CHEMICAL REVIEWS

Review

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Occurrence, Biogenesis, and Synthesis of Biologically Active Carbazole Alkaloids

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1. INTRODUCTION

1.1. General

Since our previous review,[1] there has been a tremendous development in the field of carbazole alkaloids. New synthetic methodologies have been developed, existing methodologies have been improved, and novel natural products have been isolated. In 1872, more than 100 years ago, Graebe and Glaser were the first to describe the parent compound 9*H*-carbazole (**1**) (Figure 1), which was obtained from the anthracene

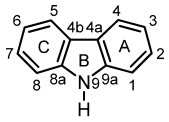

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Figure 1.

fraction of coal tar distillate.[2] Ninety years later, the disclosure of the antimicrobial properties of murrayanine (3-formyl-1-methoxycarbazole), isolated from the plant *Murraya koenigii* Spreng.,[3−5] initiated a strong interest of chemists and biologists. Since then, the intriguing structural features and promising pharmacological activities of these natural products have led to an enormous development in carbazole chemistry, which is emphasized by the large number of monographs, accounts, and reviews.[1,6−40]

The present review covers biogenesis as well as an update of carbazole chemistry based on our preceding review.[1] For the chemistry of carbazole alkaloids, we also discuss some earlier syntheses of special significance with respect to the methodology which has been applied. The classification of carbazole alkaloids used in this review is based on the ring system and the substitution pattern. The nomenclature used for carbazoles is the one that is recommended by *Chemical Abstracts*. Conventionally, tricyclic carbazole 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 9*H*-carbazole (**1**).

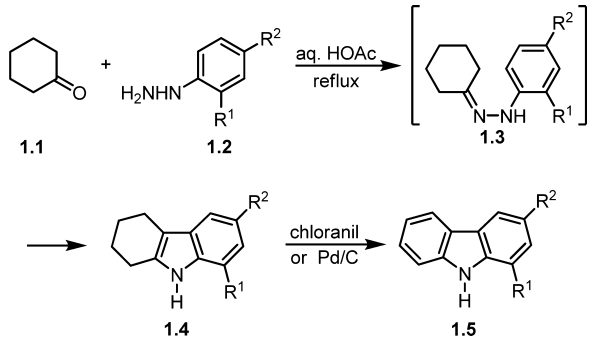
1.2. Synthetic Methods for Carbazoles

Biologically active carbazole alkaloids have been isolated from diverse natural sources and exhibit a broad range of different frameworks and functional groups. Therefore, a large number of classical and nonclassical methods have been developed for their synthesis.[1,12] Initially, the most widely used approach to carbazoles involved dehydrogenation of a 1,2,3,4-tetrahydrocarbazole. Probably the easiest way to access fully aromatized carbazoles is the construction of the central pyrrole ring by cyclization of either biphenyls with an *ortho*-nitrogen substituent or diarylamines. More recently, a variety of synthetic procedures using mild reaction conditions has been developed and some of them have proven to be general. Many of these methods afford carbazoles in good to excellent yields and use starting materials that are either commercially available or easily prepared.[1,6−12] In this section, we summarize some of the methods that have been applied frequently to the total synthesis of biologically active carbazole alkaloids.

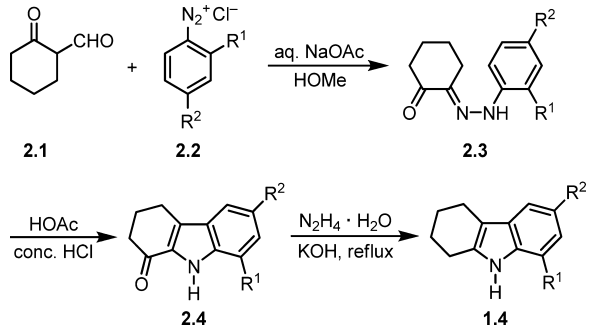
1.2.1. Fischer−Borsche Synthesis. A large number of carbazole alkaloids have been prepared via the Fischer−Borsche synthesis. Condensation of cyclohexanone (**1.1**) with phenylhydrazines **1.2** affords the arylhydrazones **1.3**. Fischer−Borsche cyclization of the arylhydrazones **1.3** forms an indole moiety and thus leads to the 1,2,3,4-tetrahydrocarbazoles **1.4**.[41,42] This reaction involves protonation, formation of a new C−C bond via a [3,3]-sigmatropic rearrangement, and elimination of ammonia. Finally, the tetrahydrocarbazoles **1.4** can be aromatized to carbazoles **1.5** by dehydrogenation using palladium on activated carbon or chloranil (Scheme 1).[43,44]

Alternatively, the hydrazones **2.3** are easily obtained by Japp−Klingemann reaction with concomitant retro-Claisen condensation of 2-formylcyclohexanone (**2.1**) and aryldiazonium salts **2.2** (Scheme 2).[45−49] Fischer−Borsche cyclization of

Scheme 1



Scheme 2



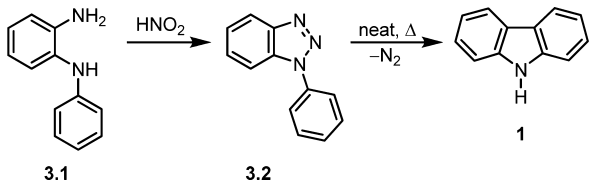
2.3 followed by deoxygenation of **2.4** represents an alternative route to the tetrahydrocarbazoles **1.4**.

In 2011, Cho and co-workers described the formation of benzo[*c*]carbazoles from 2,2′-diaminobiaryls.[50] They proposed that the reaction proceeds in close analogy to the last steps of the well-known Fischer indolization by acid-induced cyclization of an intermediate 1,1′-bi(cyclohexa-3,5-diene)-2,2′-diimine, which is formed by double imine−enamine tautomerization of the starting material.

1.2.2. Graebe−Ullmann Synthesis. The transformation of 1-phenylbenzotriazole (**3.2**) to carbazole (**1**) under thermal reaction conditions is known as Graebe−Ullmann synthesis.[51] Although this reaction proceeds almost quantitatively with unsubstituted 1-phenylbenzotriazole (**3.2**), it is very sensitive to the presence and nature of substituents. The starting material, 1-phenylbenzotriazole (**3.2**), is prepared by diazotization of *N*-(2-aminophenyl)aniline (**3.1**).[52,53] Only little is known about the mechanism of the reaction, but most likely a diradical intermediate is involved in the thermolysis of the triazole **3.2** (Scheme 3).[54]

1.2.3. Cyclization of Biarylnitrenes—Cadogan Synthesis. The deoxygenative cyclization of *o*-nitrobiphenyls **4.1** to carbazoles **4.2** in triethyl phosphite at reflux is known as Cadogan synthesis.[55] Initially, this transformation was achieved by Waterman and Vivian using stoichiometric amounts of iron oxalate at 200 °C.[56,57] However, triethyl phosphite is the most

Scheme 3



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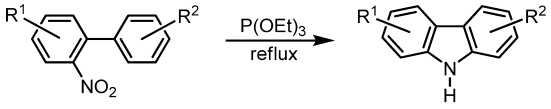
frequently used deoxygenation reagent for this transformation. Because of the tolerance of many substituents at the *o*-nitrobiaryl compound, a variety of functionalized carbazoles has been prepared by this procedure.[55] The widely accepted mechanism for this transformation involves exhaustive deoxygenation to a singlet nitrene that undergoes a C−H insertion.[58,59] Although broad in scope, the generation of large amounts of phosphorus waste represents a disadvantage of this approach.[55] Recently, this transformation has been carried out more efficiently using carbon monoxide or triphenylphosphine and analogues as stoichiometric reducing agents (Scheme 4).[60−63]

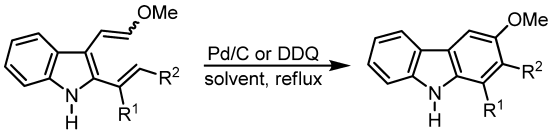
Scheme 4



4.1 4.2

1.2.4. Electrocyclic Reactions to Carbazoles. Among the various electrocyclic reactions, the transformation of 2,3-divinylindoles **5.1** to functionalized carbazoles **5.2** has been developed to an efficient method for the synthesis of a broad range of carbazole derivatives. This reaction is usually carried out at high temperatures in the presence of dehydrogenating agents such as palladium on activated carbon or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 5).[64,65]

Scheme 5

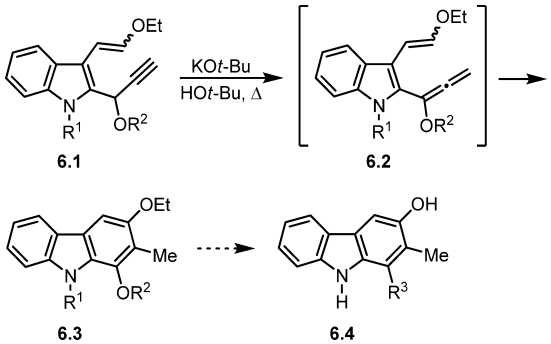


5.1 5.2

To overcome the limitations of the electrocyclic ring closure of divinylindoles, an alternative method for benzannulation has been developed in which cyclization of 2,3-difunctionalized indoles is achieved via an allene intermediate **6.2**, which is the actual starting point for the electrocyclic reaction. Thus, substituted 2-methylcarbazole derivatives **6.4** are efficiently prepared starting from 3-alkenyl-2-propargylindoles **6.1** as precursors (Scheme 6).[66,67]

A further indole benzannulation method starts from 3-(buta-1,3-dienyl)indoles **7.1** or **7.2** and has been applied to the

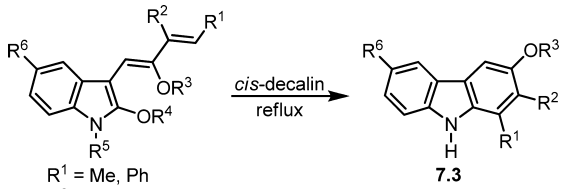
Scheme 6



6.1 6.2 6.3 6.4

synthesis of 3-oxygenated carbazoles **7.3** (Scheme 7).[68−70] This procedure involves electrocyclic ring-closure of a 3-(buta-1,3-

Scheme 7



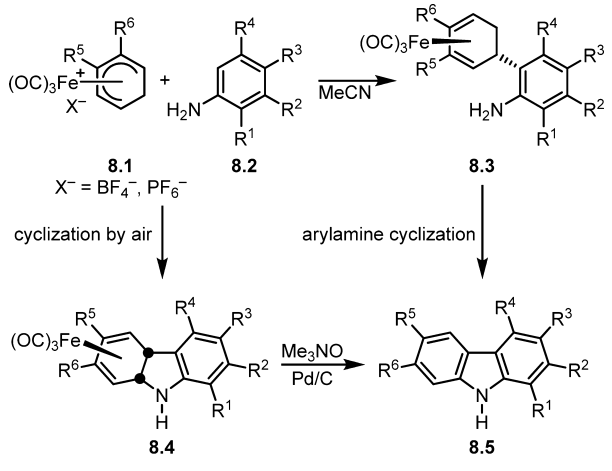
R^1 = Me, Ph
R^2 = H, Me, Et, Ph
R^6 = H, Cl, Br
7.1 R^3 = TMS; R^4 = Me; R^5 = Ac
7.2 R^3, R^4, R^5 = COOEt

7.3

dienyl)indole and subsequent aromatization to the carbazole nucleus by elimination. Following Sakamoto's protocol, the 3-(buta-1,3-dienyl)indoles **7.1** are obtained by Wittig olefination of 1-acetyl-2-methoxy-indolin-3-one.[68,69] Alternatively, 3-(buta-1,3-dienyl)indoles **7.2** can be prepared according to Beccalli by condensation of indoline-2,3-diones with α,β-unsaturated ketones.[70]

1.2.5. Iron-Mediated Carbazole Synthesis. The tricarbonyl iron-coordinated cyclohexadienylium ions **8.1** were shown to be excellent electrophiles for electrophilic aromatic substitution of functionalized electron-rich arylamines **8.2**.[71] Oxidative cyclization of the resulting arylamine-substituted tricarbonyl(η^4-cyclohexadiene)iron complexes **8.3** leads directly to carbazoles. The sequence of those two reactions represents a highly convergent route to a wide range of carbazoles. Because of the mild reaction conditions and the applicability of fully functionalized arylamines, this methodology proved to be especially advantageous for the synthesis of highly substituted carbazoles. The reaction involves consecutive iron-mediated C−C and C−N bond formations followed by aromatization (Scheme 8).[1,12,15,18,22−29,38,72−74] Knölker and co-workers have

Scheme 8



developed three alternative procedures for the iron-mediated carbazole synthesis that are distinguished by different modes for the oxidative cyclization: the arylamine cyclization, the quinone imine cyclization, and the oxidative cyclization by air.[1,12,28] The direct transformation of arylamine-substituted tricarbonyl(η^4-cyclohexadiene)iron complexes **8.3** to carbazoles **8.5** proceeds via a sequence of oxidative cyclization, aromatization, and

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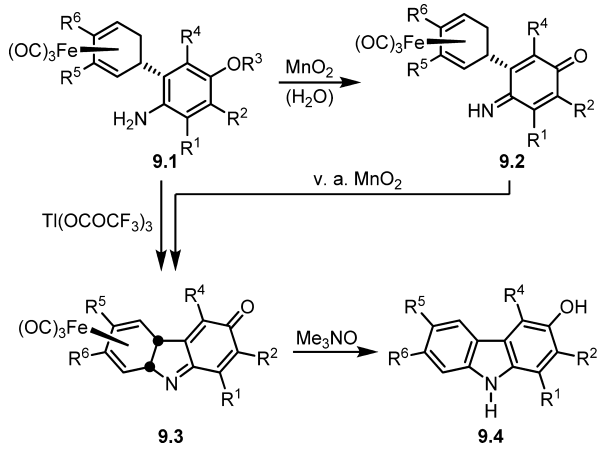
demetalation. This iron-mediated arylamine cyclization has been widely applied to the total synthesis of a broad range of 1-oxygenated, 3-oxygenated, and 3,4-dioxygenated carbazole alkaloids (Scheme 8). Alternatively, reaction of the tricarbonyl iron-coordinated cyclohexadienylium ions **8.1** with the arylamines **8.2** in air leads directly to the tricarbonyl iron-coordinated 4*a*,9*a*-dihydrocarbazoles **8.4**. Demetalation of the complexes **8.4** to the corresponding free ligands and subsequent aromatization provide the carbazoles **8.5**.

For the quinone imine cyclization, arylamine-substituted tricarbonyl(η^4-cyclohexadiene)iron complexes **9.1** are chemoselectively oxidized to the quinone imines **9.2** prior to cyclodehydrogenation. Subsequent oxidative cyclization of the complexes **9.2** affords the 4*b*,8*a*-dihydro-3*H*-carbazol-3-ones **9.3**, which on demetalation tautomerize to the 3-hydroxycarbazoles **9.4**. Thus, this cyclization mode has been used particularly for the total synthesis of 3-oxygenated carbazole alkaloids (Scheme 9).[75]

Scheme 9



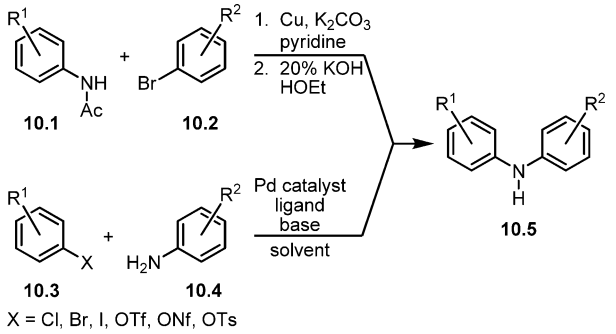
1.2.6. Palladium-Catalyzed Cyclizations to Carbazoles.

Cyclodehydrogenation of diarylamines is the most versatile and practical method for the synthesis of carbazoles. Initially, this reaction was achieved photochemically, thermally in the presence of elemental iodine (~350 °C) or platinum (~500 °C), via formation of free radicals as intermediates using benzoyl peroxide in chloroform, or by using activated metals such as degassed Raney nickel or palladium on activated carbon. However, most of these methods suffer from low to moderate yields and in some cases harsh reaction conditions.[1,7,12]

The classical method for the synthesis of the required diarylamines **10.5** is the Ullmann–Goldberg coupling of acetanilides **10.1** with bromobenzenes **10.2** and subsequent alkaline hydrolysis of the acetamide moiety (Scheme 10).[76−79] Nowadays, the palladium(0)-catalyzed Buchwald–Hartwig amination represents the preferred method for the synthesis of diarylamines.[80−85] Thus, aryl halides, aryl triflates, aryl nonaflates, and even aryl tosylates[86−88] on reaction with arylamines **10.4** directly provide diarylamines **10.5** in high yields. The advantages of the Buchwald–Hartwig protocol are application of only catalytic amounts of the transition metal (palladium[0]) and mild reaction conditions.

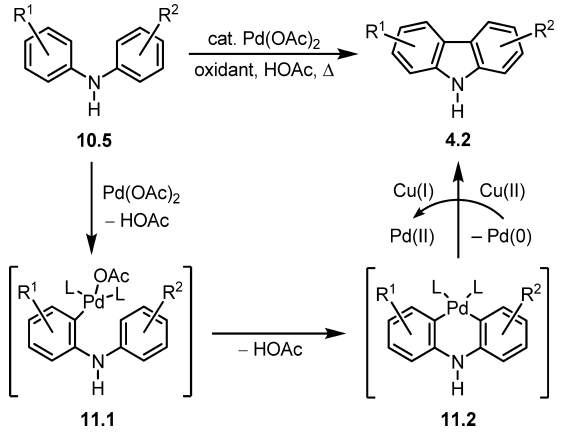
The palladium(II)-mediated oxidative cyclization of diarylamines **10.5** to carbazoles **4.2** was first reported by Åkermark and co-workers in 1975.[89] The oxidative cyclization is believed

Scheme 10



to proceed via electrophilic attack of the palladium(II) species generating a palladium complex **11.1** followed by cyclization to a palladacycle **11.2**. Reductive elimination of the palladacycle **11.2** generates the central carbon–carbon bond of the carbazole skeleton. This transformation tolerates a wide range of substituents and represents one of the most general procedures for cyclization of diarylamines to carbazole derivatives. However, stoichiometric amounts of palladium(II) acetate were required.[89] For the cyclization of diarylamines containing strong acceptor substituents, even an overstoichiometric amount of palladium(II) acetate (up to 2 equiv) had to be employed. The cyclization is promoted by trifluoroacetic acid (TFA) or methanesulfonic acid.[89] In 1994, Knölker and co-workers demonstrated for the first time that this reaction becomes catalytic in palladium by reoxidation of palladium(0) to palladium(II) using copper(II) acetate.[28,29,90−97] Since then, several alternative co-oxidants (e.g., *tert*-butyl hydroperoxide, benzoquinone, and catalytic tin(II) acetate in combination with oxygen, oxygen, and air, respectively) have been used for this transformation (Scheme 11).[98−108] Very recently, Knölker and

Scheme 11



co-workers have isolated and characterized by X-ray crystallography a palladacycle of the type **11.2**.[109] This key intermediate of the palladium(II)-catalyzed oxidative cyclization, which had been proposed by Åkermark 37 years before, was trapped by using pivaloyloxy and acetyl groups for directed palladation.

Larock and co-workers reported a one-pot, two-step method for the synthesis of carbazoles **12.4** via cross-coupling of 2-iodoanilines **12.1** (Z = I) with silylaryl triflates **12.2** (X = TMS, Y = OTf) in the presence of cesium fluoride. The reaction probably proceeds via an aryne intermediate followed by palladium(0)-catalyzed cyclization to afford carbazoles **12.4**

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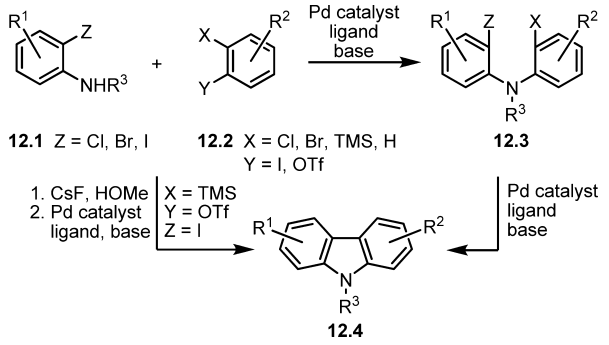
(Scheme 12).[110,111] Independently, various groups have developed alternative procedures for the cyclization of

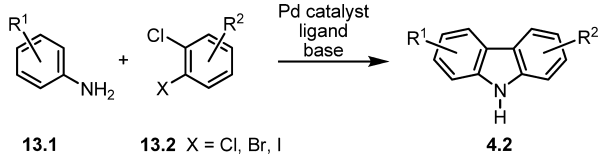
Scheme 12



halogenated diarylamines **12.3** to carbazoles **12.4**.[112−116] The advantage of these methodologies is the application of a palladium(0) species as active catalyst for the cyclization reaction, which usually allows for lower catalyst loadings and the absence of oxidizing reaction conditions. However, the starting materials (halogenated diarylamines) are not as easily accessible as the nonhalogenated diarylamines that are employed in the palladium(II)-catalyzed process described above (Scheme 11).

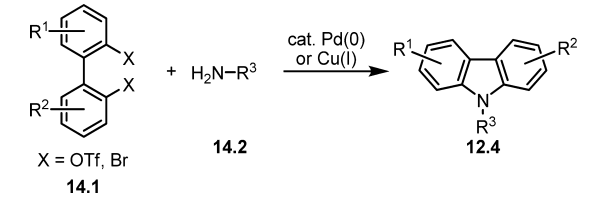
Recently, Ackermann and Althammer reported an extension of this methodology for a one-pot synthesis of carbazoles **4.2** via a domino N−H/C−H bond activation by a palladium catalyst.[117,118] Using this procedure, coupling of a range of anilines **13.1** with 1,2-dihaloarenes **13.2** led to carbazoles **4.2** (Scheme 13).

Scheme 13



An analogous approach is the synthesis of carbazoles **12.4** via 2-fold palladium(0)-catalyzed Buchwald−Hartwig coupling of biphenyl-2,2′-diyl bistriflates or the corresponding 2,2′-dihalobiphenyls **14.1** with primary amines or ammonia equivalents **14.2** (Scheme 14).[119−122] The required biphenyl-

Scheme 14



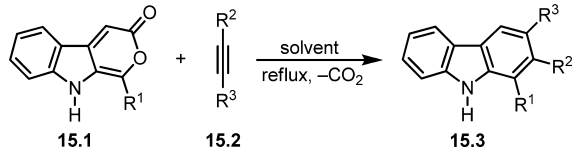
2,2′-diyl bistriflates (X = OTf) **14.1** are prepared by Suzuki−Miyaura coupling of *o*-halophenols with *o*-hydroxyphenylboronic acids.[123,124] The best ammonia equivalent for the final conversion to unprotected carbazoles **12.4** appeared to be *O*-*tert*-butyl carbamate (R^3 = Boc). Li et al. described the application of copper(I) salts to an analogous transformation.[125]

In 2005, Buchwald and co-workers described the oxidative cyclization of 2-acetamidobiphenyls to *N*-acetylcarbazoles using catalytic amounts of palladium(II) acetate in combination with copper(II) acetate under an oxygen atmosphere.[126,127] Gaunt and co-workers described an analogous approach using catalytic amounts of palladium(II) acetate and (diacetoxyiodo)benzene ($PhI(OAc)_2$) or *tert*-butyl benzoperoxoate as oxidant.[128] Youn et al. described the same approach using 2-toluenesulfonamidobiphenyls as starting material.[129] The synthesis of the carbazole nucleus from anilides and benzene by double C−H activation has been described as well.[130,131] The palladium-catalyzed cyclization of *ortho*,*ortho*-disubstituted diarylamines led to 4*a*,9*a*-dihydrocarbazole derivatives.[132−134]

1.2.7. Miscellaneous Methods. In addition to the methods described above, several alternative procedures for the construction of the carbazole framework have been developed. However, some of these methods have been used only for the synthesis of simple non-natural carbazoles.[1,12] Some recent examples include the copper- or platinum-induced cyclization of 2-aminobiphenyls,[135,136] thermal[137] or ruthenium-catalyzed[138−140] cyclization of 2-azidobiphenyls, photolytically induced cyclization of 2-chlorodiarylamide anions,[141] various benzannulation approaches,[142−163] and other cyclization reactions.[164−173] In this section, we focus on methods that have been applied to the total synthesis of naturally occurring carbazole alkaloids.

Exploitation of indolo-2,3-quinodimethanes and their cyclic analogues for the synthesis of carbazole alkaloids attracted great interest because these compounds can undergo Diels−Alder reactions with a wide variety of dienophiles to afford functionalized carbazoles.[174] Among various cyclic analogues of indolo-2,3-quinodimethanes, the pyrano[3,4-*b*]indoles **15.1** have been used for the total synthesis of a range of carbazole alkaloids. The cyclic dienes **15.1** react with dienophiles **15.2** to afford bridged intermediates, which by extrusion of carbon dioxide give rise to the carbazoles **15.3** (Scheme 15).[21,175−178]

Scheme 15



Application of Knölker's iron-mediated approach to the synthesis of 2-oxygenated tricyclic carbazoles revealed in certain cases a limitation due to moderate yields of the oxidative cyclization.[179,180] Therefore, Knölker and co-workers have developed a complementary approach via a molybdenum-mediated construction of the framework. Electrophilic aromatic substitution of electron-rich arylamines **16.2** by the cationic molybdenum complex **16.1** affords regio- and stereoselectively the molybdenum complexes **16.3**. Oxidative cyclization of **16.3** with concomitant aromatization and demetalation using activated manganese dioxide provides the carbazoles **15.3** (Scheme 16).[181]

Witulski and Alayrac utilized a Vollhardt-type cyclotrimerization of diynes **17.1** and alkynes **15.2** in the presence of catalytic amounts of Wilkinson's catalyst ($RhCl(PPh_3)_3$) for the synthesis of substituted carbazoles **17.2** (Scheme 17).[182]

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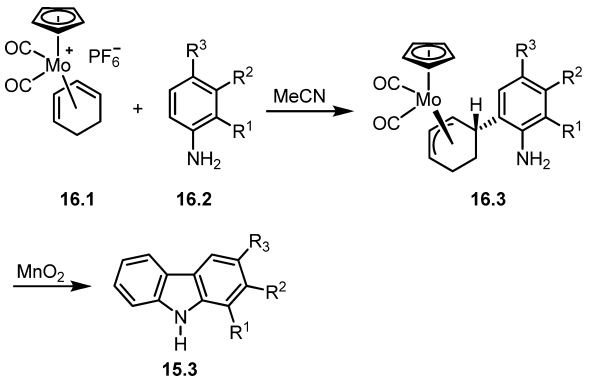
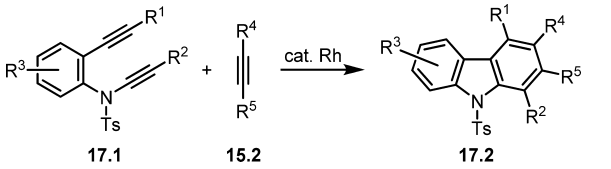
Scheme 16



Scheme 17



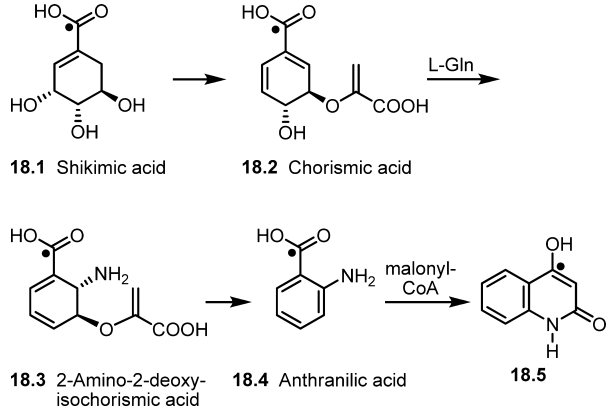
2. BIOGENESIS OF CARBAZOLE ALKALOIDS

On the basis of their natural origin, carbazole alkaloids are classified into two main groups. To the first group belong carbazole alkaloids isolated from higher plants. They generally feature a C_1-substituent at C-3 (a methyl group or its oxidized equivalents). To the second group belong carbazole alkaloids isolated from other natural sources like microorganisms, which usually lack such a carbon substituent at C-3. For both groups exceptions are known (e.g., clausine V (**161.1**) and pityriazole (**33.5**)). Because of the structural difference, one can assume that both groups of alkaloids are generated by different pathways. Some of the proposed biosynthetic routes discussed below are lacking clear experimental evidence and are based solely on rational proposals.

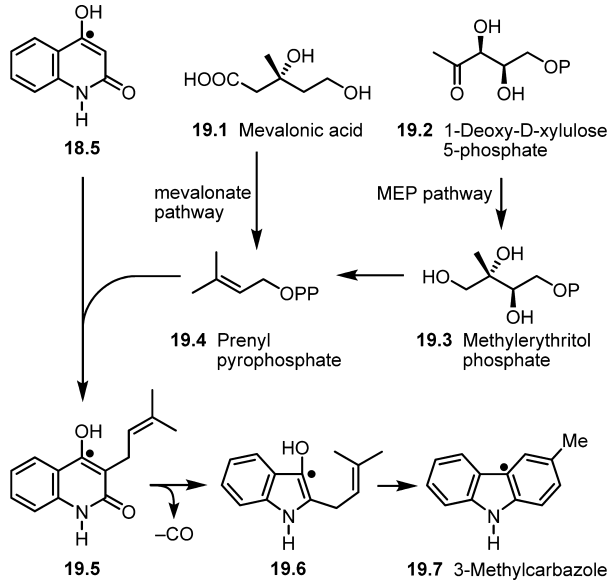
The isolation of 3-methylcarbazole (**19.7**) along with its oxidized congeners 3-formylcarbazole (**20.9**) and methyl carbazole-3-carboxylate (**20.10**) from taxonomically related plants of the family Rutaceae (genera: *Murraya, Clausena,* and *Glycosmis*) provides circumstantial evidence for in vivo oxidation of the methyl group. This hypothesis was supported by the photochemical oxidation of the methyl group at C-3 of carbazole alkaloids.[183] Further confirmation for in vivo oxidation of the methyl group at C-3 of carbazoles derives from the co-occurrence of a range of differently oxygenated 3-methylcarbazoles and their respective oxidized analogues in the same species (*Murraya*, *Clausena*, and *Glycosmis*) or at least in the same family (Rutaceae).[1,12,184,185] From these findings it has been concluded that the common precursor for carbazole alkaloids in plants is 3-methylcarbazole (**19.7**), which at later stages of the biosynthetic pathway may be oxidized at the methyl group and/or oxygenated, prenylated, or geranylated at different positions.

To date, the biosynthesis of the carbazole framework is not fully understood and is lacking experimental support. However, the so-called "anthranilic acid pathway", which proceeds via the 3-prenylquinolone (**19.5**), represents the most widely accepted proposal for the biogenesis of carbazole alkaloids in higher plants. Support for this biogenetic proposal comes from the isolation of a range of carbazole alkaloids with a carbon substituent at C-3 along with further alkaloids deriving from anthranilic acid from the taxonomically related plants of the genera *Murraya*, *Glycosmis*, and *Clausena* (Rutaceae family).[186] Thus, it has been suggested that the carbazole nucleus derives from shikimic acid (**18.1**) and prenyl pyrophosphate (**19.4**) (Schemes 18 and 19).[13,187−192] Shikimic acid (**18.1**) itself is

Scheme 18



Scheme 19



formed from 3-dehydroquinic acid by a sequence of dehydration and reduction steps and has been obtained from the fruits of the Japanese plant *Illicium religiosum* Sieb. (Japanese shikimi)[193] many years before its role in metabolism had been discovered.[187] The biogenesis of the carbazole nucleus then proceeds from shikimic acid (**18.1**) via chorismic acid (**18.2**), 2-amino-2-deoxyisochorismic acid (**18.3**), and anthranilic acid (**18.4**) to the quinolone **18.5** (Scheme 18). The quinolone **18.5** later on provides the indole unit, which corresponds to the rings B and C of the carbazole nucleus. Anthranilic acid (**18.4**) has a large abundance in plants of the Rutaceae family. Prenyl pyrophosphate provides the carbon atoms for ring A with the methyl substituent at C-3.[194]

3-Methylcarbazole (**19.7**) is considered to be formed via the 3-prenylquinolone **19.5** and the 2-prenylindole **19.6** (Scheme 19).[187−189,191,192] Prenylation of the quinolone **18.5** at C-3 by reaction with prenyl pyrophosphate (**19.4**) provides the 3-

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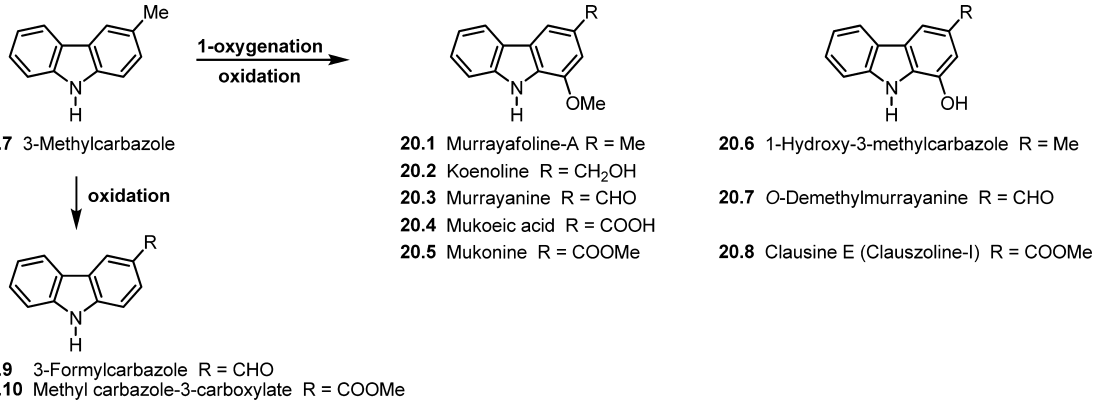
Scheme 20



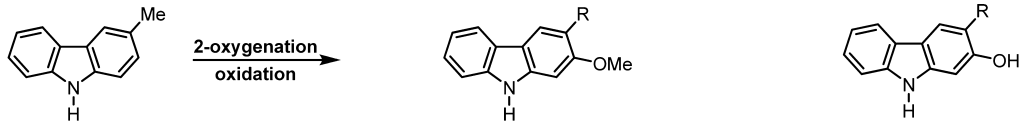
19.7 3-Methylcarbazole

20.1 Murrayafoline-A R = Me
20.2 Koenoline R = CH_2OH
20.3 Murrayanine R = CHO
20.4 Mukoeic acid R = COOH
20.5 Mukonine R = COOMe

20.6 1-Hydroxy-3-methylcarbazole R = Me
20.7 *O*-Demethylmurrayanine R = CHO
20.8 Clausine E (Clauszoline-I) R = COOMe

20.9 3-Formylcarbazole R = CHO
20.10 Methyl carbazole-3-carboxylate R = COOMe

Scheme 21



19.7 3-Methylcarbazole

21.1 2-Methoxy-3-methylcarbazole R = Me
21.2 *O*-Methylmukonal (Glycosinine) R = CHO
21.3 Clausine L R = COOMe (O-Methylmukonidine, Methyl 2-methoxycarbazole-3-carboxylate

21.4 2-Hydroxy-3-methylcarbazole R = Me
21.5 Mukonal R = CHO
21.6 Mukonidine R = COOMe

prenylquinolone **19.5**. Depending on the organism, prenyl pyrophosphate (**19.4**) can be formed via two independent pathways.[187] Mammals and fungi exclusively utilize the mevalonate pathway in which prenyl pyrophosphate (**19.4**) is derived from mevalonic acid (**19.1**). In an alternative biosynthetic route, prenyl pyrophosphate (**19.4**) is synthesized from 1-deoxy-D-xylulose 5-phosphate (**19.2**) via methylerythritol phosphate (**19.3**). The MEP pathway (methylerythritol pathway) is utilized by plants, algae, and bacteria in addition to the mevalonate pathway. Depending on where the natural product is formed, the terpenoid carbon atoms may derive from mevalonic acid (**19.1**) or from methylerythritol phosphate (**19.3**). The last steps of the biosynthesis of 3-methylcarbazole (**19.7**), the transformation of the 3-prenylquinolone **19.5** to 3-methylcarbazole (**19.7**), are lacking any experimental support. However, they are presumed to proceed via extrusion of carbon monoxide and subsequent oxidative cyclization of the intermediate 2-prenylindole **19.6** (Scheme 19).[187−189,191,192]

The occurrence of murrayanine (**20.3**) along with murrayafoline-A (**20.1**), koenoline (**20.2**), mukoeic acid (**20.4**), mukonine (**20.5**), 1-hydroxy-3-methylcarbazole (**20.6**), *O*-demethylmurrayanine (**20.7**), clausine E (clauszoline-I) (**20.8**), 3-formylcarbazole (**20.9**), methyl carbazole-3-carboxylate (**20.10**), 2-methoxy-3-methylcarbazole (**21.1**), *O*-methylmukonal (glycosinine) (**21.2**), clausine L (*O*-methylmukonidine, methyl 2-methoxycarbazole-3-carboxylate) (**21.3**), 2-hydroxy-3-methylcarbazole (**21.4**), mukonal (**21.5**), mukonidine (**21.6**), and 3-methylcarbazole (**19.7**) in taxonomically related genera of plants of the family Rutaceae (*Murraya*, *Glycosmis*, and *Clausena*) indicates the in vivo oxygenation and oxidation of 3-methylcarbazole (**19.7**) (Schemes 20 and 21).

The in vivo oxygenation of 3-methylcarbazole (**19.7**) to 2-hydroxy-3-methylcarbazoles was supported by biomimetic hydroxylation of 3-methylcarbazole (**19.7**) with Fenton's reagent (Fe^{2+}/H_2O_2) or under Udenfried's conditions (Fe^{2+}/EDTA/ascorbic acid/oxygen), a reaction which is prototypal for the oxidase function. 1-Hydroxy-3-methylcarbazole (**20.6**) was obtained by oxidation of 3-methylcarbazole (**19.7**) using Fenton's reagent, while 2-hydroxy-3-methylcarbazole (**21.4**) was formed under Udenfried's conditions. In both cases other oxidation products were formed as well.[195] An in vivo oxidation of the methyl group at C-3 to hydroxymethyl, formyl, and carboxyl groups is found for various alkaloids and has been supported by the photochemical oxidation of the methyl group at C-3 of carbazole alkaloids (Schemes 20 and 21).[183]

The 2-oxygenation of 3-methylcarbazole (**19.7**) leads to 2-hydroxy-3-methylcarbazole (**21.4**), which represents the precursor for pyranocarbazoles and furocarbazoles. This hypothesis has been supported by the isolation of mukoenine-A (girinimbilol) (**22.1**), heptaphylline (**22.2**), furostifoline (**22.3**), girinimbine (**22.4**), and murrayacine (**22.5**). Mukoenine-A (girinimbilol) (**22.1**) can be considered as the precursor for furo[3,2-*a*]- and pyrano[3,2-*a*]carbazole alkaloids. The isolation of mukoenine-A (girinimbilol) (**22.1**) and furostifoline (**22.3**) from *Murraya* species supports the proposed biosynthetic origin of the furan ring, which has been suggested to be formed via cyclization pathway (a) of the prenylated precursor **22.1**. The occurrence of mukoenine-A (girinimbilol) (**22.1**) and girinimbine (**22.4**) in *Murraya koenigii* and heptaphylline (**22.2**) and murrayacine (**22.5**) in *Clausena heptaphylla* supports the suggested biosynthetic origin of the pyran ring, which may be generated via cyclization pathway (b) from mukoenine-A (**22.1**) or heptaphylline (**22.2**), respectively (Scheme 22).[196]

Furthermore, 2-hydroxy-3-methylcarbazole (**21.4**) could represent a precursor for carbazole alkaloids with a C_{23}-skeleton. Introduction of geraniol as a C_{10}-unit at C-1 of 2-hydroxy-3-methylcarbazole (**21.4**) would yield mahanimbinol (mahanimbilol) (**23.1**). The geranyl monoterpene unit could undergo various transformations to afford isomeric carbazoles with a C_{23}-skeleton, such as mahanimbine (**23.2**), cyclomahanimbine (murrayazolidine, curryanin) (**23.3**), and bicy-

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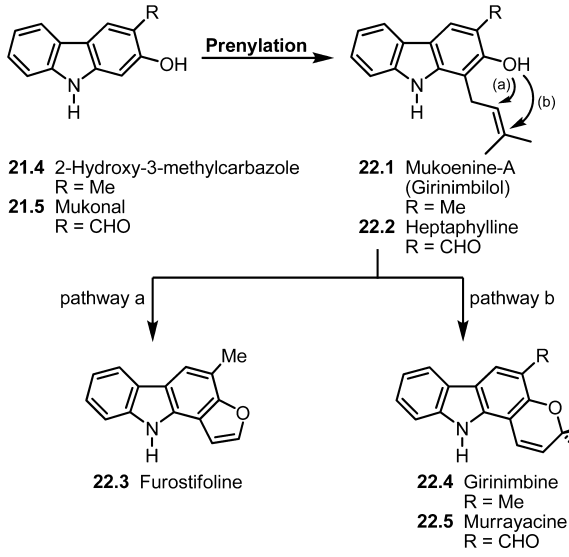
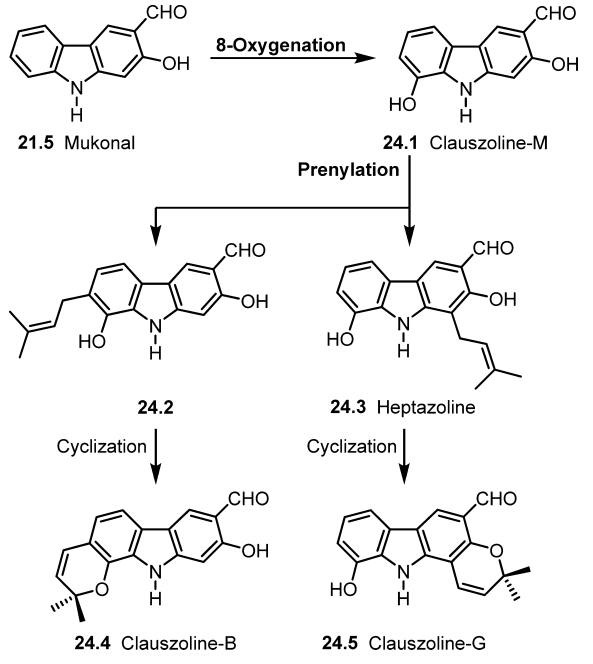
Scheme 22



clomahanimbine (**23.4**). Therefore, mahanimbinol (mahanimbilol) can be considered as the parent compound for carbazoles with a C_{23}-skeleton. The isolation of 2-hydroxy-3-methylcarbazole (**21.4**), mahanimbinol (mahanimbilol) (**23.1**), mahanimbine (**23.2**), cyclomahanimbine (murrayazolidine, curryanin) (**23.3**), and bicyclomahanimbine (**23.4**) from *Murraya koenigii* provides circumstantial evidence for the origin of the carbazole C_{23}-skeleton from the geranylated congener mahanimbinol (mahanimbilol) (**23.1**) (Scheme 23).[196,197]

Mukonal (**21.5**), an oxidation product of 2-hydroxy-3-methylcarbazole (**21.4**) (see Scheme 21), can be further hydroxylated at the C-ring of the carbazole nucleus to afford clauszoline-M (**24.1**). Addition of a C_5-unit at either ring of clauszoline-M (**24.1**) provides the prenylated carbazole derivatives **24.2** and **24.3** (heptazoline) which on cyclization lead to clauszoline-B (**24.4**) and clauszoline-G (**24.5**), respectively. The isolation of mukonal (**21.5**), clauszoline-M (**24.1**), heptazoline (**24.3**), clauszoline-B (**24.4**), and clauszoline-G (**24.5**) from taxonomically related plants of the genera *Murraya* and *Clausena* (Rutaceae family) strongly suggests that the pyranocarbazoles originate from their prenylated congeners (Scheme 24).[198]

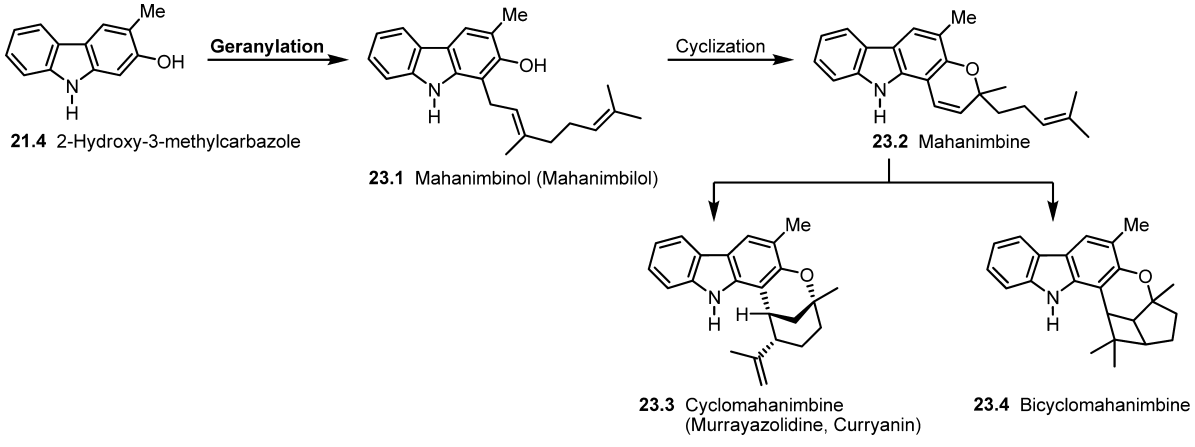
Scheme 24



Chakraborty and co-workers conducted some hydroxylation studies on 3-methylcarbazole (**19.7**) using Udenfried's conditions. In those experiments, hydroxylation was accompanied by dimerization of the carbazoles to afford biscarbazole alkaloids, which are also found in higher plants.[195,199] Thus, various natural oxidative dimerization products like murrastifoline-A (**25.1**), murrastifoline-F (**25.2**), and bismurrayafoline-A (**25.3**) could originate from murrayafoline-A (**20.1**) (Scheme 25). The co-occurrence of murrayafoline-A (**20.1**),[200,201] murrastifoline-A (**25.1**),[202] murrastifoline-F (**25.2**),[203] and bismurrayafoline-A (**25.3**)[204] in *Murraya euchrestifolia* Hayata provides strong evidence for the oxidative dimerization of murrayafoline-A (**20.1**).

Similarly, 1-hydroxy-3-methylcarbazole (**20.6**) and 2-hydroxy-3-methylcarbazole (**21.4**) could dimerize to 2,2′-bis(1-hydroxy-3-methylcarbazole) (**26.1**)[205] and bis-2-hydroxy-3-methylcarbazole [1,1′-bis(2-hydroxy-3-methylcarbazole)] (**26.2**) (Scheme 26).[181] So far, 2,2′-bis(1-hydroxy-3-methylcarbazole) (**26.1**) has not been isolated from nature. However, the isolation of 2-hydroxy-3-methylcarbazole (**21.4**)[206] and the

Scheme 23



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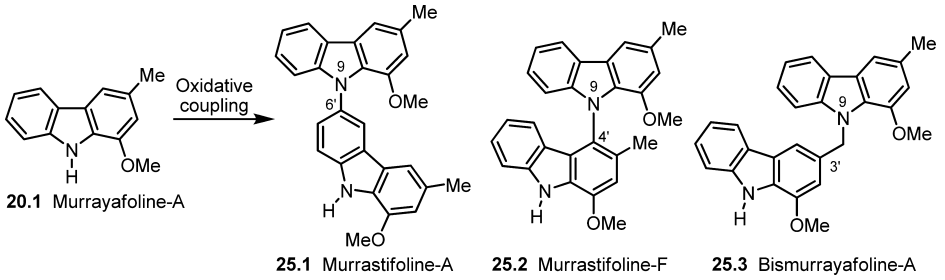
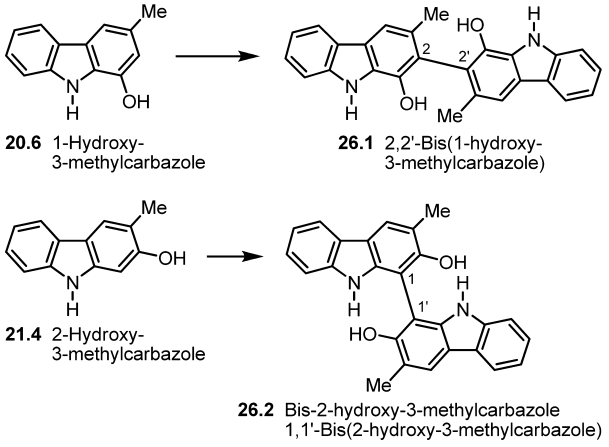
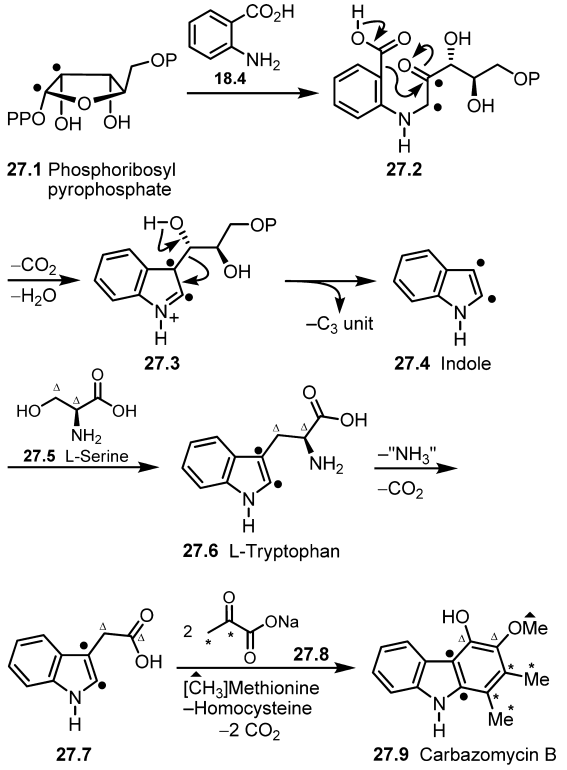
Scheme 25



Scheme 26



Scheme 27



dimer **26.2**[203] from the same plant (*Murraya koenigii*) supports the hypothesis of oxidative dimerization of 2-hydroxy-3-methylcarbazole (**21.4**).

Biogenetic studies on carbazole alkaloids from sources other than higher plants suggested an alternative pathway to these carbazoles that is based on L-tryptophan (**27.6**) as the biogenetic precursor. In 1990, Nakamura and co-workers described for the first time the biosynthetic origin of the complete carbon framework of carbazomycin B (**27.9**) isolated from a microorganism. Feeding experiments with ^{14}C- and ^{13}C-labeled compounds and subsequent measurement of radioactivity and recording of ^{13}C NMR spectra confirmed that L-tryptophan (**27.6**) provides the indole moiety as well as C-3 and C-4 of the hexasubstituted benzene ring (ring A). Thus, L-tryptophan (**27.6**) is the biogenetic precursor of carbazomycin B (**27.9**). The indole ring of L-tryptophan (**27.6**) is formed from anthranilic acid (**18.4**) by incorporation of two carbon atoms from phosphoribosyl pyrophosphate (**27.1**) with concomitant loss of the carboxyl group and dehydration (Scheme 27). The remaining ribosyl carbon atoms are subsequently removed by a retro-aldol reaction leading to a bound form of indole (**27.4**). The side chain of L-tryptophan (**27.6**) is then formed by incorporation of an L-serine (**27.5**) unit.[187] Additional feeding experiments with ^{13}C-labeled alanine, a known biosynthetic equivalent for the C_2-unit of pyruvic acid, and subsequent ^{13}C NMR measurements confirmed the origin of the C-1 and C-2 carbon atoms of the carbazole A-ring and their methyl groups. Finally, a feeding experiment using ^{13}C-labeled methionine indicated the origin of the methyl group of the methoxy substituent. From these studies it has been concluded that L-tryptophan (**27.6**), after decarboxylation and deamination, reacts with 2 molecules of sodium pyruvate (**27.8**) followed by methylation with methionine to give the carbon skeleton of carbazomycin B (**27.9**).[207,208]

The biogenesis of ellipticine (**28.9**), a member of the pyrido[4,3-*b*]carbazole alkaloid family, has attracted some attention due to the application of ellipticine derivatives in medicine. Although it still lacks complete experimental support,[209,210] elegant and rational biogenetic pathways have been suggested for the pyrido[4,3-*b*]carbazole alkaloids.[211−214] Ellipticine (**28.9**) and its natural isomer olivacine (**28.10**) are usually present in the same plants along with uleine. Therefore, it is presumed that these *Aspidosperma* alkaloids have a common biogenetic precursor. Prior to Wenkert's first detailed biogenetic proposal for ellipticine (**28.9**) and related alkaloids,[211] Woodward et al. had already suggested a biosynthetic relation of ellipticine (**28.9**) and uleine, two structurally different *Aspidosperma* alkaloids.[215] Wenkert's nontryptophan pathway is based on the common biogenetic intermediate **28.4** (Scheme 28). Compound **28.4** derives from the combination of glycosylideneanthranilic acid (**28.1**), a tryptophan precursor, with a secoprephenateformaldehyde (SPF) unit (**28.2**) or secologanin (**28.3**), as potential precursors for *Aspidosperma* alkaloids. The α-oxidation of

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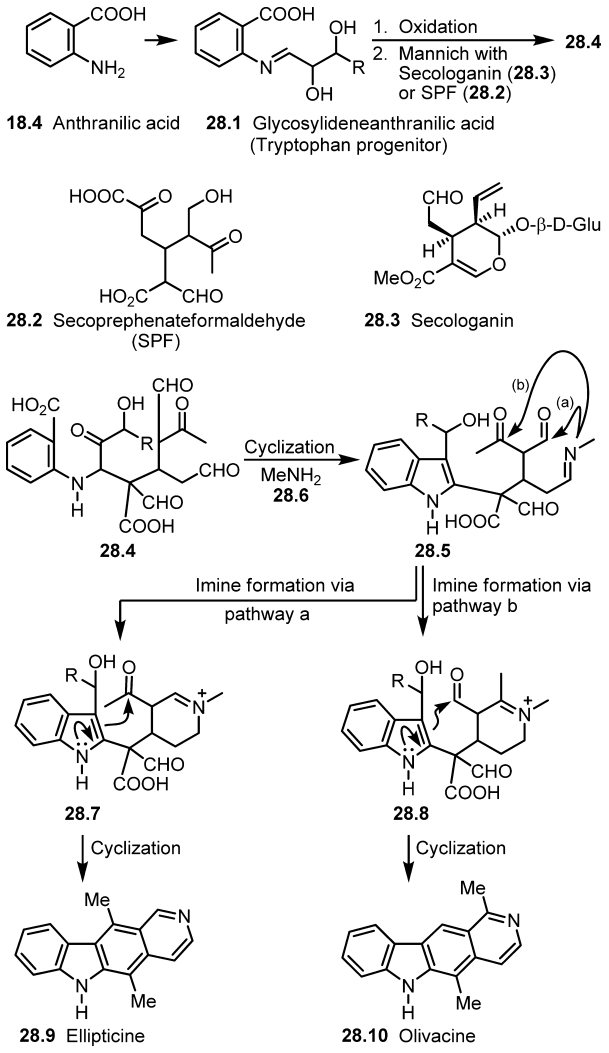
Scheme 28

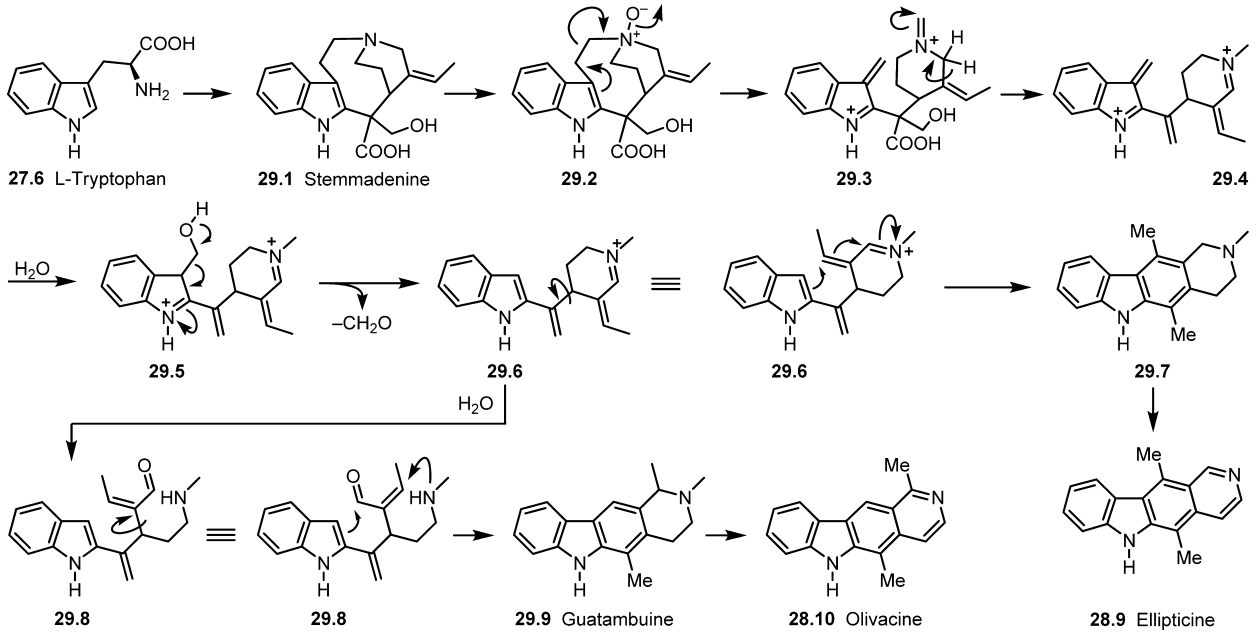


glycosylideneanthranilic acid (**28.1**) and subsequent Mannich condensation with SPF (**28.2**) or secologanin (**28.3**) would produce the α-alkyl-β-glycosylindole **28.5** as precursor for *Aspidosperma* alkaloids. This intermediate could undergo two modes of imine formation via the depicted pathways a and b to afford compounds **28.7** and **28.8**, respectively. Cyclization of **28.7** and **28.8** at the β-position of the indole and extrusion of the β-glycosyl group (retro-aldol reaction) would lead to ellipticine (**28.9**) and olivacine (**28.10**).[211]

In an alternative proposal for the biosynthesis of ellipticine (**28.9**) and olivacine (**28.10**), Potier and Janot suggested that L-tryptophan (**27.6**) is transformed into stemmadenine (**29.1**), which then serves as precursor for the pyridocarbazoles (Scheme 29).[212] However, labeling experiments with both L-tryptophan (**27.6**) and stemmadenine (**29.1**) indicated a weak incorporation for uleine and none at all for ellipticine (**28.9**) and olivacine (**28.10**).[210] Thus, this hypothesis needs further experimental support. Nevertheless, Besselièvre and Husson developed a total synthesis of ellipticine (**28.9**) and olivacine (**28.10**) based on this biogenetic model.[214] The key intermediate is the conjugated iminium salt **29.6**, which has been frequently proposed as precursor for the biogenesis of indole alkaloids. Stemmadenine *N*-oxide (**29.2**), generated from L-tryptophan (**27.6**) undergoes N−O bond cleavage followed by a series of further transformations, leading to the conjugated iminium salt **29.6** (Scheme 29).[216] An intramolecular Mannich-type reaction of **29.6** provides ellipticine (**28.9**) via intermediate **29.7**. Alternatively, hydrolysis of the conjugated iminium salt **29.6** would afford the 2-vinyl-substituted indole **29.8**, which on cyclization would lead to guatambuine (**29.9**). Demethylation and dehydrogenation of guatambuine (**29.9**) would provide olivacine (**28.10**).[212]

In 1988, the groups of Cordell[217−219] and Pearce[220] independently published preliminary results of biosynthetic studies on staurosporine (**30.3**) and rebeccamycin (**32.11**), typical representatives of indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids. Cordell's investigation on staurosporine (**30.3**) was based on feeding experiments with L-tryptophan (**27.6**) and

Scheme 29



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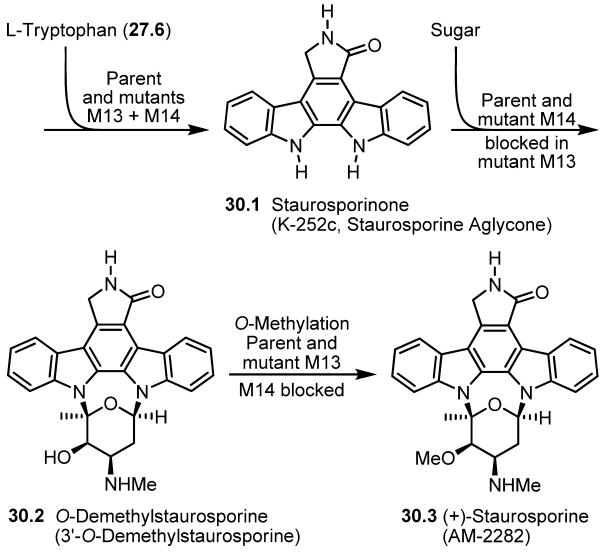
indicated that the staurosporine aglycone (**30.1**) is formed from 2 molecules of L-tryptophan (**27.6**). These experiments gave a first insight into the biosynthesis of staurosporine (**30.3**).[218,219]

Pearce's model study on the biosynthesis of rebeccamycin (**32.11**), a halogenated indolocarbazole natural product of *Lechevalieria aerocolonigenes* (former *Saccharothrix aerocolonigenes*),[221] indicated that **32.11** derives from 1 unit of D-glucose and methionine and 2 units of L-tryptophan (**27.6**). Moreover, it has been shown that the nitrogen atom of the phthalimide function does not originate from the α-amino group of one of the two tryptophan units. From these studies it was presumed that D-glucose and L-methionine are probably incorporated via UDP-glucose and *S*-adenosylmethionine.[220] L-Tryptophan (**27.6**) may be introduced via deamination to indol-3-ylpyruvic acid (**32.4**).

Until the mid-1990s, the knowledge of the biosynthesis of the pharmacologically interesting staurosporine (**30.3**) was limited to the early stages, the incorporation of L-tryptophan (**27.6**).[217,218] In 1995, Hoehn and co-workers were the first to use blocked mutants of *Streptomyces longisporoflavus* R 19 for studying the biosynthetic pathway to staurosporine (**30.3**) and isolated *O*-demethylstaurosporine (3′-*O*-demethylstaurosporine) (**30.2**) from the last step (Scheme 30).[222,223] The

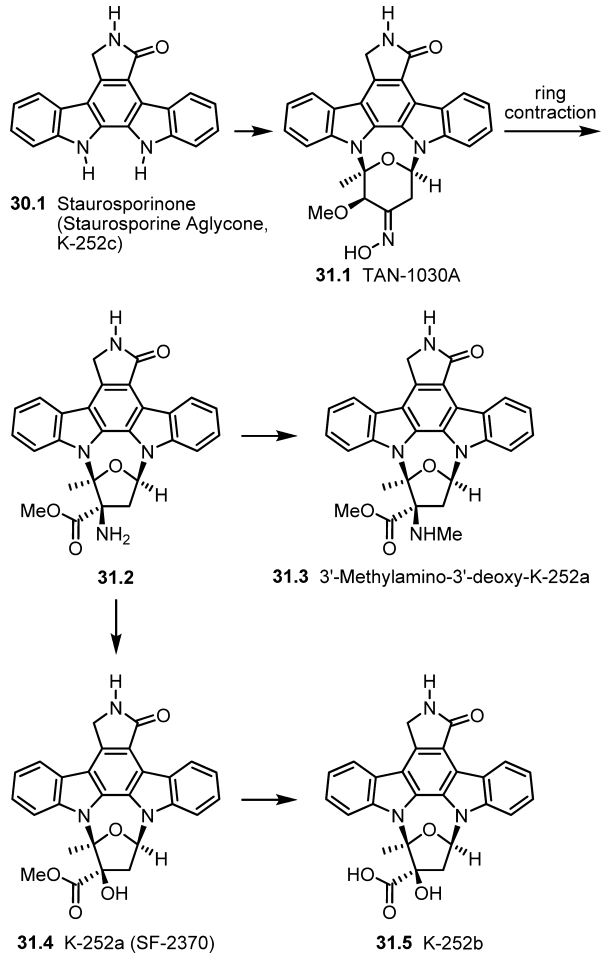
Scheme 30



staurosporine-producing strain *S. longisporoflavus* selected colony R 19/col 15 was chosen as parental strain. The blocked mutant strain M13, responsible for the production of the staurosporine aglycone (K-252c) (**30.1**), and the blocked mutant strain M14, responsible for the production of *O*-demethylstaurosporine (**30.2**), were used for the biosynthetic studies. In these studies, *O*-demethylstaurosporine (**30.2**), a direct precursor for staurosporine (**30.3**), was isolated from blocked mutants of the strain M14. Co-fermentation and bioconversion experiments excluded the possibility that *O*-demethylstaurosporine (**30.2**) was produced by demethylation of staurosporine (**30.3**). Subsequent experiments confirmed that *O*-methylation is the last step in the biosynthetic pathway of staurosporine (**30.3**).[224] The blocked mutants of strain M14 are lacking the *O*-methylase, an enzyme required for this transformation.

In 1996, Fredenhagen and co-workers proposed intermediates for the biosynthesis of K-252a (SF-2370) (**31.4**) (Scheme 31). They isolated minor metabolites closely related to either

Scheme 31



staurosporine (**30.3**) or the oxime TAN-1030A (**31.1**) from the staurosporine producing strain *S. longisporoflavus*.[225] The absolute stereochemistry of TAN-1030A (**31.1**) at the bridging atoms is similar to that of K-252a (SF-2370) (**31.4**). Thus, TAN-1030A (**31.1**) may be formed by oximation of the corresponding oxo derivative 4′-deoxime-4′-oxo-TAN-1030A, which in turn probably derives from oxidation of a sugar hydroxy group. Ring contraction of TAN-1030A (**31.1**) would lead to intermediate **31.2**.[226] Therefore, it appeared feasible that TAN-1030A (**31.1**), as biosynthetic precursor of K-252a (**31.4**), is converted to the proposed intermediate **31.2** by the microorganism. However, compound **31.2** could not be isolated from the fermentation broth. Instead, the corresponding *N*-methyl derivative, 3′-methylamino-3′-deoxy-K-252a (**31.3**), was found. It was presumed that the same enzyme that introduces the N-methyl group into staurosporine (**30.3**)[224] might be responsible for this transformation and perhaps is unable to differentiate between substrates with five- and six-membered ring systems. The free amino group of intermediate **31.2** could be converted to the hydroxy group of K-252a (**31.4**), which was found to be produced in minor amounts by the staurosporine-producing strain *S. longisporoflavus* R 19.[225] Previously, the same authors also described the isolation of various minor metabolites corresponding to

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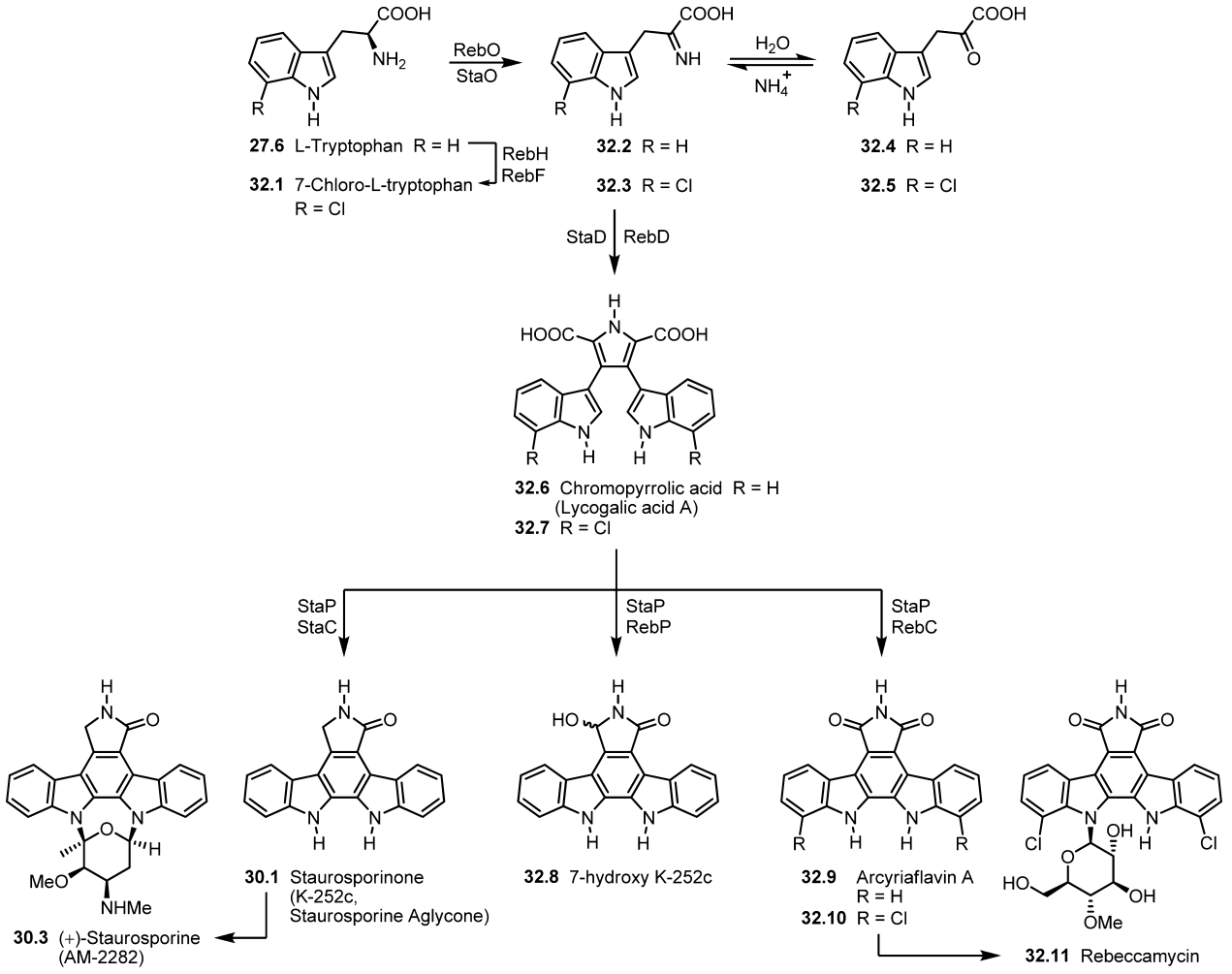
Scheme 32



staurosporine (**30.3**) and a staurosporine with a nitro function at C-4′. These studies indicated that TAN-1030A (**31.1**) is not only a key intermediate in the degradation of staurosporine (**30.3**) but also for the biosynthesis of staurosporine congeners.[227]

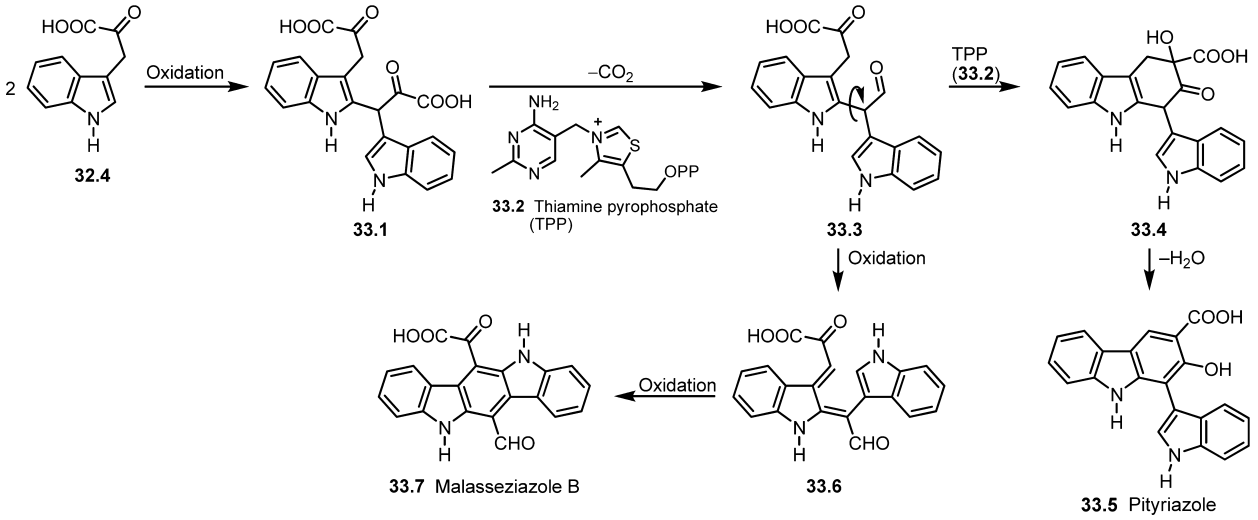
In 1994, Steglich and co-workers isolated chromopyrrolic acid (lycogalic acid A) (**32.6**) and staurosporinone (**30.1**) along with traces of arcyriaflavin A (**32.9**) and arcyriarubin A from the slime mold *Lycogala epidendrum* (Myxomycetes).[228] The co-occurrence of these alkaloids demonstrated their close biosynthetic relationship.[228−230] Prior to Steglich's report, Hoshino et al. had described compound **32.6** as a new tryptophan metabolite of a mutant of *Chromobacterium violaceum* and named it chromopyrrolic acid (**32.6**). Tracer experiments with ^{13}C-labeled L-tryptophan (**27.6**) confirmed its biosynthetic incorporation into chromopyrrolic acid (lycogalic acid A) (**32.6**) by condensation of 2 molecules of tryptophan.[231]

In 2006, Howard-Jones and Walsh reported for the first time the complete biosynthetic pathways leading to the staurosporine and rebeccamycin aglycones, K-252c (**30.1**) and 1,11-dichloroarcyriaflavin A (**32.10**) (Scheme 32).[232,233] Starting from L-tryptophan (**27.6**) and 7-chloro-L-tryptophan (**32.1**), respectively, these transformations involve a complex series of oxidative coupling reactions that are catalyzed by heme- and flavin-based enzymes. Their studies were in agreement with previously proposed biosynthetic pathways to staurosporine (**30.3**) and rebeccamycin (**32.11**), which were based on the isolation of putative intermediates by gene disruption studies of *Streptomyces sp.* TP-A0274,[234−236] *Lechevalieria* (formerly known as *Saccharothrix*), and *aerocolonigenes* ATCC 39243.[237,238] Howard-Jones and Walsh used the enzymes StaP, StaC, and RebC, and the intermediates chromopyrrolic acid (**32.6**) and dichlorochromopyrrolic acid (dichlorolycogalic acid A) **32.7** for their biosynthetic studies. The pathways to the two aglycones **30.1**, **32.9**, and **32.10** follow very similar routes. They differ only in the chlorination at C-7 of L-tryptophan en route to rebeccamycin (**32.11**) and in the oxidation state of the pyrrole-derived five-membered ring, which is converted into a maleimide for the rebeccamycin aglycone (**32.10**) and a pyrrolinone for the staurosporine aglycone (**30.1**). Subsequent N-glycosylation[235] and further modifications lead to rebeccamycin (**32.11**) and staurosporine (**30.3**).

The formation of chromopyrrolic acid (**32.6**), a biosynthetic key intermediate, was shown to proceed via condensation of 2 molecules of indol-3-ylpyruvic acid imine (**32.2**) by the combined action of RebO, an L-amino acid oxidase, and RebD (or StaD), a heme-containing oxidase (Scheme 32).[239] Moreover, StaP and StaC, or RebP and RebC, are involved in the construction of the aglycone framework. The overall reaction that converts chromopyrrolic acid (**32.6**) into the three aglycones K 252c (**30.1**), arcyriaflavin A (**32.9**), and 7-

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 33

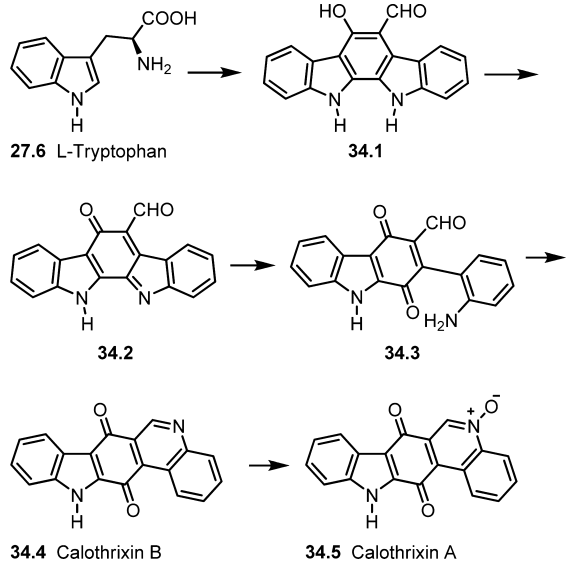


hydroxy K-252c **32.8** is catalyzed by StaP, a cytochrome P450 enzyme that is involved in the aryl−aryl coupling to generate the central six-membered ring of the indolocarbazole scaffold and in the double oxidative decarboxylation. With the ability of the StaP/StaC and StaP/RebC enzyme systems to convert possible biosynthetic intermediates into the final aglycone products, it could be demonstrated that arcyriarubin A is not an intermediate on the pathway from chromopyrrolic acid (**32.6**) to the aglycones K 252c (**30.1**), arcyriaflavin A (**32.9**), and 7-hydroxy K-252c **32.8**. The aglycones **30.1**, **32.8**, and **32.9** are not interconvertible but result from a common biosynthetic intermediate. Moreover, ^{18}O-incorporation experiments using ^{18}O-labeled dioxygen and ^{18}O-labeled water with chromopyrrolic acid (**32.6**) and the StaP/StaC and StaP/RebC enzyme systems showed that the amide oxygen of K 252c **30.1** and both oxygens of arcyriaflavin A (**32.9**) derive directly from oxygen.[232]

The co-occurrence of pityriazole (**33.5**) and the malasseziazoles A, B, and C in cultures of the human pathogenic yeast *Malassezia furfur* suggested a biogenetic relationship of these structurally different carbazoles. As proposed by Steglich and co-workers in 2005, pityriazole (**33.5**) and malasseziazole B (**33.7**) could derive from the common biogenetic precursor **33.3** via two different cyclization modes (Scheme 33).[240] Oxidative coupling of 2 molecules of indol-3-ylpyruvic acid (**32.4**) affords the dimer **33.1**, which on subsequent decarboxylation, catalyzed by thiamine pyrophosphate (TPP) (**33.2**), provides the intermediate **33.3**. Dehydrogenation of **33.3** followed by 6π-electrocyclization and aromatization leads to the indolo[3,2-*b*]carbazole malasseziazole B (**33.7**). The formation of pityriazole (**33.5**), which represents a 1-(indol-3-yl)-9*H*-carbazole derivative, can be rationalized by a TPP-catalyzed C−C bond formation of **33.3** and subsequent dehydration of the resulting α-hydroxyacid **33.4**.

In 1999, Rickards et al. proposed a biosynthetic route to the pentacyclic quinolino[4,3-*b*]carbazole-1,4-quinone alkaloids calothrixin A (**34.5**) and B (**34.4**) (Scheme 34).[241] An intermediate of this hypothesis is the indolo[2,3-*a*]carbazole **34.1**, which is closely related to the known 5-cyano-6-methoxyindolo[2,3-*a*]carbazole (**344.2**, see Scheme 344). Oxidation of the *p*-aminophenol function of metabolite **34.1** followed by hydrolytic cleavage of the resulting quinone imine

Scheme 34



34.2 leads to an *o*-aminophenyl-substituted quinone **34.3**. Condensation of the amine with the formyl group affords calothrixin B (**34.4**). N-Oxidation of **34.4** leads to calothrixin A (**34.5**). Labeling studies with L-tryptophan (**27.6**), the well-established precursor of several indolo[2,3-*a*]carbazole metabolites, confirmed the formation of the common metabolite **34.1**.[230] The co-occurrence of calothrixin A (**34.5**), B (**34.4**), and 5-cyano-6-methoxyindolo[2,3-*a*]carbazole (**344.2**) (see Scheme 344) in cyanobacteria supports this hypothetical biosynthetic pathway.

3. TRICYCLIC CARBAZOLE ALKALOIDS

In this section we discuss the naturally occurring carbazoles containing no further annulated ring or ring system. The tricyclic carbazole alkaloids have been classified by us according to their oxygenation pattern. Although the coverage of the natural products is comprehensive, the total syntheses described herein represent an update of our earlier review.[1]

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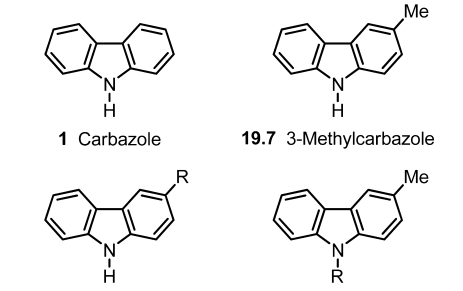
3.1. Carbazole, 3-Methylcarbazole, and Non-Oxygenated Congeners

3.1.1. Isolation from Natural Sources. Chakraborty and co-workers,[242] Joshi and Gawad,[243] and Connolly and co-workers[244] reported independently the isolation of 3-methylcarbazole (**19.7**) from the roots of different *Clausena* species, such as *Clausena heptaphylla* Wt. and Arn., *Clausena indica* Oliv., and *Clausena anisata*. Moreover, in 1987, Bhattacharyya and co-workers described the isolation of 3-methylcarbazole (**19.7**) along with carbazole (**1**) from the root bark of *Glycosmis pentaphylla* (Scheme 35).[245] This report indicated the possibility for oxidative degradation of the aromatic methyl group and, thus, supported the proposed biogenesis of carbazole alkaloids in higher plants. A decade later, 3-methylcarbazole (**19.7**) was isolated by Chakrabarty et al. from the chloroform extract of the roots of *Murraya koenigii*.[246] During their research on the antiplatelet aggregation activity of the acetone extract of the root bark of *Murraya euchrestifolia*, Wu et al. also obtained 3-methylcarbazole (**19.7**).[247]

Scheme 35



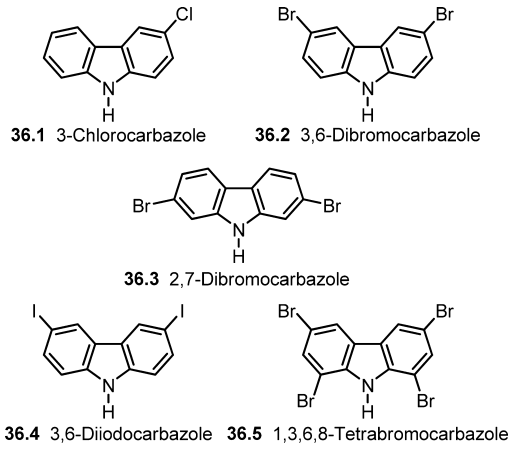
1 Carbazole
19.7 3-Methylcarbazole
20.9 3-Formylcarbazole R = CHO
20.10 Methyl carbazole-3-carboxylate R = COOMe
35.1 9-Carbethoxy-3-methylcarbazole R = COOEt
35.2 9-Formyl-3-methyl-carbazole R = CHO

In 1988, Furukawa and co-workers reported the isolation of 3-formylcarbazole (**20.9**) from the root bark of *Murraya euchrestifolia*.[248] Three years later, Li, McChesney, and El-Feraly reported the isolation of 3-formylcarbazole (**20.9**) along with methyl carbazole-3-carboxylate (**20.10**) from the roots of *Clausena lansium*.[249] Different parts of this ornamental tree are used in folk medicine in China, Taiwan, and the Philippines for the treatment of various diseases, for example, bronchitis, malaria, coughs, asthma, gastrointestinal inflammation, ulcers, influenza, colds, and colic pains.[250] 3-Formylcarbazole (**20.9**) was isolated from *G. pentaphylla* in 1992 by Bhattacharyya and co-workers.[251] Carbazole (**1**) was first obtained from the anthracene fraction of coal tar distillate in 1872 by Graebe and Glaser.[2] More than a century later, in 1987, Bhattacharyya and co-workers isolated carbazole (**1**) for the first time from a plant source (*G. pentaphylla*, see previous discussion).[245]

In 1997, Chakrabarty et al. reported the isolation of 9-carbethoxy-3-methylcarbazole (**35.1**) and 9-formyl-3-methylcarbazole (**35.2**) along with the known 3-methylcarbazole (**19.7**) from the roots of *Murraya koenigii*. These compounds were the first 9-carbonyl-substituted carbazoles from a plant source.[246] 9-Formyl-3-methylcarbazole (**35.2**) showed a weak cytotoxicity against mouse melanoma B16 and adriamycin-resistant P388 mouse leukemia cell lines.[246]

In 1983, Luk et al. identified 3-chlorocarbazole (**36.1**) from female bovine urine using a benzodiazepine receptor binding assay. This was the first isolation of a carbazole alkaloid from a mammalian source.[252] In 1999, Brown and co-workers reported the isolation of two regioisomeric dibromocarbazole alkaloids, 3,6-dibromocarbazole (**36.2**) and 2,7-dibromocarbazole (**36.3**), along with 3,6-diiodocarbazole (**36.4**) from the cyanobacterium *Kyrtuthrix maculans* from the shore of Hong Kong (Scheme 36).[253] Although these alkaloids were obtained previously by synthesis, this was the first report of their occurrence as natural products. 2,7-Dibromocarbazole (**36.3**) represents the basis for the neuroprotective compound P7C3 described by Pieper et al.[254] In 2005, Zhu and Hites described the identification of 1,3,6,8-tetrabromocarbazole (**36.5**) in the sediment cores of lake Michigan.[255] This was the first identification of a tetrahalogenated carbazole in the environment.

Scheme 36



36.1 3-Chlorocarbazole
36.2 3,6-Dibromocarbazole
36.3 2,7-Dibromocarbazole
36.4 3,6-Diiodocarbazole
36.5 1,3,6,8-Tetrabromocarbazole

3.1.2. Synthesis of 3-Methylcarbazole, 9-Carbethoxy-3-methylcarbazole, 9-Formyl-3-methylcarbazole. In 1997, Chakrabarty et al. described a synthesis for 3-methylcarbazole (**19.7**), 9-carbethoxy-3-methylcarbazole (**35.1**), and 9-formyl-3-methylcarbazole (**35.2**) to confirm the structural assignment for these natural products.[246] 3-Methylcarbazole (**19.7**), the precursor for 9-carbethoxy-3-methylcarbazole (**35.1**) and 9-formyl-3-methylcarbazole (**35.2**), was obtained by Fischer–Borsche reaction. Condensation of phenylhydrazine (**37.1**) and 4-methylcyclohexanone (**37.2**) followed by cyclization of the resulting arylhydrazone afforded the 3-methyltetrahydrocarbazole **37.3** (Scheme 37). Catalytic dehydrogenation of the tetrahydrocarbazole **37.3** provided 3-methylcarbazole (**19.7**). Base-mediated ethoxycarbonylation at the nitrogen atom of **19.7** with ethyl chloroformate led to 9-carbethoxy-3-methylcarbazole (**35.1**). Alternatively, N-formylation of 3-methylcarbazole (**19.7**) using formic acid afforded 9-formyl-3-methylcarbazole (**35.2**).

3.1.3. Syntheses of Methyl Carbazole-3-carboxylate. In 2003, Back et al. reported the synthesis of methyl carbazole-3-carboxylate (**20.10**) using a palladium-catalyzed indole annulation and subsequent Diels–Alder cycloaddition as key steps.[256] Palladium-catalyzed reaction of the 2-iodoanilide **38.1** and dienylsulfide **38.2** led to the vinylogous 2-(phenylthio)-indoline **38.3**, which on dehydrogenation with DDQ afforded the corresponding indole **38.4** (Scheme 38). Lewis acid-promoted regioselective Diels–Alder reaction of the indole **38.4** and methyl propiolate (**38.5**) with concomitant elimination of benzenethiol afforded 17% of methyl carbazole-3-carboxylate (**20.10**) along with 45% of the Cbz-

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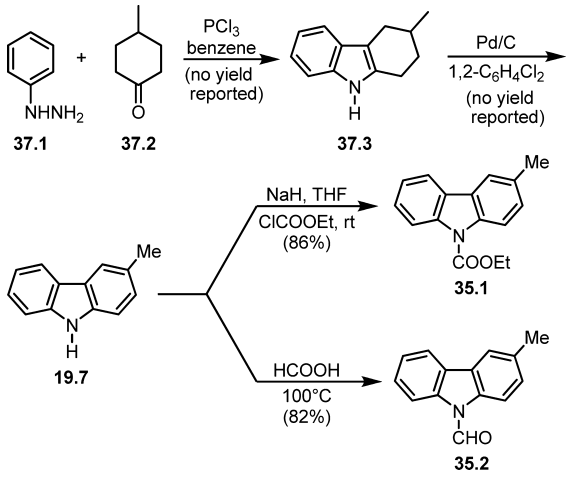
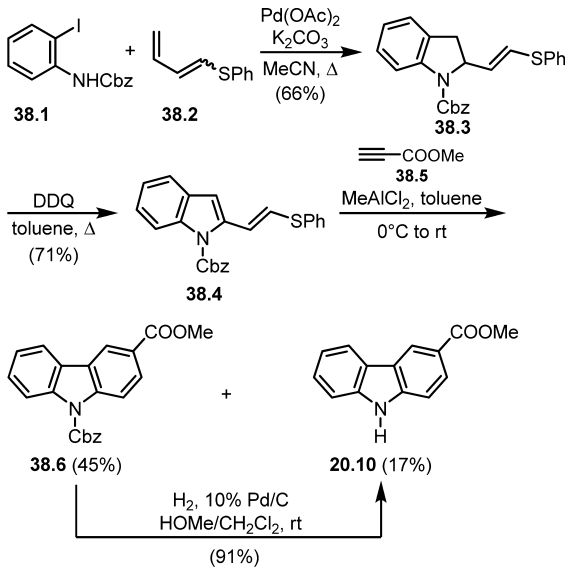
Scheme 37



Scheme 38

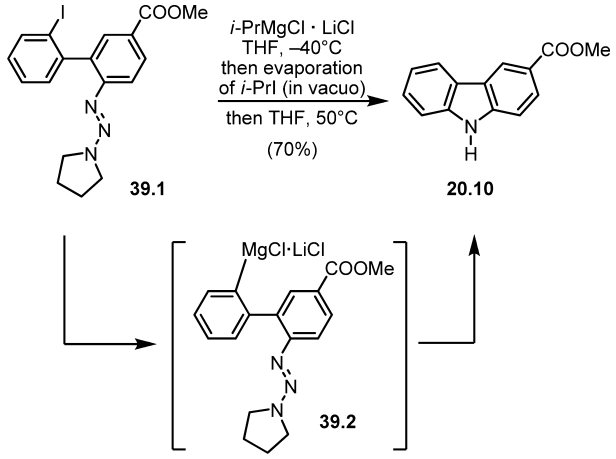


protected carbazole **38.6**. Removal of the protecting group transformed compound **38.6** into methyl carbazole-3-carboxylate (**20.10**).

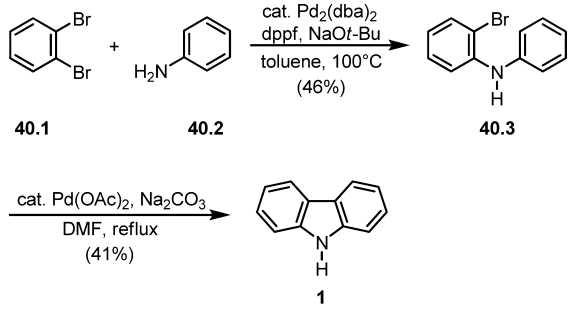
Two years later, Liu and Knochel reported a new strategy for the synthesis of methyl carbazole-3-carboxylate (**20.10**).[257] Halogen metal exchange of the iodo-substituted aryltriazene **39.1** using isopropylmagnesium chloride–lithium chloride complex followed by evaporation of isopropyl iodide and heating at 50 °C directly led to methyl carbazole-3-carboxylate (**20.10**) (Scheme 39). The reaction probably proceeds via formation of the intermediate arylmagnesium compound **39.2**, intramolecular attack of the metalated carbon atom at the triazene moiety, and elimination of *N*-(pyrrolidin-1-yl)-hydroxylamine during the aqueous workup.

3.1.4. Palladium(0)-Catalyzed Syntheses of Carbazole. In 1999, Sakamoto and co-workers reported the synthesis of carbazole (**1**) by combination of two palladium(0)-catalyzed reactions starting from *o*-dibromobenzene (**40.1**) and aniline (**40.2**). The Buchwald–Hartwig amination of *o*-dibromobenzene (**40.1**) with aniline (**40.2**) to 2-bromo-*N*-phenylaniline (**40.3**) is followed by a palladium(0)-catalyzed intramolecular arylation to provide carbazole (**1**) (Scheme 40).[112]

Scheme 39



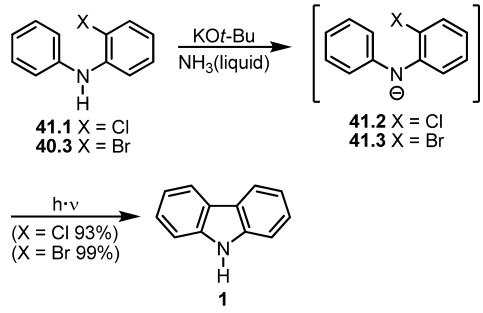
Scheme 40



In 2008, Kan and co-workers reported the synthesis of carbazole (**1**) starting from 2-iodoaniline and 2-bromophenylboronic acid. This one-pot synthesis of carbazole (**1**) was accomplished by a tandem Suzuki–Miyaura coupling and Buchwald–Hartwig amination leading to regiospecific formation of the C–C and C–N bonds.[258]

3.1.5. Synthesis of Carbazole by Photoinitiated Cyclization. In 2009, Rossi and co-workers described an approach to carbazole (**1**) and simple congeners by a photoinitiated cyclization of an *ortho*-halogenated diphenylamide anion in liquid ammonia as solvent (Scheme 41).[141] The

Scheme 41



ortho-halogenated diphenylamines **41.1** and **40.3** were synthesized by Buchwald–Hartwig amination of bromo- or iodobenzene with 2-chloroaniline and 2-bromoaniline, respectively. Addition of the diphenylamines to a solution of potassium *tert*-butoxide in liquid ammonia was followed by irradiation with a 400 W lamp with a wavelength < 350 nm for

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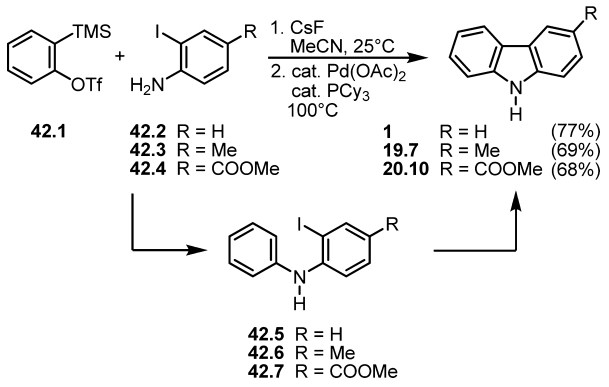
30 to 120 min. Using tetrahydrofuran (THF) or dimethylsulfoxide (DMSO) as solvent led to a slight decrease in yield (~80%) and the isolation of hydrodehalogenation products.

3.1.6. Syntheses of Carbazole, 3-Methylcarbazole, and Methyl Carbazole-3-carboxylate via Benzyne. In 2004, Liu and Larock reported a one-pot reaction for the synthesis of carbazole (**1**), 3-methylcarbazole (**19.7**), and methyl carbazole-3-carboxylate (**20.10**) (Scheme 42).[110,111]

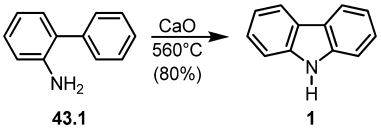
Scheme 42



Cross-coupling of benzyne, generated in situ by reaction of silylphenyl triflate **42.1** with cesium fluoride, and the *o*-iodoanilines **42.2**–**42.4** provided the *o*-iododiarylamines **42.5**–**42.7**. Subsequent palladium(0)-catalyzed intramolecular arylation by Sakamoto's procedure afforded carbazole (**1**), 3-methylcarbazole (**19.7**), and methyl carbazole-3-carboxylate (**20.10**).

3.1.7. Syntheses of Carbazole from Biaryl Precursors. In 2004, Horaguchi et al. prepared carbazole (**1**) by passing the vapor of 2-aminobiphenyl (**43.1**) over calcium oxide at 560 °C using nitrogen as carrier gas (Scheme 43).[259] Mechanistically

Scheme 43

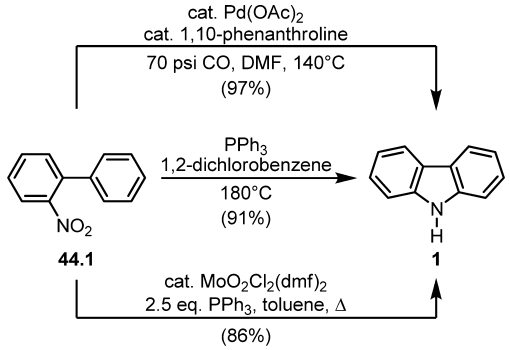


this reaction is believed to proceed via deprotonation by calcium oxide to generate an amide ion that subsequently cyclizes by attack at the phenyl substituent. Finally, elimination of a hydride ion affords carbazole (**1**).

Gaunt and co-workers described a palladium(II)-catalyzed cyclization of 2-aminobiphenyl (**43.1**) to carbazole (**1**) using either (diacetoxyiodo)benzene (34% yield) or *tert*-butyl benzoperoxoate (<10% yield) as a co-oxidant.[128] The yields could be improved by using N-monoalkylated 2-aminobiphenyls (up to 96%). Furthermore, a carbopalladation complex was isolated and characterized by X-ray analysis.

In 2004, Smitrovich and Davies reported a synthesis of carbazole (**1**) by a modification of Cadogan's procedure using a palladium-catalyzed regioselective C–H bond functionalization of 2-nitrobiphenyl (**44.1**) with CO as stoichiometric reductant (Scheme 44).[60] The mechanism of this transformation is rationalized by an exhaustive deoxygenation to generate a nitrene, which then undergoes a C–H insertion. One year later, Freeman et al. reported a similar transformation by heating 2-

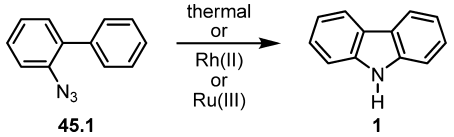
Scheme 44



nitrobiphenyl (**44.1**) and triphenylphosphine in 1,2-dichlorobenzene at 180 °C.[61] The triphenylphosphine oxide, generated during reductive cyclization, was removed by either chromatography or precipitation from hexane. In 2007, Sanz et al. reported milder reaction conditions for the same transformation by using catalytic amounts of a dichlorodioxomolybdenum(VI) complex and over-stoichiometric amounts of triphenylphosphine.[62] Moreover, the transformation was also carried out with polymer-bound triphenylphosphine.

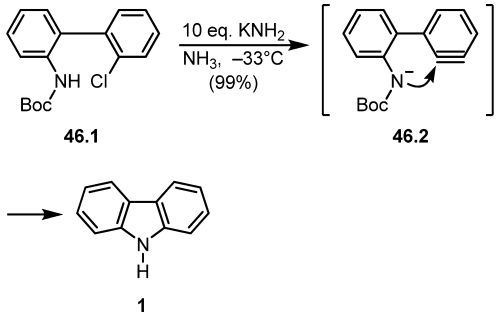
In 2007, Sapi and co-workers described the thermal cyclization of 2-azidobiphenyl (**45.1**) to carbazole (**1**) in 1,2-dichlorobenzene at reflux.[137] Smith and Brown used kerosene for the same transformation in 1951.[260] The cyclization of 2-azidobiphenyl (**45.1**) to carbazole (**1**) at lower temperatures in the presence of catalytic amounts of rhodium(II) salts has been described by Driver and co-workers (Scheme 45).[138,139] Lin, Jia, and co-workers used catalytic amounts of ruthenium(III) chloride to induce this cyclization.[140]

Scheme 45



Iwao, Watanabe, and co-workers reported a synthesis of carbazole (**1**) from biaryl **46.1** by treatment with potassium amide in liquid ammonia (Scheme 46).[261] The biaryl **46.1** was synthesized by Stille-coupling of 2-chlorobromobenzene and *N*-*tert*-butyloxycarbonyl-2-tributylstannylaniline.[262,263] Cyclization under aforementioned conditions provided carbazole (**1**), presumably via the benzyne intermediate **46.2**. In 2010,

Scheme 46



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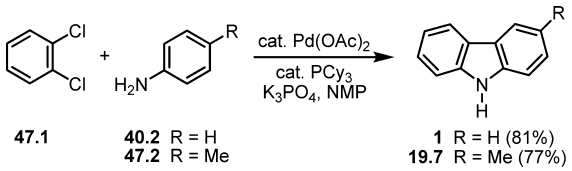
Nishiyama and co-workers applied hypervalent iodine reagents to the oxidative cyclization of *N*-acetyl-2-aminobiphenyls to carbazoles.[264]

3.1.8. Palladium(0)-Catalyzed Synthesis of Carbazole, 3-Methylcarbazole, and Methyl Carbazole-3-carboxylate. Ackermann and Althammer reported a synthesis of carbazole (**1**) and 3-methylcarbazole (**19.7**) starting from 1,2-dichlorobenzene (**47.1**) as common precursor (Scheme 47).[117]

Scheme 47

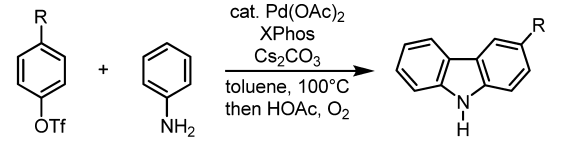


47.1 **40.2** R = H, **47.2** R = Me → **1** R = H (81%), **19.7** R = Me (77%)

Their method for construction of the carbazole framework involves a palladium(0)-catalyzed domino reaction (compare Sakamoto's procedure, section 3.1.4). Reaction of 1,2-dichlorobenzene (**47.1**) with the anilines **40.2** or **47.2** using catalytic amounts of palladium(II) acetate afforded carbazole (**1**) and 3-methylcarbazole (**19.7**) via amination and direct C−H bond arylation.

Ohno and co-workers described the synthesis of carbazole (**1**), 3-methylcarbazole (**19.7**), and methyl carbazole-3-carboxylate (**20.10**) using a one-pot N-arylation of aniline (**40.2**) by aryl triflates **48** with concomitant oxidative biaryl coupling in air or under an oxygen atmosphere (Scheme 48).[106]

Scheme 48

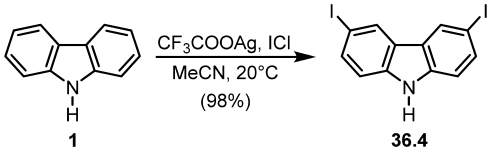


48.1 R = H, **48.2** R = Me, **48.3** R = COOMe; **40.2** → **1** R = H (69%), **19.7** R = Me (46%), **20.10** R = COOMe (64%)

Methyl carbazole-3-carboxylate (**20.10**) has also been obtained from methyl 4-aminobenzoate and phenyl triflate (**48.1**) using the same reaction conditions.

3.1.9. Syntheses of Halogenated Carbazoles. In 2001, Bonesi and Erra-Balsells described the iodination of carbazole (**1**) to 3,6-diiodocarbazole (**36.4**) by treatment with *N*-iodosuccinimide (70% yield).[265] In 2003, Filimonov et al. reported the synthesis of 3,6-diiodocarbazole (**36.4**) by 2-fold electrophilic iodination of carbazole (**1**) (Scheme 49).[266] This reaction has been achieved using a 4-fold excess of iodine chloride in the presence of silver trifluoroacetate in acetonitrile at room temperature and affords 3,6-diiodocarbazole (**36.4**) almost quantitatively.

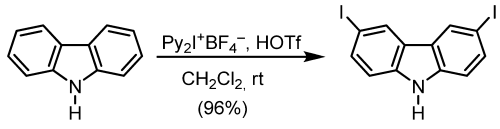
Scheme 49



1 → **36.4**

In 2006, Shimada and co-workers described a procedure for smooth diiodination of carbazole (**1**) by using bis(pyridine)-iodonium tetrafluoroborate (IPy_2BF_4) in the presence of trifluoromethanesulfonic acid in dichloromethane at room temperature (Scheme 50).[267] This method provides 3,6-diiodocarbazole (**36.4**) in 96% yield.

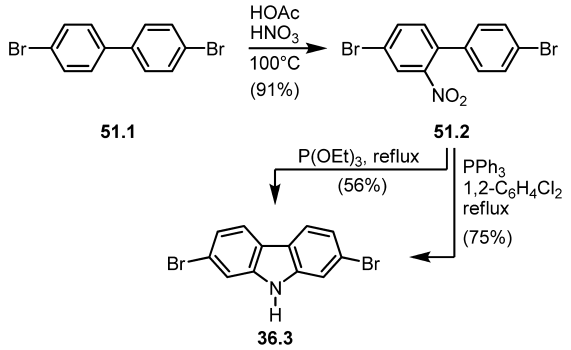
Scheme 50



1 → **36.4**

In 2003, Müllen and co-workers reported an efficient two-step synthesis of 2,7-dibromocarbazole (**36.3**) starting from commercially available 4,4′-dibromobiphenyl (**51.1**) (Scheme 51).[268] Nitration of 4,4′-dibromobiphenyl (**51.1**) with concentrated nitric acid afforded the corresponding 2-nitro derivative **51.2** in 91% yield. Reductive cyclization using Cadogan's procedure provided the carbazole **36.3** in 56% yield. Two years later, Freeman et al. used a modified procedure for cyclization of compound **51.2**.[61] Treatment of **51.2** with triphenylphosphine in 1,2-dichlorobenzene at reflux afforded 2,7-dibromocarbazole (**36.3**) in 75% yield and did not lead to the formation of unwanted byproducts.

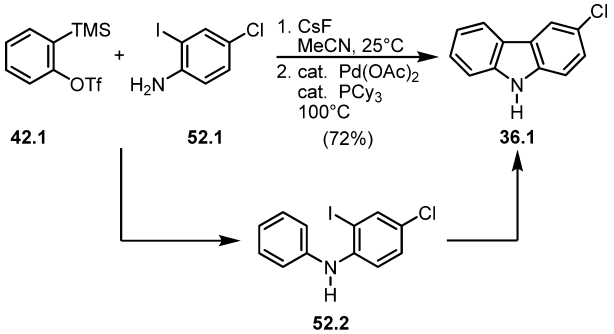
Scheme 51



51.1 → **51.2** → **36.3**

In 2007, Liu and Larock reported a one-pot synthesis of 3-chlorocarbazole (**36.1**) starting from 4-chloro-2-iodoaniline (**52.1**) and the silylphenyl triflate **42.1** (Scheme 52).[111] Reaction of the silylphenyl triflate **42.1** with **52.1** in the presence of cesium fluoride led to the diarylamine **52.2**.

Scheme 52



42.1 + **52.1** → **36.1** / **52.2**

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Subsequent palladium-catalyzed intramolecular arylation provided 3-chlorocarbazole (**36.1**) in 72% yield.

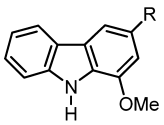
3.2. Monooxygenated Carbazole Alkaloids

This section covers the tricyclic carbazole alkaloids with only one oxygen substituent (hydroxy or methoxy group). The numbering of most of the alkaloids in this section is determined by the C_1-substituent at C-3 that is typically found in all carbazoles isolated from higher plants. Although this numbering might be in contrast to IUPAC recommendations, especially in cases of 5-, 6-, 7-, and 8-oxygenated carbazole alkaloids, we feel that this biogenesis-guided numbering provides a better understanding of the relationships between those natural products.

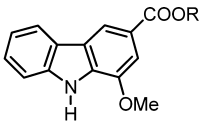
3.2.1. 1-Oxygenated Carbazole Alkaloids. *3.2.1.1. Isolation from Natural Sources.* All of the 1-oxygenated carbazole alkaloids isolated to date derive from higher plants. The genus *Murraya* (family Rutaceae), trees growing in Southern Asia, represents the major source for 1-oxygenated carbazole alkaloids. Extracts of the leaves and bark of this tree are used as a traditional folk medicine in this region for the treatment of eczema, rheumatism, and dropsy.

In 1983, Furukawa and co-workers described the isolation of murrayafoline-A (**20.1**) from the ethanol extract of the root bark of *Murraya euchrestifolia* collected in Taiwan (Scheme 53).[200,201] Two decades later, Cuong et al. isolated the same

Scheme 53



20.1 Murrayafoline-A
R = Me
20.2 Koenoline
R = CH_2OH
20.3 Murrayanine
R = CHO

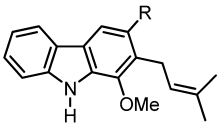


20.4 Mukoeic acid
R = H
20.5 Mukonine
R = Me

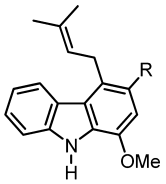
alkaloid from *Glycosmis stenocarpa* Guillaumin collected in Northern Vietnam.[269] This endemic plant is locally known as "com ruou trai hep". Fiebig et al. isolated the cytotoxic carbazole alkaloid koenoline (**20.2**) from the root bark of *Murraya koenigii*.[270] Murrayanine (**20.3**) was independently isolated from two different genera of the Rutaceae family, *Murraya koenigii*[4] and *Clausena heptaphylla*.[271] Moreover, Cuong et al. isolated murrayanine (**20.3**) from another genus of the Rutaceae family, *Glycosmis stenocarpa* Guillaumin from North Vietnam.[269] Murrayanine (**20.3**) exhibits antimicrobial properties against human pathogenic fungi.[5] Mukoeic acid (**20.4**) was isolated from the alcoholic extract of the stem bark of *Murraya koenigii*. It was the first carbazole carboxylic acid obtained from a plant.[272,273] The corresponding methyl ester, mukonine (**20.5**), was isolated from the same plant source.[6] The co-occurrence of murrayafoline-A (**20.1**), koenoline (**20.2**), murrayanine (**20.3**), mukoeic acid (**20.4**), and mukonine (**20.5**) in plants of the genus *Murraya* suggests that they might be biosynthesized by in vivo oxidation of murrayafoline-A (**20.1**) (cf. section 2).

In 1974, Joshi and Gawad isolated indizoline (**54.2**), a 2-prenylated derivative of murrayanine (**20.3**) from the roots of *Clausena indica* (Scheme 54).[243] A decade later, Bhattacharyya and Chowdhury reported the isolation of clausenapin (**54.1**) from the leaves of a different *Clausena* species, *Clausena*

Scheme 54



54.1 Clausenapin
R = Me
54.2 Indizoline
R = CHO

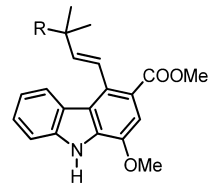


54.3 Ekeberginine
R = CHO
54.4 Clausamine D
R = COOMe

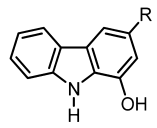
heptaphylla.[274] Prior to this report, compound **54.1** was obtained by Huang–Minlon reduction of indizoline (**54.2**).[6] Ekeberginine (**54.3**), a regioisomer of indizoline (**54.2**), was isolated from two different sources, the stem bark of *Ekebergia senegalensis* (Meliaceae)[275] and the combined extracts of the stem bark and roots of *Clausena anisata*.[244]

In 2000, Itoigawa and co-workers isolated clausamine D (**54.4**), clausamine E (**55.1**), and clausamine G (**55.2**) from branches of *Clausena anisata* (Schemes 54 and 55).[276]

Scheme 55



55.1 Clausamine E
R = OH
55.2 Clausamine G
R = OOH



20.6 1-Hydroxy-3-methylcarbazole
R = Me
20.7 *O*-Demethylmurrayanine
R = CHO
20.8 Clausine E (Clauszoline-I)
R = COOMe

Clausamine G (**55.2**) is the first example of a naturally occurring peroxygenated carbazole alkaloid and could be semisynthesized from clausamine D (**54.4**). In addition, clausamine G (**55.2**) was transformed into clausamine E (**55.1**).[276] The clausamines exhibited antitumor activity (antitumor-promoting activity against 1,3,5-triaza-7-phosphaadamantane (TPA)-induced in vitro Epstein–Barr virus early antigen (EBV-EA) activation).

In 1994, Bhattacharyya et al. described the isolation of 1-hydroxy-3-methylcarbazole (**20.6**) from the ethanol extract of the stem bark of *Murraya koenigii* (Scheme 55).[277] Connolly and co-workers isolated *O*-demethylmurrayanine (**20.7**) from the combined extracts of the stem bark and roots of *Clausena anisata*.[244] In 1996, Wu et al. reported the isolation of clausine E (**20.8**) from the methanol extract of the stem bark of *Clausena excavata* collected in Taiwan.[278] This wild shrub has been used in folk medicine for the treatment of snakebites, abdominal pain, and various infections and as a detoxification agent. One year later, Ito et al. obtained the same alkaloid from the same source in Japan and named it clauszoline-I (**20.8**).[279] Clausine E (clauszoline-I) (**20.8**) showed inhibition of rabbit platelet aggregation and vasoconstriction.[278]

In 1992, Wu and Huang isolated two 1-hydroxy-4-prenylcarbazole alkaloids from the stem bark of *Clausena excavata*, clausine D (**56.1**) and clausine F (**56.2**). Both carbazole alkaloids showed inhibition of platelet aggregation.[280] Clausamine F (**56.3**) was isolated along with other clausamine

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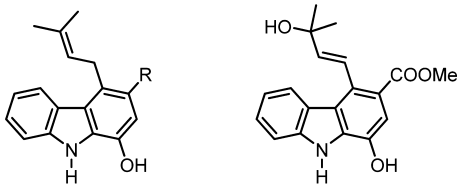
derivatives (**54.4**−**55.2**) (see Schemes 54 and 55). All these 1-oxygenated 3-methoxycarbonylcarbazoles showed antitumor activity (Scheme 56).[276]

Scheme 56

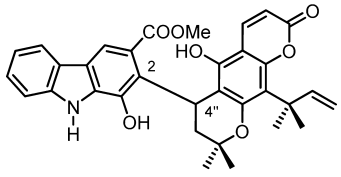


56.1 Clausine D
R = CHO
56.2 Clausine F
R = COOMe

56.3 Clausamine F

In 1996, Wu et al. isolated the optically active carbazol-2-ylpyranocoumarin carbazomarine-A (**57.1**) from the acetone extract of the root bark of *Clausena excavata* (Scheme 57).[281]

Scheme 57

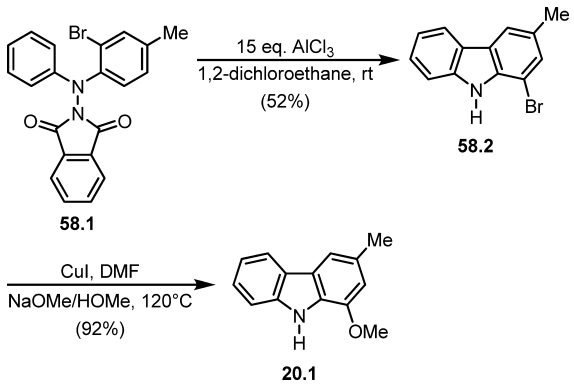


57.1 Carbazomarine-A

This natural product is the first C−C linked carbazole−pyranocoumarin conjugate found in nature. Although the value for the specific rotation of carbazomarine-A (**57.1**) is known ($[\alpha] = -27.03$, c 0.0259, $CHCl_3$), its absolute configuration has not been determined yet.

3.2.1.2. Synthesis of Murrayafoline-A (2001). Kikugawa et al. reported a total synthesis of murrayafoline-A (**20.1**) starting from the *N*-(*N*,*N*-diarylamino)phthalimide **58.1** (Scheme 58).[282] The phthalimide **58.1** was synthesized by N-phenyl-

Scheme 58



58.1

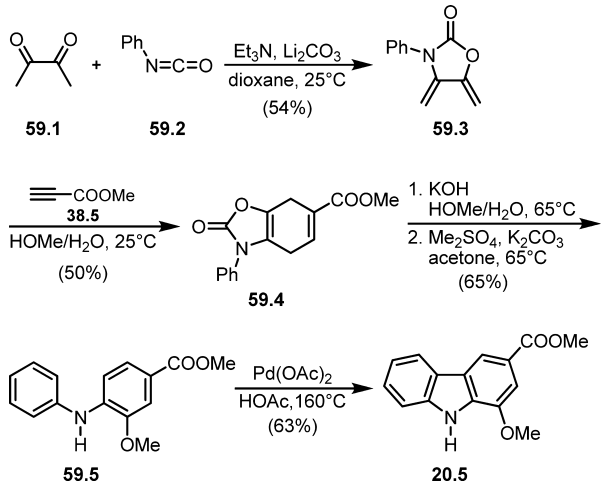
58.2

20.1

ation of the appropriate *N*-arylaminophthalimide with triphenylbismuth.[283] Reaction of the phthalimide **58.1** with aluminum trichloride in 1,2-dichloroethane afforded directly the 1-bromocarbazole **58.2** in 52% yield. This one-pot formation of the carbazole framework was rationalized by a Lewis acid-mediated generation of a diarylnitrenium ion followed by intramolecular C−C bond formation. The phthalimido group plays a pivotal role for generation of the diarylnitrenium ion. Finally, copper-mediated substitution of bromine by methoxide afforded murrayafoline-A (**20.1**) in 92% yield.

3.2.1.3. Total Synthesis of Mukonine, Murrayanine, and Murrayafoline-A. Tamariz and co-workers reported a total synthesis of murrayafoline-A (**20.1**), murrayanine (**20.3**), and mukonine (**20.5**) starting from *N*-phenyl-4,5-(dimethylene)-oxazolidin-2-one (**59.3**) (Scheme 59).[284] The key step is the

Scheme 59



59.1 **59.2** **59.3**

59.4

59.5 **20.5**

regioselective cycloaddition of diene **59.3** with an appropriate dienophile. Using a one-pot, base-mediated condensation procedure, the heterocyclic diene **59.3** was prepared in moderate yield starting from 2,3-butanedione (**59.1**) and phenyl isocyanate (**59.2**).[285−287] Diels−Alder cycloaddition of the diene **59.3** and methyl propiolate (**38.5**) afforded the cycloadduct **59.4** in 50% yield. Alkaline hydrolysis of **59.4** at elevated temperature led to cleavage of the cyclic urethane and aromatization to a diarylamine. Methyl ether formation with dimethyl sulfate to the diarylamine **59.5** was followed by palladium(II)-mediated oxidative cyclization to provide mukonine (**20.5**).

An extension of the method described above using acrolein (**60.1**) as dienophile led to the total synthesis of murrayanine (**20.3**) and murrayafoline-A (**20.1**). Lewis acid-catalyzed regioselective cycloaddition of diene **59.3** and acrolein (**60.1**) afforded compound **60.2**. In contrast to the synthesis of mukonine (**20.5**) (see Scheme 59), the cycloadduct **60.2** was aromatized to compound **60.3** prior to hydrolysis by oxidation with DDQ. Hydrolysis of **60.3** under mild alkaline conditions followed by methylation afforded the diarylamine **60.5**. A palladium(II)-promoted cyclization of **60.5** provided murrayanine (**20.3**) in 73% yield.[288] Using this route, murrayafoline-A (**20.1**) has been synthesized as well. Palladium(0)-catalyzed hydrogenation of **60.3** afforded compound **60.4** almost quantitatively. Finally, hydrolysis of the latter, methylation of the phenol, and oxidative cyclization of **60.6** using stoichiometric amounts of palladium(II) acetate provided murrayafoline-A (**20.1**) in 36% overall yield (Scheme 60).[288]

The same group subsequently reported an improved total synthesis of murrayanine (**20.3**). In contrast to the earlier routes,[284,288] catalytic amounts of palladium(0) have been used for the cyclization of the diarylamine **61.5**. A highly regioselective Lewis acid-catalyzed Diels−Alder cycloaddition

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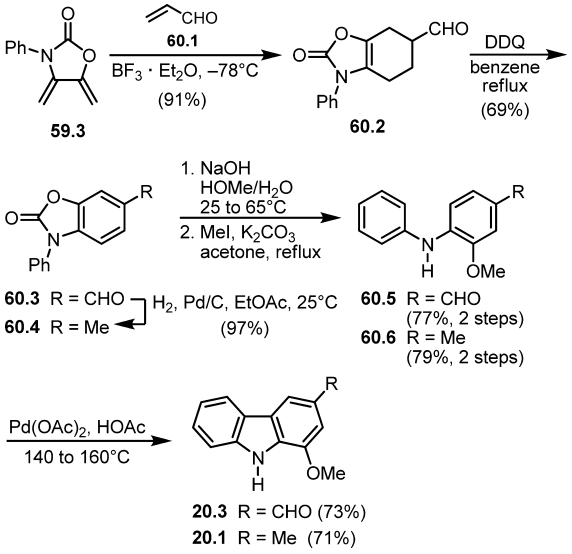
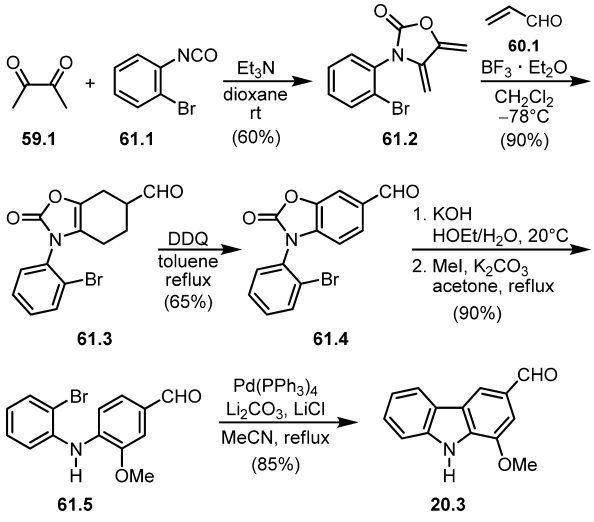
Scheme 60



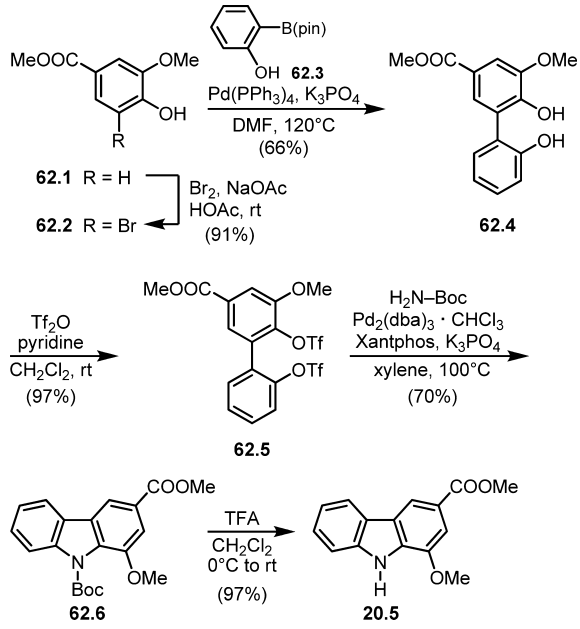
of the diene **61.2** with acrolein (**60.1**) at low temperature provided the cycloadduct **61.3** in high yield. Aromatization of **61.3** using DDQ in benzene at reflux afforded the aromatic aldehyde **61.4**. Alkaline hydrolysis followed by methylation of the resulting phenol afforded the methoxydiarylamine **61.5** in 90% yield. The palladium(0)-catalyzed Heck-type cyclization of **61.5** provided murrayanine (**20.3**) in 85% yield (Scheme 61).[289]

Scheme 61



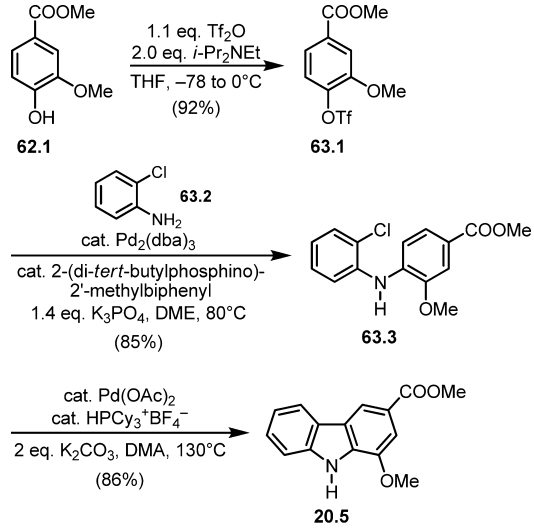
3.2.1.4. Total Synthesis of Mukonine. Nozaki and co-workers applied a double N-arylation of the ammonia surrogate *O-tert*-butyl carbamate (H_2NBoc) with the bistriflate **62.5** to the total synthesis of mukonine (**20.5**). Methyl vanillate (**62.1**) was used as starting material for the synthesis of the bistriflate **62.5**. Bromination of methyl vanillate (**62.1**) followed by Suzuki–Miyaura coupling with the boronate **62.3** afforded the biphenyl-2,2′-diol **62.4**. After transformation to the bistriflate **62.5**, double N-arylation of *O-tert*-butyl carbamate with **62.5** provided *N*-Boc-mukonine (**62.6**). Removal of the Boc group using trifluoroacetic acid led to mukonine (**20.5**) (Scheme 62).[120]

Scheme 62



3.2.1.5. Total Synthesis of Mukonine and Murrayafoline-A. In 2006, Fagnou and co-workers took advantage of the different reactivities of aryl triflates and aryl chlorides in palladium(0)-catalyzed coupling reactions to effect the total synthesis of mukonine (**20.5**).[114] A sequence of palladium(0)-catalyzed Buchwald–Hartwig amination and palladium(0)-catalyzed cyclization by a Heck-like intramolecular arylation was used to access the natural product (Scheme 63). Conversion of

Scheme 63



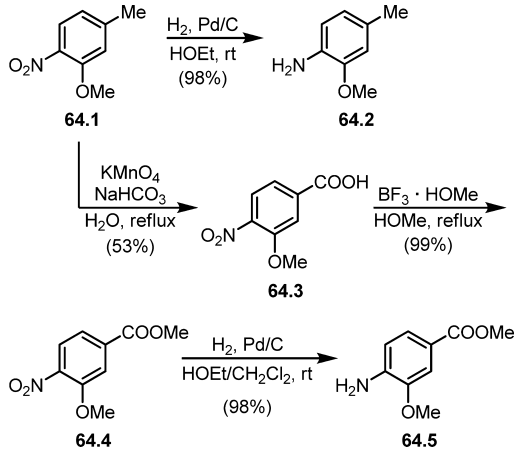
methyl vanillate (**62.1**) to the triflate **63.1** followed by Buchwald–Hartwig amination with 2-chloroaniline (**63.2**) led to the *ortho*-chlorinated diarylamine **63.3**. Palladium(0)-catalyzed cyclization of **63.3** provided mukonine (**20.5**) in 86% yield.

Two years later, the palladium(II)-catalyzed oxidative cyclization (cf. section 1.2.6) was applied to the total synthesis of murrayafoline-A (**20.1**) and an alternative synthesis of mukonine (**20.5**).[104] Both syntheses start from 2-nitro-5-

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

methylanisole (**64.1**) as common precursor (Scheme 64). Palladium(0)-catalyzed hydrogenation of the nitrobenzene **64.1**

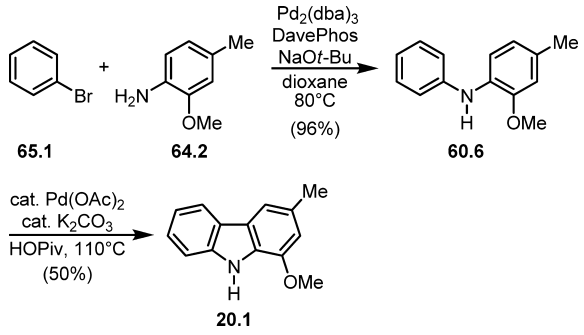
Scheme 64



afforded the aniline **64.2**. Oxidation of **64.1** to **64.3** followed by esterification to **64.4** and catalytic hydrogenation provided the methyl aminobenzoate **64.5** in 51% overall yield.

Buchwald–Hartwig coupling of 2-methoxy-4-methylaniline (**64.2**) with bromobenzene (**65.1**) afforded the diarylamine **60.6** (Scheme 65).[104] Palladium(II)-catalyzed oxidative cycliza-

Scheme 65

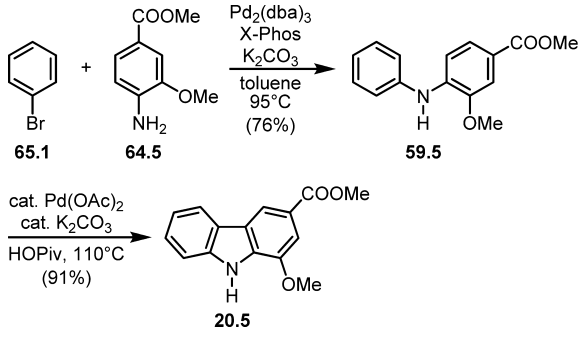


tion of **60.6** in pivalic acid in the presence of potassium carbonate provided murrayafoline-A (**20.1**) The application of pivalic acid as the solvent proved to be advantageous in comparison to acetic acid, which is usually employed. The reaction conditions are milder, and the formation of undesired byproducts is suppressed.

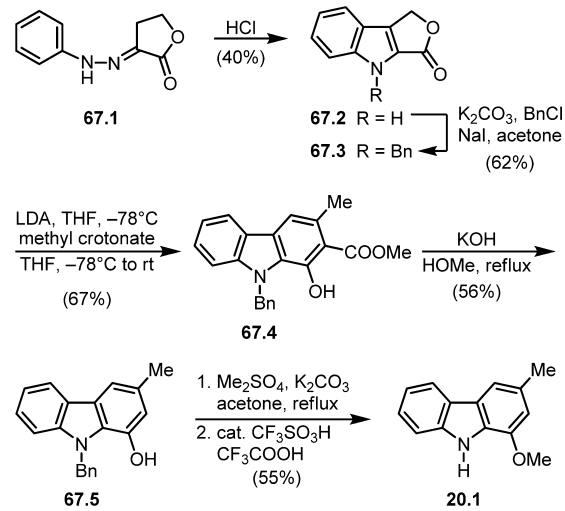
The same methodology, palladium(II)-catalyzed oxidative cyclization of a diarylamine in pivalic acid as solvent, has also been applied to the total synthesis of mukonine (**20.5**). Buchwald–Hartwig amination of bromobenzene (**65.1**) with the arylamine **64.5** furnished the diarylamine **59.5** (Scheme 66).[104] Treatment of that diarylamine with palladium(II) acetate and potassium carbonate in pivalic acid at elevated temperature led to mukonine (**20.5**) in high yield.

3.2.1.6. Total Synthesis of Murrayafoline-A (2006/2007). In 2006, Mal et al. described a total synthesis of murrayafoline-A (**20.1**) based on an anionic [4 + 2]-cycloaddition–benzannulation method (Scheme 67).[290,291] Fischer indolization of 3-(2-phenylhydrazono)dihydrofuran-2(3*H*)-one (**67.1**) followed by N-benzylation afforded the *N*-benzylfuroindolone **67.3**.[292] A formal cycloaddition of the *N*-benzylfuroindolone

Scheme 66



Scheme 67



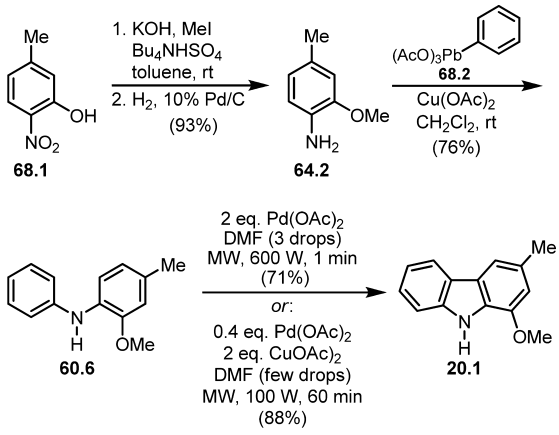
67.3 with methyl crotonate in the presence of lithium diisopropylamide (LDA) led to the 1-hydroxycarbazole **67.4**. Demethoxycarbonylation of **67.4** by heating in concentrated methanolic potassium hydroxide at reflux afforded 9-benzyl-1-hydroxy-3-methylcarbazole (**67.5**). *O*-Methylation of **67.5** and subsequent debenzylation provided murrayafoline-A (**20.1**). Subsequently, this approach has been applied to the total synthesis of more complex alkaloids (see Scheme 73).

In the same year, Menéndez and co-workers reported a new total synthesis of murrayafoline-A (**20.1**) by palladium(II)-mediated oxidative cyclization using microwave irradiation (Scheme 68).[293] O-Methylation of 5-methyl-2-nitrophenol (**68.1**) followed by catalytic hydrogenation afforded the aniline **64.2**. Arylation of the aniline **64.2** with phenyllead triacetate (**68.2**) in the presence of copper(II) acetate led to the required diarylamine **60.6** in 76% yield. Oxidative cyclization using microwave irradiation in the presence of overstoichiometric amounts of palladium(II) acetate and only a few drops of dimethylformamide (DMF) provided murrayafoline-A (**20.1**). In 2009, the same authors reported an alternative procedure for microwave-promoted oxidative cyclizations using substoichiometric amounts of palladium(II) acetate (0.4 equiv) in combination with 2 equiv of copper(II) acetate.[294]

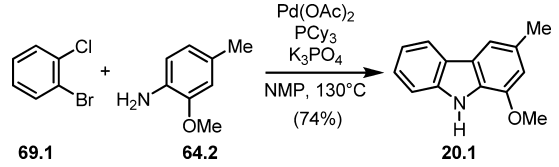
Ackermann and Althammer reported an efficient total synthesis of murrayafoline-A (**20.1**) starting from 2-methoxy-4-methylaniline (**64.2**).[117,118] The carbazole framework was constructed using a sequential palladium(0)-catalyzed Buchwald–Hartwig amination and cyclization by C–H bond activation (Scheme 69). Thus, reaction of 2-methoxy-4-

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 68



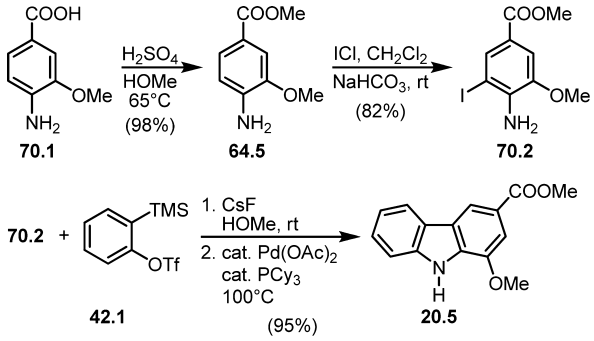
Scheme 69



methylaniline (**64.2**) and 2-chlorobromobenzene (**69.1**) in the presence of catalytic amounts of palladium provided directly murrayafoline-A (**20.1**) in 74% yield in a one-pot operation.

3.2.1.7. Total Syntheses of Mukonine (2007/2008). Liu and Larock reported a synthesis of mukonine (**20.5**) via a two-step cross coupling of the 2-iodoaniline **70.2** and the silylaryl triflate **42.1** (Scheme 70).[111] Esterification of commercially available 4-

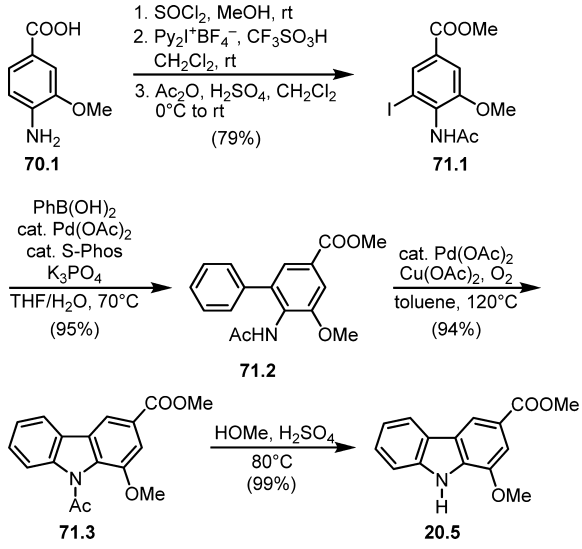
Scheme 70



amino-3-methoxybenzoic acid (**70.1**) followed by iodination of **64.5** with iodine chloride afforded the 2-iodoaniline **70.2** in two steps and 80% overall yield. Cross-coupling of **70.2** with the silylaryl triflate **42.1** was achieved by treatment with cesium fluoride. Subsequent palladium-catalyzed cyclization provided mukonine (**20.5**) in 95% yield.

Buchwald and co-workers reported a total synthesis of mukonine (**20.5**) using sequential palladium-catalyzed C−H and C−N bond-forming reactions (Scheme 71).[127] The required 2-acetamidobiphenyl **71.2** was obtained in 95% yield using a Suzuki−Miyaura cross-coupling between phenylboronic acid and the aryl iodide **71.1**. Compound **71.1** was obtained in three steps and 79% overall yield from commercially available 4-amino-3-methoxybenzoic acid (**70.1**). Reaction of **71.2** with catalytic amounts of palladium(II) acetate, copper(II) acetate,

Scheme 71



and oxygen in toluene at reflux led to 9-acetylmukonine (**71.3**) in 94% yield. Finally, acidic hydrolysis of **71.3** almost quantitatively afforded mukonine (**20.5**).

3.2.1.8. Synthesis of Mukonine and Clausine E. In 2009, Hibino and co-workers described the total synthesis of mukonine (**20.5**) and clausine E (**20.8**) using the electrocyclic ring-closure of an allene as the key step.[295] Addition of lithiated ethyl propynoate to the methoxymethyl (MOM)-protected indole **72.1**[296] followed by MOM protection of the resulting alcohol led to the cyclization precursor **72.2** (Scheme 72). Treatment of **72.2** with potassium *tert*-butoxide induced the formation of allene **72.3**, which underwent electrocyclization with concomitant ester cleavage to the carbazole-3-carboxylic acid **72.4**. Formation of the methyl ester, oxidation to the aldehyde, and acidic removal of the MOM groups led to the 1-hydroxycarbazole-2-carbaldehyde **72.5**. For the synthesis of mukonine (**20.5**), the hydroxy group was transformed into the corresponding methyl ether **72.6**. Dakin reaction followed by esterification of the resulting 2-hydroxycarbazole with *N*-phenyl bis(trifluoromethanesulfonimide) and subsequent palladium(0)-catalyzed defunctionalization led to mukonine (**20.5**).

For the synthesis of clausine E (**20.8**), 1-hydroxycarbazole **72.5** was transformed into the corresponding benzyl ether **72.7**. The total synthesis of clausine E (**20.8**) was achieved by applying the same sequence as described for the total synthesis of mukonine (**20.5**).

3.2.1.9. Synthesis on Clausamine D and Clausine F. In 2010, Jana and Mal described the application of their anionic [4 + 2]-cycloaddition−benzannulation method (see Scheme 67) to the synthesis of clausamine D (**54.4**) and clausine F (**56.2**).[297] Reaction of the *N*-benzylfuro[3,4-*b*]indolone **67.3** and dimethyl fumarate in the presence of lithium *tert*-butoxide and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) led to a 1-hydroxycarbazole that was directly transformed into the methyl ether **73.1** (Scheme 73). Cleavage of the protecting groups, O-prenylation, and aryl-Claisen rearrangement with subsequent Cope rearrangement led to the 4-prenylated carbazole **73.3**. Ester cleavage in refluxing methanol also led to decarboxylation at C-2 to give the carboxylic acid **73.4**. Methyl ester formation afforded clausine F (**56.2**), which was then transformed into clausamine D (**54.4**).

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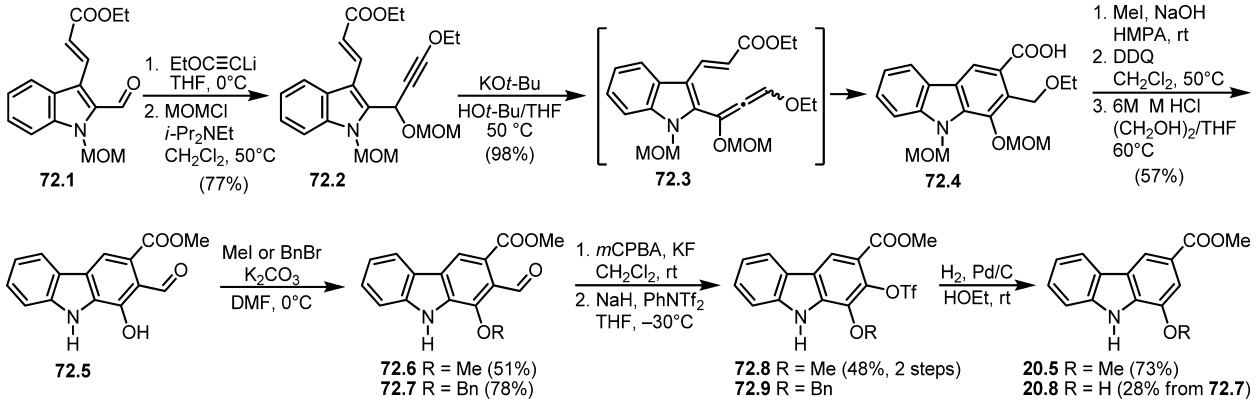
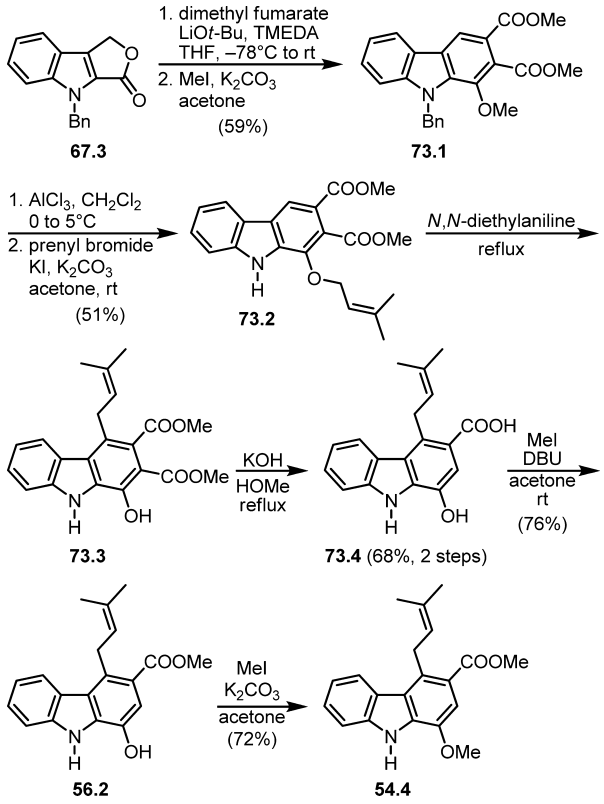
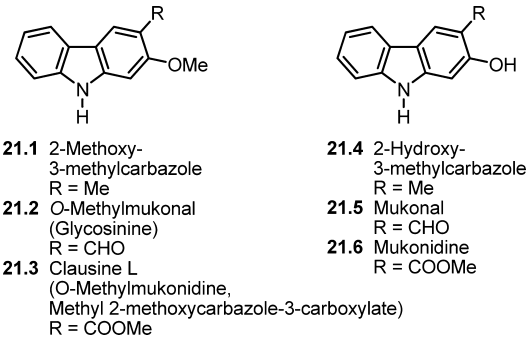
Scheme 72



Scheme 73



Scheme 74



3.2.2. 2-Oxygenated Carbazole Alkaloids. *3.2.2.1. Isolation from Natural Sources.* A large number of 2-oxygenated carbazole alkaloids has been isolated from *Murraya koenigii*. In 1985, Bhattacharyya and Chowdhury reported the isolation of 2-methoxy-3-methylcarbazole (**21.1**) from the petroleum ether extract of the seeds of *Murraya koenigii* (Scheme 74).[298] Five years later, Lange and co-workers isolated *O*-methylmukonal (**21.2**) from the roots of *Murraya siamensis*.[299] In 1992, Bhattacharyya and co-workers obtained the same alkaloid from the roots of a different natural source, *Glycosmis pentaphylla*, and named it glycosinine (**21.2**).[251] Recently, Kongkathip et al. isolated *O*-methylmukonal (**21.2**) from the rhizomes and roots of *Clausena excavata*.[300] *O*-Methylmukonal (**21.2**) exhibits anti-HIV-1 activity.[300] In 1993, Wu et al. reported the isolation of clausine L (*O*-methylmukonidine) (**21.3**) from the leaves of *Clausena excavata*.[301] One year later, Bhattacharyya et al. isolated the same alkaloid from the stem bark of *Murraya koenigii* and named it methyl 2-methoxycarbazole-3-carboxylate (**21.3**).[277] In the mid-1980s, Bhattacharyya et al. isolated 2-hydroxy-3-methylcarbazole (**21.4**)[206] and mukonal (**21.5**)[198] from the root and the stem bark of *Murraya koenigii*. In 1978, Chakraborty et al. reported the isolation of a compound from the stem bark of *Murraya koenigii* that was assigned as methyl 2-hydroxycarbazole-3-carboxylate (**21.6**). This compound was named mukonidine (**21.6**).[302] During their studies on the antiplatelet aggregation activity of the leaves of *Clausena excavata*, Wu et al. also isolated mukonidine (**21.6**) along with its *O*-methyl derivative, clausine L (**21.3**).[301] However, the physical and spectroscopic data of Chakraborty's mukonidine were not in agreement with those of Wu's mukonidine (**21.6**).[301,302] On the basis of the agreement of the data for Knölker's synthetic mukonidine (**21.6**) with those of Wu's mukonidine (**21.6**),[301] it was concluded that Chakraborty's mukonidine may have a different structure.[96,97,180,303,304]

Mukoenine-A (**22.1**) was obtained in 1993 by Furukawa and co-workers from the roots and stem bark of *Murraya koenigii*[203] and in the following year by Reisch et al.[305] from the stem bark of the same natural source (Scheme 75). However, Reisch et al. named the natural product girinimbilol (**22.1**). The geranyl-substituted mahanimbinol (**23.1**) was first isolated in 1980 by Rama Rao et al. from the benzene extract of the stem wood of *Murraya koenigii*.[306] In 1994, Reisch et al. extracted the same natural product from the stem bark of the same plant and named it mahanimbilol (**23.1**).[305] Six years later, Boyd and co-workers reported the isolation of mahanimbilol (**23.1**) from the organic extract of *Murraya siamensis*.[307] In 1967, Joshi et al. isolated heptaphylline (**22.2**) from the hexane extract of the roots of *Clausena heptaphylla*.[308] Mukoenine-B (**75.1**) was obtained in 1993 by Furukawa and co-workers from the

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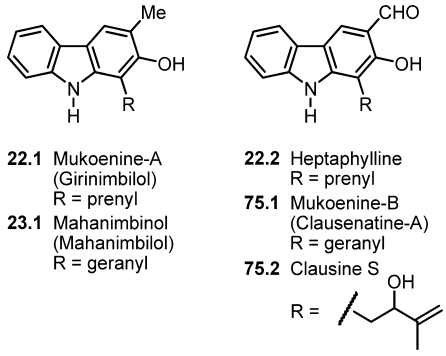
acetone extract of the roots of *Murraya koenigii*.[203] Six years later, Wu et al. described the isolation of the same carbazole from the root bark of *Clausena excavata* and named it clausenatine-A (**75.1**). Clausine S (**75.2**) was isolated by Wu et al. along with mukoenine-B (clausenatine-A) (**75.1**) from the same natural source. Although clausine S (**75.2**) was obtained in optically active form ($[\alpha]_D$ = +159.09, c 0.0022, HOMe), the absolute stereochemistry is still unknown.[309]

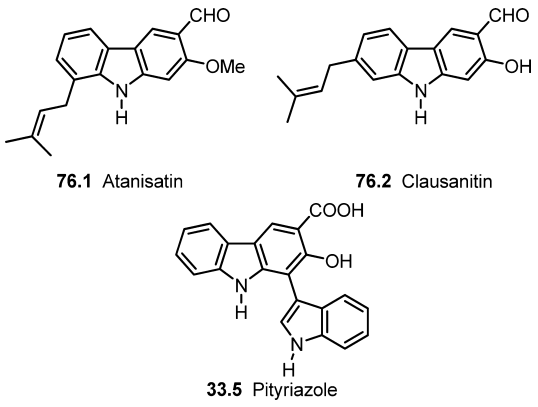
Scheme 75



22.1 Mukoenine-A (Girinimbilol) R = prenyl
23.1 Mahanimbinol (Mahanimbilol) R = geranyl
22.2 Heptaphylline R = prenyl
75.1 Mukoenine-B (Clausenatine-A) R = geranyl
75.2 Clausine S R =

Atanisatin (**76.1**) and clausanitin (**76.2**) were isolated in 1975 by Okorie from the hexane extract of the stem and the roots of *Clausena anisata* (Scheme 76).[310] In addition to their

Scheme 76



76.1 Atanisatin **76.2** Clausanitin
33.5 Pityriazole

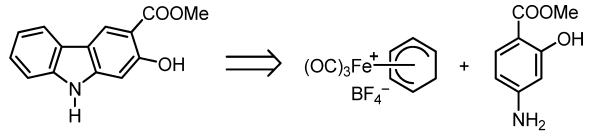
difference in the C-2 oxygen substituent, both alkaloids differ also in the position of the prenyl group. In 2005, Steglich and co-workers described the isolation of the tryptophan metabolite pityriazole (**33.5**) from cultures of the human pathogenic yeast *Malassezia furfur*.[240] Remarkably, this alkaloid possesses a C_1-substituent at C-3 even though it has not been isolated from a higher plant.

Despite the fact that a large number of 2-oxygenated tricyclic carbazole alkaloids have been isolated from various natural sources, only few syntheses are known for this class of alkaloids. Total syntheses reported prior to 2001 were covered in our earlier review.[1]

3.2.2.2. Total Synthesis of Mukonidine. Knölker and co-workers described the total synthesis of mukonidine (**21.6**) based on an iron-mediated approach.[180] Retrosynthetic analysis of mukonidine (**21.6**) led to the iron complex salt **77.1** and the arylamine **77.2** as building blocks (Scheme 77).

Esterification of commercial 4-aminosalicylic acid (**78.1**) with diazomethane led quantitatively to the arylamine **77.2** (Scheme

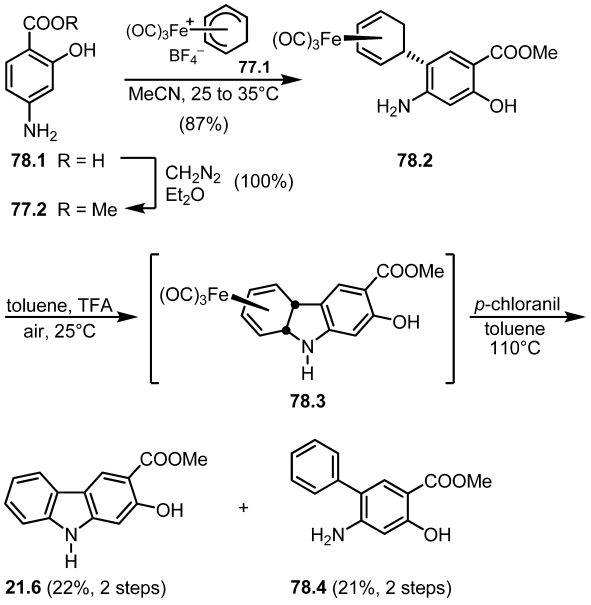
Scheme 77



21.6 Mukonidine **77.1** **77.2**

78).[179] On a large scale, sulfuric acid/methanol was used for this conversion (93% yield).[180] The electrophilic aromatic

Scheme 78



78.2
78.3
21.6 (22%, 2 steps) **78.4** (21%, 2 steps)

substitution of the arylamine **77.2** by reaction with the iron complex salt **77.1** afforded the iron complex **78.2** in 87% yield. All attempts to achieve an iron-mediated oxidative cyclization of complex **78.2** using very active manganese dioxide, iodine in pyridine, or ferrocenium hexafluorophosphate failed, which was ascribed to the free hydroxy group present in this substrate. Finally, oxidative cyclization of complex **78.2** was achieved in air at room temperature in the presence of trifluoroacetic acid and afforded the tricarbonyl iron-coordinated dihydrocarbazole **78.3**. Oxidation of complex **78.3** with *p*-chloranil (tetrachloro-1,4-benzoquinone) afforded mukonidine (**21.6**) in 22% yield along with the biaryl derivative **78.4**. Complex **78.3** could also successfully be transformed to mukonidine (**21.6**) by demetalation with trimethylamine *N*-oxide and subsequent catalytic dehydrogenation with palladium on activated carbon (11% yield based on **77.1**).[180,304] Various other efforts to transform complex **78.3** to mukonidine (**21.6**) using very active manganese dioxide or ferrocenium hexafluorophosphate failed and resulted in complete decomposition.

3.2.2.3. Synthesis of O-Methylmukonal. In 2007, St. Jean Jr. et al. reported a concise total synthesis of *O*-methylmukonal (**21.2**) starting from 4-fluoro-2-hydroxybenzaldehyde (**79.1**) and the boronic ester **79.4** (Scheme 79).[311] Methylation of the hydroxybenzaldehyde **79.1** followed by bromination of the resulting anisole **79.2** with *N*-bromosuccinimide (NBS) afforded the bromo derivative **79.3**. A tandem process of palladium-catalyzed microwave-assisted Suzuki–Miyaura cross-coupling of **79.3** with the boronate **79.4** and subsequent S_NAr-reaction provides *N*-tosyl-*O*-methylmukonal. Deprotection with

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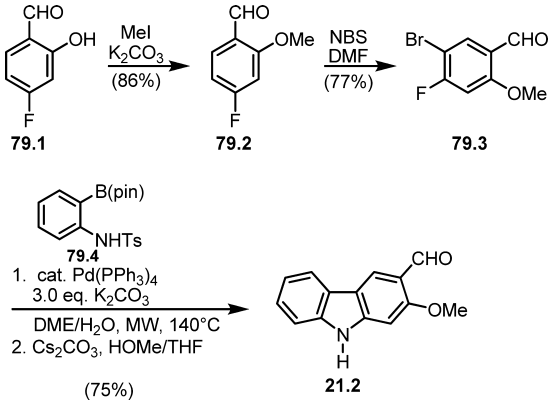
Scheme 79

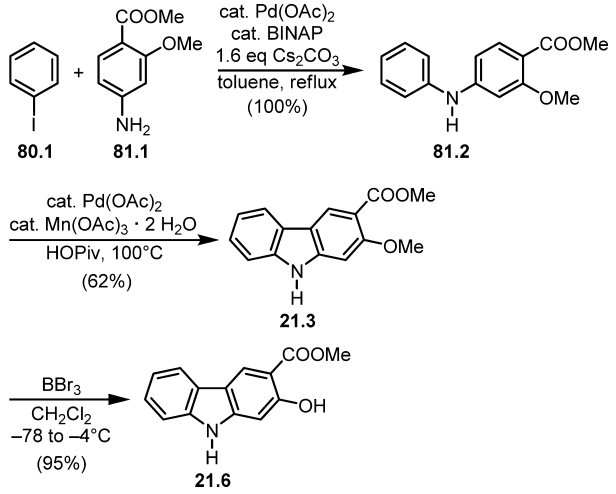


cesium carbonate afforded *O*-methylmukonal (glycosinine) (**21.2**) in 50% overall yield based on the benzaldehyde **79.1**.

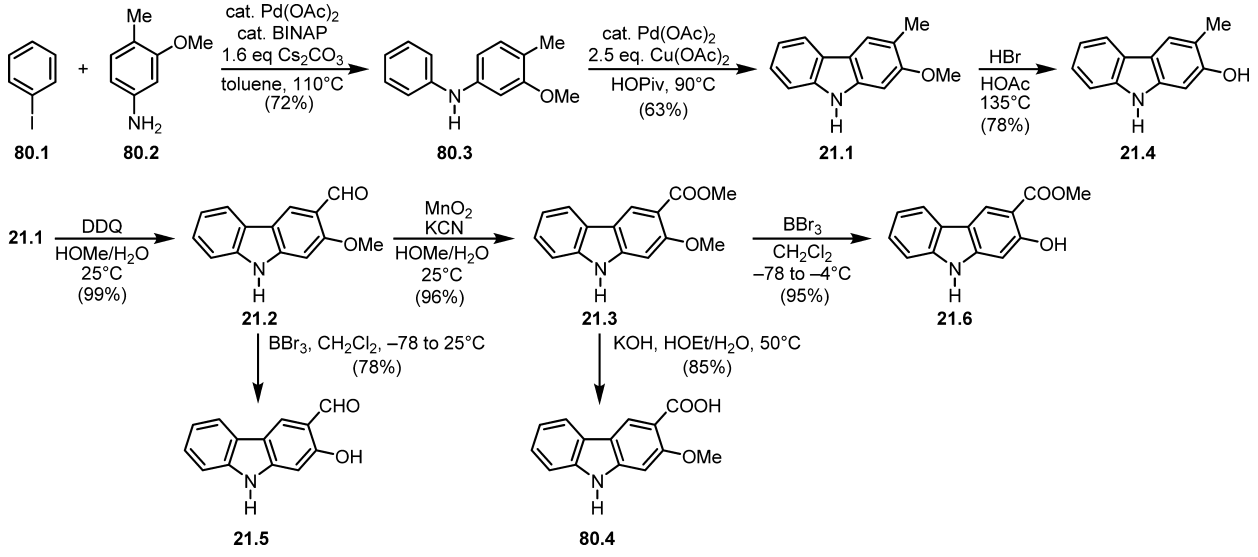
3.2.2.4. Total Synthesis of 2-Methoxy-3-methylcarbazole, 2-Hydroxy-3-methylcarbazole, O-Methylmukonal, Mukonal, Clausine L, Mukonidine, and Pityriazole. In 2008, Knölker and co-workers described the synthesis of 2-methoxy-3-methylcarbazole (**21.1**) and its transformation into the 2-oxygenated carbazole alkaloids 2-hydroxy-3-methylcarbazole (**21.4**), *O*-methylmukonal (**21.2**), mukonal (**21.5**), clausine L (**21.3**), and mukonidine (**21.6**) (Scheme 80).[97] The relay compound, 2-methoxy-3-methylcarbazole (**21.1**), was obtained using a palladium-catalyzed route starting from iodobenzene (**80.1**) and 3-methoxy-4-methylaniline (**80.2**). Buchwald–Hartwig coupling of iodobenzene (**80.1**) and 3-methoxy-4-methylaniline (**80.2**) provided the diarylamine **80.3** in 72% yield. Palladium(II)-catalyzed oxidative cyclization of the diarylamine **80.3** using copper(II) acetate as reoxidant afforded 2-methoxy-3-methylcarbazole (**21.1**) in 63% yield along with 26% of recovered diarylamine **80.3**. Using common functional group transformations, 2-methoxy-3-methylcarbazole (**21.1**) was converted to the other 2-oxygenated carbazole alkaloids. Cleavage of the methyl ether of **21.1** with hydrogen bromide/acetic acid gave 2-hydroxy-3-methylcarbazole (**21.4**). Oxidation of **21.1** with DDQ afforded almost quantitatively *O*-methylmukonal (**21.2**), which on demethylation with boron tribromide provided mukonal (**21.5**). Oxidation of *O*-methylmukonal (**21.2**) with manganese dioxide in methanol in the presence of potassium cyanide[312] provided clausine L (**21.3**). Cleavage of the methyl ether of clausine L (**21.3**) led to mukonidine (**21.6**), whereas ester cleavage afforded the isomukonidine **80.4**, a potential structural alternative for Chakraborty's mukonidine.[97]

Knölker and co-workers also described an improved synthesis of clausine L (**21.3**) and mukonidine (**21.6**) starting from iodobenzene (**80.1**) and commercial methyl 4-amino-2-methoxybenzoate (**81.1**) (Scheme 81).[96] Palladium(0)-catalyzed Buchwald–Hartwig amination of iodobenzene (**80.1**) with the amine **81.1** led to the diarylamine **81.2**. Subsequent palladium(II)-catalyzed oxidative cyclization via double C–H bond activation afforded clausine L (**21.3**) in two steps and 62% overall yield (alternative route: four steps and 43% overall yield).[97] Cleavage of the methyl ether of clausine L (**21.3**) provided mukonidine (**21.6**) in 95% yield. Thus, mukonidine

Scheme 81



Scheme 80

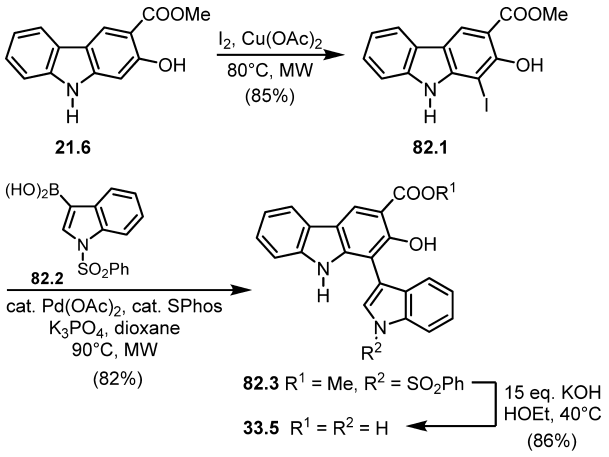


dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

(**21.6**) was obtained in three steps and 59% overall yield[96] (alternative route: five steps and 41% overall yield).[97]

For the total synthesis of pityriazole (**33.5**), the indolyl substituent at C-1 was introduced via Suzuki–Miyaura coupling of 1-iodomukonidine (**82.1**) with indol-3-ylboronic acid **82.2** (Scheme 82).[96] Microwave-assisted electrophilic iodination of

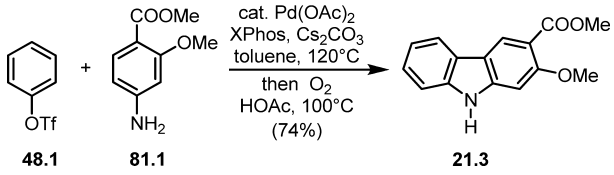
Scheme 82



mukonidine (**21.6**) with iodine and copper(II) acetate afforded 1-iodomukonidine (**82.1**) in 85% yield. Palladium-catalyzed coupling of the 1-iodocarbazole **82.1** and the indol-3-ylboronic acid **82.2** furnished the 1-(indol-3-yl)carbazole **82.3**. Cleavage of the ester and the benzenesulfonyl group under alkaline conditions provided pityriazole (**33.5**) in 86% yield.

3.2.2.5. Synthesis of Clausine L and 2-Methoxy-3-methylcarbazole. On the basis of their one-pot procedure for N-arylation and oxidative coupling (see Scheme 48), Fujii, Ohno, and co-workers described the synthesis of clausine L (**21.3**) from phenyl triflate (**48.1**) and the aniline derivative **81.1** (Scheme 83).[106] After completion of the Buchwald–

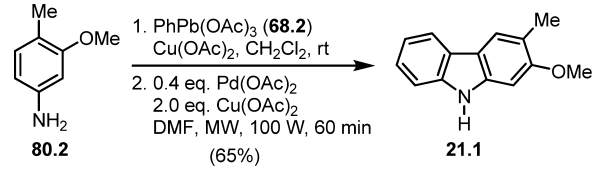
Scheme 83



Hartwig amination, acetic acid was added and the flask was put under an oxygen atmosphere to effect the oxidative cyclization.

Menéndez and co-workers reported a lead-mediated total synthesis of 2-methoxy-3-methylcarbazole (**21.1**) (Scheme 84).[294] The same approach has also been applied to the total synthesis of murrayafoline-A (**20.1**) (see section 3.2.1.6, Scheme 68). The aniline **80.2** was used as starting material

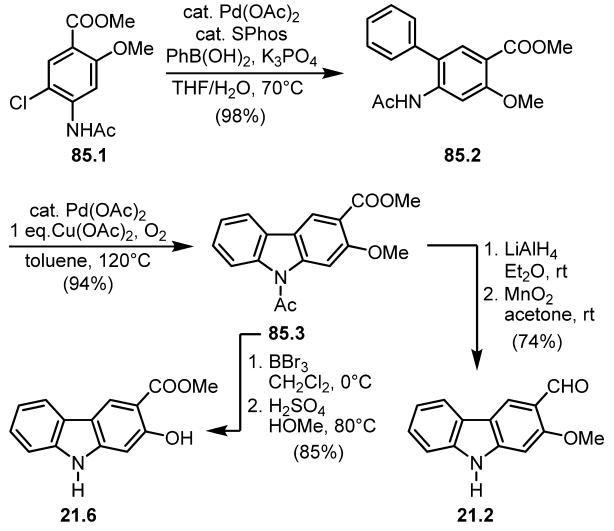
Scheme 84



and was prepared from 2-methyl-5-nitrophenol by methyl ether formation and subsequent hydrogenation. N-Phenylation of 3-methoxy-4-methylaniline (**80.2**) with phenyllead triacetate (**68.2**) followed by oxidative cyclization in the microwave afforded 2-methoxy-3-methylcarbazole (**21.1**).

3.2.2.6. Synthesis of O-Methylmukonal and Mukonidine. On the basis of the oxidative cyclization of *N*-acetyl-2-aminobiphenyls (see Scheme 71), Buchwald and co-workers developed a synthetic route to *O*-methylmukonal (**21.2**) and mukonidine (**21.6**) (Scheme 85).[127] The 9-acetylcarbazole

Scheme 85



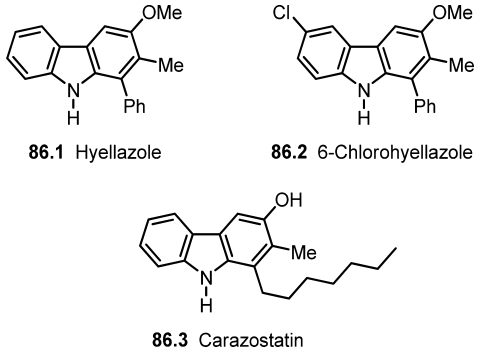
85.3, which serves as a common intermediate for both alkaloids, was prepared in two steps and 92% overall yield from the commercially available aryl chloride **85.1** by a sequence of Suzuki–Miyaura coupling and oxidative cyclization. Reduction of the methyl ester group of **85.3** with concomitant cleavage of the acetamide moiety and subsequent oxidation of the resulting benzylic alcohol afforded *O*-methylmukonal (glycosinine) (**21.2**) in 74% yield. Cleavage of the methyl ether of **85.3** followed by acidic hydrolysis of the acetamide afforded mukonidine (**21.6**) in 85% yield.

3.2.3. 3-Oxygenated Carbazole Alkaloids. This section covers carbazole alkaloids that lack a C_1-substituent at the 3-position of either benzene ring of the carbazole nucleus. Carbazoles with an oxygen substituent at C-3 and a carbon substituent at C-6 (IUPAC numbering) are formally 3-oxygenated carbazoles as well but have been classified by us as 6-oxygenated carbazoles and are discussed in section 3.2.5 (vide infra).

3.2.3.1. Isolation from Natural Sources. Until the late 1970s, tricyclic carbazole alkaloids have been isolated mainly from different plant sources. These carbazole alkaloids exhibit a C_1-substituent at C-3 as the common structural feature (see above). However, in 1979 Moore and co-workers obtained for the first time two unusual, nonbasic 3-oxygenated carbazole alkaloids from the blue-green algae *Hyella caespitosa*. Unlike the carbazole alkaloids isolated from terrestrial plants, hyellazole (**86.1**) and 6-chlorohyellazole (**86.2**) lack a C_1-substituent at C-3 (Scheme 86).[313] Ten years after Moore's discovery, Kato et al. isolated carazostatin (**86.3**) from *Streptomyces chromofuscus*. Carazostatin (**86.3**) is a radical scavenger and is more active than 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT).[314] Moreover,

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

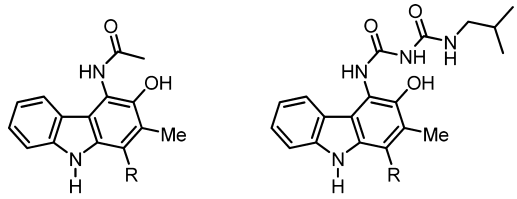
Scheme 86



carazostatin (**86.3**) exhibits a strong inhibitory activity against the free radical-induced lipid peroxidation in liposomal membranes and is a stronger antioxidant than α-tocopherol.[315,316]

In 1990, Seto and co-workers reported the isolation of the antiostatins A_1 (**87.1**), A_2 (**87.2**), A_3 (**87.3**), A_4 (**87.4**), B_2 (**87.5**), B_3 (**87.6**), B_4 (**87.7**), and B_5 (**87.8**) from *Streptomyces cyaneus* 2007-SV_1 (Scheme 87).[317] Seto and co-workers did not

Scheme 87



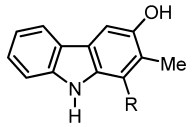
87.1 Antiostatin A_1 R = $(CH_2)_4Me$
87.2 Antiostatin A_2 R = $(CH_2)_2CHMeCH_2Me$
87.3 Antiostatin A_3 R = $(CH_2)_4CHMe_2$
87.4 Antiostatin A_4 R = $(CH_2)_6Me$
87.5 Antiostatin B_2 R = $(CH_2)_5Me$
87.6 Antiostatin B_3 R = $(CH_2)_4CHMe_2$
87.7 Antiostatin B_4 R = $(CH_2)_6Me$
87.8 Antiostatin B_5 R = $(CH_2)_5CHMe_2$

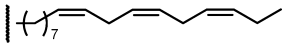
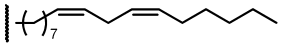
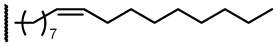
report whether or not antiostatin A_2 (**87.2**) was obtained as an optically active compound. The antiostatins are the first carbazole alkaloids with an acetamido group or a biuret side chain at C-4. They showed a strong inhibitory activity against free radical-induced lipid peroxidation.

The lipocarbazoles A1–A4 (**88.1–88.4**) were isolated in 2009 by Süssmuth, Fiedler, and co-workers from the fermentation broth of the actinomycete *Tsukamurella pseudomonae* Acta 1857 (Scheme 88).[318] A C_{17} alkyl side-chain at C-1 is the common structural element of the lipocarbazoles A1–A4 (**88.1–88.4**). The structures of the lipocarbazoles were assigned based on NMR and MS/MS experiments and later confirmed by total synthesis. The lipocarbazoles A3 (**88.3**) and A4 (**88.4**) showed antioxidative activity in a DPPH (1,1-diphenyl-2-picrylhydrazyl)-based assay.

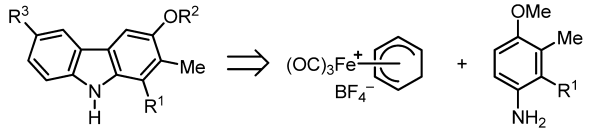
3.2.3.2. Total Synthesis of Carazostatin, Hyellazole, and 6-Chlorohyellazole. Knölker and co-workers have developed a synthetic route to the structurally related alkaloids carazostatin (**86.3**), hyellazole (**86.1**), and 6-chlorohyellazole (**86.2**) based on their iron-mediated approach. Retrosynthetic analysis led to the iron complex salt **77.1** and the corresponding arylamines **89.1** and **89.2** as precursors (Scheme 89).

Scheme 88



88.1 Lipocarbazole A1 R = 
88.2 Lipocarbazole A2 R = 
88.3 Lipocarbazole A3 R = 
88.4 Lipocarbazole A4 R = n-$C_{17}H_{35}$

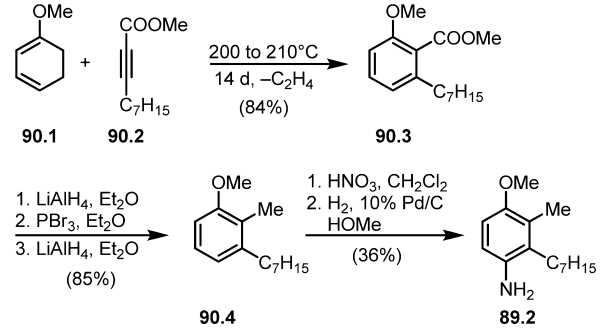
Scheme 89



86.1 Hyellazole
R^1 = Ph; R^2 = Me; R^3 = H
86.2 6-Chlorohyellazole
R^1 = Ph; R^2 = Me; R^3 = Cl
86.3 Carazostatin
R^1 = C_7H_{15}; R^2, R^3 = H
77.1
89.1 R^1 = Ph
89.2 R^1 = C_7H_{15}

The arylamine **89.2**, required for the total synthesis of carazostatin (**86.3**), was prepared starting from 1-methoxycyclohexa-1,3-diene (**90.1**) and methyl 2-decynoate (**90.2**) (Scheme 90).[319,320] Diels–Alder cycloaddition of **90.1** and

Scheme 90

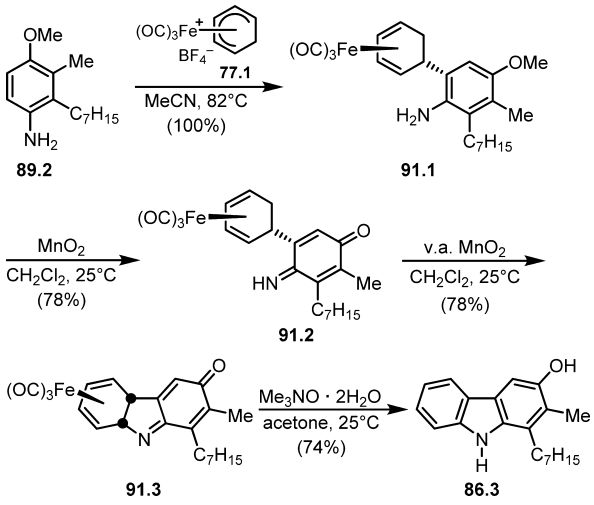


90.2 with concomitant retro-Diels–Alder reaction by extrusion of ethylene afforded methyl 2-heptyl-6-methoxybenzoate (**90.3**). Using a three-step procedure, the methoxycarbonyl group of compound **90.3** was transformed into a methyl group to give 3-heptyl-2-methylanisole (**90.4**). Nitration of the anisole **90.4** and subsequent catalytic hydrogenation led to the desired arylamine **89.2** in six steps and 26% overall yield.

Electrophilic aromatic substitution of the arylamine **89.2** by reaction with the iron complex salt **77.1** afforded quantitatively the iron complex **91.1** (Scheme 91).[319,320] Oxidation of that iron complex with commercial manganese dioxide led to the quinone imine **91.2**. Further oxidation with Fatiadi's very active manganese dioxide[321] finally gave the tricarbonyl iron-coordinated 4*b*,8*a*-dihydrocarbazole-3-one **91.3**. This very mild two-step oxidation/cyclization sequence of complexes like **91.1** has been called quinone imine cyclization (see section 1.2.5, Scheme 9). Remarkably, the tricarbonyl iron–cyclohexadiene complex is not affected by commercial manganese dioxide. The highly active manganese dioxide described by Fatiadi then induces an oxidative cyclization without destroying

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

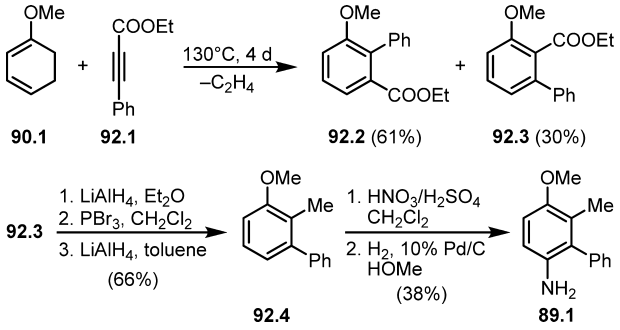
Scheme 91



the tricarbonyl iron complex. Demetalation of complex **91.3** was achieved by using trimethylamine *N*-oxide. Concomitant tautomerization provided carazostatin (**86.3**) in 74% yield.

For the synthesis of hyellazole (**86.1**), the required arylamine **89.1** was prepared via Diels–Alder reaction of 1-methoxycyclohexa-1,3-diene (**90.1**) and ethyl phenylpropynoate **92.1** (Scheme 92).[322,323] The desired biphenyl **92.3** was transformed

Scheme 92

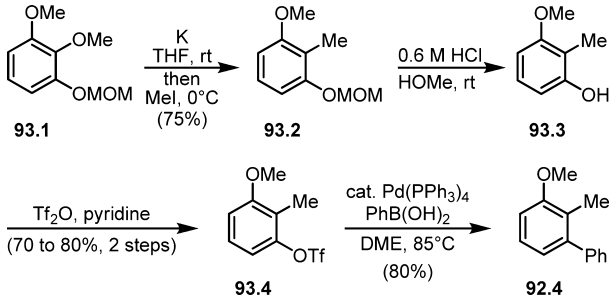


to the 2-aminobiphenyl **89.1** by a similar sequence of transformations as shown in Scheme 90. This approach provides the arylamine **89.1** in six steps and 7% overall yield based on 1-methoxycyclohexa-1,3-diene (**90.1**).

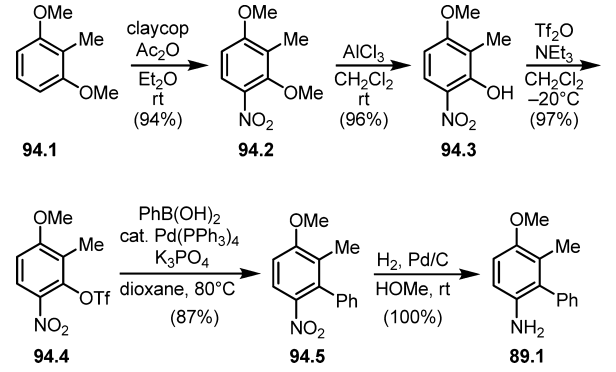
The drawback of the synthesis described above is the preferential formation of the undesired regioisomer **92.2** (61% yield) in the Diels–Alder reaction. Therefore, the overall yield of the intermediate biphenyl derivative **92.4** was limited to 20%. However, Azzena et al. reported an alternative route to compound **92.4** starting from 1,2-dimethoxy-3-(methoxymethyl)benzene (**93.1**) (Scheme 93).[324] The key step of that approach is a Suzuki–Miyaura cross-coupling of the triflate **93.4** with phenylboronic acid. This procedure provides the biphenyl derivative **92.4** in four steps and 48% overall yield based on compound **93.1**. The biphenyl **92.4** was then converted to the arylamine **89.1** as described above, and **89.1** was obtained in six steps and 18% overall yield based on 1,2-dimethoxy-3-(methoxymethyl)benzene (**93.1**).

For the synthesis of 6-chlorohyellazole (**86.2**), Knölker et al. developed an improved route to arylamine **89.1** starting from commercially available 2,6-dimethoxytoluene (**94.1**) (Scheme 94).[325] Nitration of **94.1** using claycop selectively afforded the

Scheme 93



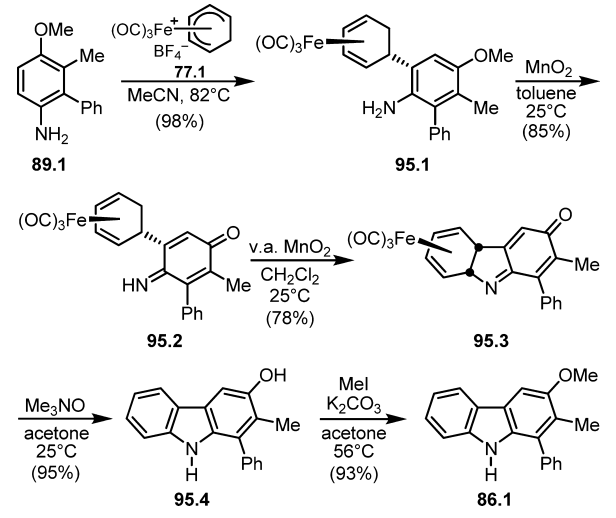
Scheme 94



desired 4-nitroanisole **94.2**. Regioselective methyl ether cleavage to the phenol **94.3** followed by esterification and subsequent Suzuki–Miyaura cross-coupling of the resulting triflate **94.4** with phenylboronic acid led to the biphenyl derivative **94.5**. Finally, catalytic hydrogenation of **94.5** afforded the arylamine **89.1**. The improved synthesis provides the arylamine **89.1** in five steps and 76% overall yield (Diels–Alder approach: six steps, 7% overall yield (Scheme 92); Suzuki–Miyaura approach: six steps, 18% overall yield (Scheme 93)).

Electrophilic substitution of the arylamine **89.1** by reaction with the complex salt **77.1** provided the iron complex **95.1** in excellent yield (Scheme 95).[322,323] Sequential highly chemoselective oxidation of the iron complex **95.1**, first with commercial manganese dioxide and in a second oxidation

Scheme 95



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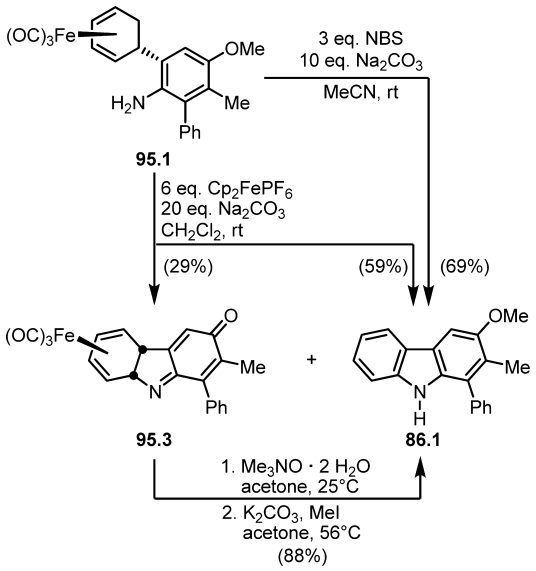
step with Fatiadi's very active manganese dioxide, provided via the quinone imine **95.2** the tricarbonyliron-coordinated 4*b*,8*a*-dihydrocarbazole-3-one **95.3**. Demetalation of the tricarbonyl iron-coordinated 4*b*,8*a*-dihydrocarbazole-3-one (**95.3**) followed by selective O-methylation afforded hyellazole (**86.1**).

A more direct method for the oxidative cyclization of complex **95.1** to hyellazole (**86.1**) is the iron-mediated arylamine cyclization (Scheme 96).[322,323] Treatment of iron

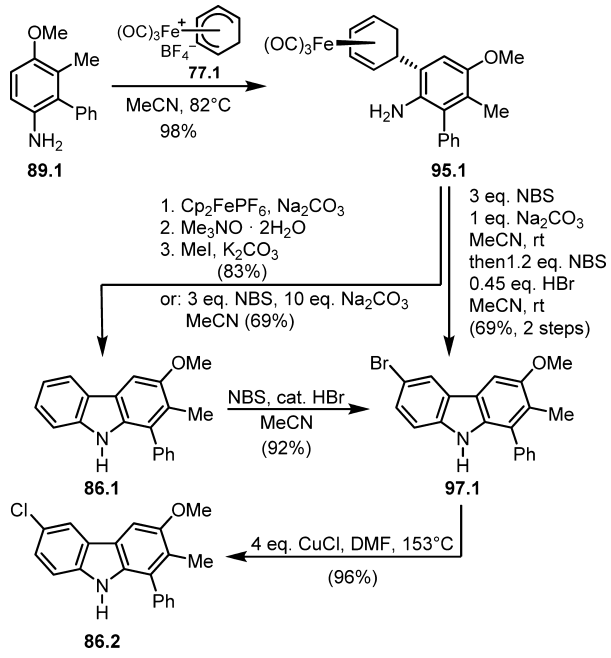
Scheme 96



complex **95.1** with ferrocenium hexafluorophosphate in the presence of sodium carbonate provided hyellazole (**86.1**) along with complex **95.3**, which was converted to the natural product as described above. Alternatively, treatment of complex **95.1** with *N*-bromosuccinimide (NBS) in the presence of sodium carbonate led to hyellazole (**86.1**) in 69% yield.[325] The complex **95.3** was not obtained as a byproduct under these conditions. Thus, the shortest route to the natural product **86.1** is the oxidative cyclization of **95.1** using *N*-bromosuccinimide. It provides hyellazole (**86.1**) in two steps and 68% yield based on the iron complex salt **77.1**. Oxidative cyclization of complex **95.1** with ferrocenium hexafluorophosphate inclusive conversion of the byproduct **95.3** leads to hyellazole (**86.1**) in four steps and 83% yield. Application of the quinone imine cyclization provided hyellazole (**86.1**) in five steps and only 57% yield based on the iron complex salt **77.1**. Taking into account the improved synthesis of arylamine **89.1**, hyellazole (**86.1**) can be obtained in eight steps and 63% overall yield based on 2,6-dimethoxytoluene (**94.1**).

An attempted direct conversion of hyellazole (**86.1**) into 6-chlorohyellazole (**86.2**) by reaction with *N*-chlorosuccinimide (NCS) in the presence of a catalytic amount of hydrochloric acid led exclusively to 4-chlorohyellazole.[325] In contrast, bromination of **86.1** using NBS provided exclusively 6-bromohyellazole (**97.1**) (Scheme 97). A straightforward one-pot transformation of the iron complex **95.1** to 6-bromohyellazole (**97.1**) was achieved by reaction of **95.1** with an excess of NBS and switching from conditions for oxidative cyclization (basic reaction medium) to conditions for electrophilic substitution (acidic reaction medium). Finally, halogen exchange with 4 equiv of copper(I) chloride in DMF at reflux was used for the transformation of 6-bromohyellazole

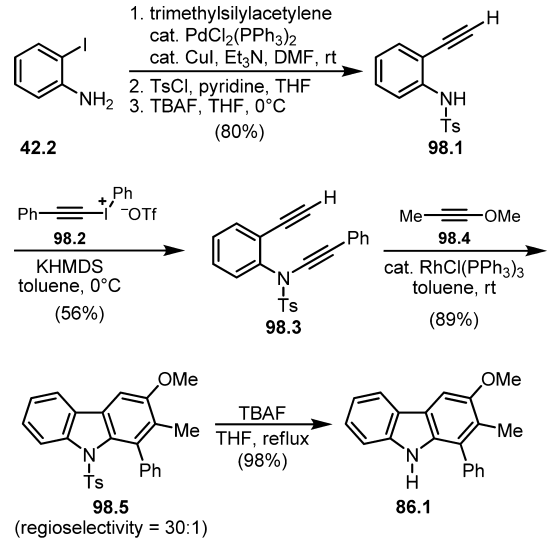
Scheme 97



(**97.1**) into 6-chlorohyellazole (**86.2**) in nearly quantitative yield. Using this sequence, 6-chlorohyellazole (**86.2**) is available in three steps and 65% overall yield (or four steps and 72% overall yield) based on the iron complex salt **77.1** (Scheme 97).

In 2002, Witulski and Alayrac reported the total synthesis of hyellazole (**86.1**) via a Vollhardt-type rhodium-catalyzed alkyne cyclotrimerization (Scheme 98).[182] The diyne **98.3** was

Scheme 98



obtained in four steps starting from 2-iodoaniline (**42.2**). Sonogashira–Hagihara coupling[326−328] of 2-iodoaniline (**42.2**) with trimethylsilylacetylene followed by N-tosylation and protodesilylation afforded the alkyne **98.1**. Alkynylation of compound **98.1** with the alkynyliodonium triflate **98.2** led to diyne **98.3**. A Vollhardt-type cyclization of the diyne **98.3** and 1-methoxypropyne (**98.4**) using Wilkinson's catalyst afforded *N*-tosylhyellazole (**98.5**) along with an undesired regioisomer in a ratio of 30:1 and 89% yield. The minor regioisomer

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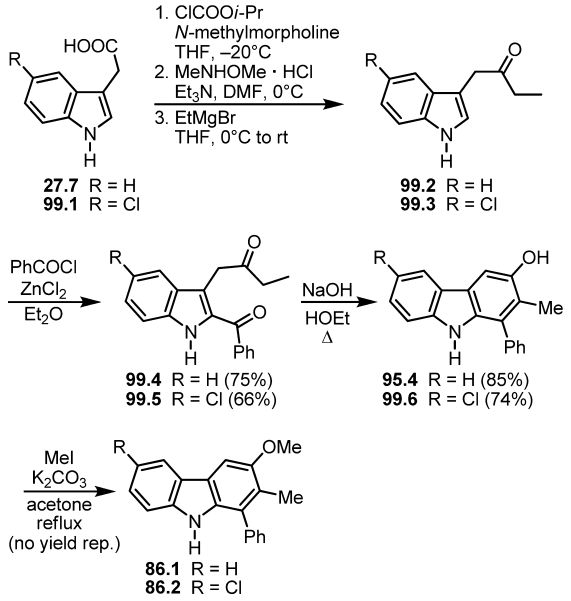
resulted from the alternative ("wrong") incorporation of the unsymmetrical alkyne. Finally, isomerically pure hyellazole (**86.1**) was obtained in 98% yield by removal of the tosyl group of **98.5** with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran at reflux followed by crystallization.

Two years later, Duval and Cuny reported a further total synthesis of hyellazole (**86.1**) and 6-chlorohyellazole (**86.2**) via the diketoindoles **99.4** and **99.5** as intermediates (Scheme 99).[329] Conversion of the indol-3-ylacetic acids **27.7** and **99.1**

Scheme 99

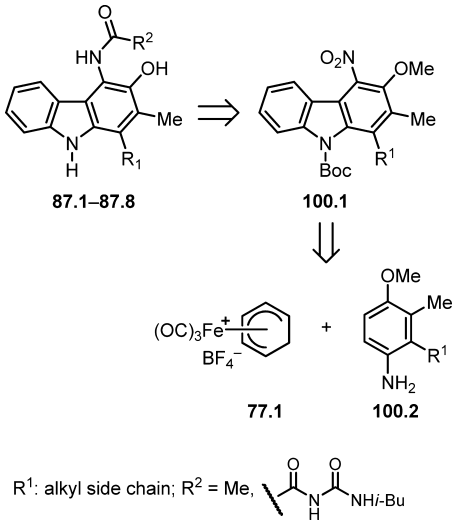


into the corresponding Weinreb amides followed by addition of ethylmagnesium bromide and Friedel–Crafts reaction with benzoyl chloride provided the diketoindoles **99.4** and **99.5** in 75% and 66% overall yield, respectively. The intramolecular aldol condensations of **99.4** and **99.5** were induced by treatment with sodium hydroxide and led to the 3-hydroxycarbazoles **95.4** and **99.6** in 85% and 74% yields, respectively. Finally, O-methylation using methyl iodide in the presence of potassium carbonate in acetone at reflux afforded hyellazole (**86.1**) and 6-chlorohyellazole (**86.2**).

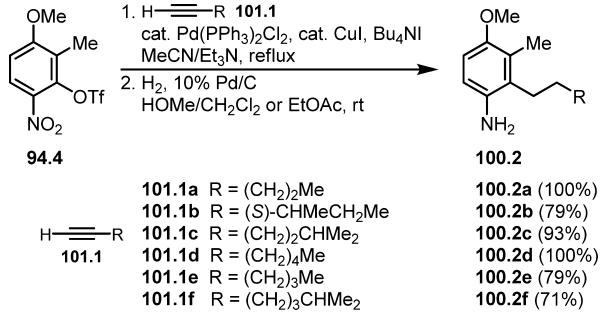
3.2.3.3. Syntheses of Antiostatins. In 2009, Knölker and co-workers described the first synthetic access to the whole series of the antiostatins A as well as to the antiostatins B (**87.1**–**87.8**). The iron-mediated approach started from the iron complex salt **77.1** and the arylamines **100.2** using the 4-nitro-*N*-Boc-carbazoles **100.1** as intermediates (Scheme 100).[330]

The arylamines **100.2a**–**100.2f** were prepared in two steps from the triflate **94.4**, which is easily accessible in three steps from 2,6-dimethoxytoluene (**94.1**). Previously, triflate **94.4** has been used by Knölker et al. as a precursor for the total synthesis of hyellazole (**86.1**) and 6-chlorohyellazole (**86.2**) (see Scheme 94).[325] The alkyl side-chains at C-1 were introduced by Sonogashira coupling of the aryl triflate **94.4** and the corresponding alkyne followed by catalytic hydrogenation (Scheme 101). Except for **101.1b** and **101.1f**, all alkynes were commercially available. By adaptation of a literature procedure, 6-methylhept-1-yne (**101.1f**) was prepared in two steps from 1-bromo-4-methylpentane.[331] In analogy to other chiral carbazole alkaloids, such as carbazomadurin B (**185.2**) (see Scheme 185),[332,333] an *S*-configuration was assumed for

Scheme 100



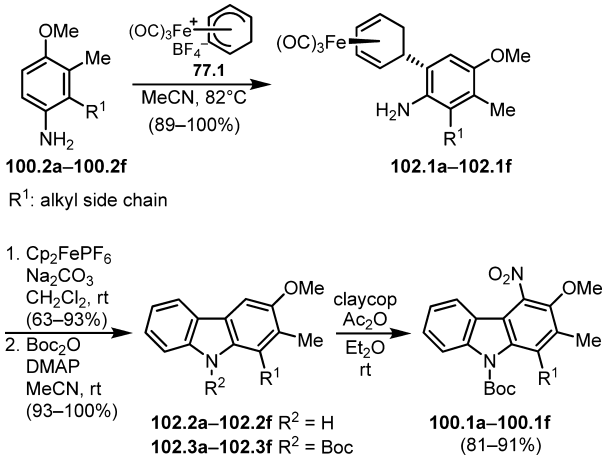
Scheme 101



antiostatin A_2 (**87.2**). Thus, (*S*)-3-methylpent-1-yne (**101.1b**) was prepared in three steps from commercial (*S*)-2-methylbutan-1-ol by oxidation with the Dess–Martin reagent[334] and subsequent Corey–Fuchs homologation to the terminal alkyne.[335,336]

Electrophilic substitution of the arylamines **100.2** by reaction with the iron complex salt **77.1** led to the iron complexes **102.1** (Scheme 102).[330] Oxidative cyclization of **102.1a**–**102.1f** with an excess of ferrocenium hexafluorophosphate in the presence of sodium carbonate provided the corresponding carbazoles

Scheme 102



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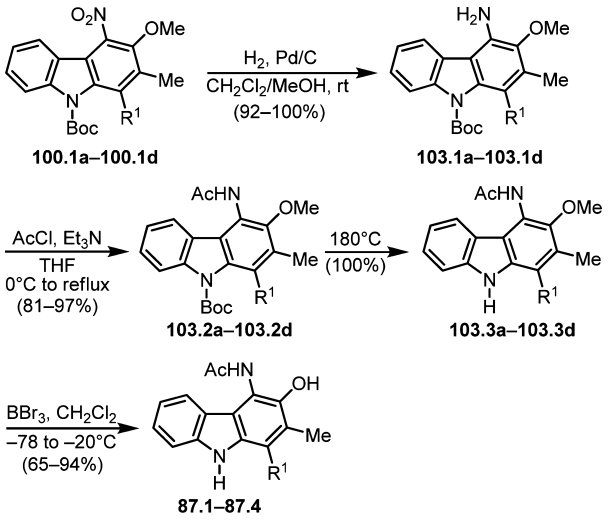
102.2, which were then transformed to the corresponding *N*-Boc-carbazoles **102.3a−102.3f** to facilitate nitration. Direct nitration of the unprotected carbazoles **102.2** proved to be uncompetitive to the protecting-group variant. Treatment with claycop finally afforded the N-protected 4-nitrocarbazoles **100.1** in excellent yields.

Catalytic hydrogenation of the *N*-Boc-4-nitrocarbazoles **100.1a−d** afforded the *N*-Boc-4-aminocarbazoles **103.1a−d** as precursors for the antiostatin A series (Scheme 103).[330] After

Scheme 103

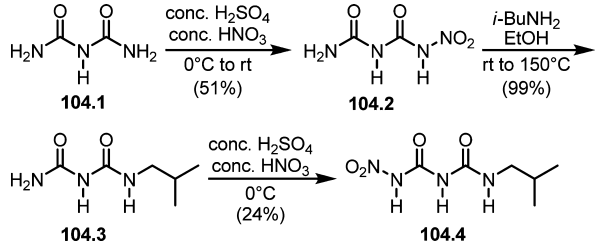


acetylation of the aminocarbazoles **103.1**, the corresponding acetamides **103.2a−d** were transformed to the *O*-methylantiostatins (**103.3**) by removal of the Boc group under thermal conditions. Finally, cleavage of the methyl ether provided the antiostatins A_1, (*S*)-A_2, A_3, and A_4 (**87.1−87.4**).

For an access to the B-series of the antiostatins, Knölker et al. needed to devise a method for the introduction of the isobutylbiuret side chain. A solution was provided by the observation of Davis and Blanchard, that heating of nitrobiuret in the presence of an amine leads to N-substituted biurets.[337] Using the procedure reported by Thiele and Uhlfelder,[338] biuret (**104.1**) was nitrated to give 1-nitrobiuret (**104.2**) (Scheme 104). Reaction of **104.2** with isobutylamine afforded 1-isobutylbiuret (**104.3**). Finally, a second nitration provided 5-isobutyl-1-nitrobiuret (**104.4**).[330]

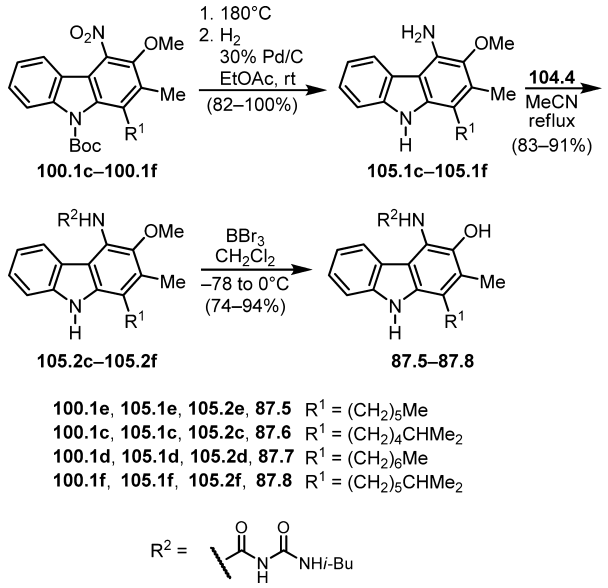
For the total synthesis of the antiostatin B series, the unprotected 4-aminocarbazoles **105.1c−f** were prepared in

Scheme 104



excellent yields by heating the *N*-Boc-4-nitrocarbazoles **100.1c−f** without solvent followed by catalytic hydrogenation (Scheme 105). Reaction of the aminocarbazoles **105.1c−f** with

Scheme 105



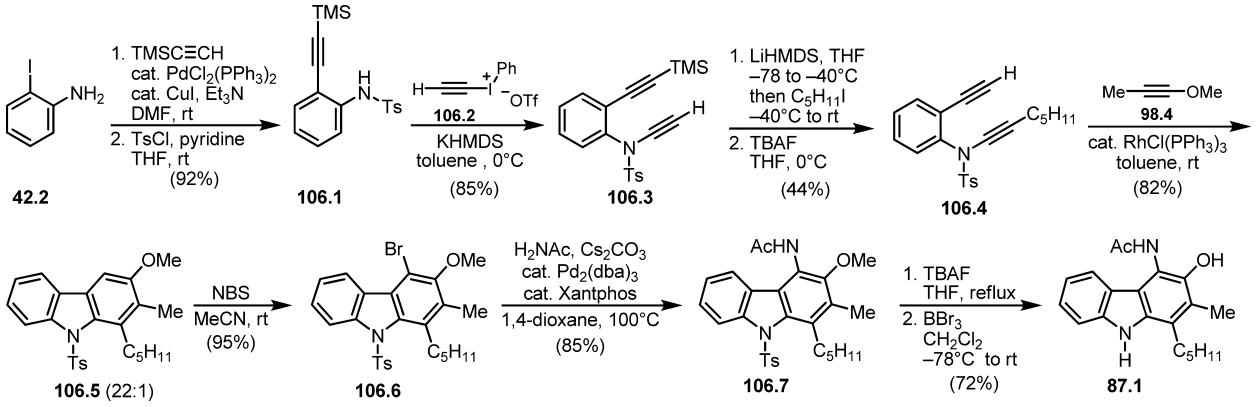
5-isobutyl-1-nitrobiuret (**104.4**) in acetonitrile at reflux afforded the 5-isobutyl-1-(carbazol-4-yl)biurets **105.2c−f**. Finally, cleavage of the methyl ether provided the antiostatins B_2 to B_5 (**87.5−87.8**).[330]

In the same year, Witulski and co-workers reported the total synthesis of antiostatin A_1 (**87.1**) using a chemo- and regioselective rhodium-catalyzed Vollhardt-type alkyne cyclotrimerization followed by a palladium-catalyzed amidation.[339] Sonogashira−Hagihara coupling of 2-iodoaniline (**42.2**) and trimethylsilylacetylene led to the corresponding alkyne derivative, which on tosylation afforded the anilide **106.1** (Scheme 106). Ethynylation of **106.1** at the nitrogen atom using the alkynyliodonium salt **106.2** followed by alkylation of the resulting ynamide **106.3** with iodopentane and desilylation with TBAF afforded the diyne **106.4** in 37% yield. A Vollhardt-type cycloaddition of diyne **106.4** and 1-methoxypropyne (**98.4**) in the presence of catalytic amounts of Wilkinson's catalyst in toluene afforded the carbazole **106.5** in 82% yield (ratio of regioisomers = 22:1). Regioselective bromination of **106.5** with NBS and subsequent Buchwald−Hartwig-type amidation of **106.6** with acetamide afforded the corresponding 4-acetamidocarbazole **106.7**. Detosylation of **106.7** with TBAF in toluene at reflux followed by demethylation of the resulting *O*-methylantiostatin A_1 provided antiostatin A_1 (**87.1**) in 72% yield over two steps.

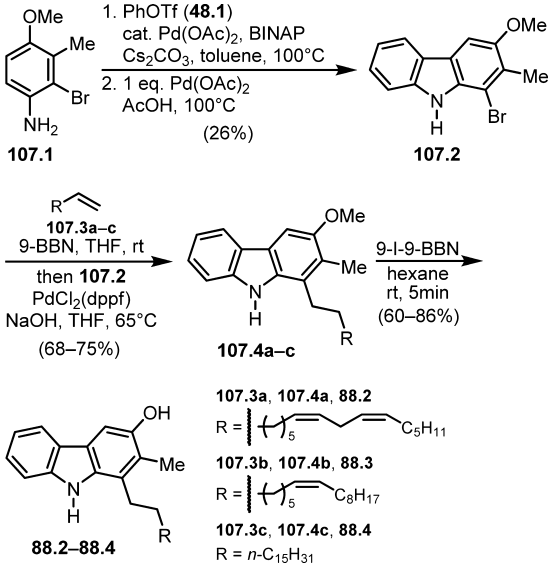
3.2.3.4. Synthesis of Lipocarbazoles A2−A4. Hänchen and Süssmuth described the total synthesis of the lipocarbazoles A2−A4 (**88.2−88.4**) together with the isolation from the actinomycete *Tsukamurella pseudomonae* Acta 1857.[340] The carbazole core was synthesized by Buchwald−Hartwig reaction of phenyl triflate (**48.1**) and the 2-bromoaniline **107.1** followed by oxidative cyclization to the 1-bromocarbazole **107.2** using stoichiometric amounts of palladium(II) acetate (Scheme 107). The arylamine **107.1** was prepared in five steps from 2-bromo-6-nitrotoluene following a synthetic route developed by Knölker and Knöll (see Scheme 188).[341] After synthesis of

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 106



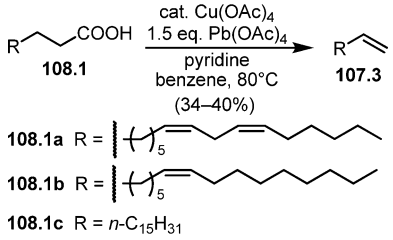
Scheme 107



the carbazole core, the alkyl side chains were introduced by Suzuki–Miyaura coupling of the 1-bromocarbazole **107.2** and in situ generated alkylboranes. Hydroboration of the alkenes **107.3a–c** with 9-borabicyclo[3.3.1]nonane (9-BBN) and direct coupling of the resulting alkylboranes with the 1-bromocarbazole **107.2** provided the *O*-methyllipocarbazoles **107.4a–c** in good yields. The required olefins **107.3** were prepared from the C_1-homologous carboxylic acids in moderate yield (Scheme 108). Finally, cleavage of the methyl ether at C-3 using 9-iodo-9-BBN led to the lipocarbazoles A2 (**88.2**), A3 (**88.3**), and A4 (**88.4**) (Scheme 107).

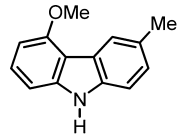
3.2.4. 5-Oxygenated Carbazole Alkaloids. In 2001, Chakravarty et al. reported the isolation and structural

Scheme 108



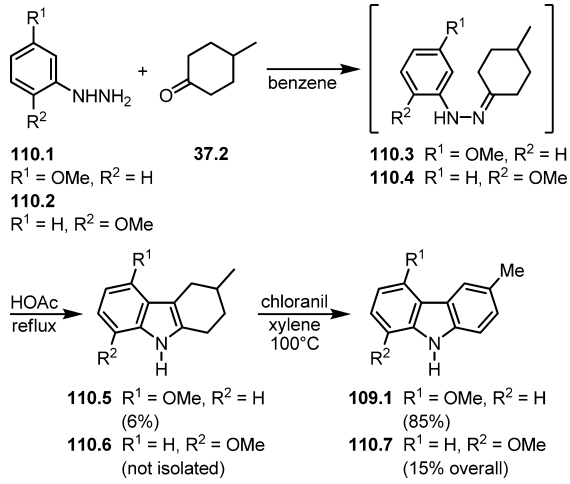
elucidation of glycoborine (**109.1**) from the petroleum ether extract of the roots of *Glycosmis arborea* (Scheme 109).[342] Nine

Scheme 109



years earlier, Bhattacharyya and co-workers had already reported the isolation of 5-methoxy-3-methylcarbazole and had named it glycozolicine.[251] Both groups reported the synthesis of 5-methoxy-3-methylcarbazole based on a Fischer indole cyclization (see Schemes 110 and 111) to confirm their

Scheme 110



structural assignments. However, in contrast to Bhattacharyya, Chakravarty et al. also synthesized 8-methoxy-3-methylcarbazole. Comparison of the NMR data of the synthetic compounds and the natural products led to a reassignment of Bhattacharyya's glycozolicine (**110.7**) as 8-methoxy-3-methylcarbazole (see Scheme 129). In 2011, Cheenpracha and Laphookhieo reported the isolation of 5-methoxy-3-methylcarbazole from the roots and twigs of *Glycosmis macrophylla* and named the compound glycrophylamine (**109.1**).[343]

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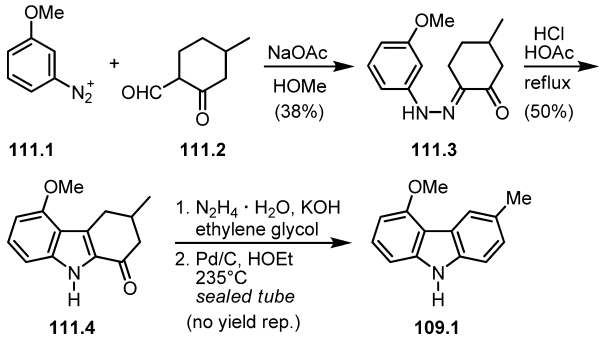
Scheme 111



Laphookhieo's NMR data of the natural product are virtually identical to those of Chakravarty's glycoborine (**109.1**).

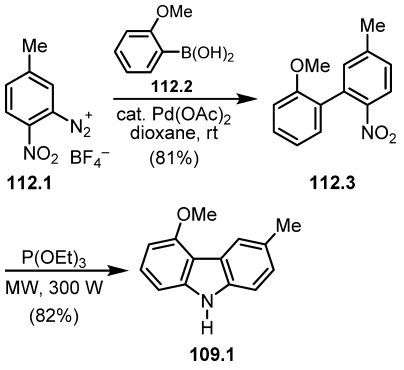
In Chakravarty's synthesis of glycoborine (**109.1**), first the hydrazone **110.3** was formed from 4-methylcyclohexanone (**37.2**) and 3-methoxyphenylhydrazine (**110.1**) in benzene (Scheme 110).[342] Removal of the solvent and heating the hydrazone in acetic acid at reflux led to a mixture of 5-methoxy-3-methyl-1,2,3,4-tetrahydrocarbazole (**110.5**) and 7-methoxy-3-methyl-1,2,3,4-tetrahydrocarbazole in a ratio of 1:9 in favor of the undesired regioisomer. Aromatization of compound **110.5** provided glycoborine (**109.1**) by heating with chloranil in xylene at 100 °C. The same reaction sequence also led to 8-methoxy-3-methylcarbazole (glycozolicine) (**110.7**) using 1-methoxyphenylhydrazine (**110.2**) as starting material.

Bhattacharyya's synthesis of glycoborine (**109.1**) was based on a Japp–Klingemann approach (Scheme 111).[251] Reaction of 2-formyl-5-methylcyclohexanone (**111.2**) and the diazonium salt **111.1** formed from *m*-anisidine (procedure not reported) in the presence of sodium acetate gave the hydrazone **111.3**. Cyclization in a mixture of acetic acid and concentrated hydrochloric acid at reflux led to a mixture of 5-methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**111.4**) and the undesired regioisomer 7-methoxy-3-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (no ratio reported, combined yield = 50%). Wolff–Kizhner reduction and aromatization with palladium on activated carbon provided 5-methoxy-3-methylcarbazole (glycoborine) (**109.1**). Surprisingly, in the hands of Bhattacharyya and co-workers, the synthetic product was indistinguishable from glycozolicine (8-methoxy-3-methylcarbazole) (**110.7**) with respect to UV, IR, melting point, and even mixed melting point.

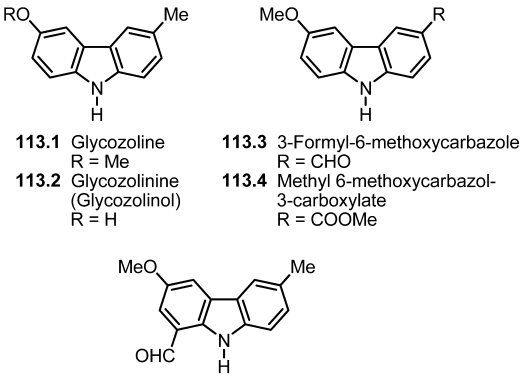
In 2008, Kuethe and Childers reported a synthesis of glycoborine (**109.1**) using a Cadogan cyclization as the key step.[344] Suzuki–Miyaura coupling of the diazonium salt **112.1** and 2-methoxyphenylboronic acid (**112.2**) afforded the 2-nitrobiphenyl **112.3** in high yield (Scheme 112). Cyclization using triethyl phosphite under microwave irradiation led to glycoborine (**109.1**). The spectroscopic data of the compound obtained by Kuethe and Childers matched those reported by Chakravarty.

3.2.5. 6-Oxygenated Carbazole Alkaloids. *3.2.5.1. Isolation from Natural Sources.* Glycozoline (**113.1**), the first C-ring oxygenated carbazole obtained from natural sources, was isolated in 1966 by Chakraborty from the stem bark of *Glycosmis pentaphylla* (Scheme 113).[345,346] In 1991, the same alkaloid was isolated by Li, McChesney, and El-Feraly from the roots of *Clausena lansium*.[249] Eight years later, Chakravarty et al. isolated glycozoline (**113.1**) from the roots of a different plant of the family Rutaceae, *Glycosmis arborea*.[347] In 1983,

Scheme 112



Scheme 113



Mukherjee et al. reported the isolation and structural elucidation of glycozolinine (**113.2**) from the seeds of *G. pentaphylla*.[348] In the following year, Bhattacharyya et al. isolated the same compound from the same natural source and named it glycozolinol (**113.2**).[349] Li, McChesney, and El-Feraly described the isolation of 3-formyl-6-methoxycarbazole (**113.3**) and methyl 6-methoxycarbazole-3-carboxylate (**113.4**) from the ethanol extract of the roots of *Clausena lansium*.[249] Franzblau and co-workers isolated 3-formyl-6-methoxycarbazole (**113.3**) from the stem bark of *Micromelum hirsutum* and found an in vitro anti-tuberculosis (TB) activity against the $H_{37}Rv$ strain of *Mycobacterium tuberculosis*.[350] Chowdhury et al. isolated 8-formyl-6-methoxy-3-methylcarbazole (1-formyl-3-methoxy-6-methylcarbazole) (**113.5**) from the leaves of *Murraya koenigii*. This alkaloid showed an inhibitory activity against Gram-negative bacteria and fungi.[351]

In 1989, Reisch and co-workers reported the isolation of glycomaurrol (**114.1**) from the dichloromethane extract of the stem bark of *Glycosmis mauritiana* (Scheme 114).[352] Glycomaurrol (**114.1**) can be considered as biogenetic precursor of glycomaurin (eustifoline-A) (**238.1**), a pyrano[2,3-*c*]carbazole that may result from an intramolecular attack of the C-6 hydroxy group at the double bond of the prenyl group to form the pyran ring (see Scheme 238). One year later, Ito and Furukawa isolated eustifoline-C (**114.2**) from the root bark of *Murraya euchrestifolia* Hayata collected in Taiwan in December.[353] In analogy to the relationship between glycomaurrol (**114.1**) and glycomaurin (eustifoline-A) (**238.1**), eustifoline-C (**114.2**) can be considered as a biogenetic precursor of eustifoline-B (**238.2**) (see Scheme 238). In 2005, Franzblau and co-workers isolated micromeline

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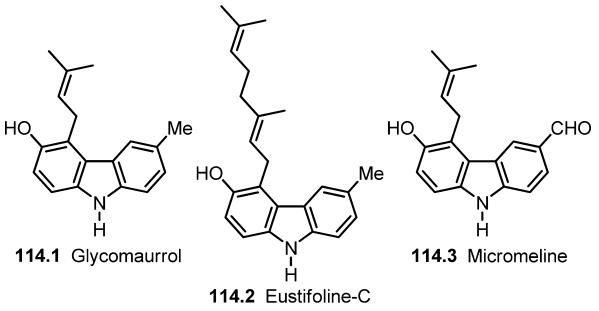
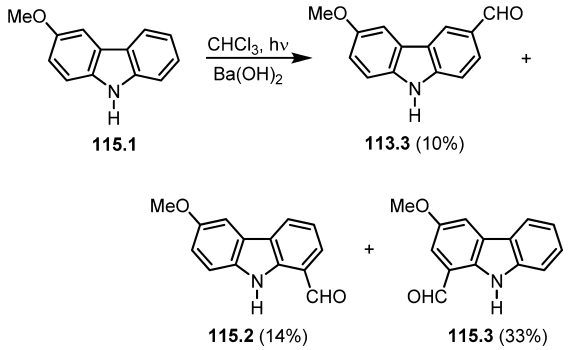
Scheme 114



(**114.3**) from the dichloromethane extract of the stem bark of *Micromelum hirsutum* (Scheme 114). This compound exhibited an in vitro anti-TB activity against the $H_{37}Rv$ strain of *Mycobacterium tuberculosis* and against the Erdman strain of *Mycobacterium tuberculosis* in a J774 mouse macrophage model.[350]

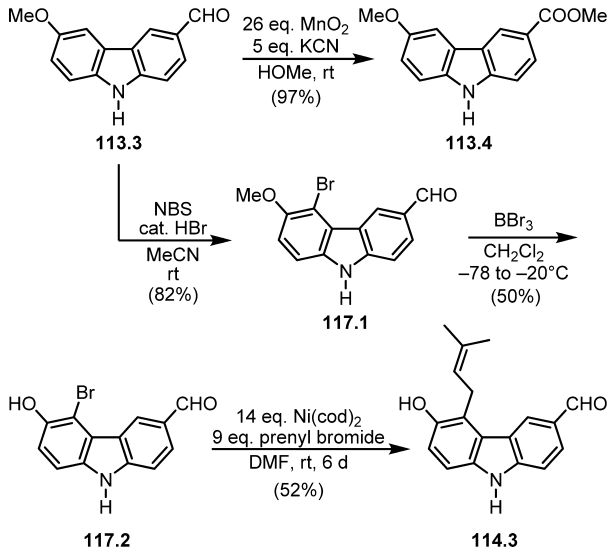
3.2.5.2. Total Synthesis of 3-Formyl-6-methoxycarbazole. During photoformylation studies of methoxycarbazoles with chloroform in diffuse daylight, Chowdhury and Saha obtained 3-formyl-6-methoxycarbazole (**113.3**). In this transformation, the desired 3-formyl-6-methoxycarbazole (**113.3**) was formed only as minor product in 10% yield along with other regioisomeric formylcarbazoles (**115.2**, 14% yield, and **115.3**, 33% yield). The high yield of 1-formyl-3-methoxycarbazole (**115.3**) suggests that the methoxy group activates the corresponding benzene ring toward photoformylation (Scheme 115).[354]

Scheme 115



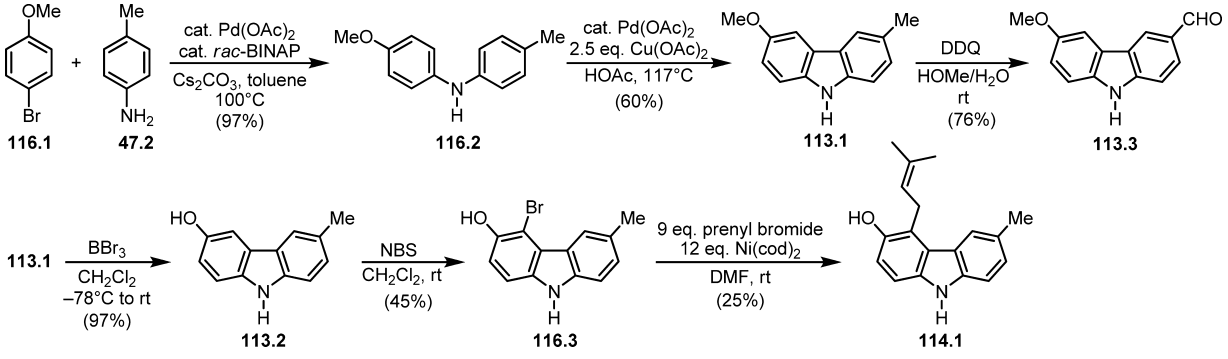
3.2.5.3. Total Syntheses of Glycozoline, Glycozolinine (Glycozolinol), Glycomaurrol, 3-Formyl-6-methoxycarbazole, Methyl 6-methoxycarbazole-3-carboxylate, and Micromeline. Using a palladium-catalyzed approach, Knölker and coworkers described the total synthesis of glycozoline (**113.1**), glycozolinine (glycozolinol) (**113.2**), 3-formyl-6-methoxycarbazole (**113.3**), methyl 6-methoxycarbazole-3-carboxylate (**113.4**), glycomaurrol (**114.1**), and micromeline (**114.3**).[95] The palladium(0)-catalyzed coupling of 4-bromoanisole (**116.1**) and *p*-toluidine (**47.2**) followed by palladium(II)-catalyzed oxidative cyclization afforded directly glycozoline (**113.1**) (Scheme 116). Glycozoline (**113.1**) was used as relay compound for the synthesis of the other carbazole alkaloids (Schemes 116 and 117).[95] Cleavage of the methyl ether with boron tribromide transformed glycozoline (**113.1**) to glycozolinine (**113.2**) (Scheme 116). Regioselective bromination of **113.2** at C-5 and subsequent nickel-mediated prenylation[355,356] of the 5-bromocarbazole **116.3** afforded glycomaurrol (**114.1**). Oxidation of glycozoline (**113.1**) with DDQ provided 3-formyl-6-methoxycarbazole (**113.3**).

Scheme 117



Oxidation of 3-formyl-6-methoxycarbazole (**113.3**) with manganese dioxide in the presence of potassium cyanide in methanol afforded methyl 6-methoxycarbazole-3-carboxylate (**113.4**) (Scheme 117).[95] Electrophilic bromination of 3-formyl-6-methoxycarbazole (**113.3**) led to the corresponding 5-bromocarbazole **117.1**. Cleavage of the methyl ether of compound **117.1** to the corresponding 5-bromo-6-hydrox-

Scheme 116



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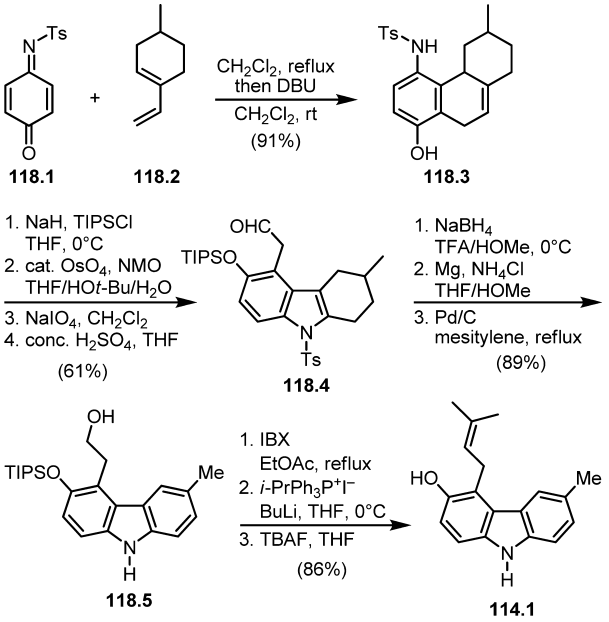
ycarbazole **117.2** followed by nickel-mediated prenylation provided micromeline (**114.3**)

3.2.5.4. Total Synthesis of Glycomaurrol and Eustifoline-C. Lebold and Kerr described a total synthesis of glycomaurrol (**114.1**) and eustifoline-C (**114.2**) starting from the quinone imine **118.1** and the diene **118.2** (Scheme 118).[357] Key steps

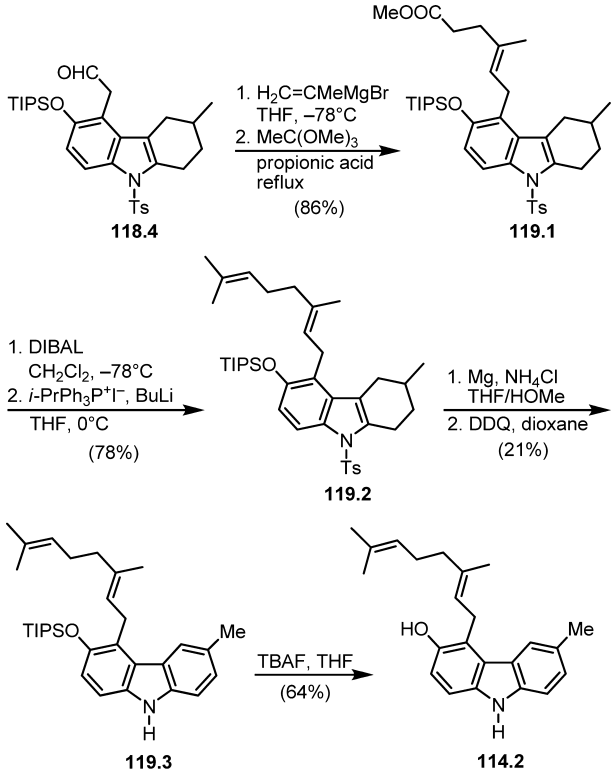
Scheme 118



are Diels–Alder reaction of the quinone imine **118.1** followed by Plieninger indolization of the adduct **118.3** to the tetrahydrocarbazole framework **118.4**. Reaction of the quinone imine **118.1** and diene **118.2** in dichloromethane at reflux followed by treatment of the resulting cycloadduct with catalytic amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the desired hexahydrophenanthrene **118.3** as a 1:1 mixture of diastereoisomers in 91% yield. Without isolation, both diastereoisomers of the hexahydrophenanthrene **118.3** were transformed to the tetrahydrocarbazole **118.4** via triisopropylsilyl protection of the phenolic OH group, oxidative cleavage of the olefinic double bond, and treatment of the resulting dicarbonyl compound with acid. Using this four-step sequence, the tetrahydrocarbazole **118.4** was obtained in 61% yield. Compound **118.4** was then transformed to the carbazole **118.5** in 89% yield by a three-step sequence of reduction, removal of the tosyl group by treatment with magnesium metal in a mixture of methanol, THF, and aqueous ammonium chloride, and finally dehydrogenation. This sequence was necessary to effect a smooth removal of the tosyl group and aromatization. Reoxidation of the 2-hydroxyethyl side-chain in **118.5** with 2-iodoxybenzoic acid (IBX) afforded the corresponding aldehyde, which on olefination with isopropyltriphenylphosphonium iodide followed by desilylation with TBAF provided glycomaurrol (**114.1**) in 11 steps and 42% overall yield.

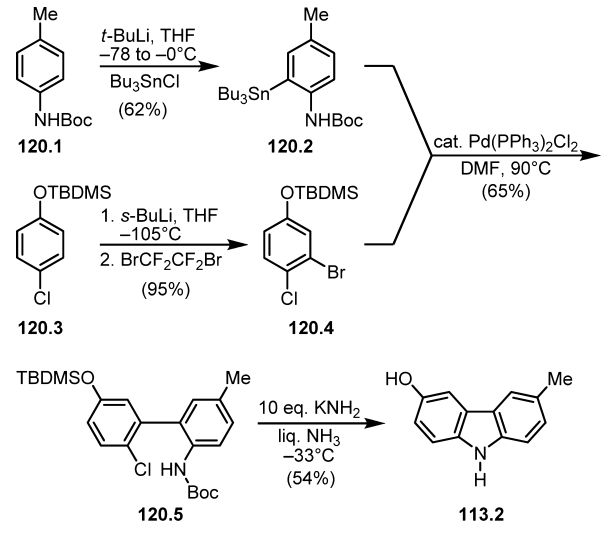
For the synthesis of eustifoline-C (**114.2**), a geranyl side-chain was introduced at C-5 of the tetrahydrocarbazole **118.4**. Reaction of **118.4** with isopropenylmagnesium bromide followed by a Johnson–Claisen rearrangement provided the ester **119.1** with an *E*-configuration of the double bond. Selective reduction to the aldehyde using diisobutylaluminum hydride (DIBAL) and subsequent olefination with isopropyltriphenylphosphonium iodide afforded the tetrahydrocarbazole **119.2** in 78% overall yield. Removal of the tosyl group followed by aromatization using DDQ provided *O*-triisopropylsilyleustifoline-C (**119.3**). Finally, desilylation with TBAF afforded eustifoline-C (**114.2**) in 64% yield (Scheme 119).[357]

Scheme 119



3.2.5.5. Synthesis of Glycozolinine and Glycozoline. Iwao, Watanabe, and co-workers described an access to glycozolinine (**113.2**) using a potassium amide-induced cyclization of a Boc-protected 2-aminobiphenyl (Scheme 120 and also see Scheme 46).[261] *ortho*-Lithiation of *N*-(*tert*-butoxycarbonyl)-4-methylaniline (**120.1**) followed by reaction with Bu_3SnCl afforded the

Scheme 120



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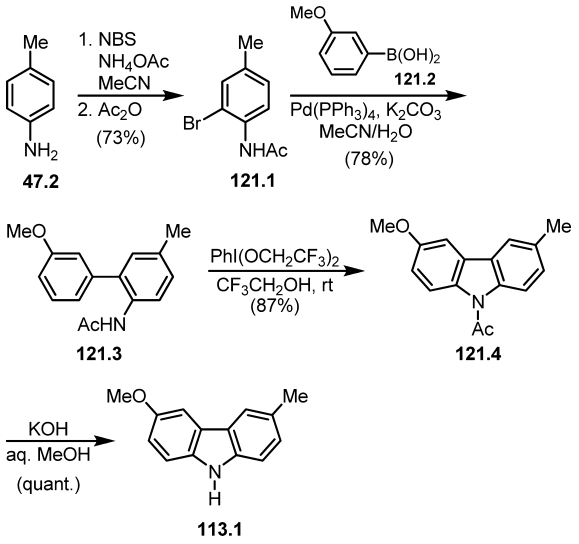
stannane **120.2** in 62% yield. Palladium-catalyzed cross-coupling of compound **120.2** with the bromoarene **120.4** in DMF at 90 °C afforded the biphenyl derivative **120.5** in 65% yield. The bromide **120.4** was prepared by *ortho*-lithiation of 1-(*tert*-butyldimethylsilyloxy)-4-chlorobenzene (**120.3**) and subsequent treatment with 1,2-dibromo-1,1,2,2-tetrafluoroethane. Finally, treatment of **120.5** with an excess of potassium amide in liquid ammonia led directly to glycozolinine (**113.2**) in 54% yield (Scheme 120).

Nishiyama and co-workers reported the total synthesis of glycozoline (**113.1**) using a hypervalent iodine-induced oxidative cyclization of the 2-acetamidobiphenyl **121.3** (Scheme 121).[264] The biphenyl **121.3** was synthesized from

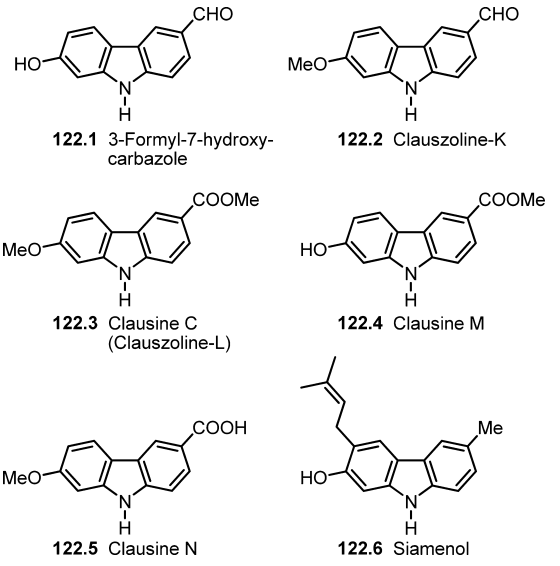
Scheme 121



p-toluidine (**47.2**) in a three-step sequence of bromination, N-acetylation, and Suzuki–Miyaura coupling in good yield. Oxidative cyclization to the carbazole **121.4** was induced by treatment of the 2-acetamidobiphenyl **121.3** with [bis(2,2,2-trifluoroethoxy)iodo]benzene in 2,2,2-trifluoroethanol at room temperature. The unusual hypervalent iodine reagent was generated by electrolysis of a solution of iodobenzene in 2,2,2-trifluoroethanol in the presence of lithium perchlorate. This procedure proved to be superior to treatment of the 2-acetamidobiphenyl **121.3** with [bis(2,2,2-trifluoroacetoxy)-iodo]benzene (PIFA), which provided the desired carbazole in only 58% yield. Cleavage of the acetyl protecting group finally furnished glycozoline (**113.1**).

3.2.6. 7-Oxygenated Carbazole Alkaloids. *3.2.6.1. Isolation from Natural Sources.* The first 7-oxygenated carbazole obtained from natural sources, 3-formyl-7-hydroxycarbazole (**122.1**), was isolated by Furukawa and co-workers from the root bark of *Murraya euchrestifolia* in 1992 (Scheme 122).[358] Five years later, the same group isolated clauszoline-K (**122.2**) from the acetone extract of the stem bark of *Clausena excavata*.[279,309] In 1996, Wu et al. reported the isolation of clausine C (**122.3**) from the methanol extract of the same plant.[359] One year later, Ito et al. also isolated **122.3** from *Clausena excavata* and named it clauszoline-L (**122.3**).[279] In 1999, Wu et al. reported the isolation of clausine M (**122.4**) and clausine N (**122.5**) from the acetone extract of the root bark of *Clausena excavata*.[309] Siamenol (**122.6**) was isolated by Boyd and co-workers in a bioassay-guided fractionation of the

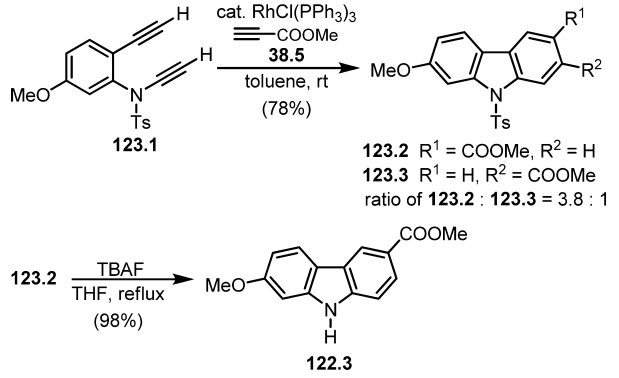
Scheme 122



organic extract of *Murraya siamensis*. This alkaloid showed anti-HIV activity.[307]

3.2.6.2. Total Synthesis of Clausine C (Clauszoline-L). Witulski and Alayrac reported a synthesis of clausine C (clauszoline-L) (**122.3**) using a rhodium-catalyzed Vollhardt-type cyclization of the diyne **123.1** and methyl propiolate (**38.5**) (Scheme 123).[182] The diyne precursor **123.1** was

Scheme 123

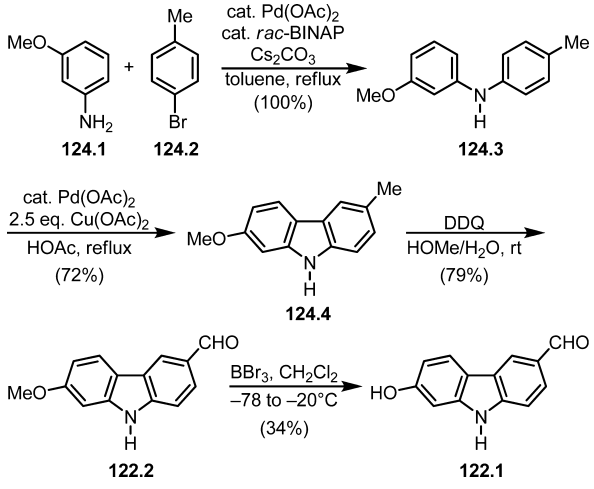


obtained from 2-iodo-5-methoxyaniline in an analogous way as described for diyne **98.3** in the synthesis of hyellazole (**86.1**) (see Scheme 98). The alkyne cyclization of **123.1** and **38.5** using Wilkinson's catalyst provided *N*-tosylclausine C (**123.2**) and the undesired regioisomer **123.3** in a ratio of 3.8:1 (78% yield). Deprotection of *N*-tosylclausine C (**123.2**) with TBAF in tetrahydrofuran at reflux afforded clausine C (**122.3**).

3.2.6.3. Total Syntheses of Clauszoline-K, 3-Formyl-7-hydroxycarbazole, Clausine C (Clauszoline-L), Clausine M, Clausine N, and Siamenol. Using a palladium-catalyzed approach, Knölker and co-workers described the total synthesis of a range of 7-oxygenated carbazole alkaloids: 3-formyl-7-hydroxycarbazole (**122.1**), clauszoline-K (**122.2**), clausine C (**122.3**), clausine M (**122.4**), clausine N (**122.5**), and siamenol (**122.6**) (Schemes 124–126).[94] 7-Methoxy-3-methylcarbazole (**124.4**) served as the common synthetic precursor for these carbazole alkaloids and was obtained in two steps from commercially available starting materials. A palladium(0)-

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

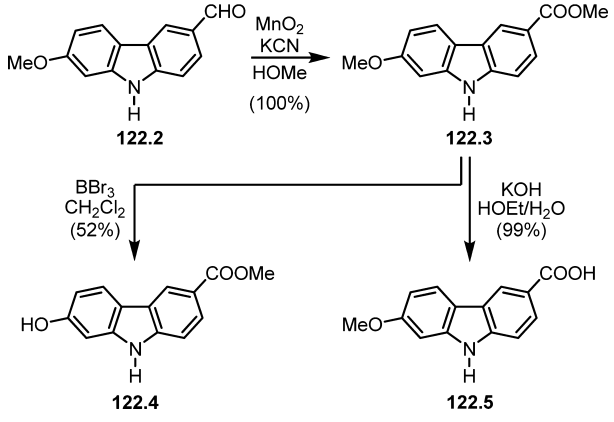
Scheme 124



catalyzed Buchwald–Hartwig amination of *p*-bromotoluene (**124.2**) with *m*-anisidine (**124.1**) afforded quantitatively the corresponding diarylamine **124.3**. Oxidative cyclization of **124.3** using catalytic amounts of palladium(II) acetate provided 7-methoxy-3-methylcarbazole (**124.4**) in 72% yield. Oxidation of **124.4** with DDQ led to clauszoline-K (**122.2**). Finally, cleavage of the methyl ether using boron tribromide led to 3-formyl-7-hydroxycarbazole (**122.1**) (Scheme 124).[94]

Clauszoline-K (**122.2**) was quantitatively transformed to clausine C (**122.3**) by oxidation with manganese dioxide in the presence of potassium cyanide in methanol (Scheme 125).

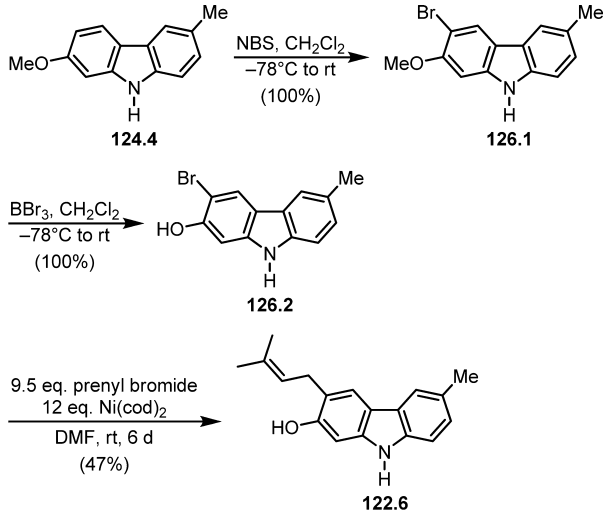
Scheme 125



Hydrolysis of the ester group of clausine C (**122.3**) afforded almost quantitatively clausine N (**122.5**), whereas ether cleavage led to clausine M (**122.4**).[94]

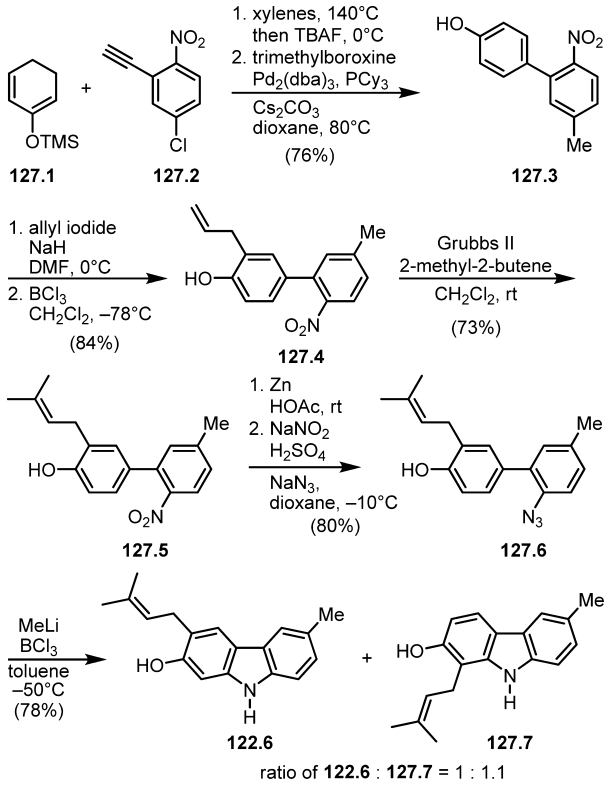
The synthesis of siamenol (**122.6**) also starts from the relay compound 7-methoxy-3-methylcarbazole (**124.4**) (Scheme 126). The prenyl side-chain at C-6 was introduced by a nickel-mediated coupling using the dimeric π-prenylnickel bromide complex, prepared in situ from prenyl bromide and bis(1,5-cyclooctadiene)nickel(0) [Ni(cod)$_2$]. Electrophilic bromination of the carbazole **124.4** with NBS afforded quantitatively the corresponding 6-bromocarbazole **126.1**. Cleavage of the methyl ether to give **126.2** followed by treatment with the dimeric π-prenylnickel bromide complex afforded after purification by high-performance liquid chromatography (HPLC) pure siamenol (**122.6**) in 47% yield.[94]

Scheme 126



3.2.6.4. Synthesis of Siamenol from a Biphenyl. Carter and co-workers reported a synthesis of siamenol (**122.6**) starting from diene **127.1** and alkyne **127.2** (Scheme 127).[360] Alkyne

Scheme 127



127.2 was obtained in three steps from 5-chloro-2-nitrobenzoic acid. Diels–Alder cycloaddition of diene **127.1** and alkyne **127.2** in the presence of TBAF with concomitant retro-Diels–Alder reaction by extrusion of ethylene and a palladium-catalyzed Suzuki–Miyaura coupling of the resulting chlorinated biphenyl with trimethylboroxine led to compound **127.3**. Transformation of **127.3** to the allyl ether and subsequent Claisen rearrangement in the presence of boron trichloride afforded the allyl derivative **127.4**. An olefin cross-metathesis of the allyl derivative **127.4** with 2-methyl-2-butene using second-

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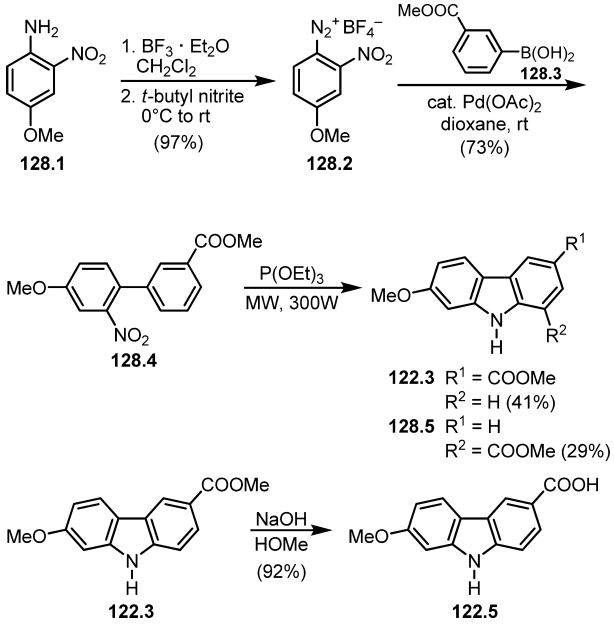
generation Grubbs catalyst provided the prenyl derivative **127.5** in 73% yield. Reduction of the nitro group with zinc/acetic acid to the corresponding amine followed by diazotization and displacement by an azide group led to the 2-azidobiphenyl **127.6**. An attempted Lewis acid-promoted cyclization of **127.6** using boron trichloride in toluene at low temperature did not result in any cyclization, probably due to the influence of the free phenolic group. Finally, deprotonation of **127.6** with methyllithium followed by addition of boron trichloride at low temperature afforded siamenol (**122.6**) and the regioisomeric carbazole **127.7** in a 1:1.1 ratio (78% yield).

3.2.6.5. Total Synthesis of Clausine C and Clausine N. Recently, Kuethe and Childers reported a synthesis of clausine C (**122.3**) and clausine N (**122.5**) using the 2-nitrobiphenyl **128.4** as the central intermediate. Key steps are a Suzuki–Miyaura cross-coupling and a Cadogan cyclization (Scheme 128).[344] Using Doyle's protocol,[361] commercially available 4-

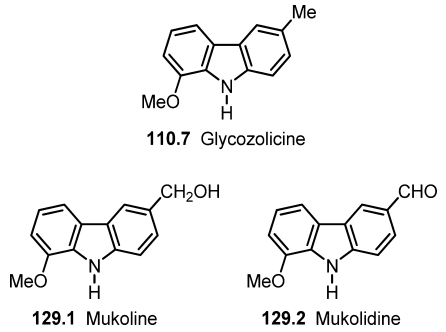
Scheme 128



methoxy-2-nitroaniline (**128.1**) was converted to the 2-nitrobenzene diazonium tetrafluoroborate **128.2**. Suzuki–Miyaura cross-coupling of **128.2** with the phenylboronic acid **128.3** provided the nitrobiphenyl **128.4**. Reductive cyclization of **128.4** under microwave (MW) irradiation in triethyl phosphite afforded directly clausine C (**122.3**) in 41% yield along with 29% of the regioisomeric carbazole **128.5**. Saponification of the methyl ester of clausine C (**122.3**) led to clausine N (**122.5**) in 92% yield.

3.2.7. 8-Oxygenated Carbazole Alkaloids. In 1992, Bhattacharyya and co-workers reported the isolation of glycozolicine (**110.7**) from the roots of *Glycosmis pentaphylla* (Scheme 129). Originally, its structure was assigned as 5-methoxy-3-methylcarbazole (glycoborine) (**109.1**).[251] Nine years later, Chakravarty et al. reassigned glycozolicine (**110.7**) as 8-methoxy-3-methylcarbazole based on synthesis and comparison of the spectroscopic data (cf. Scheme 110).[342] In the course of these studies, a synthetic access to glycozolicine (**110.7**) has been described (see section 3.2.4.). In 1982, Chakraborty and co-workers reported the isolation of mukoline (**129.1**) and mukolidine (**129.2**) from the benzene extract of

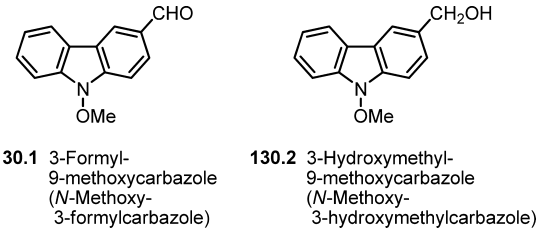
Scheme 129



the roots of *Murraya koenigii* Spreng.[362] These compounds are oxidized derivatives of glycozolicine (**110.7**). In 2011, Tamariz and co-workers described the total synthesis of all three 8-oxygenated carbazole alkaloids using a Lewis acid-mediated Diels–Alder cycloaddition strategy (see Addendum).[363]

3.2.8. 9-Oxygenated Carbazole Alkaloids. *3.2.8.1. Isolation from Natural Sources.* So far, only two carbazole alkaloids of this category have been found in nature, both isolated from the plant *Murraya euchrestifolia* (Rutaceae family). In 1988, Furukawa and co-workers described the isolation of *N*-methoxy-3-formylcarbazole (**130.1**) from the root bark of *Murraya euchrestifolia* Hayata (Scheme 130).[248] This was the

Scheme 130



first example of a naturally occurring 9-oxygenated tricyclic carbazole alkaloid. Four years later, the same group obtained *N*-methoxy-3-hydroxymethylcarbazole (**130.2**) from the acetone extract of the dried root bark of the same plant.[358]

3.2.8.2. Total Syntheses of 9-Oxygenated Carbazole Alkaloids. In 1990, Kawasaki and Somei reported the first total synthesis of 3-formyl-9-methoxycarbazole (**130.1**) starting from the racemic *cis*-hexahydrocarbazole **131.1** (Scheme 131).[364] Protection of the NH group by reaction with methyl chloroformate in dichloromethane and triethylamine provided the *N*-methoxycarbonyl derivative **131.2**. Regioselective iodination of **131.2** using iodine and sodium periodate in sulfuric acid followed by basic hydrolysis afforded the hexahydro-3-iodocarbazole **131.4**. Using a literature procedure,[365] compound **131.4** was transformed to 1,2,3,4-tetrahydro-6-iodo-9-methoxycarbazole (**131.5**) in two steps and 37% yield. Halogen–metal exchange of **131.5** using butyllithium followed by reaction with DMF led to 6-formyl-1,2,3,4-tetrahydro-9-methoxycarbazole, which was then aromatized by treatment with DDQ in benzene to provide 3-formyl-9-methoxycarbazole (**130.1**).[364]

Thirteen years later, Selvakumar et al. reported a second total synthesis of 3-formyl-9-methoxycarbazole (**130.1**) using a ring-closing metathesis as key step (Scheme 132).[366] Nucleophilic aromatic substitution at 3-fluoro-4-nitrotoluene **132.1** with methyl cyanoacetate provided almost quantitatively the

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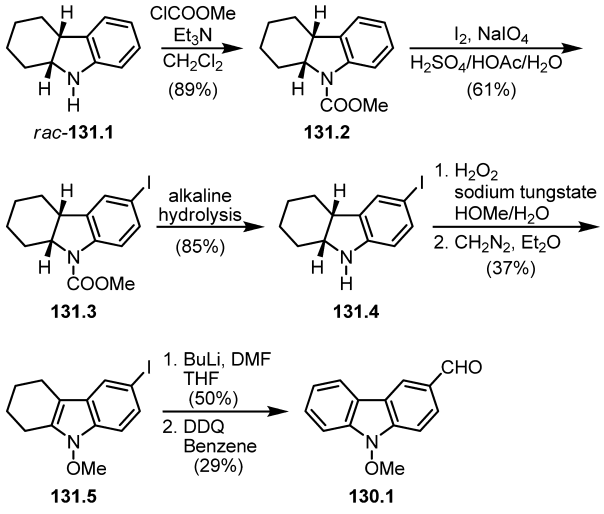
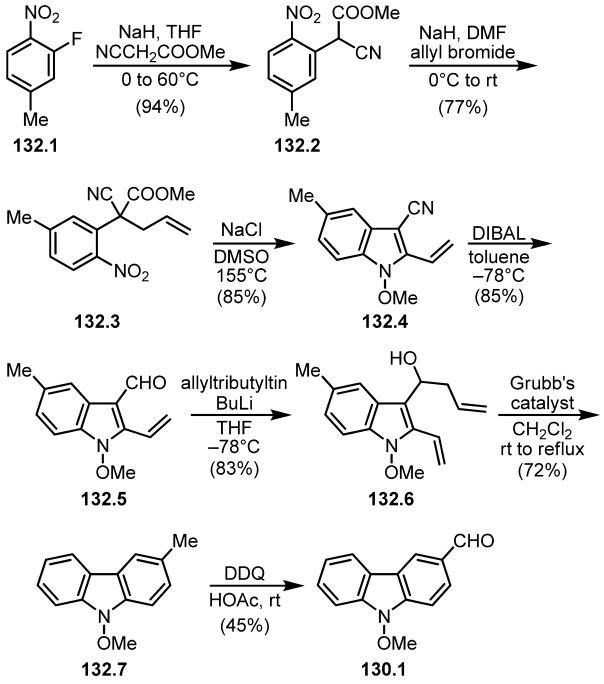
Scheme 131



Scheme 132



cyanoester **132.2**. Alkylation of **132.2** with allyl bromide followed by cyclization and decarboxylation[367] of **132.3** in a solution of sodium chloride in DMSO at 155 °C led to the desired 1-methoxyindole **132.4**. Reduction of the nitrile **132.4** with DIBAL followed by allylation of the resulting aldehyde **132.5** using allyltributyltin afforded the alcohol **132.6**. Ring-closing metathesis of **132.6** using Grubb's catalyst and concomitant aromatization led to 9-methoxy-3-methylcarbazole (**132.7**). Oxidation of **132.7** with DDQ in acetic acid afforded 3-formyl-9-methoxycarbazole (**130.1**).[366]

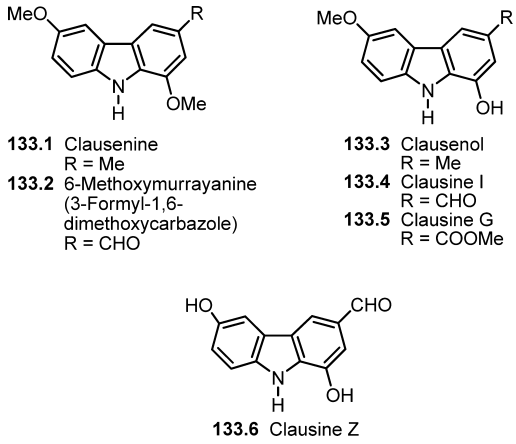
3.3. Dioxygenated Carbazole Alkaloids

This section covers all tricyclic dioxygenated carbazole alkaloids, most of them having a methyl group or oxidized analogues (−CH_2OH, −CHO, −COOH, COOMe) at C-3. The further classification depends on the position of the two oxygen substituents.

3.3.1. 1,6-Dioxygenated Carbazole Alkaloids.

3.3.1.1. Isolation from Natural Sources. So far, six carbazole alkaloids of this category have been identified, all of them isolated from plants of the species *Clausena* (family Rutaceae). In 1991, the first 1,6-dioxygenated carbazole alkaloid, 6-methoxymurrayanine (3-formyl-1,6-dimethoxycarbazole) (**133.2**), was isolated by El-Feraly and co-workers from the roots of *Clausena lansium* (Scheme 133).[249] Four years later,

Scheme 133



Chowdhury and co-workers isolated clausenine (**133.1**) and clausenol (**133.3**) from the ethanol extract of the stem bark of *Clausena anisata*.[368] Both alkaloids showed antibiotic activity. Clausenol (**133.3**) was nearly as active against some bacteria as streptomycin. In 1996, Wu et al. isolated clausine I (**133.4**) from the stem bark of *Clausena excavata* collected in Taiwan.[278] This alkaloid showed inhibition of rabbit platelet aggregation and vasoconstriction. Clausine I (**133.4**) and clausine E (clauszoline-I) (**20.8**) (see Scheme 55) have the same molecular formula. Moreover, clausine I (**133.4**) is a regioisomer of lansine (**150.4**) (see Scheme 150). Also in 1996, Wu et al. isolated clausine G (**133.5**) from the methanol extract of the stem bark of *Clausena excavata*.[359] In 2005, Potterat et al. reported the isolation of clausine Z (**133.6**) from an ethanol extract of the stem and leaves of *Clausena excavata* Burm.[369] Clausine Z (**133.6**) exhibits an inhibitory activity against cyclin-dependent kinase 5 (CDK5) and showed a protective effect on cerebral granule neurons against free radical-induced cell death.

3.3.1.2. Total Synthesis of Clausenol and Clausenine. In 1995, Chowdhury and co-workers synthesized clausenol (**133.3**) and clausenine (**133.1**) to confirm the structural assignments.[368] Japp−Klingemann reaction of 2-formyl-5-methylcyclohexanone (**111.2**) with 4-methoxybenzene diazonium chloride (**134.1**) afforded the hydrazone **134.2**. Subsequent Fischer−Borsche cyclization of the hydrazone **134.2** in concentrated hydrochloric and acetic acid led to the 1-oxotetrahydrocarbazole **134.3**. Palladium-catalyzed dehydrogenation of **134.3** gave clausenol (**133.3**), which on methylation with diazomethane provided clausenine (**133.1**) (Scheme 134).[368] Chowdhury's synthesis afforded clausenol (**133.3**) in three steps and 7% overall yield. By modification of some reaction conditions in Chowdhury's synthesis, Lin and Zhang described an improved synthesis of clausenol (**133.3**) (three steps, 17% overall yield).[370,371]

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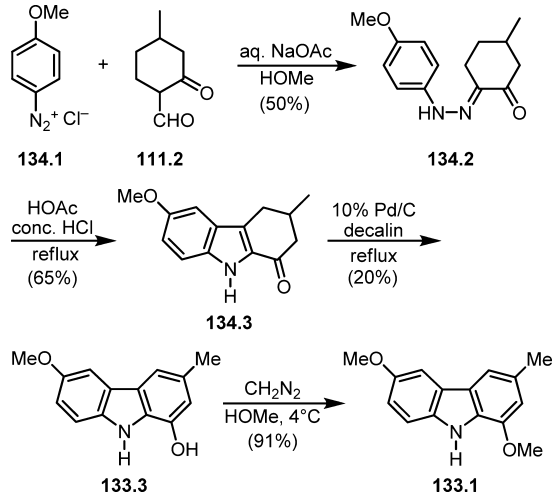
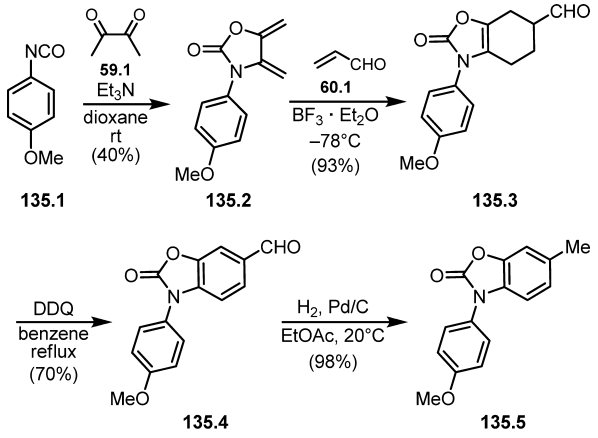
Scheme 134



3.3.1.3. Total Synthesis of 6-Methoxymurrayanine and Clausenine. In 2007, Tamariz and co-workers reported the total synthesis of 6-methoxymurrayanine (**133.2**) and clausenine (**133.1**) based on a Diels–Alder cycloaddition of the diene **135.2** (Schemes 135–138).[372] Using a previously described

Scheme 135

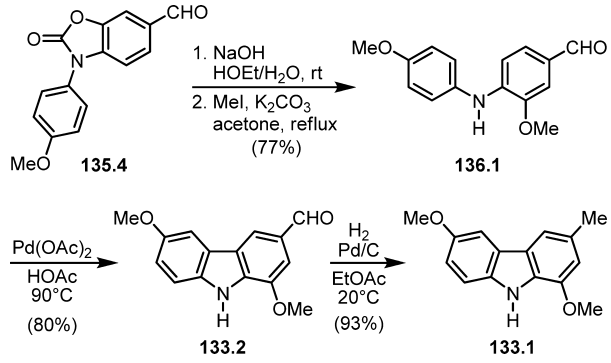


procedure,[285–287] the diene **135.2** was prepared in moderate yield by reaction of butane-2,3-dione (**59.1**) with 4-methoxyphenyl isocyanate (**135.1**). The Lewis acid-promoted regioselective cycloaddition of diene **135.2** and acrolein (**60.1**) provided compound **135.3**, which on aromatization afforded the benzoxazolone **135.4**, a key intermediate for the synthesis of 6-methoxymurrayanine (**133.2**) and clausenine (**133.1**) (Scheme 135). Hydrogenation of the formyl group provided the corresponding methylbenzoxazolone **135.5**, a precursor for an alternative route to clausenine (**133.1**).[372]

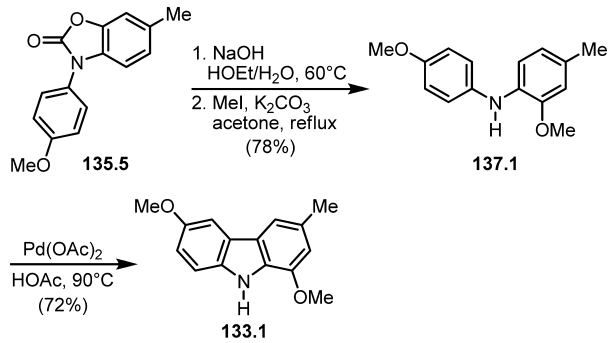
Cleavage of the oxazolone moiety of the formylbenzoxazolone **135.4** followed by O-methylation led to the corresponding diarylamine **136.1** (Scheme 136). Palladium(II)-mediated oxidative cyclization of **136.1** afforded 6-methoxymurrayanine (**133.2**). Finally, 6-methoxymurrayanine (**133.2**) was converted to clausenine (**133.1**) by catalytic hydrogenation.[372]

A more direct approach to clausenine (**133.1**) was achieved from the methylbenzoxazolone **135.5** (Scheme 137). Hydrolysis of **135.5** followed by O-methylation afforded the

Scheme 136



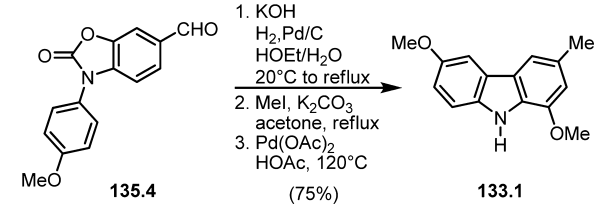
Scheme 137



diarylamine **137.1**. Palladium(II)-mediated oxidative cyclization of **137.1** provided clausenine (**133.1**) in 72% yield.[372]

An improved synthesis of clausenine (**133.1**) was achieved by using a three-step procedure without purification of intermediates (compare Scheme 136). Palladium-catalyzed hydrogenation of the benzoxazolone **135.4** in the presence of potassium hydroxide afforded the corresponding phenol, which on successive treatment of the crude product with methyl iodide and palladium(II) acetate led to clausenine (**133.1**) in 75% overall yield based on the formylbenzoxazolone **135.4** (Scheme 138).[372]

Scheme 138



3.3.1.4. Total Synthesis of Clausenine, 6-Methoxymurrayanine, Clausine Z, Clausine G, Clausenol, and Clausine I. Using a palladium-catalyzed construction of the carbazole framework, Börger and Knölker reported the total synthesis of a series of 1,6-dioxygenated carbazole alkaloids: clausenine (**133.1**), 6-methoxymurrayanine (**133.2**), clausenol (**133.3**), clausine I (**133.4**), clausine G (**133.5**), and clausine Z (**133.6**) (Schemes 139–144).[373] Acid-catalyzed esterification of the benzoic acid **70.1** followed by a palladium(0)-catalyzed Buchwald–Hartwig coupling of the resulting methyl 4-amino-3-methoxybenzoate (**64.5**) with 4-bromoanisole (**116.1**) afforded the diarylamine **139.1** (Scheme 139). Finally, oxidative

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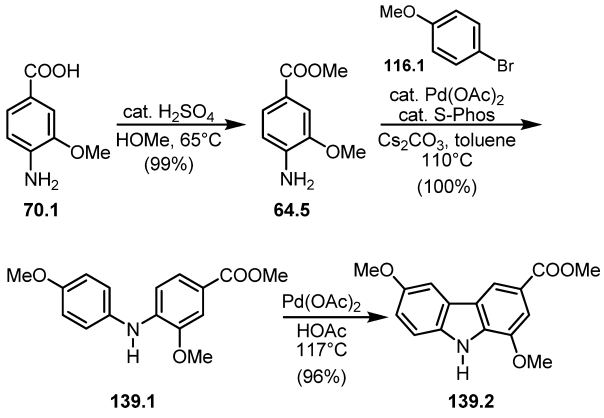
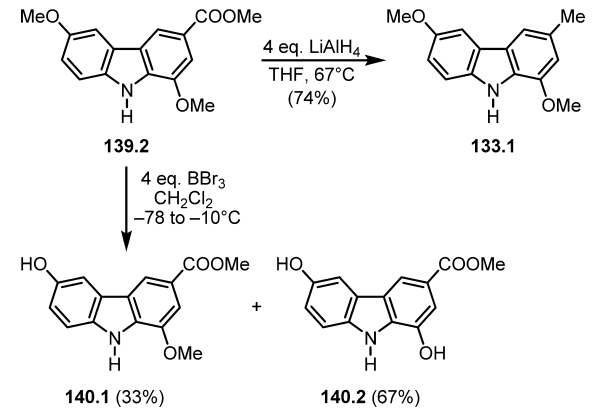
Scheme 139



cyclization of **139.1** using palladium(II) acetate afforded the carbazole **139.2** almost quantitatively in three steps based on the commercial benzoic acid **70.1**.[373]

Reduction of carbazole **139.2** with an excess of lithium aluminum hydride directly provided clausenine (**133.1**) (Scheme 140). A selective cleavage of the methyl ether at C-1 would have led to clausine G (**133.5**). However, reaction of carbazole **139.2** with 4 equiv of boron tribromide at low temperature provided the 1,6-dihydroxycarbazole **140.2** in 67% yield along with isoclausine G (**140.1**) in 33% yield.[373] Thus, an orthogonal protecting group strategy was developed for the synthesis of clausine G (**133.5**).

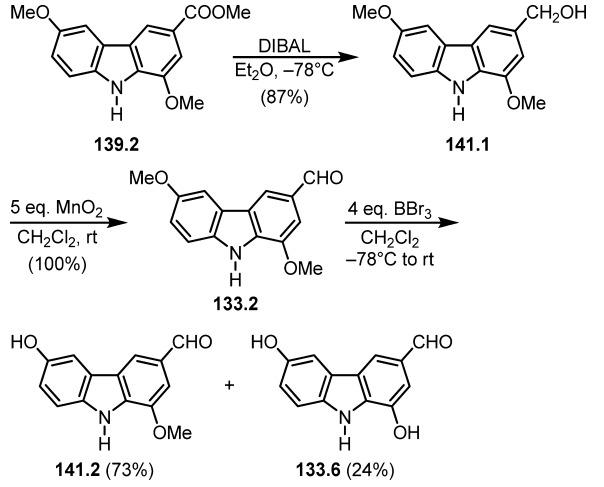
Scheme 140



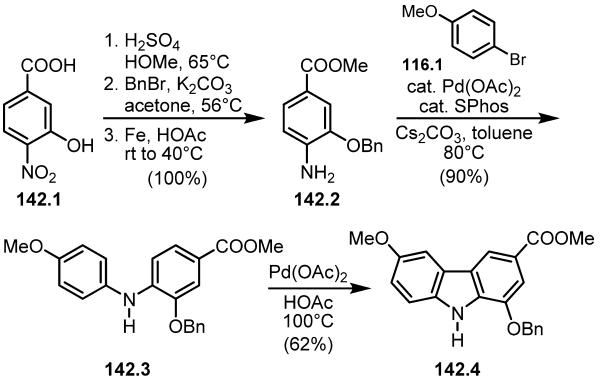
Reduction of the carbazole **139.2** with DIBAL afforded the carbinol **141.1**, which on subsequent oxidation with activated manganese dioxide afforded 6-methoxymurrayanine (**133.2**). Reaction of **133.2** with 4 equiv of boron tribromide at low temperature afforded isoclausine I (**141.2**) in 73% yield along with clausine Z (**133.6**) (24% yield) (Scheme 141).[373] This result confirmed the selective cleavage of the C-6 methyl ether described above for carbazole **139.2**.

The total synthesis of the 1-hydroxy-6-methoxycarbazoles clausenol (**133.3**), clausine I (**133.4**), and clausine G (**133.5**) required a strategy that employs a protecting group at C-1 that can be removed selectively in the presence of the C-6 methyl ether (Scheme 142).[373] The *O*-benzyl analogue of arylamine **64.5** (see Scheme 139) was synthesized by acid-catalyzed esterification of commercial 3-hydroxy-4-nitrobenzoic acid (**142.1**) with methanol followed by O-benzylation and subsequent reduction of the nitro group to provide the

Scheme 141



Scheme 142

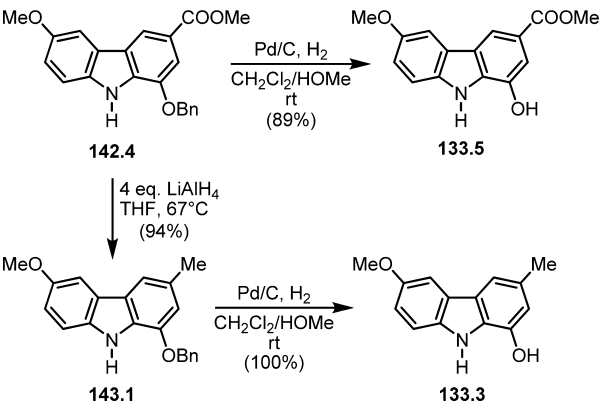


benzyl-protected arylamine **142.2**. Buchwald–Hartwig coupling of **142.2** with 4-bromoanisole (**116.1**) and oxidative cyclization of the resulting diarylamine **142.3** provided the 1-benzyloxycarbazole **142.4**.

Palladium-catalyzed deprotection of **142.4** afforded clausine G (**133.5**) (Scheme 143).[373] Reduction of **142.4** with an excess of lithium aluminum hydride to the carbazole **143.1** and subsequent debenzylation provided clausenol (**133.3**).

Reduction of carbazole **142.4** with DIBAL led to the carbinol **144.1**, which on subsequent oxidation with activated manganese dioxide afforded the 3-formylcarbazole **144.2**

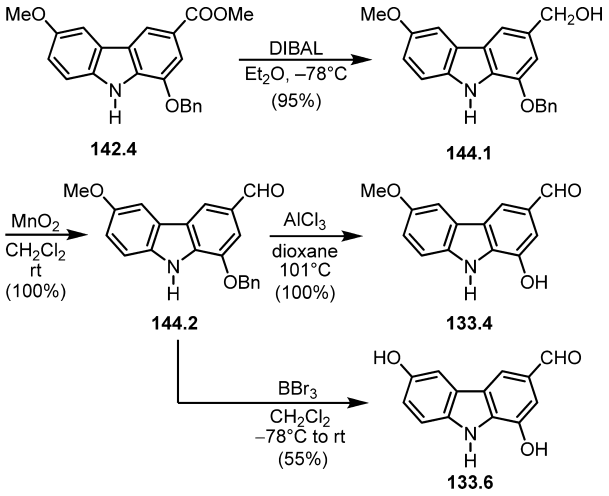
Scheme 143



dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

(Scheme 144).[373] Chemoselective cleavage of the benzyl ether using a large excess of aluminum trichloride in dioxane at reflux

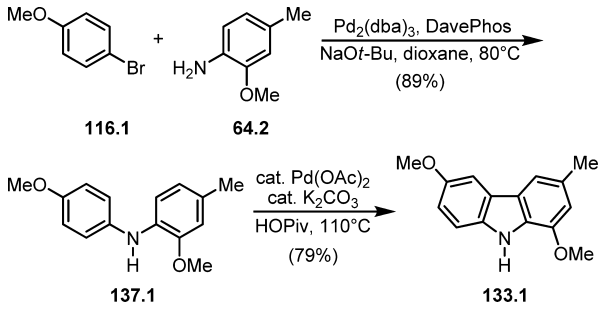
Scheme 144



afforded clausine I (**133.4**), whereas cleavage of both ethers with boron tribromide provided clausine Z (**133.6**) in 55% yield.

3.3.1.5. Total Synthesis of Clausenine. In 2008, Fagnou and co-workers reported a total synthesis of clausenine (**133.1**) by sequential palladium-catalyzed inter- and intramolecular arylation (Scheme 145).[104] Buchwald–Hartwig coupling of 2-

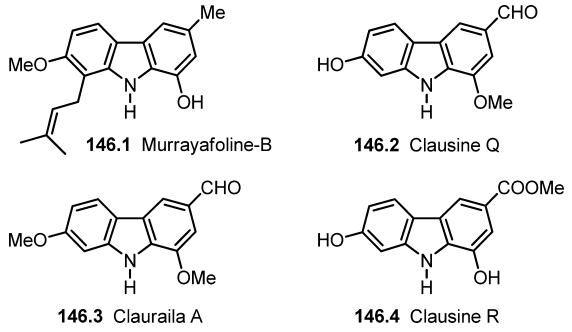
Scheme 145



methoxy-4-methylaniline (**64.2**) with 4-bromoanisole (**116.1**) afforded the diarylamine **137.1** in 89% yield. The palladium-(II)-catalyzed oxidative cyclization of **137.1** in pivalic acid provided clausenine (**133.1**).

3.3.2. 1,7-Dioxygenated Carbazole Alkaloids. In 1985, Furukawa et al. reported the first isolation of a 1,7-dioxygenated carbazole alkaloid, murrayafoline B (**146.1**), from the ethanol extract of the dried root bark of *Murraya euchrestifolia* Hayata collected in Taiwan.[201] Fourteen years later, Wu et al. isolated two further 1,7-dioxygenated carbazole alkaloids, clausine Q (**146.2**) and clausine R (**146.4**), from the acetone extract of the root bark of *Clausena excavata* (Scheme 146).[309] In 2011, Yenjai and co-workers isolated another 1,7-dioxygenated carbazole alkaloid. Clauraila A (**146.3**), the O-methyl derivative of clausine Q, was obtained from the roots of *Clausena harmandiana* together with other known and previously unknown carbazoles.[374] *Clausena harmandiana* is known in Thai as "Song Fa" and has been used as a health-promoting herb and for the treatment of stomachache and headache.

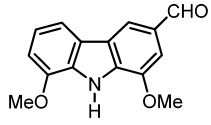
Scheme 146



Murrayafoline-B (**146.1**) was synthesized one year after its isolation, as discussed in our earlier review.[1] The first syntheses of clausine Q (**146.2**) and clausine R (**146.4**) have been reported recently by Knölker et al. (see Addendum).[375]

3.3.3. 1,8-Dioxygenated Carbazole Alkaloids. Until now, only one example of a 1,8-dioxygenated carbazole alkaloid has been found in a plant of the Rutaceae family. In 1995, Chowdhury and co-workers described the isolation of clausenal (**147.1**) from the ethanol extract of the leaves of *Clausena heptaphylla* (Scheme 147).[376] Clausenal (**147.1**) exhibited

Scheme 147

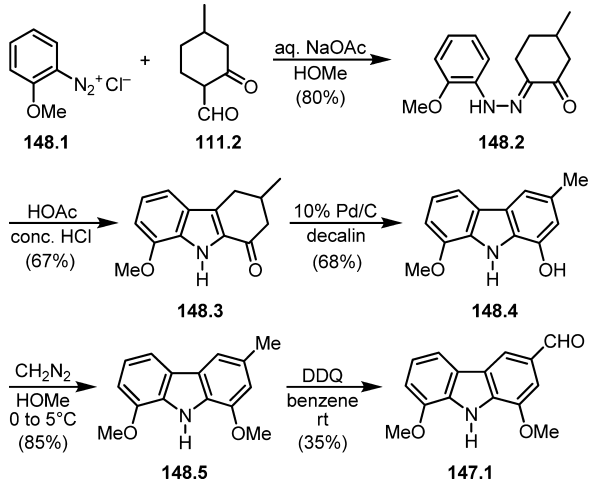


147.1 Clausenal

promising antimicrobial activity against fungi and Gram-positive and Gram-negative bacteria.

Together with its isolation from nature, Chowdhury and co-workers described a synthesis of clausenal (**147.1**) to confirm the structural assignment (Scheme 148).[376] Japp–Klingemann reaction of 2-formyl-5-methylcyclohexanone (**111.2**) with 2-methoxybenzenediazonium chloride (**148.1**) afforded the hydrazone **148.2**. Fischer–Borsche cyclization of the hydrazone **148.2** in a mixture of acetic acid and concentrated hydrochloric acid led to the 1-oxotetrahydrocarbazole **148.3**. Palladium-

Scheme 148

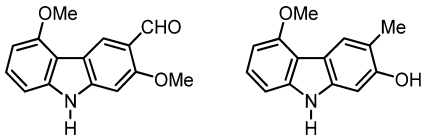


dx.doi.org/10.1021/cr200447s | Chem. Rev. 2012, 112, 3193–3328

catalyzed dehydrogenation of **148.3** in boiling decalin gave 1-hydroxy-8-methoxy-3-methylcarbazole (**148.4**), which on O-methylation with diazomethane provided 1,8-dimethoxy-3-methylcarbazole (**148.5**). Finally, oxidation of **148.5** with DDQ afforded clausenal (**147.1**).

3.3.4. 2,5-Dioxygenated Carbazole Alkaloids. In 2004, Itoigawa, Furukawa, and co-workers isolated glybomine A (**149.1**) from the acetone extract of the stem of *Glycosmis arborea* collected at Mymensing in Dhaka, Bangladesh (Scheme 149).[377] Although glybomine A (**149.1**) was claimed as the first

Scheme 149



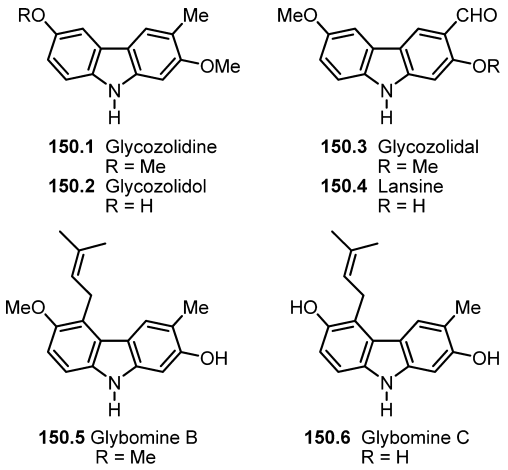
149.1 Glybomine A **149.2** Carbalexin A

2,5-dioxygenated carbazole alkaloid from natural sources, Greger and co-workers had already reported in 2001 the isolation of carbalexin A (**149.2**) from the methanol extract of the leaves of *Glycosmis pentaphylla* and *Glycosmis parviflora*.[378] Stress like wounding, UV irradiation, or treatment with the fungus *Botrytis cinerea* was shown to induce formation of a series of carbazole alkaloids in the leaves of these plants with carbalexin A (**149.2**) as major component. Carbalexin A (**149.2**) is also 2,5-dioxygenated and showed a strong antifungal activity in bioautographic tests on thin-layer chromatography (TLC) plates with *Cladosporium herbarum*.

3.3.5. 2,6-Dioxygenated Carbazole Alkaloids.

3.3.5.1. Isolation from Natural Sources. In 1966, Chakraborty et al. described the isolation of glycozolidine (**150.1**) from the petroleum ether extract of the root bark of *Glycosmis pentaphylla* (Scheme 150).[379,380] Glycozolidine (**150.1**) was

Scheme 150

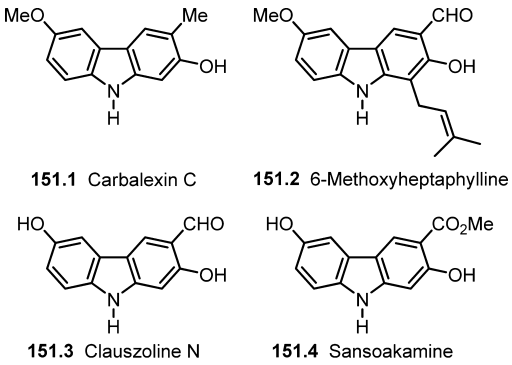


150.1 Glycozolidine R = Me
150.2 Glycozolidol R = H
150.3 Glycozolidal R = Me
150.4 Lansine R = H
150.5 Glybomine B R = Me
150.6 Glybomine C R = H

the first 2,6-dioxygenated carbazole alkaloid obtained from a natural source. The same compound was found by Chakravarty et al. in 1999 in the roots of *Glycosmis arborea*.[347] Glycozolidol (**150.2**) was obtained by Bhattacharyya et al. from the roots of *Glycosmis pentaphylla* in 1985.[381] A bioactivity against Gram-positive and Gram-negative bacteria has been shown for glycozolidol (**150.2**). Glycozolidal (**150.3**) was also isolated from the roots of *Glycosmis pentaphylla* by Bhattacharyya and Chowdhury.[382] This alkaloid was considered to be a biosynthetic oxidation product of glycozolidine (**150.1**), which was isolated from the same natural source. Prior to its isolation from nature, compound **150.3** was known by synthesis as the *O*-methyl derivative of lansine (**150.4**), which was isolated first by Kapil and co-workers in 1980 from the ethanol extract of the leaves of *Clausena lansium*.[383] In 2004, Itoigawa, Furukawa, and co-workers reported the isolation of glybomine B (**150.5**) and glybomine C (**150.6**) along with glybomine A (**149.1**) (see Scheme 149) from the acetone extract of the stem of *Glycosmis arborea* collected at Mymensing in Dhaka, Bangladesh.[377] Glybomine B (**150.5**) and glybomine C (**150.6**) showed significant antitumor-promoting activity, which was confirmed by the inhibiting effect of these alkaloids in conjunction with the tumor promoter 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA).

In 2001, Greger and co-workers reported the isolation of the stress-induced alkaloid carbalexin C (**151.1**) from the methanol extract of the leaves of *Glycosmis parviflora* (Scheme 151).[378]

Scheme 151



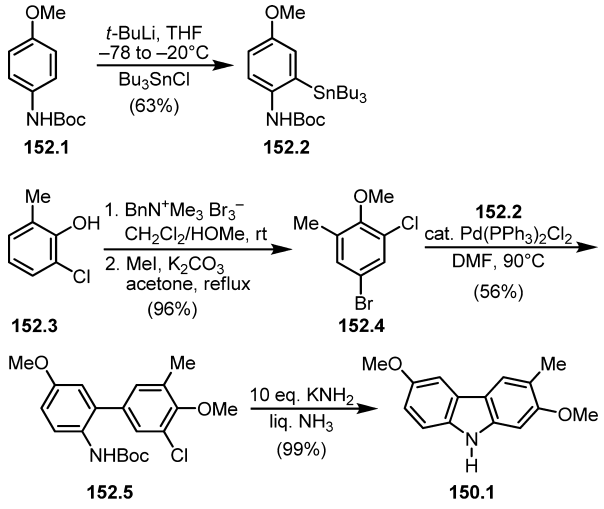
151.1 Carbalexin C **151.2** 6-Methoxyheptaphylline
151.3 Clauszoline N **151.4** Sansoakamine

Carbalexin C (**151.1**) showed a strong antifungal activity in bioautographic tests on TLC plates with *Cladosporium herbarum*. 6-Methoxyheptaphylline (**151.2**) was isolated in 1972 by Joshi et al. from the hexane extract of the roots of *Clausena indica* Oliv.[384] A further 2,6-dioxygenated carbazole has been isolated from *Clausena vestita* D. D. Tao, an endemic Chinese species. Zhao and co-workers obtained clauszoline N (**151.3**) as a yellow powder by ethanol extraction of the whole plant (Scheme 151).[385] Sansoakamine (**151.4**) was isolated in 2010 by Sripisut and Laphookhieo from the stem of *Clausena excavata* collected in Southern Thailand.[386]

3.3.5.2. Total Syntheses of Glycozolidine. In 1993, Iwao, Watanabe, and co-workers reported the total synthesis of glycozolidine (**150.1**) using a Stille-coupling with a subsequent aryne-mediated cyclization as key steps, a strategy which was applied before by the same authors to the synthesis of carbazole (**1**) and glycozolinine (**113.2**) (see Schemes 46 and 120).[261] The required arylstannane **152.2** was prepared by *ortho*-lithiation of the aniline **152.1** followed by stannylation with tributyltin chloride (Scheme 152). The bromochlorobenzene **152.4** was obtained from 2-chloro-6-methylphenol (**152.3**) by sequential bromination and methylation. Stille cross-coupling of the arylstannane **152.2** with **152.4** afforded the biphenyl **152.5** in 56% yield. Reaction of **152.5** with an excess of potassium amide in liquid ammonia provided glycozolidine (**150.1**) almost quantitatively by elimination to an aryne, cyclization, and cleavage of the Boc group.

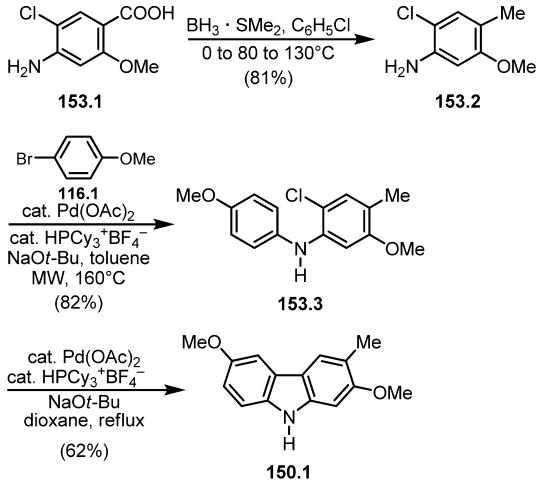
dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 152



Bedford and Betham's synthetic strategy relies on a palladium(0)-catalyzed cyclization of a 2-halogenated diarylamine using commercially available 4-bromoanisole (**116.1**) and the benzoic acid **153.1** (also commercially available) as starting materials (Scheme 153).[387] The 2-chloroaniline **153.2**

Scheme 153

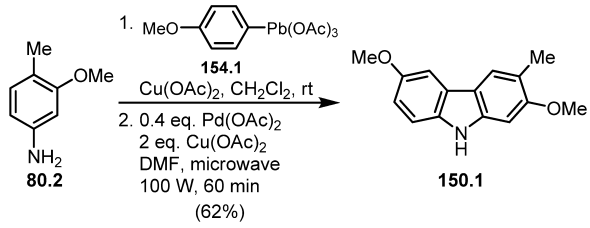


was readily prepared in one step by reduction of the carboxylic acid of **153.1** to a methyl group using the method developed by Le Corre and co-workers.[388] Buchwald–Hartwig amination of 4-bromoanisole (**116.1**) with the 2-chloroaniline **153.2** afforded the diarylamine **153.3**. Palladium(0)-catalyzed cyclization of **153.3** in 1,4-dioxane at reflux provided glycozolidine (**150.1**) via C–H bond activation.

In 2009, Menéndez and co-workers reported an approach to glycozolidine (**150.1**) based on the N-arylation of an aniline with an aryl lead compound (see Schemes 68 and 84). Thus, reaction of (*p*-methoxyphenyl)lead triacetate (**154.1**) with the arylamine **80.2** followed by palladium(II)-catalyzed oxidative cyclization of the intermediate diarylamine afforded glycozolidine (**150.1**) in good yield (Scheme 154).[294]

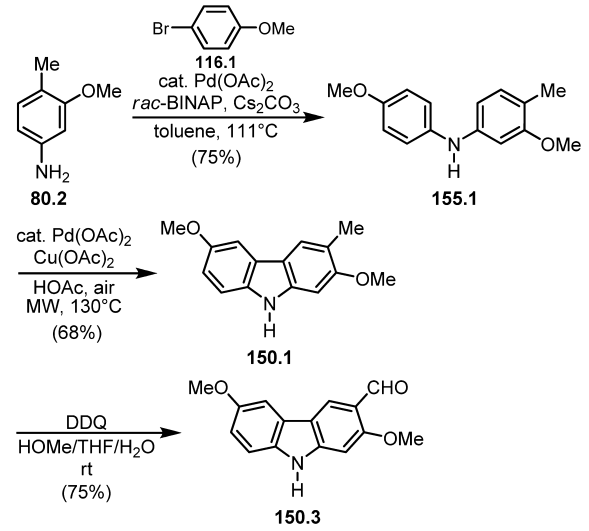
3.3.5.3. Total Synthesis of Glycozolidine, Glycozolidal, Glycozolidol, Carbalexin C, and Lansine. Schmidt and Knölker applied a palladium(II)-catalyzed oxidative cyclization of diarylamines to short and efficient syntheses of a range of

Scheme 154



2,6-dioxygenated carbazole alkaloids.[389] The required diarylamines were synthesized by Buchwald–Hartwig amination of commercially available or easily accessible precursors. Thus, palladium(0)-catalyzed coupling of 4-bromoanisol (**116.1**) and 3-methoxy-4-methylaniline (**80.2**) furnished the diarylamine **155.1** (Scheme 155), which is the direct precursor for

Scheme 155



glycozolidine (**150.1**). Oxidative cyclization of **155.1** with catalytic amounts of palladium(II) acetate in the presence of copper(II) acetate and air with microwave heating led directly to glycozolidine (**150.1**) in good yield. Oxidation of glycozolidine (**150.1**) with DDQ afforded glycozolidal (**150.3**).

A similar strategy was employed for the total synthesis of glycozolidol (**150.2**) (Scheme 156). Buchwald–Hartwig amination of benzyl 4-bromophenyl ether (**156.1**) and 3-methoxy-4-methylaniline (**80.2**) followed by palladium(II)-catalyzed cyclization of the diarylamine **156.2** and final hydrogenolytic debenzylation of the carbazole **156.3** afforded glycozolidol (**150.2**) in three steps and 45% overall yield.

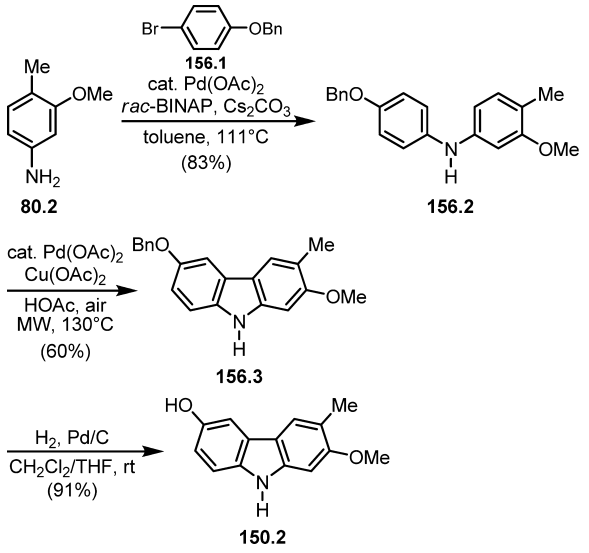
For the total synthesis of lansine (**150.4**) and carbalexin C (**151.1**), the silyl-protected aniline **157.1** was prepared first (Scheme 157). Buchwald–Hartwig amination and followed by palladium(II)-catalyzed oxidative cyclization of the resulting diarylamine **157.2** provided the silyl-protected carbazole **157.3**. Removal of the silyl group afforded lansine (**150.4**). Oxidation of the methyl group at C-3 of **157.3** led to the 3-formylcarbazole **157.4**, which was then deprotected to give carbalexin C (**151.1**).

3.3.6. 2,7-Dioxygenated Carbazole Alkaloids.

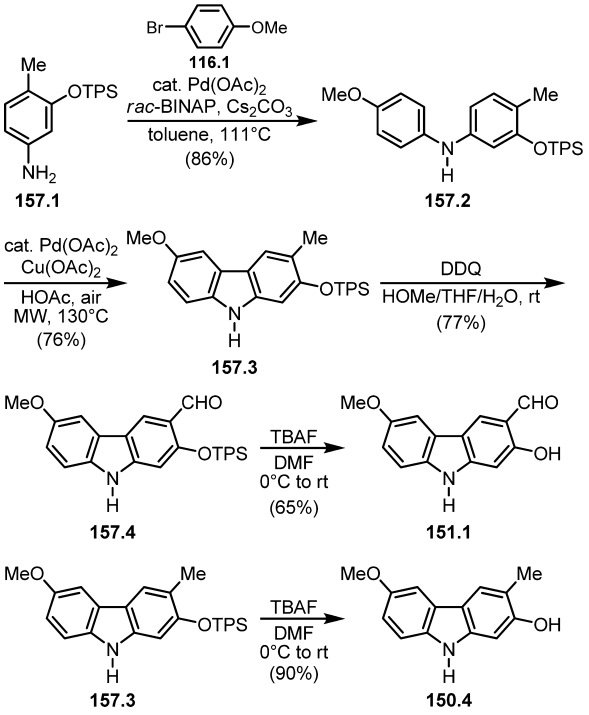
3.3.6.1. Isolation from Natural Sources. The first 2,7-dioxygenated carbazole, murrayaline-A (**158.1**), was isolated in 1986 by Furukawa et al. from the root bark of *Murraya*

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 156

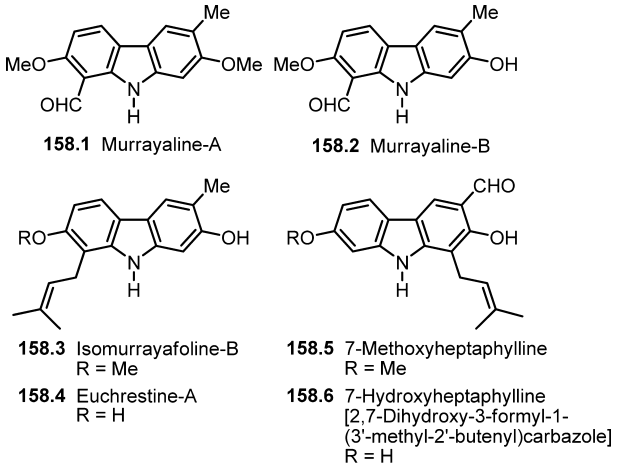


Scheme 157

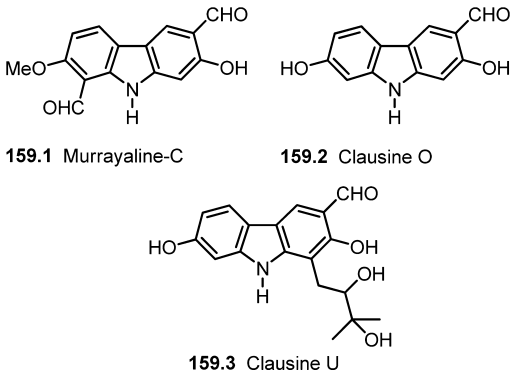


euchrestifolia Hayata collected in Taiwan (Scheme 158).[390,391] Five years later, the same group described additional compounds from the stem bark of the same natural source and named them in a similar manner: murrayaline-B (**158.2**), murrayaline-C (**159.1**), and murrayaline-D (**162.2**) (Schemes 158, 159, and 162, respectively).[391] In 1987, Furukawa and co-workers reported the isolation of isomurrayafoline-B (**158.3**), also from the stem bark of *Murraya euchrestifolia* Hayata collected in Taiwan.[392] The same group also reported the isolation of euchrestine-A (**158.4**) from the stem bark of *Murraya euchrestifolia* Hayata.[393] 7-Methoxyheptaphylline (**158.5**) and 2-hydroxy-3-formyl-7-methoxycarbazole (7-methoxymukonal) (**160.2**) (Scheme 160) were obtained by Pummangura and co-workers in 1988 from the root bark of *Clausena harmandiana*.[394] The extracts of this plant have been

Scheme 158



Scheme 159



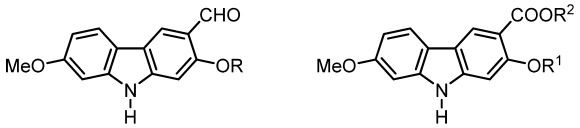
used in folk medicine for the treatment of stomachache and fever. In 2011, Yenjai and co-workers described the derivatization of 7-methoxyheptaphylline (**158.5**) and heptaphylline (**22.2**) and probed the cytotoxicity of the resulting compounds against the NCI-H187 cell line.[395] In 1995, Kumar et al. isolated 2,7-dihydroxy-3-formyl-1-(3′-methyl-2′-butenyl)-carbazole (7-hydroxyheptaphylline) (**158.6**) from the dichloromethane extract of the root bark of *Clausena lansium*.[396] Clausine O (**159.2**) and clausine U (**159.3**) were isolated by Wu et al. in 1999 from the acetone extract of the root bark of *Clausena excavata* (Scheme 159).[309]

In 1990, Lange and co-workers isolated 3-formyl-2,7-dimethoxycarbazole (7-methoxy-*O*-methylmukonal) (**160.1**) from the ethanol extract of the roots of *Murraya siamensis* (Scheme 160).[299] Fifteen years later, Kongkathip et al. isolated the same natural product from the rhizomes and roots of another Rutaceae species, *Clausena excavata*.[300] 7-Methoxy-*O*-methylmukonal (**160.1**) was the first carbazole alkaloid found to exhibit anti-HIV-1 activity.

Wu et al. reported the isolation of clausine H (**160.3**) and clausine K (**160.4**) from the stem bark of *Clausena excavata* (Scheme 160) in 1996.[278] Both alkaloids showed inhibition of rabbit platelet aggregation and vasoconstriction. One year later, Ito et al. isolated the same two alkaloids from the same natural source and named them clauszoline-C (**160.3**) and clauszoline-J (**160.4**), respectively.[279] In 2005, Kongkathip et al. isolated clausine K (clauszoline-J) (**160.4**) from the rhizomes and roots of *Clausena excavata* and reported its anti-HIV-1 activity.[300] Two years later, Taufiq-Yap et al. described the cytotoxic

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 160



160.1 7-Methoxy-*O*-methylmukonal (3-Formyl-2,7-dimethoxycarbazole) R = Me

160.2 7-Methoxymukonal (2-Hydroxy-3-formyl-7-methoxycarbazole) R = H

160.3 Clausine H (Clauszoline-C) R^1, R^2 = Me

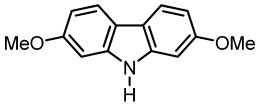
160.4 Clausine K (Clauszoline-J) R^1 = Me; R^2 = H

160.5 Clausine-TY R^1 = H; R^2 = Me

carbazole alkaloid clausine-TY (**160.5**) along with the previously known clausines H (**160.3**) and B (**195.4**) (see Scheme 195). These alkaloids were obtained from the ethyl acetate extract of the stem bark of *Clausena excavata*.[397] Clausine-TY (**160.5**) exhibited a significant cytotoxicity against the CEM-SS cell line.

In 1999, Wu et al. obtained clausine V (**161.1**) from the acetone extract of the root bark of *Clausena excavata* (Scheme 161).[309] In contrast to the usual structural pattern, clausine V

Scheme 161



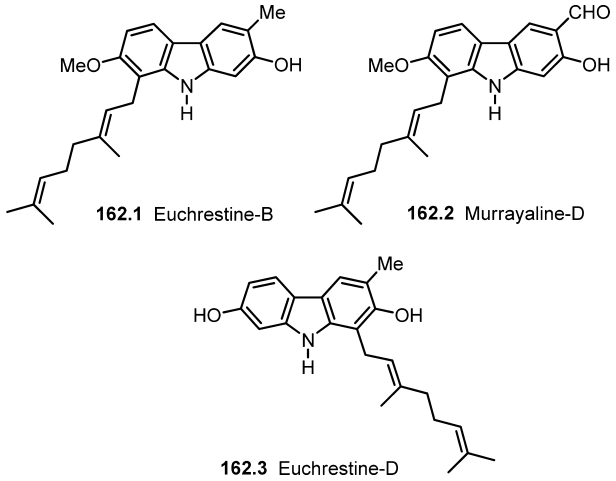
161.1 Clausine V

(**161.1**) does not have the C_1-substituent at C-3 that is typically found in carbazole alkaloids from higher plants. One might speculate that this alkaloid is formed by decarboxylation of clausine K (**160.4**), which was isolated from the same natural source. Prior to its isolation, Kapil, Popli, and co-workers synthesized clausine V (**161.1**) and studied the antiviral activity of this compound along with several *N*- and *O*-alkylcarbazoles (see Scheme 166).[398]

In 1991, Furukawa and co-workers reported the isolation of a number of geranyl-substituted carbazole alkaloids from the stem bark of *Murraya euchrestifolia* Hayata: euchrestine-B (**162.1**), murrayaline D (**162.2**), euchrestine-D (**162.3**), euchrestine-C (**163.1**), and euchrestine-E (**163.3**). The chiral euchrestine-E (**163.3**) was obtained as a racemic mixture (Schemes 162 and 163).[391,393] The co-occurrence of euchrestine-C (**163.1**), euchrestine-E (**163.3**), and the pyranocarbazole pyrayafoline D (**220.3**) supports the proposed mechanism for pyran annulations in biological systems.[187] Epoxidation of the double bond would be followed by a nucleophilic attack of the phenolic hydroxy group at the tertiary carbon atom of the epoxide. Finally, dehydration would lead to pyrayafoline D (**220.3**). As one would expect, pyrayafoline D (**220.3**) was obtained as a racemate as well as euchrestine-E (**163.3**). Murrayanol (**163.2**), the monomethyl ether derivative of euchrestine-C (**163.1**), was isolated by Reisch et al. in 1992 from the fruits of *Murraya koenigii* together with other carbazole alkaloids.[399]

3.3.6.2. Total Syntheses of Clausine O, 7-Methoxy-O-methylmukonal, Clausine H (Clauszoline-C), and Clausine K (Clauszoline-J). In 2005, Knölker and co-workers reported a short and efficient access to a series of 2,7-dioxygenated carbazole alkaloids: clausine O (**159.2**), 7-methoxy-*O*-methylmukonal (**160.1**), clausine H (clauszoline-C) (**160.3**), and clausine K (clauszoline-J) (**160.4**) (Schemes 164 and 165).[400]

Scheme 162

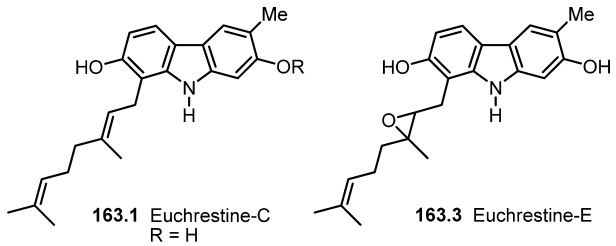


162.1 Euchrestine-B

162.2 Murrayaline-D

162.3 Euchrestine-D

Scheme 163

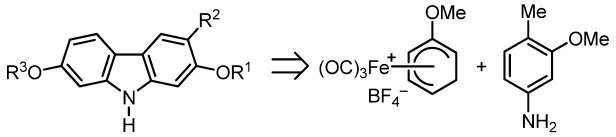


163.1 Euchrestine-C R = H

163.2 Murrayanol R = Me

163.3 Euchrestine-E

Scheme 164



159.2 Clausine O R^1,R^3 = H; R^2 = CHO

160.1 7-Methoxy-*O*-methylmukonal R^1,R^3 = Me; R^2 = CHO

160.3 Clausine H (Clauszoline-C) R^1,R^3 = Me; R^2 = COOMe

160.4 Clausine K (Clauszoline-J) R^1,R^3 = Me; R^2 = COOH

164.1

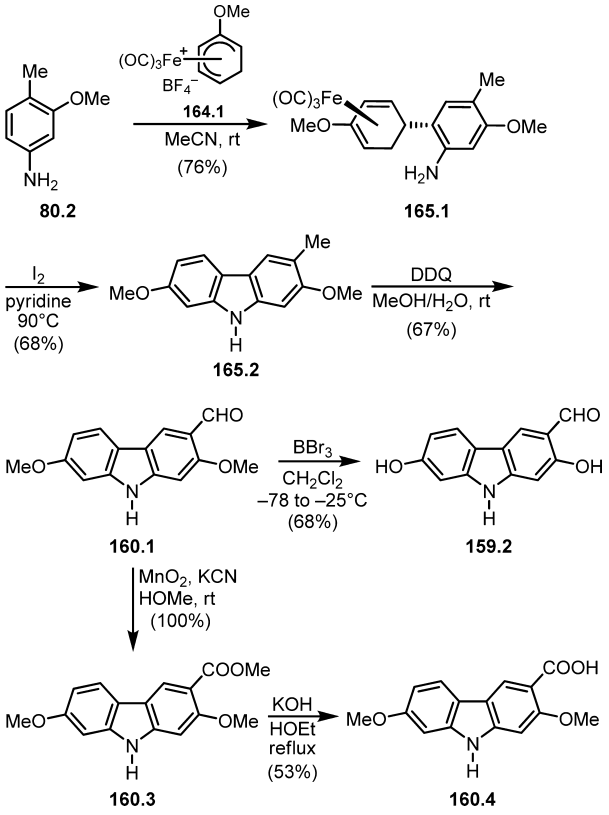
80.2

Using the iron-mediated arylamine cyclization as the key step, the aforementioned 2,7-dioxygenated carbazole alkaloids were obtained starting from the amine **80.2** and the 2-methoxy-substituted iron complex salt **164.1**.

Electrophilic substitution by reaction of the 2-methoxy-substituted iron complex salt **164.1** with 3-methoxy-4-methylaniline (**80.2**) afforded the iron complex **165.1** in 76% yield (Scheme 165).[400] Reaction of complex **165.1** with iodine in pyridine at 90 °C provided directly 2,7-dimethoxy-3-methylcarbazole (**165.2**) by iron-mediated cyclization with concomitant aromatization and demetalation. Finally, oxidation of the carbazole **165.2** with DDQ led to 7-methoxy-*O*-methylmukonal (**160.1**), a crucial precursor for the synthesis of further 2,7-dioxygenated carbazoles. Cleavage of both methyl ethers of **160.1** on reaction with boron tribromide led to

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

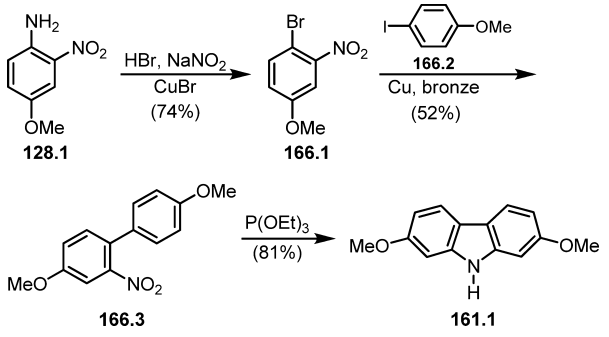
Scheme 165



clausine O (**159.2**). Oxidation of **160.1** with manganese dioxide in methanol in the presence of potassium cyanide afforded quantitatively clausine H (clauszoline-C) (**160.3**), which on alkaline saponification afforded clausine K (clauszoline-J) (**160.4**).

3.3.6.3. Total Syntheses of Clausine V. Prior to the isolation of clausine V (**161.1**), Hsieh and Litt reported the synthesis of 2,7-dimethoxycarbazole (clausine V) (**161.1**) starting from commercially available 4-methoxy-2-nitroaniline (**128.1**) and 4-iodoanisole (**166.2**) (Scheme 166).[401] This synthesis was

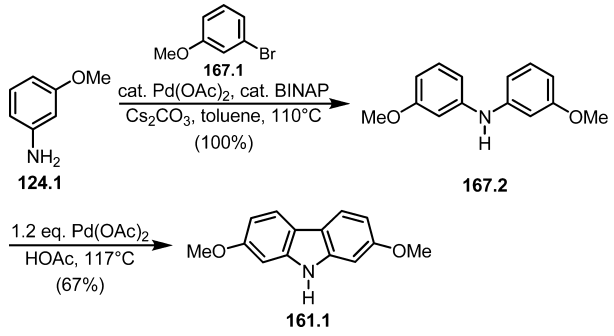
Scheme 166



carried out for the preparation of carbazole-containing polymers to investigate their electrical and photophysical properties. Treatment of 4-methoxy-2-nitroaniline (**128.1**) with sodium nitrite in hydrobromic acid followed by addition of copper(I) bromide to the intermediate diazonium salt afforded the bromonitrobenzene **166.1**. Using Ullmann conditions, coupling of **166.1** with 4-iodoanisole (**166.2**) afforded *o*-nitrobiphenyl **166.3** in 52% yield. Finally, Cadogan's reductive cyclization of **166.3** with triethyl phosphite led to 2,7-dimethoxycarbazole (clausine V) (**161.1**) in 81% yield.

In 2008, Knölker and co-workers reported an efficient two-step synthesis of clausine V (**161.1**) starting from commercially available 3-bromoanisole (**167.1**) and *m*-anisidine (**124.1**) (Scheme 167).[97] This method involves two consecutive

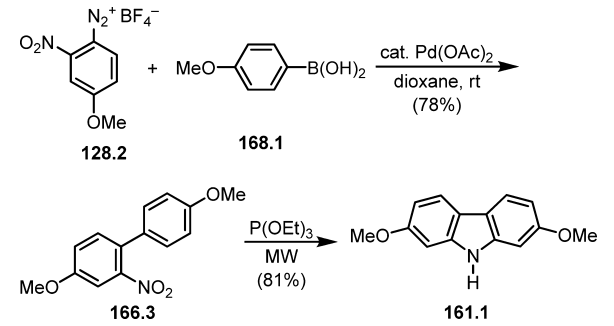
Scheme 167



palladium-catalyzed reactions for the amination and double C−H bond activation. Coupling of 3-bromoanisole (**167.1**) with *m*-anisidine (**124.1**) using palladium(0)-catalyzed Buchwald−Hartwig amination led to the diarylamine **167.2**, which on palladium(II)-catalyzed intramolecular oxidative cyclization afforded clausine V (**161.1**) in two steps and 67% overall yield.

In the same year, Kuethe and Childers reported a further synthesis of clausine V (**161.1**) starting from the aryldiazonium tetrafluoroborate **128.2** and 4-methoxyphenylboronic acid (**168.1**) (Scheme 168).[344] Suzuki−Miyaura cross-coupling of

Scheme 168



the diazonium salt **128.2** with 4-methoxyphenylboronic acid (**168.1**) in the presence of catalytic amounts of palladium(II) acetate provided the required 2-nitrobiphenyl derivative **166.3** in high yield. Finally, in analogy to Hsieh and Litt's procedure,[401] the nitrobiphenyl **166.3** was cleanly transformed to clausine V (**161.1**) in 81% yield using microwave (MW) conditions.

3.3.7. 2,8-Dioxygenated Carbazole Alkaloids.

3.3.7.1. Isolation from Natural Sources. So far all known 2,8-dioxygenated carbazole alkaloids were isolated from plants of the Rutaceae family. In 1970, Chakraborty et al. reported the isolation of the first 2,8-dioxygenated carbazole alkaloid, heptazoline (**24.3**), from the stem bark of *Clausena heptaphylla* (Scheme 169).[402] In 1996, Ito et al. reported the isolation of clauszoline-D (**169.1**) and clauszoline-F (**169.2**) from the stem bark of *Clausena excavata* collected in Singapore.[403]

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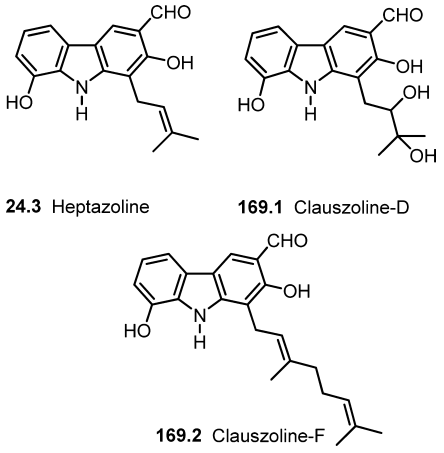
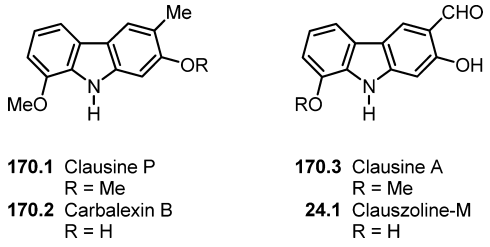
Scheme 169



In 1999, Wu et al. isolated clausine P (**170.1**) from the acetone extract of the root bark of *Clausena excavata* (Scheme 170).[309] Two years later, Greger and co-workers described the

Scheme 170



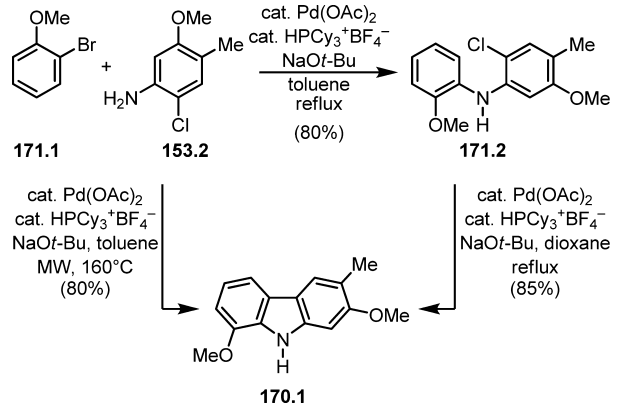
stress-induced formation of the phytoalexin carbalexin B (**170.2**), isolated from the methanol extract of the leaves of *Glycosmis parviflora*.[378] This compound showed a strong antifungal activity in bioautographic tests on TLC plates with *Cladosporium herbarum*. In 1996, Wu et al. isolated clausine A (**170.3**) from a methanol extract of the stem bark of *Clausena excavata*.[359] One year later, Ito et al. reported the isolation of clauszoline-M (**24.1**) from the acetone extract of the leaves of the same *Clausena* plant.[279]

3.3.7.2. Palladium-Catalyzed Total Synthesis of Clausine P. In 2006, Bedford and Betham reported the first total synthesis of clausine P (**170.1**) starting from the 2-chloroaniline **153.2**, which was obtained in a one-pot operation starting from the commercial benzoic acid **153.1** (see Scheme 153).[387] The Buchwald–Hartwig amination of 2-bromoanisole (**171.1**) with the chloroaniline **153.2** afforded the diarylamine **171.2** (Scheme 171). Finally, intramolecular Heck-like cyclization via C–H-bond activation under thermal conditions in 1,4-dioxane and catalytic amounts of palladium(0) afforded clausine P (**170.1**). This two-step amination/C–H bond activation methodology afforded clausine P (**170.1**) in 68% overall yield. Alternatively, clausine P (**170.1**) was also obtained in an improved procedure via a one-pot tandem process carrying out the same reactions under microwave irradiation at 160 °C in toluene. Under these reaction conditions, clausine P (**170.1**) was obtained in 80% yield.

3.3.8. 3,4-Dioxygenated Carbazole Alkaloids.

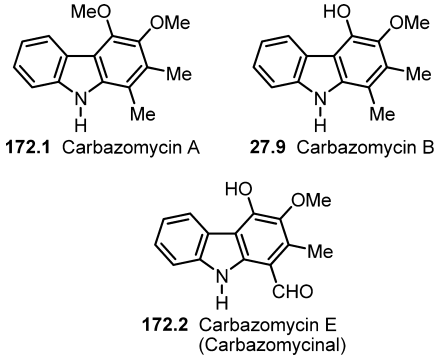
3.3.8.1. Isolation from Natural Sources. All known 3,4-dioxygenated carbazole alkaloids were isolated from microorganisms, e.g., various *Streptomyces* species. In 1980, Nakamura

Scheme 171



and co-workers reported the isolation of the first 3,4-dioxygenated carbazoles, carbazomycin A (**172.1**) and carbazomycin B (**27.9**), from *Streptoverticillium ehimense* H 1051-MY 10 (Scheme 172).[404−406] These structurally unique

Scheme 172

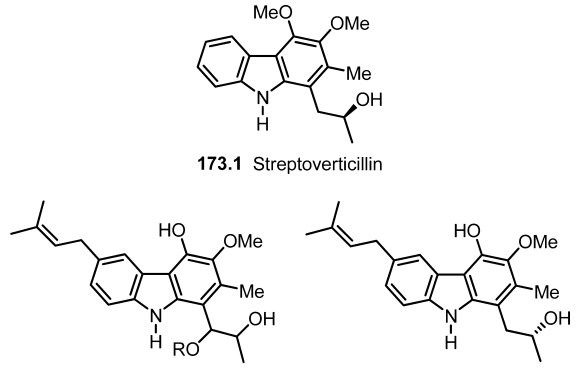


alkaloids biogenetically derive from tryptophan[207] and represent the first antibiotics with a carbazole framework. Carbazomycin A (**172.1**) and B (**27.9**) inhibit the growth of phytopathogenic fungi and show antibacterial and antiyeast activities.[404] Furthermore, carbazomycin B (**27.9**) inhibits 5-lipoxygenase[407] and also showed inhibitory activity against lipid peroxidation induced by free radicals.[316] In 1986, Marumo and co-workers isolated carbazomycin E (carbazomycinal) (**172.2**) from a different *Streptoverticillium* species of the strain KCC U-0166.[408] One year later, Nakamura and co-workers described carbazomycin B (**27.9**) along with carbazomycin A (**172.1**) and carbazomycin E (**172.2**) as minor components of the culture broth of *S. ehimense* H 1051-MY 10.[409]

Streptoverticillin (**173.1**) was isolated by Wei and co-workers from the mycelial solid culture of *Streptoverticillium morookaense* in 2007 (Scheme 173).[410] This compound was obtained from nature in optically active form ($[\alpha]_D^{20}$ = +18.4, c 0.179, HOMe) and has shown antifungal activity against *Peronophythora litchii*, one of the main pathogens causing litchi fruit rot. By comparison of the sign of the optical rotation value with that of (*R*)-neocarazostatin B (**173.4**) as reported by Knölker and co-workers,[411] it was presumed that streptoverticillin (**173.1**) has an *S*-configuration at the stereogenic center.[410] In 2011, Knölker and co-workers described the total synthesis of (*S*)-streptoverticillin (**173.1**) and (*R*)-streptoverticillin [(*R*)-**173.1**] and confirmed the *S*-configuration for the natural product (see Addendum).[412]

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 173



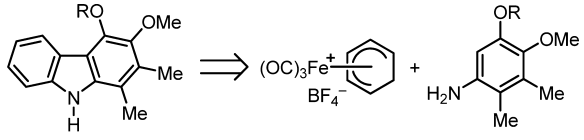
173.1 Streptoverticillin

173.2 Neocarazostatin A R = H
173.3 Neocarazostatin C R = Me
173.4 Neocarazostatin B

In 1991, Kato et al. reported the isolation of the neocarazostatins A (**173.2**), B (**173.4**), and C (**173.3**) from the cultures of *Streptomyces* species GP 38. Although isolated in optically active form, the absolute configurations of the neocarazostatins A (**173.2**) ($[\alpha]_D^{26}$ = −36.0, c 0.1, HOMe), B (**173.4**) ($[\alpha]_D^{26}$ = −24.0, c 0.1, HOMe), and C (**173.3**) ($[\alpha]_D^{26}$ = −92.0, c 0.1, HOMe) have not been determined.[413] However, Knölker and co-workers have assigned the absolute configuration of neocarazostatin B (**173.4**) as (*R*) by enantioselective total synthesis of the natural product.[411] Compounds **173.2**−**173.4** exhibit a strong inhibitory activity against free radical-induced lipid peroxidation.

3.3.8.2. Total Synthesis of Carbazomycin A and Carbazomycin B. Since their isolation, several total syntheses using different strategies have been reported for carbazomycin A (**172.1**) and B (**27.9**). Among the various methods, the iron-mediated synthesis provides the carbazomycins A and B on a large scale in excellent overall yield with a minimum number of steps. On the basis of this approach, the retrosynthetic analysis of carbazomycin A (**172.1**) and B (**27.9**) leads to the iron complex salt **77.1** and the fully functionalized arylamines **174.1** and **174.2** as synthetic precursors (Scheme 174).[414]

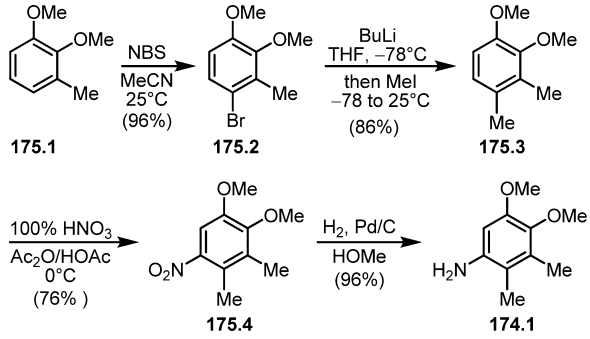
Scheme 174



172.1 Carbazomycin A R = Me
27.9 Carbazomycin B R = H
77.1
174.1 R = Me
174.2 R = Ac

The arylamine **174.1**, required for the total synthesis of carbazomycin A (**172.1**), was synthesized from commercially available 3-methylveratrole (**175.1**) (Scheme 175).[414,415] Electrophilic bromination of **175.1** afforded regioselectively the 4-bromoanisole **175.2**. Halogen−metal exchange with butyllithium and subsequent quenching of the intermediate aryllithium with iodomethane afforded 3,4-dimethylveratrole (**175.3**). Regioselective nitration of **175.3** with fuming nitric acid in a mixture of acetic anhydride and glacial acetic acid provided the nitrobenzene **175.4**. Finally, catalytic hydrogenation of **175.4** with palladium on activated carbon led to the

Scheme 175

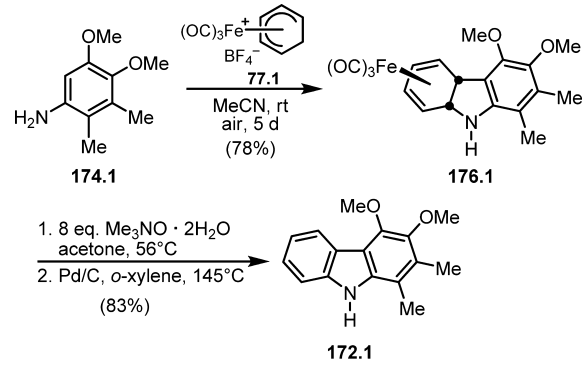


175.1 **175.2** **175.3** **175.4** **174.1**

arylamine **174.1**, which was thus obtained in four steps and 60% overall yield.

Using the iron-mediated one-pot oxidative coupling procedure by oxidation with air (cf. Scheme 8), the arylamine **174.1** was transformed to the iron-coordinated dihydrocarbazole **176.1** (Scheme 176)[414] Finally, demetalation of **176.1**

Scheme 176

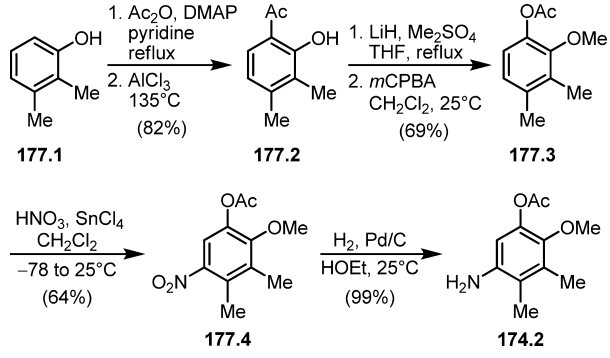


174.1 **176.1** **172.1**

followed by aromatization led to carbazomycin A (**172.1**). This three-step procedure provides carbazomycin A (**172.1**) in 65% overall yield based on the iron complex salt **77.1**.

2,3-Dimethylphenol (**177.1**) was used as starting material to access the arylamine **174.2**, which was required for the total synthesis of carbazomycin B (**27.9**) (Scheme 177).[416] The second oxygen substituent in the *ortho*-position relative to the hydroxy group was introduced by O-acetylation of **177.1** followed by *ortho*-selective Fries rearrangement of the intermediate acetoxy derivative to the desired acetophenone **177.2**. O-Methylation followed by Baeyer−Villiger oxidation afforded the acetoxy derivative **177.3**. Regioselective nitration

Scheme 177



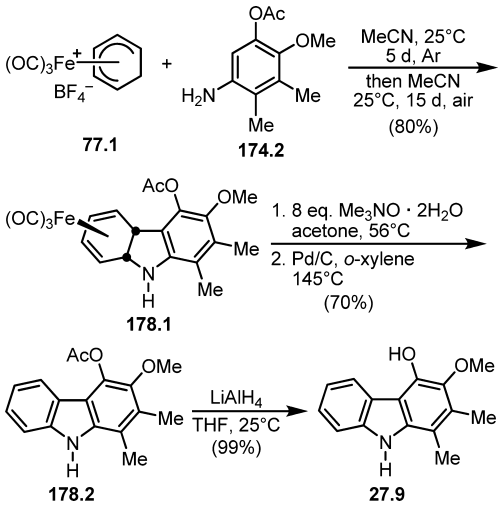
177.1 **177.2** **177.3** **177.4** **174.2**

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

of **177.3** using a preformed complex of fuming nitric acid and $SnCl_4$ at −78 °C afforded the desired 5-nitrophenyl acetate **177.4**. Finally, catalytic hydrogenation of **177.4** led to the arylamine **174.2** in almost quantitative yield.

Oxidative coupling of the iron complex salt **77.1** and the arylamine **174.2** in the presence of air afforded the tricarbonyl-(η^4-4*b*,8*a*-dihydro-9*H*-carbazole) iron complex **178.1** (Scheme 178).[414] Demetalation of **178.1** followed by aromatization led

Scheme 178

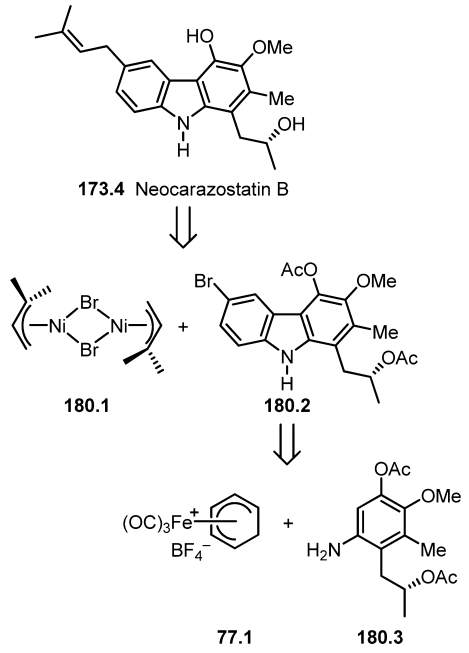


to *O*-acetylcarbazomycin B (**178.2**). Finally, ester cleavage provided carbazomycin B (**27.9**) almost quantitatively. Using this procedure, carbazomycin B (**27.9**) was obtained in five steps and 55% overall yield based on the iron complex salt **77.1**.

In 2004, Crich and Rumthao also reported a synthesis of carbazomycin B (**27.9**) (Scheme 179).[417] Their approach involves the addition of a phenyl radical to the highly functionalized (iodophenyl)carbamate **179.2** followed by cyclization and dehydrogenative aromatization. The (iodophenyl)carbamate **179.2** was obtained from the 5-nitrophenyl acetate **177.4**, which was prepared following Knölker's route (see Scheme 177). After deacetylation of **177.4**, the corresponding phenol was subjected to iodination and reacetylation to afford 6-iodo-2-methoxy-3,4-dimethyl-5-nitrophenyl acetate (**179.1**) in 72% yield. Reduction of **179.1** with iron and iron(III) chloride in acetic acid followed by reaction with methyl chloroformate led to the (iodophenyl)-carbamate **179.2**. Reaction of **179.2** with diphenyl diselenide, tributyltin hydride, and azobisisobutyronitrile (AIBN) in benzene at reflux gave the adduct **179.4** in 40% yield along with 8% of recovered substrate **179.2** and 12% of the hydrodeiodinated carbamate **179.3**. Reaction of **179.4** with phenylselenyl bromide in dichloromethane afforded the phenylselenenyltetrahydrocarbazole **179.5**. Oxidative deselenation followed by aromatization with an excess of *tert*-butyl hydroperoxide led to the fully aromatized carbazole **179.6**. Finally, saponification of **179.6** using methanolic sodium hydroxide afforded carbazomycin B (**27.9**) in nine steps and 6% overall yield based on **177.4**.

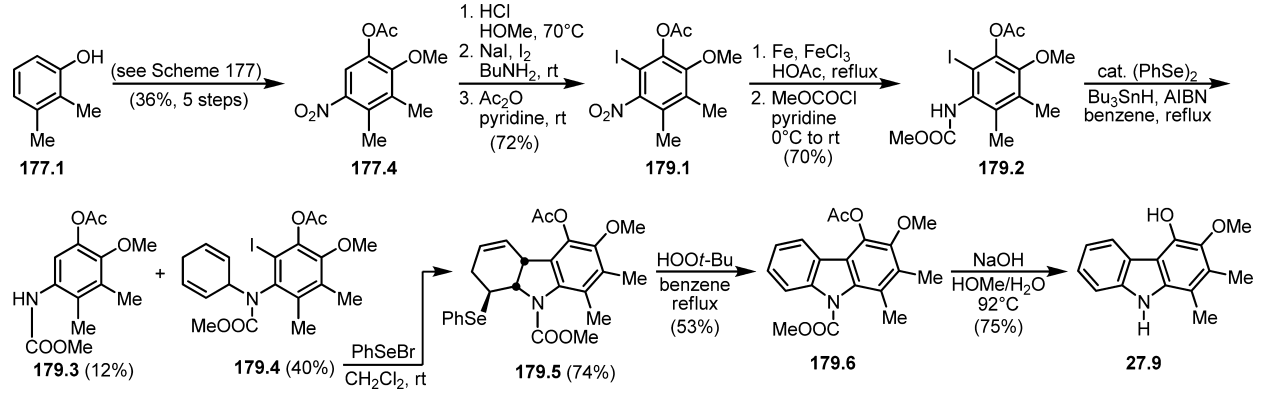
3.3.8.3. Enantioselective Total Synthesis of Neocarazostatin B. In 2006, Knölker and co-workers reported the first enantioselective total synthesis of neocarazostatin B (**173.4**) (Scheme 180).[411] The protected 6-bromocarbazole **180.2**, the

Scheme 180



key intermediate of this synthesis, was prepared in a highly convergent manner using the iron-mediated approach with the fully functionalized chiral arylamine **180.3** and the iron complex salt **77.1** as building blocks.

Scheme 179



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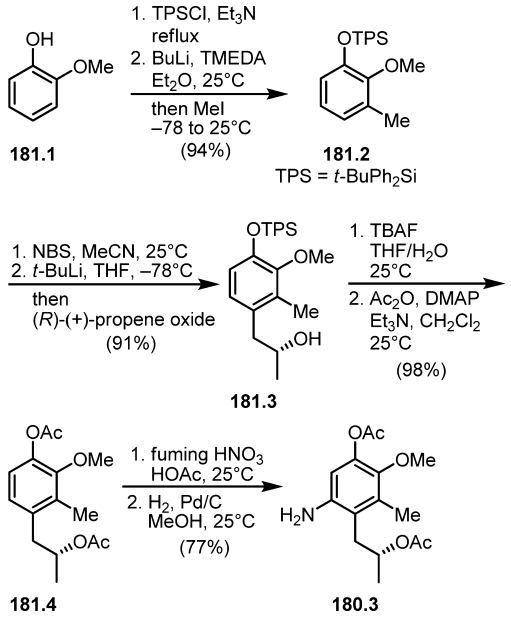
The chiral arylamine **180.3** with an *R*-configuration at the stereogenic center was obtained from commercial guaiacol (**181.1**) in 8 steps and 65% overall yield.[411] Previously, for the total synthesis of racemic neocarazostatin B (±)-(**173.4**), the analogous racemic arylamine (±)-**180.3** had been prepared in 10 steps and 14% overall yield based on *o*-cresol.[418] Protection of guaiacol (**181.1**) as *tert*-butyldiphenylsilyl (TPS) ether and subsequent *ortho*-directed lithiation followed by methylation of the intermediate lithium derivative afforded the 2,3-dioxygenated toluene **181.2** (Scheme 181). The required chiral side-

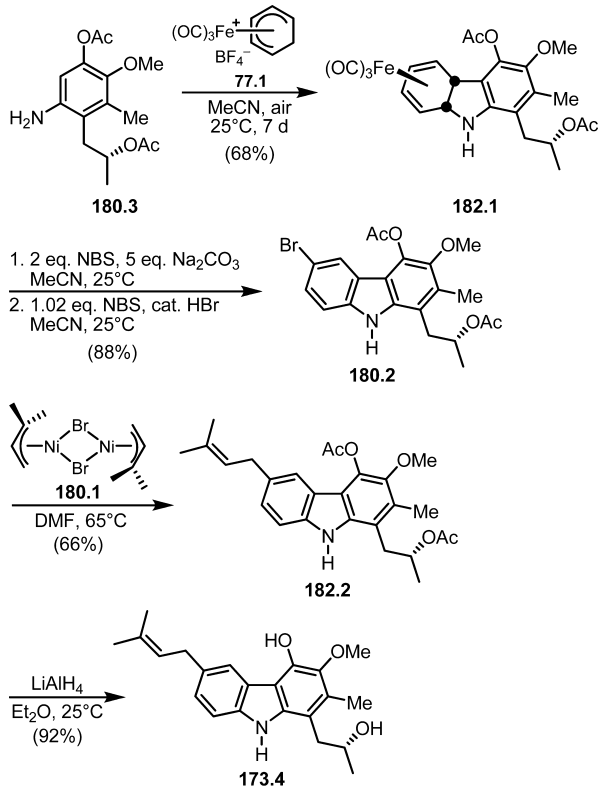
Scheme 181



chain for *R*-neocarazostatin B (**173.4**) was derived from (*R*)-(+)-propene oxide. Hydrolytic kinetic resolution (HKR) of racemic propene oxide using Jacobsen's (*R*,*R*)-(salen)cobalt(II) complex provided (*R*)-(+)-propene oxide (enantiomeric excess (ee) ≥ 99%).[419−421] Regioselective bromination of **181.2** followed by halogen−metal exchange and ring-opening of (*R*)-(+)-propene oxide by the intermediate aryllithium provided the (*R*)-2-hydroxypropylarene **181.3**. After removal of the silyl protecting group using TBAF, the corresponding phenol derivative was subjected to acetylation to afford the diacetate **181.4**. Regioselective nitration with fuming nitric acid in glacial acetic acid followed by catalytic hydrogenation provided the arylamine **180.3** with an (*R*)-configuration at the side-chain.[411]

One-pot reaction of the iron complex salt **77.1** with the (*R*)-arylamine **180.3** in air provided the tricarbonyliron-coordinated 4*b*,8*a*-dihydrocarbazole iron complex **182.1** via a sequential C−C and C−N bond formation (Scheme 182).[411] Aromatization with concomitant demetalation of complex **182.1** using NBS under basic reaction conditions led to the free carbazole. Electrophilic bromination with NBS under acidic reaction conditions furnished the 6-bromocarbazole **180.2**. Coupling of the 6-bromocarbazole **180.2** with 2 equiv of the dimeric π-prenyl nickel bromide complex **180.1**, prepared from prenyl bromide and tetracarbonyl nickel(0), afforded di(*O*-acetyl)-neocarazostatin B (**182.2**) in 66% yield along with some hydrodebrominated product. Finally, reductive cleavage of both ester groups by reaction with lithium aluminum hydride provided (*R*)-(−)-neocarazostatin B (**173.4**). This synthesis

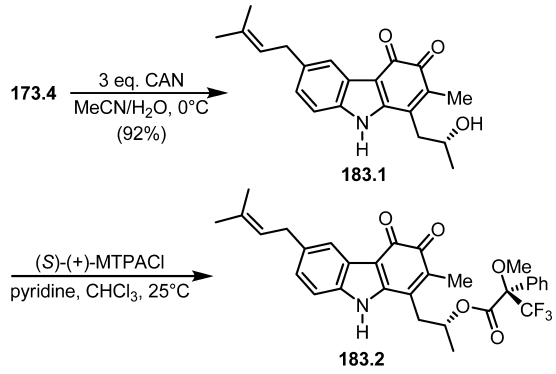
Scheme 182



provides enantiopure (*R*)-(−)-neocarazostatin B (**173.4**) in 5 steps and 36% overall yield based on the iron complex salt **77.1**.

For an additional confirmation of the absolute configuration, (*R*)-(−)-neocarazostatin B (**173.4**) was oxidized to (*R*)-carquinostatin A (**183.1**) using ceric ammonium nitrate (CAN) (Scheme 183).[411] The identity of the absolute

Scheme 183

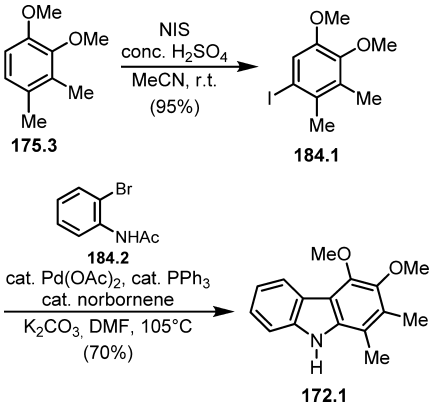


configuration of (*R*)-(−)-neocarazostatin B (**173.4**) and (*R*)-carquinostatin A (**183.1**) and also their optical purity (ee ≥ 99%) has been additionally confirmed by transformation of (*R*)-carquinostatin A (**183.1**) to the known (*R*,*R*)-Mosher ester **183.2** by reaction with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MTPACl).

3.3.8.4. Total Synthesis of Carbazomycin A. Recently, Catellani and co-workers reported the total synthesis of carbazomycin A (**172.1**) by a one-pot sequential palladium-catalyzed C−C and C−N bond formation (Scheme 184).[422,423] Iodination of 3,4-dimethylveratrole **175.3**, which was prepared

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 184

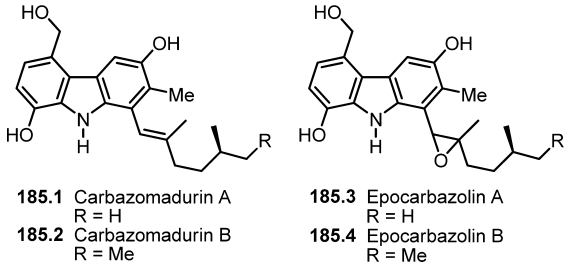


following Knölker's route (see Scheme 175),[414] provided the iodobenzene **184.1**. Coupling of 1-iodo-4,5-dimethoxy-2,3-dimethylbenzene (**184.1**) and commercial 2-bromo-*N*-acetylaniline (**184.2**) in the presence of a catalytic amount of palladium(II) acetate, norbornene, and triphenylphosphine directly afforded carbazomycin A (**172.1**) in 4 steps and 55% overall yield.

3.3.9. 3,8-Dioxygenated Carbazole Alkaloids.

3.3.9.1. Isolation from Natural Sources. Like the 3,4-dioxygenated carbazole alkaloids, this family of dioxygenated carbazole alkaloids has been isolated only from microorganisms, such as the *Actinomadura* and *Streptomyces* species. The neuronal cell-protecting substances carbazomadurin A (**185.1**) and carbazomadurin B (**185.2**) were first obtained in 1997 by Seto and co-workers from *Actinomadura madurae* 2808-SV1 (Scheme 185).[332] Carbazomadurin B (**185.2**) was

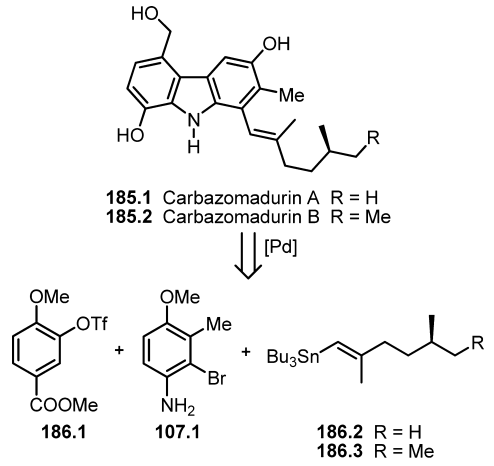
Scheme 185



isolated in optically active form ($[\alpha]_D^{24}$ = +4.0, c 0.05, HOMe). By total synthesis Knöll and Knölker have assigned an (*S*)-configuration to natural carbazomadurin B (**185.2**).[333] Both alkaloids, **185.1** and **185.2**, exhibit a strong neuronal cell-protecting activity against L-glutamate-induced cell death.[332] In 1993, a research group of Bristol–Myers in Japan isolated epocarbazolin A (**185.3**) and epocarbazolin B (**185.4**) as carbazole antibiotics from the culture broth of *Streptomyces anulatus* T688-8.[424] These compounds were the first carbazole alkaloids with an epoxide function. In fact, they represent the epoxides of carbazomadurin A (**185.1**) and carbazomadurin B (**185.2**). Epocarbazolin A (**185.3**) ($[\alpha]_D^{26}$ = +75, c 0.5, HOMe) and epocarbazolin B (**185.4**) ($[\alpha]_D^{26}$ = +78, c 0.5, HOMe) were obtained from nature in optically active form. However, their absolute configurations are not known. Both alkaloids showed a potent 5-lipoxygenase inhibitory activity and a weak antibacterial activity.

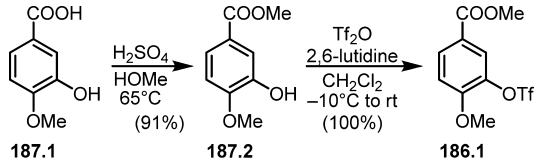
3.3.9.2. Palladium(0)-Catalyzed Synthesis of Carbazomadurin A, Carbazomadurin B, (±)-Epocarbazolin A, and Epocarbazolin B. Knölker and Knöll described the first total synthesis of carbazomadurin A (**185.1**) and B (**185.2**) using a sequence of three different palladium-catalyzed cross-coupling reactions of the three building blocks **107.1** and **186.1**–**186.3** (Scheme 186).[333,341]

Scheme 186



The first building block, the aryl triflate **186.1**, was available in 2 steps and 91% overall yield from isovanillic acid (**187.1**) (Scheme 187).[341] Acid-catalyzed esterification of **187.1** to the

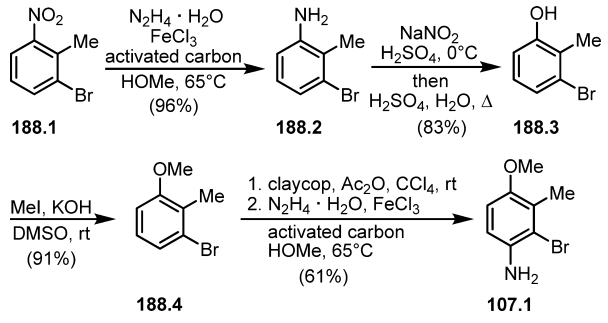
Scheme 187



corresponding methyl ester **187.2** was followed by reaction with triflic anhydride using 2,6-lutidine as base to afford the desired triflate **186.1**.

The second building block, arylamine **107.1**, was prepared from 2-bromo-6-nitrotoluene (**188.1**) in 5 steps and 44% overall yield (Scheme 188).[341] Transfer hydrogenation of **188.1** using hydrazine hydrate afforded 3-bromo-2-methylaniline (**188.2**), which was converted to the corresponding phenol **188.3** via diazotization and hydrolysis of the diazonium salt. Methyl ether formation to give the anisole **188.4** was followed

Scheme 188

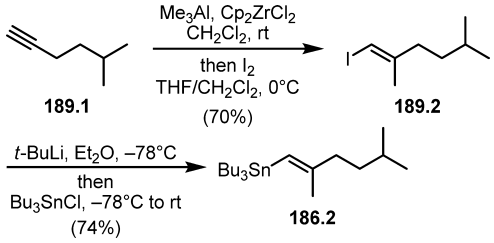


dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

by regioselective nitration using claycop to afford the corresponding 4-nitroanisole. Transfer hydrogenation using hydrazine hydrate led to the arylamine **107.1**. Later, this synthetic approach to the arylamine **107.1** was modified by Hänchen and Süssmuth in their synthesis of the lipocarbazoles A2−A4 (**88.2**−**88.4**) (see Scheme 107).[340]

The alkyl side-chains at C-1 of carbazomadurin A (**185.1**) and B (**185.2**) were introduced by Stille coupling of a 1-halogenated carbazole with the vinylstannanes **186.2** and **186.3** (third building block) (Scheme 186).[341] The stereospecific construction of the trisubstituted double bond of the vinyl stannanes **186.2** and **186.3** was achieved by application of Negishi's zirconium-catalyzed carboalumination of the alkynes **189.1** and **190.4**.[341,333] Reaction of 5-methyl-1-hexyne (**189.1**) with trimethylaluminum in the presence of di-(cyclopentadienyl)zirconium dichloride followed by addition of iodine afforded the vinyl iodide **189.2** with the required *E*-configuration of the double bond (Scheme 189). Halogen−

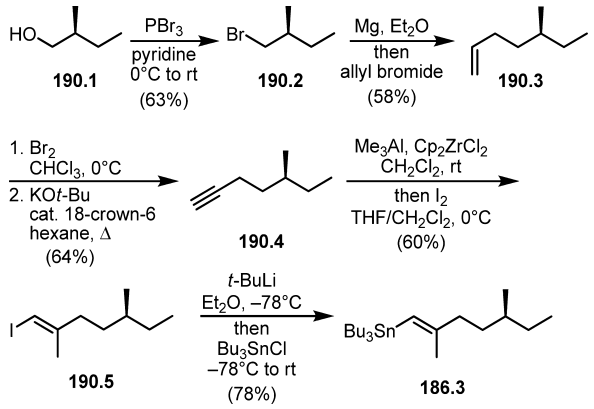
Scheme 189



metal exchange with *tert*-butyllithium and reaction of the intermediate vinyllithium compound with tributyltin chloride provided the vinylstannane **186.2**.

Assuming an *S*-configuration for carbazomadurin B (**185.2**), the synthesis of the chiral alkenylstannane **186.3** has been accomplished in 6 steps and 11% overall yield from commercial (*S*)-(−)-2-methyl-1-butanol (**190.1**) (Scheme 190). After the

Scheme 190



enantiomeric purity was confirmed for **190.1** (ee ≥ 99%), it was transformed to the corresponding bromo derivative **190.2**. Conversion of **190.2** to the Grignard reagent and Wurtz coupling with allyl bromide led to the alkene **190.3**. Addition of bromine was followed by double elimination using potassium *tert*-butoxide as base in the presence of catalytic amounts of 18-crown-6 to provide (*S*)-(+)-5-methyl-1-heptyne (**190.4**). Compound **190.4** was then transformed to the vinylstannane **186.3** in 2 steps and 47% overall yield using the same sequence of reactions as shown in Scheme 189 for the transformation of the alkene **189.1** to the vinylstannane **186.2**.[333]

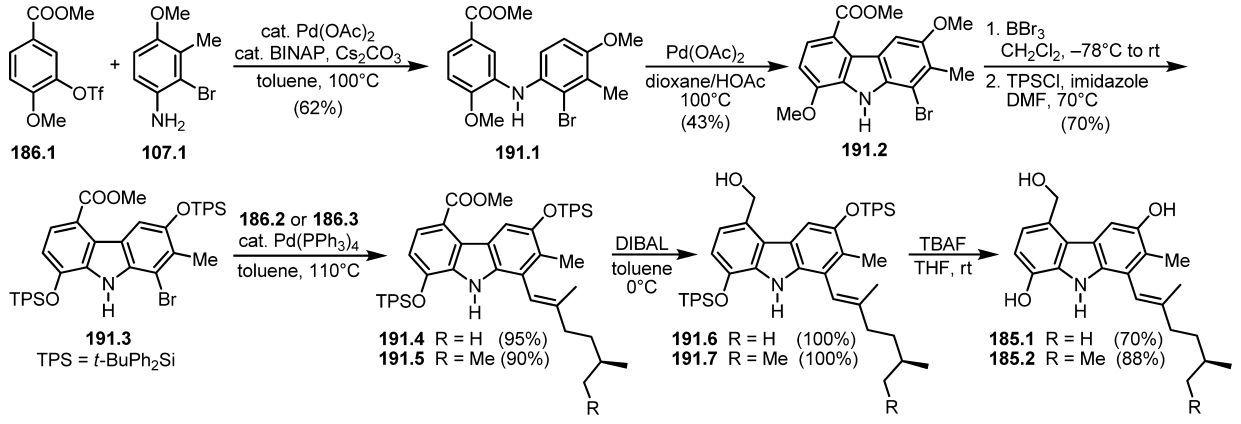
The palladium(0)-catalyzed Buchwald−Hartwig coupling of the aryl triflate **186.1** and the arylamine **107.1** afforded the diarylamine **191.1** (Scheme 191).[333] Subsequent palladium(II)-mediated oxidative cyclization of **191.1** led to the pentasubstituted carbazole **191.2**. A change of the protecting groups was achieved by cleavage of both methyl ethers followed by double silylation to afford the bis(*tert*-butyldiphenylsilyl) ether **191.3**. Palladium(0)-catalyzed Stille coupling of the 1-bromocarbazole **191.3** and the 1-(*E*)-alkenylstannanes **186.2** and **186.3** furnished the 1-alkenylcarbazoles **191.4** and **191.5**, respectively. Reduction of the methyl ester using DIBAL led to the corresponding benzylic alcohols **191.6** and **191.7** as common precursors for the carbazomadurins and the epocarbazolins. Finally, removal of both silyl protecting groups from the intermediates **191.6** and **191.7** with TBAF provided carbazomadurin A (**185.1**) and carbazomadurin B (**185.2**).[333,341] On the basis of this synthesis and comparison of the specific rotation with natural carbazomadurin B (**185.2**), an (*S*)-configuration has been assigned to the stereogenic center in the side-chain of the natural product.

Knöll and Knölker also investigated the possibility to transform carbazomadurin A (**185.1**) and B (**185.2**) into epocarbazolin A (**185.3**) and B (**185.4**) by epoxidation. All attempts to achieve a direct conversion of the carbazomadurins A (**185.1**) and B (**185.2**) or of the disilyl-protected carbazomadurins A (**191.6**) and B (**191.7**) were unsuccessful and led to complete decomposition.[425] Therefore, prior to epoxidation, the disilyl-protected carbazomadurins A (**191.6**) and B (**191.7**) were transformed quantitatively into the corresponding trisilyl-protected carbazomadurins A (**192.1**) and B (**192.2**) by reaction with *tert*-butyldiphenylsilyl chloride (TPSCl) in the presence of stoichiometric amounts of dimethylaminopyridine (DMAP) (Scheme 192). Epoxidation of the fully protected carbazomadurins A (**192.1**) and B (**192.2**) with dimethyldioxirane at −20 °C (yield 53%) followed by desilylation provided racemic epocarbazolin A (*rac*-**185.3**) and epocarbazolin B (**185.4**) as a mixture of diastereoisomers. Following the same approach, Knöll and Knölker also described the total synthesis of non-natural (−)-epocarbazolin A [(−)-**185.3**]. Asymmetric epoxidation of the trisilyl-protected carbazomadurin A (**192.1**) under Shi's conditions[426] and subsequent deprotection led to (−)-**185.3** in approximately 73% ee. The absolute configuration of (−)-**185.3** has not been assigned.

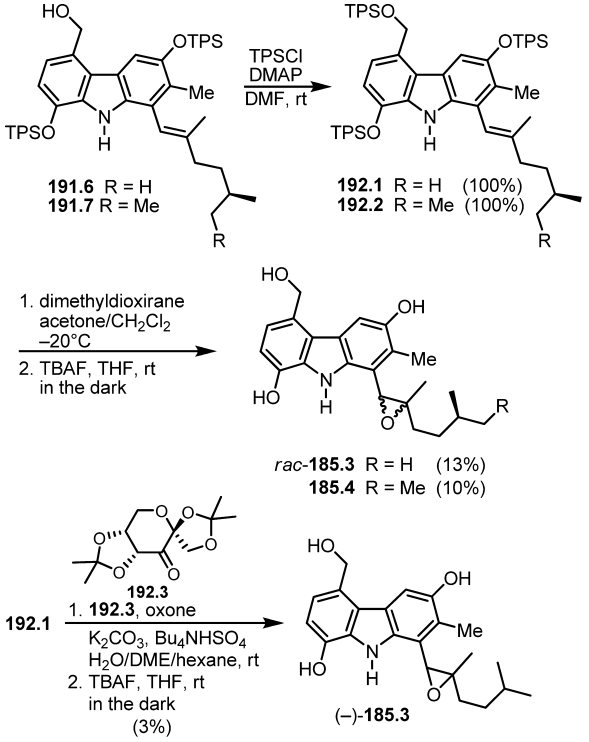
3.3.9.3. Synthesis of Carbazomadurin A by Benzannulation. In 2010, Choshi, Hibino, and co-workers reported the second synthesis of carbazomadurin A (**185.1**) using an electrocyclic ring-closure of an allene for the construction of the carbazole nucleus (Scheme 193).[427] The required MOM-protected propargyl alcohol **193.5** was synthesized from the indole-3-carboxylate **193.1**, which was obtained by a literature-known Reissert synthesis.[428] Formylation of **193.1** at C-4, reduction of the resulting aldehyde, and MOM protection led to the ethyl indole-2-carboxylate **193.2**. Reduction of the ethyl ester to a benzylic alcohol followed by oxidation with manganese dioxide and iodination of the indole-2-carbaldehyde afforded the 3-iodoindole-2-carbaldehyde **193.3**. Stille coupling of **193.3** and (2-ethoxyvinyl)stannane (**193.4**) followed by addition of ethynylmagnesium bromide and MOM protection of the alcohol furnished **193.5**, the precursor for the electrocyclic ring-closure. Treatment of **193.5** with TBAF at

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

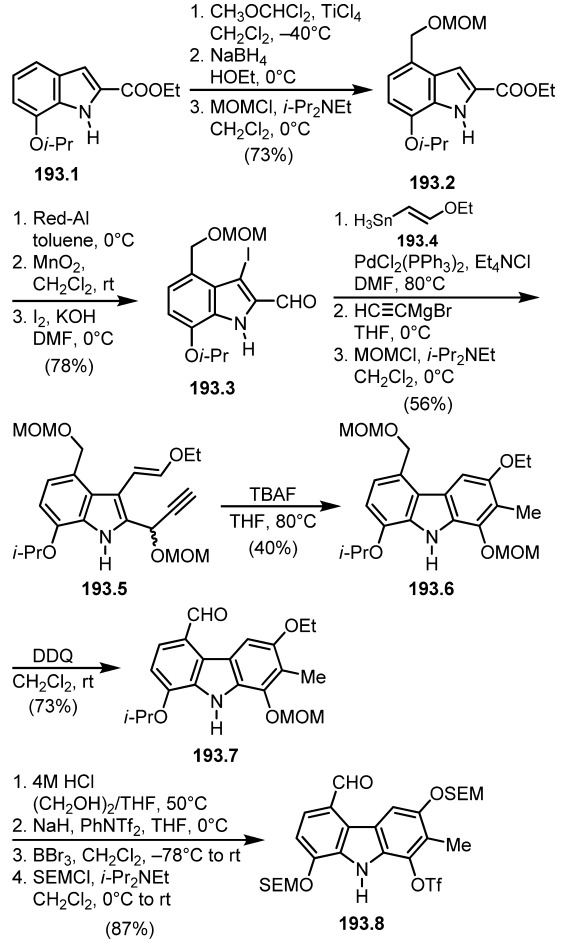
Scheme 191



Scheme 192



Scheme 193



elevated temperature afforded the carbazole **193.6** in moderate yield. Strong basic conditions (cf. Scheme 72) did not provide any carbazole. Direct oxidation of the MOM-protected benzylic alcohol with DDQ[429] to the aldehyde **193.7** followed by several modifications of the remaining protective groups led to the protected triflate **193.8**.

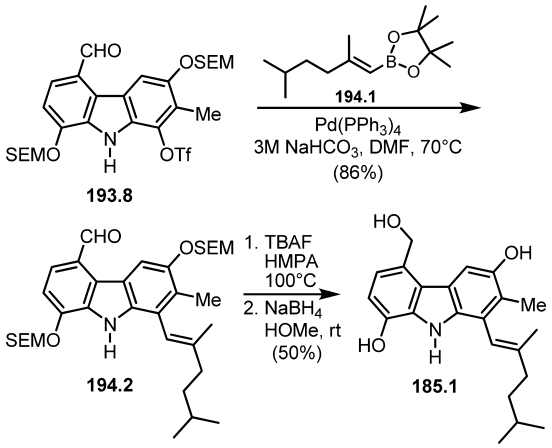
The side-chain at C-1 of carbazomadurin A (**185.1**) was introduced by Suzuki–Miyaura coupling of the triflate **193.8** and the boronate **194.1** (Scheme 194). The boronate **194.1** was obtained from 5-methylhexyne (**189.1**) in 3 steps using a sequence similar to the one developed by Knölker and co-workers for the synthesis of the analogous stannane **186.2** (depicted in Scheme 189). Finally, removal of the SEM groups and treatment of the resulting 3,8-dihydroxycarbazole-5-carbaldehyde with sodium borohydride led to carbazomadurin A (**185.1**) in 21 steps and 1.3% overall yield.

3.4. Trioxygenated Carbazole Alkaloids

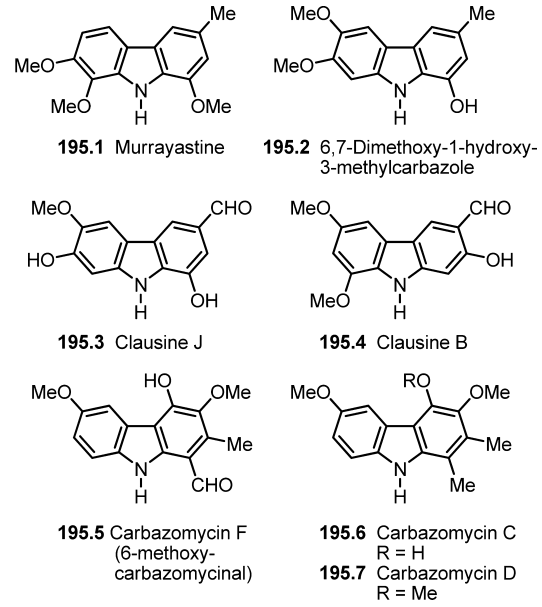
Various trioxygenated carbazoles with diverse oxygenation patterns have been isolated from natural sources. However, since there are only few members of this class of natural products known, this section is not divided into further subsections. The first trioxygenated carbazole was described by Furukawa et al. in 1986. Murrayastine (**195.1**), a 1,7,8-trioxygenated carbazole, was isolated from the stem bark of *Murraya euchrestifolia* Hayata collected in Taiwan (Scheme 195).[390] In 2001, Chowdhury, Mukherjee, and co-workers reported the isolation of 6,7-dimethoxy-1-hydroxy-3-methyl-

dx.doi.org/10.1021/cr200447s | Chem. Rev. 2012, 112, 3193–3328

Scheme 194



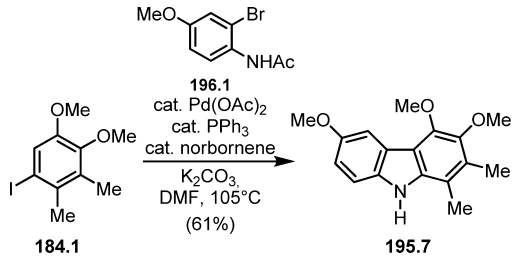
Scheme 195



carbazole (**195.2**) from the petroleum ether extract of the leaves of *Murraya koenigii*.[351] This natural product exhibited a high activity against Gram-positive and Gram-negative bacteria and against fungi. Prior to its isolation from nature, Saha and Chowdhury had obtained 6,7-dimethoxy-1-hydroxy-3-methylcarbazole (**195.2**) as an intermediate in the course of the total synthesis of koeniginequinone B (**198.3**).[430] Clausine J (**195.3**)[359] and clausine B[278] (**195.4**) (Scheme 195) were first obtained by Wu et al. from the methanol extract of the stem bark of *Clausena excavata* in 1996. Clausine B (**195.4**) showed inhibition of rabbit platelet aggregation and caused vasoconstriction. In 1986, Marumo and co-workers reported the isolation of carbazomycin F (6-methoxycarbazomycinal) (**195.5**) along with carbazomycin E (carbazomycinal) (**172.2**) (see Scheme 172) from the strain KCC U-0166 of a *Streptoverticillium* species (Scheme 195).[408] One year later, Nakamura and co-workers reported the isolation of carbazomycin C (**195.6**) and D (**195.7**) along with carbazomycin F (**195.5**) from the culture broth of *Streptoverticillium ehimense* 1051-MY 10.[409] Carbazomycin C (**195.6**) was shown to inhibit 5-lipoxygenase. In 1997, Knölker and Schlechtingen described an iron-mediated total synthesis of carbazomycin C (**195.6**) and D (**195.7**).[431]

In 2010, Catellani and co-workers described the total synthesis of carbazomycin D (**195.7**) using a one-pot palladium-catalyzed C−N- and C−C-bond formation approach (Scheme 196).[423] The same route had already been applied by

Scheme 196

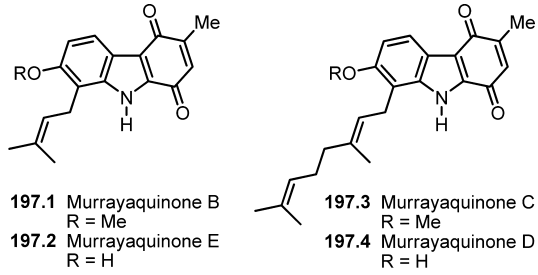


Catellani and co-workers to the total synthesis of carbazomycin A (**172.1**) (see Scheme 184). Iodination of 1,2-dimethoxy-3,4-dimethylbenzene (**175.3**), Knölker's precursor for the total synthesis of carbazomycin A (**172.1**) and B (**27.9**),[414] led to the iodoarene **184.1**. Coupling of **184.1** and the bromoacetanilide (**196.1**) provided carbazomycin D (**195.7**) in 61% yield.

3.5. Carbazole-1,4-quinone Alkaloids

3.5.1. Isolation from Natural Sources. Carbazolequinone alkaloids formally represent oxygenated carbazoles as well. Because of the different properties of a quinone in comparison to a dihydroxybenzene (or a dimethoxybenzene), the carbazolequinone alkaloids are discussed in a separate section.[432,433] Except clausenaquinone A (**198.4**) and **198.5**, all of the nine naturally occurring tricyclic carbazole-1,4-quinone alkaloids known so far have a 3-methylcarbazole-1,4-quinone framework and have been isolated from different *Murraya* plants (Schemes 197 and 198). In 1983, Furukawa and

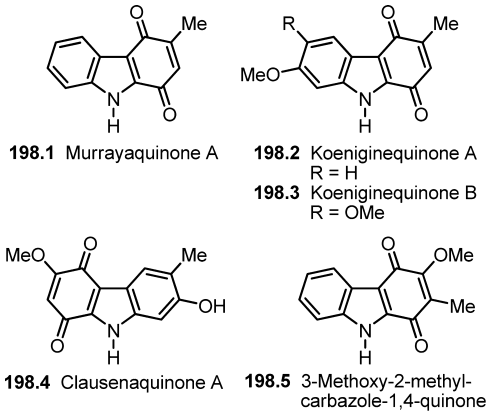
Scheme 197



co-workers isolated the first carbazole-1,4-quinone alkaloid murrayaquinone B (**197.1**) from the root bark of *Murraya euchrestifolia* Hayata.[200,201] In the following years, the same group isolated further carbazole-1,4-quinone alkaloids: the murrayaquinones A (**198.1**),[200,201] C (**197.3**),[200,201] D (**197.4**),[201] and E (**197.2**)[391] from the root or stem bark of the same plant. Except murrayaquinone A (**198.1**), all murrayaquinones have a hydroxy or methoxy substituent at C-7 and a prenyl or geranyl side chain at C-8. Murrayaquinone A (**198.1**) exhibited a significant cytotoxicity against SK-MEL-5 and Colo-205 cells. In contrast, the more lipophilic murrayaquinone B (**197.1**) showed only marginal inhibition of leukemia (CCRF-CEM) and was not cytotoxic against

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 198



several cell lines.[434] Moreover, murrayaquinone A (**198.1**) also showed cardiotonic activity.[435]

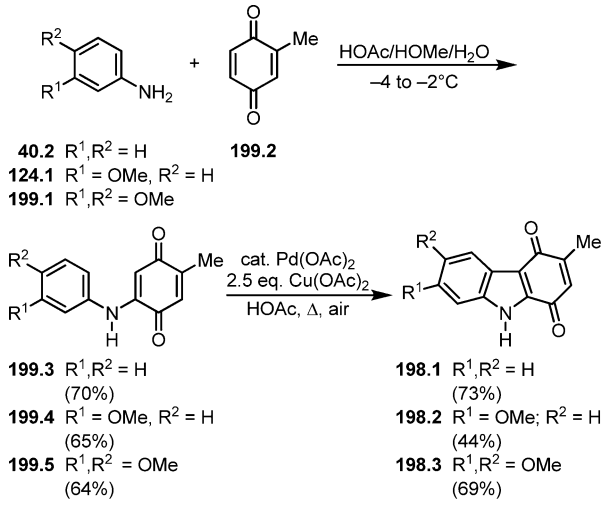
In 1998, Saha and Chowdhury isolated koeniginequinone A (**198.2**) and B (**198.3**) from the ethanol extract of the stem bark of *Murraya koenigii* Spreng (Scheme 198).[430] This was the first report of a carbazole-1,4-quinone alkaloid from this plant. In 1994, Wu et al. isolated clausenaquinone A (**198.4**) from the stem bark of a further plant of the Rutaceae family, *Clausena excavata*.[436] This alkaloid showed potent inhibitory activity of rabbit platelet aggregation induced by arachidonic acid, as well as cytotoxicity toward HCT-8, RPMI-7951, and TE671 tumor cells.[436] It should be noted that clausenaquinone A (**198.4**) is not a carbazole-1,4-quinone but a carbazole-5,8-quinone (based on numbering with the methyl group at C-3), which makes this natural product unique among the carbazolequinones. In 2011, Lumyong and co-workers isolated 3-methoxy-2-methylcarbazole-1,4-quinone **198.5** from the crude extract of *Streptomyces* CMU-JT005.[437] This compound had already been known as a synthetic intermediate[91−93,438−440] and has shown promising antituberculosis activity.[34,441]

Since the isolation of the first carbazole-1,4-quinone alkaloid from natural sources, many total syntheses have appeared for these natural products.[12] In 1994, Furukawa published the first review covering solely the isolation and synthesis of carbazole-1,4-quinone alkaloids.[432] Six years later, Fillion and co-workers published a comprehensive review on the isolation and synthesis of various natural and non-natural carbazole-1,4-quinone alkaloids.[433] In contrast to other sections, this section also covers formal total syntheses.

3.5.2. Total Synthesis of Carbazole-1,4-quinone Alkaloids. In 2003, Knölker and Reddy reported an efficient short route for the total synthesis of murrayaquinone A (**198.1**), koeniginequinone A (**198.2**), and koeniginequinone B (**198.3**) (Scheme 199).[442] This method involves a palladium(II)-catalyzed oxidative cyclization of the 5-arylamino-2-methyl-1,4-benzoquinones **199.3**−**199.5** as the key step. Using Musso's conditions,[443] the arylaminobenzoquinones **199.3**−**199.5** were obtained by addition of 2-methyl-1,4-benzoquinone (**199.2**) and the arylamines **40.2**, **124.1**, and **199.1**. Finally, palladium(II)-catalyzed cyclization of **199.3**−**199.5** afforded murrayaquinone A (**198.1**), koeniginequinone A (**198.2**), and koeniginequinone B (**198.3**).

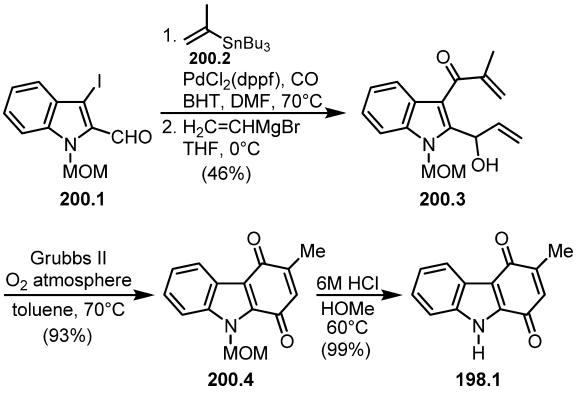
3.5.3. Total Synthesis of Murrayaquinone A. Choshi, Hibino, and co-workers described the total synthesis of murrayaquinone A (**198.1**) by a ring-closing metathesis of a 2,3-diallyl-substituted indole under an oxygen atmosphere

Scheme 199



(Scheme 200).[444] Palladium-catalyzed vinylcarbonylation of the literature known *N*-methoxymethyl-2-formyl-3-iodoindole

Scheme 200



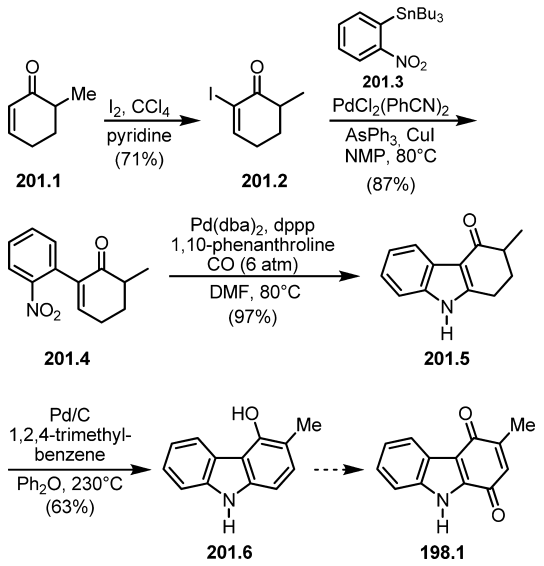
(**200.1**)[67] followed by addition of vinylmagnesium bromide led to the substituted indole **200.3**, the precursor for the ring-closing metathesis. Heating of **200.3** in the presence of Grubbs' second-generation catalyst under an oxygen atmosphere led to the desired cyclization with concomitant oxidation of the hydroxy group at C-2 of the carbazole core. Unfortunately, the authors did not mention the amount of Grubbs' catalyst used. Cleavage of the methoxymethyl protecting group at the nitrogen atom finally furnished murrayaquinone A (**198.1**).

3.5.4. Formal Synthesis of Murrayaquinone A. In 1988, Martin and Moody described the transformation of murrayafoline-A (**20.1**) into murrayaquinone A (**198.1**) by methyl ether cleavage and subsequent oxidation with Fremy's salt ($K_2[ON(SO_3)_2]$).[445] Thus, all syntheses of murrayafoline-A (**20.1**) also constitute formal total syntheses of murrayaquinone A (**198.1**).

Scott and Söderberg reported a formal total synthesis of murrayaquinone A (**198.1**) from the tetrahydrocarbazol-4-one **201.5** via 4-hydroxy-3-methylcarbazole (**201.6**) (Scheme 201).[446] The key steps are an intermolecular Stille cross-coupling reaction and a palladium-catalyzed reductive N-heteroannulation. Iodination of 6-methyl-2-cyclohexenone (**201.1**) afforded the corresponding 2-iodo derivative **201.2**. Stille cross-coupling of the vinyl iodide **201.2** and the arylstannane **201.3** led to the annulation precursor **201.4**.

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 201



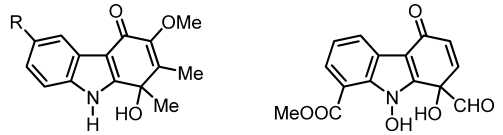
Reductive cyclization of the 2-nitrotetrahydrobiphenyl **201.4** afforded almost quantitatively the tetrahydrocarbazolone **201.5**. Dehydrogenation of **201.5** with palladium on activated carbon in a mixture of diphenyl ether and 1,2,4-trimethylbenzene at 230 °C afforded 4-hydroxy-3-methylcarbazole (**201.6**), a precursor of murrayaquinone A (**198.1**).[446] Oxidation of the 4-hydroxycarbazole **201.6** with Fremy's salt ($K_2[ON(SO_3)_2]$) using Matsuo and Ishida's procedure[447,448] is known to afford murrayaquinone A (**198.1**) in good yield.

In 2011, Saha and co-workers described the oxidation of 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones to carbazole-1,4-quinones with solid-supported ceric ammonium nitrate (CAN–SiO_2).[449] This procedure was applied to the total synthesis of murrayaquinone A (**198.1**) and koeniginequinone A (**198.2**).

3.6. Carbazole-1,4-quinol Alkaloids

In 1988, Nakamura and co-workers reported the isolation of carbazomycin G (**202.1**) and H (**202.2**), new members of the carbazomycin family with a carbazole-1,4-quinol framework, from the culture broth of *Streptoverticillium ehimense* (Scheme 202).[450] Although these compounds have a stereogenic center

Scheme 202



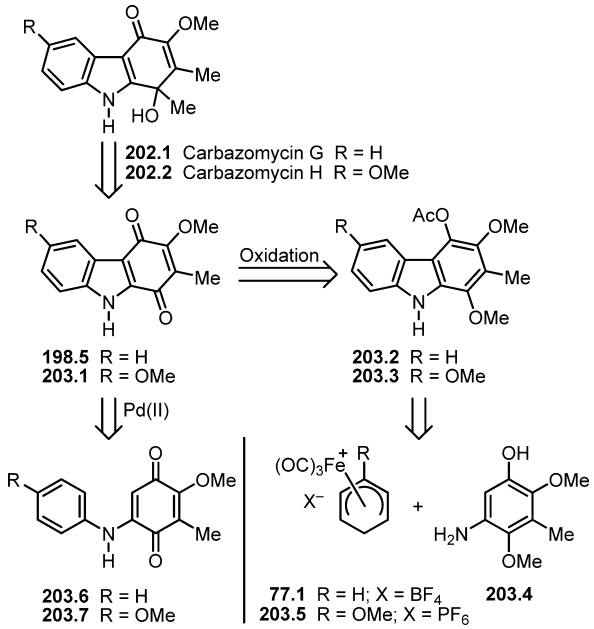
202.1 Carbazomycin G R = H
202.2 Carbazomycin H R = OMe
202.3 Coproverdine

at C-1, they were obtained from nature in racemic form. Carbazomycin G showed a moderate antifungal activity against *Trichophyton* species.

In 2002, Munro and co-workers isolated coproverdine (**202.3**), a further carbazole-1,4-quinol alkaloid, during a bioassay-directed fractionation of a New Zealand ascidian.[451] Although this alkaloid was isolated from nature in optically active form ($[\alpha]_D^{20}$ −8.0, c 0.36, HOEt), its absolute configuration is not known. Coproverdine (**202.3**) showed cytotoxic activity against a variety of murine and human tumor cell lines. Thus, coproverdine (**202.3**) was responsible for the antitumor activity observed for the crude extract.

Knölker and Reddy described two different synthetic approaches to the carbazomycins G (**202.1**) and H (**202.2**) using the carbazole-1,4-quinones **198.5** and **203.1** as central intermediates.[1] For the iron-mediated synthesis of the carbazomycins G (**202.1**) and H (**202.2**), the compounds **198.5** and **203.1** are easily obtained by oxidation of the *O*-acetylcarbazoles **203.2** and **203.3**, which in turn are accessible by coupling of the arylamine **203.4** with the corresponding iron complex salts **77.1** and **203.5**.[438,440] Alternatively, the carbazole-1,4-quinones **198.5** and **203.1** can be obtained via a palladium(II)-catalyzed oxidative cyclization of the corresponding arylaminobenzo-1,4-quinones **203.6** and **203.7** (Scheme 203).[91] Hibino and co-workers described a total

Scheme 203



synthesis of carbazomycin G (**202.1**) using an electrocyclic reaction as the key step.[439]

3.7. Carbazole-3,4-quinone Alkaloids

3.7.1. Isolation from Natural Sources. In the early 1990s, Seto and co-workers reported the isolation of a series of carbazole-3,4-quinone alkaloids from various *Streptomyces* species.[452] In 1993, carquinostatin A (**183.1**), the first example of a carbazole-3,4-quinone alkaloid, was isolated from *Streptomyces exfoliates* 2419-SVT2 (Scheme 204). This alkaloid was shown to be a potent neuronal cell-protecting substance that also exhibits free radical scavenging activity. Carquinostatin A (**183.1**) was isolated from nature in enantiopure form, and the absolute stereochemistry of the stereogenic center at C-2′ was assigned to be *R* by Mosher's method. Although carquinostatin A (**183.1**) was obtained in enantiopure form, the optical rotation could not be measured due to its strong absorption of visible light. One year later, carquinostatin B (**204.1**), a further 6-prenylcarbazole-3,4-quinone alkaloid, was isolated from the same *Streptomyces* species.[453,454] This alkaloid was shown to be a hydroxycarquinostatin A with potent neuronal cell-protecting activity. Carquinostatin B (**204.1**) was

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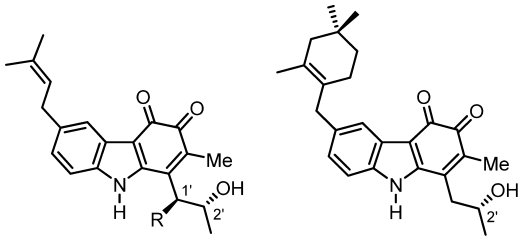
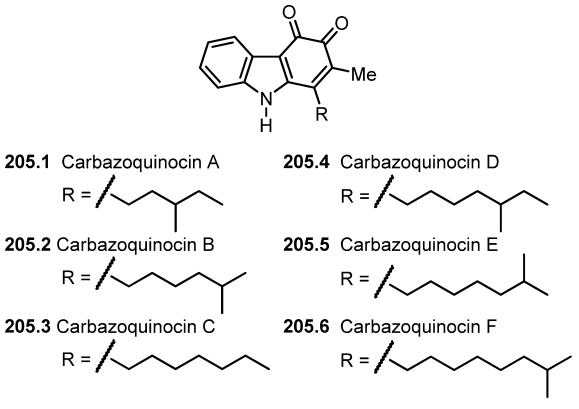
Scheme 204



obtained from nature in enantiopure form. However, no optical rotation value was reported because, like carquinostatin A (**183.1**), carquinostatin B (**204.1**) exhibited a strong absorption of visible light. In analogy to carquinostatin A (**183.1**), the absolute configuration at C-2′ was assigned to be *R*. On the basis of nuclear Overhauser effects (NOE) studies of the acetonide of carquinostatin B, the absolute configuration at C-1′ was assigned to be *S*. In 1998, Laatsch and co-workers reported the isolation of carquinostatin A (**183.1**) and B (CS-79B) (**204.1**) from a *Streptomyces tendae* bald mutant, generated by the addition of acriflavine.[455] These authors also reported an antibacterial activity of the aforementioned alkaloids. In 1995, lavanduquinocin (**204.2**), a structurally intriguing carbazole-3,4-quinone alkaloid with a monoterpenoid *β*-cyclolavandulyl side-chain at C-6, was isolated from *Streptomyces viridochromogenes* 2942-SVS3.[456] Lavanduquinocin (**204.2**) exhibited a strong neuronal cell-protecting activity due to its antioxidative activity. Similar to carquinostatin A (**183.1**), lavanduquinocin (**204.2**) did not show any optical rotation due to its strong absorption. However, based on Mosher's method, the absolute stereochemistry at C-2′ was determined to be *R*.[456]

Further carbazole-3,4-quinone alkaloids, the carbazoquinocins A (**205.1**), B (**205.2**), C (**205.3**), D (**205.4**), E (**205.5**), and F (**205.6**), were isolated by Seto and co-workers from *Streptomyces violaceus* 2448-SVT2 in 1995 (Scheme 205).[457]

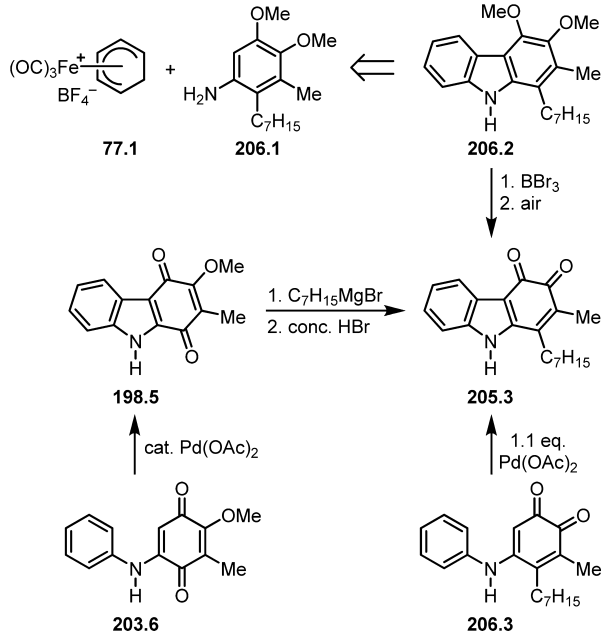
Scheme 205



These alkaloids differ in the alkyl substitution at C-1 and show a strong inhibitory activity against lipid peroxidation induced by free radicals. Carbazoquinocin A (**205.1**) and D (**205.4**) have a stereogenic center in the alkyl side-chain of C-1 and were shown to be optically active. The absolute configuration was not assigned during isolation. In 1996, Shin and Ogasawara described the enantioselective synthesis of (−)-(*S*)-carbazoquinocin A [(−)-(*S*)-**205.1**] and (−)-(*S*)-carbazoquinocin D [(−)-(*S*)-**205.4**].[458] Because of the deep coloring, they were unable to measure the exact optical rotation of the synthetic material, but it was established that the sign of the optical rotation was the same for both synthetic (−)-(*S*)-**205.1** and natural carbazoquinocin A (**205.1**). Thus, natural carbazoquinocin A (**205.1**) most likely has an (*S*)-configuration. However, because of the low amounts of natural carbazoquinocin D (**205.4**), such an assignment could not be made for **205.4**.

3.7.2. Total Synthesis of Carbazoquinocin C. In 1997, Hibino and co-workers described the total synthesis of the carbazoquinocins B−F (**205.2**−**205.6**) using an electrocyclization as key step (see Scheme 6).[67] In the same year, Knölker and Fröhner described the total synthesis of carbazoquinocin C (**205.3**) based on an iron-mediated approach (Scheme 206).[459]

Scheme 206



In the following years, Knölker and co-workers also developed palladium-mediated and palladium-catalyzed syntheses of carbazoquinocin C (**205.3**).[92,93,460] For the iron-mediated approach, the 3,4-dimethoxycarbazole **206.2** was synthesized. Electrophilic aromatic substitution of the arylamine **206.1** with the iron-complex salt **77.1** and cyclization by air led to a 4*a*,9*a*-dihydrocarbazole−tricarbonyliron complex. Subsequent demetalation and aromatization provided the 3,4-dimethoxycarbazole **206.2**. Cleavage of both methyl ethers with boron tribromide followed by oxidation in air led to carbazoquinocin C (**205.3**) in 5 steps and 42% overall yield based on the iron-complex salt **77.1**. Reaction of aniline (**40.2**) and 2 equiv of 2-methoxy-3-methyl-1,4-benzoquinone led to the anilinobenzoquinone **203.6**, the precursor for Knölker's palladium-catalyzed synthesis of carbazoquinocin C (**205.3**). Palladium-catalyzed oxidative cyclization of the anilinobenzoquinone **203.6** afforded the carbazolequinone **198.5**. The carbazolequinone **198.5** has also been an intermediate in Knölker's total synthesis of carbazomycin G (**202.1**) (see Scheme 203).[91] More recently, the carbazolequinone **198.5** has been identified as a natural product by Laatsch, Lumyong, and co-workers.[437] Addition of heptylmagnesium chloride to **198.5** and treatment of the intermediate quinol with hydrobromic acid provided carbazo-

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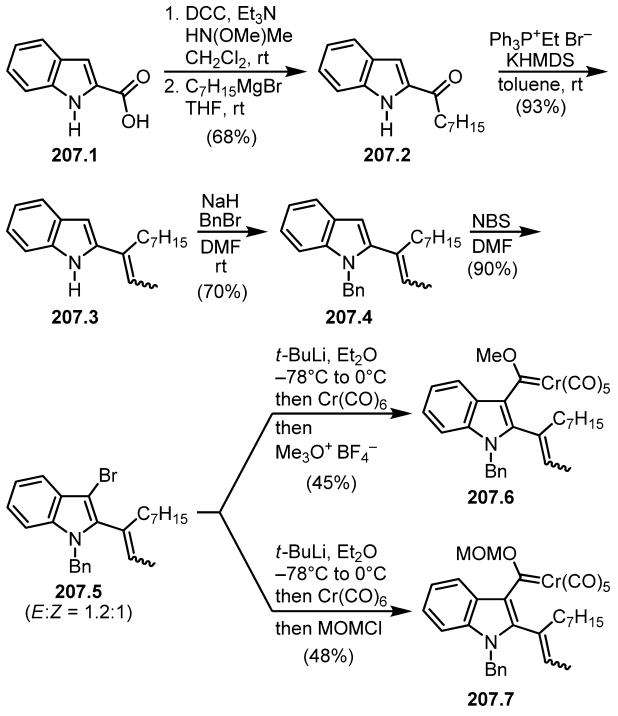
quinocin C (**205.3**). The palladium-catalyzed route provided carbazoquinocin C (**205.3**) in 4 steps and 36% overall yield.[92,93] The anilino-*ortho*-quinone **206.3** was used as precursor for Knölker's palladium-mediated synthesis of carbazoquinocin C (**205.3**).[460] Oxidative cyclization of **206.3** using stoichiometric amounts of palladium(II) acetate led directly to carbazoquinocin C (**205.3**). The palladium-mediated approach provided natural **205.3** in 5 steps and 21% overall yield.

In 2000, Aygün and Pindur reported the total synthesis of carbazoquinocin C (**205.3**) starting from *N*-(benzenesulfonyl)-indole.[461−463] The key step of their methodology is a cyclization of a 2-vinylindole with oxalyl chloride. Carbazoquinocin C (**205.3**) was obtained in 3 steps and 28−34% overall yield. The same procedure was applied to the synthesis of a range of carbazole-3,4-quinones for biological studies.

3.7.3. Total Synthesis of Carbazoquinocin C via a Fischer Carbene. Rawat and Wulff reported a total synthesis of carbazoquinocin C (**205.3**) starting from indole-2-carboxylic acid (**207.1**) (Scheme 207).[464] This methodology involves a

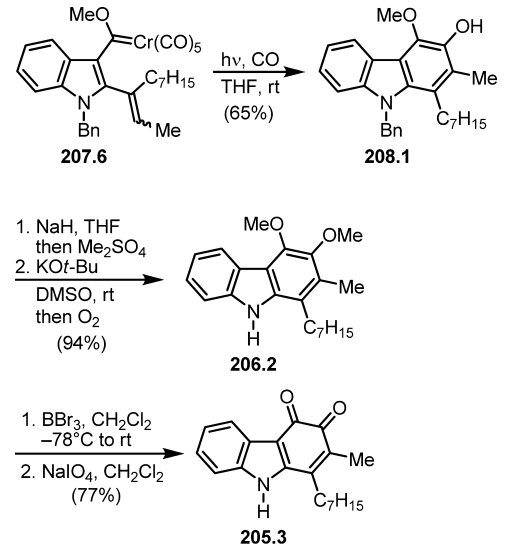
Scheme 207



photoinduced *o*-benzannulation of the Fischer carbene complexes **207.6** and **207.7**. The fully functionalized 2-vinylindol-3-ylcarbene complexes **207.6** and **207.7** required for the synthesis of carbazoquinocin C (**205.3**) were prepared from the commercially available indole-2-carboxylic acid (**207.1**). The heptyl-2-indolyl ketone **207.2** was obtained from the acid **207.1** via addition of a Grignard reagent to the corresponding Weinreb amide. After Wittig olefination of the indolyl ketone **207.2**, the 2-vinylindole **207.3** was protected to afford the corresponding *N*-benzyl derivative **207.4**, which on bromination led to the carbene precursor **207.5**. Using the standard Fischer procedure, the 3-bromo derivative **207.5** was transformed to the carbene complexes **207.6** and **207.7** in moderate yields.

Without purification, the carbene complex **207.6** was subjected to a photolytically induced benzannulation under carbon monoxide atmosphere to give the *N*-benzylcarbazole **208.1** (Scheme 208). After O-methylation, the nitrogen atom

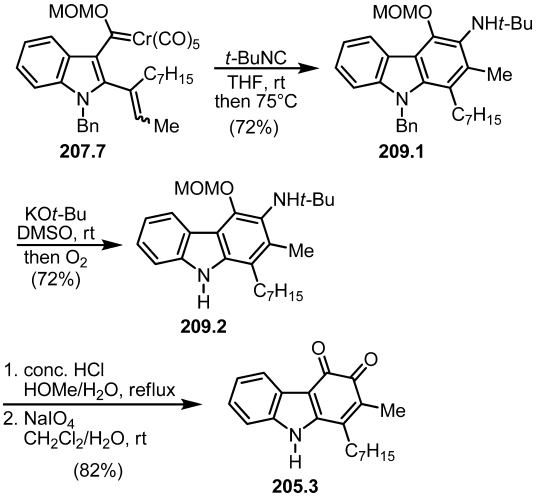
Scheme 208



was deprotected with potassium *tert*-butoxide in DMSO in the presence of oxygen to afford the 3,4-dimethoxycarbazole **206.2**. Compound **206.2** has already been a precursor in Knölker's iron-mediated synthesis of carbazoquinocin C (**205.3**) (Scheme 206).[459] Finally, following a two-step sequence of demethylation with boron tribromide and oxidation using sodium periodate, the 3,4-dimethoxycarbazole **206.2** was transformed to carbazoquinocin C (**205.3**).[464]

An alternative synthesis of carbazoquinocin C (**205.3**) was achieved by thermal benzannulation of the carbene complex **207.7** (Scheme 209). Thus, reaction of carbene complex **207.7** with *tert*-butylisonitrile in tetrahydrofuran at reflux gave the *N*-benzyl carbazole **209.1** in 72% yield. After debenzylation, the resulting (*tert*-butylamino)carbazole **209.2** was subjected to cleavage of the MOM group followed by oxidation of the intermediate 4-hydroxycarbazole with sodium periodate to

Scheme 209



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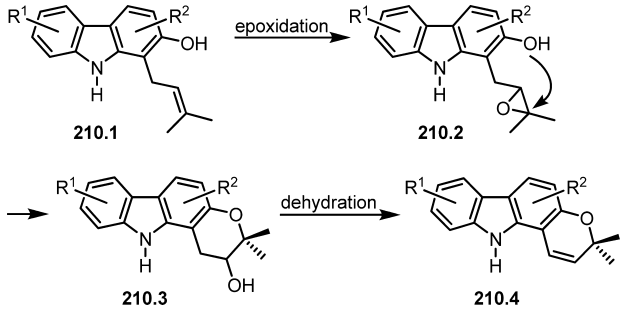
afford carbazoquinocin C (**205.3**).[464] In 2007, Hibino and co-workers reported an enantioselective synthesis of deprenyl carquinostatin A and de-*β*-cyclolavandulyl lavanduquinocin using a Lipase QLM (Meito)-catalyzed enantioselective acetylation of the racemic compounds.[465]

4. PYRANOCARBAZOLE ALKALOIDS

This section covers all pyranocarbazole alkaloids obtained from higher plants. It is divided into several sections based on the mode of pyran annulation. The pyran ring in this class of alkaloids probably derives from an oxidative cyclization of an *o*-hydroxyprenyl- or an *o*-hydroxygeranylcarbazole. The biosynthetic mechanism is unknown. One might speculate that the initial reaction is an epoxidation of the double bond of the prenyl or geranyl group followed by nucleophilic attack of the phenolic hydroxy group and elimination of water (Scheme 210). The co-occurrence of euchrestine-C (**163.1**), the

Scheme 210



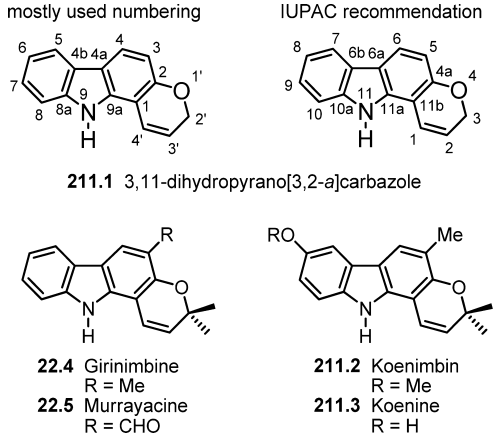
corresponding epoxide euchrestine-E (**163.3**), and pyrayafoline D (**220.3**) in the same natural source supports this biosynthetic hypothesis.

4.1. Pyrano[3,2-*a*]carbazole Alkaloids

The carbazoles in the present section are all derivatives of 3,11-dihydropyrano[3,2-*a*]carbazole (**211.1**). The positions of substituents are usually assigned using a non-IUPAC nomenclature (Scheme 211). The carbon atoms and the nitrogen atom of the carbazole part are numbered as in the nonannulated case (1−9), and the oxygen atom and the carbon atoms of the annulated pyran ring are designated 1′−4′.

4.1.1. Isolation from Natural Sources. Girinimbine (**22.4**), the first pyrano[3,2-*a*]carbazole alkaloid from natural

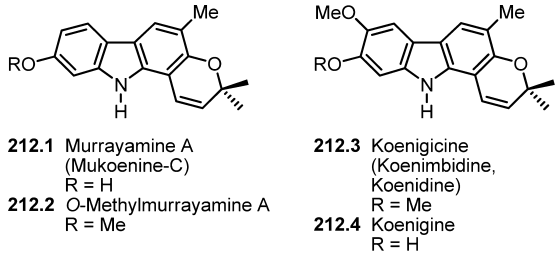
Scheme 211



sources, was isolated by Chakraborty et al. in 1964 from the stem bark of *Murraya koenigii* (Scheme 211).[3] Eight years later, Joshi et al. reported the isolation of the same compound from the roots of a different plant, *Clausena heptaphylla*.[466] On the basis of chemical degradation studies, Chakraborty et al. proposed that the pyran ring and the aromatic methyl group in girinimbine are located at different benzene rings of the carbazole framework.[3] In 1969, Dutta and Quasim proposed that in girinimbine (**22.4**) the pyran ring and the methyl group are present in the same benzene ring of the carbazole framework.[467] This structural assignment was based on NMR studies and additionally was in agreement with Joshi's biogenetic considerations.[466,468] Independently, Chakraborty and co-workers reported the isolation of murrayacine (**22.5**), a formyl analogue of girinimbine, from two different natural sources, *Murraya koenigii*[469,470] and *Clausena heptaphylla*.[471] In 1968, Narasimhan et al. reported the isolation of koenimbin (**211.2**) from the fruits of *Murraya koenigii*.[472] One year later, Kapil and co-workers isolated the same alkaloid from the leaves of the same plant.[190] Koenine (**211.3**), an *O*-demethylkoenimbine, was obtained in 1970 by Narasimhan et al. from the leaves of *Murraya koenigii*.[473]

In 1991, Wu reported the isolation of murrayamine A (**212.1**), a 7-hydroxygirinimbine, from the leaves of a different *Murraya* plant, *Murraya euchrestifolia* (Scheme 212).[474] Two

Scheme 212



years later, Furukawa and co-workers isolated the same carbazole alkaloid from the acetone extract of the roots of *Murraya koenigii* and named it mukoenine-C.[203] *O*-Methylmurrayamine A (**212.2**) was isolated by Nakatani and co-workers in 2003 from the leaves of *Murraya koenigii*.[475] This alkaloid has shown radical scavenging activity against the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. Prior to this report, **212.2** has been known as a synthetic derivative of murrayamine A, which was obtained by O-methylation of **212.1** with diazomethane.[474] In 1969, Kapil and co-workers isolated koenigicine (**212.3**), a 6,7-dimethoxygirinimbine, from the leaves of *Murraya koenigii*.[190] Only one year later, Joshi and Narasimhan independently isolated the same alkaloid from the same natural source. Joshi called the compound koenimbidine,[468] whereas Narasimhan et al. named it koenidine.[473] During their investigation Narasimhan et al. also isolated koenine (**211.3**) (see Scheme 211) and koenigine (**212.4**) along with koenidine (koenigicine) (**212.3**).[473] These alkaloids differ in the oxygen substitution at C-6 and C-7.

A further 6,7-dimethoxy derivative of girinimbine (**22.4**) was isolated in 2008 by Banerji and co-workers. The new natural product was named kurryam (**213.1**) and differs from koenigicine (**212.3**) by an additional hydroxy group at C-4 (Scheme 213).[476] Kurryam (**213.1**) was obtained from the hexane extract of the seeds of *Murraya koenigii* Spreng. along with the known koenimbin (**211.2**) and koenigine (**212.4**).

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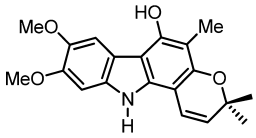
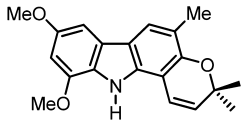
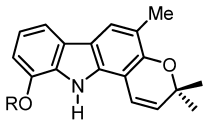
Scheme 213



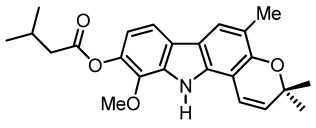
213.1 Kurryam



213.2 Mukonicine



213.3 Mupamine R = Me
213.4 Clauraila B R = H

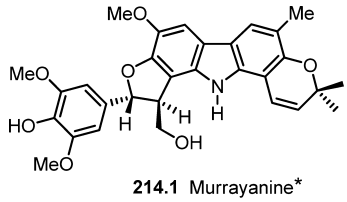


213.5 7-Isovaleryloxy-8-methoxygirinimbine

The same authors also reported an antidiarrheal activity of kurryam (**213.1**) and related alkaloids in rats shortly after the isolation from natural sources.[477] In 1983, Ganguly and co-workers reported the isolation of mukonicine (**213.2**), a 6,8-dimethoxygirinimbine, from the ethanol extract of the leaves of *Murraya koenigii*.[478] Mupamine (**213.3**), the 8-methoxy derivative of girinimbine (**22.4**), was isolated by Mester and Reisch in 1977 from the methanol extract of the root bark of *Clausena anisata*.[479] The corresponding 8-hydroxycarbazole was isolated in 2011 by Yenjai and co-workers from the roots of *Clausena harmandiana* and named clauraila B (**213.4**).[374] Tripathi and co-workers described 7-isovaleryloxy-8-methoxygirinimbine (**213.5**), another oxygenated girinimbine derivative, in 2006.[480] This compound was obtained from the leaves of *Murraya koenigii*, collected in Uttar Pradesh in India. However, no spectroscopic data have been provided for **213.5**.

In 2003, Hao et al. isolated an optically active carbazole alkaloid from the ethanol extract of the aerial parts of *Murraya koenigii* collected in China and named it "murrayanine" ($[\alpha]_D^{25}$ = +8.0, c 0.74, HOMe). However, since 1965, 3-formyl-1-methoxycarbazole (**20.3**) (see Scheme 53), isolated by Chakraborty and co-workers from the stem bark of the same plant, has been known as murrayanine.[4,271] Therefore, Hao's murrayanine is now called "murrayanine*" (**214.1**) (Scheme 214). In addition to the pyran ring, this alkaloid also shows an

Scheme 214

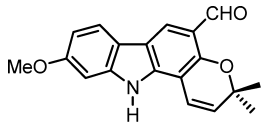


214.1 Murrayanine*

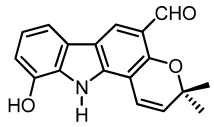
annulated furan ring featuring a unique trioxygenated phenyl substituent and a hydroxymethyl side-chain.[481] This structural motif is not found in any other known carbazole alkaloid. The constitution and relative stereochemistry were assigned based on NMR experiments. The absolute configuration has not been assigned yet.

In 1990, Lange and co-workers isolated 7-methoxymurrayacine (**215.1**) from the ethanol extract of the roots of *Murraya siamensis*.[299] In Thailand, the root powder of this plant mixed with water is used for the treatment of eye sores, snakebites, and tuberculosis. Six years later, clauszoline-G (**24.5**), the 8-hydroxy-derivative of murrayacine (**22.5**), was obtained by Ito et al. from the acetone extract of the stem bark of *Clausena excavata* collected in Singapore.[403] In 1974, Chakraborty et al. isolated heptazolidine (**215.2**) from a different *Clausena* plant, *Clausena heptaphylla*.[482] In heptazolidine (**215.2**) the annulated pyran ring and the C_1 side-chain, which is characteristic for carbazole alkaloids isolated from higher plants, are located at different benzene rings of the carbazole core. Ten years later, Chowdhury and co-workers isolated heptazolicine (**215.3**) from the roots of the same natural source.[483] Heptazolicine (**215.3**) features the same substitution pattern as clauszoline-G (**24.5**) but contains a saturated pyran ring.

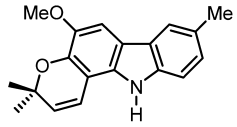
Scheme 215



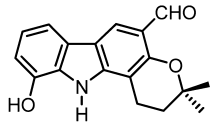
215.1 7-Methoxymurrayacine



24.5 Clauszoline-G



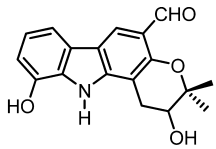
215.2 Heptazolidine



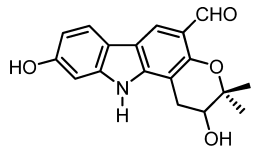
215.3 Heptazolicine

In addition to the alkaloids described above, a variety of pyrano[3,2-*a*]carbazoles with an oxygenated pyran ring have been obtained from natural sources (Scheme 216). In 1996, Ito

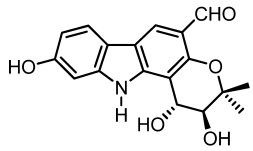
Scheme 216



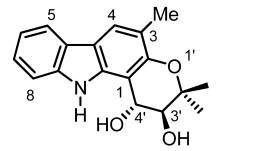
216.1 Clauszoline-E



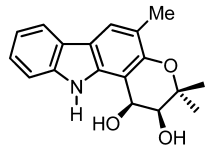
216.2 Clausine-T



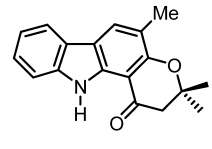
216.3 Clausine-W



216.4 (–)-*trans*-Dihydroxygirinimbine



216.5 *cis*-Dihydroxygirinimbine



216.6 Euchrestifoline

et al. isolated racemic clauszoline-E (**216.1**) from the acetone extract of the stem bark of *Clausena excavata* collected in Singapore.[403] One year later, Wu et al. reported the isolation of clausine-T (**216.2**) and clausine-W (**216.3**) from the acetone extract of the root bark of the same plant collected in Taiwan.[484] Although clausine-T (**216.2**) ($[\alpha]_D$ = −82.1, c 0.0341, HOMe) and clausine-W (**216.3**) ($[\alpha]_D$ = −3.41, c 1.002, HOMe) were obtained from nature in optically active

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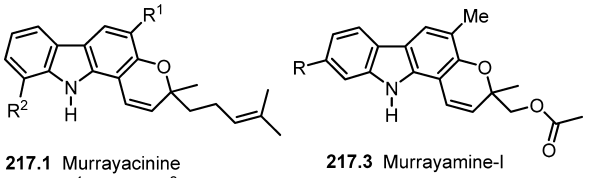
form, their absolute configurations are still unknown. In 1985, Furukawa et al. isolated (−)-*trans*-dihydroxygirinimbine (**216.4**) from the root bark of *Murraya euchrestifolia* Hayata collected in Taiwan. This natural product was also obtained in optically active form ($[\alpha]_D$ = −4, HOMe), but the absolute configuration was not assigned during isolation (Scheme 216).[485] Twenty-five years later Knölker and co-workers described the enantioselective total synthesis of (−)-*trans*-dihydroxygirinimbine (**216.4**) and assigned the absolute configuration as (3′*S*,4′*R*).[486] The diastereoisomeric *cis*-dihydroxygirinimbine (**216.5**) was isolated by Furukawa as well. In contrast to (−)-*trans*-dihydroxygirinimbine (**216.4**), *cis*-dihydroxygirinimbine (**216.5**) was obtained as a racemate from the extract of the dried roots of *Murraya koenigii* collected in Bangladesh.[486,487] Euchrestifoline (**216.6**) was described by Wu et al. in 1996 in a report on phytochemical studies.[488] The natural product **216.6** was obtained from the leaves of *Murraya euchrestifolia* collected in spring.

In 1974, Chakraborty et al. reported the isolation of murrayacinine (**217.1**) (Scheme 217), a formyl analogue of

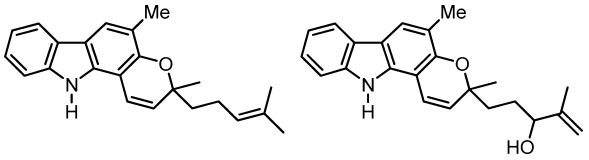
Scheme 217



217.1 Murrayacinine
R^1 = CHO; R^2 = H
217.2 Murrayamine-B
R^1 = Me; R^2 = OMe

217.3 Murrayamine-I
R = OH
217.4 Murrayamine-K
R = H

Scheme 218



218.1 (+)-Mahanimbine
23.2 (±)-Mahanimbine

218.2 Mahanimboline
(Murrayamine-C*)

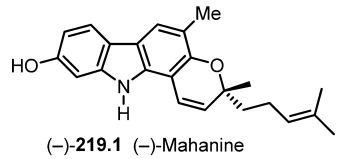
(±)-mahanimbine (**23.2**) (see Scheme 218) from the stem bark of *Murraya koenigii* Spreng. Because of the low amounts of material, it was impossible to determine the optical activity.[489] Murrayamine-B (**217.2**) was obtained as a racemate by Wu in 1991 from the leaves of *Murraya euchrestifolia* collected in Taiwan.[474] Five years later, the same group reported the isolation of two further compounds with the same basic skeleton. Murrayamine-I (**217.3**) and murrayamine-K (**217.4**) were isolated from the acetone extract of the leaves of the same *Murraya* plant collected in November.[490]

In 1966, Chakraborty et al. isolated (+)-mahanimbine (**218.1**) from *Murraya koenigii* Spreng (Scheme 218).[491] Two years later, Narasimhan et al. isolated the same alkaloid from the fruits of the same plant and corrected Chakraborty's structural assignment.[194,472] Although this alkaloid was obtained in optically active form ($[\alpha]_D$ = +52), the absolute configuration is still unknown. Later, two groups independently isolated racemic mahanimbine (**23.2**) from two further *Murraya* plants, *Murraya euchrestifolia*[201] and *Murraya siamensis*.[307] Recently, an acetylcholinesterase inhibitory potential has been described for mahanimbine (**23.2**) or (**218.1**) and a *Murraya koenigii* extract.[492] The authors did not specify whether racemic or enantiopure mahanimbine was tested.

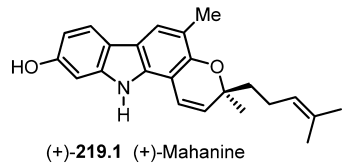
In 1979, Chakraborty et al. isolated a pyranocarbazole from the root bark of *Murraya koenigii*, assigned the structure of **218.2** to that alkaloid, and named it mahanimboline (**218.2**).[493] Wu, Furukawa, and co-workers reported in 1992 the isolation of a compound with the same structure from the fruits of *Murraya euchrestifolia* collected in Taiwan and named it murrayamine-C (**218.2**).[494] We will refer to this compound as "murrayamine-C*" because, one year before, Wu had already named a structurally different carbazole murrayamine-C (**221.1**) (see Scheme 221).[474] Murrayamine-C* (**218.2**) was obtained as optically inactive compound. A comparison of the spectroscopic data of mahanimboline (**218.2**) with those of murrayamine-C* (**218.2**) showed that they are structurally different compounds. Therefore, at least one of these alkaloids must have a different structure, which still has to be assigned.

In 1970, Narasimhan et al. isolated the optically active (−)-mahanine [(−)-**219.1**] ($[\alpha]_D$ = −24.4), a 7-hydroxymahanimbine, from the leaves of *Murraya koenigii* collected on the campus of University of Poona (Scheme 219).[194,473] The

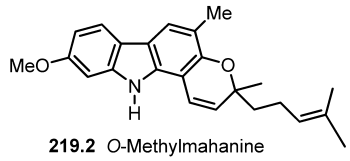
Scheme 219



(−)-**219.1** (−)-Mahanine



(+)-**219.1** (+)-Mahanine



219.2 *O*-Methylmahanine

enantiomer, (+)-mahanine [(+)-**219.1**], was obtained three decades later by Nakatani and co-workers from the dichloromethane extract of the leaves of *Murraya koenigii* collected in Malaysia ($[\alpha]_D^{25}$ = +7.6, c 5.38, $CHCl_3$).[495] In 1999, Ramsewak et al. conducted a bioassay-guided fractionation of the acetone extract of the leaves of *Murraya koenigii* collected in a greenhouse at Michigan State University. In the course of these studies, mahanine (**219.1**) was obtained as well. The authors did not comment on the optical activity.[496] Wu described the isolation of (+)-mahanine [(+)-**219.1**] from a different *Murraya* plant, *Murraya euchrestifolia* ($[\alpha]_D$ = +34, c 2.0, $CHCl_3$). The CD spectrum of Wu's (+)-mahanine [(+)-**219.1**] showed a positive Cotton effect in the region of 265−276 nm due to the styrene chromophore. On the basis of Crabbé and Klyne's work on the circular dichroism of aromatic compounds,[497] an (*S*) configuration has been assigned to (+)-mahanine [(+)-**219.1**]. Thus, (−)-mahanine [(−)-**219.1**]

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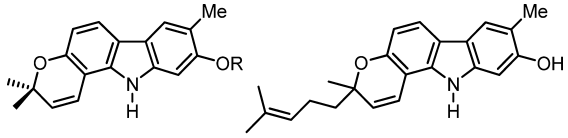
probably has an *R*-configuration.[474] In 2002, (+)-mahanine [(+)-**219.1**] was also isolated by Nakahara during a bioactivity-guided fractionation of the methanol extract of the twigs of *Micromelum minutum*.[498] Mahanine (**219.1**) has shown a wide range of biological activities, including cytotoxicity against human leukemia cells (HL60),[498−500] (U937),[501] antimutagenicity against heterocyclic amines such as 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-1), antimicrobial activity against *Bacillus cereus* and *Staphylococcus aureus*,[498] and inhibition of growth of prostate cancer cells.[502]

O-Methylmahanine (**219.2**) was obtained by Nakatani and co-workers in 2003 from the dichloromethane extract of the leaves of *Murraya koenigii*.[475] Although this alkaloid was isolated in optically active form ($[\alpha]_D^{25}$ = +3.0, c 0.10, $CHCl_3$), the absolute configuration is still unknown. *O*-Methylmahanine (**219.2**) showed radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals.[475] Prior to that report, the same compound was synthesized in racemic form as DL-*O*-methylmahanine.[503]

In 1986, Furukawa et al. reported the isolation of pyrayafoline A (**220.1**) from the stem bark of *Murraya euchrestifolia* (Scheme 220).[390,393] Five years later, the same

Scheme 220



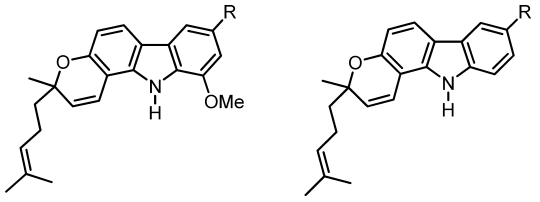
220.1 Pyrayafoline A R = Me
220.2 Pyrayafoline C R = H
220.3 Pyrayafoline D (Isomahanine)

group obtained two further pyrano[3,2-*a*]carbazole alkaloids from the same natural source, pyrayafoline C (**220.2**) and the optically inactive pyrayafoline D (**220.3**).[393] Reisch et al. reported the isolation of pyrayafoline D (**220.3**) from the methanol extract of the fruits of *Murraya koenigii* and named it isomahanine (**220.3**). Reisch and co-workers did not report whether or not **220.3** was obtained as an optically active compound.[399] In 2003, Nakatani and co-workers reported the isolation of pyrayafoline D (isomahanine) (**220.3**) from the dichloromethane extract of the leaves of *Murraya koenigii* in optically active form ($[\alpha]_D^{25}$ = −38.2, c 0.22, $CHCl_3$). The absolute configuration of (**220.3**) has not been assigned yet.[475] Pyrayafoline D (isomahanine) (**220.3**) showed radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals[475] and significant cytotoxicity against human leukemia cells HL60.[500]

In 1991, Wu et al. isolated the optically inactive murrayamine-C (**221.1**) from the leaves of *Murraya euchrestifolia* (Scheme 221).[474] The structure was assigned based on NMR experiments and the mass fragment ions. Murrayamine-N (**221.2**), a formyl analogue of murrayamine-C (**221.1**), and murrayamine-J (**221.3**) were also obtained by Wu et al. from the acetone extract of the leaves of *Murraya euchrestifolia* collected in Taiwan in November.[490] The optical properties of these alkaloids were not mentioned.

Joshi et al. described the isolation of (−)-isomahanimbine (**221.4**), a methyl analogue of murrayamine-J (**221.3**), from the leaves of *Murraya koenigii*. Although, (−)-isomahanimbine (**221.4**) was isolated from nature in optically active form ($[\alpha]_D$

Scheme 221

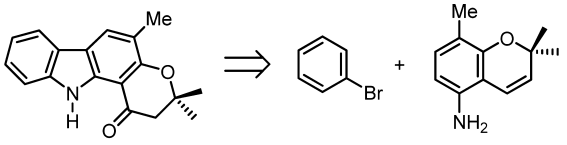


221.1 Murrayamine-C R = Me
221.2 Murrayamine-N R = CHO
221.3 Murrayamine-J R = CHO
221.4 (−)-Isomahanimbine R = Me
221.5 (+)-Mahanimbicine R = Me

= −6.0, c 2.1, $CHCl_3$), the absolute configuration has not been assigned.[468] In the same year, Kapil and co-workers isolated the enantiomeric (+)-**221.4** ($[\alpha]_D^{30}$ = +18.6, c 0.86, $CHCl_3$) from the same natural source and named it mahanimbicine (**221.5**). The absolute configuration of this alkaloid has also not been assigned.[504]

4.1.2. Palladium-Catalyzed Synthesis of Euchrestifoline and Girinimbine. Recently, Gruner and Knölker reported the total synthesis of euchrestifoline (**216.6**) using a one-pot Wacker oxidation and double aromatic C−H bond activation.[505] Euchrestifoline (**216.6**) was then transformed into girinimbine (**22.4**). Retrosynthetic analysis of euchrestifoline (**216.6**) based on this approach led to bromobenzene (**65.1**) and the aminochromene **222.1** as building blocks (Scheme 222).

Scheme 222



216.6 Euchrestifoline **65.1** **222.1**

The aminochromene **222.1** was prepared starting from commercially available 2-methyl-3-butyn-2-ol (**223.1**) and 2-methyl-5-nitrophenol (**223.3**). Reaction of 2-methyl-3-butyn-2-ol (**223.1**) with trifluoroacetic anhydride (TFAA) led to the corresponding trifluoroacetate **223.2** (Scheme 223). Without purification, the trifluoroacetate **223.2** was treated with 2-methyl-5-nitrophenol (**223.3**) to afford the corresponding aryl propargyl ether **223.4**. Thermally induced [3,3]-sigmatropic rearrangement with in situ rearomatization and cyclization afforded the nitrochromene **223.5**. Finally, reduction of **223.5** using iron in glacial acetic acid led quantitatively to the aminochromene **222.1**. Using this improved approach, the aminochromene **222.1** is available in 3 steps and 70% overall yield based on the nitrophenol **223.3**[505] (previous synthesis: 3 steps, 60% overall yield based on **223.3**).[506]

Buchwald−Hartwig amination of bromobenzene (**65.1**) with the aminochromene **222.1** afforded the diarylamine **224.1** (Scheme 224).[505] Under optimized reaction conditions, the diarylamine **224.1** was transformed directly into euchrestifoline (**216.6**) by heating of **224.1** for 2 days in a mixture of acetic acid and water (10:1) in the presence of catalytic amounts of palladium(II) acetate and copper(II) acetate. Alternatively, heating of the diarylamine **224.1** in a mixture of acetic acid and water in the presence of catalytic amounts of palladium(II)

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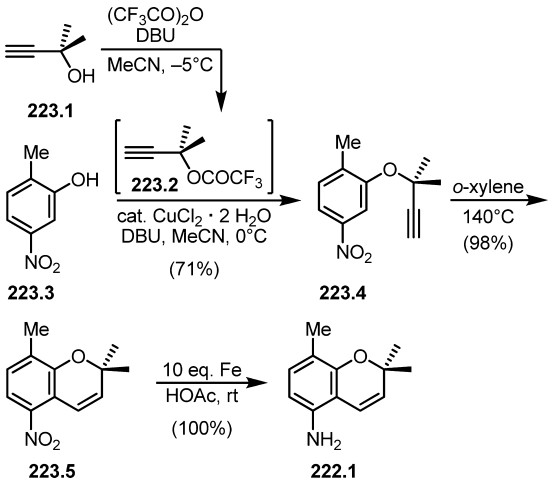
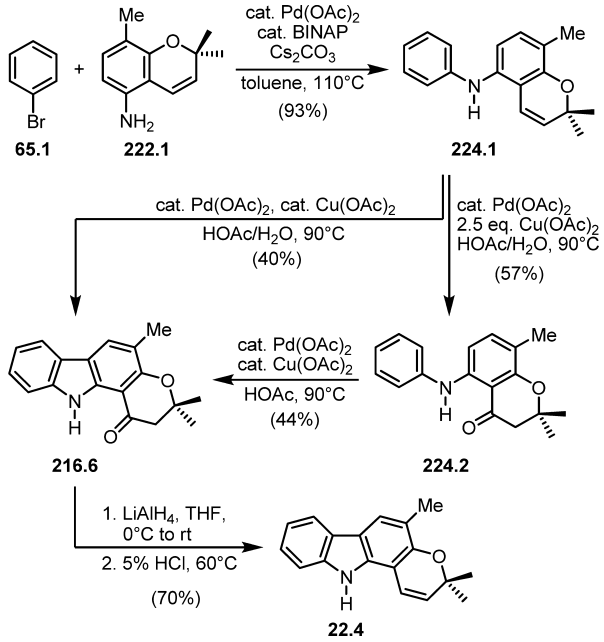
Scheme 223



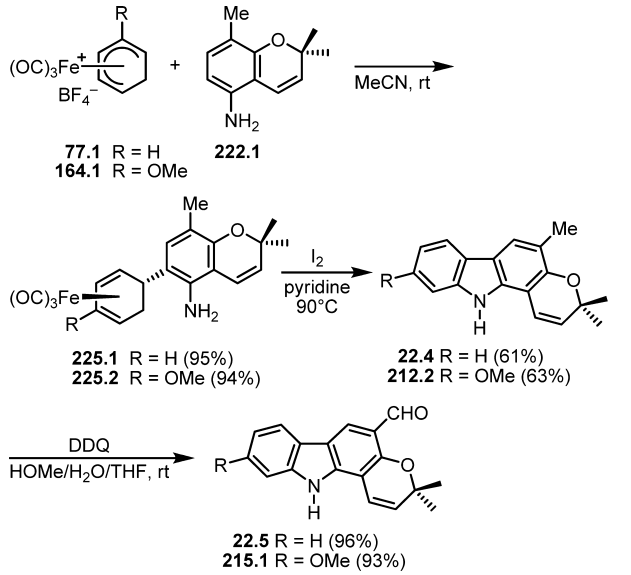
Scheme 224



acetate and an excess of copper(II) acetate at 90 °C for 5 h induced a Wacker oxidation to the chromanone **224.2**. The chromanone **224.2** was then cyclized to euchrestifoline (**216.6**) in 44% yield under the aforementioned conditions or by extension of the reaction time for the Wacker process to 24 h (yield 26%). Thus, Gruner and Knölker have shown that the one-pot transformation of **224.1** into euchrestifoline (**216.6**) consists of a two-step sequence of Wacker oxidation of the chromene double bond followed by a palladium(II)-catalyzed oxidative cyclization of a diarylamine to the carbazole ring system. Finally, conversion of euchrestifoline (**216.6**) to girinimbine (**22.4**) was achieved by reduction of **216.6** with lithium aluminum hydride and subsequent acid-catalyzed elimination of water.

4.1.3. Iron-Mediated Synthesis of Pyrano[3,2-*a*]-carbazole Alkaloids. In 2011, Knölker and co-workers described an iron-mediated approach to the synthesis of several pyrano[3,2-*a*]carbazole alkaloids.[486] Key steps are the consecutive formation of the C–C and C–N bonds by an electrophilic aromatic substitution of the aminochromene **222.1** with the iron complex salts **77.1** and **164.1** followed by oxidative cyclization of the resulting iron complexes **225.1** and **225.2**, respectively (Scheme 225). The aminochromene

Scheme 225



222.1 has already been used by Knölker and Hofmann for the molybdenum-mediated[506] and the palladium-catalyzed synthesis (see above) of girinimbine (**22.4**) and related compounds. Electrophilic aromatic substitution of **222.1** with the unsubstituted iron complex salt **77.1** regioselectively afforded the iron diene complex **225.1** in near quantitative yield. The central pyrrole ring was then formed by oxidation of the diene–iron complex with iodine in pyridine at elevated temperature to give girinimbine (**22.4**) in good yield. Oxidation of the methyl group at C-3 of the carbazole moiety with DDQ led to the carbazole-3-carbaldehyde murrayacine (**22.5**). The same sequence of steps afforded *O*-methylmurrayamine A (**212.2**) and 7-methoxymurrayacine (**215.1**) using the 2-methoxy-substituted iron complex salt **164.1** as starting material.

Knölker and co-workers have applied three different synthetic strategies to the total synthesis of girinimbine (**22.4**) (for an overview of synthetic strategies used by others, see ref 1). The first strategy relied on formation of the C–C bond of the central pyrrole ring by reaction of the aminochromene **222.1** and the molybdenum complex salt **16.1** followed by oxidative cyclization of the intermediate molybdenum allyl complex with manganese dioxide to form the C–N bond (Scheme 226) (2 steps, 11% overall yield).[506] In the palladium-catalyzed synthesis, first the C–N bond is formed by a Buchwald–Hartwig amination of bromobenzene (**65.1**) with the aminochromene **222.1**. A palladium(II)-catalyzed oxidative cyclization of the diarylamine **224.1** led to euchrestifoline (**216.6**), which was then transformed into girinimbine (**22.4**) (see Scheme 224). The palladium-catalyzed synthesis furnished girinimbine (**22.4**) in 4 steps and 26% overall yield.[505] The third route is the iron-mediated synthesis (Scheme 225; 2 steps, 58% overall yield).[486] A comparison of the three methods reveals that in the present case the iron-mediated synthesis is superior to the other two methods and provides the best overall yield of girinimbine (**22.4**).

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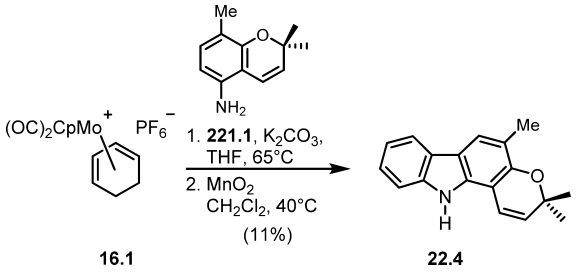
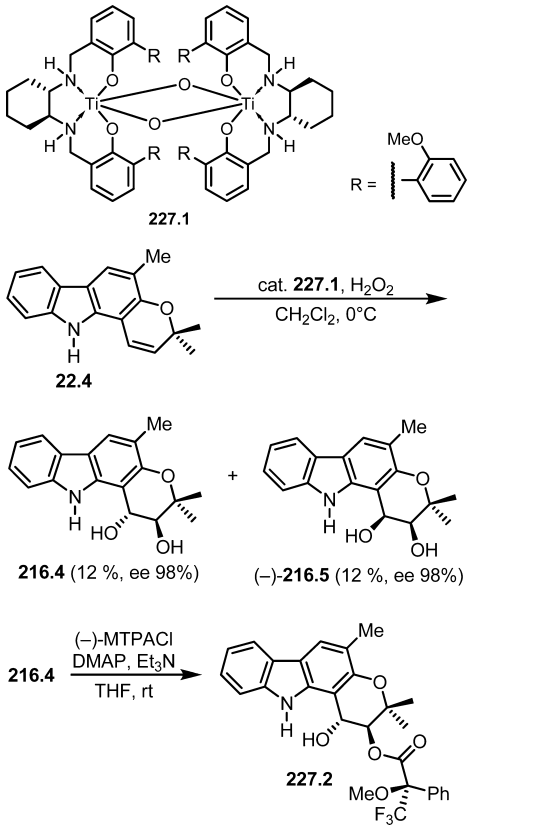
Scheme 226



For the total synthesis of enantiopure (−)-*trans*-dihydroxygirinimbine (**216.4**), Knölker et al. envisaged an enantioselective epoxidation of girinimbine (**22.4**) followed by a regio- and stereoselective ring-opening of the epoxide by hydrolysis (Scheme 227). However, oxidation of girinimbine (**22.4**) with hydrogen peroxide in the presence of catalytic amounts of the dimeric titanium salan complex **227.1** (developed by the Katsuki group) directly afforded a mixture of (−)-*trans*-dihydroxygirinimbine (**216.4**) and (−)-*cis*-dihydroxygirinimbine [(−)-**216.5**] (ratio of diastereoisomers = 1:1), both in very high enantioselectivity (ee ≥ 98%). Apparently, the intermediate epoxide is very prone to hydrolysis, a feature which Knölker and Hofmann already observed in their first synthesis of racemic *trans*- and *cis*-dihydroxygirinimbine [(±)-**216.4** and **216.5**].[506] Esterification of (−)-*trans*-dihydroxygirinimbine (**216.4**) with (*R*)-(−)-1-methoxy-1-(trifluoromethyl)-phenylacetyl chloride [(−)-MTPACl] led to the (*S*)-Mosher ester **227.2**. The ester **227.2** was used for the assignment of the absolute configuration of (−)-*trans*-dihydroxygirinimbine (**216.4**) according to Mosher's method.[507]

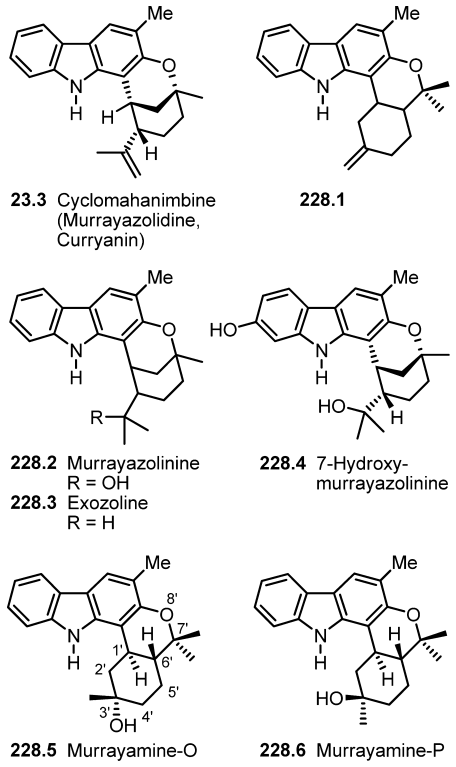
Scheme 227



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

4.2.1. Isolation from Natural Sources. In 1969, Kapil and co-workers isolated the pentacyclic pyrano[3,2-*a*]carbazole alkaloid **23.3** from the leaves of *Murraya koenigii* Spreng. in racemic form and named it cyclomahanimbine (**23.3**) (Scheme 228).[508] In the same year, Dutta et al. reported the isolation of curryanin from *Murraya koenigii* Spreng. and assigned its structure as **228.1**.[509] Curryanin was obtained in racemic form. The name curryanin derives from the vernacular name of this plant: currypatta or curry-leaf tree. In 1970, Chakraborty et al. reported the isolation of the same alkaloid in optically active form ($[\alpha]_D^{30}$ = +20, $CHCl_3$) from the stem bark of the same source, named it murrayazolidine, and assigned the structure **228.1**.[510] Independently from each other, Bandaranayake et al.[197] and Narasimhan et al.[511] examined the structure of optically active murrayazolidine and racemic curryanin and reassigned both as **23.3**. Thus, Kapil's cyclomahanimbine (**23.3**), Dutta's curryanin, and Chakraborty's murrayazolidine are identical compounds. In 1983, Furukawa and co-workers reported the relative stereochemistry of cyclomahanimbine (**23.3**) based on an X-ray crystal structure analysis of (±)-murrafoline-A (**250.1**) (see Scheme 250), an aryl−pyran-linked biscarbazole of girinimbine (**22.4**) and cyclomahanimbine (**23.3**).[512,513] Two years later, the same group reported the isolation of racemic cyclomahanimbine (**23.3**) from the root bark of *Murraya euchrestifolia* Hayata collected in Taiwan.[201] In 1974, Chakraborty et al. revised their earlier assignment for optically active murrayazolidine to racemic cyclomahanimbine (**23.3**).[514] In 1992, Reisch et al. also reported the isolation of murrayazolidine (**23.3**) from the dichloromethane extract of the fruits of *Murraya koenigii*. They confirmed the relative stereochemistry of murrayazolidine (**23.3**) by an X-ray analysis

Scheme 228



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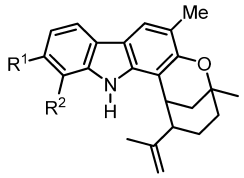
and showed that it is identical to cyclomahanimbine and curryanin.[399]

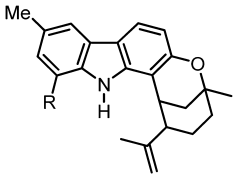
In 1973, Chakraborty et al. reported the isolation of murrayazolinine (**228.2**) from the stem bark of *Murraya koenigii*.[515] Exozoline (**228.3**) was isolated by Ganguly and Sarkar from the leaves of *Murraya exotica* 5 years later.[516] In 2011, Sim and Teh isolated 7-hydroxymurrayazolinine (**228.4**) from the ethanol extract of the leaves of *Murraya koenigii* collected in Malaysia in May.[517] The structure was assigned based on NMR experiments. The authors did not comment on the optical activity. In 1995, Wu et al. reported the isolation of two C-3′ epimeric cannabinol-skeletal carbazole alkaloids (see Scheme 228 for numbering as used by Wu), murrayamine-O (**228.5**) and murrayamine-P (**228.6**), from the root bark of *Murraya euchrestifolia*.[518] Although these two diastereoisomeric alkaloids were obtained in optically active form ($[\alpha]_D$ = −137.6, c 0.07, $CHCl_3$ for **228.5** and $[\alpha]_D$ = +92, c 0.015, $CHCl_3$ for **228.6**), their absolute configurations are not known. However, the relative configurations of **228.5** and **228.6** were assigned based on 2D-NMR studies.

In 1995, Wu et al. reported the isolation of murrayamine-D (**229.1**) from the acetone extract of the leaves of *Murraya euchrestifolia* collected during winter (Scheme 229).[519] This

Scheme 229



229.1 Murrayamine-D
R^1 = OH; R^2 = H
229.2 Murrayamine-H
R^1 = H; R^2 = OMe

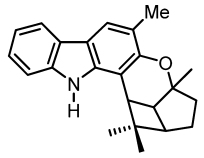


229.3 Murrayamine-F
R = OMe
229.4 Murrayamine-G
R = H

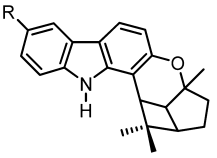
compound has the same bicyclic terpenoid skeleton as murrayazolidine (**23.3**) (see Scheme 228) with a hydroxy group at C-7 of the carbazole nucleus. Therefore, murrayamine-D (**229.1**) is a 7-hydroxymurrayazolidine. Wu et al. did not mention whether or not murrayamine-D (**229.1**) was obtained in optically active form. One year later, the same group isolated murrayamine-H (**229.2**), murrayamine-F (**229.3**), and murrayamine-G (**229.4**) from the leaves of the same plant collected in spring, indicating a strong seasonal variation of carbazole alkaloid biosynthesis. Wu et al. did not report whether these alkaloids showed any optical activity or if they were obtained as racemates.[488] The seasonal variation of biologically active carbazole alkaloids might serve as an explanation for the dependency of the pharmacological activity of the extract of this traditional Chinese medicinal plant on the collection time.

In 1969, Kapil and co-workers reported the isolation of bicyclomahanimbine (**23.4**) from the leaves of *Murraya koenigii* (Scheme 230).[508] Although this alkaloid was obtained in optically active form ($[\alpha]_D^{23}$ = −1.23, $CHCl_3$), the absolute configuration is not known. One year later, the same authors reported the isolation of bicyclomahanimbicine (**230.1**), an isomer of bicyclomahanimbine (**23.4**), from the same natural source. The authors did not mention any optical activity.[504] Four years after the isolation from natural sources, Bandaranayake et al. revised the original structures of **23.4** and **230.1**.[197] The revision of the original structures was based on NMR experiments and comparison with similar compounds.

Scheme 230



23.4 Bicyclomahanimbine



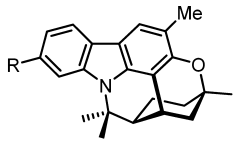
230.1 Bicyclomahanimbicine
R = Me
230.2 Murrayamine-M
R = CHO

Bicyclomahanimbine (**23.4**) was also obtained by Wu et al. in 1995 from the leaves of *Murraya euchrestifolia*.[519] One year later, the same group isolated murrayamine-M (**230.2**), a formyl analogue of bicyclomahanimbicine (**230.1**), from the acetone extract of the leaves of the same plant. The authors did not comment on the optical activity of this natural product.[490]

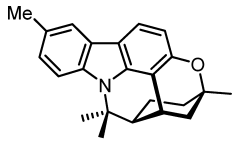
In 1969, Dutta et al. isolated racemic curryangin (**231.1**) from the stem bark of *Murraya koenigii* (Scheme 231).[520] In the same year, Kapil and co-workers isolated the same alkaloid also in racemic form from the leaves of the same plant and named it mahanimbidine (**231.1**).[508] Three years later, Chakraborty and co-workers reported the isolation of the same compound from the alcoholic extract of the stem bark of *Murraya koenigii* and named it murrayazoline (**231.1**).[521] By single-crystal X-ray analysis, it was shown that this compound was obtained in racemic form (space group $P2_1/c$). In 1985, Furukawa et al. isolated the same alkaloid in optically active form ($[\alpha]_D$ = +2.25, $CHCl_3$) from the root bark of a different *Murraya* species, *Murraya euchrestifolia* Hayata, and named it (+)-murrayazoline [(+)-**231.1**] without assignment of the absolute configuration.[201] Murrayamine-E (**231.2**), a 7-hydroxymurrayazoline, was isolated by Wu et al. in 1995 from the leaves of *Murraya euchrestifolia* collected in Taiwan in winter. This alkaloid was isolated in optically active form ($[\alpha]_D$ = −39.68, c 0.133, $CHCl_3$). The absolute configuration was not assigned. However, the relative stereochemistry was confirmed by 2D-NMR spectroscopy and X-ray analysis.[519]

In 1982, Chakraborty and co-workers reported the isolation of isomurrayazoline (**231.3**), a regioisomer of murrayazoline (**231.1**), from the benzene extract of the stem bark of *Murraya koenigii*.[522] Although this alkaloid was obtained from nature in optically active form ($[\alpha]_D$ = −7.33, $CHCl_3$), its absolute configuration is not known.

Scheme 231



231.1 (+)-Murrayazoline
(Mahanimbidine, Curryangin)
R = H
231.2 Murrayamine-E
R = OH



231.3 Isomurrayazoline

The hexacyclic pyrano[3,2-*a*]carbazole alkaloid murrayazolinol (**232.1**) was described by Chakraborty and co-workers in 1989 as a minor constituent of the root bark of *Murraya koenigii*.[523] In 1994, this alkaloid was also obtained by Ahmad as a minor natural product from the benzene extract of the root bark of *Murraya exotica*, a different *Murraya* species (Scheme

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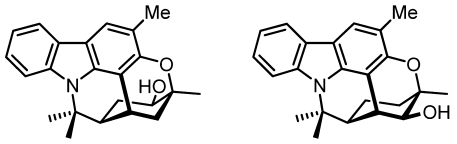
232).[524] Murrayakoeninol (**232.2**), a further hydroxylated derivative of murrayazoline (**231.1**), was isolated in 2009 by

Scheme 232

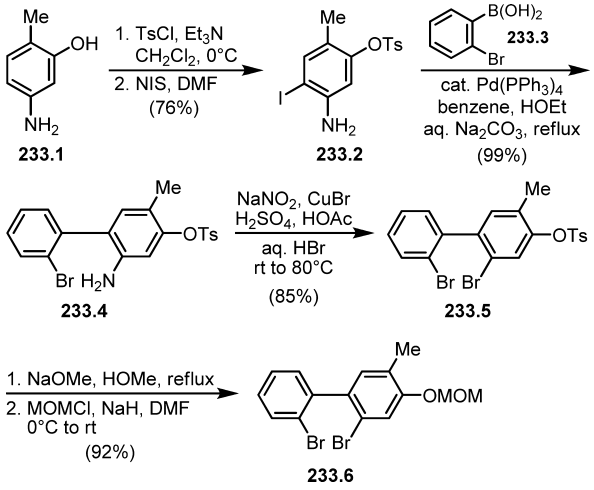


232.1 Murrayazolinol **232.2** Murrayakoeninol

Mukhapadhyay and co-workers from the leaves of *Murraya koenigii*.[525] The structure of murrayakoeninol (**232.2**) has been assigned based on NMR experiments and by comparison of the spectroscopic data with those of known compounds. Murrayakoeninol (**232.2**) was obtained in optically active form ($[\alpha]_D$ = −1.03, c 0.001, $CHCl_3$). However, the absolute configuration was not assigned.

4.2.2. Total Synthesis of (±)-Murrayazoline. Recently, Chida and co-workers reported a total synthesis of (±)-murrayazoline [(±)-**231.1**] using a combination of a 2-fold Buchwald−Hartwig amination, intramolecular Friedel−Crafts-type Michael addition, and palladium-catalyzed C−O coupling (Schemes 233−235).[526] The first fragment required

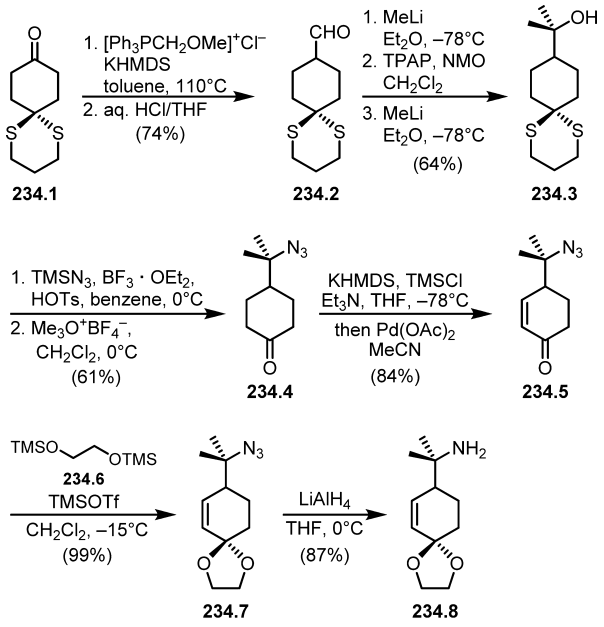
Scheme 233



for the construction of the carbazole core, the dibromobiphenyl **233.6**, was prepared starting from commercially available 5-amino-2-methylphenol (**233.1**). O-Tosylation of **233.1** followed by iodination led to the iodoaniline **233.2**. Suzuki−Miyaura cross-coupling of **233.2** with 2-bromophenylboronic acid (**233.3**) afforded the biphenyl **233.4** almost quantitatively. Using standard Sandmeyer conditions, the aminobiphenyl **233.4** was then transformed to the corresponding dibromobiphenyl derivative **233.5**. An exchange of the protecting group in **233.5** was achieved by detosylation and subsequent methoxymethylation to afford the MOM derivative **233.6**.[526]

The second building block, amine **234.8**, was prepared from the known 1,5-dithiaspiro[5,5]undecan-9-one (**234.1**) (Scheme 234).[526] Wittig reaction of the monothioacetal **234.1** with (methoxymethyl)triphenylphosphonium chloride followed by acid hydrolysis afforded the aldehyde **234.2**. Reaction of **234.2** with methyllithium followed by oxidation of the resulting alcohol afforded a methyl ketone, which on further addition of

Scheme 234



methyllithium provided the tertiary alcohol **234.3** in 64% yield. Lewis acid-promoted reaction of **234.3** with trimethylsilyl azide and subsequent deprotection of the thioacetal group using trimethyloxonium tetrafluoroborate afforded the azide **234.4** in 61% yield. Ito−Saegusa oxidation of **234.4** to the cyclohexenone **234.5** was followed by protection of the carbonyl group in **234.5** by treatment with ethylenediol bis(trimethylsilyl) ether (**234.6**) to give the ethylene ketal **234.7**. Reduction of the azide function in **234.7** with lithium aluminum hydride provided amine **234.8**.

Double N-arylation of the 2,2′-dibromobiphenyl **233.6** with the amine **234.8** afforded the desired N-substituted carbazole **235.1** in 59% yield (Scheme 235).[526] Using catalytic amounts of tris(dibenzylideneacetone)dipalladium(0) and XPhos as ligand in the presence of sodium *tert*-butoxide as base in toluene at elevated temperature gave the best yields. Treatment of **235.1** with scandium triflate in a mixture of dichloromethane and water at 120 °C resulted in deprotection of the ethylene ketal as well as intramolecular Friedel−Crafts-type Michael addition and removal of the MOM group to give the pentacyclic ketone **235.3** in 73% yield. After conversion of **235.3** into the corresponding triflate **235.4**, addition of methylmagnesium bromide to **235.4** led to the tertiary alcohol **235.5** as a single diastereoisomer in 77% yield. Finally, intramolecular etherification of the tertiary alcohol using Buchwald−Hartwig conditions provided (±)-murrayazoline [(±)-**231.1**] in 80% yield.

4.3. Pyrano[2,3-*a*]carbazole Alkaloids

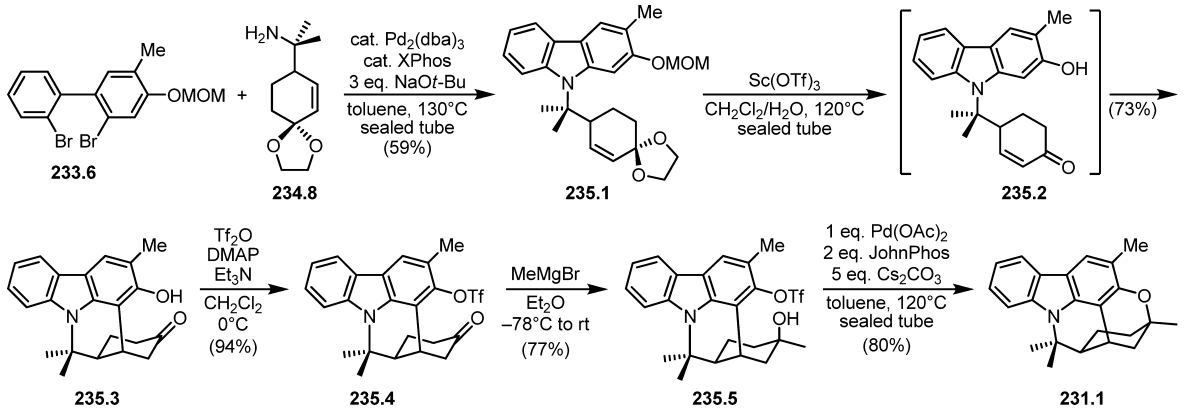
In 1996, Ito et al. reported the isolation of the first pyrano[2,3-*a*]carbazole alkaloids, clauszoline-A (**236.1**) and clauszoline-B (**24.4**), from the acetone extract of the stem bark of *Clausena excavata* collected in Singapore (Scheme 236).[403] One year later, the same group isolated a further pyrano[2,3-*a*]carbazole alkaloid, clauszoline-H (**236.2**), from the roots of the same *Clausena* plant collected in Japan.[279]

4.4. Pyrano[2,3-*b*]carbazole Alkaloids

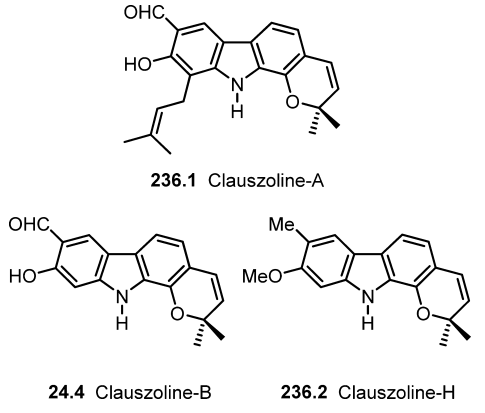
In 1991, Furukawa and co-workers isolated the first pyrano[2,3-*b*]carbazole alkaloid, pyrayafoline-B (**237.1**), from the stem

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 235

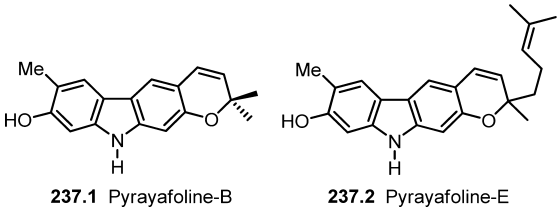


Scheme 236



bark of *Murraya euchrestifolia* collected in May in Taiwan.[393] In the same year, the same group isolated a further pyrano[2,3-*b*]carbazole alkaloid, pyrayafoline-E (**237.2**), from the stem bark of the same natural source (Scheme 237).[391] Pyrayafoline-E (**237.2**) was obtained as an optically inactive compound.

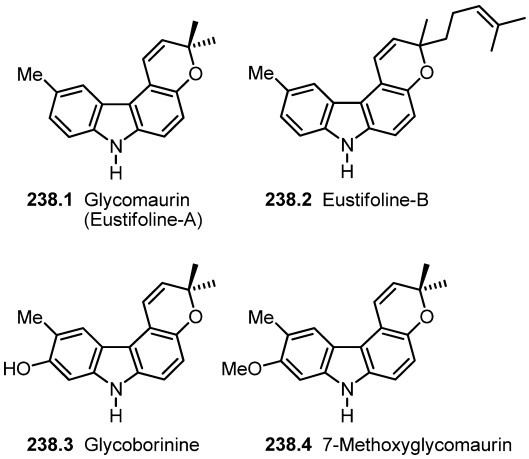
Scheme 237



4.5. Pyrano[2,3-*c*]carbazole Alkaloids

4.5.1. Isolation from Natural Sources. In 1989, Reisch and co-workers reported the isolation of the first pyrano[2,3-*c*]carbazole alkaloid, glycomaurin (**238.1**), from the dichloromethane extract of the stem bark of *Glycosmis mauritiana* collected in Sri Lanka (Scheme 238).[352] One year later, Ito and Furukawa reported the isolation of the same alkaloid from the acetone extract of the root bark of *Murraya euchrestifolia* and named it eustifoline-A (**238.1**).[353] Together with eustifoline-A (**238.1**), Ito and Furukawa also isolated the corresponding prenyl analogue, eustifoline-B (**238.2**). Although eustifoline-B (**238.2**) possesses a stereogenic carbon atom, the authors did not comment on the optical activity. In 1999, Chakravarty et al.

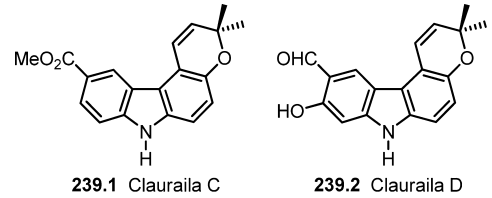
Scheme 238



reported the isolation of glycoborinine (**238.3**) from the roots of *Glycosmis arborea*.[347] This indigenous Indian plant is known as *Ashshoura*, *Bon-numbu*. The extracts of *Glycosmis arborea* are locally used for the treatment of fever, liver complaints, and certain other diseases. 7-Methoxyglycomaurin (**238.4**), the *O*-methyl derivative of glycoborinine (**238.3**), was isolated already in 1998 by Rahmanil and co-workers from the bark of *Glycosmis rupestris* Ridely.[527] The roots of this plant have been used in folk medicine for the treatment of fever and swollen spleen and as a digestion stimulant.

Clauraila C (**239.1**) and D (**239.2**) were isolated in 2011 (Scheme 239). Yenjai and co-workers obtained these two pyrano[2,3-*c*]carbazoles together with other carbazoles from the roots of *Clausena harmandiana*.[374] Clauraila C (**239.1**) can be regarded as an oxidation product of glycomaurin (eustifoline-A) (**238.1**), whereas clauraila D (**239.2**) represents an oxidation product of glycoborinine (**238.3**).

Scheme 239



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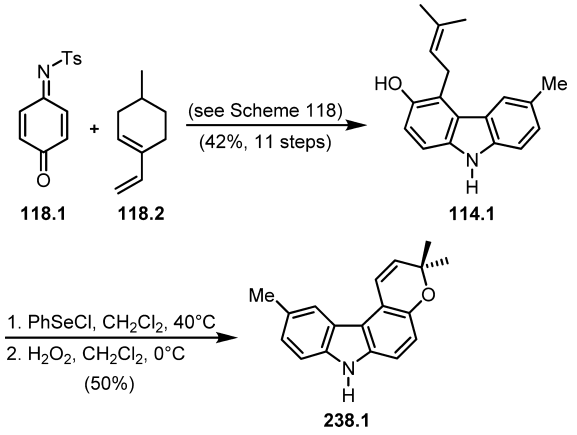
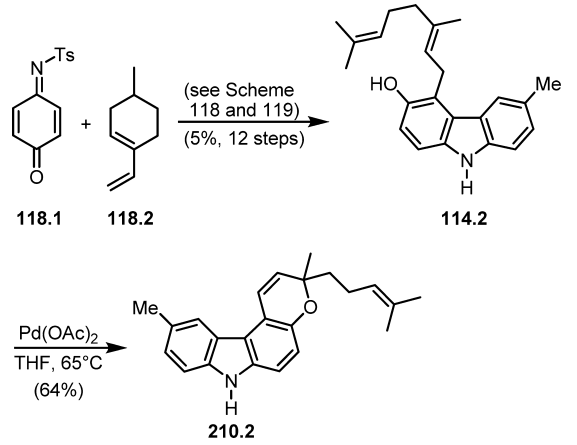
4.5.2. Total Synthesis of Glycomaurin (Eustifoline-A) and Eustifoline-B. In 2007, Lebold and Kerr reported the total synthesis of glycomaurin (eustifoline-A) (**238.1**) and eustifoline-B (**238.2**) using glycomaurrol (**114.1**) and eustifoline-C (**114.2**) as intermediates.[357] Glycomaurrol (**114.1**) was obtained in 11 steps and 42% overall yield starting from the readily available quinone imine **118.1** and diene **118.2** (see Scheme 118). Cyclization of glycomaurrol (**114.1**) with phenylselenyl chloride followed by oxidation with H_2O_2 afforded glycomaurin (eustifoline-A) (**238.1**) in 50% yield over 2 steps (Scheme 240).[357]

Scheme 240



Eustifoline-C (**114.2**) was prepared in 12 steps and 5% overall yield starting from the same precursors, quinone imine **118.1** and diene **118.2** (see Scheme 119). Oxidative cyclization of eustifoline-C (**114.2**) using palladium(II) acetate afforded eustifoline-B (**238.2**) in 64% yield (Scheme 241).[357]

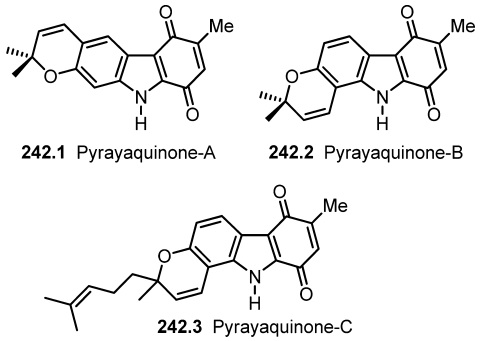
Scheme 241



4.6. Pyranocarbazole-1,4-quinone Alkaloids

In 1985, Furukawa et al. reported the isolation of the first pyranocarbazole-1,4-quinone alkaloids, pyrayaquinone-A (**242.1**) and pyrayaquinone-B (**242.2**), from the acetone extract of the root bark of *Murraya euchrestifolia* collected in Taiwan in December (Scheme 242).[528] Three years later, the same group isolated a further pyranocarbazole-1,4-quinone alkaloid, pyrayaquinone-C (**242.3**), from the root bark of the same *Murraya* plant.[248] Furukawa and co-workers did not describe whether pyrayaquinone-C (**242.3**) was obtained as an optically active compound.

Scheme 242



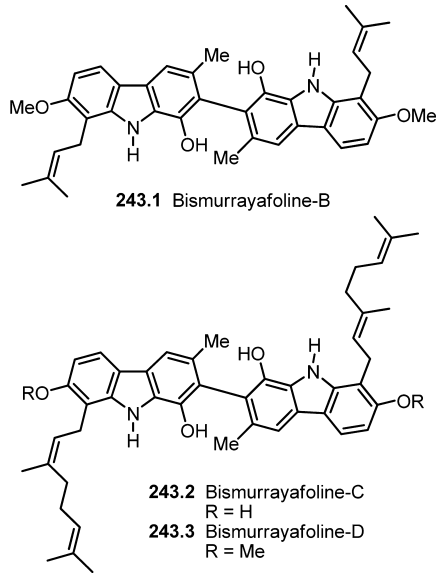
5. BISCARBAZOLE ALKALOIDS

The biscarbazole alkaloids contain known monomeric carbazoles as structural subunits. To date, the majority of all known biscarbazole alkaloids have been isolated from plants of two genera of the family Rutaceae, *Murraya* and *Clausena*. The biscarbazoles often co-occur with the monomeric carbazoles in the root bark, stem bark, and the leaves of these plants. Some biscarbazole alkaloids are axially chiral. The aspect of atropisomerism has been investigated only recently.[529] 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 to the biological activity.[1,12,530,531] Since 1983, a large number of biscarbazoles with different linkage modes between the two carbazole units has been isolated. Thus, the biscarbazole section of this review has been divided into subsections based on the different carbazole linkages.

5.1. Aryl−Aryl-Linked Biscarbazole Alkaloids

5.1.1. Isolation from Natural Sources. In 1983, Furukawa et al. isolated the first biscarbazole alkaloid, bismurrayafoline-B (**243.1**), from *Murraya euchrestifolia* Hayata collected in Taiwan in February (Scheme 243). It has not been

Scheme 243



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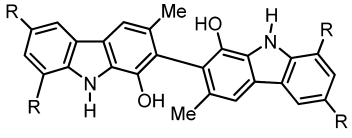
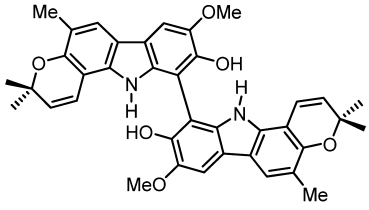
reported whether or not bismurrayafoline-B (**243.1**) showed any optical activity.[204] Eight years later, Furukawa and co-workers reported the isolation of further aryl−aryl-linked biscarbazole alkaloids from the stem bark of the same plant: bismurrayafoline-C (**243.2**) and bismurrayafoline-D (**243.3**), the dimethyl ether of bismurrayafoline-C (**243.2**). The authors did not comment on the potential optical activity.[391]

In 1995, Bringmann et al. reported on the antiplasmodial activity of the non-natural 2,2′-bis(1-hydroxy-3-methylcarbazole) (**26.1**) against *Plasmodium falciparum* in vitro (Scheme 244).[205] Bringmann et al. also described an antimalarial activity

Scheme 244



26.1 Bis(*O*-demethylmurrayafoline A) R = H
244.1 Clausenamine-A R = OMe



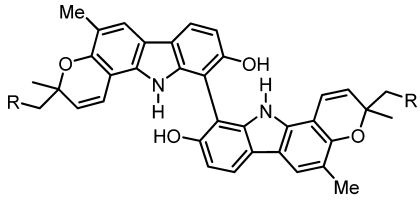
244.2 8,8″-Biskoenigine

of **26.1**, its enantiomeric resolution, and the chiroptical properties of this compound.

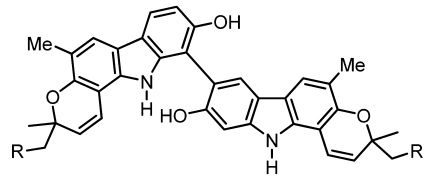
Clausenamine-A (**244.1**) was isolated in 1996 by Wu et al. from the methanol extract of the stem bark of *Clausena excavata*.[281] Four years later, Zhang and Lin reported the in vitro cytotoxic activity of clausenamine-A (**244.1**) and its synthetic analogues against a variety of human cancer cell lines.[532] In 2003, Hao et al. isolated 8,8″-biskoenigine (**244.2**) from the ethanol extract of *Murraya koenigii*.[481] Although this alkaloid was isolated in optically active form ($[\alpha]_D^{25}$ = +139.6, c 1.0, $CHCl_3$), the absolute configuration is not known. 8,8″-Biskoenigine (**244.2**) exhibits antiosteoporotic activity in the CAT-B model.

In 1991, Wu et al. reported the isolation of bis-7-hydroxygirinimbine-A (**245.1**) and bis-7-hydroxygirinimbine-B (**245.3**) from the acetone extract of the leaves of *Murraya euchrestifolia* Hayata collected in Taiwan (Scheme 245).[533] The authors did not investigate the optical activity of these alkaloids. In 1993, Furukawa et al. reported the isolation of bismahanine (**245.4**) from the acetone extract of the stem bark of *Murraya koenigii*.[203] A decade later, Nakatani et al. isolated the same alkaloid in optically active form ($[\alpha]_D^{25}$ = +4.0, c 0.65, $CHCl_3$) from the dichloromethane extract of the leaves of *Murraya koenigii*.[475] Along with bismahanine (**245.4**), they obtained a further optically active aryl−aryl-linked biscarbazole alkaloid, bispyrayafoline (**245.2**) ($[\alpha]_D^{25}$ = +22.2, c 0.09, $CHCl_3$). Although these alkaloids were isolated in enantiopure form, their absolute configurations are still unknown. Both compounds showed a radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals.

Scheme 245



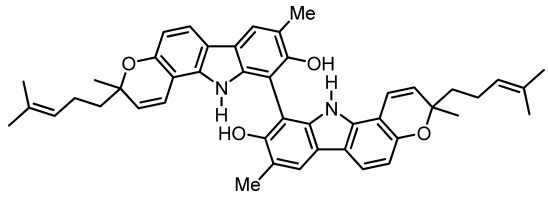
245.1 Bis-7-hydroxygirinimbine-A R = H
245.2 Bispyrayafoline R =



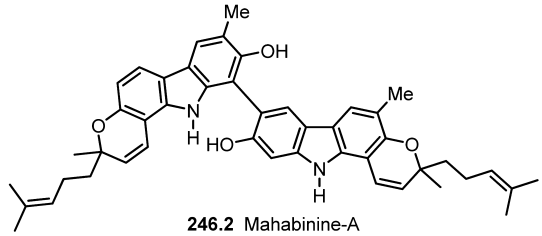
245.3 Bis-7-hydroxygirinimbine-B R = H
245.4 Bismahanine R =

In 2004, Cuong et al. reported the isolation of bisisomahanine (**246.1**) from the acetone extract of the roots of *Glycosmis stenocarpa* collected in North Vietnam (Scheme 246).[269] Bisisomahanine (**246.1**) was obtained in optically

Scheme 246



246.1 Bisisomahanine



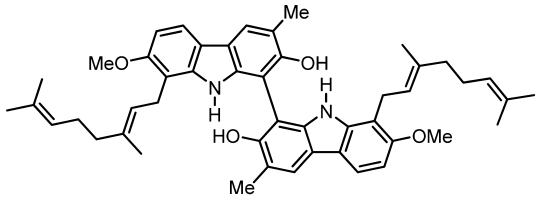
246.2 Mahabinine-A

active form ($[\alpha]_D^{20}$ = −13.1, c 0.25, $CHCl_3$). However, the absolute configuration is not known. In 2003, Nakatani et al. reported the isolation of **246.2** in optically active form ($[\alpha]_D^{25}$ = +55.0, c 0.12, $CHCl_3$) from the leaves of *Murraya koenigii*.[475] The absolute configuration of this alkaloid was not assigned. This alkaloid showed radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals. Three years later, Itoigawa and co-workers isolated the same compound from the same source and named it mahabinine-A (**246.2**).[500] Mahabinine-A (**246.2**) induced apoptosis in HL-60 cells by activation of the caspase-9/caspace-3 pathway, through mitochondrial dysfunction.

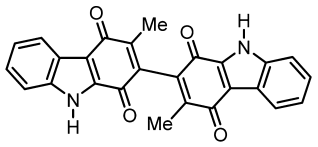
In 1993, Furukawa and co-workers reported the isolation of bis-2-hydroxy-3-methylcarbazole (**26.2**), bismurrayaquinone-A (**247.2**), and bikoeniquinone-A (**247.3**) from the acetone extract of the root bark of *Murraya koenigii* (Scheme 247).[203]

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

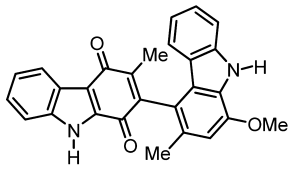
Scheme 247



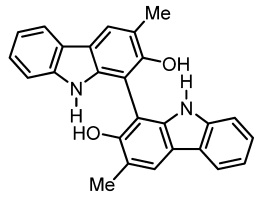
247.1 Bismurrayafoline E



247.2 Bismurrayaquinone-A



247.3 Bikoeniquinone-A

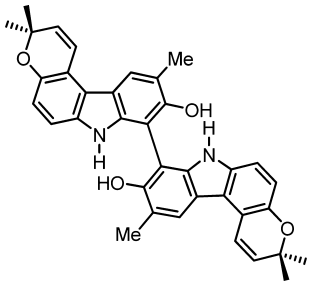


26.2 Bis-2-hydroxy-3-methyl-carbazole 1,1'-Bis(2-hydroxy-3-methylcarbazole)

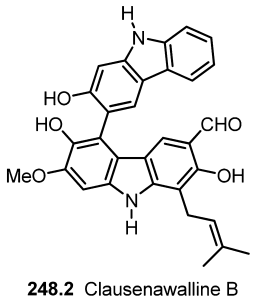
Bismurrayaquinone-A (**247.2**) and bikoeniquinone-A (**247.3**) are the first examples of dimeric carbazolequinone alkaloids isolated from nature. It has not been reported whether either of these two dimeric carbazole alkaloids showed any optical activity. However, 2 years later, Bringmann et al. described the enantiomeric resolution and the chiroptical properties of bismurrayaquinone-A (**247.2**).[534] In 2011, Thomson and co-workers reported the enantioselective total synthesis of (+)-bismurrayaquinone-A [(+)-**247.2**] and experiments toward atropisomerization (see Addendum).[535] In 1999, Rashid and co-workers isolated bismurrayafoline E (**247.1**) from the ethanol extract of the leaves of *Murraya koenigii*.[536] Bismurrayafoline E (**247.1**) is isomeric to the aryl−aryl-linked biscarbazole alkaloid bismurrayafoline-D (**243.3**) (see Scheme 243).

Clausenawalline A (**248.1**), a glycoborinine (**238.3**) homodimer, was isolated by Laphookhieo and co-workers in 2011 (Scheme 248).[537] The natural product was obtained from an acetone extract of the roots of *Clausena wallichi*. In the same publication, Laphookhieo also described clausenawalline B (**248.2**), which was obtained from the same natural source.

Scheme 248



248.1 Clausenawalline A

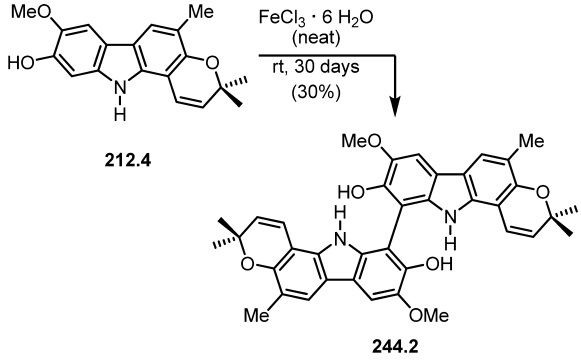


248.2 Clausenawalline B

Clausenawalline B (**248.2**) is a heterodimer of two carbazoles that have not been obtained from natural sources yet. Interestingly, the smaller fragment does not bear the C_1-substituent at C-3 that is typically found in carbazoles from higher plants. The structures of the two new dimeric carbazole alkaloids were assigned based on NMR data.

5.1.2. Synthesis of 8,8″-Biskoenigine. To confirm the structure assigned to 8,8″-biskoenigine (**244.2**), Hao and co-workers reported the oxidative dimerization of koenigine (**212.4**) to 8,8″-biskoenigine (**244.2**) (Scheme 249).[481] Thus,

Scheme 249



212.4

244.2

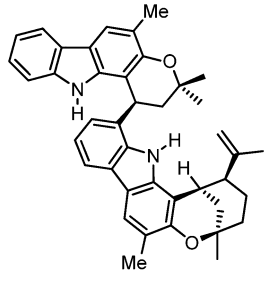
treatment of koenigine (**212.4**) with iron(III) chloride (neat) at room temperature for 30 days was employed to effect the desired oxidative coupling to 8,8″-biskoenigine (**244.2**) in 30% yield.

5.2. Aryl−Pyran-Linked Biscarbazole Alkaloids

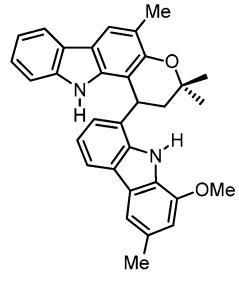
In 1983, Furukawa and co-workers isolated murrafoline-A [(±)-murrafoline] (**250.1**) from the acetone extract of the root bark of *Murraya euchrestifolia* (Scheme 250).[512] This biscarbazole occurs in nature in racemic form and consists of a dihydrogirinimbine unit [cf. girinimbine (**22.4**)] (see Scheme 211) attached at C-4 of the pyran ring to C-8 of the carbazole core of cyclomahanimbine (**23.3**) (see Scheme 228). Both monomeric carbazole alkaloids co-occur with murrafoline-A (**250.1**). The structure and relative stereochemistry of murrafoline-A (**250.1**) was confirmed by an X-ray analysis.[512,513]

In 1985 and 1993, Furukawa et al. described further aryl−pyran-linked biscarbazole alkaloids obtained from the same natural source: murrafoline-B (**250.2**),[513,538] murrafoline-C (**251.1**),[513,538] murrafoline-D (**251.3**),[513] murrafoline-G (**252.1**),[513] and murrafoline-H (**252.2**) (Schemes 250−252).[513] A further biscarbazole alkaloid, murrafoline-I (**251.2**), was isolated in 2006 by Furukawa et al. from the

Scheme 250



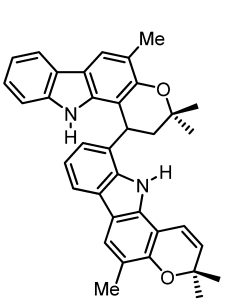
250.1 Murrafoline-A [(±)-Murrafoline]



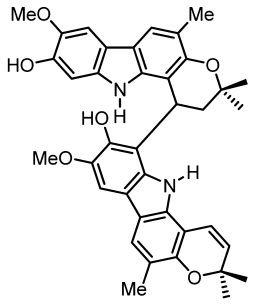
250.2 Murrafoline-B

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

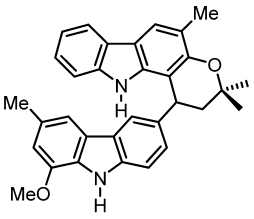
Scheme 251



251.1 Murrafoline-C

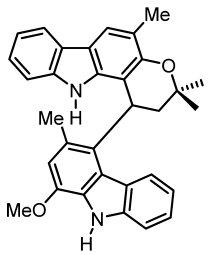


251.2 Murrafoline-I

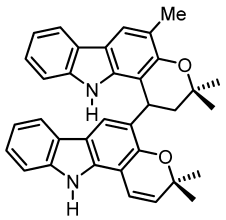


251.3 Murrafoline-D

Scheme 252



252.1 Murrafoline-G



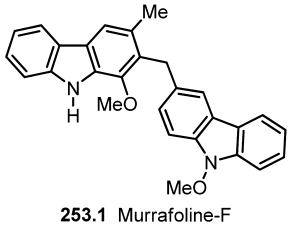
252.2 Murrafoline-H

acetone extract of the leaves of *Murraya koenigii* collected in Bangladesh in April.[500] Murrafoline-I (**251.2**) induced apoptosis in human leukemia cells (HL60) by activation of the caspase-9/caspase-3 pathway, through mitochondrial dysfunction. The common structural feature of all murrafoline congeners is the presence of a dihydrogirinimbine subunit, which is attached at C-4 of the pyran ring to a second carbazole moiety. The murrafolines were obtained from nature in racemic form.[513,538]

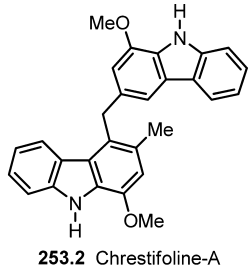
5.3. Aryl−3-Methyl-Linked Biscarbazole Alkaloids

In 1988, Furukawa and co-workers reported the isolation of murrafoline-F (**253.1**) from the acetone extract of the root bark of *Murraya euchrestifolia* Hayata collected in Taiwan in December (Scheme 253).[248] This was the first example of an

Scheme 253



253.1 Murrafoline-F



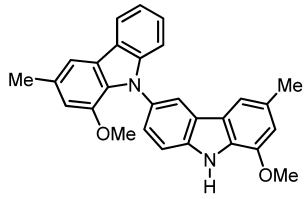
253.2 Chrestifoline-A

N-methoxy-biscarbazole alkaloid isolated from nature. Two years later, the same group isolated a further aryl−3-methyl-linked biscarbazole, chrestifoline-A (**253.2**), from the root bark of *Murraya euchrestifolia*.[202] In 2001, Bringmann and Tasler obtained chrestifoline-A (**253.2**) by reaction of murrayafoline-A (**20.1**) and koenoline (**20.2**) under acidic conditions.[539]

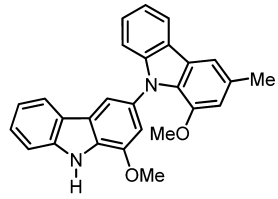
5.4. N−Aryl-Linked Biscarbazole Alkaloids

5.4.1. Isolation from Natural Sources. In 1990, Furukawa and co-workers isolated murrastifoline-A (**25.1**) and murrastifoline-B (**254.1**) from the root bark of *Murraya euchrestifolia* (Scheme 254).[202] Three years later, the same

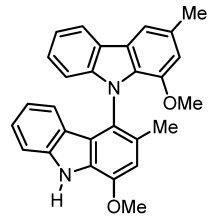
Scheme 254



25.1 Murrastifoline-A



254.1 Murrastifoline-B



25.2 Murrastifoline-F

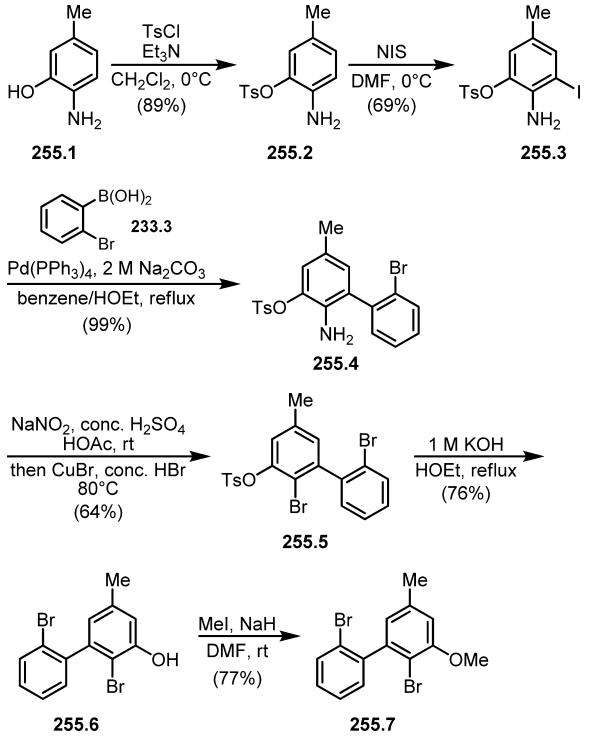
authors reported a further murrastifoline derivative, murrastifoline-F (**25.2**), from *Murraya koenigii*.[203] The common structural feature of the murrastifolines is the presence of a 1-methoxy-3-methylcarbazole, which is attached via the carbazole nitrogen atom to a second carbazole moiety. No optical rotation was mentioned for any of these alkaloids. However, in 2001, Bringmann et al. described the enantiomeric resolution and chiroptical properties of murrastifoline-F (**25.2**).[540]

5.4.2. Total Synthesis of Murrastifoline-A. In 2005, Chida and co-workers reported the total synthesis of murrastifoline-A (**25.1**) using a palladium-catalyzed double N-arylation of the 6-aminocarbazole **256.7** with the dibromobiphenyl derivative **255.7** (Schemes 255−257).[121,122] Both components were obtained from the common precursor 2-amino-5-methylphenol (**255.1**). The synthesis of dibromobiphenyl derivative **255.7** started from the known tosylate **255.2**, prepared by O-tosylation of the commercially available phenol **255.1**. Iodination of **255.2** with *N*-iodosuccinimide (NIS) afforded the corresponding iodoaniline **255.3**, which on Suzuki−Miyaura cross-coupling with 2-bromophenylboronic acid (**233.3**) afforded almost quantitatively the aminobiphenyl **255.4**. Using Sandmeyer reaction conditions, the aminobiphenyl **255.4** was transformed to the dibromobiphenyl **255.5**. After removal of the tosyl group of **255.5** by alkaline hydrolysis, the corresponding phenol derivative **255.6** was subjected to O-methylation to afford the 2,2′-dibromobiphenyl **255.7**.[121,122]

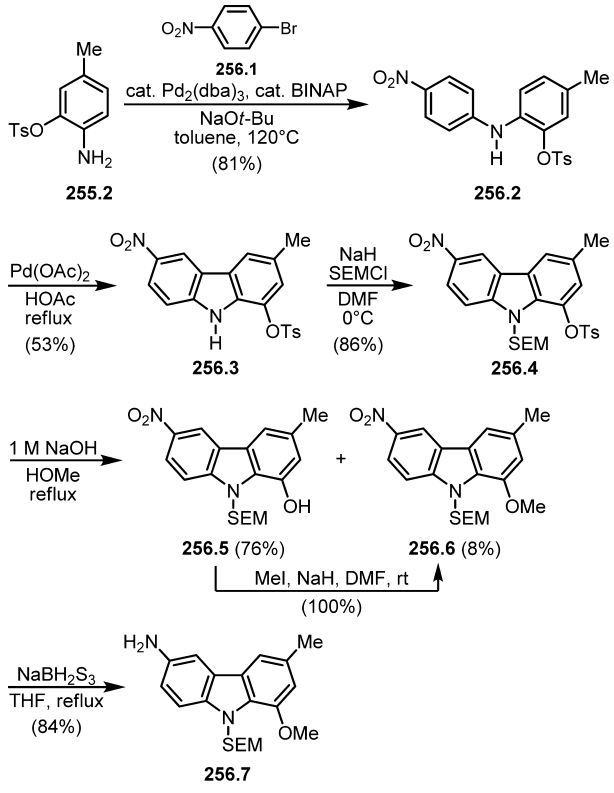
The 6-aminocarbazole **256.7** was synthesized starting from the tosyl derivative **255.2** and 4-bromonitrobenzene (**256.1**) (Scheme 256). Buchwald−Hartwig N-arylation of 4-bromonitrobenzene (**256.1**) with the aniline **255.2** afforded the

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 255



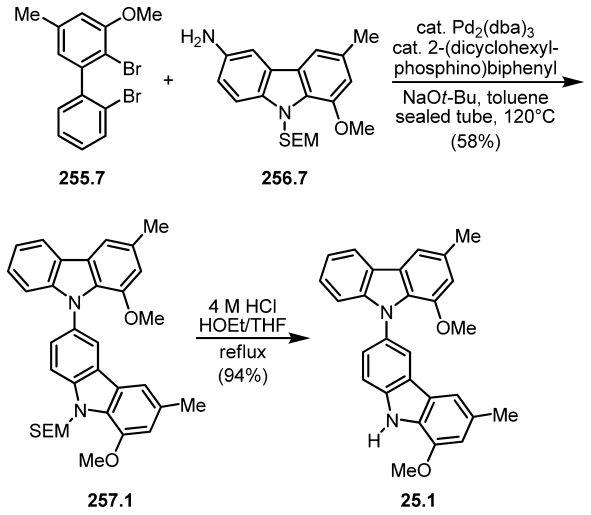
Scheme 256



diarylamine **256.2** in 81% yield. Reaction of **256.2** with an excess of palladium(II) acetate in acetic acid provided the carbazole **256.3**. After protection of the nitrogen in **256.3** with the (2-trimethylsilylethoxy)methyl (SEM) group, the corresponding N-protected carbazole **256.4** was subjected to alkaline hydrolysis to afford the hydroxycarbazole **256.5** along with the methyl ether **256.6**. The hydroxycarbazole **256.5** was then also transformed to the O-methyl derivative **256.6** in quantitative yield. Finally, reaction of **256.6** with sulfurated sodium borohydride ($NaBH_2S_3$)[541] afforded the 6-aminocarbazole **256.7**.[121,122]

Double N-arylation of **256.7** with the dibromobiphenyl **255.7** in toluene at 120 °C in the presence of $Pd_2(dba)_3$, sodium *tert*-butoxide, and 2-(dicyclohexylphosphino)biphenyl as ligand afforded the protected biscarbazole **257.1** (Scheme 257). Finally, the SEM group was removed under acidic conditions to afford murrastifoline-A (**25.1**).[121,122]

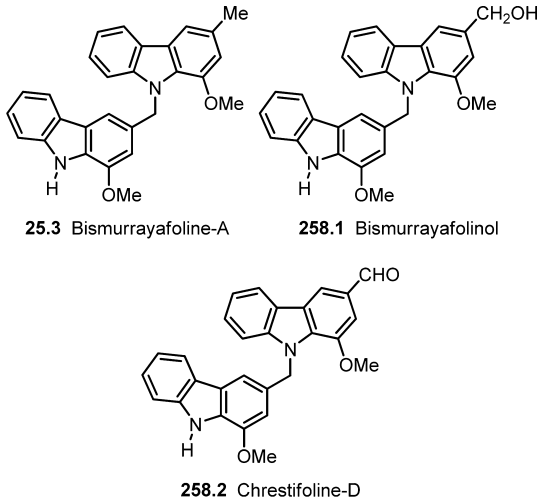
Scheme 257



5.5. N–3-Methyl-Linked Biscarbazole Alkaloids

In 1983, Furukawa et al. reported the isolation of bismurrayafoline-A (**25.3**), the first N–3-methyl-linked biscarbazole alkaloid, from *Murraya euchrestifolia* Hayata collected in Taiwan in February (Scheme 258).[204] In 1987 and 1992, Furukawa and co-workers obtained bismurrayafolinol (**258.1**)[392] and chrestifoline-D (**258.2**),[358] oxidized derivatives of bismurrayafoline-A (**25.3**), from the same natural source. The co-occurrence of all these alkaloids in *Murraya euchrestifolia* suggests that they are

Scheme 258

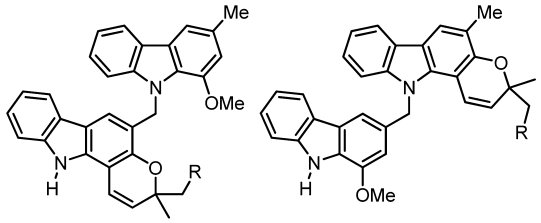


dx.doi.org/10.1021/cr200447s | Chem. Rev. 2012, 112, 3193–3328

biosynthesized by in vivo oxidation of bismurrayafoline-A (**25.3**).

In 1988, Furukawa and co-workers isolated murrafoline-E (**259.1**) from the root bark of *Murraya euchrestifolia* (Scheme 259).[248] Two years later, the same group isolated further N−3-

Scheme 259



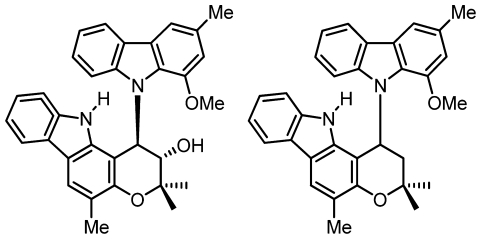
259.1 Murrafoline-E R = H
259.2 Murrastifoline-C R = prenyl
259.3 Chrestifoline-B R = H
259.4 Chrestifoline-C R = prenyl

methyl-linked biscarbazoles: murrastifoline-C (**259.2**), chrestifoline-B (**259.3**), and chrestifoline-C (**259.4**) from *Murraya euchrestifolia*.[202] The chrestifolines contain 1-methoxy-3-methylcarbazole [murrayafoline-A (**20.1**)] (see Scheme 53) as common structural subunit, which is attached at the C-3 methyl group to a second carbazole. Chrestifoline-C (**259.4**) was isolated from nature in optically active form ($[\alpha]_D$ = −5.6, c 0.054, $CHCl_3$). However, the absolute configuration is not known.[202]

5.6. N−Pyran-Linked Biscarbazole Alkaloids

In 1990, Furukawa and co-workers reported the isolation of murrastifoline-D (**260.1**) from the root bark of *Murraya euchrestifolia* (Scheme 260).[202] Murrastifoline-D (**260.1**) did

Scheme 260



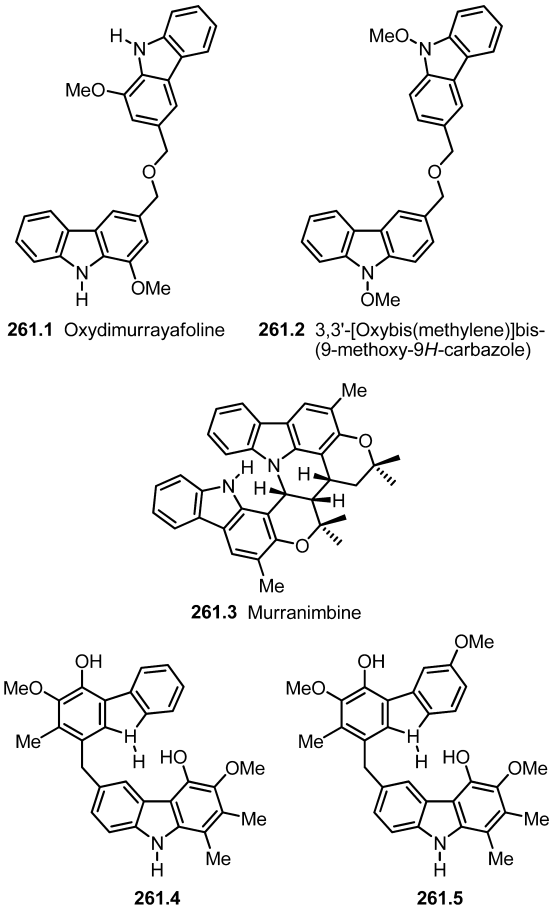
260.1 Murrastifoline-D
260.2 Murrastifoline-E

not exhibit any optical activity. In the same year, Murrastifoline-E (**260.2**) was isolated by Furukawa et al. from the same natural source.[353] In contrast to murrastifoline-D (**260.1**), murrastifoline-E (**259.2**) was obtained in optically active form ($[\alpha]_D$ = −5.7, c 0.035, $CHCl_3$). However, the absolute configuration is not known.

5.7. Miscellaneous Biscarbazole Alkaloids

In 1987, Furukawa and co-workers described the isolation of oxidimurrayafoline (**261.1**) from the root bark of *Murraya euchrestifolia* (Scheme 261). This alkaloid represents the first example of a dimeric carbazole alkaloid with an ether linkage.[392] In 2005, Rahman and Gray isolated 3,3′-[oxybis(methylene)]-bis(9-methoxy-9*H*-carbazole) (**261.2**) from the stem bark of *Murraya koenigii*.[542] This alkaloid is the first example of an ether-linked symmetrical biscarbazole with *N*-methoxycarbazole units and has shown potent activity against Gram-negative bacteria and fungi.[542] Murranimbine (**261.3**), a homodimer of

Scheme 261

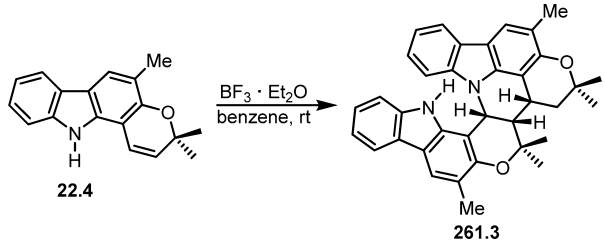


261.1 Oxydimurrayafoline
261.2 3,3′-[Oxybis(methylene)]bis-(9-methoxy-9*H*-carbazole)
261.3 Murranimbine
261.4
261.5

girinimbine (**22.4**), was obtained in 1991 as a racemate by Ito and Furukawa from the acetone extract of the root bark of *Murraya euchrestifolia* collected in Taiwan. The relative stereochemistry of this alkaloid was assigned based on 2D-NMR studies.[543] In 2011, Pittayakhajonwut and co-workers isolated compounds **261.4** and **261.5** from *Streptomyces* sp. BCC26924 together with the known carbazomycin A (**172.1**), B (**27.9**), C (**195.6**), and D (**195.7**) and a closely related tetrahydrocarbazole.[544] The structures of **261.4** and **261.5** were assigned based on NMR experiments. Both alkaloids showed some antimalaria and antituberculosis activity. The authors did not assign a common name.

In 2010, Chakraborty and Mukhopadhyay reported the dimerization of girinimbine (**22.4**) to murranimbine (**261.3**) (Scheme 262). Treatment of 50 mg of **22.4** with boron trifluoride−diethyl ether complex led to 30 mg of a crude product from which murranimbine (**261.3**) was isolated by preparative TLC.[545] The non-natural dimer of koenigicine

Scheme 262



22.4
261.3

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

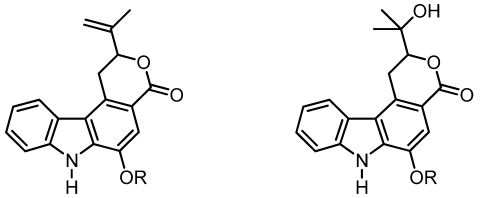
(**212.3**) was synthesized as well using the same reaction conditions.

6. CARBAZOLELACTONE ALKALOIDS

6.1. Isolation from Natural Sources

The δ-lactone carbazole alkaloids feature a carbazole framework with an annulated δ-lactone ring. So far, all alkaloids of this class are oxygenated at C-1 of the carbazole framework. The δ-lactone is fused either at C-3/C-4 or at C-2/C-3 of the carbazole ring system. The clausamines A–C (**263.1**–**263.3**) were the first naturally occurring carbazole alkaloids with a lactone moiety (Scheme 263). In 1998, Ito et al. isolated

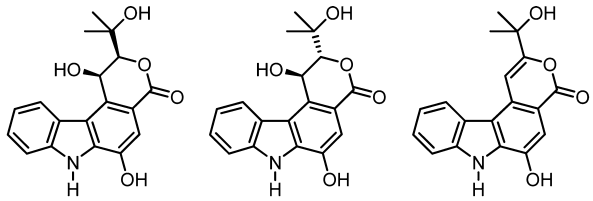
Scheme 263



263.1 Clausamine-A R = H
263.2 Clausamine-B R = Me
263.3 Clausamine-C R = Me
263.4 Clausevatine-D R = H

clausamine-A (**263.1**), -B (**263.2**), and -C (**263.3**) in racemic form ($[\alpha]_D$ = 0, c 0.0372–0.082, $CHCl_3$) from the branches of *Clausena anisata* collected in Taiwan.[546] Two years later, Ito et al. reported the antitumor-promoting properties of clausamine-A, -B, and -C during short-term in vitro assays of TPA-induced EBV-EA activation in Raji cells.[276] In 1998, Wu et al. reported the isolation of further carbazole lactone alkaloids from the root bark of *Clausena anisata*: clausevatine-D (**263.4**), -E (**264.1**), -F (**264.2**), and -G (**264.3**) (Schemes 263 and 264).[547] In Taiwan,

Scheme 264

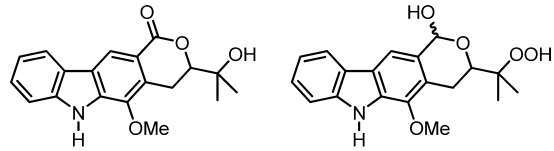


264.1 Clausevatine-E **264.2** Clausevatine-F **264.3** Clausevatine-G

this wild shrub is used in folk medicine for the treatment of snakebites and abdominal pain and also as a detoxificant. The absolute configurations of the optically active clausevatine-D (**263.4**) ($[\alpha]_D$ = −5.7, c 0.932, HOMe), clausevatine-E (**264.1**) ($[\alpha]_D$ = −92.4, c 0.0552, HOMe), and clausevatine-F (**264.2**) ($[\alpha]_D$ = −199, c 0.0203, HOMe) are not known.[547]

In contrast to the clausamines and clausevatines, mafaicheenamine A (**265.1**) and B (**265.2**) feature a pyrano[4,3-*b*]carbazole framework (Scheme 265). Both alkaloids, mafaicheenamine A (**265.1**) and mafaicheenamine B (**265.2**), were isolated by Maneerat and Laphookhieo from the twigs of *Clausena lansium*.[250] The name mafaicheenamine is derived from "mafaicheen", the local Thai name of *C. lansium*. The structures of both alkaloids were assigned based on NMR and MS experiments. The absolute configurations of the optically active mafaicheenamine A (**265.1**) ($[\alpha]_D^{26}$ = +81.37, c 0.02, HOMe) and mafaicheenamine B (**265.2**) ($[\alpha]_D^{24}$ = +32.47, c 0.02, HOMe) have not been determined.

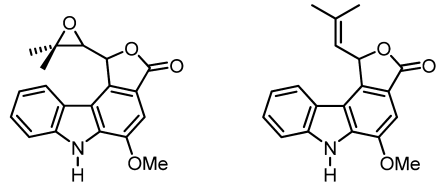
Scheme 265



265.1 Mafaicheenamine A **265.2** Mafaicheenamine B

Furanoclausamine A (**266.1**) and furanoclausamine B (**266.2**) were obtained in 2009 by Furukawa and co-workers from the acetone extract of *Clausena anisata* (Willd.) Oliv. collected in Thailand (Scheme 266).[548] Both alkaloids feature a

Scheme 266



266.1 Furanoclausamine A **266.2** Furanoclausamine B

furo[3,4-*c*]carbazole framework. Like the δ-lactone carbazole alkaloids, the furanoclausamines are oxygenated at C-1 of the carbazole ring system. The structures have been assigned based on IR, MS, ^{1}H NMR, ^{13}C NMR, and 2D NMR experiments. Furanoclausamine A (**266.1**) ($[\alpha]_D^{25}$ = −33, c 0.042, HOMe) and furanoclausamine B (**266.2**) ($[\alpha]_D^{25}$ = −20, c 0.075, HOMe) were isolated as optically active compounds. The absolute configurations of furanoclausamine A (**266.1**) and furanoclausamine B (**266.2**) and the relative configuration of furanoclausamine A (**266.1**) were not determined.

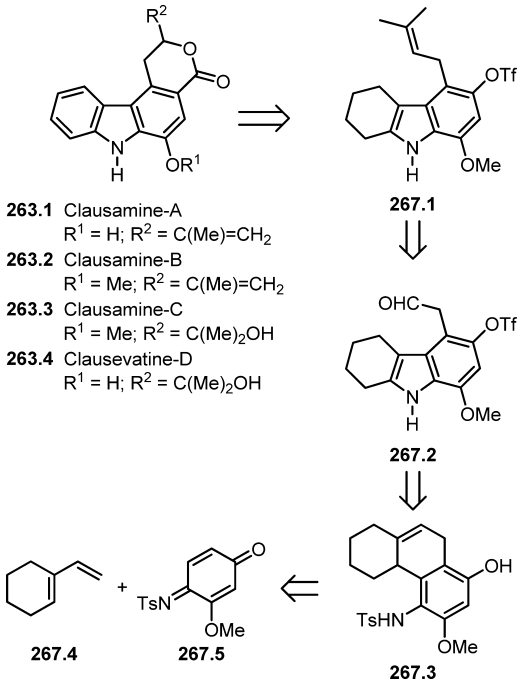
6.2. Total Synthesis of Clausamine-A, -B, and -C and Clausevatine-D

In 2008, Lebold and Kerr reported the first total synthesis of clausamine-A (**263.1**), B (**263.2**), C (**263.3**), and clausevatine D (**263.4**) using the prenylated tetrahydrocarbazole **267.1** as intermediate (Scheme 267). An asymmetric dihydroxylation was used to establish the stereogenic center of the natural products. Intermediate **267.1** derives from the tetrahydrocarbazole **267.2**. The aldehyde **267.2** was accessible from the hexahydrophenanthrene **267.3**, which was synthesized by a Diels–Alder cycloaddition of the diene **267.4** and the quinone imine **267.5**.[549]

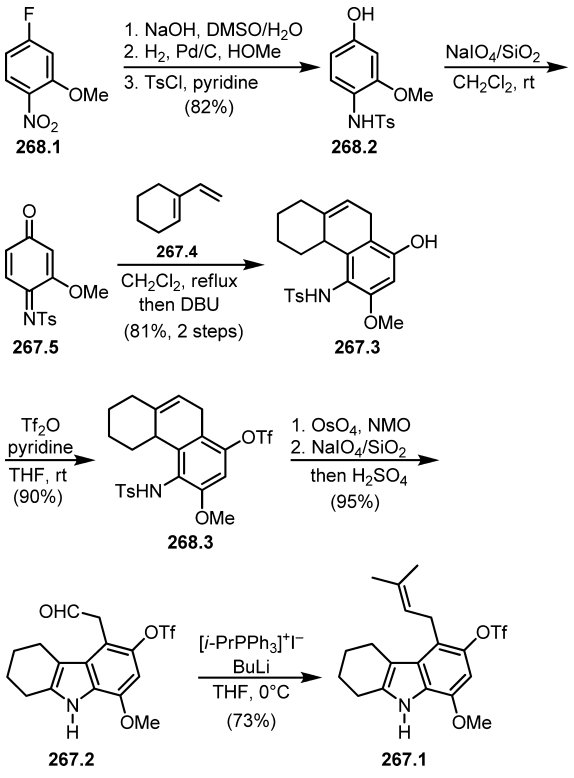
For the synthesis of the required quinone imine **267.5**, 4-fluoro-2-methoxynitrobenzene (**268.1**) was transformed to the tosylated aminophenol **268.2** in 3 steps and 82% overall yield involving a sequence of nucleophilic aromatic substitution, reduction of the nitro group, and tosylation of the resulting amine (Scheme 268).[549] Oxidation of **268.2** with sodium periodate/silica gel afforded the desired quinone imine **267.5**. Diels–Alder cycloaddition of **267.5** and **267.4** in dichloromethane at reflux in the presence of a catalytic amount of DBU directly provided the aromatized product **267.3**. Conversion of the phenol **267.3** to the corresponding triflate **268.3** was achieved using triflic anhydride and pyridine. The dihydronaphthalene **268.3** was then transformed to the tetrahydrocarbazole **267.2** in 95% yield by oxidative cleavage of the double bond followed by treatment of the resulting dicarbonyl compound

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 267



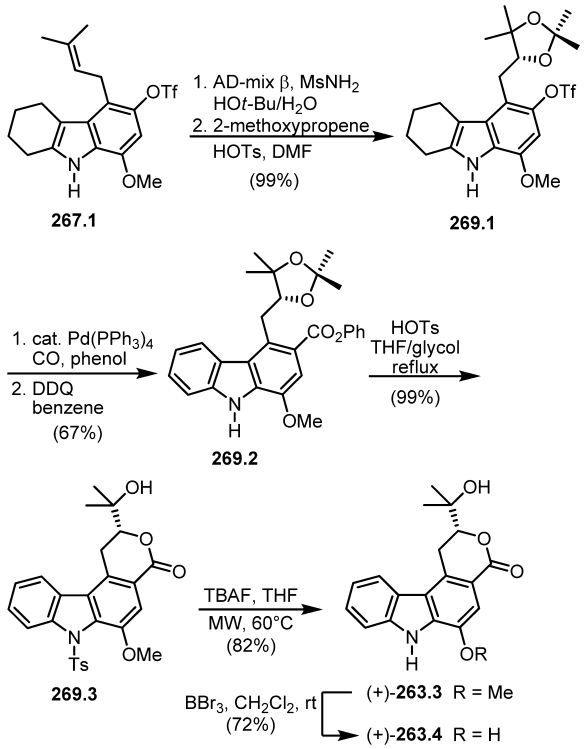
Scheme 268



with sulfuric acid. Wittig reaction of **267.2** with deprotonated isopropyltriphenylphosphonium iodide afforded the desired prenylated tetrahydrocarbazole **267.1**.

Sharpless asymmetric dihydroxylation of the prenylated tetrahydrocarbazole **267.1** with $(DHQD)_2PHAL$ afforded a diol (ee = 45%), which on further reaction with 2-methoxypropene under acidic conditions provided the acetonide **269.1** almost quantitatively (Scheme 269). Using a

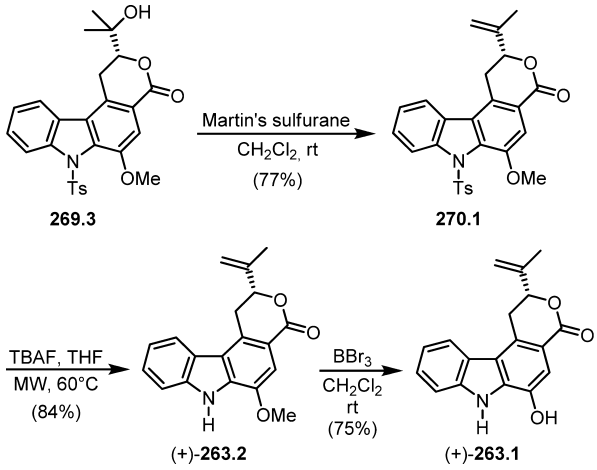
Scheme 269



palladium-catalyzed carbonylation, the acetonide **269.1** was transformed to the corresponding phenyl ester, which on aromatization by reaction with DDQ afforded the carbazole **269.2**. Deprotection of the acetonide with *p*-toluenesulfonic acid in ethylene glycol afforded *N*-tosyl clausamine C (**269.3**) almost quantitatively. Finally, removal of the tosyl group in **269.3** with TBAF afforded (+)-clausamine C [(+)-**263.3**] ($[\alpha]_D$ = +50.0, c 0.036, $CHCl_3$, ee ≈ 47%). Cleavage of the methyl ether with boron tribromide transformed (+)-clausamine C [(+)-**263.3**] to (+)-clausevatine-D [(+)-**263.4**] ($[\alpha]_D$ = +50.7, c 1.380, HOMe, ee ≈ 49%) in 72% yield.[549]

Reaction of *N*-tosyl clausamine C (**269.3**) with Martin's sulfurane followed by detosylation of **270.1** with TBAF afforded (+)-clausamine-B [(+)-**263.2**] ($[\alpha]_D$ = +62.8, c 0.083, $CHCl_3$, ee ≈ 46%) in 84% yield (Scheme 270). Finally, cleavage of the methyl ether of (+)-clausamine-B [(+)-**263.2**]

Scheme 270



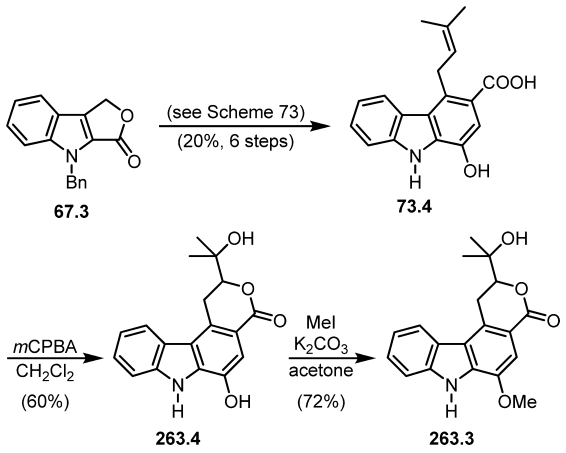
dx.doi.org/10.1021/cr200447s | Chem. Rev. 2012, 112, 3193−3328

by treatment with boron tribromide led to (+)-clausamine-A [(+)-**263.1**] ($[\alpha]_D$ = +33.2, c 0.063, $CHCl_3$, ee ≈ 35%) in 75% yield.[549]

6.3. Total Synthesis of Clausamine-C and Clausevatine-D

Jana and Mal described the total synthesis of clausamine-C (**263.3**) and clausevatine-D (**263.4**) using the 4-prenylcarbazole **73.4** as an intermediate.[297] This compound has been utilized by the same authors for the total synthesis of clausamine D (**54.4**) and clausine F (**56.2**) (Scheme 73). Carbazole **73.4** was obtained from the indole **67.3** in 6 steps using an anionic [4 + 2]-cycloaddition−benzannulation (Scheme 271) and a *para*-Claisen rearrangement as key steps. Epoxidation of the prenyl side-chain of **73.4** and concomitant nucleophilic epoxide opening by the carboxyl group led directly to clausevatine-D (**263.4**) in 60% yield. Chemoselective O-methylation of the phenol hydroxy group provided clausamine-C (**263.3**).

Scheme 271



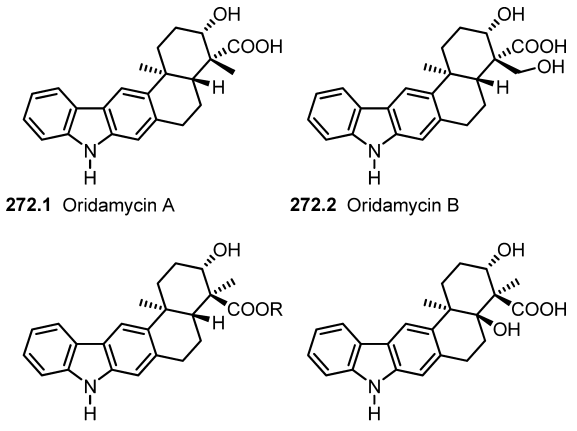
7. TERPENOID CARBAZOLE ALKALOIDS

7.1. Isolation from Natural Sources

The present section describes carbazoles that are derived from indolosesquiterpenes and indoloditerpenes. The carbazole core in these compounds is formed by cyclization of a part of the sesqui- or diterpene moiety of the indoloterpene to an additional benzene ring that is annulated to the indole skeleton. This biogenetic route distinguishes the carbazoles in the present section from the cyclic monoterpenoid pyrano[3,2-*a*]carbazole alkaloids discussed in section 4.2. The terpenoid side-chain of those compounds was added to a preformed carbazole skeleton, and therefore, the cyclic monoterpenoid pyrano[3,2-*a*]carbazole alkaloids are biogenetic derivatives of 3-methylcarbazole (**19.7**). Consequently, the cyclic monoterpenoid pyrano[3,2-*a*]carbazole alkaloids have all been isolated from higher plants while the terpenoid carbazole alkaloids of the present section have been obtained from microorganisms. The alkaloids in Scheme 272 consist of an indole ring system and 15 additional carbon atoms (indolosesquiterpenes). Alternatively, one could regard these alkaloids as carbazolomonoterpenes (2-methylcarbazole and a C_{10} moiety).

Oridamycin A (**272.1**) and B (**272.2**) were isolated by Imamura and co-workers from the fermentation broth of *Streptomyces* sp. KS84, obtained from a soil sample collected in

Scheme 272



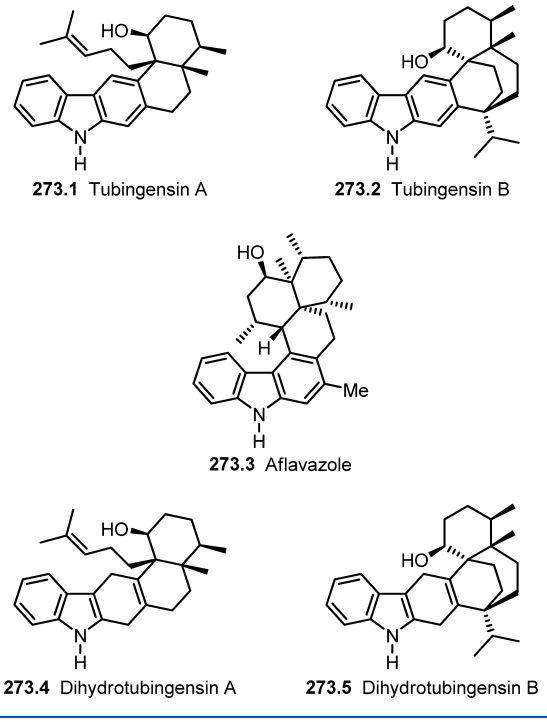
272.1 Oridamycin A
272.2 Oridamycin B
272.3 Xiamycin A (R = H)
272.4 Xiamycin A methyl ester (R = Me)
272.5 Xiamycin B

Uji City, Japan (Scheme 272).[550] Both alkaloids were isolated in 2010 in optically active form (oridamycin A (**272.1**), $[\alpha]_D^{20}$ = +92, c 0.10, HOMe; oridamycin B (**273.2**), $[\alpha]_D^{20}$ = +110, c 0.02, HOMe). The relative configuration of oridamycin A (**272.1**) was assigned based on NMR experiments. Furthermore, oridamycin A (**272.1**) was transformed into the corresponding (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid esters. The absolute configuration was then assigned based on a modification of Mosher's method.[507,551] Oridamycin A (**272.1**) and B (**272.2**) showed biological activity against *Saprolegnia parasitica*, a water mold that infects freshwater fish and ova. Also in 2010, xiamycin A (**272.3**) ($[\alpha]_D^{21}$ = +137.6, c 5.3, HOMe) and its methyl ester **272.4** ($[\alpha]_D^{21}$ = +162.4, c 1.3, HOMe) were obtained by Hertweck and co-workers from *Streptomyces* sp. GT2002/1503, an endophyte of the mangrove plant *Bruguiera gymnorrhiza*.[552] One year later, the same group isolated the analogous xiamycin B (**272.5**) ($[\alpha]_D^{20}$ = −75, c 0.01, HOMe) along with xiamycin A (**272.3**) and related alkaloids from *Streptomyces* sp. HKI0595, an endophyte of the mangrove *Kandelia candel*.[553] The relative configuration of xiamycin A (**272.3**) was assigned based on NMR experiments and unequivocally confirmed by a single-crystal X-ray analysis. The absolute configuration was assigned based on the modified Mosher method.[507,551] Xiamycin A (**272.3**), xiamycin A methyl ester (**272.4**), and xiamycin B (**272.5**) showed antibacterial properties. In addition, xiamycin A (**272.3**) also exhibited a moderate anti-HIV activity.

Tubingensin A (**273.1**) and congeners are derived from an indole moiety and a C_{20} unit and therefore can be classified as indoloditerpenes (Scheme 273). Alternatively, they could be regarded as carbazolosesquiterpenes (2-methylcarbazole and a C_{15} moiety). Tubingensin A (**273.1**) was isolated in 1989 by Gloer and co-workers from the hexane extract of the sclerotia of the fungus *Aspergillus tubingensis*.[554] Tubingensin A (**273.1**) exhibits potent activity against the agriculturally important crop pest caused by *Heliothis zea* and displays in vitro antiviral activity against the herpes simplex virus type 1.[554] Also in 1989, Gloer et al. described the isolation of the cytotoxic hexacyclic carbazole alkaloid tubingensin B (**273.2**) from the same source.[555] This alkaloid exhibits similar activity to that of tubingensin A but was more cytotoxic to HeLa cells (IC_{50} 4 μg mL^{-1} for **273.2** vs 23 μg mL^{-1} for **273.1**). One year later, the same group isolated a new anti-insect carbazole metabolite,

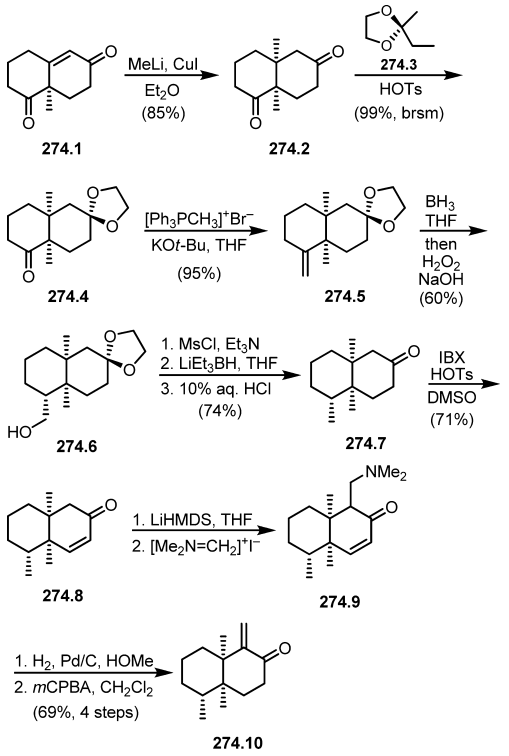
dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 273



273.1 Tubingensin A
273.2 Tubingensin B
273.3 Aflavazole
273.4 Dihydrotubingensin A
273.5 Dihydrotubingensin B

Scheme 274



aflavazole (**273.3**), from the chloroform extract of the sclerotia of a different *Aspergillus* species, *A. flavus*.[556] Aflavazole (**273.3**) showed a strong antifeedant activity against the fungivorous beetle *Carpophilus hemipterus*. Tubingensin A (**273.1**) ($[\alpha]_D^{20}$ = +13.6, c 1.0, $CHCl_3$),[554] tubingensin B (**273.2**) ($[\alpha]_D$ = −6.7, c 0.80, $CHCl_3$),[555] and aflavazole (**273.3**) ($[\alpha]_D$ = +2.8, c 0.35, HOMe)[556] were isolated from nature in optically active form (Scheme 273).

In 2001, Sings et al. isolated dihydrotubingensin A (**273.4**) and dihydrotubingensin B (**273.5**) along with the previously known tubingensin A (**273.1**) and tubingensin B (**273.2**) from the fungus *Aspergillus tubingensis* (ATCC 76608, Trichocomaceae).[557] The dihydrotubingensins A (**273.4**) and B (**273.5**) were the first dihydrocarbazole alkaloids isolated from a living system. Dihydrotubingensin B (**273.5**) was obtained in optically active form ($[\alpha]_D^{20}$ = −50.0, c 0.1, HOMe). In contrast, no value for the optical rotation of dihydrotubingensin A was reported. The co-occurrence of all these alkaloids in the extract of *A. tubingensis* suggests that the dihydrotubingensins A and B are the biogenetic precursors for the tubingensins A and B, which may be formed by oxidation of the dihydrocarbazole unit.

7.2. Synthetic Approach to Terpenoid Carbazole Alkaloids

Although terpenoid carbazole alkaloids with interesting biological activities have been known since the late 1980s, there is still no total synthesis reported for any member of this class of compounds. However, Bonjoch and co-workers reported a synthesis of the pentacyclic framework of tubingensin A (see structure **275.6** in Scheme 275) starting from the Wieland–Miescher ketone (**274.1**).[558] Conjugate addition of lithium dimethylcopper to **274.1** afforded the diketone **274.2** with the desired quaternary center (Scheme 274). Chemoselective protection of the less-hindered ketone in **274.2** with 2-ethyl-2-methyl-1,3-dioxolane (**274.3**) in acidic medium afforded the ketal **274.4** in 99% yield based on recovered starting material (brsm) **274.2**. Wittig methylenation of the carbonyl group in **274.4** gave the *cis*-dimethyldecalin **274.5**. Hydroboration of **274.5** led to the corresponding alcohol **274.6**. Removal of the hydroxy group by mesylation, superhydride reduction, and acidic workup led to the stereochemically pure ketone **274.7**. Oxidation of **274.7** with IBX afforded the enone **274.8**. Reaction of the lithium enolate of **274.8** with Eschenmoser's salt, hydrogenation of the crude polar amine **274.9**, followed by oxidation with *meta*-chloroperbenzoic acid (*m*CPBA) and Cope elimination afforded the exocyclic enone **274.10**. This synthetic sequence led to the enone **274.10** in 11 steps in 18% overall yield starting from Wieland–Miescher ketone (**274.1**).

Robinson annulation of enone **274.10** with 1-(2-nitrophenyl)propan-2-one (**275.1**) in a biphasic system (toluene/60% aqueous KOH) afforded via intermediate **275.3** the cyclohexanone **275.4** as a single diastereoisomer. Elimination of the hydroxy group to a conjugated enone was not observed. Reduction of **275.4** with zinc afforded smoothly the annulated indole **275.5** in 81% yield. Elimination of the tertiary alcohol with *p*-toluenesulfonic acid in toluene at reflux led to a dihydro derivative that, by spontaneous oxidation under the reaction conditions, provided compound **275.6** (Scheme 275).[558]

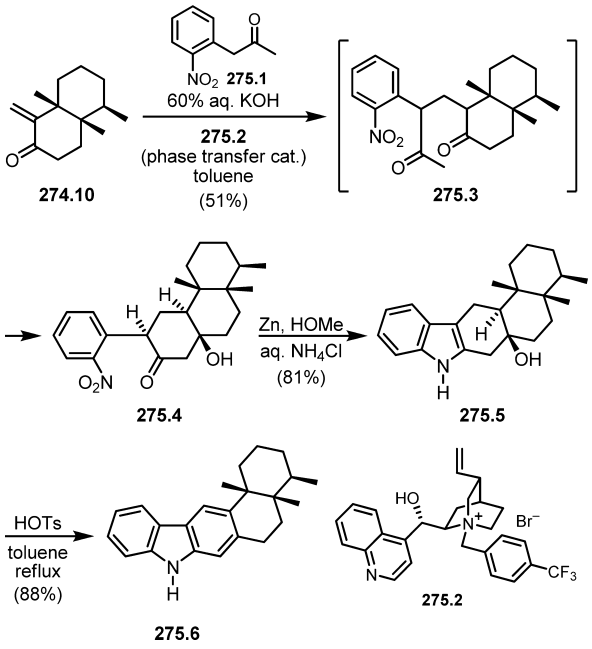
8. BENZOCARBAZOLE ALKALOIDS

8.1. Isolation from Natural Sources

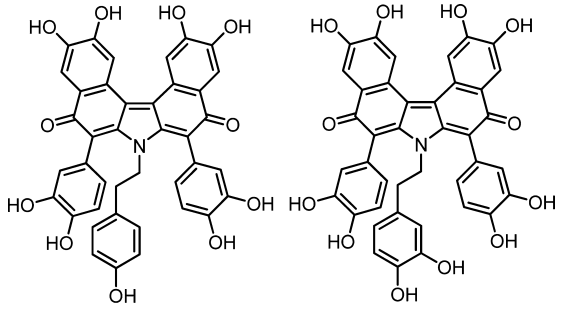
All naturally occurring benzannulated carbazoles obtained so far have a dibenzo[*c*,*g*]carbazole skeleton and were isolated from marine sources. In 1993, Chan et al. isolated the benzocarbazole alkaloid purpurone (**276.1**) from the marine sponge *Iotrochota* sp. at the Koror island, Palau (Scheme 276).[559] Purpurone (**276.1**), as indicated by its name, is purple in color. Purpurone (**276.1**) is the first example of a benzocarbazole alkaloid with a biphenylene quinone methide functionality. It was found that this alkaloid showed ATP-citrate lyase (ACL)

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 275



Scheme 276



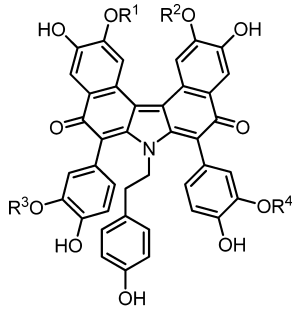
276.1 Purpurone

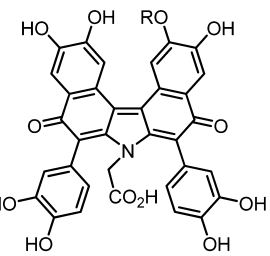
276.2 Ningalin D

inhibitory activity. Four years later, Kang and Fenical reported the isolation of ningalin D (**276.2**) from a marine ascidian of the genus *Didemnum* collected in Western Australia, near Ningaloo Reef.[560] Because of restricted rotation and the apparent helicity, purpurone (**276.1**)[559] and ningalin D (**276.2**)[560] could be chiral. However, both alkaloids were obtained as optically inactive compounds.

In 2010, Li, Bringmann, Lin, and co-workers described 10 further dibenzo[*c*,*g*]carbazole alkaloids (Scheme 277).[561] The baculiferins A–H (**277.1**–**277.8**) are sulfuric acid esters of purpurone (**276.1**). Baculiferin L (**277.9**) and M (**277.10**) possess an acetic acid side-chain at the carbazole nitrogen atom instead of the phenylethyl group, which is found in purpurone (**276.1**), ningalin D (**276.2**), and the baculiferins A–H (**277.1**–**277.8**). The baculiferins L (**277.9**), M (**277.10**), and A–H (**277.1**–**277.8**) were obtained from the ethanol extract of the Chinese marine sponge *Iotrochota baculifera* together with purpurone (**276.1**), ningalin D (**276.2**), and further related compounds. The structures have been assigned based on NMR and electrospray ionization (ESI)-MS data. The authors also reported an inhibitory activity of the baculiferins against the HIV-1 IIIB virus.

Scheme 277





277.1 Baculiferin A
$R^1 = SO_3H$; $R^2,R^3,R^4 = H$

277.2 Baculiferin B
$R^3 = SO_3H$; $R^1,R^2,R^4 = H$

277.3 Baculiferin C
$R^3,R^4 = SO_3H$; $R^1,R^2 = H$

277.4 Baculiferin D
$R^1, R^2 = SO_3H$; $R^3,R^4 = H$

277.5 Baculiferin E
$R^1, R^3 = SO_3H$; $R^2,R^4 = H$

277.6 Baculiferin F
$R^1,R^4 = SO_3H$; $R^2,R^3 = H$

277.7 Baculiferin G
$R^1,R^3,R^4 = SO_3H$; $R^2 = H$

277.8 Baculiferin H
$R^1,R^2,R^3 = SO_3H$; $R^4 = H$

277.9 Baculiferin L
R = H

277.10 Baculiferin M
$R = SO_3H$

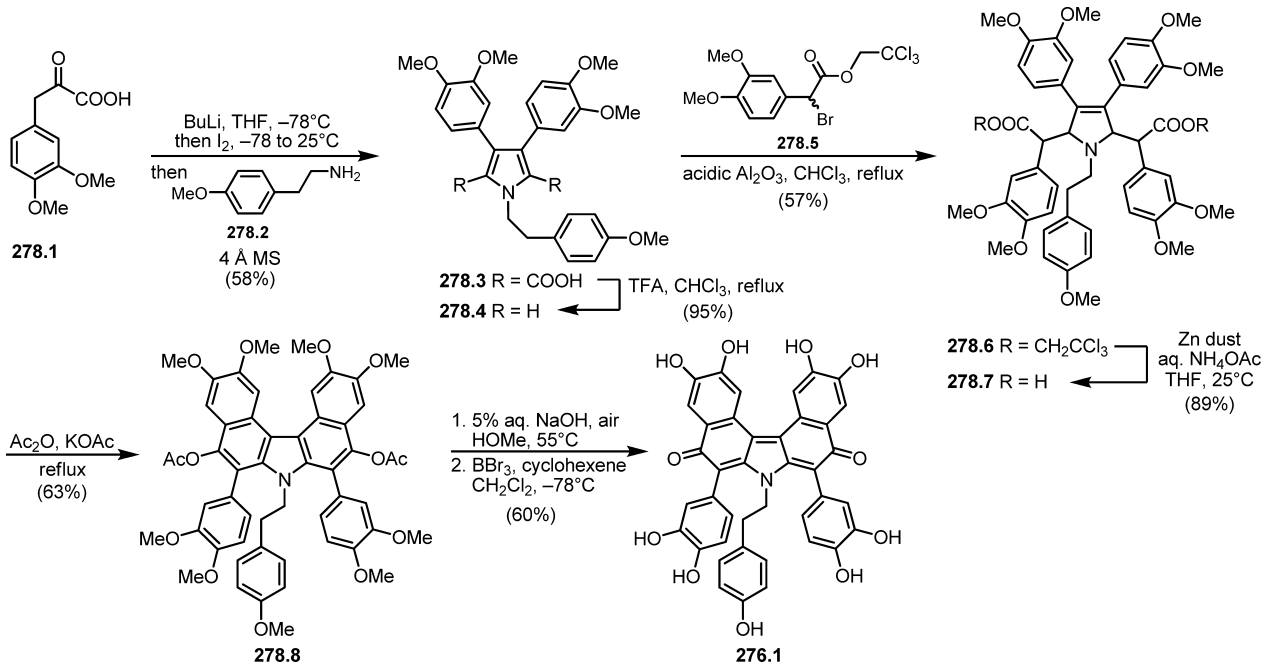
8.2. Synthesis of Benzocarbazole Alkaloids

Prior to the isolation of the natural benzocarbazole alkaloids purpurone (**276.1**) and ningalin D (**276.2**), various isomeric benzocarbazoles were synthesized. A range of useful pharmacological properties associated with this class of compounds[1,12] induced a widespread interest in the synthesis of non-natural benzocarbazoles. The methods used for the synthesis of various benzocarbazole derivatives range from polar (ionic) over radical to pericyclic reactions. Moreover, a number of transition metal-mediated reactions has been employed.[1,12] Recent approaches to non-natural benzocarbazoles include the synthesis via intramolecular Michael addition of (2-aminoaryl)-substituted naphthoquinones,[562] benzannulation of substituted indoles via electrocyclization,[563] and cyclocondensation of carbazolylidenemalononitriles and acetylenic esters.[564]

8.2.1. Syntheses of Purpurone. Seven years after the isolation from natural sources, Peschko and Steglich reported the first total synthesis of purpurone (**276.1**).[565] Oxidative dimerization of two molecules of the arylpyruvic acid **278.1**, followed by condensation of the resulting 1,4-diketone with *O*-methyltyramine (**278.2**), formed the N-substituted 3,4-diarylpyrrole-2,5-dicarboxylic acid **278.3**, which was used as core pyrrole unit (Scheme 278). Decarboxylation of **278.3** with trifluoroacetic acid in chloroform at reflux afforded the pyrrole **278.4** almost quantitatively. Two-fold Friedel–Crafts alkylation of pyrrole **278.4** with the bromoester **278.5** in the presence of a large excess of acidic alumina led to the key intermediate **278.6**. Cleavage of the ester groups in **278.6** under mild conditions by reaction with zinc and aqueous ammonium acetate in tetrahydrofuran followed by regioselective cyclization of the diacid **278.7** on heating with acetic anhydride and potassium acetate provided the diacetate **278.8**. Saponification of **278.8** with aqueous sodium hydroxide in methanol followed by exhaustive methyl ether cleavage with an excess of boron tribromide in dichloromethane using cyclohexene as a bromine

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

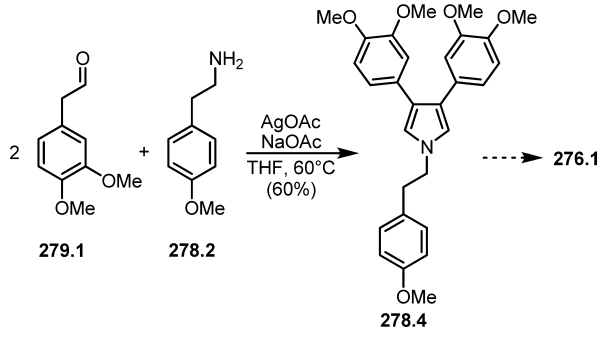
Scheme 278



scavenger led to purpurone (**276.1**) in 7 steps and 10% overall yield.

Jia and co-workers described a one-step access to the pyrrole **278.4** by silver(I)-mediated oxidative cyclocondensation of the phenylacetaldehyde **279.1** and *O*-methyltyramine (**278.2**) (Scheme 279).[566] The pyrrole **278.4** was subsequently transformed into purpurone (**276.1**) following Steglich's route.

Scheme 279



8.2.2. Total Synthesis of Ningalin D. In 2005, Boger and co-workers reported the first total synthesis of ningalin D (**276.2**) starting from the diphenylacetylene **280.1** and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**280.2**).[567] The key step of this approach is the formation of a fully substituted pyrrole ring via an inverse electron demand hetero-Diels–Alder reaction of a diazadiene followed by reductive ring-contraction of the resulting 1,2-diazine.[567] The [4 + 2]-cycloaddition reaction of **280.1** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**280.2**) in toluene at reflux led to the symmetrical 1,2-diazine **280.3** (Scheme 280). Reductive ring-contraction of **280.3** by treatment with zinc and trifluoroacetic acid followed by N-alkylation of the resulting pyrrole with the arylethyl iodide **280.4** afforded the corresponding *N*-alkyl pyrrole **280.5**. A double Dieckmann condensation of **280.5** by treatment with sodium hydride afforded the bisphenol **280.6**. Conversion of the bisphenol **280.6** into the corresponding bistriflate **280.7** followed by 2-fold Suzuki–Miyaura coupling with 3,4-dimethoxyphenylboronic acid (**280.8**) provided the diester **280.9**. Hydrolysis of the diester **280.9** by reaction with potassium *tert*-butoxide afforded the dicarboxylic acid **280.10**. Using modified conditions for the Curtius rearrangement [diphenyl phosphorazidate (DPPA) and Hünig's base], the dicarboxylic acid **280.10** was transformed to the corresponding diisocyanate, which on in situ hydrolysis and oxidation afforded permethylningalin D (**280.11**) in 70% yield. Finally, exhaustive demethylation of **280.11** with an excess of boron tribromide led almost quantitatively to ningalin D (**276.2**).

9. FUROCARBAZOLE ALKALOIDS

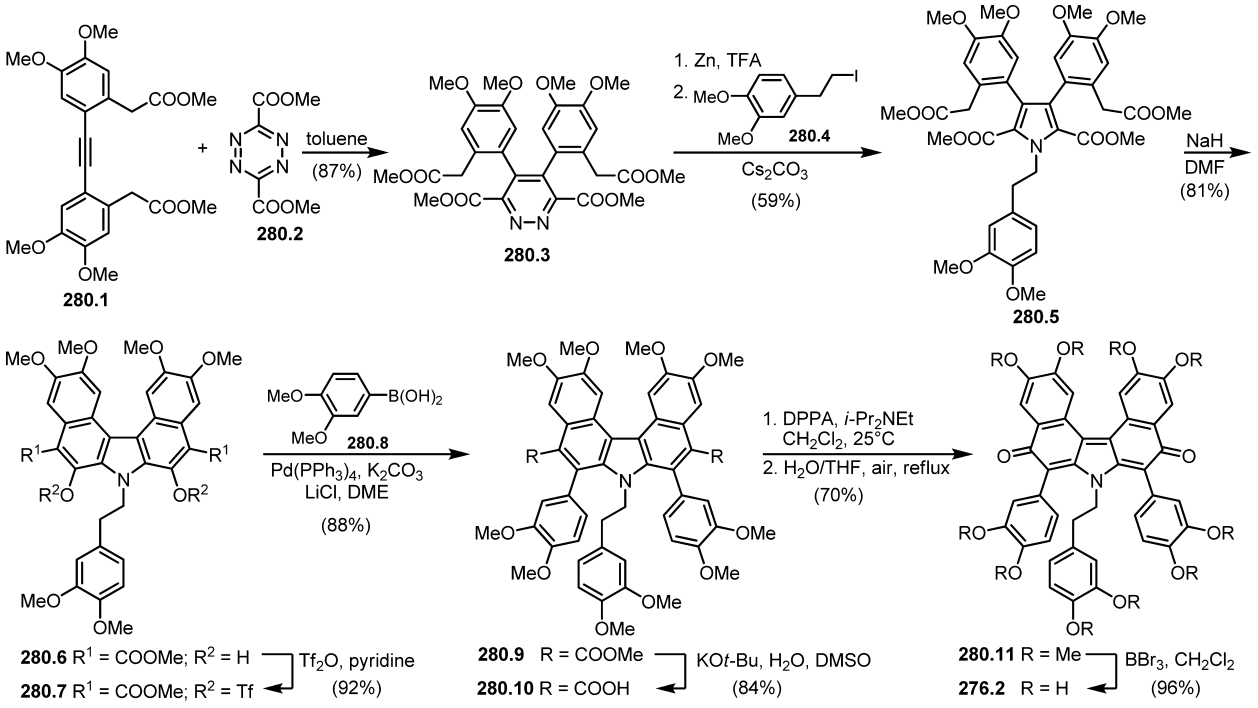
Carbazole alkaloids fused to a furan ring represent a relatively young and rare class of natural products. Until today, only four furocarbazole alkaloids have been found in nature. On the basis of the annulation mode of the furan ring at the carbazole framework, this group is divided into two subclasses. In 2004, Knölker and co-workers have summarized the occurrence, biological activity, and total synthesis of furocarbazoles.[568,569]

9.1. Furo[3,2-*a*]carbazole Alkaloids

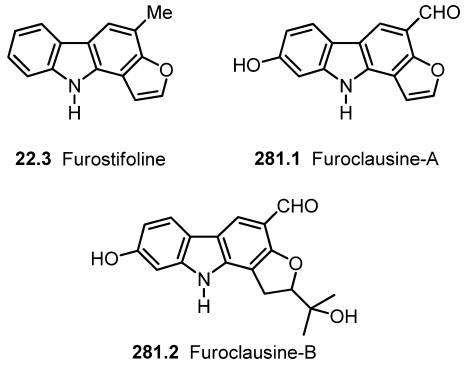
9.1.1. Isolation from Natural Sources. In 1990, Ito and Furukawa described the isolation of the first furo[3,2-*a*]carbazole alkaloid, furostifoline (**22.3**), from the root bark of *Murraya euchrestifolia* Hayata collected in the central and southern parts of Taiwan in December (Scheme 281).[353] The leaves and bark extracts of this plant have been used in folk medicine. Seven years later, Wu et al. reported the isolation of two further furocarbazole alkaloids, furoclausine-A (**281.1**) and furoclausine-B (**281.2**), from the acetone extract of the root bark of a different plant source, *Clausena excavata*.[484] Furoclausine-B (**281.2**) was isolated from nature in optically active form ($[\alpha]_D$ = −32.73, c 0.022, HOMe). However, the absolute stereochemistry of furoclausine-B (**281.2**) is still unknown.[484]

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

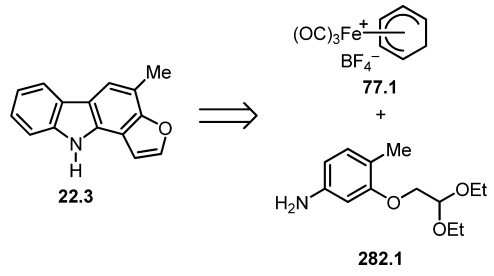
Scheme 280



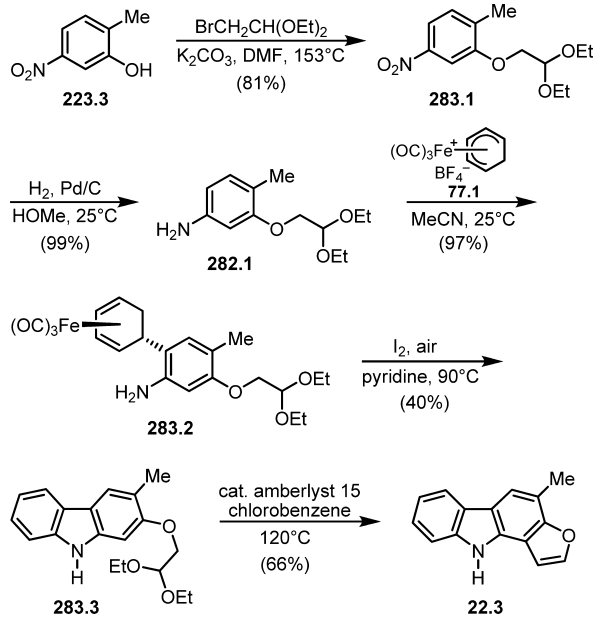
Scheme 281



Scheme 282



Scheme 283



9.1.2. Knölker's Total Synthesis of Furostifoline. In 1996, Knölker and Fröhner reported the first total synthesis of furostifoline (**22.3**).[570] Four years later, the same authors described an improved route to the same natural product.[571] In the new approach, the carbazole nucleus is formed first followed by annulation of the furan ring. This constitutes a reversal of the sequence for the two cyclization reactions as compared to Knölker's earlier synthesis. The iron complex salt **77.1** and the arylamine **282.1** were used as synthetic precursors (Scheme 282).

The required arylamine **282.1** was prepared starting from the commercial 2-methyl-5-nitrophenol (**223.3**) over 2 steps in 80% yield (Scheme 283).[571] Alkylation of **223.3** with bromoacetaldehyde diethyl acetal, a well-established C_2-building block for the synthesis of benzofurans, led to the ether **283.1**. Catalytic hydrogenation of the nitro derivative **283.1** afforded almost quantitatively the corresponding arylamine **282.1**. Electrophilic aromatic substitution of the arylamine **282.1** with the iron complex salt **77.1** in acetonitrile at room temperature provided the iron complex **283.2** almost quantitatively. The iron-mediated arylamine cyclization of

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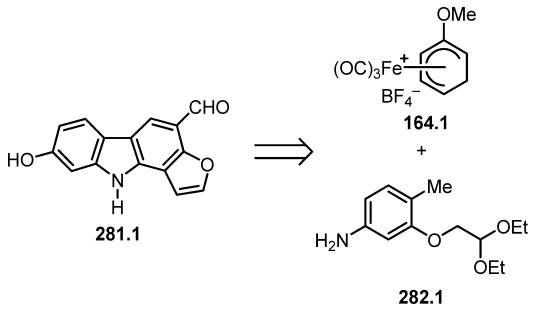
complex **283.2** with iodine in pyridine led to the carbazole **283.3**. Annulation of the furan ring by reaction of the carbazole **283.3** with catalytic amounts of amberlyst 15 in chlorobenzene at 120 °C afforded directly furostifoline (**22.3**). This synthesis provides furostifoline (**22.3**) in only 5 steps and 21% overall yield based on the nitrophenol **223.3**.[571] In comparison, Knölker's first synthesis led to the natural product in 7 steps and 19% overall yield based on the same starting material.[570]

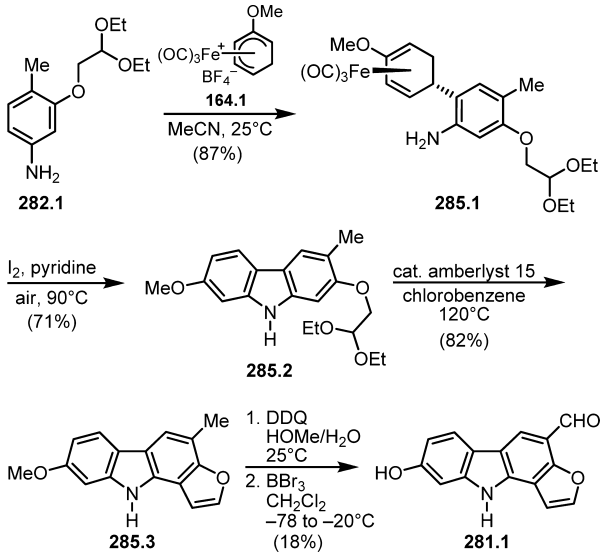
9.1.3. Total Synthesis of Furoclausine-A. In 2004, Knölker and Krahl described the first total synthesis of furoclausine-A (**281.1**).[572] The synthetic approach was based on the improved route to furostifoline (**22.3**) (see Scheme 283).[571] The arylamine **282.1** and tricarbonyl(η^5-2-methoxycyclohexadienylium)iron tetrafluoroborate (**164.1**) were used as precursors (Scheme 284).

Scheme 284



Electrophilic substitution of the arylamine **282.1** with the iron complex salt **164.1** afforded regioselectively the iron complex **285.1** (Scheme 285). As one would expect, the yield

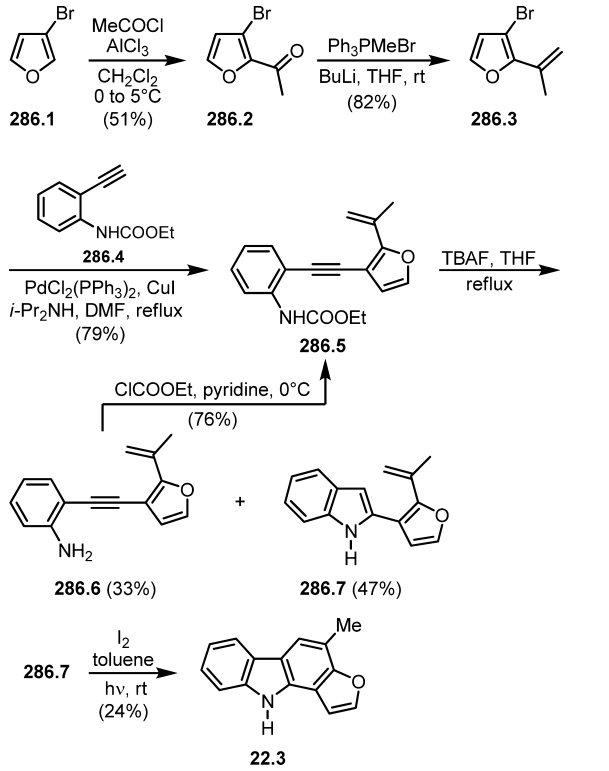
Scheme 285



for the electrophilic aromatic substitution of **282.1** with the methoxy-substituted iron complex salt **164.1** was slightly lower as compared to the analogous reaction with the more electrophilic unsubstituted iron complex salt **77.1**. In contrast, the oxidative cyclization of complex **285.1** to the carbazole **285.2** with iodine in pyridine proceeded in a much better yield than the cyclization of **283.2** under the same reaction conditions. Annulation of the furan ring by heating the carbazole **285.2** with catalytic amounts of amberlyst 15 in chlorobenzene at 120 °C afforded 8-methoxyfurostifoline (**285.3**). Oxidation of the methyl group of **285.3** to a formyl group with DDQ and subsequent cleavage of the methyl ether finally provided furoclausine-A (**281.1**) in 5 steps and 9% overall yield based on the iron complex salt **164.1**.[572]

9.1.4. Yasuhara's Total Synthesis of Furostifoline. In 2002, Yasuhara et al. reported a synthesis of furostifoline (**22.3**) by oxidative photocyclization of 3-(indol-2-yl)-2-(propen-2-yl)furan (**286.7**) (Scheme 286).[573] Friedel–Crafts acylation of

Scheme 286



3-bromofuran (**286.1**) led to 2-acetyl-3-bromofuran (**286.2**), which was obtained in 51% yield. Wittig reaction of **286.2** with methyltriphenylphosphonium bromide and butyllithium provided 3-bromo-2-(propen-2-yl)furan (**286.3**). Sonogashira coupling of **286.3** with ethyl 2-ethynylphenylcarbamate (**286.4**) afforded the N-protected 2-[(2-(propen-2-yl)furan-3-yl)ethynyl]aniline **286.5**. TBAF-promoted cyclization of **286.5** led to 3-(indol-2-yl)-2-(propen-2-yl)furan (**286.7**) in 47% yield along with the deprotected aniline **286.6** in 33% yield. Compound **286.6** was recycled to the *N*-ethoxycarbonyl derivative **286.5** in 76% yield by protection of the amino group. Finally, photocyclization of **286.7** with catalytic amounts of iodine in toluene afforded furostifoline (**22.3**) in 5 steps and 4% overall yield.[573]

9.2. Furo[2,3-*c*]carbazole Alkaloids

9.2.1. Isolation from Natural Sources. Up to today, only one naturally occurring furo[2,3-*c*]carbazole is known. Eustifoline-D (**287.1**) was described by Ito and Furukawa in 1990 (Scheme 287).[353] The natural product was obtained along with its regioisomer furostifoline (**22.3**) (see Scheme 281) from the root bark of *Murraya euchrestifolia* Hayata. The extract of the leaves and bark of this plant have been used as folk medicine in China.

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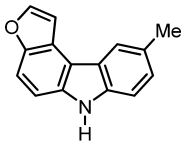
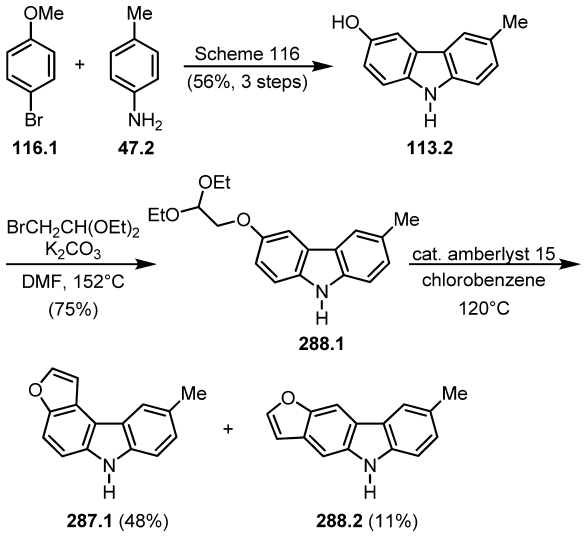
Scheme 287



287.1 Eustifoline-D

9.2.2. Total Synthesis of Eustifoline-D. In 2007, Knölker and co-workers reported the first total synthesis of eustifoline-D (**287.1**) starting from glycozolinine (**113.2**), which was obtained in 3 steps and 56% overall yield from 4-bromoanisole (**116.1**) and *p*-toluidine (**47.2**) (Scheme 288).[95] Williamson

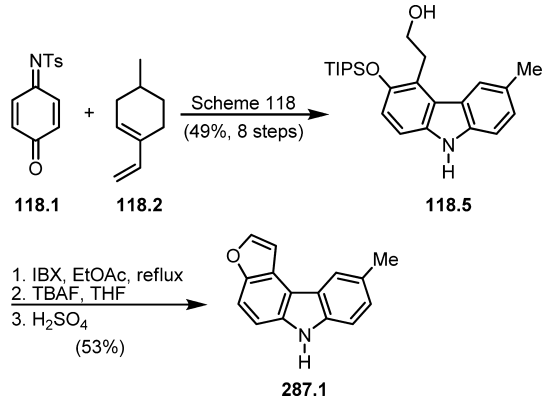
Scheme 288



ether synthesis of **113.2** with bromoacetaldehyde diethyl acetal afforded compound **288.1**. The cyclization of **288.1** using catalytic amounts of amberlyst 15 in chlorobenzene at reflux afforded eustifoline-D (**287.1**) along with isoeustifoline-D (**288.2**) in a ratio of 4.3:1. This route provides eustifoline-D (**287.1**) in 5 steps and 20% overall yield based on 4-bromoanisole (**116.1**).

Later in the same year, Lebold and Kerr reported a synthesis of eustifoline-D (**287.1**) via the carbazole **118.5**, which has been an intermediate in their total synthesis of glycomaurrol (**114.1**) (Scheme 289).[357] Oxidation of the hydroxy group of

Scheme 289



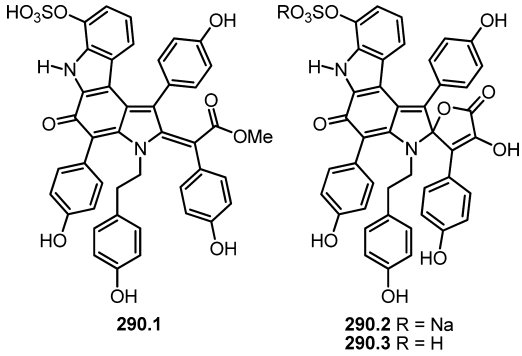
118.5 with IBX afforded the corresponding carbazol-5-ylacetaldehyde. Removal of the silyl group with TBAF was followed by treatment with sulfuric acid to induce the cyclodehydratization to eustifoline-D (**287.1**).

10. PYRROLO[2,3-*c*]CARBAZOLE ALKALOIDS

10.1. Isolation from Natural Sources

Since the late 1980s, pyrrolocarbazoles emerged as a new class of heteroaryl-condensed carbazoles. These compounds attracted strong interest due to their broad spectrum of biological activities, such as anticancer, antidiabetic, neurotropic, and protein kinase C (PKC) inhibitory properties.[12,574] However, for a decade pyrrolocarbazoles have been solely of synthetic origin. In 1993, Sato et al. isolated the pyrrolo[2,3-*c*]carbazole alkaloids **290.1**, **290.2**, and **290.3** from the methanol extract of the marine sponge *Dictyodendrilla* sp. (Scheme 290).[575] These

Scheme 290



compounds exhibited inhibitory activity against bovine lens aldose reductase. Although **290.2** and **290.3** have a stereogenic center, they have been isolated from nature in optically inactive form (no Cotton effect).

A decade later, Fusetani and co-workers reported the isolation of further pyrrolo[2,3-*c*]carbazole alkaloids, the dictyodendrins A (**291.1**), B (**291.2**), C (**291.3**), D (**291.4**), and E (**291.5**), along with the previously known carbazole alkaloid **290.2** in a bioassay-guided fractionation of the Japanese marine sponge *Dictyodendrilla verongiformis* (Scheme 291).[576] Despite the presence of a stereogenic center, the circular dichroism (CD) spectrum of dictyodendrin A (**291.1**) shows no Cotton effect, indicating that the natural product has been isolated in racemic form. This assumption was supported by reverse-phase chiral HPLC. The dictyodendrins A–E (**291.1**–**291.5**) were the first marine natural products to exhibit a telomerase-inhibitory activity. Consequently, a number of non-natural pyrrolo[2,3-*c*]carbazoles have been prepared for structure–activity relationship studies.[577−581]

10.2. Total Synthesis of Dictyodendrin B, C, and E

Two years after the isolation, Fürstner et al. reported the first total synthesis of dictyodendrin B (**291.2**),[582,583] C (**291.3**),[583] and E (**291.5**)[583] in the form of their ammonium salts from the common pyrrolocarbazole precursor **293.2** using a McMurry coupling and a 6π-electrocyclization as key steps. The synthesis of the relay compound **293.2** starts from the readily available 3-hydroxy-2-nitroacetophenone (**292.1**).[582,583] First, **292.1** was transformed into the corresponding isopropyl ether (Scheme 292). Base-induced aldol condensation with *p*-methoxybenzaldehyde (**292.2**) to the chalcone **292.3** was followed by pyrrole

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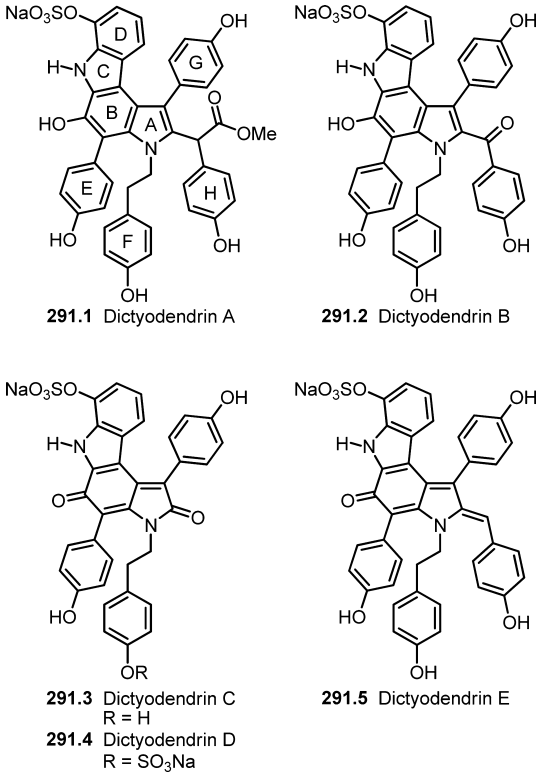
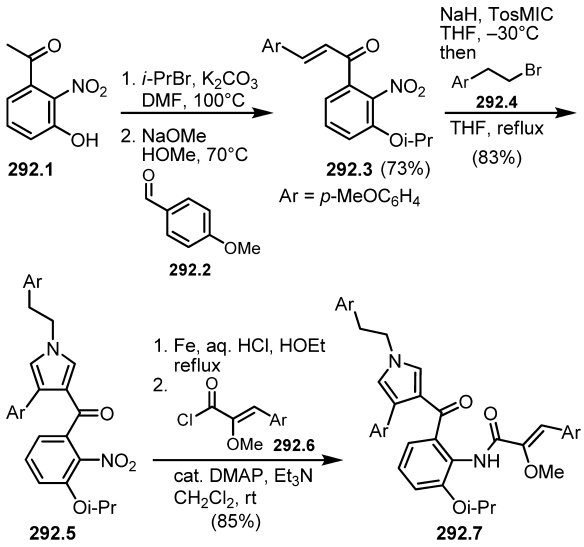
Scheme 291



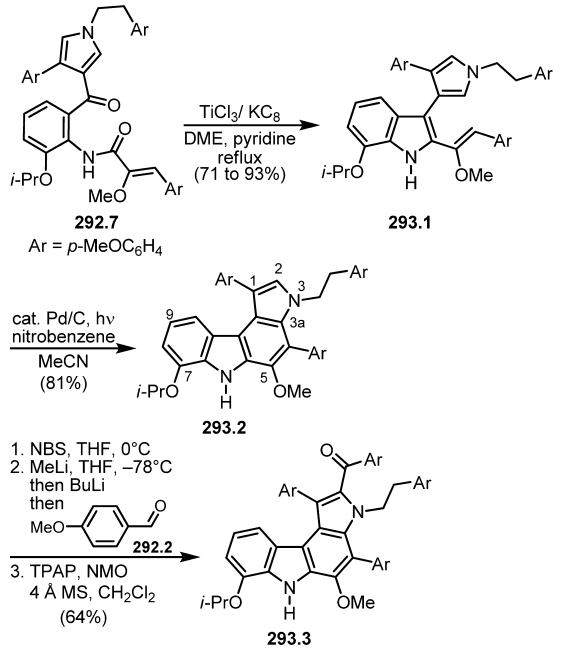
Scheme 292



annulation with *p*-toluenesulfonylmethyl isocyanide (TosMIC) in the presence of sodium hydride at low temperature and in situ N-alkylation with 4-methoxyphenethyl bromide (**292.4**) to the substituted *N*-alkyl pyrrole **292.5**. Reduction of the nitro group in **292.5** with iron under acidic conditions (aqueous hydrochloric acid) led almost quantitatively to the corresponding aniline. Subsequent treatment with the acid chloride **292.6** provided the amide **292.7**.

Intramolecular McMurry coupling of the ketoamide **292.7** using low-valent titanium on graphite, prepared from titanium(III) chloride and 2 equiv of potassium–graphite (KC_8), in 1,2-dimethoxyethane (DME) at reflux provided the indole **293.1** in up to 93% yield (Scheme 293).[582,583] Irradiation of **293.1** with

Scheme 293



UV light in acetonitrile and nitrobenzene in the presence of palladium on activated carbon induced a 6π-electrocyclization followed by aromatization to give the pyrrolo[2,3-*c*]carbazole **293.2**. The carbazole **293.2** was then used as a relay compound for the synthesis of the dictyodendrins B (**291.2**), C (**291.3**), and E (**291.5**).

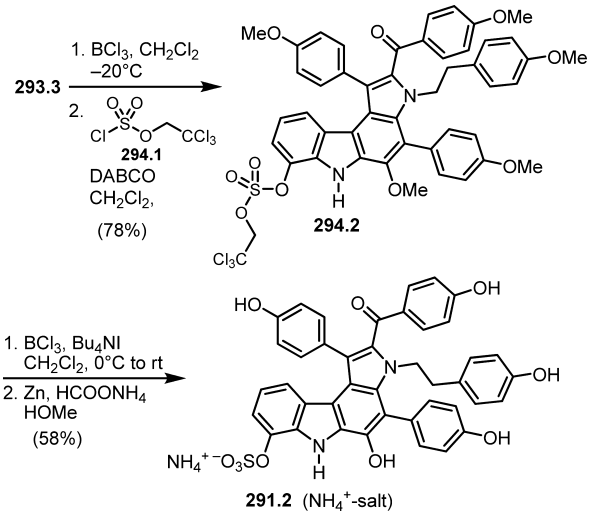
For the synthesis of dictyodendrin B (**291.2**), the pyrrolocarbazole **293.2** was subjected to regioselective bromination at C-2 with NBS to afford an unstable 2-bromopyrrolo[2,3-*c*]carbazole. Deprotonation of the carbazole nitrogen atom, halogen–metal exchange with butyllithium, and subsequent quenching of the intermediate lithio species with *p*-methoxybenzaldehyde (**292.2**) led to a secondary alcohol that was oxidized to the ketone **293.3** using catalytic amounts of tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) as the stoichiometric oxidant. The more direct approach, Friedel–Crafts acylation at C-2 of **293.2** with 4-methoxybenzoyl chloride using either titanium(IV) chloride, tin(IV) chloride, or boron trifluoride as the Lewis acid, had failed.

Chemoselective cleavage of the isopropyl ether in **293.3** with BCl_3 and reaction of the resulting pyrrolo[2,3-*c*]carbazol-7-ol with 2,2,2-trichloroethyl chlorosulfonate (**294.1**) afforded the aryl sulfate **294.2** in 78% yield (Scheme 294).[582,583] Exhaustive demethylation of **294.2** was achieved with BCl_3 and substoichiometric amounts of tetrabutylammonium iodide (TBAI). Subsequent reductive cleavage of the trichloroethyl ester with zinc and ammonium formate led to the ammonium salt of dictyodendrin B (**291.2**).

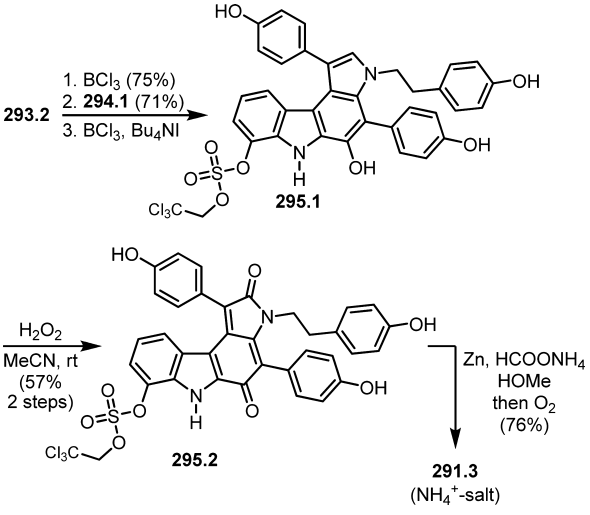
For the total synthesis of dictyodendrin C (**291.3**), the isopropyl ether in the relay compound **293.2** was first cleaved chemoselectively with boron trichloride (Scheme 295). Esterification of the free hydroxy group at C-7 with 2,2,2-trichloroethyl chlorosulfonate (**294.1**) and subsequent cleavage of all methyl ethers using boron trichloride in the presence of tetrabutylammonium iodide provided the tetraol **295.1**. Treatment with hydrogen peroxide in acetonitrile effected a chemoselective oxidation of the pyrrolo[2,3-*c*]carbazol-5-ol

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 294



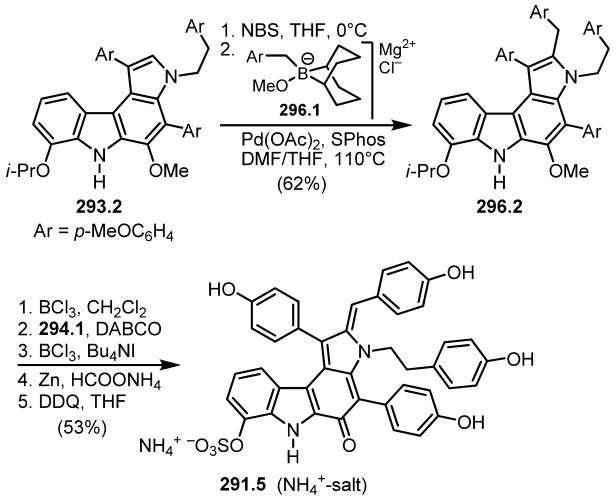
Scheme 295



core of **295.1** to the pyrrolo[2,3-*c*]carbazole-2,5-dione **295.2**. Finally, reductive cleavage of the trichloroethyl ester with an excess of zinc dust and ammonium formate in methanol followed by stirring the reaction mixture under an oxygen atmosphere afforded the ammonium salt of dictyodendrin C (**291.3**) in 76% yield.[583]

The total synthesis of dictyodendrin E (**291.5**) was also achieved using the pyrrolo[2,3-*c*]carbazole **293.2** as an intermediate. The required benzylidene substituent at C-2 was introduced by a Suzuki–Miyaura coupling (Scheme 296). Regioselective bromination of **293.2** using NBS followed by treatment with the borate complex **296.1** in the presence of palladium(II) acetate and SPhos provided the benzylated compound **296.2** in good yield. The borate complex **296.1** was generated in situ from 9-methoxy-9-borabicyclo[3.3.1]nonane (9-MeO-9-BBN) and *p*-methoxybenzylmagnesium chloride. The final steps in the total synthesis of dictyodendrin E (**291.5**) are analogous to those of the total synthesis of dictyodendrin B (**291.2**) and C (**291.3**). Chemoselective cleavage of the isopropyl ether in **296.2** with boron trichloride was followed by esterification of the free hydroxy group with 2,2,2-trichloroethyl chlorosulfonate (**294.1**), exhaustive cleavage of the methyl ethers, and cleavage of the trichloroethyl ester

Scheme 296



by treatment with zinc and ammonium formate. Finally, oxidation of the resulting 2-benzylated pyrrolo[2,3-*c*]carbazol-5-ol to a quinone methide with DDQ afforded the ammonium salt of dictyodendrin E (**291.5**).[583] The approach to the dictyodendrins B (**291.2**), C (**291.3**), and E (**291.5**) has been subsequently applied by Fürstner and co-workers to the synthesis of non-natural derivatives of the dictyodendrins.[580]

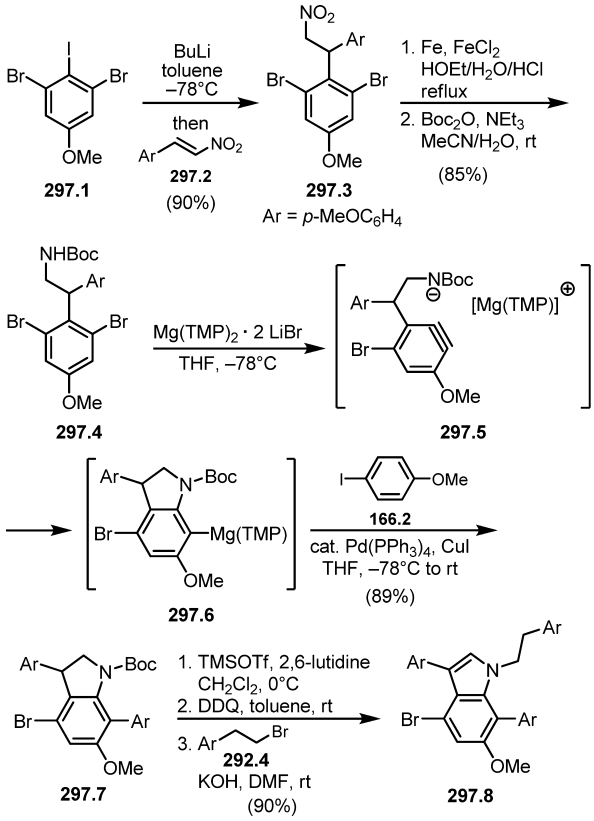
10.3. Total Synthesis of Dictyodendrins A–E

Tokuyama and co-workers developed a synthetic route to the whole series of the dictyodendrins A–E (**291.1**–**291.5**).[584,585] Key steps are the formation of an indole ring system via an aryne intermediate and a thermally induced cyclization of an 2-azidobiphenyl to the carbazole ring system. In contrast to Fürstner's approach (see previous discussion), the A/B-ring system is constructed first. Tokuyama's route starts from the literature-known 3,5-dibromo-4-iodoanisole (**297.1**). Chemoselective halogen–metal exchange of the iodine atom using butyllithium and 1,4-addition of the lithiated arene to the *ω*-nitrostyrene **297.2** provided the nitroethyl-substituted anisole **297.3** in high yield (Scheme 297). Reduction of the nitro group to an amine and protection of the amino group as *tert*-butyl carbamate led to the dibromo compound **297.4**. Treatment of **297.4** with magnesium bis(tetramethylpiperidide)–lithium bromide complex induced the formation of aryne **297.5**. Intramolecular nucleophilic addition of the deprotonated carbamate unit led to the arylmagnesium species **297.6**. An in situ Kumada-type cross-coupling reaction of the indol-7-ylmagnesium compound **297.6** with 4-iodoanisole (**166.2**) afforded the dihydroindole **297.7**. Cleavage of the Boc group was followed by aromatization with DDQ and N-alkylation using *para*-methoxyphenethyl bromide (**292.4**). The resulting alkylated indole **297.8** was used as a relay compound for the total syntheses of dictyodendrin A (**291.1**), B (**291.2**), C (**291.3**), and E (**291.5**).

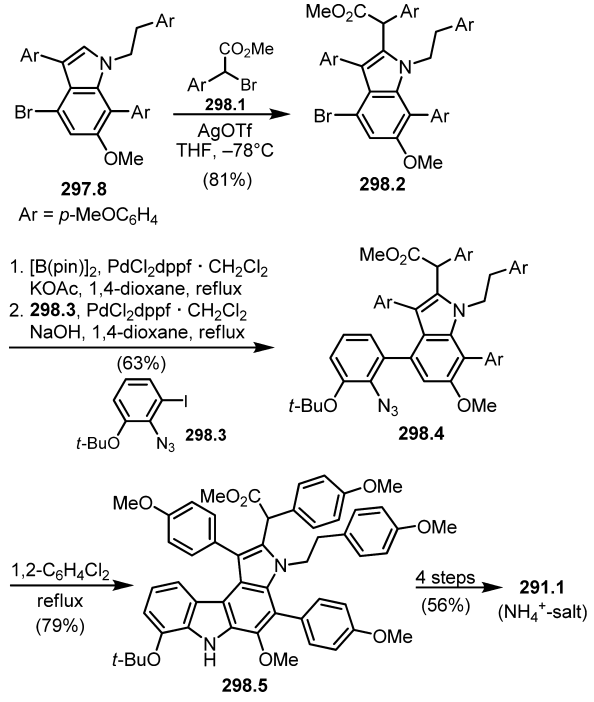
The side-chain at C-2 of the pyrrolo[2,3-*c*]carbazole core of dictyodendrin A (**291.1**) was introduced by a Friedel–Crafts-type alkylation of indole **297.8** with methyl 2-bromo-2-(4-methoxyphenyl)acetate (**298.1**) in the presence of silver triflate (Scheme 298). Borylation at C-4 of the indole ring system with bis(pinacolato)diboron ([B(pin)]$_2$) under Suzuki–Miyaura conditions was followed by Suzuki–Miyaura coupling with 2-azido-3-*tert*-butoxyiodobenzene (**298.3**). Thus, the *ortho*-azidobiphenyl derivative **298.4** was obtained from a halo-

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 297



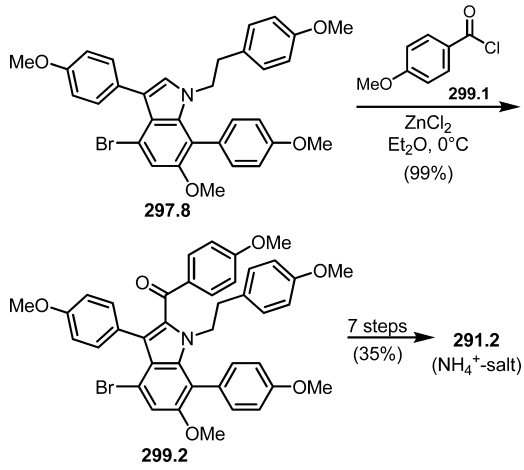
Scheme 298



genated indole by 2-fold Suzuki–Miyaura coupling in good yield. The *ortho*-azidobiphenyl **298.4** was then heated in 1,2-dichlorobenzene at reflux. Thermally induced cyclization with concomitant loss of dinitrogen afforded the pyrrolocarbazole **298.5**. The carbazole **298.5** was then transformed into the ammonium salt of dictyodendrin A (**291.1**) using the same sequence of reactions as reported by Fürstner for the transformation of the analogous **293.3** into dictyodendrin B (**291.2**) (see Scheme 294). The same sequence of transformations has also been applied to the total syntheses of dictyodendrins B–E (**291.2**– **291.5**).

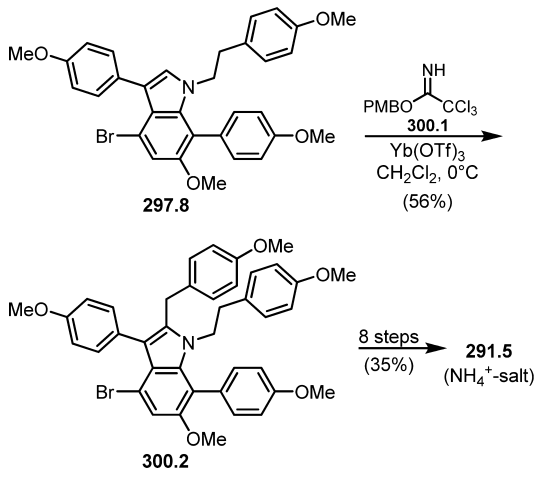
Friedel–Crafts acylation of the relay compound **297.8** with *p*-methoxybenzoyl chloride (**299.1**) using zinc(II) chloride as Lewis acid led to the 4-bromoindole **299.2**, the precursor for the total synthesis of dictyodendrin B (**291.2**) (Scheme 299).

Scheme 299



The side-chain of dictyodendrin E (**291.5**) was introduced by acid-induced alkylation of **297.8** with 4-methoxybenzyl 2,2,2-trichloroacetimidate (**300.1**) (Scheme 300).

Scheme 300



For the total synthesis of the ammonium salt of dictyodendrin C (**291.3**), the relay compound **297.8** was first borylated by Suzuki–Miyaura coupling with bis(pinacolato)-diboron (Scheme 301). Suzuki–Miyaura coupling with 2-azido-3-*tert*-butoxy-iodobenzene (**298.3**) and subsequent thermal cyclization of the azidobiphenyl **301.1** led to the pyrrolocarbazole **301.2**. Compound **301.2** was then transformed into dictyodendrin C (**291.3**) following Fürstner's route (see Scheme 295). Dictyodendrin D (**291.4**) was obtained from the benzyl-protected **302.1** in an analogous way (Scheme 302).

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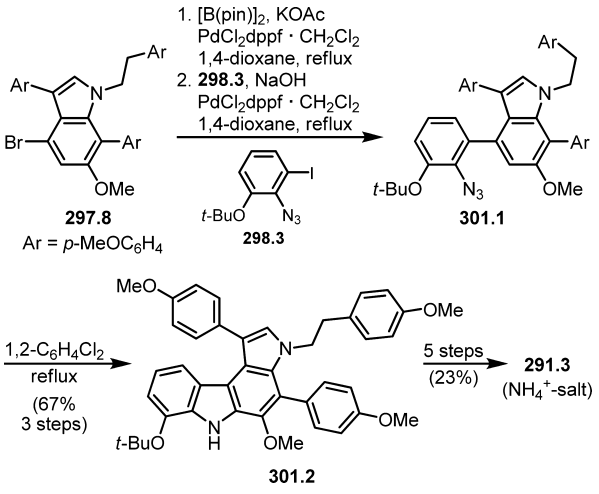
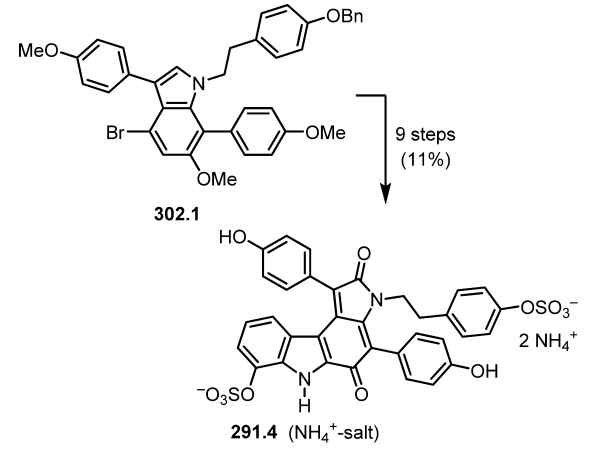
Scheme 301



Scheme 302



10.4. Formal Synthesis of Dictyodendrin B

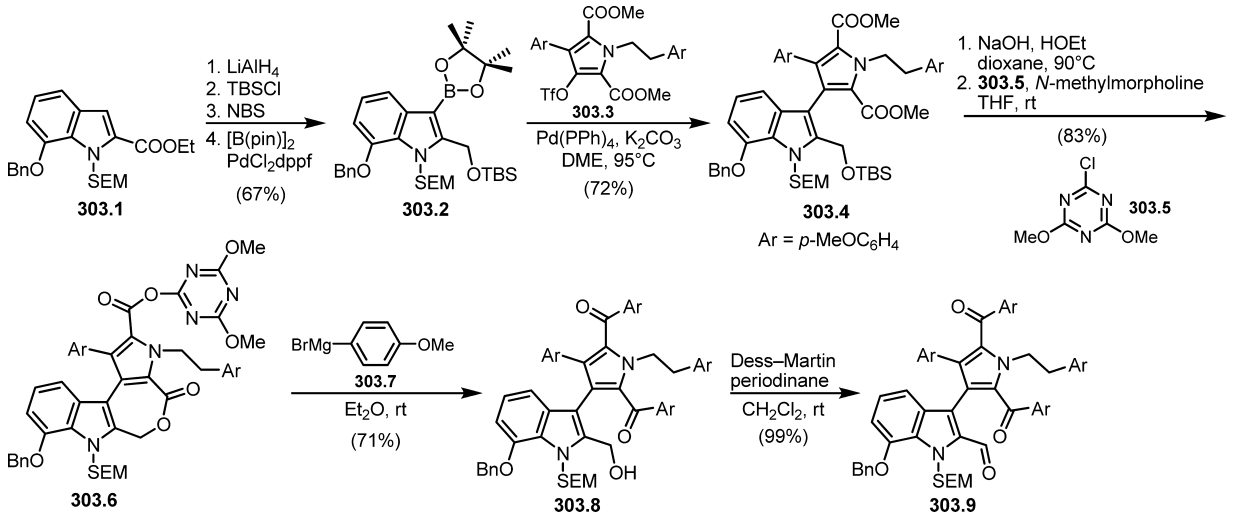
Ishibashi and co-workers devised an approach to dictyodendrin B (**291.2**) using a samarium(II) iodide-induced carbonyl coupling reaction as the key step (Scheme 303).[586] Indole **303.1** is easily available by Reissert synthesis using 3-benzyloxy-2-nitrotoluene as starting material. Reduction of the ester group at C-2 and silyl protection of the resulting hydroxymethyl side-chain was followed by regioselective bromination at C-3 of the indole ring system. Subsequent palladium-catalyzed borylation using bis(pinacolato)diboron furnished the indol-3-ylboronic acid derivative **303.2**. Suzuki–Miyaura coupling of the boronate **303.2** with the literature-known pyrrol-3-yl triflate **303.3**[587] afforded the 3-pyrrolylindole **303.4** in good yield. Treatment of **303.4** with sodium hydroxide in ethanol led to cleavage of the methyl esters and deprotection of the hydroxymethyl unit at C-2 of the indole system. Activation of the carboxyl groups with 2-chloro-4,6-dimethoxy-1,3,5-triazine (**303.5**) furnished the ε-lactone **303.6**. Addition of 4-methoxyphenylmagnesium bromide to both carbonyl groups followed by Dess–Martin-oxidation of **303.8** afforded compound **303.9**, the precursor for the cyclization reaction.

Treatment of **303.9** with samarium(II) iodide in THF at room temperature induced the desired carbonyl coupling reaction to the 4,5-dihydroxytetrahydropyrrolo[2,3-*c*]carbazole **304.1** (Scheme 304). Aromatization was then achieved by acetic anhydride-mediated elimination reaction of the tertiary alcohol with concomitant acetylation of the hydroxy group at C-5. The acetoxy group at C-5 was then transformed into a methoxy group by treatment with sodium methoxide followed by immediate O-alkylation with methyl iodide to provide compound **304.2**. The SEM (2-[trimethylsilyl]ethoxymethyl) protecting group at the carbazole nitrogen atom was removed under acidic conditions. Finally, hydrogenolytic cleavage of the benzyl ether at C-7 afforded the phenol **304.3**, which had been an intermediate in Fürstner's total synthesis of dictyodendrin B (**291.2**) (see Scheme 294).

10.5. Synthesis of the Pyrrolo[2,3-*c*]carbazole Core of the Dictyodendrins

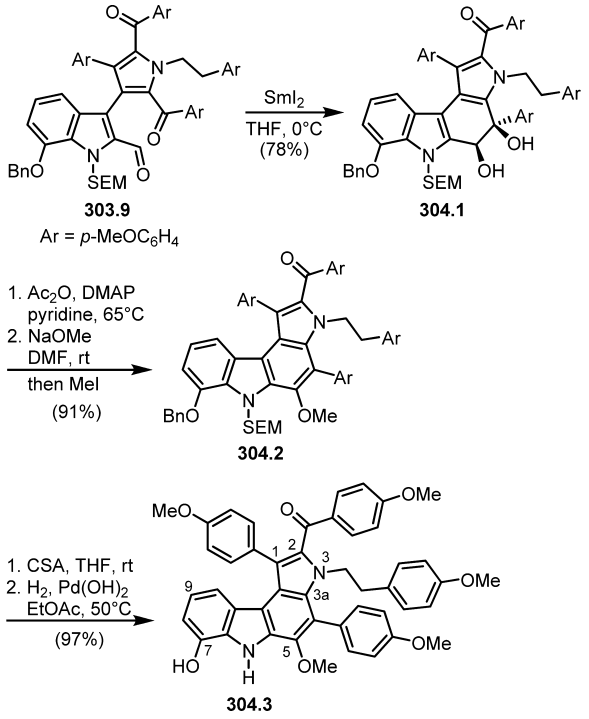
Ayats, Álvarez, and co-workers reported a convergent synthesis of the pyrrolo[2,3-*c*]carbazole core of the common framework of the dictyodendrins A (**291.1**) and B (**291.2**) using the pyrrole **305.6** and the indole **306.5** as advanced intermediates (Schemes 305–307).[581] Their approach is based on sequential Suzuki–Miyaura cross-coupling reactions and a tandem photochemical 6π-electrocyclization/aromatization as the key step. A bromine–lithium exchange of 3-bromo-*N*-(triisopropylsilyl)pyrrole (**305.1**) followed by reaction with

Scheme 303

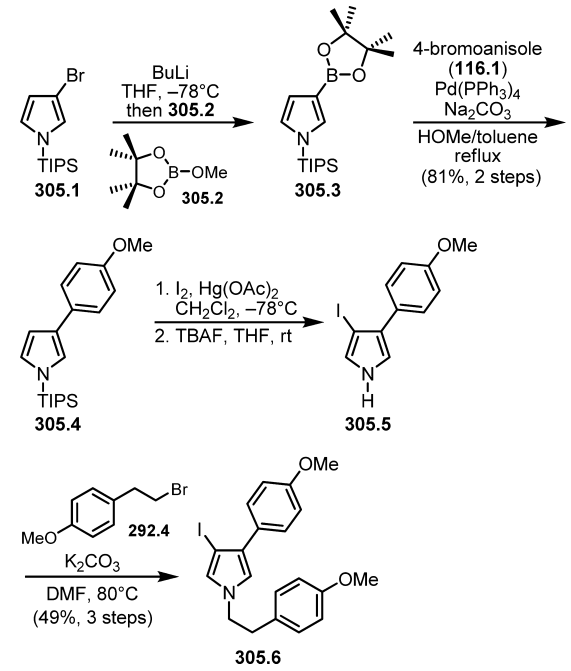


dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 304



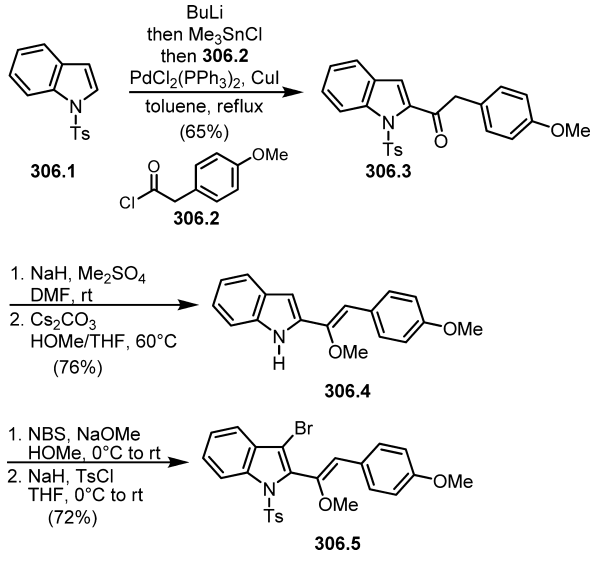
Scheme 305



commercially available 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [MeOB(pin)] (**305.2**) afforded the pyrrol-3-ylboronic acid ester **305.3** (Scheme 305). Suzuki–Miyaura cross-coupling of **305.3** and 4-bromoanisole (**116.1**) led to the pyrrole **305.4**. Iodination with molecular iodine in the presence of mercuric acetate at −78 °C followed by deprotection using TBAF afforded the 3-iodopyrrole **305.5**. Subsequent alkylation with 4-methoxyphenethyl bromide (**292.4**) finally provided the *N*-alkylpyrrole **305.6**, the first precursor for the projected synthesis, in 40% overall yield.

The second precursor, indole **306.5**, was prepared from *N*-tosylindole (**306.1**). Lithiation of **306.1** was followed by transmetalation with trimethyltin chloride and palladium-catalyzed coupling with the acid chloride **306.2** to give the 2-acylindole **306.3** (Scheme 306). Deprotonation of **306.3** with

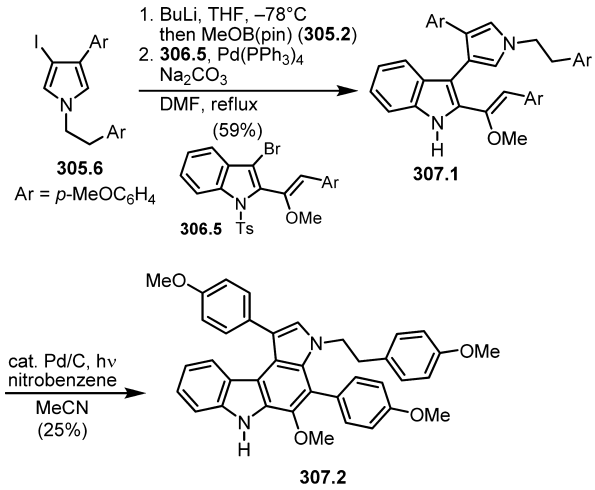
Scheme 306



sodium hydride and reaction with dimethyl sulfate followed by cleavage of the tosyl protecting group led to the methyl enol ether **306.4**. Electrophilic substitution at C-3 of the indole ring system with NBS in the presence of sodium methoxide in methanol and reprotection of the indole nitrogen atom with tosyl chloride afforded the desired 3-bromoindole **306.5** in 36% overall yield.[581]

The pyrrolo[2,3-*c*]carbazole core of the dictyodendrins was then assembled from the two halogenated precursor compounds **305.6** and **306.5** (Scheme 307). Halogen–metal exchange of the iodopyrrole **305.6** with butyllithium followed by treatment of the resulting pyrrol-3-yllithium with 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**305.2**) and subsequent Suzuki–Miyaura coupling with the 3-bromoindole **306.5** led to the 2,3-disubstituted indole **307.1**. Irradiation of a solution of **307.1** in acetonitrile with a medium-pressure Hg

Scheme 307



dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

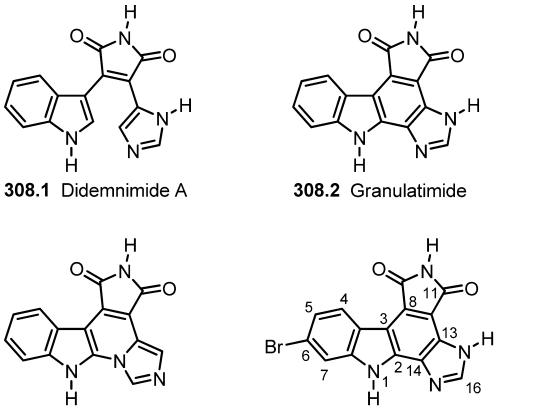
lamp in the presence of palladium on activated carbon and nitrobenzene induced a photochemical 6π-electrocyclization with concomitant aromatization to the desired pyrrolo[2,3-*c*]carbazole derivative **307.2** in 25% yield. Compound **307.2** has the pyrrolo[2,3-*c*]carbazole framework that is characteristic for the dictyodendrins A (**291.1**) and B (**291.2**). However, **307.2** lacks the oxygen substituent at C-8 of the carbazole ring system.[581]

11. IMIDAZO[4,5-*a*]PYRROLO[3,4-*c*]CARBAZOLE ALKALOIDS

11.1. Isolation from Natural Sources

So far, only two imidazo[4,5-*a*]pyrrolo[3,4-*c*]carbazole alkaloids have been obtained from natural sources. In the late 1990s, Berlinck et al. isolated two novel alkaloids, granulatimide (**308.2**) and isogranulatimide (**308.3**), in a bioassay-guided fractionation of the crude methanol extract of the ascidian *Didemnum granulatum* collected in Southern Brazil (Scheme 308).[588] Granulatimide (**308.2**) and isogranulatimide (**308.3**) were obtained along with the previously known didemnimide A (**308.1**).[589] From a biogenetic perspective, it appears that didemnimide A (**308.1**) represents the precursor for the two pentacyclic alkaloids granulatimide (**308.2**) and isogranulatimide (**308.3**). Granulatimide (**308.2**) and isogranulatimide (**308.3**) represent a new class of G2-specific cell cycle checkpoint inhibitors, and they are the first being identified in a rational screening program.[588] In early 2001, Berlinck and co-workers reported the isolation of 6-bromogranulatimide (**308.4**) along with the known granulatimide (**308.2**) from the same Brazilian marine invertebrate.[590] Imidazo[4,5-*a*]pyrrolo-[3,4-*c*]carbazoles and structural isomers showed potentially useful interactions with the cell division cycle.[591−593]

Scheme 308

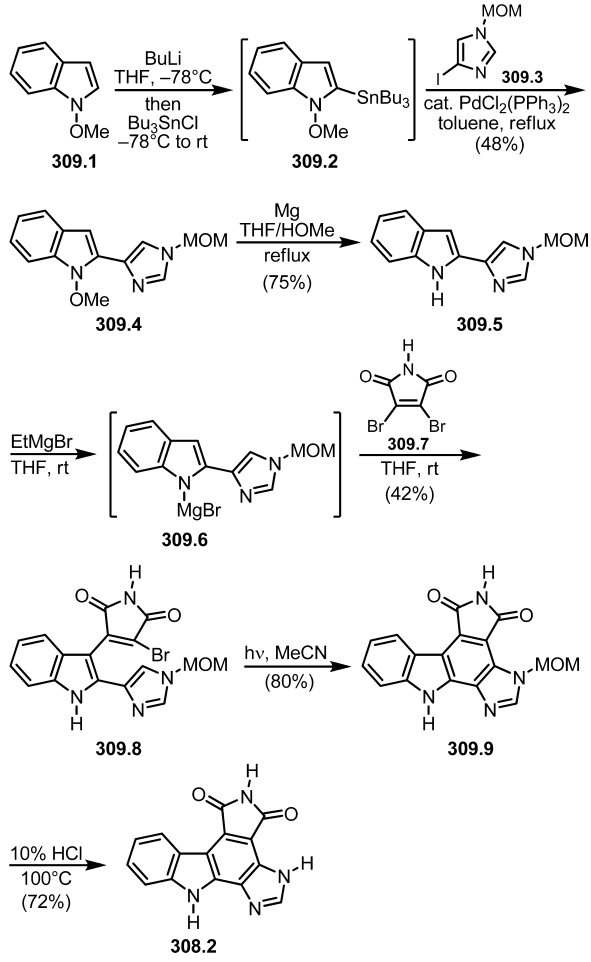


11.2. Total Synthesis of Imidazo[4,5-*a*]pyrrolo[3,4-*c*]carbazole Alkaloids

Both members of the imidazo[4,5-*a*]pyrrolo[3,4-*c*]carbazole alkaloid family have shown G2 checkpoint inhibitor activity and represent promising targets for the development of new anticancer agents. Therefore, in addition to the synthesis of the naturally occurring imidazo[4,5-*a*]pyrrolo[3,4-*c*]carbazole alkaloids **308.2** and **308.4**, a wide range of synthetic analogues has been described for structure−activity studies.[1,12]

In 2002, Murase and co-workers reported a synthesis of granulatimide (**308.2**) starting from 1-methoxyindole (**309.1**) (Scheme 309).[594] Regioselective lithiation of 1-methoxyindole (**309.1**) with butyllithium followed by quenching of the intermediate 2-lithio derivative with chlorotributylstannane led to the 2-stannylindole **309.2**. Stille coupling reaction of **309.2** with 4-iodo-1-(methoxymethyl)imidazole (**309.3**) in the presence of bis(triphenylphosphine)palladium(II) chloride afforded the corresponding coupling product **309.4**, the key intermediate for the synthesis of granulatimide. Reductive removal of the methoxy group at the nitrogen atom by treatment with magnesium in methanol led to the MOM-protected indol-2-ylimidazole **309.5**. Addition of ethylmagnesium bromide to **309.5** afforded the corresponding N-metalated compound **309.6**, which on reaction with 2,3-dibromomaleimide (**309.7**) provided the coupling product **309.8**. Using a modification of Piers' procedure for the photocyclization,[595] compound **309.8** was transformed to the MOM-protected granulatimide **309.9**. Finally, removal of the MOM group in **309.9** led to granulatimide (**308.2**) in 72% yield. Further applications of this approach led to structural analogues of granulatimide (**308.2**): 10-methylgranulatimide and 10,17-dimethylgranulatimide.[594] One year later, the same group reported an extension of their methodology, which was applied to the synthesis of a range of granulatimide derivatives.[596] Prudhomme and co-workers reported the synthesis of a series of granulatimide and isogranulatimide isomers and analogues bearing modified heterocycles.[597−601]

Scheme 309



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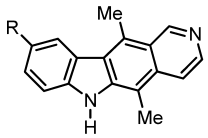
12. PYRIDO[4,3-*b*]CARBAZOLE ALKALOIDS

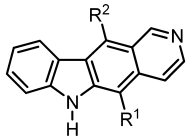
12.1. Isolation from Natural Sources

The pyrido[4,3-*b*]carbazole alkaloids constitute a group of naturally occurring biologically active compounds that has been known for more than 40 years. In 1959, Goodwin et al. reported the isolation of ellipticine (**28.9**) and 9-methoxyellipticine (**310.1**), fully aromatized pyrido[4,3-*b*]carbazole alkaloids, from the leaves of *Ochrosia elliptica* Labill. and *Ochrosia sandwicensis* A.DC. of the Apocynaceae family (Scheme 310).[602] In the following years, other groups reported

Scheme 310



28.9 Ellipticine
R = H
310.1 9-Methoxyellipticine
R = OMe
310.2 10-Hydroxyellipticine
(9-Hydroxyellipticine)
R = OH



310.3 17-Oxoellipticine
(13-Oxoellipticine,
5-Formylellipticine)
R^1 = CHO; R^2 = Me
310.4 18-Hydroxyellipticine
(12-Hydroxyellipticine,
5-Methyl-6*H*-pyrido[4,3-*b*]-
carbazole-11-methanol)
R^1 = Me; R^2 = CH_2OH

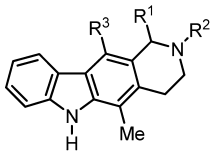
the isolation of the same alkaloids from different plants of the Apocynaceae family, *Aspidosperma subincanum* Mart.,[215] *Ochrosia maculata* Jacq. (*Ochrosia borbonica* Gmel.),[603] *Bleekeria vitiensis*,[604] *Ochrosia moorei*,[605] *Ochrosia acuminata*,[606] as well as from the Loganiaceae family, *Strychnos dinklagei* Gilg.[607] In 1982, Michel et al. isolated further ellipticine congeners from the stem bark of *Strychnos dinklagei* Gilg. The compounds were named 10-hydroxyellipticine (**310.2**), 17-oxoellipticine (**310.3**), and 18-hydroxyellipticine (**310.4**), based on an unusual numbering of the framework.[608]

Since the first isolation of ellipticine (**28.9**) and its congeners from natural sources and the discovery of their anticancer activity in various human tumor systems, pyrido[4,3-*b*]-carbazole alkaloids have attracted a widespread interest in chemistry, biology, and pharmacology. The antineoplastic property of ellipticine (**28.9**) was considered to be based mainly on DNA intercalation and/or inhibition of topoisomerase II. Moreover, it has been demonstrated in vitro and in vivo that ellipticine (**28.9**) binds covalently to DNA after being enzymatically activated by cytochrome P450 or peroxidase.[609,610]

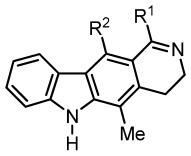
With the commercialization of some ellipticine derivatives and their clinical use for treatment of myeloblastic leukemia, advanced breast cancer, and other solid tumors,[611−615] the chemistry and biology of pyridocarbazoles underwent a tremendous development. This is emphasized by several comprehensive reviews covering the synthesis and biological activity of ellipticines.[1,12,213,616−628]

In 1957, Schmutz et al. reported the isolation of (+)-guatambuine (u-alkaloid C) [(+)-**29.9**] from *Aspidosperma ulei* Markgr. (Scheme 311).[629,630] In 1959, Carvalho-Ferreira et al. isolated the same alkaloid from a different *Aspidosperma* species, *Aspidosperma longipetiolatum* Kuhlm. (*Aspidosperma pyricollum* Müll. Arg.).[631,632] In Brazil this plant is known as *Guatambu amarelo*. In 1960, Ondetti and Deulofeu reported the isolation of (+)-guatambuine [(+)-**29.9**] from the root bark

Scheme 311



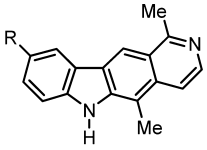
29.9 Guatambuine
(u-Alkaloid C)
R^1,R^2 = Me; R^3 = H
311.1 *N*-Methyltetrahydroellipticine
R^1 = H; R^2,R^3 = Me
311.2 Janetine
R^1 = Me; R^2,R^3 = H



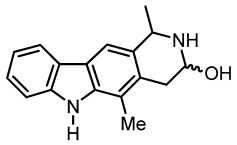
311.3 3,4-Dihydroellipticine
(u-Alkaloid D)
R^1 = H; R^2 = Me
311.4 3,4-Dihydroolivacine
R^1 = Me; R^2 = H

of *Aspidosperma australe* Müll. Arg. along with (−)-guatambuine [(−)-**29.9**], and from the stem bark (±)-guatambuine (**29.9**) and olivacine (**28.10**) (Scheme 312).[633,634] It is

Scheme 312



28.10 Olivacine
R = H
312.1 9-Methoxyolivacine
R = OMe



312.2 3-Hydroxytetrahydro-
olivacine

noteworthy that both enantiomers and racemic guatambuine have been isolated from the same natural source. Although (+)-guatambuine [(+)-**29.9**] ($[\alpha]_D^{25}$ = +112.0, c 0.990, pyridine),[630] ($[\alpha]_D^{25}$ = +106, pyridine),[631] ($[\alpha]_D^{29}$ = +112.0 ± 3.0, c 0.485, pyridine), and (−)-guatambuine [(−)-**29.9**] ($[\alpha]_D^{26}$ = −106.0 ± 2.0, pyridine) were isolated in optically active form, their absolute stereochemistry is still not known.[633,634] Woodward et al. reported the isolation of *N*-methyltetrahydroellipticine (**311.1**) from *Aspidosperma subincanum* Mart. in 1959.[215] In 1967, Burnell and Casa reported the isolation of (±)-guatambuine (**29.9**) from the bark of a different *Aspidosperma* species, *Aspidosperma vargasii* A. DC. along with *N*-methyltetrahydroellipticine (**311.1**) and 9-methoxyolivacine (**312.1**).[635]

Janetine (**311.2**), 3,4-dihydroolivacine (**311.4**), olivacine (**28.10**), and 3-hydroxytetrahydroolivacine (**312.2**) were isolated in 1995 by Moreti et al. from the stem bark of *Peschiera buchtienii* (H.J.P.Winkl.) Markgr. (*Tabernaemontana cymosa* Jacq.).[636] This tree is common in the Chapare regions of Bolivia and locally used for the treatment of leishmaniasis. Although janetine (**311.2**) was isolated from nature in optically active form ($[\alpha]_D$ = +8, c 0.95, HOEt), the absolute stereochemistry is not known.[636] Schmutz and Hunziker reported the isolation of 3,4-dihydroellipticine (u-alkaloid D) (**311.3**) from *Aspidosperma ulei* Markgr.[630] The known 3,4-dihydroellipticine (**311.3**) was obtained as an inseparable mixture with 3,4-dihydroolivacine (**311.4**) by Lehner and Schmutz from the same natural source.[637] In 1961, Büchi et al. reported the isolation of 3,4-dihydroellipticine (**311.3**) along with *N*-methyltetrahydroellipticine (**311.1**) and ellipticine (**28.9**) (see Scheme 310) from a different *Aspidosperma* species, *Aspidosperma subincanum* Mart.[638] Michel et al. reported the isolation of 3,4-dihydroellipticine (**311.3**) from the stem bark of *Strychnos dinklagei* Gilg (Loganiaceae).[608] Olivacine (**28.10**)

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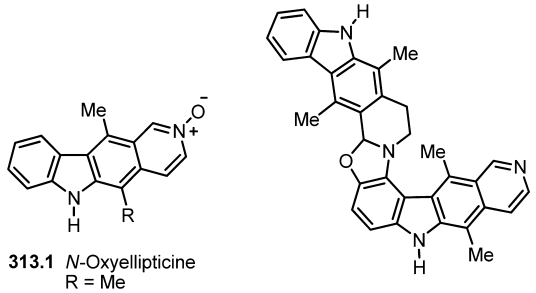
was first obtained by Schmutz and Hunziker from *Aspidosperma olivaceum* Müll. Arg. (Apocynaceae) in 1958.[639] In the following years, olivacine (**28.10**) has also been isolated from different members of the Apocynaceae family: *Aspidosperma longepetiolatum* Kuhlm.,[632] *Aspidosperma australe* Müll. Arg.,[640] and *Tabernaemontana psychotriifolia* Kunth (*Tabernaemontana cymosa* Jacq.).[641]

In 1981, Potier and co-workers reported the isolation of *N*-oxyellipticine (**313.1**) from the trunk bark of *Ochrosia moorei* (Scheme 313).[605] In the following year, Michel et al. reported

Scheme 313



313.1 *N*-Oxyellipticine R = Me
313.2 *N*-Oxy-5-formylellipticine R = CHO
313.3 Strellidimine

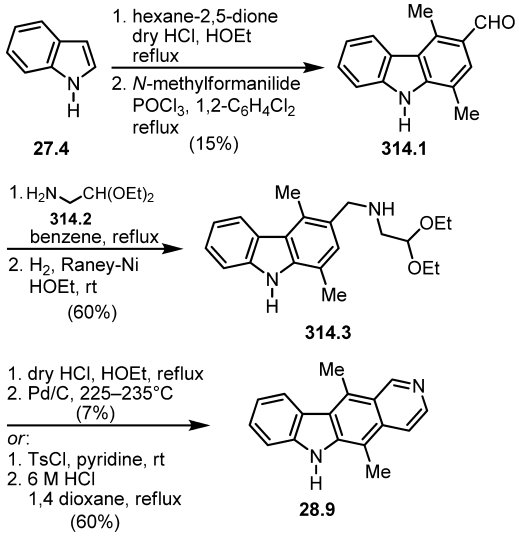
the isolation of a further *N*-oxyellipticine derivative, *N*-oxy-5-formylellipticine (**313.2**), from the stem bark of *Strychnos dinklagei* Gilg (Loganiaceae).[608] Strellidimine (**313.3**), the first naturally occurring bispyridocarbazole alkaloid, was isolated in 1987 by Michel et al. from the bark of the same African tree.[642] It is evident that this optically inactive alkaloid is formed in vivo by coupling of 9-hydroxyellipticine (**310.2**) (see Scheme 310) and 3,4-dihydroellipticine (**311.3**) (see Scheme 311), both of which co-occur in the bark of *S. dinklagei*.

12.2. Synthesis of Pyrido[4,3-*b*]carbazoles

With the disclosure of the antitumor activity of ellipticine (**28.9**) and 9-methoxyellipticine (**310.1**) in several animal and human tumor systems, the pyrido[4,3-*b*]carbazole alkaloids became promising targets for many synthetic groups[1,213,616−628] and inspired the synthesis of a broad range of synthetic analogues.[643−655] In 1977, Bergman and Carlsson described a highly efficient three-step route to ellipticine (**28.9**) via condensation of 2-ethylindole with 3-acetylpyridine followed by N-alkylation and pyrolysis (65% overall yield).[656] One year later, the same authors reported a related approach to olivacine (**28.10**) starting from 2-ethylindole and 3-formyl-2-methylpyridine.[657] In the present section, we describe synthetic approaches that appeared after 2002 and, therefore, have not been covered in earlier reviews. However, for comparison we included two classical approaches.

12.2.1. Saxton's Total Synthesis of Ellipticine. In 1962, Cranwell and Saxton described a straightforward synthesis of ellipticine using a Pomeranz−Fritsch cyclization as key step.[658] Condensation of indole (**27.4**) with hexane-2,5-dione in the presence of gaseous HCl in ethanol followed by Vilsmeier formylation led to 3-formyl-1,4-dimethylcarbazole (**314.1**) (Scheme 314). Imine formation by reaction with **314.2** and hydrogenation of the resulting imine led to the secondary amine **314.3**. Acid-catalyzed cyclization of the amine **314.3** followed by solvent-free dehydrogenation with palladium on activated carbon led to ellipticine (**28.9**) in low yield. All attempts to directly induce cyclization of the imine, which was

Scheme 314



obtained from condensation of 3-formyl-1,4-dimethylcarbazole (**314.1**) and 2,2-diethoxyethylamine (**314.2**), had failed.

In 1974, Jackson and co-workers improved the efficiency of that approach by application of an improved procedure for the Pomeranz−Fritsch cyclization.[659,660] Tosylation of the secondary amine in **314.3** followed by heating of the tosylamide in a mixture of hydrochloric acid and 1,4-dioxane provided ellipticine (**28.9**) in 60% yield based on the amine **314.3**. Chern and co-workers reported that the overall yield can be further improved by conducting several of the steps shown in Scheme 314 in the microwave.[661]

12.2.2. Husson's Total Synthesis of Guatambuine, Olivacine, and Ellipticine. In 1981, Besselièvre and Husson described an elegant approach to olivacine (**28.10**) and ellipticine (**28.9**) and suggested its biomimetic character (see section 2).[214] The synthetic strategy was inspired by Joule and co-workers' synthesis of the biogenetically related uleine.[662] *N*-(Benzenesulfonyl)indole (**306.1a**) was used as the starting material. Lithiation at C-2 followed by addition of pyridine-4-carbaldehyde (**315.1**) and basic cleavage of the sulfonyl protecting group led to the secondary alcohol **315.2** (Scheme 315). The bridged compound **315.5** was obtained from **315.2** in 4 steps following the procedures reported by Joule (overall yield reported by Joule, 32%).[662] The acid-catalyzed cyclization of the allylamine **315.3** to compound **315.5** probably starts with an initial acid-induced transformation of the enone to the iminium salt **315.4** via the dienol. Addition of methyllithium to the ketone **315.5** led to a tertiary alcohol that was then treated with acetyl chloride to effect elimination of acetic acid and an acetamide to give the aromatic ring-opening product **315.6**. A Bischler−Napieralski cyclization with phosphoryl chloride followed by reduction of the intermediate iminium salt led to guatambuine (**29.9**). Dehydrogenation and concomitant demethylation with palladium on activated carbon in boiling decalin finally afforded olivacine (**28.10**) in 11 steps and 2% overall yield.

In the same paper, Besselièvre and Husson also described an improved route to olivacine (**28.10**) starting from 4-acetylpyridine (**316.1**) (Scheme 316).[214] Formation of the ethyleneacetal was followed by N-methylation and double reduction to the tetrahydropyridine **316.2**. Reaction of **316.2** with indole (**27.4**) in refluxing aqueous acetic acid led directly

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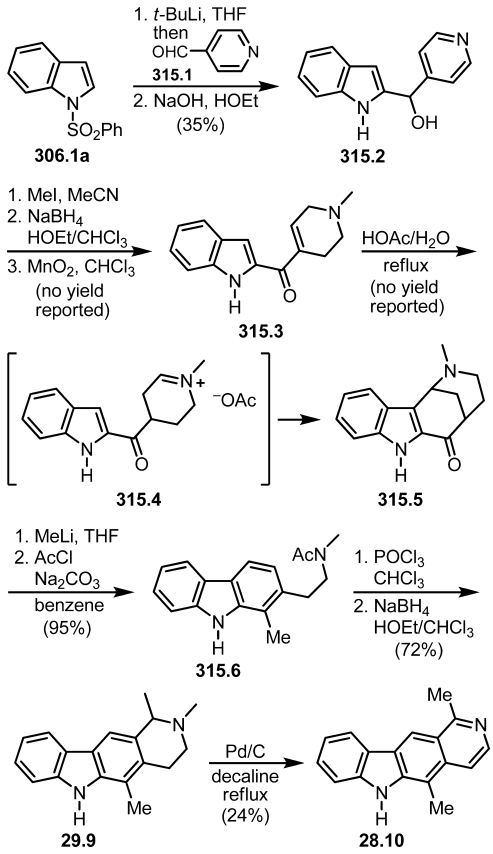
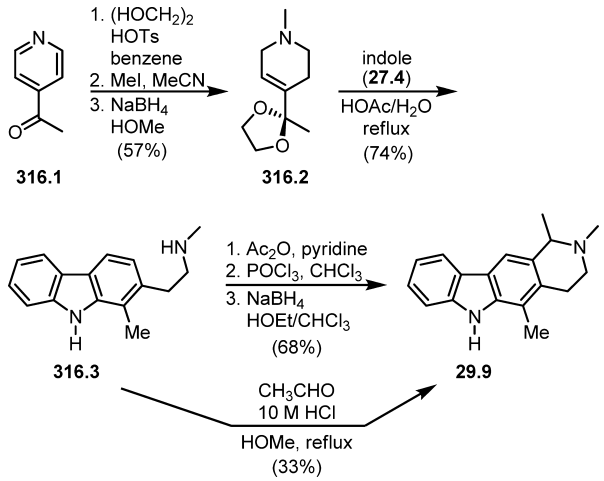
Scheme 315



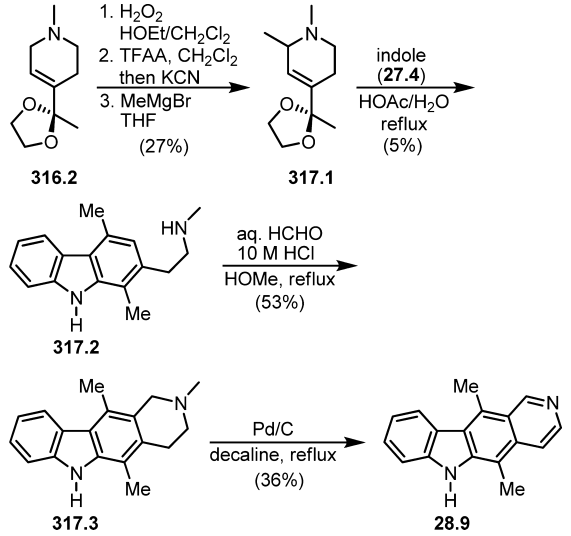
Scheme 316



to the 2-(2-aminoethyl)carbazole **316.3**. N-Acetylation of the secondary amino group of compound **316.3** gave carbazole **315.6**, which was then transformed to guatambuine (**29.9**) as described above (see Scheme 315). Alternatively, Pictet–Spengler reaction of **316.3** with acetaldehyde in methanol at reflux under acidic conditions afforded directly guatambuine (**29.9**). Thus, guatambuine (**29.9**) was obtained in 7 steps and 29% overall yield or in only 5 steps and 14% overall yield. Because guatambuine (**29.9**) can be transformed into olivacine (**28.10**) by dehydrogenation with palladium on activated carbon (see Scheme 315), olivacine (**28.10**) is accessible in 8 steps and 7% overall yield or in only 6 steps and 3% overall yield.

The shortest synthetic route to olivacine (**28.10**) was then modified and adapted to the total synthesis of ellipticine (**28.9**). First, the tetrahydropyridine **316.2** was transformed into the 1,6-dimethyl-1,2,3,6-tetrahydropyridine **317.1** via a sequence of oxidation to the *N*-oxide, generation of an iminium salt with trifluoroacetic anhydride, addition of cyanide, and nucleophilic displacement of cyanide by methylmagnesium bromide (Scheme 317). The resulting tetrahydropyridine **317.1** and

Scheme 317



indole (**27.4**) were then heated at reflux in aqueous acetic acid to give the 2-(2-aminoethyl)carbazole **317.2** in low yield. The authors assumed that the low yield for this step in comparison to the reaction of indole (**27.4**) and **316.2** is due to a less efficient nucleophilic attack of indole (**27.4**) at the more-hindered iminium salt, which is formed in situ from **317.1**. Pictet–Spengler reaction of **317.2** with aqueous formaldehyde to the tetrahydropyrido[4,3-*b*]carbazole **317.3** followed by aromatization and demethylation led to ellipticine (**28.9**) in 9 steps and 0.1% overall yield.

12.2.3. Miki's Total Synthesis of Olivacine and Ellipticine. In 2004, Miki et al. reported the total synthesis of olivacine (**28.10**) and ellipticine (**28.9**) starting from common precursors, *N*-benzylindole-2,3-dicarboxylic anhydride (**318.1**) and 2,4,6-trimethoxypyridine (**318.2**) (Scheme 318).[663,664] Previously, the same group had already reported a synthesis of ellipticine (**28.9**) starting from the same indole precursor **318.1**.[665−667] Friedel–Crafts acylation of 2,4,6-trimethoxypyridine (**318.2**) with *N*-benzylindole-2,3-dicarboxylic anhydride (**318.1**) in the presence of titanium(IV) chloride in dichloromethane afforded regioselectively the 3-acylindole-2-carboxylic acid **318.3**, which was transformed to ketone **318.4** by reaction with copper chromite in quinoline.[663,664] The ketone **318.4** was transformed to the monomethyl derivative **318.5** by regioselective methyl ether cleavage with 47% hydrobromic acid, treatment with triflic anhydride (Tf_2O), and subsequent reaction of the corresponding triflate with MeMgBr in the presence of $NiCl_2(dppe)_2$ (70% yield over 3 steps).[663] Regioselective O-demethylation of **318.5** by treatment with boron tribromide followed by reductive removal of the ketone oxygen atom with diborane and subsequent

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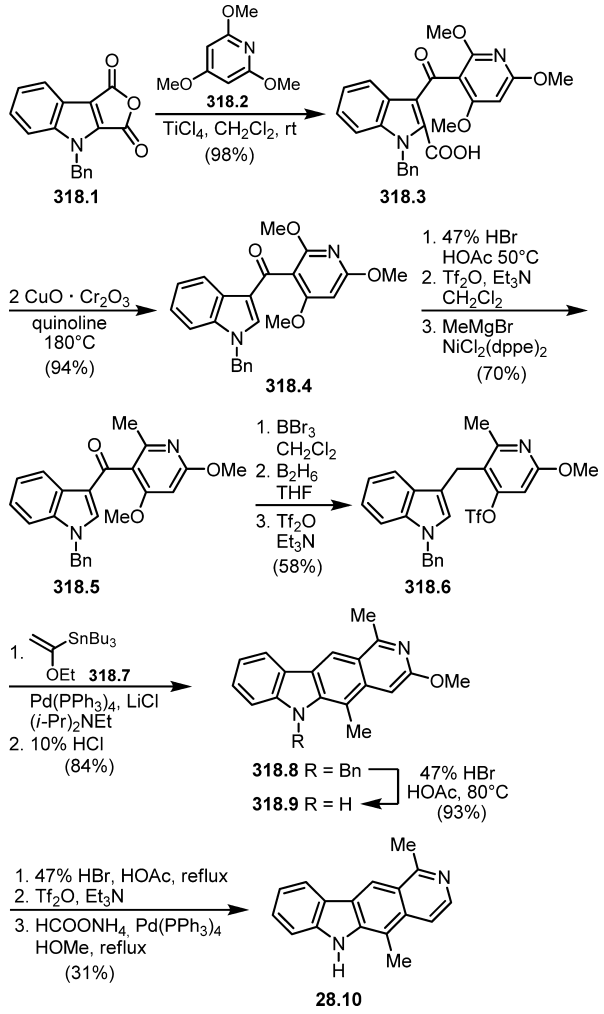
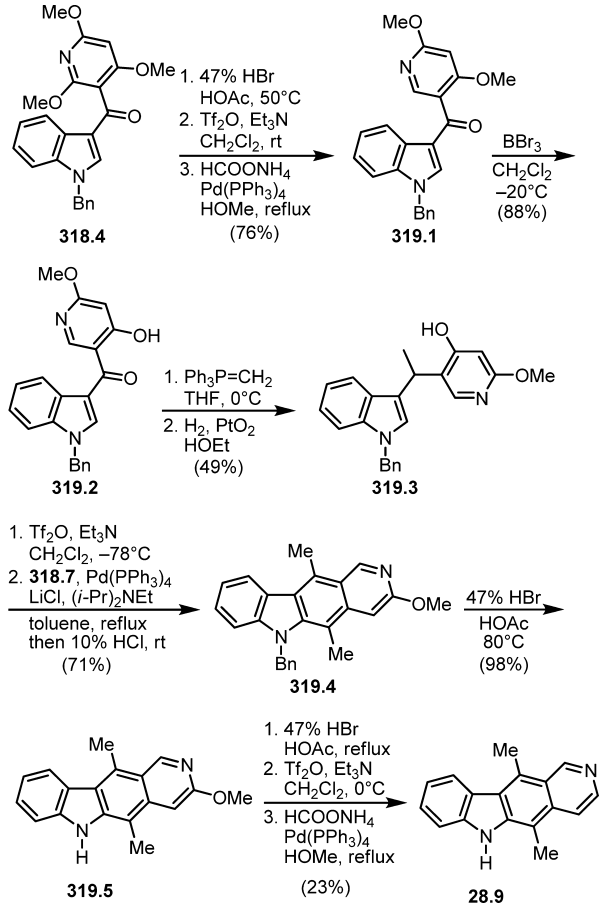
Scheme 318



Scheme 319



treatment with triflic anhydride (Tf_2O) afforded the 4-pyridyl triflate **318.6**. Palladium(0)-catalyzed cross-coupling of **318.6** with (1-ethoxyvinyl)tributyltin (**318.7**) followed by cyclization of the intermediate ethoxyvinyl derivative with 10% hydrochloric acid afforded 6-benzyl-3-methoxyolivacine (**318.8**) in 84% yield. Debenzylation of **318.8** with 47% hydrobromic acid afforded 3-methoxyolivacine (**318.9**). After O-demethylation of **318.9**, the corresponding hydroxy derivative was transformed to the triflate, which on subsequent treatment with ammonium formate in the presence of $Pd(PPh_3)_4$ in hot methanol led to olivacine (**28.10**).[663]

For the synthesis of ellipticine (**28.9**), the required 2,4-dimethoxy derivative **319.1** was prepared over 3 steps in 76% yield starting from the ketone **318.4**. Thus, regioselective demethylation of **318.4** with 47% hydrobromic acid in hot acetic acid followed by treatment with triflic anhydride (Tf_2O) gave the corresponding triflate, which on reduction with ammonium formate in the presence of palladium on activated carbon was transformed to the 2,4-dimethoxy derivative **319.1** (Scheme 319). Regioselective O-demethylation of the 4-methoxy group of **319.1** was performed by treatment with boron tribromide to provide the 4-hydroxy compound **319.2**. Wittig olefination of the keto derivative **319.2** to the corresponding olefin followed by catalytic hydrogenation in the presence of Adam's catalyst (PtO_2) afforded compound **319.3**. Transformation of **319.3** to the corresponding triflate by reaction with triflic anhydride in the presence of triethylamine, palladium(0)-catalyzed cross-coupling with (1-ethoxyvinyl)-tributyltin (**318.7**), and subsequent cyclization of the intermediate ethoxyvinyl derivative with 10% hydrochloric acid afforded 6-benzyl-3-methoxyellipticine (**319.4**) in 71% yield. Finally, 6-benzyl-3-methoxyellipticine (**319.4**) was converted to ellipticine (**28.9**) in 4 steps and 23% yield by a similar sequence as described above (see Scheme 318).[664]

12.2.4. Formal Synthesis of Ellipticine and Olivacine, Total Synthesis of Guatambuine. In 2005, Bennasar et al. reported a formal synthesis of ellipticine (**28.9**) starting from the 3-formylindole **320.1** and 3-pyridylmagnesium bromide (**320.2**).[668] The key step of this approach is a regioselective cyclization of a 2-indolylacyl radical (in situ generated from the *N*-benzyl selenoester **320.5**) to the 4-position of the pyridine ring. Reaction of **320.1** with 3-pyridylmagnesium bromide (**320.2**) followed by triethylsilane reduction of the resulting carbinol **320.3** led to the ester **320.4** in 55% yield (Scheme 320). Hydrolysis of **320.4** followed by phenylselenation of the corresponding carboxylic acid gave the selenoester **320.5**. The 2-indolylacyl radical generated from the selenoester **320.5** underwent a regioselective cyclization to afford the *N*-benzylellipticine quinone **320.6**.[668] The transformation of the *N*-benzylellipticine quinone **320.6** to ellipticine (**28.9**) has been described by others.[666,669,670]

One year later, Bennasar et al. adapted the above protocol to the total synthesis of (±)-guatambuine (**29.9**) starting from the unprotected 3-formylindole **321.1** (Scheme 321).[671] Following a similar reaction sequence as used for the formal synthesis of

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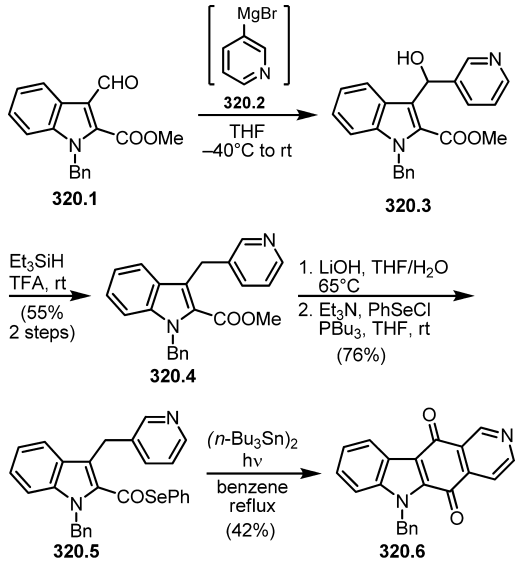
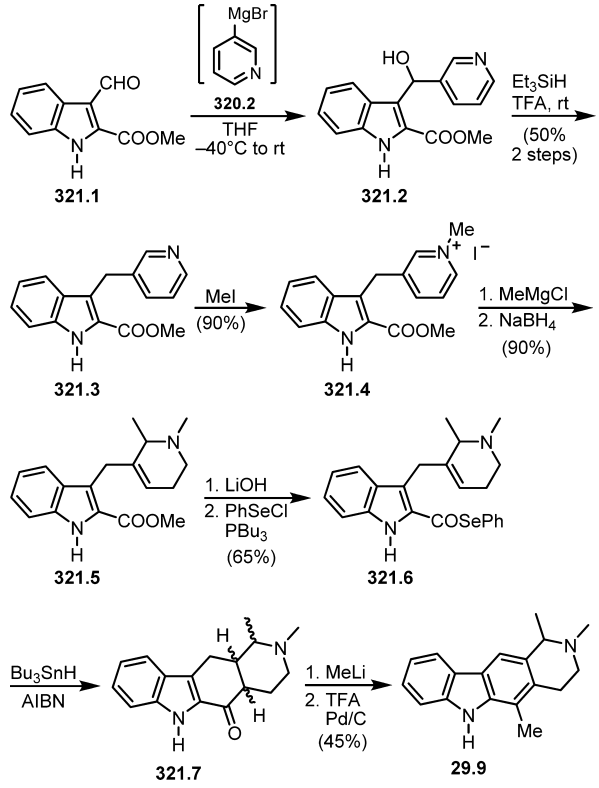
Scheme 320



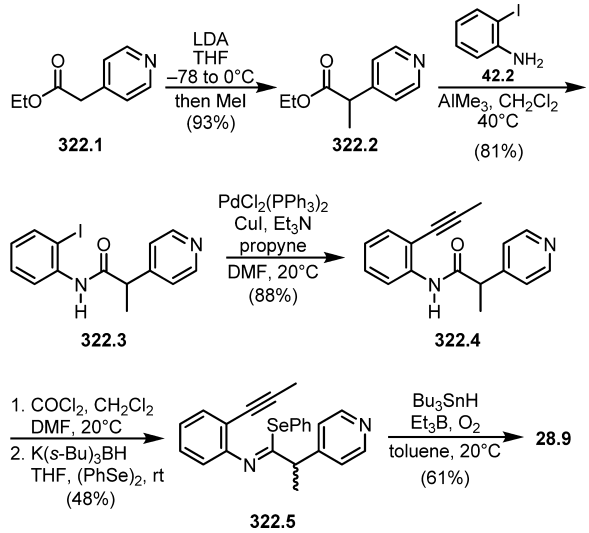
Scheme 321



ellipticine (**28.9**) (see Scheme 320),[668] compound **321.1** was transformed to the pyridylmethylindole **321.3** over 2 steps in 50% yield. After alkylation of the pyridine nitrogen atom with methyl iodide, the *N*-methylpyridinium salt **321.4** was reacted with methylmagnesium chloride followed by reduction of the intermediate 2,3-disubstituted dihydropyridine to afford the tetrahydropyridine **321.5**. Hydrolysis of **321.5** led to the corresponding carboxylic acid, which on phenylselenation afforded the selenoester **321.6**. Radical cyclization of **321.6** in benzene solution led to a stereoisomeric mixture of the pyridocarbazole **321.7**. This reaction probably proceeds through the formation of a 2-indolylacyl radical, which initiates the desired 6-endo cyclization without interference of the indole N–H. Finally, the pyridocarbazole **321.7** was transformed into (±)-guatambuine (**29.9**) by reaction with methyllithium, followed by dehydration with concomitant dehydrogenation of the carbinol using trifluoroacetic acid and palladium on activated carbon.[671] Previously, (±)-guatambuine (**29.9**) had been transformed to olivacine (**28.10**) by dealkylative aromatization (see Scheme 315).[214,634]

12.2.5. Bowman's Total Synthesis of Ellipticine. In 2005, Bowman and co-workers reported the total synthesis of ellipticine (**28.9**) based on an imidoyl radical cascade reaction.[672] The required imidoyl radical was generated from the imidoyl selenide **322.5** (Scheme 322). Reaction of ethyl 2-

Scheme 322



(4-pyridyl)acetate (**322.1**) with lithium diisopropylamide followed by addition of methyl iodide led to the corresponding methyl derivative **322.2**. Treatment of **322.2** with 2-iodoaniline (**42.2**) in the presence of trimethylaluminum afforded the amide **322.3**. Sonogashira coupling of propyne with the amide **322.3** afforded the aryl acetylene **322.4**. The aryl acetylene **322.4** was transformed to the imidoyl selenide **322.5** by reaction with oxalyl chloride followed by K-Selectride treatment in the presence of diphenyl diselenide. Finally, the imidoyl selenide **322.5** was converted to ellipticine (**28.9**) in a one-pot operation by reaction with tributyltin hydride in the presence of triethylborane and oxygen.

12.2.6. Mal's Formal Synthesis of Ellipticine. In 2005, Mal et al. reported a formal synthesis of ellipticine (**28.9**) starting from the furoindolone **67.2** (Scheme 323).[291,292] First, the nitrogen atom of furoindolone **67.2** was protected as the ethyl carbamate **323.1**. Anionic [4 + 2]-cycloaddition of the deprotonated furoindolone **323.2** with 3-pyridyne (**323.3**), prepared in situ from 3-bromopyridine, afforded an inseparable mixture of the ellipticine quinone **323.4** and the isoellipticine quinone **323.5** in a ratio of 2:1 (45% combined yield). The quinones **323.4** and **323.5** had been transformed to ellipticine (**28.9**) and isoellipticine (**323.6**) previously by others.[673–675]

12.2.7. Ho's Total Synthesis of Ellipticine. Ho and Hsieh reported a total synthesis of ellipticine (**28.9**) starting from 4,7-dimethyl-1*H*-indene, which was first oxidized to 4,7-dimethyl-indan-2-one (**324.1**).[676] Reduction of 4,7-dimethyl-indan-2-one (**324.1**) using sodium borohydride provided the alcohol **324.2**

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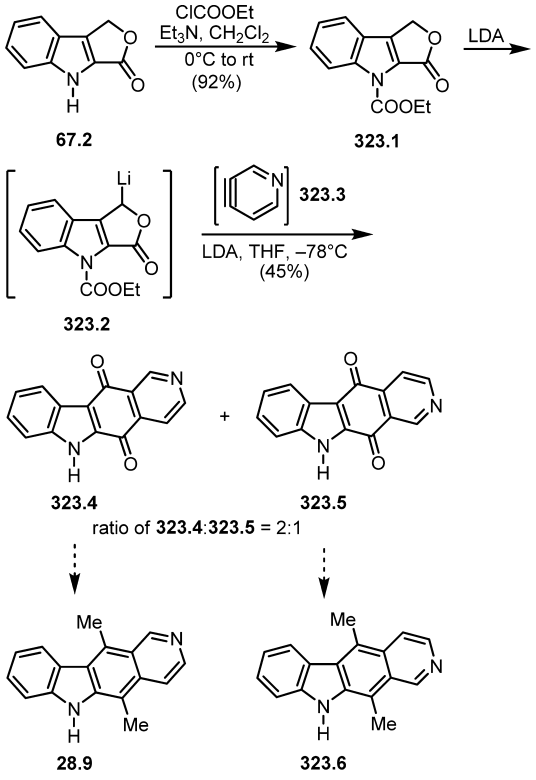
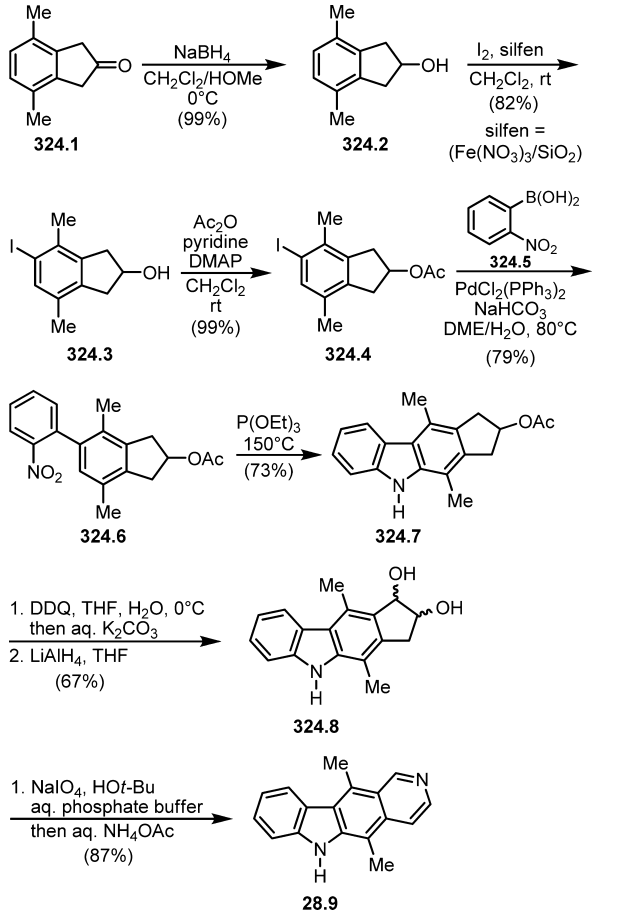
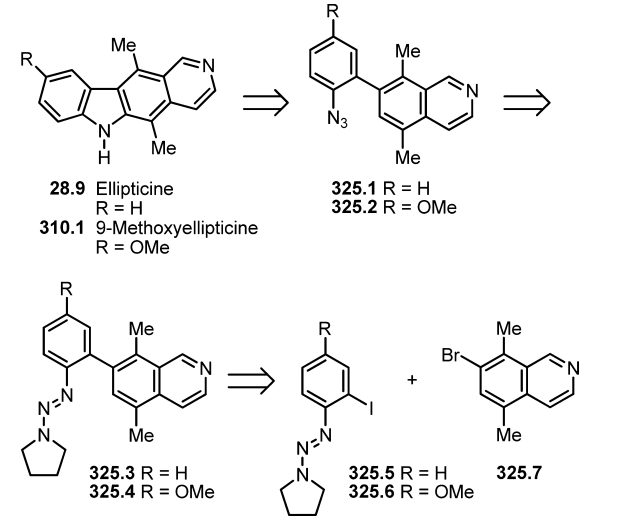
Scheme 323



Scheme 324



Scheme 325



almost quantitatively (Scheme 324). After iodination of **324.2**, the corresponding iodo derivative **324.3** was transformed to the acetate **324.4**. Suzuki–Miyaura coupling of the latter with 2-nitrophenylboronic acid (**324.5**) afforded the nitrobiaryl **324.6** in 79% yield. Cadogan cyclization of **324.6** using triethyl phosphite at high temperature led to the carbazole **324.7** in 73% yield. Oxidation of **324.7** with DDQ followed by in situ reduction of the keto acetate led to the stereoisomeric diols **324.8**. Oxidative cleavage of **324.8** with sodium periodate and heterocyclization of the intermediate dicarbonyl derivative with ammonium acetate provided ellipticine (**28.9**).[676]

12.2.8. Knochel's Total Synthesis of Ellipticine and 9-Methoxyellipticine. In 2007, Liu and Knochel reported a synthesis of ellipticine (**28.9**) and 9-methoxyellipticine (**310.1**) using a three-step sequence of Negishi cross-coupling, azidation, and cyclization (Scheme 325).[677] The precursors were prepared by reaction of the zinc species of 1-(2-iodophenylazo)pyrrolidines **325.5** and **325.6** with 7-bromo-5,8-dimethylisoquinoline (**325.7**) to give the aryl triazenes **325.3** and **325.4**. The aryl triazenes **325.3** and **325.4** were then converted to the aryl azides **325.1** and **325.2**. These underwent thermal cyclization to ellipticine (**28.9**) and 9-methoxyellipticine (**310.1**). The 1-(2-iodophenylazo)pyrrolidines **325.5** and **325.6** were prepared from the corresponding *ortho*-iodoanilines using a sequence of diazotation followed by treatment of the diazonium salts with pyrrolidine.

7-Bromo-5,8-dimethylisoquinoline (**325.7**) was prepared starting from 1,4-dibromo-2,5-dimethylbenzene (**326.1**) (Scheme 326). Reaction of **326.1** with butyllithium and quenching of the intermediate aryllithium with DMF afforded the aldehyde **326.2** almost quantitatively. After reaction of the aryl aldehyde **326.2** with sodium borohydride, the corresponding benzyl alcohol **326.3** was transformed to the benzyl chloride **326.4** using thionyl chloride. Alkylation of diethyl malonate with the benzyl chloride **326.4** provided the diester **326.5** in 88% yield. Hydrolysis and decarboxylation gave the corresponding carboxylic acid **326.6** in 83% yield. Polyphosphoric acid (PPA)-catalyzed ring-closure afforded the indanone **326.7**, which was then reduced to the corresponding indanol followed by elimination with a catalytic amount of *p*-toluenesulfonic acid in benzene at reflux to afford the indene **326.8** in 78% yield. Ozonolysis of **326.8** followed by reductive

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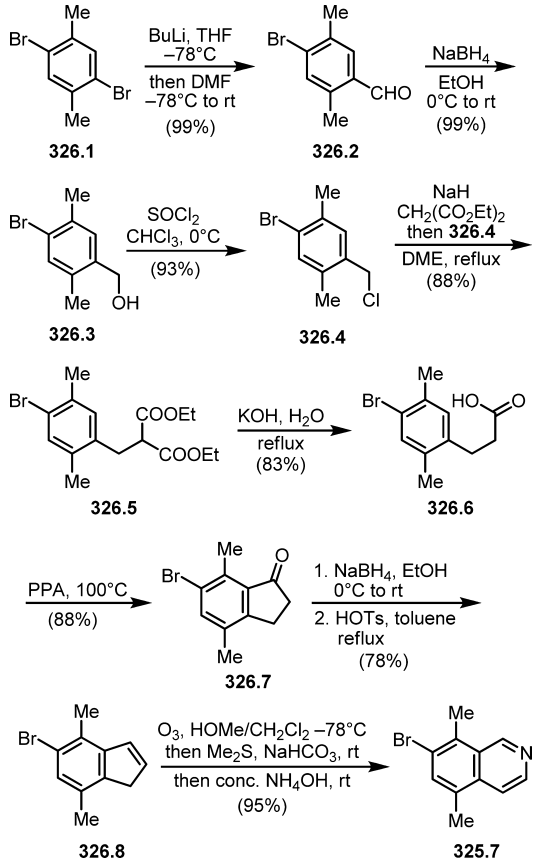
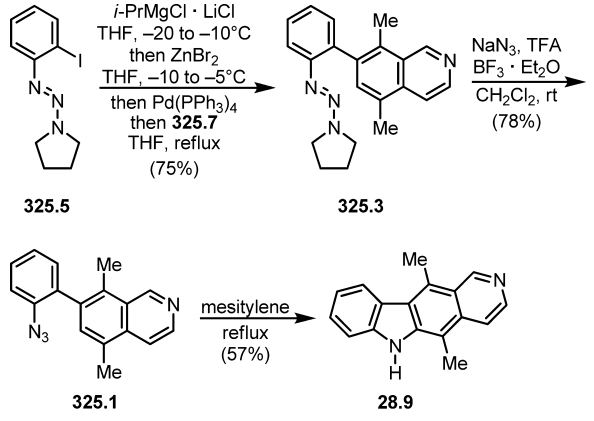
Scheme 326



workup with dimethyl sulfide and treatment with ammonium hydroxide provided the desired 7-bromoisoquinoline **325.7**.[677]

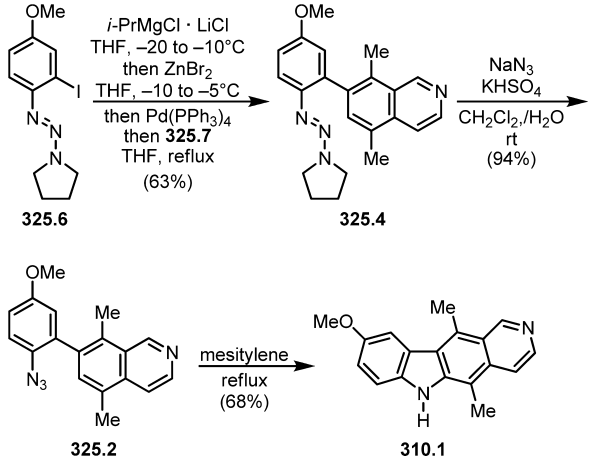
For the synthesis of ellipticine (**28.9**), the triazene **325.5** was subjected to an iodine–magnesium exchange with isopropylmagnesium chloride–lithium chloride complex followed by transmetalation with zinc(II) bromide to afford an organozinc intermediate, which on Negishi cross-coupling with the 7-bromoisoquinoline **325.7** led to the polyfunctionalized aryl triazene **325.3** (Scheme 327). Addition of boron trifluoride–diethyl ether complex and trifluoroacetic acid in dichloromethane in the presence of sodium azide to **325.3** afforded the corresponding aryl azide **325.1**. Thermal cyclization in mesitylene at reflux afforded ellipticine (**28.9**) by loss of dinitrogen and C–H insertion of the intermediate nitrene.[677]

Scheme 327



The total synthesis of 9-methoxyellipticine (**310.1**) was accomplished in an analogous fashion (Scheme 328).

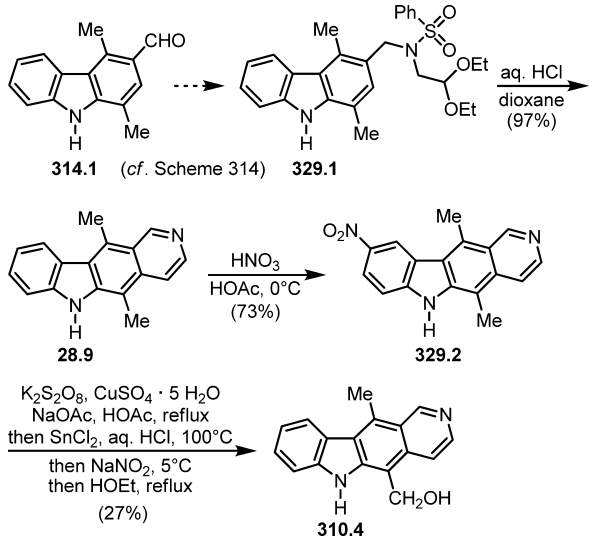
Scheme 328



Halogen–metal exchange of 1-(4-methoxy-2-iodophenylazo)-pyrrolidine (**325.6**) led to a Grignard reagent that was transmetalated with zinc(II) bromide to afford the corresponding zinc intermediate. The same reaction sequence as depicted in Scheme 327 provided 9-methoxyellipticine (**310.1**) over 3 steps in 40% yield based on triazene **325.6**. An extension of this methodology led to isoellipticine and 7-ethoxycarbonylisoellipticine.[677]

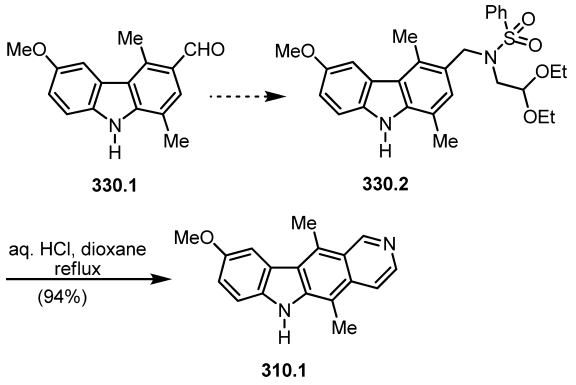
12.2.9. Dračínský's Total Synthesis of Ellipticine, 12-Hydroxyellipticine, and 9-Methoxyellipticine. In 2007, Dračínský et al. reported an efficient modification of previous syntheses of ellipticine (**28.9**) and 9-methoxyellipticine (**310.1**). This route also led to a new synthesis of 12-hydroxyellipticine (**310.4**).[678] The approach starts from the known 1,4-dimethylcarbazole-3-carbaldehyde precursors **314.1** and **330.1**, respectively, and applies the procedure of Jackson and Shannon (Schemes 329 and 330).[660] Using optimized reaction conditions, the acid-mediated cyclization of the carbazole *N*-benzenesulfonamide **329.1** in boiling dioxane afforded ellipticine (**28.9**) almost quantitatively (Scheme

Scheme 329

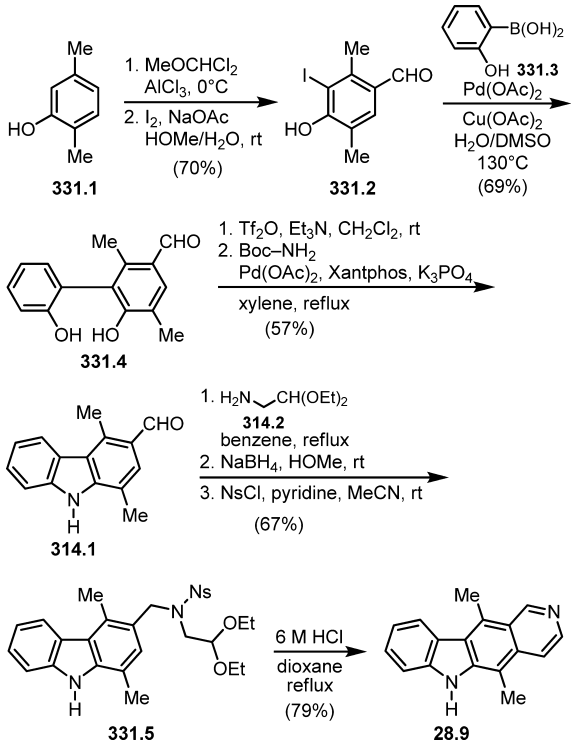


dx.doi.org/10.1021/cr200447s | Chem. Rev. 2012, 112, 3193–3328

Scheme 330



Scheme 331



329).[678] Mechanistically, this reaction probably involves ring-closure followed by elimination of ethanol and benzenesulfinic acid. For the synthesis of 12-hydroxyellipticine (**310.4**), ellipticine (**28.9**) was first nitrated to provide 9-nitroellipticine (**329.2**). The 12-methyl group of compound **329.2** was then oxidized to a hydroxymethyl unit with potassium peroxodisulfate ($K_2S_2O_8$). All attempts toward direct oxidation of ellipticine (**28.9**) had failed. The nitro group was then removed in a two-step sequence. Reduction with tin(II) chloride followed by diazotation of the resulting amino derivative and thermal decomposition of the diazonium salt in ethanol at reflux provided 12-hydroxyellipticine (**310.4**). After purification by preparative HPLC, this reaction sequence led to 12-hydroxyellipticine (**310.4**) in 19% yield over 5 steps. Starting from 5-methoxy-1,4-dimethylcarbazole-3-carbaldehyde (**330.1**), the same sequence of transformations as described above led to 9-methoxyellipticine (**310.1**) in 94% yield (Scheme 330).[678]

12.2.10. Konakahara's Total Synthesis of Ellipticine. In 2010, Konakahara and co-workers accomplished the total synthesis of ellipticine (**28.9**) using a double Buchwald–Hartwig amination of a biphenyl-2,2′-diyl bistriflate as the key step.[679] The required biphenyl-2,2′-diol precursor was synthesized in 3 steps from 2,5-dimethylphenol (**331.1**) (Scheme 331). Friedel–Crafts alkylation of **331.1** with dichloromethyl methyl ether led, after hydrolysis, to 2,5-dimethyl-4-hydroxybenzaldehyde, which was smoothly converted to the iodophenol **331.2** by treatment with iodine in the presence of sodium acetate. Phosphine-free Suzuki–Miyaura coupling with 2-hydroxyphenylboronic acid (**331.3**) led to the desired biphenyl-2,2′-diol **331.4** in 69% yield. This reaction required considerable optimization, and a large variety of palladium sources and solvent systems were screened. Optimal results were achieved when **331.2** and **331.3** were heated in a 1:1 mixture of DMSO and water in the presence of 2 mol % of palladium(II) acetate, 5 mol % of copper(II) acetate dihydrate, and 3 equiv of sodium carbonate. Reaction of the biphenyl-2,2′-diol **331.4** with trifluoromethanesulfonic anhydride led to the corresponding biphenyl-2,2′-diyl bistriflate. Buchwald–Hartwig coupling with *tert*-butyl carbamate in xylene at reflux furnished the 3-formylcarbazole **314.1**, which had previously been transformed into ellipticine (**28.9**).[658,660] In a slight modification of the original procedure, Konakahara and co-workers converted the 3-formylcarbazole **314.1** into ellipticine (**28.9**). Imine formation with 2,2-diethoxyethylamine (**314.2**) followed by reduction and N-sulfonylation with 2-nitrobenzenesulfonyl chloride (NsCl) led to the cyclization precursor **331.5**. Treatment with hydrochloric acid in 1,4-dioxane at reflux induced a Pomeranz–Fritsch cyclization with concomitant aromatization to ellipticine (**28.9**).

12.2.11. Ishikura's Formal Synthesis of Olivacine. Ishikura et al. described a formal synthesis of olivacine (**28.10**) starting from *N*-Boc-indole (**332.1**) (Scheme 332).[680] The key step of Ishikura's approach is a palladium-catalyzed tandem cyclization–cross-coupling reaction of an indolylborate with the vinyl bromide **332.3**. The desired indolylborate **332.2** was formed in situ by treatment of *N*-Boc-indole (**332.1**) with *tert*-butyllithium followed by addition of triethylborane. Palladium-catalyzed coupling of the vinyl bromide **332.3** and the indolylborate **332.2** led to the hexatriene **332.4**. Irradiation of **332.4** with a high-pressure mercury lamp in benzene at room temperature induced an electrocyclic reaction and oxidation which furnished the tetrahydropyridocarbazole **332.5** in moderate yield. Removal of the Cbz protecting group of **332.5** by catalytic hydrogenation provided **332.6** in 90% yield. Oxidation of the tetrahydropyridocarbazole **332.6** with manganese dioxide in ethyl acetate at room temperature afforded the pyridocarbazole **332.7** and the dihydrocarbazole **332.8** in 10% and 25% yield, respectively. The pyridocarbazole **332.7** could selectively be prepared in 60% yield by heating of **332.6** with manganese dioxide in ethyl acetate at reflux. Finally, the Boc group of **332.7** was removed by treatment with cesium carbonate in methanol/tetrahydrofuran at elevated temperature to provide 1-demethylolivacine (**332.9**). The conversion of **332.9** to olivacine (**28.10**) has already been described by Kutney et al.[681]

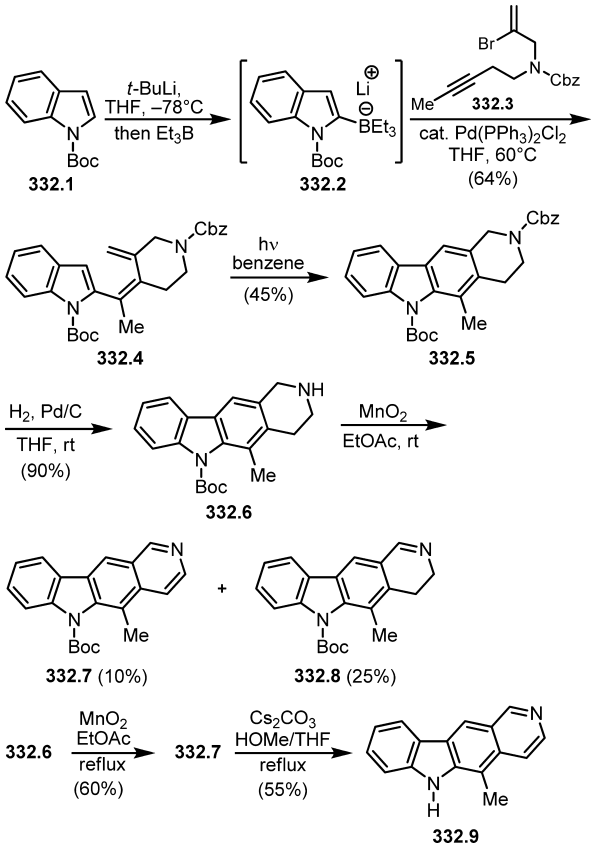
13. QUINOLINO[4,3-*b*]CARBAZOLE ALKALOIDS

13.1. Isolation from Natural Sources

According to the Hantzsch–Widman nomenclature, the quinolino[4,3-*b*]carbazole framework should preferably be named as indolo[3,2-*j*]phenanthridine. However, the non-recommended name has been chosen as the title of the present

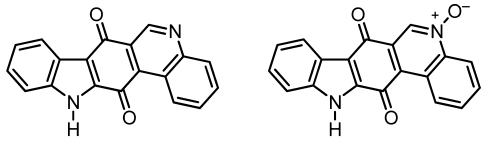
dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 332



section to put this class of alkaloids into the context of this review. Calothrixin A (**34.5**) and its *N*-deoxy derivative, calothrixin B (**34.4**), are the only quinolino[4,3-*b*]carbazole alkaloids known so far (Scheme 333). Both have been obtained

Scheme 333



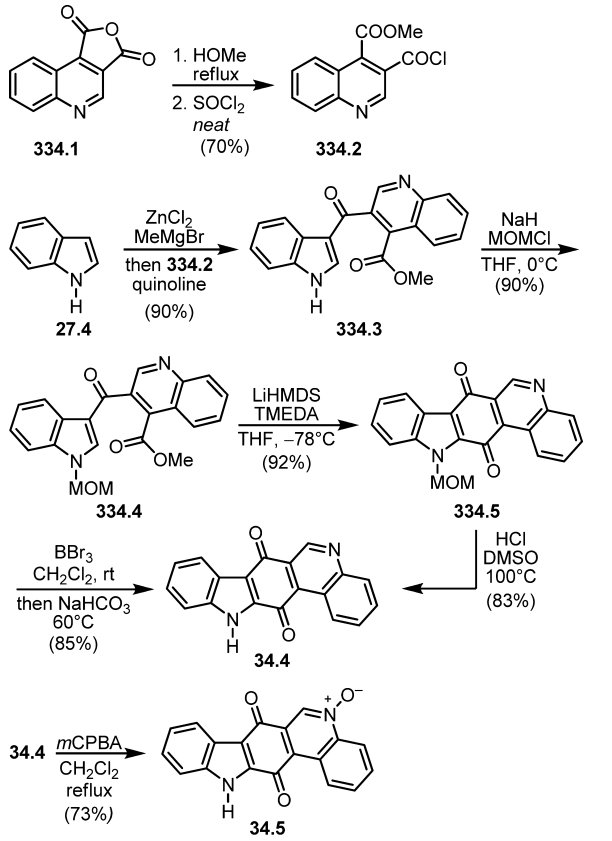
in 1999 by Rickards, Smith, and co-workers from a bioassay-guided fractionation of photoautotrophic cultures of two strains of *Calothrix* cyanobacteria (a blue-green alga).[241]

The quinolino[4,3-*b*]carbazole-1,4-quinones calothrixin A (**34.5**) and B (**34.4**) inhibit the growth of a chloroquine-resistant strain of the malaria parasite *Plasmodium falciparum* and human HeLa cancer cells.[241] Subsequent investigations also revealed that calothrixin A (**34.5**) is redox-active and induces the intracellular formation of reactive oxygen species.[682] Very recently, Hecht and co-workers described calothrixin A (**34.5**) and B (**34.4**) and their O- and N-methylated derivatives as human DNA topoisomerase I poisons, capable of stabilizing the enzyme−DNA covalent binary complex and mediating topoisomerase I-dependent cell death.[683] Because of the wide range of biological activities, various synthetic methods have been developed for the synthesis of calothrixins.[12,684,685]

13.2. Syntheses of Calothrixin A and B via Friedel−Crafts acylation

In 2002, Chai and co-workers reported a simple and concise route to calothrixin B (**34.4**) starting from indole (**27.4**) and the readily available quinoline-3,4-dicarboxylic anhydride (**334.1**) (Scheme 334).[686−688] Anhydride **334.1** was first

Scheme 334

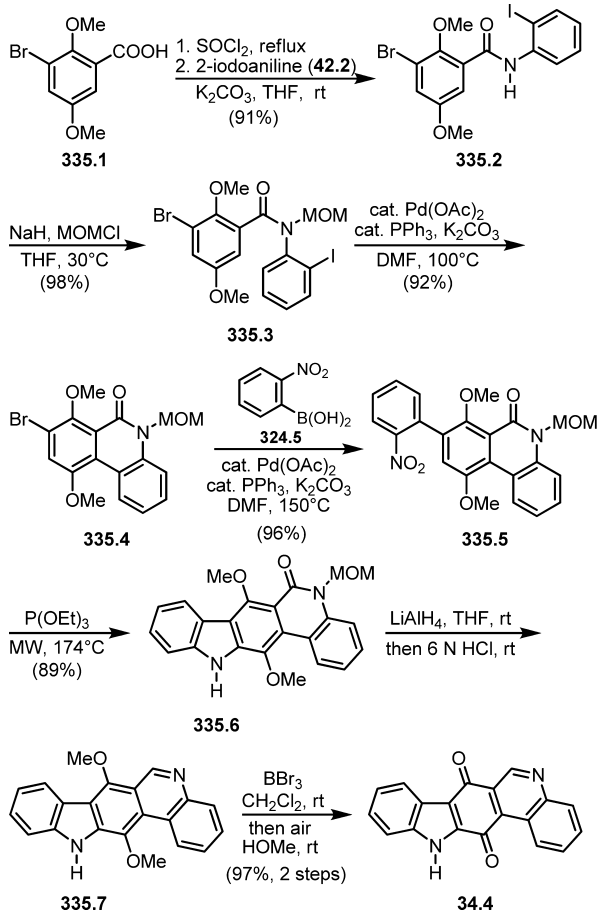


transformed into the acid chloride **334.2**, which was then used for a Friedel−Crafts acylation. The diarylketone **334.3** was obtained in 90% yield by deprotonation of indole (**27.4**) with methylmagnesium bromide in the presence of zinc chloride followed by addition of the acid chloride **334.2**. After protection of the indole nitrogen atom, the corresponding *N*-MOM derivative **334.4** was subjected to lithiation with lithium hexamethyldisilazide (LiHMDS) in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine followed by intramolecular nucleophilic substitution of the ester to afford *N*-MOM-calothrixin B (**334.5**). Cleavage of the *N*-MOM group by dissolving **334.5** in DMSO under acidic conditions, or alternatively by treatment with boron tribromide, afforded calothrixin B (**34.4**). Transformation of calothrixin B (**34.4**) to calothrixin A (**34.5**) was achieved by using *m*CPBA as oxidant following a procedure reported by Kelly et al.[689]

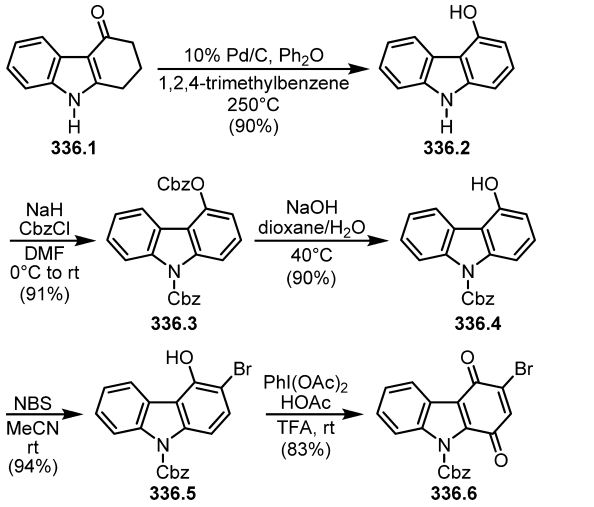
Five years later, the same authors reported an efficient palladium-catalyzed route for the synthesis of calothrixin B (**34.4**) using the phenanthridinone **335.4** and 2-nitrophenylboronic acid (**324.5**) as precursors (Scheme 335).[690] The benzoic acid **335.1** was transformed into the acid chloride and coupled with 2-iodoaniline (**42.2**) to afford the amide **335.2**. Transformation of the amide **335.2** to the MOM-protected amide **335.3** followed by a palladium-catalyzed Heck

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

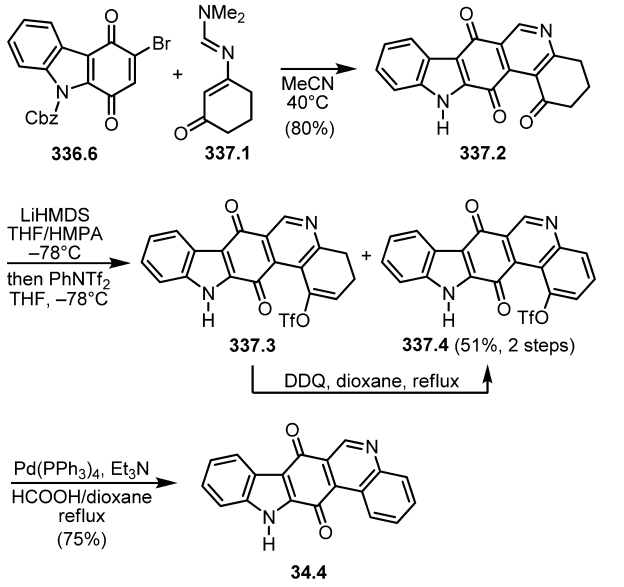
Scheme 335



Scheme 336



Scheme 337



cyclization afforded the phenanthridinone **335.4**. Suzuki–Miyaura coupling of the bromophenanthridinone **335.4** with 2-nitrophenylboronic acid (**324.5**) afforded the *o*-nitrophenylphenanthridinone **335.5**. Cadogan cyclization of **335.5** provided the indolophenanthridinone **335.6** in 89% yield. Reduction of the amide group of **335.6** with lithium aluminum hydride followed by acidic workup afforded the dimethoxyindolophenanthridine derivative **335.7**. Oxidative demethylation of **335.7** with an excess of boron tribromide followed by quenching with anhydrous methanol and stirring in the presence of air afforded calothrixin B (**34.4**) in 97% yield.

13.3. Synthesis of Calothrixin B via Diels–Alder Cycloaddition

In 2004, Guingant and co-workers reported a new and efficient synthesis of calothrixin B (**34.4**) via a hetero-Diels–Alder reaction of the 3-bromocarbazole-1,4-dione **336.6** and the 2-aza-1,3-diene **337.1** (Schemes 336 and 337).[691,692] Dehydrogenation of tetrahydro-4*H*-carbazol-4-one (**336.1**) using palladium on activated carbon afforded 4-hydroxy-9*H*-carbazole (**336.2**), which on bis-protection by the Cbz group led to **336.3**. Chemoselective monodeprotection of **336.3** with aqueous sodium hydroxide followed by bromination of the *N*-Cbz-protected 4-hydroxy-9*H*-carbazole **336.4** with NBS afforded the 3-bromocarbazole **336.5**. Finally, oxidation of compound **336.5** with diacetoxyiodobenzene ($PhI(OAc)_2$) provided the desired dienophile **336.6** in 83% yield.

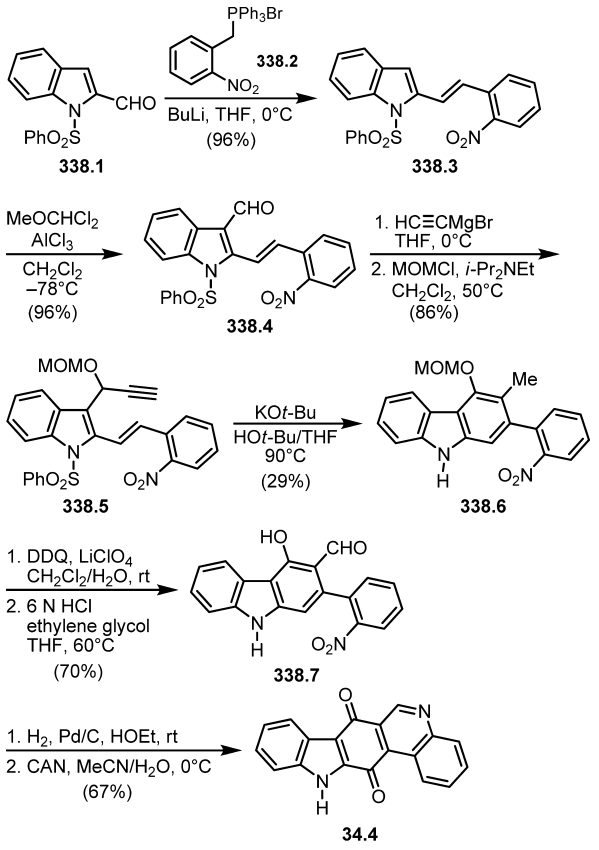
Diels–Alder cycloaddition of **336.6** and the 2-azadiene **337.1** in acetonitrile at 40 °C afforded the cycloadduct **337.2** in 80% yield, along with 5% of the Cbz-protected cycloadduct. The in situ removal of the Cbz group is ascribed to the liberated dimethylamine hydrobromide. Deprotonation of **337.2** followed by treatment with *N*-phenyl-bis(trifluoromethanesulfonimide) afforded a mixture of vinyl triflate **337.3** and aryl triflate **337.4**. Without separation, this mixture was heated in dioxane in the presence of DDQ to afford the pure aryl triflate **337.4** in 51% yield. Finally, a palladium(0)-catalyzed defunctionalization of **337.4** led to calothrixin B (**34.4**).[691,692] Recently, an extension of this methodology led to a calothrixin B isomer, which has been used for an investigation of the biological activity of this class of compounds.[693]

13.4. Syntheses of Calothrixin A and B via Electrocyclic Reaction

In 2005, Hibino et al. reported a new synthesis of calothrixin B (**34.4**) starting from 2-formyl-*N*-benzenesulfonylindole (**338.1**) (Scheme 338).[694] The key step of this synthesis is an allene-mediated electrocyclic reaction of a 6π-electron system involving the indole-2,3-bond. Wittig olefination of **338.1** with (2-nitrobenzyl)triphenylphosphonium bromide (**338.2**)

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

Scheme 338



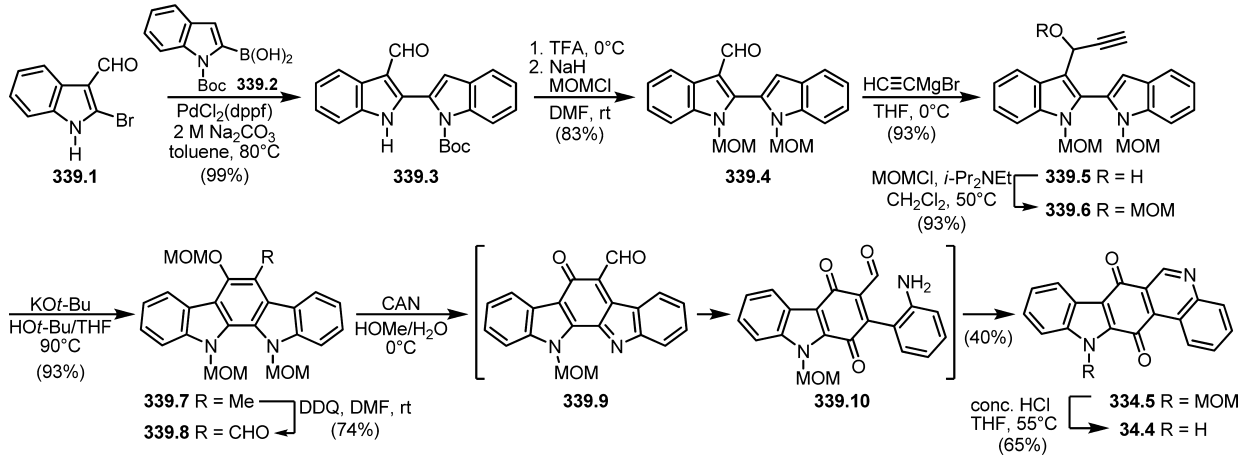
gave the *trans*-styrylindole **338.3**. Reaction of **338.3** with 1,1-dichloromethyl methyl ether in the presence of $AlCl_3$ afforded the 3-formylindole **338.4**. The Grignard reaction of **338.4** with ethynylmagnesium bromide led to the corresponding propargyl alcohol, which was protected as methoxymethyl ether **338.5**. The propargyl ether **338.5** was subjected to an allene-mediated electrocyclic reaction with potassium *tert*-butoxide in *tert*-butanol and tetrahydrofuran at 90 °C to afford the required 4-oxygenated carbazole **338.6**. Oxidation of **338.6** with DDQ in the presence of lithium perchlorate and removal of the MOM group gave the 3-formyl-4-hydroxy-carbazole **338.7**. Reduction of the nitro group of **338.7** with palladium on activated carbon, followed by intramolecular condensation and subsequent oxidation to a quinone with ceric ammonium nitrate, provided calothrixin B (**34.4**) in 67% yield.

In the following year, Hibino and co-workers described a biomimetic approach to calothrixin B (**34.4**) via the 6-formylindolo[2,3-*a*]carbazole **339.8** (Scheme 339).[695,696] The key step of their approach is an electrocyclic reaction of a 2,2′-biindole involving both 2,3-indole double bonds via an allene intermediate. Suzuki–Miyaura coupling of **339.1** with the indol-2-ylboronic acid **339.2** led to the 2,2′-biindole derivative **339.3**. Cleavage of the *N*-Boc group followed by protection of both nitrogen atoms afforded the di-MOM-protected biindole **339.4**. Grignard reaction of **339.4** with ethynylmagnesium bromide yielded the propargyl alcohol **339.5**, which was protected with MOMCl to afford the MOM ether **339.6**. An allene-mediated electrocyclic reaction of **339.6** led to the desired indolocarbazole **339.7**. Oxidation of the 6-methylindolocarbazole **339.7** to 6-formylindolocarbazole **339.8** was achieved by reaction with DDQ, which on further oxidation with ceric ammonium nitrate led to *N*-MOM-calothrixin B (**334.5**) involving the quinone imine **339.9** and the quinone **339.10** as intermediates. Finally, cleavage of the MOM group using Kelly's procedure[689] afforded calothrixin B (**34.4**) in 65% yield.

Using Hibino's 6-formylindolo[2,3-*a*]carbazole intermediate **339.8**,[695] Moody and co-workers reported in 2007 a second biomimetic synthesis of calothrixin B (**34.4**) starting from indigo (**340.1**) (Scheme 340).[697,698] Following Somei's procedure, the *cis*-chlorohydrin **340.2** was obtained in 3 steps and 68% overall yield from indigo (**340.1**) (see Scheme 348).[699−701] Reduction of the chlorohydrin **340.2** afforded the known 5-hydroxyindolo[2,3-*a*]carbazole (**340.3**), which on subsequent Vilsmeier formylation provided 5-hydroxyindolo-[2,3-*a*]carbazole-6-carboxaldehyde (**34.1**). Reaction of **34.1** with an excess of chloromethyl methyl ether (MOMCl) afforded the tris-MOM-protected compound **339.8**, an intermediate of Hibino's biomimetic approach. Thus, following Hibino's protocol,[695] the indolocarbazole **339.8** was transformed to calothrixin B (**34.4**) in 2 steps and 26% overall yield.

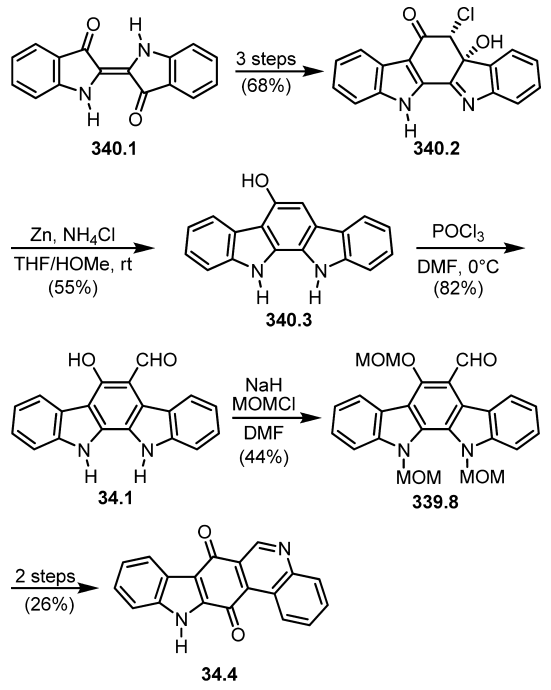
In 2011, Ishikura and co-workers also reported a total synthesis of the calothrixins A (**34.5**) and B (**34.4**) using an electrocyclic ring-closure as the key step (Schemes 341 and 342).[702] The synthetic route was based on the same approach that already had been successfully applied to the formal synthesis of olivacine (**28.10**) (see section 12.2.11). The

Scheme 339

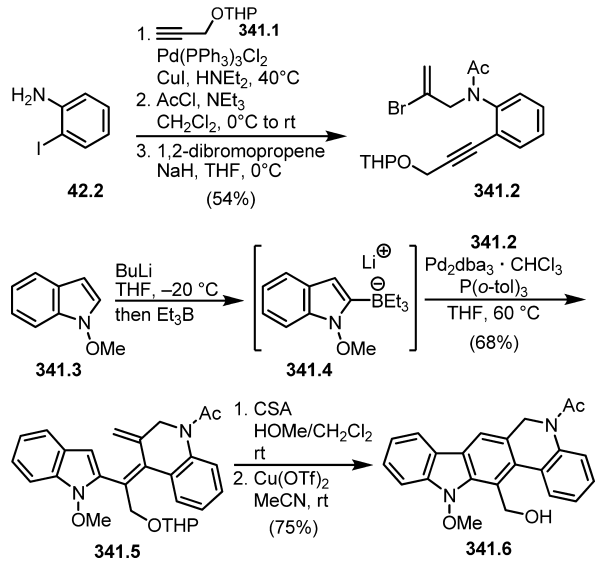


dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

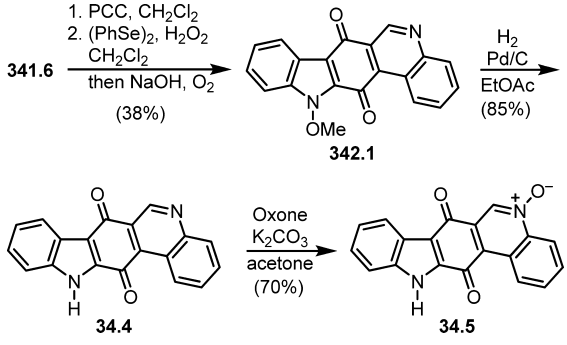
Scheme 340



Scheme 341



Scheme 342



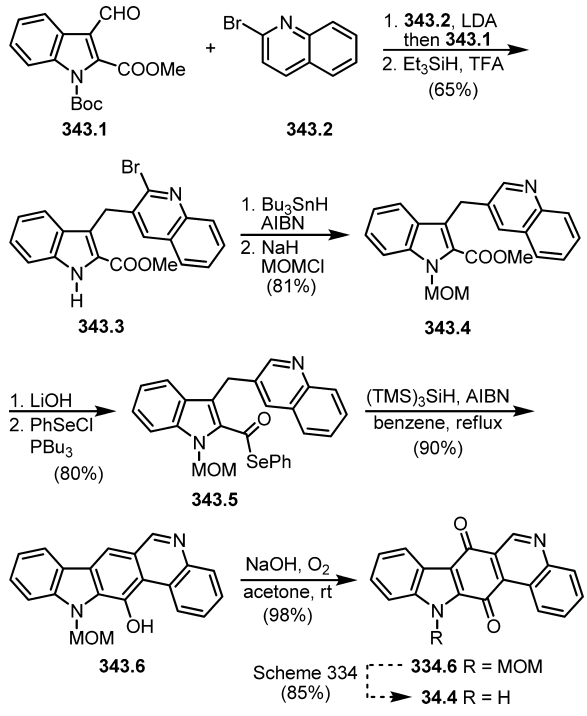
precursor for the electrocyclization was synthesized by Suzuki–Miyaura coupling of an indol-2-ylborate and a vinyl bromide. Sonogashira coupling of 2-iodoaniline (**42.2**) and tetrahydropyranyl-protected propargyl alcohol **341.1** followed by N-acetylation and N-alkylation provided the required vinyl bromide **341.2**. Lithiation of *N*-methoxyindole (**341.3**) followed by treatment with triethylborane led to the triethylindol-2-ylborate **341.4**, which was directly used for a Suzuki–Miyaura cross-coupling with the vinyl bromide **341.2** to give the cyclization precursor **341.5**. Deprotection with camphorsulfonic acid led to the free alcohol, which was then treated with stoichiometric amounts of copper(II) triflate–toluene complex in acetonitrile at room temperature. The thermally induced electrocyclic ring-closure was accompanied by aromatization to the dihydroquinolinocarbazole **341.6**.

The hydroxymethyl group in **341.6** was then oxidized to a formyl group with PCC (pyridinium chlorochromate). Treatment with diphenyl diselenide in the presence of hydrogen peroxide led to *N*-methoxycalothrixin B (**342.1**) and a partially oxidized byproduct, which was further converted to **342.1** by resubjecting it to the diphenyl diselenide/hydrogen peroxide oxidation (Scheme 342). Hydrogenolysis of the oxygen–nitrogen bond led to calothrixin B (**34.4**), which was then oxidized to calothrixin A (**34.5**) using oxone as oxidant.

13.5. Radical-Based Route to Calothrixin B

In 2006, Bennasar et al. reported a radical-based approach that generates the framework of calothrixin B (**34.4**) by a regioselective intramolecular acylation of a quinoline (Scheme 343).[703] Chemoselective reaction of 3-lithio-2-bromoquinoline, generated in situ from 2-bromoquinoline **343.2**, with the 3-formylindole **343.1** followed by reduction of the resulting carbinol with triethylsilane afforded the 2-bromoquinoline derivative **343.3** in 65% yield. Reaction of **343.3** with tributyltinhydride and protection of the indole nitrogen with chloromethyl methyl ether led to the *N*-MOM indole **343.4** in

Scheme 343



dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

81% yield. Saponification of the methyl ester **343.4** followed by phenylselenation of the intermediate carboxylic acid gave the required selenoester **343.5**. Treatment of the selenoester **343.5** with tris(trimethylsilyl)silane in the presence of the radical initiator azobisisobutyronitrile at 80 °C led to the hydroxyquinolino[4,3-*b*]carbazole **343.6**. Mild oxidation of the phenol **343.6** with molecular oxygen in basic medium provided almost quantitatively *N*-MOM-calothrixin B (**334.5**), a known intermediate for the synthesis of calothrixin B (**34.4**).

14. INDOLOCARBAZOLE ALKALOIDS

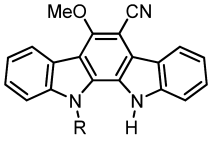
The indolocarbazoles, a well-known family of biologically active carbazole alkaloids, have an indole moiety fused to one of the benzo rings of the carbazole framework. On the basis of the mode of indole annulation at the carbazole framework, they are classified in five possible isomeric ring systems.[1,704] The indolo[2,3-*a*]carbazoles have been studied most extensively, because numerous alkaloids with this framework have shown a wide range of potent biological activities such as antifungal, hypotensive, antimicrobial, protein kinase C (PKC) inhibition, and antiplatelet aggregation properties.[12,705−708] However, the enormous interest in these compounds derives from their potent antitumor activity. Currently, several indolo[2,3-*a*]-carbazole alkaloids are in clinical trials for potential use in cancer therapy. Also several derivatives of the isomeric ring systems displayed promising biological activities and interesting physical properties. These aspects have been summarized previously in several accounts and comprehensive reviews.[12,229,230,705−716] Moreover, in 2002, Knölker and Reddy covered various aspects of the isolation, synthesis, and biological activities of indolocarbazoles.[1] Herein, we summarize the literature since then including a few earlier milestone syntheses of natural indolocarbazoles. Because of the enormous growth of publications in this field of research, the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles are discussed separately from the indolo[2,3-*a*]carbazoles without the annulated pyrrole ring.

14.1. Indolo[2,3-*a*]carbazole Alkaloids

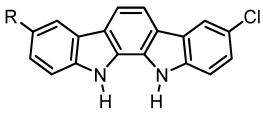
14.1.1. Isolation from Natural Sources. In 1990, Moore and co-workers isolated 5-cyano-6-methoxy-11-methylindolo-[2,3-*a*]carbazole (6-methoxy-11-methyl-11,12-dihydroindolo-[2,3-*a*]carbazole-5-carbonitrile) (**344.1**) from the ethanol extract of the blue−green alga *Nostoc sphaericum* EX-5-1 (Scheme 344).[717] The corresponding normethyl derivative 5-cyano-6-methoxyindolo[2,3-*a*]carbazole (6-methoxy-11,12-dihydroindolo[2,3-*a*]carbazole-5-carbonitrile) (**344.2**) was obtained along with **344.1** as minor component from the same source. The indolo[2,3-*a*]carbazole alkaloids **344.1** and **344.2** were the first natural products with a simple indolo[2,3-*a*]carbazole skeleton (no annulated pyrrole ring). Moreover, **344.1** and **344.2** exhibited moderate activity against herpes simplex virus type 2 and were weakly cytotoxic against murine and human cancer cell lines.[717]

In 1991, Bonjouklian et al. reported the discovery of the tjipanazoles **344.3**−**347.2**, an extraordinary group containing some unprecedented chlorine-substituted and *N*-glycosidic indolo[2,3-*a*]carbazoles, from a bioactivity-directed investigation of the blue−green alga *Tolypothrix tjipanasensis* (strain DB-1-1) collected in Vero Beach, Florida (Schemes 344−347).[718]

Scheme 344

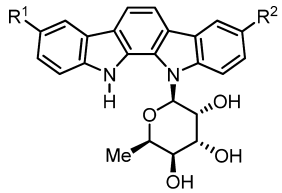


344.1 R = Me
344.2 R = H

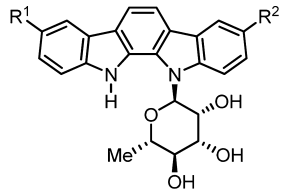


344.3 Tjipanazole D R = Cl
344.4 Tjipanazole I R = H

Scheme 345

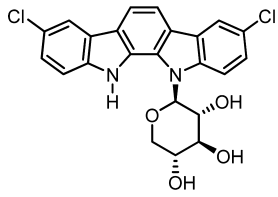


345.1 Tjipanazole A1 R^1,R^2 = Cl
345.2 Tjipanazole C1 R^1 = Cl; R^2 = H
345.3 Tjipanazole C2 R^1 = H; R^2 = Cl
345.4 Tjipanazole G1 R^1,R^2 = H

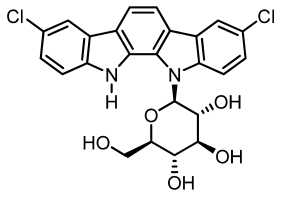


345.5 Tjipanazole A2 R^1,R^2 = Cl
345.6 Tjipanazole C3 R^1 = Cl; R^2 = H
345.7 Tjipanazole C4 R^1 = H; R^2 = Cl
345.8 Tjipanazole G2 R^1,R^2 = H

Scheme 346

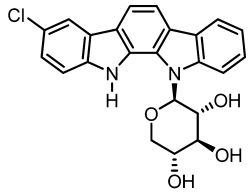


346.1 Tjipanazole B

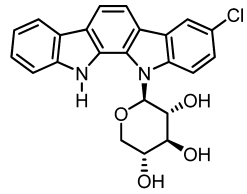


346.2 Tjipanazole E

Scheme 347



347.1 Tjipanazole F1



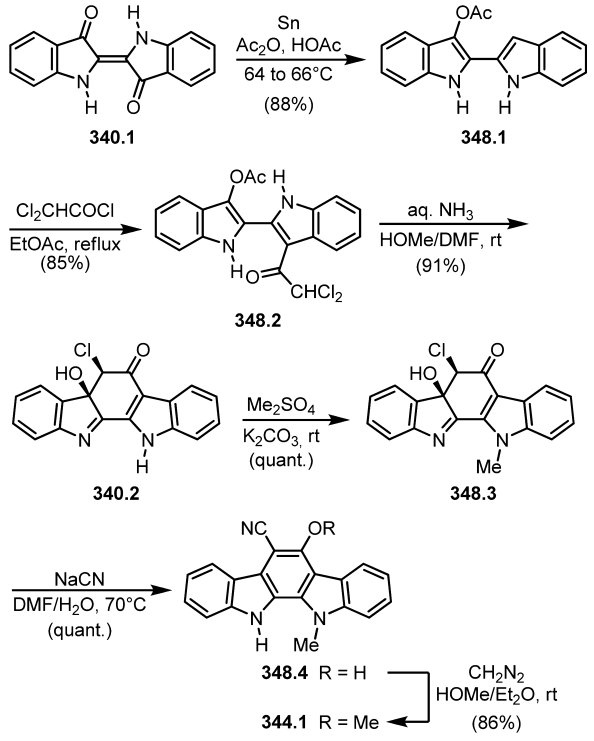
347.2 Tjipanazole F2

Tjipanazoles D (**344.3**) and I (**344.4**) are chlorinated indolo[2,3-*a*]carbazoles. Tjipanazole G1 (**345.4**) and G2 (**345.8**) are nonchlorinated indolo[2,3-*a*]carbazole *N*-glycosides, and the tjipanazoles A1 (**345.1**), A2 (**345.5**), B (**346.1**), C1 (**345.2**), C2 (**345.3**), C3 (**345.6**), C4 (**345.7**), E (**346.2**), F1 (**347.1**), and F2 (**347.2**) are chlorinated indolo[2,3-*a*]carbazole *N*-glycosides. Tjipanazole A1 (**345.1**) and A2 (**345.5**) exhibited a selective fungicidal activity against rice blast and leaf rust wheat infections.[718] Tjipanazole D (**344.3**) was also isolated from a different terrestrial blue−green alga, *Fischerella ambigua*.[719,720]

14.1.2. Synthesis of 5-Cyano-6-methoxy-11-methylindolo[2,3-*a*]carbazole. In 1997, Somei and co-workers reported the synthesis of 5-cyano-6-methoxy-11-methylindolo[2,3-*a*]carbazole (**344.1**) starting from indigo (**340.1**) (Scheme 348).[699−701] Reduction of **340.1** with tin in acetic acid/acetic anhydride afforded 3-acetoxy-2,2′-biindole

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 348

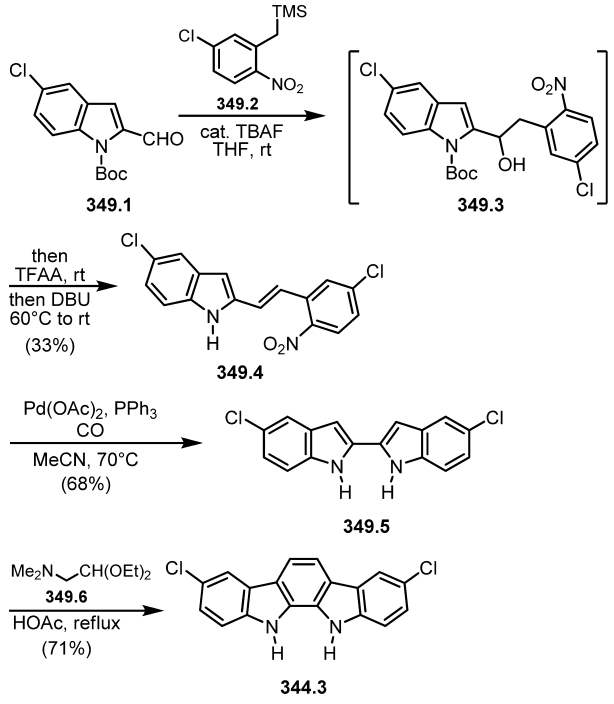


(**348.1**) in 88% yield. Heating of compound **348.1** with dichloroacetyl chloride in ethyl acetate at reflux provided 3-acetoxy-3′-dichloroacetyl-2,2′-biindole (**348.2**) in 85% yield. Treatment of **348.2** with aqueous ammonia in methanol/DMF at room temperature led to the indolo[2,3-*a*]carbazole derivative **340.2**. After N-methylation of **340.2**, the corresponding *N*-methyl derivative **348.3** was subjected to reductive cyanation to afford 5-cyano-6-hydroxy-11-methylindolo[2,3-*a*]carbazole (**348.4**). Finally, O-methylation of **348.4** with diazomethane afforded 5-cyano-6-methoxy-11-methylindolo-[2,3-*a*]carbazole (**344.1**) in 86% yield. On the basis of this approach, the same group subsequently reported the synthesis of a range of analogous compounds for bioactivity tests.[721]

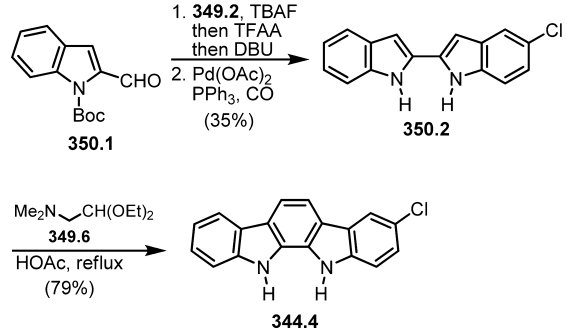
14.1.3. Total Synthesis of Tjipanazoles B, D, E, and I. In 2003, Kuethe et al. reported the total synthesis of the tjipanazoles B (**346.1**), D (**344.3**), E (**346.2**), and I (**344.4**) starting from the indolecarbaldehydes **349.1** and **350.1** (Schemes 349−351).[722] The indolocarbazole ring system is formed by a C_2-insertion into a 2,2′-biindole compound. Tjipanazoles B (**346.1**), D (**344.3**), and E (**346.2**) were synthesized starting from the 5-chloroindole-2-carbaldehyde **349.1**. The *trans*-alkene **349.4** was synthesized in a one-pot operation by treatment of the indole carbaldehyde **349.1** with the benzyl(trimethyl)silane **349.2** in the presence of catalytic amounts of TBAF followed by acylation with trifluoroacetic anhydride and elimination of the intermediate trifluoroacetate with DBU (Scheme 349). The reaction probably proceeds via the alcohol **349.3**, which is formed by the addition of a benzyl anion to the aldehyde **349.1**. Reductive cyclization of **349.4** using Cadogan/Sundberg conditions led to the 2,2′-biindole **349.5**. Finally, condensation with dimethylaminoacetaldehyde diethyl acetal (**349.6**) in acetic acid afforded tjipanazole D (**344.3**) in 71% yield.[722]

Tjipanazole I (**344.4**) was obtained in 5 steps and 28% overall yield via a similar sequence starting from *N*-Boc-indole-2-carbaldehyde (**350.1**) and the benzylsilane **349.2** (Scheme 350).[722]

Scheme 349



Scheme 350

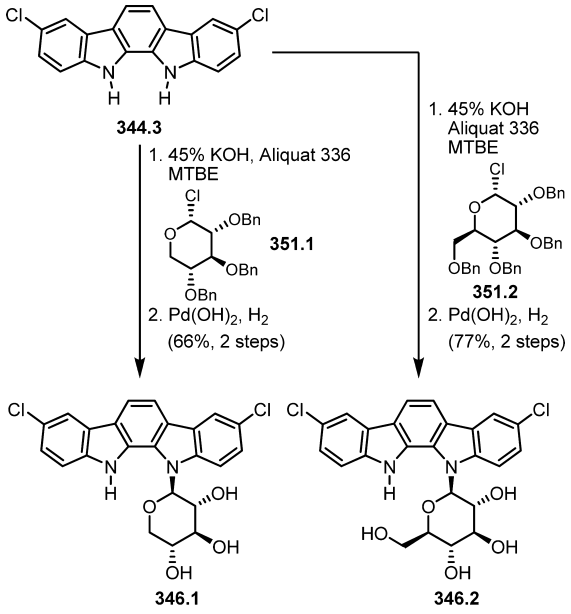


In addition, Kuethe et al. described the first total synthesis of tjipanazoles B (**346.1**) and E (**346.2**) by glycosylation of tjipanazole D (**344.3**) (Scheme 351). For the synthesis of tjipanazole B (**346.1**), **344.3** and benzyl protected α-D-xylopyranosyl chloride **351.1** were stirred in a biphasic mixture of methyl *tert*-butyl ether and aqueous potassium hydroxide using Aliquat 336 as phase-transfer catalyst followed by hydrogenation with palladium(II)hydroxide to provide tjipanazole B (**346.1**) in 2 steps and 66% yield. Using the same approach, tjipanazole E (**346.2**) was obtained in 2 steps and 77% yield from tjipanazole D (**344.3**) and the benzyl-protected α-D-glucopyranosyl chloride **351.2**.[722]

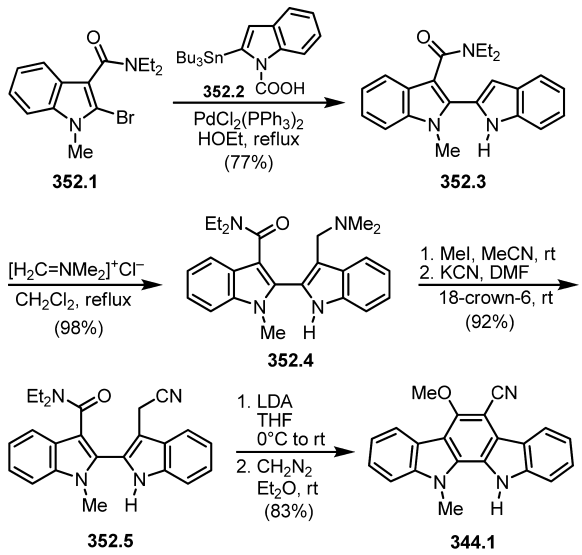
14.1.4. Synthesis of 5-Cyano-6-methoxy-11-methylindolo[2,3-*a*]carbazole. In 2004, Cai and Snieckus reported the synthesis of 5-cyano-6-methoxy-11-methylindolo-[2,3-*a*]carbazole (**344.1**) starting from the easily accessible 2-bromoindole-3-carboxamide **352.1** and the 2-stannylated indole-*N*-carboxylic acid **352.2** (Scheme 352).[723] This approach takes advantage of an efficient Stille cross-coupling

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 351



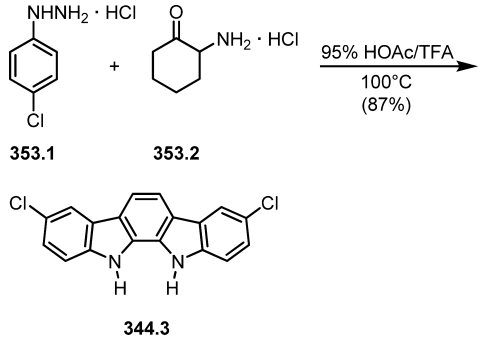
Scheme 352



strategy for the construction of the indolo[2,3-*a*]carbazole framework. Thus, coupling of the bromoindole **352.1** with the indol-2-ylstannane **352.2** provided the biindole derivative **352.3** in 77% yield. Reaction of **352.3** with Eschenmoser's salt afforded the gramine **352.4**. Sequential N-alkylation with methyl iodide and nucleophilic displacement with potassium cyanide in combination with 18-crown-6 afforded the biindolylacetonitrile **352.5**. Finally, treatment with lithium diisopropylamide induced a cyclocondensation that was followed by immediate methylation of the resulting unstable phenol with diazomethane. Thus, 5-cyano-6-methoxy-11-methylindolo[2,3-*a*]carbazole (**344.1**) was obtained in 6 steps and 58% overall yield based on the bromoindole **352.1**.

14.1.5. Total Synthesis of Tjipanazole D. In 2005, Hu and Chen reported an efficient one-pot synthesis of tjipanazole D (**344.3**) starting from 4-chlorophenylhydrazine hydrochloride (**353.1**) and 2-aminocyclohexanone hydrochloride (**353.2**) via Fischer indole synthesis (Scheme 353).[724] Double

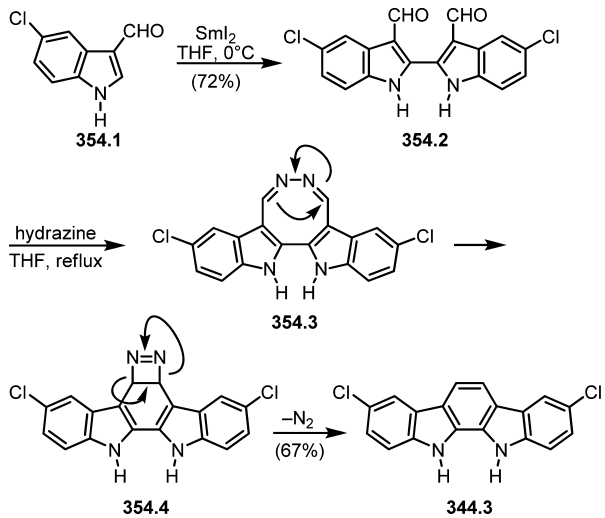
Scheme 353



Fischer indolization of **353.2** with 4-chlorophenylhydrazine hydrochloride (**353.1**) afforded tjipanazole D (**344.3**) in 87% yield.

In the same year, Banerji et al. reported a two-step synthesis of tjipanazole D (**344.3**) from 5-chloroindole-3-carbaldehyde (**354.1**) using single electron transfer (SET) conditions (Scheme 354).[725] Reaction of the 3-formylindole **354.1** with

Scheme 354



samarium(II) iodide in tetrahydrofuran afforded the 2,2′-biindole **354.2**. Heating of **354.2** with hydrazine in tetrahydrofuran at reflux led to tjipanazole D (**344.3**) in 67% yield. The reaction is believed to involve a cyclocondensation to **354.3** followed by an electrocyclic diazacyclobutene formation to **354.4** and subsequent elimination of dinitrogen.

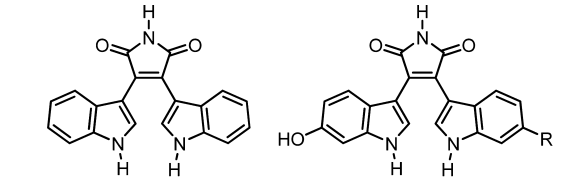
14.2. 2,3-Bis(indol-3-yl)maleimide Alkaloids

14.2.1. Isolation from Natural Sources. 2,3-Bis(indol-3-yl)maleimide alkaloids do not contain a carbazole ring system. However, they are considered to be biogenetic precursors for the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles and, therefore, have been included in the present review.[229,230]

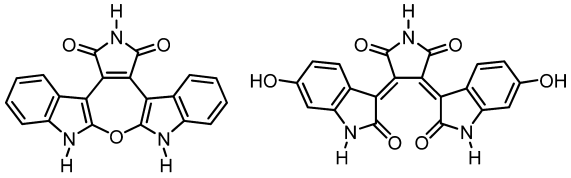
In the early 1980s, Steglich and co-workers reported the isolation of a series of biogenetically closely related 2,3-bis(indol-3-yl)maleimide alkaloids (Schemes 355 and 356). Arcyriarubins A (**355.1**), B (**355.2**), and C (**355.3**),[710,726,727] dihydroarcyriarubin B (**355.4**),[710] arcyroxepin A (**356.1**),[710,726,727] and arcyriaverdin C (**356.2**)[710] as well as the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids arcyriaflavin B (**363.1**) and C (**363.2**)[726] (see Scheme 363) were obtained

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 355



Scheme 356

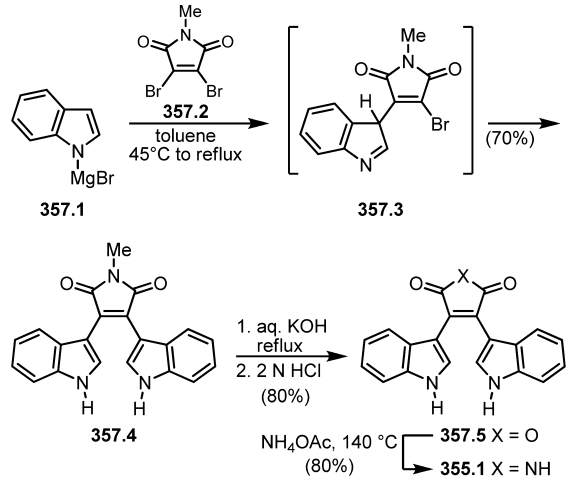


from the red sporangia of the slime mold *Arcyria denudata*. Arcyriarubin A (**355.1**) was present in this slime mold in only small amounts.[229,710] Similar to the arcyriaflavins, the arcyriarubins also exhibit moderate antibiotic and antifungal activities.[710]

In 2003, Ishibashi and co-workers isolated a further, biogenetically closely related 2,3-bis(indol-3-yl)maleimide alkaloid, dihydroarcyriarubin C (**355.5**), along with the previously known arcyriarubin C (**355.3**) and arcyriaflavin C (**363.2**) (see Scheme 363) from different fruit bodies of the myxomycete *Arcyria ferruginea* collected in Kochi prefecture, Japan.[728] The CD spectrum of dihydroarcyriarubin C (**355.5**) indicated that this natural product was obtained in racemic form, and the ^{1}H NMR data confirmed a *trans*-stereochemistry for the protons of the dihydromaleimide ring.[728] Biosynthetically, all these compounds may derive by several oxygenations and oxidative cyclizations from arcyriarubin A (**355.1**). In addition to the compounds discussed above, further 2,3-bis(indol-3-yl)maleimides have been described that are not direct precursors for indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazoles.[228,729−736]

14.2.2. Synthesis of Arcyriarubin A and Arcyriarubin B. Eight years after the original isolation, Steglich and co-workers reported the first synthesis of arcyriarubin A (**355.1**) and arcyriarubin B (**355.2**) by reaction of indolylmagnesium bromide (**357.1**) with 2,3-dibromo-*N*-methylmaleimide (**357.2**) (Scheme 357).[737] Condensation of **357.1** with **357.2** in toluene afforded the diindolyl compound **357.4** in 70% yield by addition of 2 molecules of indolylmagnesium bromide (**357.1**) to **357.2** via the monoadduct **357.3**. The course of the reaction is strongly dependent on the solvent (see below). Conversion of **357.4** to arcyriarubin A (**355.1**) was achieved by alkaline hydrolysis to the cyclic anhydride **357.5**, which on

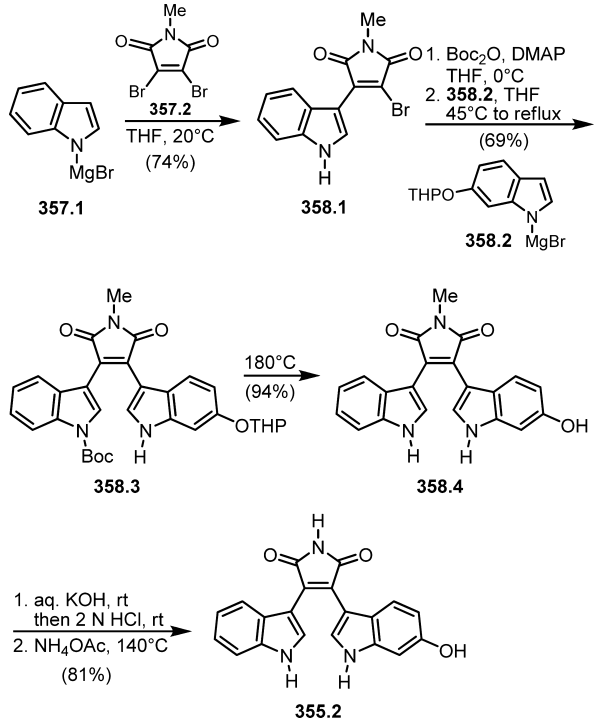
Scheme 357



heating with ammonium acetate afforded arcyriarubin A (**355.1**).

The unsymmetrically substituted compound **358.4**, required for the synthesis of arcyriarubin B (**355.2**), was obtained in 4 steps and 48% overall yield from indolylmagnesium bromide (**357.1**), 2,3-dibromo-*N*-methylmaleimide (**357.2**), and 6-(tetrahydropyranyloxy)indolylmagnesium bromide (**358.2**) (Scheme 358).[737] Addition of **357.1** to **357.2** in tetrahydrofur-

Scheme 358



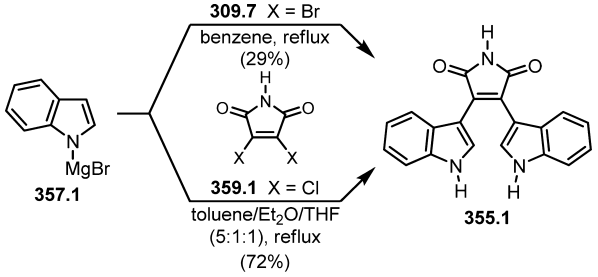
an afforded the monosubstituted product **358.1** via isomerization of the primary adduct **357.3**. Transformation of **358.1** to the Boc derivative followed by addition of 6-(tetrahydropyranyloxy)indolylmagnesium bromide (**358.2**) afforded the diindolyl derivative **358.3** in 69% yield. Deprotection of **358.3** by heating at 180 °C afforded the hydroxy derivative **358.4**. Conversion of the methylimide to the imide following the same route as described above for the

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

synthesis of arcyriarubin A (**355.1**) provided arcyriarubin B (**355.2**).

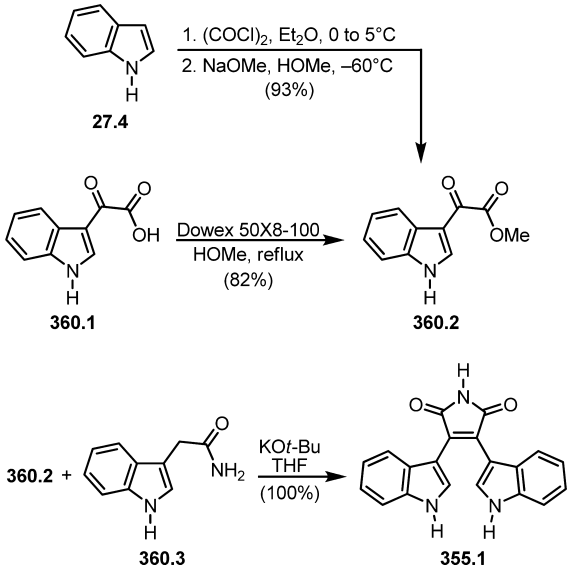
In 1993, Hill and co-workers reported a one-step synthesis of arcyriarubin A (**355.1**) by direct condensation of 2,3-dibromomaleimide (**309.7**) with 4 equiv of indolylmagnesium bromide (**357.1**) in benzene at reflux (Scheme 359). The yield, however, was only 29%.[738] Two years later, Faul et al. described an improved one-step approach to arcyriarubin A (**355.1**) (72% yield) using 2,3-dichloromaleimide (**359.1**) in a 5:1:1 toluene/ether/tetrahydrofuran solvent mixture.[739]

Scheme 359



Faul et al. reported an alternative method for the synthesis of arcyriarubin A (**355.1**). The natural product was obtained by condensation of the readily available indol-3-ylglyoxyl ester **360.2** with indol-3-ylacetamide (**360.3**) (Scheme 360).[740]

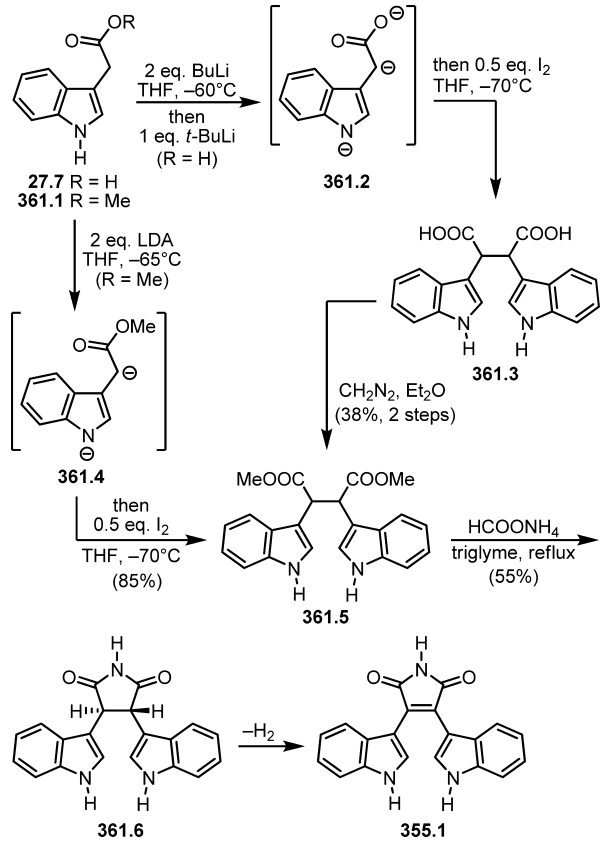
Scheme 360



Methyl indol-3-ylglyoxylate (**360.2**) was prepared either by treatment of indole (**27.4**) with oxalyl chloride and subsequent addition of sodium methoxide at low temperature, or by heating indol-3-ylglyoxylic acid (**360.1**) in methanol at reflux in presence of a Dowex 50×8-100 ion-exchange resin. Finally, base-mediated (KO*t*-Bu) condensation of **360.2** with **360.3** led quantitatively to arcyriarubin A (**355.1**).

Bergman et al. reported a biomimetic synthesis of arcyriarubin A (**355.1**) by oxidative coupling of the trianion **361.2** derived from indol-3-ylacetic acid (**27.7**) or, alternatively, the dianion **361.4** derived from methyl indol-3-ylacetate (**361.1**) (Scheme 361).[741] Sequential addition of 2 equiv of butyllithium and 1 equiv of *tert*-butyllithium to indol-3-yl acetic

Scheme 361

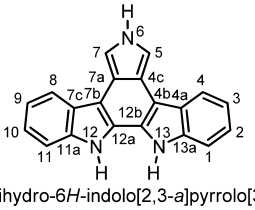


acid (**27.7**) afforded the trianion **361.2**, which on iodine-mediated oxidative coupling followed by acidic workup afforded the diacid **361.3**. Treatment of **361.3** with diazomethane provided diindolylsuccinic acid methyl ester **361.5** as a diastereomeric mixture in 2 steps and 38% overall yield. Alternatively, the diester **361.5** could be prepared in much better overall yield (85%) by iodine-mediated oxidative coupling of the dianion **361.4**, obtained by addition of 2 equiv of lithium diisopropylamide to methyl indol-3-ylacetate (**361.1**). Heating of the diastereoisomeric mixture of the diester **361.5** with ammonium formate in triglyme at reflux led exclusively to the *trans*-imide **361.6**, which was explained by cyclization of only one of the two diastereoisomers to the imide. Dehydrogenation of **361.6** afforded arcyriarubin A (**355.1**). Unfortunately, the authors did not provide any experimental details on that transformation.

14.3. Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole Alkaloids

The vast majority of naturally occurring indolocarbazole alkaloids are derivatives of the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole ring system **362.1** (Scheme 362). Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole natural products have been known

Scheme 362



362.1 12,13-Dihydro-6*H*-indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole

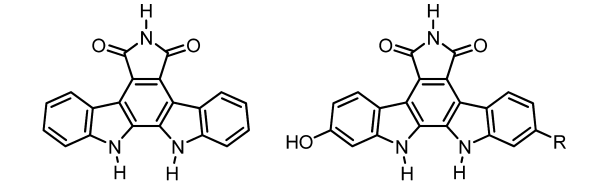
dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

for more than 30 years. They have been isolated from diverse natural sources: prokaryotes (actinomycetes, cyanobacteria, and β-proteobacteria) and eukaryotes (myxomycetes, basidiomycetes, and marine invertebrates). Indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles have shown a broad range of potent biological activities: antifungal, antimicrobial, antiviral, antitumor, antihypertensive, and antiplatelet aggregation activities. The discovery that these natural products are potent inhibitors of protein kinase C (PKC) has received special attention and induced extensive investigations.

14.3.1. Isolation from Natural Sources. The indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids have been isolated either as aglycones or as glycosides. Depending on their structure and mechanism of action, the latter can be divided into two classes. The members of the staurosporine and K252a class contain two glycosidic bonds linked to the indolocarbazole framework and are inhibitors of protein kinases. The indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole glycosides with only one glycosidic linkage to the indolocarbazole framework, such as rebeccamycin (**32.11**) and related natural products, bind to DNA and have antitumor properties.

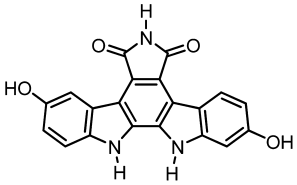
In 1980, Steglich and co-workers reported the isolation of arcyriaflavins B (**363.1**) and C (**363.2**) from the fruit bodies of the slime mold *Arcyria denudata* (myxomycetes) (Scheme 363).[710,726,727] Two years later, Steglich and co-workers

Scheme 363

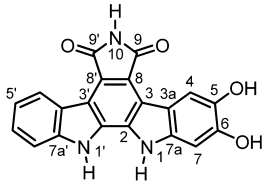


32.9 Arcyriaflavin A

363.1 Arcyriaflavin B R = H
363.2 Arcyriaflavin C R = OH



363.3 Arcyriaflavin D

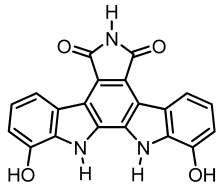


363.4 5,6-Dihydroxyarcyriaflavin A (2,3-Dihydroxyarcyriaflavin A)

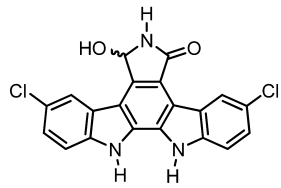
isolated the same natural products from a different slime mold, *Metatrichia vesparium* (myxomycetes).[742] In the following years, arcyriaflavin A (**32.9**) was isolated from a different *Arcyria* species, *A. nutans*,[229,710] and arcyriaflavin D (**363.3**) was isolated from another slime mold, *Dictydiaethalium plumbeum*.[710] Except arcyriaflavin A (**32.9**), which has no hydroxy groups, the other arcyriaflavins were classified based on the number and positions of the hydroxy groups present in the indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole framework. The arcyriaflavins exhibit moderate antibiotic and antifungal activities.[710] In 1994, McConnell et al. reported the isolation of arcyriaflavin A (**32.9**) from the marine ascidian *Eudistoma* sp. collected off the coast of West Africa.[743] In 2003, Ishibashi and co-workers isolated arcyriaflavin C (**363.2**) from another *Arcyria* species, *A. ferruginea*.[728] Moreover, arcyriaflavin C (**363.2**) has been isolated along with arcyriaflavin B (**363.1**) from the slime mold *Tubifera casparyi*.[728] Arcyriaflavin C (**363.2**) showed cell cycle inhibition at the G1 and G2/M stages at nanomolar concentrations. Two years later, Ishibasi and co-workers isolated a further dihydroxy derivative of arcyriaflavin A, 5,6-dihydroxyarcyriaflavin A (2,3-dihydroxyarcyriaflavin A) (**363.4**), from field-collected fruit bodies of the myxomycete *Lycogala epidendrum* along with the known arcyriarubin A (**355.1**) (see Scheme 355), arcyriaflavin A (**32.9**), arcyriaflavin B (**363.1**), and staurosporinone (**30.1**) (see Scheme 365). 5,6-Dihydroxyarcyriaflavin A (**363.4**) has shown cytotoxicity against HeLa, Jurkat, and vincristine-resistant KB/VJ300 cells.[732]

In 1991, Kojiri et al. reported the isolation of BE-13793C (**364.1**), a compound isomeric to the arcyriaflavins C (**363.2**) and D (**363.3**) (see Schemes 363 and 364), from the culture

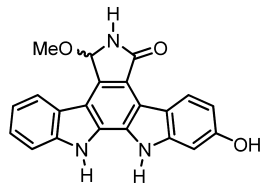
Scheme 364



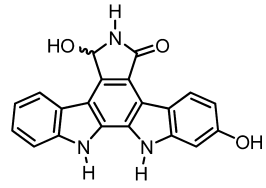
364.1 BE-13793C



364.2 Tjipanazole J



364.3 6-Hydroxy-9'-methoxy-staurosporinone



364.4 6,9'-Dihydroxy-staurosporinone

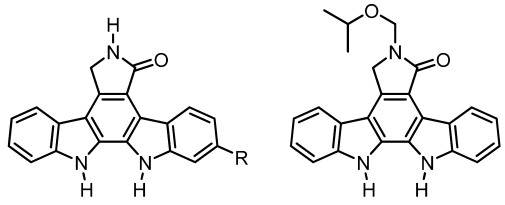
broth of *Streptoverticillium mobaraense* strain BA13793 collected in Seto, Aichi prefecture, Japan.[744] BE-13793C (**364.1**) showed a strong inhibitory activity against topoisomerases I and II and inhibited the growth of doxorubicin- or vincristine-resistant P388 murine leukemia cell lines, as well as their parent P388 cell line. In the same year, Bonjouklian et al. reported the isolation of 15 different tjipanazoles from the extract of the blue–green alga *Tolypothrix tjipanasensis* (strain DB-1-1).[718] Among these 15 tjipanazoles, only tjipanazole J (**364.2**) has an indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole framework similar to the aglycone of 7-hydroxy-TAN-1030A (**374.3**), UCN-01 (**375.1**), and UCN-02 (**375.2**) (see Schemes 374 and 375), whereas the others have a simple indolo[2,3-*a*]carbazole framework.

In 2010, Ishibashi and co-workers described two further alkaloids with the same lactam motif as in tjipanazole J (**364.2**).[745] 6-Hydroxy-9′-methoxystaurosporinone (**364.3**) was obtained from an extract of the myxomycete *Perichaena chrysosperma* (Scheme 364). The analogous 6,9′-dihydroxy-staurosporinone (**364.4**) was isolated from the myxomycete *Arcyria cinera*. Both alkaloids were isolated as racemic mixtures. The structures were assigned based on their NMR spectra and by comparison with analogous compounds.

In 1986, Nakanishi et al. reported the isolation of K-252c (**30.1**) from the culture broth of *Nocardiopsis* sp. K-290 (Scheme 365).[746,747] The structure of K-252c (**30.1**) represents the aglycone of staurosporine (**30.3**) (see Scheme 366), which had been isolated almost a decade before. Therefore, **30.1** is also called staurosporinone. In 1994, Horton et al. isolated staurosporinone (K-252c) (**30.1**) from the marine ascidian

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

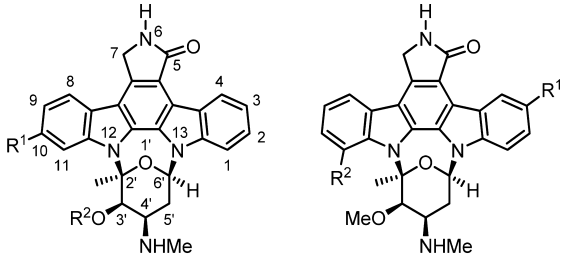
Scheme 365



30.1 Staurosporinone (K-252c) Staurosporine Aglycone R = H
365.1 6-Hydroxystaurosporinone (2-Hydroxystaurosporinone) R = OH

365.2 6-Isopropoxymethyl-staurosporinone

Scheme 366



30.3 (+)-Staurosporine (AM-2282) R^1 = H; R^2 = Me
366.1 TAN-999 R^1 = OMe; R^2 = Me
30.2 *O*-Demethylstaurosporine (3'-Demethoxy-3'-hydroxystaurosporine CGP 58 546) R^1,R^2 = H

366.2 11-Hydroxystaurosporine R^1 = H; R^2 = OH
366.3 3,11-Dihydroxy-staurosporine R^1,R^2 = OH
366.4 3-Hydroxystaurosporine R^1 = OH, R^2 = H

Eudistoma sp., collected off the coast of West Africa.[743] Staurosporinone (K-252c) (**30.1**) exhibited a strong inhibition of protein kinase C (PKC) isoenzymes[743,746] and a potent in vitro cytotoxicity against the human lung cancer A549 and murine leukemia P388 cell lines.[743] In 1996, Cai et al. described the isolation of a 6-alkylated derivative of staurosporinone (**30.1**), 6-isopropoxymethyl-K-252c (**365.2**), from *Streptomyces longisporoflavus* strain R-19.[748] In 2005, Ishibashi et al. isolated 6-hydroxystaurosporinone (2-hydroxystaurosporinone) (**365.1**) from field-collected fruit bodies of the myxomycete *Lycogala epidendrum* along with the previously known arcyriarubin A (**355.1**) (see Scheme 355), arcyriaflavin A (**32.9**), arcyriaflavin B (**363.1**) (see Scheme 363), and staurosporinone (**30.1**).[732] 6-Hydroxystaurosporinone (**365.1**) has shown cytotoxicity against HeLa, Jurkat, and vincristine-resistant KB/VJ300 cells, as well as an inhibition of protein tyrosine kinase activity (Scheme 365).

In 1977, Ōmura et al. isolated the first indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloid **30.3** from a culture of an actinomycete (*Streptomyces* strain AM-2282) while screening for microbial alkaloids (Scheme 366).[749] The strain AM-2282 (NRRL 11184, ATCC 55006) has been renamed because of repeated revisions of the taxonomy of the soil *Actinomyces* as *Streptomyces staurosporeus* AM-2287 in 1977,[749] *Saccharothrix aerocolonigenes* subsp. *staurosporea* AM 2282 in 1995,[750] and *Lentzea albida* in 2002.[751] Initially, this alkaloid was known as AM-2282, but later it was named staurosporine (**30.3**).[752,753] In the following years, the same alkaloid was also isolated from several other actinomycetes.[754,755] Staurosporine (**30.3**) was obtained from nature in optically active form ($[\alpha]_D^{25}$ = +35.0, c 1.0, HOMe).[749] The absolute configuration of this alkaloid was initially assigned from circular dichroism (CD) measurements.[756] However, the original assignment was revised based on anomalous dispersion measurements of crystalline 4′-*N*-methylstaurosporine methiodide, which was prepared from staurosporine (**30.3**). On the basis of this X-ray crystallographic analysis, the absolute stereochemistry of staurosporine (**30.3**) was revised to be 2′*S*, 3′*R*, 4′*R*, and 6′*R*.[757] Staurosporine (**30.3**) shows promising biological activities: antimicrobial, antihypertensive, and cytotoxic properties, nanomolar inhibition of protein serine/threonine kinases (such as PKC and protein tyrosine kinase), and inhibition of platelet aggregation.[758]

In 1989, Tanida et al. described the isolation of TAN-999 (**366.1**), a 10-methoxy derivative of staurosporine (**30.3**), from the culture broth of *Nocardiopsis dassonvillei* C-71425 in optically active form ($[\alpha]_D^{24}$ = +42.0, c 0.50, DMF).[759−761] TAN-999 (**366.1**) functions as a macrophage activator, potentially useful for the treatment of mycosis, bacterial infection, and cancer. Six years later, Hoehn et al. from Ciba−Geigy isolated *O*-demethylstaurosporine (3′-demethoxy-3′-hydroxystaurosporine) (CGP 58 546) (**30.2**) in optically active form ($[\alpha]_D^{20}$ = +82.0 ± 1.1, c 1.0, DMSO) from a blocked mutant of *S. longisporoflavus* R 19.[223] The staurosporine derivative **30.2** was less potent than (+)-staurosporine (**30.3**) but showed a more selective inhibition pattern against PKC subtypes α, β-2, and γ.

In 1992, Kinnel and Scheuer isolated 11-hydroxystaurosporine (**366.2**) and 3,11-dihydroxystaurosporine (**366.3**) from the brown tunicate *Eudistoma* sp. collected in Sapwale Bay, Phonpei, Micronesia.[762] This was the first example of naturally occurring indolo[2,3-*a*]carbazoles from a marine organism. On the basis of the specific rotation of **366.2** ($[\alpha]_D$ = +10.3, c 0.3, HOMe) and the close similarity of their CD spectra, the absolute configuration of these alkaloids was presumed to be the same as that of (+)-staurosporine (**30.3**) and RK-286C (**372.3**) (see Scheme 372). The compounds **366.2** and **366.3** were active against human nasopharyngeal cancer cells. Moreover, 11-hydroxystaurosporine (**366.2**) is more potent than staurosporine (**30.3**) in protein kinase C (PKC) inhibition. Seven years later, Boyd and co-workers reported the isolation of 11-hydroxy-4′-*N*-demethylstaurosporine (**368.2**) (see Scheme 368), a new staurosporine analogue, along with the known 3,11-dihydroxystaurosporine (**366.3**) from the prosobranch mollusk *Coriocella nigra* collected around Cebu in the Philippines.[763] Strong similarities between the CD spectra of 3,11-dihydroxystaurosporine (**366.3**) and 11-hydroxystaurosporine (**366.2**) indicated that they have the same absolute configuration (Scheme 366).

Schupp et al. isolated a series of staurosporine derivatives, 3-hydroxystaurosporine (**366.4**) (Scheme 366), 3-hydroxy-3′-*O*-demethylstaurosporine (3-hydroxy-3′-demethoxy-3′-hydroxystaurosporine) (**367.4**) (Scheme 367), and 4′-*N*-demethylstaurosporine (**368.3**) (Scheme 368), along with the previously known staurosporinone (**30.1**) (Scheme 365), (+)-staurosporine (**30.3**), *O*-demethylstaurosporine (**30.2**) (Scheme 365), and 11-hydroxy-4′-*N*-demethylstaurosporine (**368.2**) (Scheme 368) from the marine ascidian *Eudistoma toealensis* and its predator, the marine flatworm *Pseudoceros* sp.[764] Except for 3-hydroxy-3′-*O*-demethylstaurosporine (**367.4**) (Scheme 367) and 11-hydroxy-4′-*N*-demethylstaurosporine (**368.2**) (Scheme

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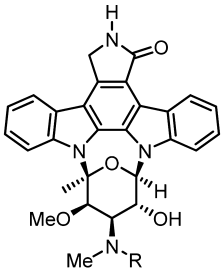
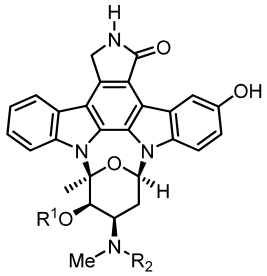
Scheme 367

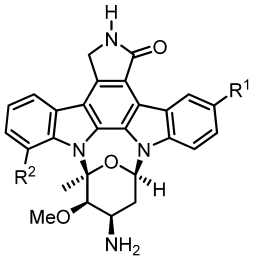


367.1 4′-*N*-Methyl-5′-hydroxystaurosporine
R = Me
367.2 5′-Hydroxystaurosporine
R = H

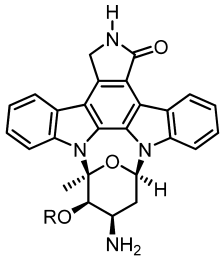


367.3 3-Hydroxy-4′-*N*-methylstaurosporine
R^1, R^2 = Me
367.4 3-Hydroxy-3′-*O*-demethylstaurosporine (3-Hydroxy-3′-demethoxy-3′-hydroxystaurosporine)
R^1, R^2 = H

Scheme 368



368.1 3-Hydroxy-4′-*N*-demethylstaurosporine
R^1 = OH; R^2 = H
368.2 11-Hydroxy-4′-*N*-demethylstaurosporine
R^1 = H; R^2 = OH

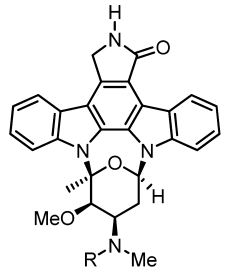


368.3 4′-*N*-Demethylstaurosporine
R = Me
368.4 3′-*O*-Demethyl-4′-*N*-demethylstaurosporine
R = Me

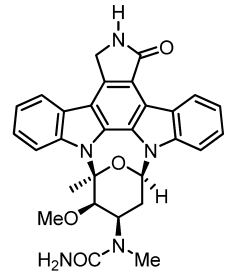
368), these staurosporine derivatives have been isolated in their protonated form.

In 2000, Baz, Millán, and co-workers isolated 4′-*N*-methyl-5′-hydroxystaurosporine (**367.1**) and 5′-hydroxystaurosporine (**367.2**) along with the known staurosporine (**30.3**) from the culture broth of a marine *Micromonospora* sp. (strain L-31-CLCO-002) (Scheme 367).[765] These alkaloids were isolated in enantiopure form with a specific rotation of $[\alpha]_D^{25}$ = +30.0 (c 0.11, $CHCl_3$) for 4′-*N*-methyl-5′-hydroxystaurosporine (**367.1**) and $[\alpha]_D^{25}$ = +53.0 (c 0.10, $CHCl_3$) for 5′-hydroxystaurosporine (**367.2**). The relative configuration of these staurosporine analogues was determined by NMR analysis. Two years later, Schupp et al. reported the isolation of 3-hydroxy-4′-*N*-methylstaurosporine (**367.3**) (Scheme 367), 3-hydroxy-4′-*N*-demethylstaurosporine (**368.1**), and 3′-*O*-demethyl-4′-*N*-demethylstaurosporine (**368.4**) (Scheme 368) along with the previously known 11-hydroxystaurosporine (**366.2**) (Scheme 366) and *N*-methylstaurosporine (**369.1**) (Scheme 369) from the marine ascidian *Eudistoma toealensis* and the predatory flatworm *Pseudoceros* sp. (Pseudocerotidae).[766] Comparison of the CD spectra of these staurosporine derivatives with that of (+)-staurosporine (**30.3**) confirmed that the absolute configuration is identical to that of (+)-staurosporine (**30.3**) with a 2′*S*,3′*R*,4′*R*,6′*R*-configuration (Scheme 366). Prior to Schupp's report, *N*-methylstaurosporine (**369.1**) was already known by Cai et al. at Ciba–Geigy from *S. longisporoflavus*.[225]

Scheme 369



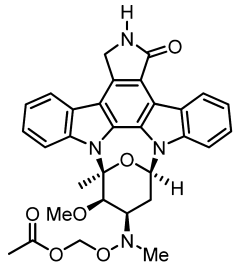
369.1 *N*-Methylstaurosporine
R = Me
369.2 *N*-Formylstaurosporine
R = CHO



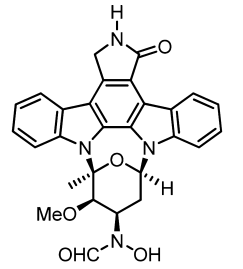
369.3 *N*-Carboxamidostaurosporine

In 1995, Cai et al. reported the isolation of various minor metabolites related to staurosporine (**30.3**), *N*-formylstaurosporine (**369.2**) (Scheme 369), *N*-acetoxymethoxystaurosporine (**370.1**), 4′-*N*-demethyl-*N*-formyl-*N*-hydroxystaurosporine (**370.2**), and 4′-demethylamino-4′-nitrostaurosporine (**370.3**) (Scheme 370) from the staurosporine-producing strain *S. longsporoflavus* R-19.[227] All these compounds inhibited protein kinase C (PKC) at nanomolar concentrations. Prior to this report, *N*-methylstaurosporine (**369.1**) was described in the patent literature as PKC inhibitor.[767]

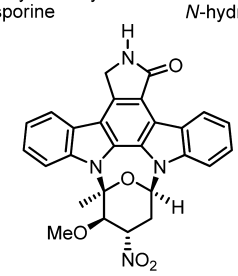
Scheme 370



370.1 *N*-Acetoxymethoxystaurosporine



370.2 4′-*N*-Demethyl-*N*-formyl-*N*-hydroxystaurosporine



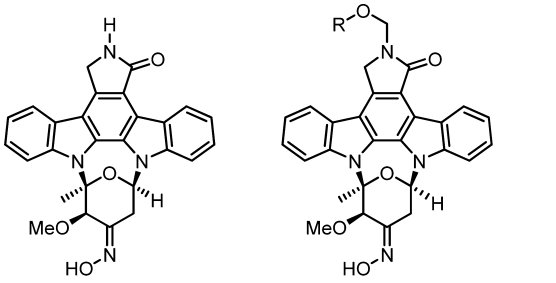
370.3 4′-Demethylamino-4′-nitrostaurosporine

In 2006, Laatsch and co-workers obtained *N*-carboxamidostaurosporine (**369.3**) along with the previously isolated staurosporine (**30.3**) and *N*-formylstaurosporine (**369.2**) from a marine *Streptomyces* sp. of the Jiaozhou Bay of Qindao in China (Scheme 369).[768] Compared to *N*-formylstaurosporine (**369.2**), *N*-carboxamidostaurosporine (**369.3**) showed a highly selective in vitro antitumor activity at micromolar concentrations against a wide range of human tumor cell lines.

In 1989, Tanida et al. isolated an oxime analogue of staurosporine, TAN-1030A (**31.1**), from the culture broth of *Streptomyces* sp. C-71799 along with TAN-999 (**366.1**) and the previously known (+)-staurosporine (**30.3**) (Scheme 371).[760,761] TAN-1030A (**31.1**) was shown to enhance nonspecific phagocytic activity and the expression of Fcγ

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

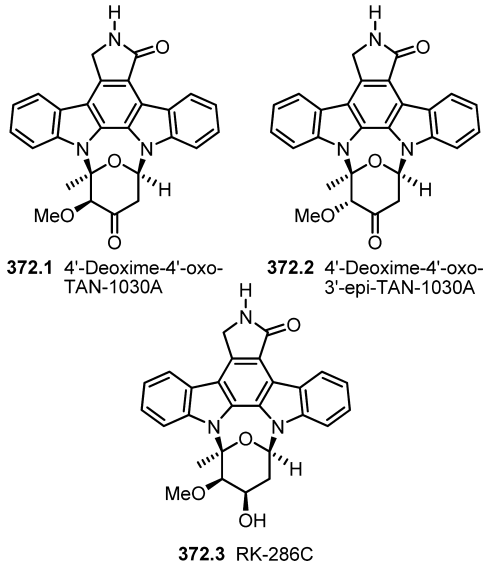
Scheme 371



receptors in murine macrophage cell lines, to increase lysosomal enzyme activity in these cells, and to activate macrophage function in mice. Six years later, Cai et al. isolated the same alkaloid from a different *Streptomyces* sp., *S. longisporoflavus* R19 strain, collected in Ellora, India.[227] In 1996, Cai et al. isolated several metabolites related to TAN-1030A (**31.1**) from the staurosporine-producing strain R-19 *S. longisporoflavus*: 6-methoxymethyl-TAN-1030A (**371.1**), 6-isopropoxymethyl-TAN-1030A (**371.2**), 4′-deoxime-4′-oxo-TAN-1030A (**372.1**), and 4′-deoxime-4′-oxo-3′-epi-TAN-1030A (**372.2**) (Schemes 371 and 372).[748] Among these TAN-1030A derivatives, only 4′-deoxime-4′-oxo-TAN-1030A (**372.1**) and 4′-deoxime-4′-oxo-3′-epi-TAN-1030A (**372.2**) show an inhibition of protein kinase C (PKC) at micromolar concentrations.

In 1990, Isono and co-workers reported the isolation of RK-286C (**372.3**) from the culture filtrate and the mycelium extract of *Streptomyces* sp. RK-286 (Scheme 372).[769] This alkaloid was

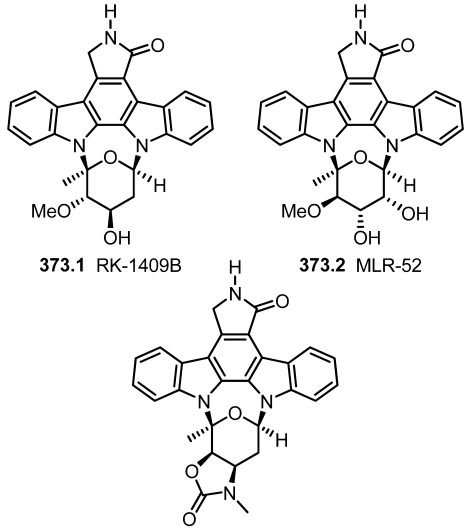
Scheme 372



obtained from nature in optically active form ($[\alpha]_D^{20}$ = +45.3, c 0.22, EtOAc). On the basis of similar CD curves of RK-286C (**372.3**) and (+)-staurosporine (**30.3**),[756] it was concluded that they have the same absolute configuration (see Scheme 366). RK-286C (**372.3**) shows in vitro PKC inhibitory activity and inhibition of platelet aggregation, as well as weak antimicrobial and antifungal activity.[769]

Two years later, Isono and co-workers isolated the 3′-epimer of RK-286C (**372.3**), RK-1409B (**373.1**), from the culture broth of *Streptomyces platensis* subsp. *malvinus* RK-1409 (Scheme 373).[770] Compound **373.1** was isolated in optically

Scheme 373



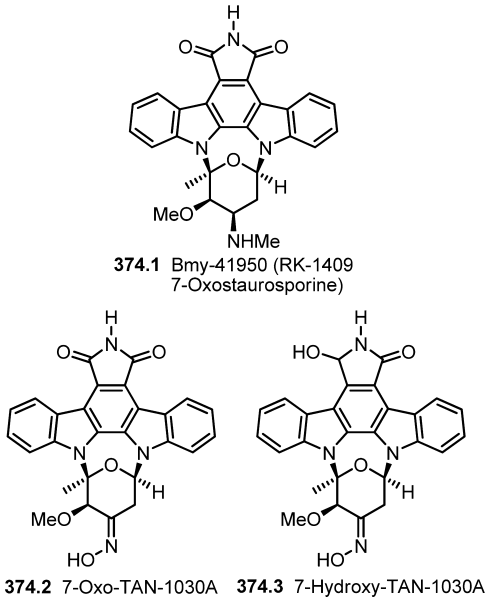
active form ($[\alpha]_D^{22}$ = +147.0, c 0.2, DMSO). A close comparison of the CD spectrum of RK-1409B (**373.1**) with those of RK-286C (**372.3**) and (+)-staurosporine (**30.3**) indicated the relative and absolute stereochemistry of this alkaloid, which is a 4′-demethylamino-4′-hydroxy-3′-epistaurosporine. Thus, RK-1409B (**373.1**) is a C3′-stereoisomer of RK-286C (**372.3**). RK-1409B (**373.1**) showed in vitro PKC inhibition, inhibition of the cell cycle progression in the G2 phase with polyploid DNA, and weak antifungal activity.

In 1994, McAlpine et al. isolated MLR-52 (**373.2**) along with staurosporine (**30.3**) in a bioassay-guided fractionation of the fermentation broth and mycelia of *Streptomyces* sp. AB 1869R-359 (Scheme 373).[771] Compound **373.2** was obtained in optically active form ($[\alpha]_D^{22}$ = +68.0, c 0.093, HOMe) and showed an inhibition of PKC and a potent in vitro immunosuppressive activity. In 2005, Han et al. isolated ZHD-0501 (**373.3**) in a bioassay-guided fractionation from the fermentation broth of the marine *Actinomadura* sp. 007 collected in Jiaozhou Bay, China.[772] This alkaloid was the first example of a staurosporine derivative with a heterocycle fused to the pyran ring. ZHD-0501 (**373.3**) was obtained from nature in optically active form ($[\alpha]_D^{20}$ = +83.2, c 0.10, HOMe) and exhibited an inhibition of the proliferation of mammalian cancer cells.

In 1990, researchers at Bristol−Myers Squibb reported the isolation of Bmy-41950 (**374.1**) from *Streptomyces staurosporeus* strain R10069 (ATCC 55006) (Scheme 374).[773] This compound showed in vitro activity against human colon cancer cells (HCT-116). Two years later, Isono et al. reported the isolation of the same natural product from *Streptomyces platensis* subsp. *malvinus* RK-1409 and named it RK-1409 (7-oxostaurosporine) (**374.1**).[774,775] Bmy-41950 (**374.1**) was obtained from nature in optically active form ($[\alpha]_D^{20}$ = +38.3, c 0.06, $CHCl_3$).[775] The protein kinase C (PKC) inhibitor RK-1409 (**374.1**) exhibited antitumor and also weak antimicrobial activity against *Chlorella vulgaris* and *Pyricularia*

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 374



374.1 Bmy-41950 (RK-1409 7-Oxostaurosporine)

374.2 7-Oxo-TAN-1030A **374.3** 7-Hydroxy-TAN-1030A

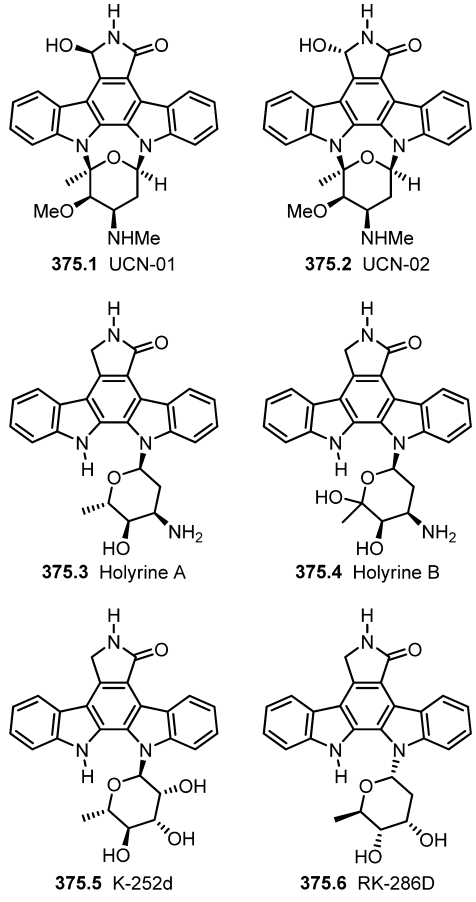
oryzae.[774] In 1996, Cai et al. isolated the 7-oxygenated TAN-1030A derivatives 7-oxo-TAN-1030A (**374.2**) and 7-hydroxy-TAN-1030A (**374.3**) (Scheme 374) along with the known 7-hydroxy derivative of (+)-staurosporine, UCN-01 (**375.1**), from *Streptomyces longisporoflavus* strain R-19 (Scheme 375).[748] The stereochemistry of the hydroxy group at C-7 could not be assigned.

Prior to Cai's report, Takahashi and co-workers isolated UCN-01 (**375.1**) from *Streptomyces* strain N-71 collected in the Yamaguchi Prefecture in Japan (Scheme 375).[776,777] UCN-01 (**375.1**) showed inhibition of protein kinase C (PKC) and protein kinase A (PKA), in vivo antitumor activity against murine lymphatic leukemia P388, and cytotoxic effects on the growth of HeLa S3 cells. UCN-01 (**375.1**) was isolated from nature in optically active form ($[\alpha]_D^{22}$ = +132.0, c 0.3, HOMe). On the basis of its CD spectrum, an *R*-configuration was assigned to the stereogenic center of the pyrrole ring of UCN-01 (**375.1**).[748]

In 1989, Takahashi et al. reported also the isolation of UCN-01 (**375.1**) along with the previously unknown C-7-epimer UCN-02 (**375.2**) from *Streptomyces* sp. strain N-126.[778,779] UCN-02 (**375.2**) was also isolated in optically active form ($[\alpha]_D^{22}$ = −38.6, c 0.35, HOMe). On the basis of the known configuration at C-7 for UCN-01 (**375.1**),[748] UCN-02 (**375.2**) was assigned to have an *S*-configuration at the stereogenic center of the pyrrole ring. In acid or alkaline buffer media, UCN-01 (**375.1**) and UCN-02 (**375.2**) are in equilibrium. UCN-02 (**375.2**) inhibits PKC and PKA and shows cytotoxic effects on the growth of HeLa S3 cells.[779]

In 1999, Bernan, Andersen, and co-workers reported the isolation of holyrine A (**375.3**) and holyrine B (**375.4**) along with the previously known K-252d (**375.5**), (+)-staurosporine (**30.3**), and *O*-demethylstaurosporine (**30.2**) from cultures of the marine *Actinomycete* strain N96C-47 collected in the North Atlantic Ocean near Holyrood, Newfoundland (Scheme 375).[780] Holyrine A (**375.3**) and holyrine B (**375.4**) resemble K-252d (**375.5**) and rebeccamycin (**32.11**) (see Scheme 377) by having only a single attachment of their sugar moiety to the aromatic framework. Holyrine A (**375.3**) exhibited activity in MAPK and ERK kinase assays. Prior to Bernan and Andersen's report, Nakanishi et al. had already reported the isolation of K-252d (**375.5**) along with K-252b (**31.5**) (see Scheme 376) and K-252c (staurosporinone) (**30.1**) from the culture broth of *Nocardiopsis* sp. K-290.[746] All these alkaloids showed strong inhibition of protein kinase C (PKC). K-252d (**375.5**) ($[\alpha]_D^{20}$ = +35.0, c 0.4, HOMe) and K-252b (**31.5**) ($[\alpha]_D^{20}$ = +97.0, c 0.6, DMF) were obtained from nature in optically active form.[746,747] In 1992, Isono et al. isolated the indolocarbazole antibiotic RK-286D (**375.6**) along with the previously known (+)-staurosporine (AM-2282) (**30.3**) and RK-286C (**372.3**) from the mycelial cake of *Streptomyces* sp. RK-286.[781] The alkaloid **375.6** was obtained from nature in optically active form ($[\alpha]_D^{20}$ = −60.0, c 0.13, HOMe) and showed a weak inhibition of PKC (Scheme 375).

Scheme 375



375.1 UCN-01 **375.2** UCN-02

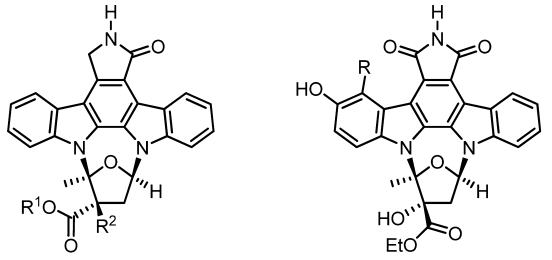
375.3 Holyrine A **375.4** Holyrine B

375.5 K-252d **375.6** RK-286D

In 1985, Kase and co-workers reported the isolation of K-252a (previously named K-252) (**31.4**) from the culture broth of *Nocardiopsis* sp.[782] The alkaloid K-252a (**31.4**) was obtained in optically active form ($[\alpha]_D^{20}$ = +52.0, c 0.1, HOMe) (Scheme 376).[747,783] In the same year, Sezaki et al. isolated the same natural product from a different natural source, *Actinomadura* sp., and named it SF-2370.[784] The antibiotic K-252a (SF-2370) (**31.4**) showed an extremely potent inhibition of protein kinase C (PKC) and/or calmodulin[782,783] as well as weak antibacterial and antifungal activities.[784] In 1996, Cai et al. from Ciba−Geigy isolated 3′-methylamino-3′-deoxy-K-252a (**31.3**) along with the previously known K-252c (**30.1**) (see Scheme 365) and K-252a (**31.4**) from *Streptomyces longisporoflavus* R-19 (Scheme 376).[225] This alkaloid inhibits porcine PKC at a similar concentration as K-252a (**31.4**). In

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 376



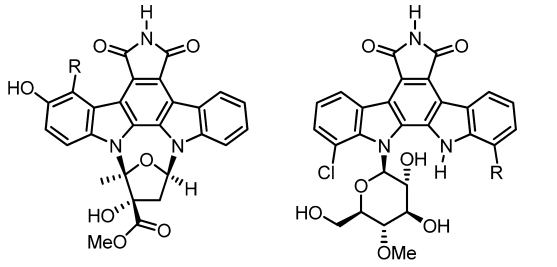
31.3 3'-Methylamino-3'-deoxy-K-252a R^1 = Me; R^2 = NHMe
31.4 K-252a (SF-2370) R^1 = Me; R^2 = OH
31.5 K-252b R^1 = H; R^2 = OH

376.1 (+)-Indocarbazostatin R = H
376.2 (−)-Indocarbazostatin B R = NH_2

2002, Ubukata and co-workers isolated (+)-indocarbazostatin (**376.1**) and (−)-indocarbazostatin B (**376.2**) from a culture broth of *Streptomyces* sp. TA-0403.[785,786]

Two years later, Ubukata and co-workers described the isolation of further indocarbazostatin derivatives, (+)-indocarbazostatin C (**377.1**) and (−)-indocarbazostatin D (**377.2**) (Scheme 377), along with the previously known (+)-indocarbazostatin (**376.1**) and (−)-indocarbazostatin B (**376.2**) (Scheme 376) from a different mutant strain, *Streptomyces* sp. MUV-6-83.[787] These compounds represent methyl ester analogues of (+)-indocarbazostatin (**376.1**) and (−)-indocarbazostatin B (**376.2**). The indocarbazostatins are novel inhibitors of nerve growth factor (NGF)-induced neuronal differentiation in PC12 cells at nanomolar concentrations.[785,787] (+)-Indocarbazostatin (**376.1**) ($[\alpha]_D^{26}$ = +51.3, c 0.05, HOMe),[786] (−)-indocarbazostatin B (**376.2**) ($[\alpha]_D^{26}$ = −48.7, c 0.05, HOMe),[786] (+)-indocarbazostatin C (**377.1**) ($[\alpha]_D^{26}$ = +50.0, c 0.05, HOMe),[787] and (−)-indocarbazostatin D (**377.2**) ($[\alpha]_D^{26}$ = −44.0, c 0.05, HOMe)[787] were isolated from nature in optically active form. The relative and absolute configurations were assigned based on CD analyses and MM2, MOPAC, and CONFLEX calculations.[786,787]

Scheme 377



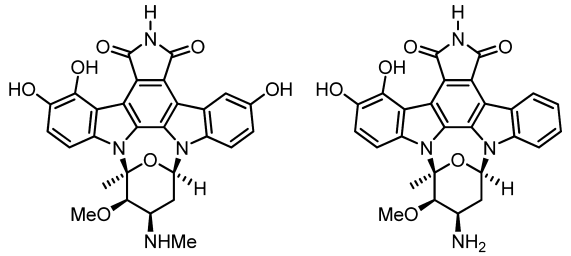
377.1 (+)-Indocarbazostatin C R = H
377.2 (−)-Indocarbazostatin D R = NH_2

32.11 Rebeccamycin R = Cl
377.3 1-Dechlororebeccamycin R = H

In 1985, researchers at Bristol−Myers reported the isolation of rebeccamycin (**32.11**)[788−790] and 1-dechlororebeccamycin (**377.3**)[791] from fermentations of the actinomycete *Saccharothrix aerocolonigenes* (formerly *Nocardia aerocoligenes*), strain C38383-RK-2 (ATCC 39243) (Scheme 377). In 2001, the genus name for strain ATCC 39243 was changed from *Saccharothrix* to *Lechevalieria*.[221] Rebeccamycin (**32.11**) ($[\alpha]_D^{20}$ = +143.0, c 1.02, THF)[788,792] and 1-dechlororebeccamycin (**377.3**) ($[\alpha]_D^{20}$ = +128.1, c 1.01, THF)[791,792] were isolated from nature in optically active form. The absolute configuration of rebeccamycin (**32.11**) was assigned based on X-ray analysis.[788] Rebeccamycin (**32.11**) shows a broad spectrum of antitumor activities (e.g., against several murine tumor cells: P388 leukemia, L1210 leukemia, B16 melanoma, and human lung adenocarcinoma cells).[789,793] 1-Dechlororebeccamycin (**377.3**) inhibits the growth of Gram-positive and Gram-negative bacteria as well as mammalian neoplasms, such as murine leukemia P388.[791]

In 2008, Reyes and co-workers described the isolation of 7-oxo-3,8,9-trihydroxystaurosporine (**378.1**) and 7-oxo-8,9-dihydroxy-4′-*N*-demethylstaurosporine (**378.2**) from the ascidian *Cystodytes solitus* Monniot, collected in Tanzania (Scheme 378).[794] Both alkaloids were obtained by a bioassay-guided fractionation of extracts of that organism. The structures of **378.1** and **378.2** were assigned based on their UV and NMR spectra.

Scheme 378

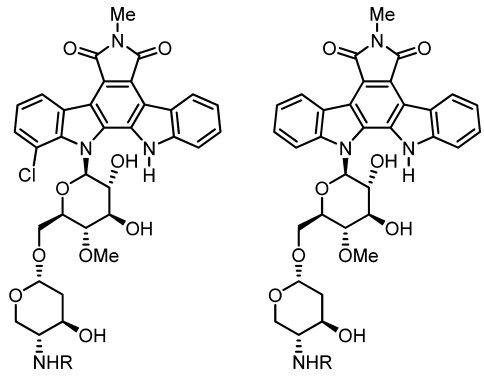


378.1 7-Oxo-3,8,9-trihydroxy-staurosporine

378.2 7-Oxo-8,9-dihydroxy-4′-*N*-demethyl-staurosporine

One year after the isolation of rebeccamycin (**32.11**), researchers at Bristol−Myers and Schering Plough reported the isolation of AT2433-A1 (**379.1**), AT2433-A2 (**379.2**), AT2433-B1 (**379.3**), and AT2433-B2 (**379.4**) from the cultured broth of *Actinomadura melliaura* ATCC 39691 [previously known as *Actinomadura melliaura* sp. nov. (SCC 1655)] (Scheme 379).[795−797] These alkaloids are structurally related to rebeccamycin (**32.11**) and were active against Gram-positive bacteria, such as *Micrococcus lutea* (ATCC 9341), *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (A 9537),

Scheme 379

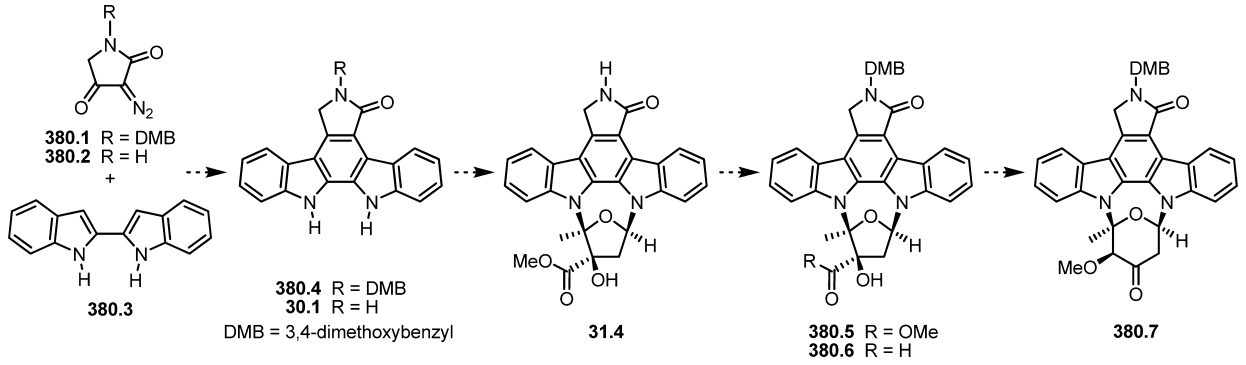


379.1 AT2433-A1 R = Me
379.2 AT2433-A2 R = H

379.3 AT2433-B1 R = Me
379.4 AT2433-B2 R = H

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 380



Streptococcus faecalis (A 20688), and *Streptococcus faecium* (ATCC 9790). Moreover, AT2433-B2 (**379.4**) showed activity against the Gram-negative bacterium *Escherichia coli* SS 1431. In addition, AT2433-A1 (**379.1**) and AT2433-B1 (**379.3**) exhibited antitumor activity against murine leukemia cells P388.[795,797]

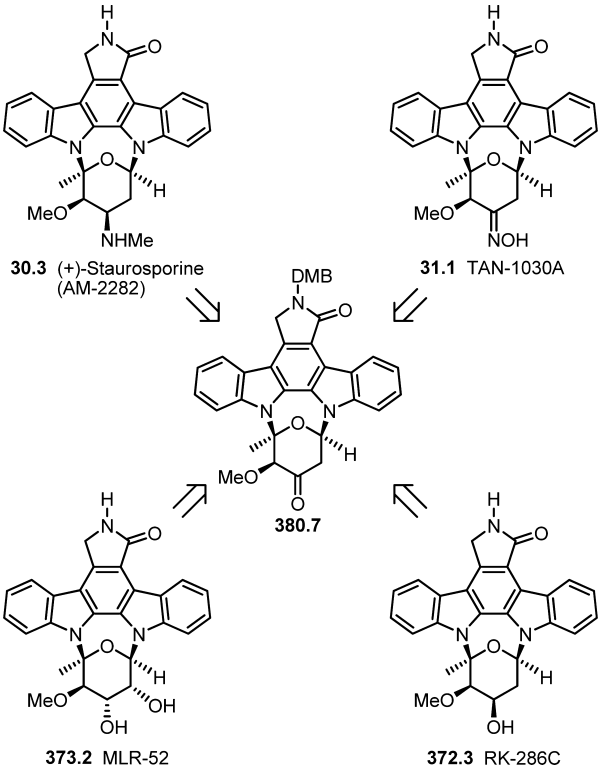
14.3.2. Synthesis of Indolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole Alkaloids. The alkaloids described above have attracted an enormous interest, both from the viewpoint of natural product synthesis and because of their biological activity.[593,713,798−802] Although already published in 1995, Wood et al.'s imaginative approach to a series of indolocarbazole alkaloids has been included in the present review.[803−806]

14.3.2.1. Total Synthesis of Staurosporinone (K-252c), (+)-K-252a, (+)-Staurosporine, (−)-TAN-1030A, (+)-RK-286C, and (+)-MLR-52. Wood and co-workers developed an elegant strategy for the total synthesis of a series of indolocarbazole alkaloids: staurosporinone (K-252c) (**30.1**), (+)-K-252a (SF-2370) (**31.4**), (+)-staurosporine (**30.3**), (−)-TAN-1030A (**31.1**), (+)-RK-286C (**372.3**), and (+)-MLR-52 (**373.2**). The crucial intermediate, the α-methoxy ketone **380.7**, was conveniently generated by a Tiffeneau−Demjanov-like ring-expansion of the furanosylated indolocarbazole **380.6** (Scheme 380).[803−806] This common intermediate contains all stereogenic centers required for the synthesis of **30.3**, **31.1**, **372.3**, and **373.3**, and additional stereocontrolled functionalizations at C-4′ and C-5′ are feasible. For the synthesis of (+)-K-252a (**31.4**), a single-step cycloglycosidation of the selectively protected aglycone **380.4** with an appropriate furanose was envisaged. The protected aglycone **380.4** derived from a rhodium-catalyzed coupling of 2,2′-biindole (**380.3**) with the α-diazo-β-keto-γ-lactam **380.1** (Scheme 380).

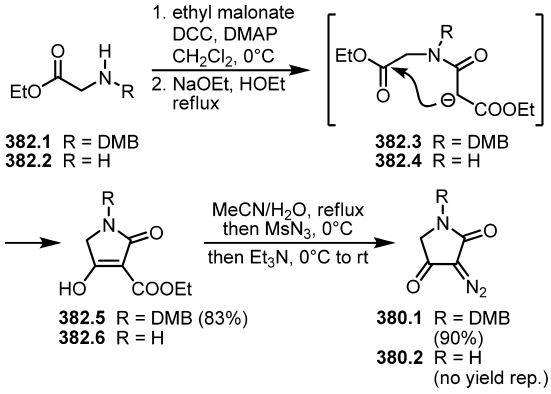
Starting from ketone **380.7**, a reductive amination was envisaged to produce staurosporine (**30.3**) (Scheme 381). Formation of the oxime would lead to (−)-TAN-1030A (**31.1**). Reduction at C-4′ from the convex face would provide (+)-RK-286C (**372.3**). Elimination of either the C-4′-amino group of **30.3** (via Cope elimination) or the C-4′-hydroxy group of **372.3** (via dehydration with Martin's sulfurane or Burgess dehydration) followed by dihydroxylation would provide (+)-MLR-52 (**373.2**).

For the synthesis of the diazolactams **380.1** and **380.2**, the glycine esters **382.1** and **382.2** were transformed to the lactams **382.5** and **382.6** by DCC/DMAP-promoted coupling with monoethyl malonate followed by Dieckmann cyclization (DCC = 1,3-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine) (Scheme 382). Using a one-pot decarboethoxylation/diazo-transfer procedure, the lactams **382.5** and **382.6** were transformed to the diazolactams **380.1** and **380.2** by heating in wet acetonitrile followed by treatment with mesyl azide in triethylamine.

Scheme 381



Scheme 382



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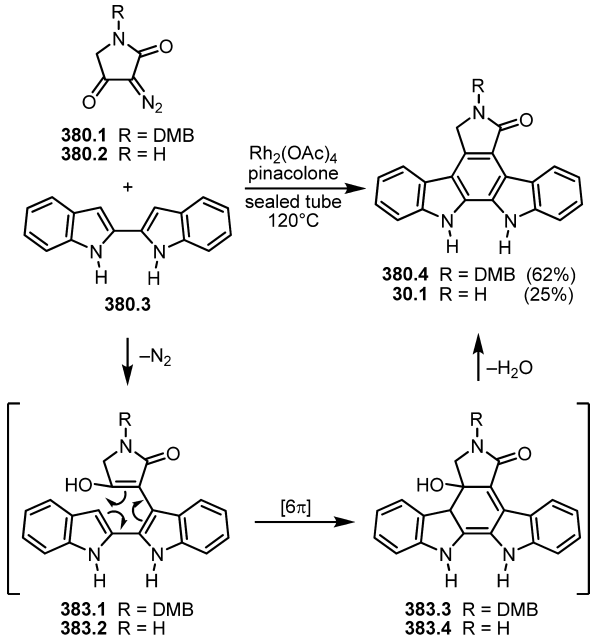
Double Madelung cyclization as reported by Bergman provided 2,2′-biindole (**380.3**).[807] Coupling of the diazolactam **380.2** with 2,2′-biindole (**380.3**) in the presence of catalytic amounts of dirhodium tetraacetate ($Rh_2(OAc)_4$) using degassed pinacolone (*tert*-butyl methyl ketone) as solvent provided directly staurosporinone (K-252c) (**30.1**) in 25% yield (Scheme 383).[803,805] The protected aglycone **380.4** was

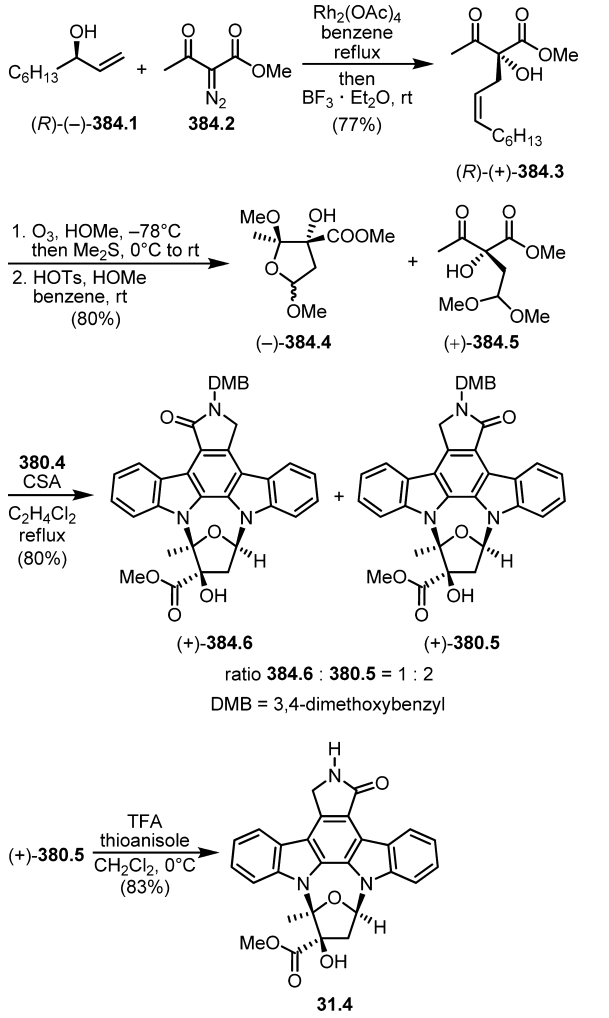
Scheme 383



obtained from the 3,4-dimethoxybenzyl protected lactam **380.1** in 62% yield using the same approach. The annulation is believed to proceed via the intermediates **383.1**/**383.2** and **383.3**/**383.4**.

For the asymmetric synthesis of the furanose (−)-**384.4**, a novel tandem [3,3]/[1,2]-rearrangement protocol was developed starting from (*R*)-(−)-1-nonen-3-ol [(*R*)-(−)-**384.1**] and methyl 2-diazo-3-oxobutyrate (**384.2**) (Scheme 384). Reaction of (*R*)-(−)-**384.1** and **384.2** in the presence of catalytic amounts of dirhodium tetraacetate followed by addition of boron trifluoride etherate afforded (*R*)-(+)-**384.3** in 77% yield. Ozonolysis of (*R*)-(+)-**384.3** and subsequent acid-mediated cyclization provided a mixture of (−)-**384.4** (as a mixture of anomers) and (+)-**384.5** in 80% yield. A McCombie cycloglycosidation of the 3,4-dimethoxybenzyl (DMB)-protected aglycone **380.4** with a mixture of (−)-**384.4** and (+)-**384.5** in 1,2-dichloroethane using camphorsulfonic acid (CSA) as catalyst afforded a regioisomeric mixture of the furanosylated indolocarbazoles (+)-**384.6** and (+)-**380.5** (ratio = 1:2) in 80% yield. This reaction led selectively to a stereochemistry with the C-3′ hydroxy group oriented *syn* to the indolocarbazole moiety. Moreover, the major regioisomer corresponded to the *N*-protected K-252a (**380.5**). Thus, removal of the DMB group using trifluoroacetic acid and thioanisole as cation scavenger provided (+)-K-252a (**31.4**) in 83% yield.[803,805] The same route was applied to the synthesis of racemic K-252a and non-natural (−)-K-252a using the DMB-protected aglycone **380.4** and the carbohydrates (±)-**384.4**/(±)-**384.5** and (+)-**384.4**/(−)-**384.5** as precursors.[803,805]

Scheme 384



The N-protected K-252a **380.5** was then transformed to the α-hydroxyketone (+)-**385.2**, which was used as the common synthetic precursor for the synthesis of an entire family of glycosylated indolocarbazoles: (+)-staurosporine (**30.3**), (−)-TAN-1030A (**31.1**), (+)-RK-286C (**372.3**), and (+)-MLR-52 (**373.2**). Thus, compound **380.5** was subjected to a regio- and stereoselective ring-expansion (Scheme 385). Reduction of (+)-**380.5** to the alcohol (+)-**385.1** using lithium borohydride followed by Moffatt−Pfitzner oxidation provided the aldehyde (+)-**380.6**. Treatment of aldehyde (+)-**380.6** with boron trifluoride etherate induced a rearrangement with ring-expansion to the α-hydroxyketone (+)-**385.2**.[804,806] Unexpectedly, exposure of (+)-**385.2** to copper(I) chloride in methanol at elevated temperature induced a ring-contraction back to **380.5**, the starting material of this sequence of transformations.

For the synthesis of (+)-MLR-52 (**373.2**) and (+)-RK-286C (**372.3**), the α-hydroxyketone (+)-**385.2** was first reduced to the diol (+)-**386.1** using sodium borohydride (Scheme 386). Selective alkylation at the C-3′ hydroxy group with sodium hydride and iodomethane provided the alcohol (+)-**386.2** 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 (+)-**386.2** with trifluoroacetic acid in anisole afforded (+)-RK-286C (**372.3**) in 75% yield. Dehydration of the alcohol (+)-**386.2** using Martin's sulfurane led to the olefin

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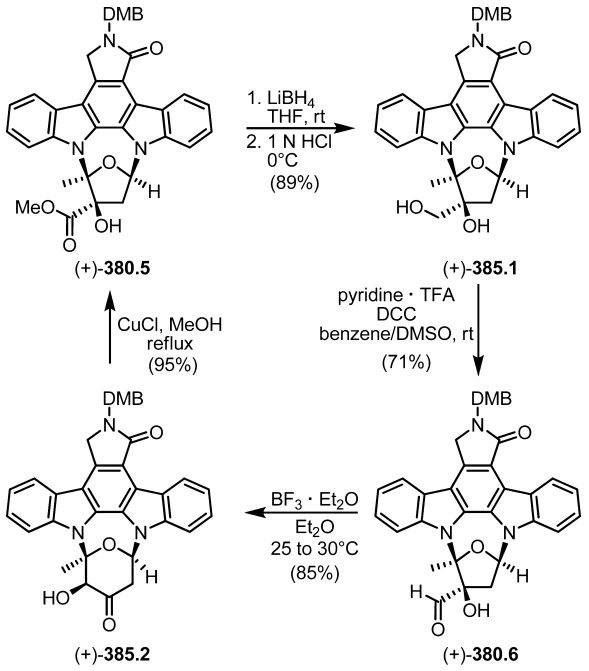
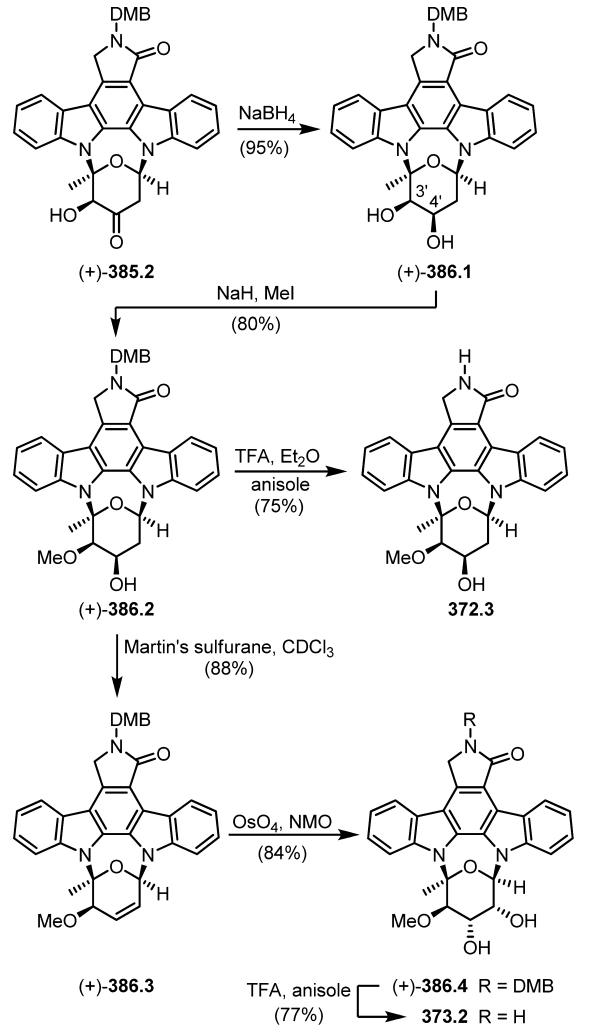
Scheme 385



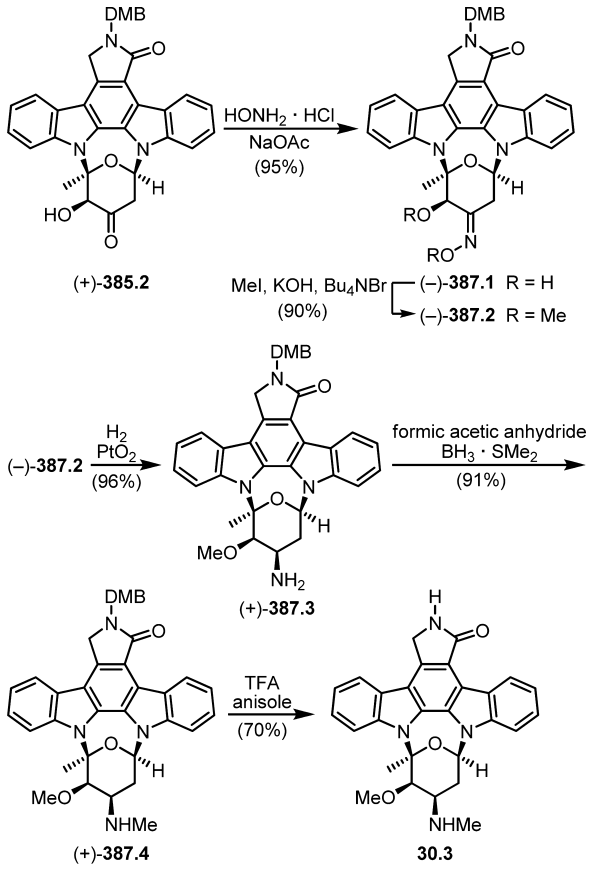
Scheme 386



(+)-**386.3**, which by stereoselective dihydroxylation with osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO) led to the dihydroxy derivative (+)-**386.4**. Finally, removal of the DMB protecting group of (+)-**386.4** provided (+)-MLR-52 (**373.2**) in 77% yield.[804,806]

Condensation of the α-hydroxyketone (+)-**385.2** with hydroxylamine hydrochloride gave the oxime (−)-**387.1**, a precursor for the synthesis of (+)-staurosporine (**30.3**), in 95% yield (Scheme 387). Double methylation of (−)-**387.1** using

Scheme 387



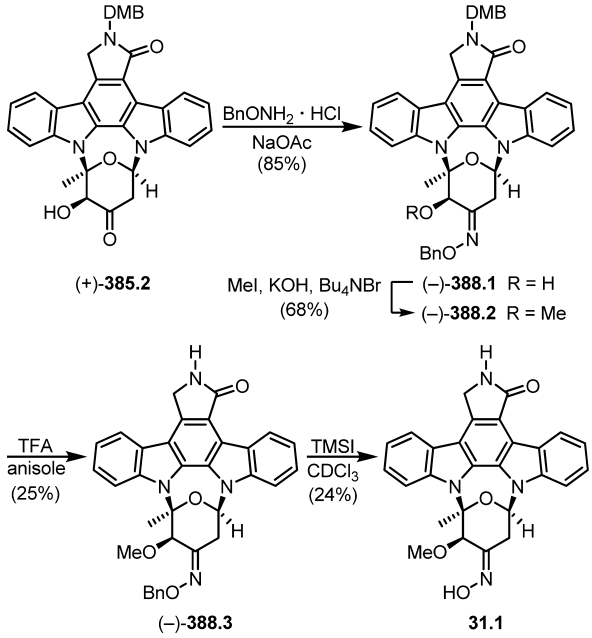
phase-transfer conditions afforded the corresponding dimethyl derivative (−)-**387.2**. Stereoselective hydrogenation of (−)-**387.2** using Adam's catalyst led to the amine (+)-**387.3**. Subsequent monomethylation led to the DMB-protected staurosporine (**387.4**), which on deprotection provided (+)-staurosporine (**30.3**).[804,806]

Reaction of the α-hydroxyketone (+)-**385.2** with *O*-benzylhydroxylamine hydrochloride followed by O-methylation of the resulting benzyl-protected oxime (−)-**388.1** under phase-transfer conditions led to the corresponding methyl derivative (−)-**388.2** (Scheme 388).[806] Removal of the DMB protecting group of (−)-**388.2** and subsequent debenzylation of (−)-**388.3** with iodotrimethylsilane afforded (−)-TAN-1030A (**31.1**).

In an extension of their original work, Wood et al. applied the rhodium-carbenoid approach to the synthesis of C7−methyl derivatives of K-252a,[808] C-2′−alkyl derivatives of (±)-K-252a,[809] and (−)-(7*S*)- and (+)-(7*R*)-K-252a dimers.[810] These investigations focused on the development of specific kinase inhibitors.[811]

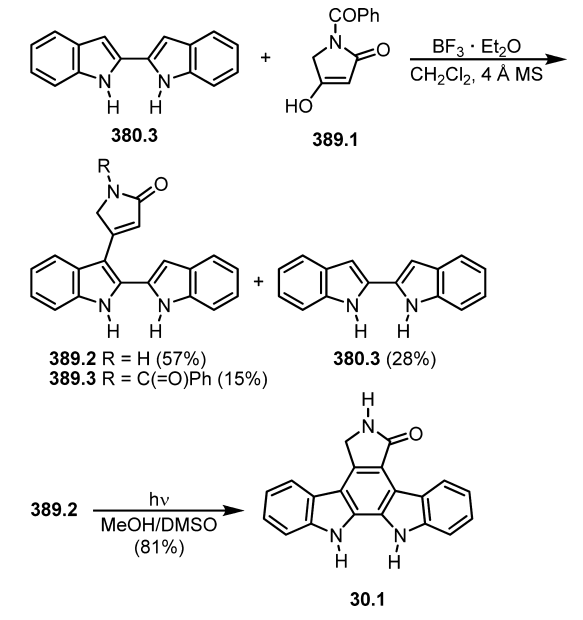
dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

Scheme 388



14.3.2.2. Total Syntheses of Staurosporinone (K-252c). In 2003, Lobo, Prabhakar, and co-workers described a new synthesis of staurosporinone (K-252c) (**30.1**) starting from 2,2′-biindole (**380.3**) and the lactam **389.1** (Scheme 389).[812]

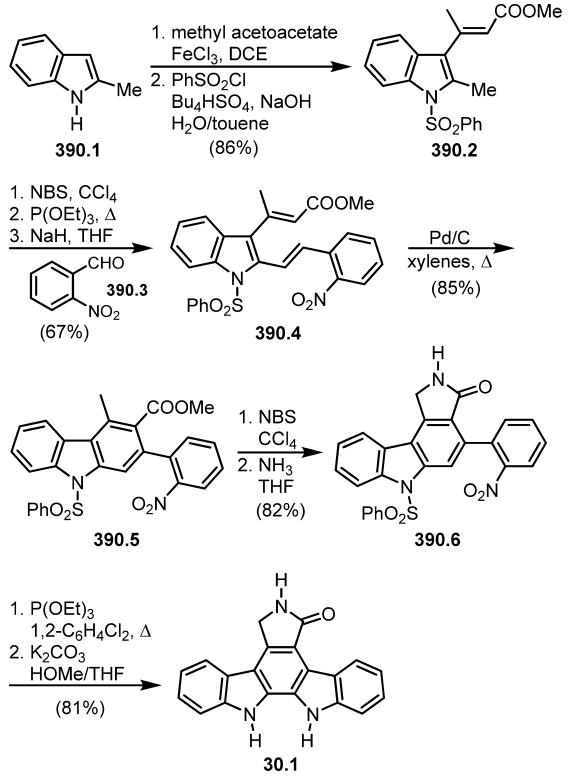
Scheme 389



The lactam **389.1** is easily accessible in 2 steps from Meldrum's acid and hippuric acid.[813] Heating a solution of **380.3** and **389.1** in dichloromethane at reflux in the presence of boron trifluoride etherate and activated molecular sieves (4 Å) afforded the desired lactam **389.2** in 57% yield along with 15% of the imide **389.3** (the immediate precursor of **389.2**) and 28% of unreacted 2,2′-biindole (**380.3**). Photocyclization of **389.2** in methanol/dimethylsulfoxide (5:1) provided staurosporinone (K-252c) (**30.1**) in 81% yield. One year later, the same group extended the aforementioned approach to the synthesis of N-protected staurosporinones.[814] This approach was developed to differentiate between the two indole nitrogen atoms for a projected synthesis of monoglycosidic indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids.

Rajeshwaran and Mohanakrishnan also developed a new synthetic route to the staurosporine aglycone (**30.1**) using 2-methylindole (**390.1**) as starting material (Scheme 390).[815]

Scheme 390



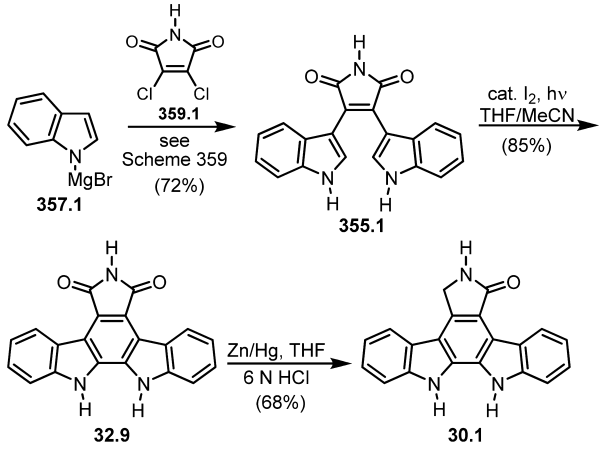
Key steps are an electrocyclic ring-closure for the formation of the central benzene ring and a Cadogan cyclization. Iron(III) chloride-catalyzed condensation of 2-methylindole (**390.1**) and methyl acetoacetate followed by protection of the indole nitrogen atom led to the 3-vinylindole **390.2**. Radical bromination of the methyl group was followed by a Michaelis–Arbuzov reaction and subsequent Horner–Wadsworth–Emmons reaction with 2-nitrobenzaldehyde (**390.3**) to give the cyclization precursor **390.4**. Thermally induced 6π-electrocyclization with concomitant aromatization in the presence of palladium on activated carbon furnished the 2-arylcarbazole **390.5**. The lactam ring was formed by a sequence of radical bromination at the C-4 methyl group of the carbazole ring followed by nucleophilic displacement with ammonia. Treatment of the resulting pyrrolo[3,4-*c*]carbazole **390.6** with triethyl phosphite at elevated temperature induced a Cadogan cyclization to the desired indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole. Finally, removal of the benzenesulfonyl protecting group by basic hydrolysis provided the staurosporine aglycone (staurosporinone, K-252c) (**30.1**) in 10 steps and 33% overall yield. Following the same synthetic route, Rajeshwaran and Mohanakrishnan also prepared some substituted derivatives of staurosporinone (**30.1**).[815]

14.3.2.3. Total Synthesis of Arcyriaflavin A and Staurosporinone (K-252c). In 2003, Uang and co-workers reported a facile synthesis of staurosporinone (K-252c) (**30.1**) starting

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

from arcyriarubin A (**355.1**),[816] which was readily obtained using Faul et al.'s procedure.[739] Oxidative photocyclization of the diindolylmaleimide **355.1** in the presence of a catalytic amount of iodine led to arcyriaflavin A (**32.9**) (Scheme 391).

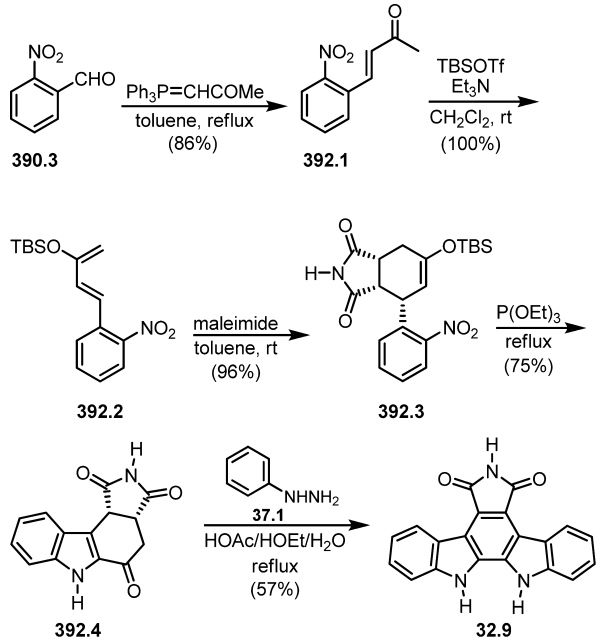
Scheme 391



Reduction of **32.9** using modified Clemmensen conditions (heating with zinc amalgam in a mixture of 6 N HCl and tetrahydrofuran at reflux) afforded staurosporinone (**30.1**) in 68% yield.

14.3.2.4. Total Synthesis of Arcyriaflavin A. In 2005, Tomé and co-workers described a synthesis of arcyriaflavin A (**32.9**)[817] based on a modification of their earlier approach.[818] Wittig olefination of commercially available 2-nitrobenzaldehyde (**390.3**) led to the enone **392.1** (Scheme 392). Reaction of **392.1** with *tert*-butyldimethylsilyl triflate (TBSOTf) in the presence of triethylamine afforded the arylsilyloxydiene **392.2**. Diels–Alder cycloaddition of the diene **392.2** with maleimide provided the cycloadduct **392.3** in 96% yield. Reductive cyclization of **392.3** using Cadogan's conditions by heating with triethyl phosphite led to the tetrahydrocarbazolone **392.4**

Scheme 392



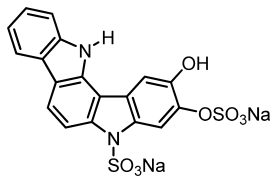
via a nucleophilic attack of the silyl enol ether at the intermediate electrophilic nitrene. Finally, Fischer indolization of **392.4** by reaction with phenylhydrazine (**37.1**) provided directly arcyriaflavin A (**32.9**). This method was also applied to the synthesis of an unsymmetrical analogue of arcyriaflavin A.[817]

In addition to the synthesis of the natural indolocarbazole alkaloids described above, a large variety of synthetic indolocarbazoles has been reported in order to develop potential candidates for the treatment of cancer and other diseases.[714,729,736,819–861] A quite interesting approach was developed by Meggers and co-workers, who prepared a range of carbazole–metal complexes that are inspired by staurosporine (**30.3**) and analogues.[862–866]

14.4. Indolo[3,2-*a*]carbazole Alkaloids

14.4.1. Isolation from Natural Sources. From the five possible isomeric indolocarbazole alkaloids, the indolo[3,2-*a*]carbazole ring system received little attention, and only in early 2000 a derivative with this framework was found in nature.[1,12,704,867] During the studies on the aqueous extract of the sponge *Ancorina* sp. collected in New Zealand, Boyd and co-workers isolated ancorinazole (**393.1**) (Scheme 393).[867] This is the first and to date the only indolo[3,2-*a*]carbazole obtained from a natural source.

Scheme 393



393.1 Ancorinazole

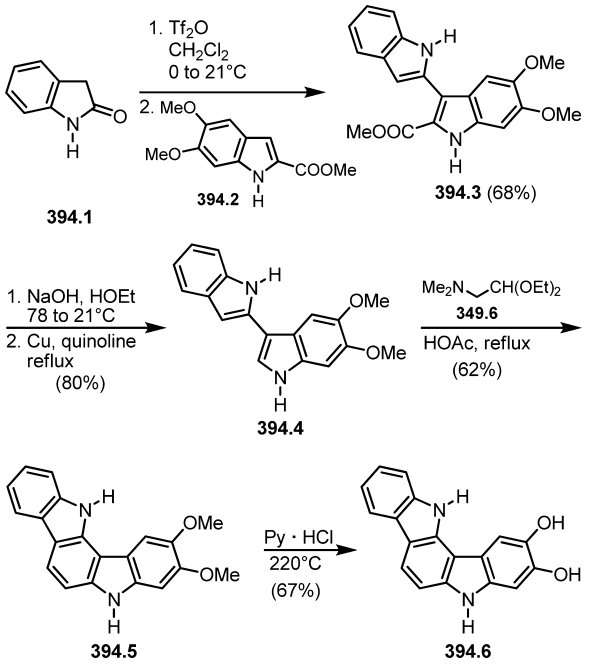
14.4.2. Synthesis of the Indolo[3,2-a]carbazole Core of Ancorinazole. For the only natural product of this family, ancorinazole (**393.1**), no total synthesis has been reported so far.[704,868] However in 1999, Bergman and co-workers reported a synthetic route to the skeleton of this natural product.[869,870] Their approach starts from indolin-2-one (**394.1**) and involves an annulation of the 2,3′-biindole (**394.4**) with a C_2-building block as key step (Scheme 394). Reaction of **394.1** with trifluoromethanesulfonic anhydride followed by addition of methyl 5,6-dimethoxyindole-2-carboxylate (**394.2**) afforded the 2,3′-biindole derivative **394.3**. Saponification and subsequent decarboxylation provided the desired 2,3′-biindole **394.4**. Condensation of **394.4** with dimethylaminoacetaldehyde diethyl acetal (**349.6**) in acetic acid at reflux afforded the indolo[3,2-*a*]carbazole **394.5** in 62% yield. The moderate yield of this step was explained by the tendency of the 2,3′-biindole precursor **394.4** to undergo polymerization. Finally, methyl ether cleavage of **394.5** provided compound **394.6**, which displays the same oxygenation pattern as ancorinazole (**393.1**). In 2011, Cachet and co-workers described the synthesis of a 7-phenyl-substituted indolo[3,2-*a*]carbazole by a one-pot homodimerization of indole and reaction with a nitrostyrene in the presence of tin(II) chloride and manganese dioxide.[871]

14.5. Indolo[3,2-*b*]carbazole Alkaloids

Prior to the isolation of natural indolo[3,2-*b*]carbazole alkaloids, synthetic derivatives attracted strong interest, because these carbazoles have a similar biological activity as the

dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193–3328

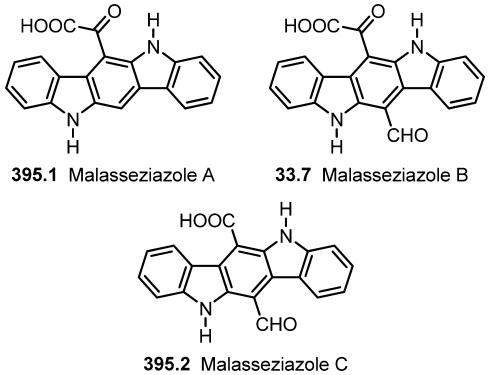
Scheme 394



environmental pollutant TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin). The TCDD receptor (Ah-receptor) is very important in the primary detoxification of unpolar substances, as this receptor triggers the expression of many enzymes (including cytochrome P-4501A1 or CYP1A1) involved in this process.[704]

In 2005, Steglich and co-workers isolated the malasseziazoles A (**395.1**), B (**33.7**), and C (**395.2**) from the lipophilic yeast *Malassezia furfur* (Scheme 395).[240] *Malassezia furfur* is part of

Scheme 395



the residential flora of human skin but is also responsible for skin disorders like pityriasis versicolor. This skin disease is manifested by flaky lesions with variable coloration and fluorescence. To date, this is the only report of naturally occurring indolo[3,2-*b*]carbazole alkaloids.

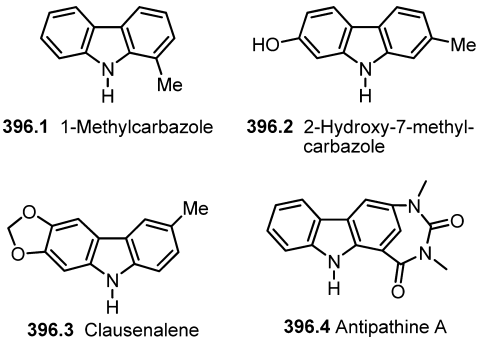
Since the isolation of the malasseziazoles, there are no reports of their synthesis. However, there are many reports on the synthesis of synthetic indolo[3,2-*b*]carbazole derivatives because most of them function as agonists at the TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) receptor (Ah-receptor).[872−876] In addition, various synthetic indolo[3,2-*b*]-carbazole derivatives have shown great potential as materials in electronic devices such as light-emitting diodes (LEDs), field-effect transistors (FETs), thin-film transistors (TFTs), and photovoltaic cells.[877−881]

15. MISCELLANEOUS CARBAZOLES

15.1. Isolation from Natural Sources

This section covers carbazole alkaloids with a substitution pattern that does not fit into a common category and, therefore, cannot be classified in one of the sections described above. In 1991, Dillman and Cardellina II isolated 1-methylcarbazole (**396.1**) from the extract of the sponge *Tedania ignis* in the shallow waters of Bermuda (scheme 396).[882] Prior to this

Scheme 396



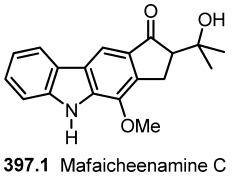
report, in 1968, Hoffmann et al. detected 1-methylcarbazole (**396.1**) along with other methylcarbazoles as major components of the condensate of cigarette smoke.[883] 1-Methylcarbazole exhibits insecticidal and antimicrobial activity[884] and was shown to be nonmutagenic.[885]

In 1993, Kusano et al. reported the isolation of 2-hydroxy-7-methylcarbazole (**396.2**) from the methanol extract of the aerial parts of *Cimicifuga simplex*.[886] In the same year, Bhattacharyya et al. described clausenalene (**396.3**), which was isolated from the stem bark of *Clausena heptaphylla*.[887] This was the first report of a methylenedioxycarbazole alkaloid from a plant source. The structure was assigned based on spectroscopic data and confirmed by total synthesis (see below). Clausenalene (**396.3**) inhibited the growth of both Gram-positive and Gram-negative bacteria.

In 2009, Qi et al. isolated antipathine A (**396.4**) from the extract of the black coral *Antipathes dichotoma* in the South China Sea (Scheme 396).[888] These zoanthid black corals have been applied in Chinese folk medicine and show diverse pharmaceutical functions, such as relieving fever. Antipathine A (**396.4**) exhibited moderate cytotoxicity against human stomach carcinoma SGC-7901 cell line as well as human liver carcinoma HepG2 cell line. Subsequently, the structural assignment for antipathine A (**396.4**) has been questioned because of its ring strain.[889,890]

In 2010, Maneerat and Laphookhieo reported the isolation of mafaicheenamine C (**397.1**) (Scheme 397).[250] This compound

Scheme 397



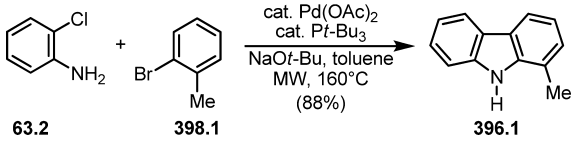
dx.doi.org/10.1021/cr200447s | *Chem. Rev.* 2012, 112, 3193−3328

displays an unprecedented cyclopenta[*b*]carbazole skeleton. Mafaicheenamine C (**397.1**) was obtained from the twigs of *Clausena lansium* together with mafaicheenamine A (**265.1**), mafaicheenamine B (**265.2**), and the previously known indizoline (**54.2**), lansine (**150.4**), glycozolidal (**150.3**), and murrayanine (**20.3**). The structure of the new alkaloid **397.1** was assigned based on HMBC (heteronuclear multiple bond correlation) experiments. Mafaicheenamine C (**397.1**) was isolated as an optically active compound ($[\alpha]_D^{26}$ = +64.25, c 0.02, HOMe). However, the absolute configuration has not yet been assigned.

15.2. Synthesis of 1-Methylcarbazole

In 2006, Bedford and Betham reported a synthesis of 1-methylcarbazole (**396.1**) starting from commercially available 2-chloroaniline (**63.2**) and 2-bromotoluene (**398.1**) (Scheme 398).[387] The palladium(0)-catalyzed coupling of 2-chloroaniline (**63.2**) and 2-bromotoluene (**398.1**) using microwave conditions provided 1-methylcarbazole (**396.1**) in a one-pot operation in 88% yield.

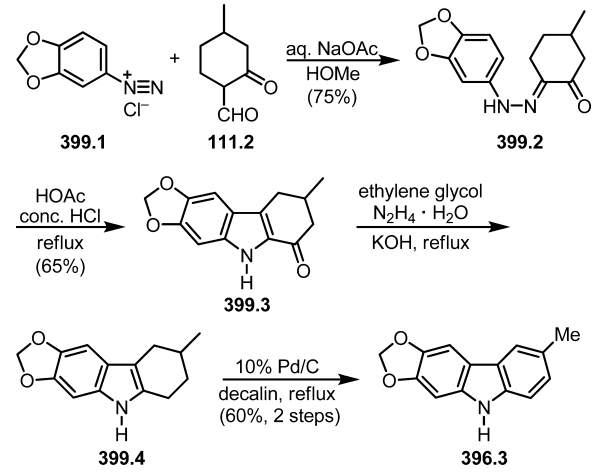
Scheme 398



15.3. Total Syntheses of Clausenalene

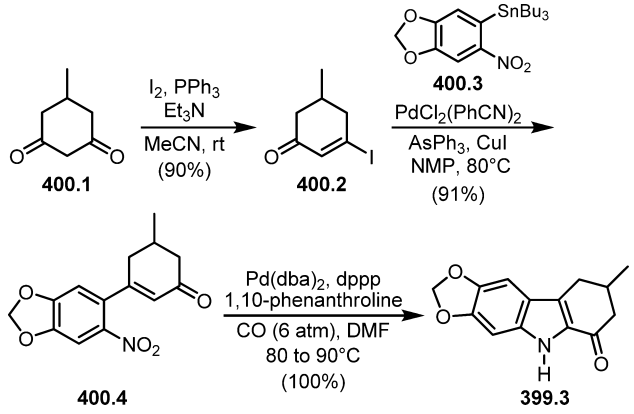
In 1993, Bhattacharyya et al. reported the first total synthesis of clausenalene (**396.3**) in order to confirm the structure.[887] Condensation of the diazonium salt **399.1** with 2-hydroxymethylene-5-methylcyclohexanone (**111.2**) afforded in a Japp–Klingemann reaction the phenylhydrazone **399.2** (Scheme 399). Subsequent Fischer–Borsche reaction provided the 1-oxotetrahydrocarbazole **399.3**. Deoxygenation of **399.3** by Wolff–Kishner reduction gave 3-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydrocarbazole (**399.4**), which on aromatization with palladium on activated carbon in decalin led to clausenalene (**396.3**).

Scheme 399



Söderberg and co-workers reported a formal synthesis of clausenalene (**396.3**) starting from 5-methylcyclohexane-1,3-dione (**400.1**) using two sequential palladium-catalyzed reactions (Scheme 400).[891] Iodination of **400.1** and Stille cross-coupling of the resulting iodo derivative **400.2** with the arylstannane **400.3** afforded compound **400.4**. Intramolecular reductive N-heteroannulation of **400.4** provided quantitatively 3-methyl-6,7-methylenedioxy-1-oxo-1,2,3,4-tetrahydrocarbazole (**399.3**), a known precursor for clausenalene (**396.3**) (see Scheme 399).[887]

Scheme 400



16. ADDENDUM

16.1. Total Synthesis of Siamenol, Clauszoline-K, 3-Formyl-7-hydroxycarbazole, Clausine N, Clausine C (Clauszoline-L), and Clausine M

In 2011, Ma and co-workers described the total synthesis of a range of 7-oxygenated carbazole alkaloids using a gold-catalyzed cyclization of an allenyl-substituted indole as the key step (Schemes 401–403).[892] For the synthesis of siamenol (**122.6**), methoxyallene (**401.2**) was first deprotonated with butyllithium at low temperature to generate 1-methoxyallenyllithium. Addition of *N*-benzyl-5-methylindole-2-carbaldehyde (**401.1**) led to the allenylmethyl-substituted indole **401.3** (Scheme 401). Treatment of compound **401.3** with catalytic amounts of gold(I) chloride in toluene at room temperature induced cyclization with concomitant dehydration to give the benzyl-protected 3-methyl-7-methoxycarbazole **401.4** in 81% yield. The same transformation could also be induced by stirring of the (allenylmethyl)carbazole **401.3** with catalytic amounts of platinum(II) chloride (61% yield). Regioselective bromination at C-6 with *N*-bromosuccinimide and debenzylation by treatment with potassium *tert*-butoxide in dimethylsulfoxide under oxygen atmosphere provided the carbazole **126.1**. The methyl ether at C-7 was cleaved using boron tribromide, and the resulting hydroxycarbazole was O-acylated to the carbazol-7-yl acetate **401.5**. Prenylation by Suzuki coupling with prenylboronic acid pinacol ester (4,4,5,5-tetramethyl-2-(3-methylbut-2-enyl)-1,3,2-dioxaborolane) (**401.6**) and cleavage of the acetyl group provided siamenol (**122.6**) in 7 steps and 19% overall yield based on the indole **401.1**.

N-Benzyl-5-bromoindole-2-carbaldehyde (**402.1**) was used as starting material for the synthesis of clauszoline-K (**122.2**), 3-formyl-7-hydroxycarbazole (**122.1**), clausine N (**122.5**), clausine C (clauszoline-L) (**122.3**), and clausine M (**122.4**) (Schemes 402 and 403). Addition of 1-methoxyallenyllithium to the indole-2-carbaldehyde **402.1** furnished the (allenylmethyl)indole **402.2**. Cyclization with concomitant dehydration was achieved as described above by treatment

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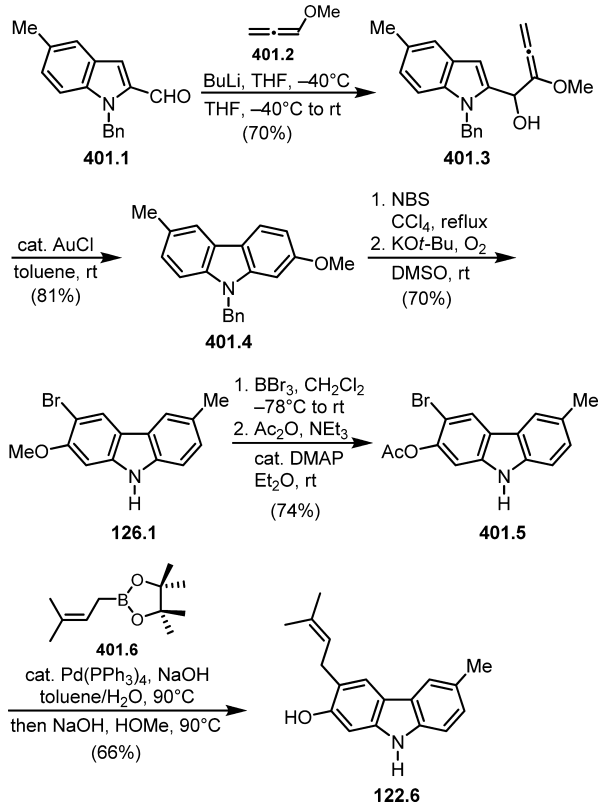
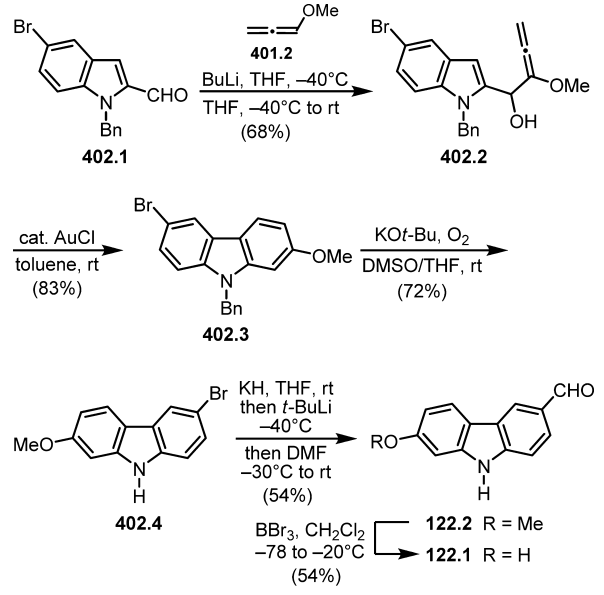
Scheme 401

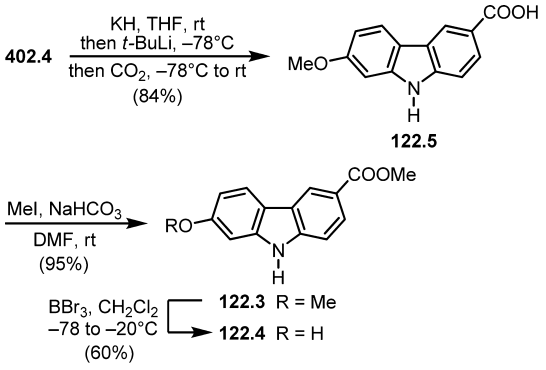


Scheme 402



with catalytic amounts of gold(I) chloride and provided the 6-bromocarbazole **402.3** in 83% yield. Debenzylation with potassium *tert*-butoxide under oxygen atmosphere led to 6-bromo-2-methoxycarbazole (**402.4**), which was used as precursor for the synthesis of the natural products **122.1**–**122.5**. Deprotonation of **402.4** with potassium hydride, halogen–metal exchange, and addition of dimethylformamide provided, after workup, clauszoline-K (**122.2**) in 4 steps and 22% yield based on the bromoindole **402.1**. Methyl ether cleavage as described previously by Knölker et al. (see Scheme 124)[94] led to 3-formyl-7-hydroxycarbazole (**122.1**). For the synthesis of clausine N (**122.5**), the bromocarbazole **402.4** was again first deprotonated with potassium hydride. Bromine–lithium exchange and treatment with gaseous carbon dioxide afforded clausine N (**122.5**) in 4 steps and 34% yield based on the bromoindole **402.1**. (Scheme 403). Methyl ester formation by treatment with methyl iodide led to clausine C (clauszoline-L) (**122.3**). Clausine M (**122.4**) was obtained from clausine C (clauszoline-L) (**122.3**) by methyl ether cleavage with boron tribromide as reported before by Knölker and co-workers (see Scheme 125).[94] Ma's approach provided clausine C (clauszoline-L) (**122.3**) in 5 steps and 32% yield and clausine M (**122.4**) in 6 steps and 19% yield based on the bromoindole **402.1**.

Scheme 403



16.2. Total Synthesis of Glycozolicine, Mukoline, and Mukolidine

In 2011, Tamariz and co-workers described the total synthesis of the 8-oxygenated carbazole alkaloids glycozolicine (**110.7**), mukoline (**129.1**), and mukolidine (**129.2**).[363] The key step is a boron trifluoride-mediated Diels–Alder cycloaddition of the dimethyleneoxazolidinone **404.2** and acrolein (**60.1**) (Scheme 404). An analogous approach has been described by the same group for the total synthesis of 1-oxygenated (see section 3.2.1.3) and 1,6-dioxygenated carbazole alkaloids (see section 3.3.1.3). Condensation of 4-methylphenyl isocyanate (**404.1**) and biacetyl (**59.1**) led to the dimethylene compound **404.2**, which was employed as dienophile in a Diels–Alder reaction with acrolein (**60.1**). The resulting annulated cyclohexene **404.3** was aromatized to the 2-oxobenzoxazole **404.4** by oxidation with DDQ. Cleavage of the cyclic carbamate and subsequent O-methylation led to the diarylamine **404.5**. Treatment of compound **404.5** with catalytic amounts of palladium(II) acetate and stoichiometric amounts of copper(II) acetate under microwave heating induced the oxidative cyclization and loss of the formyl group to give glycozolicine (**110.7**). The decarbonylation is probably promoted by an intermediate palladium(0) species that is formed during the oxidative cyclization. The palladium(0) is reoxidized to palladium(II) by copper(II) acetate as reported previously by Knölker and co-workers.[90,389] Tamariz' approach provided glycozolicine (**110.7**) in 6 steps and 27% overall yield. Oxidation of the methyl group at C-3 with DDQ led to mukolidine (**129.2**). Reduction of the formyl group of mukolidine (**129.2**) to a hydroxymethylene unit provided mukoline (**129.1**).

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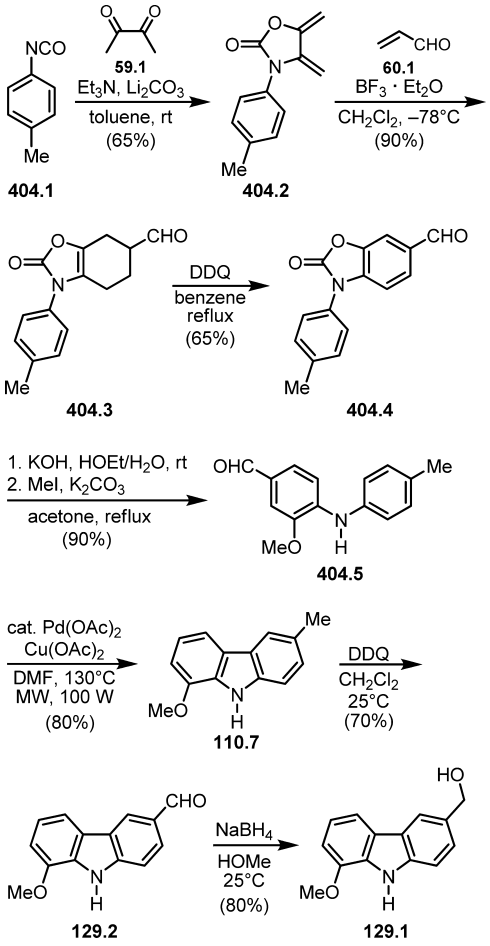
Scheme 404



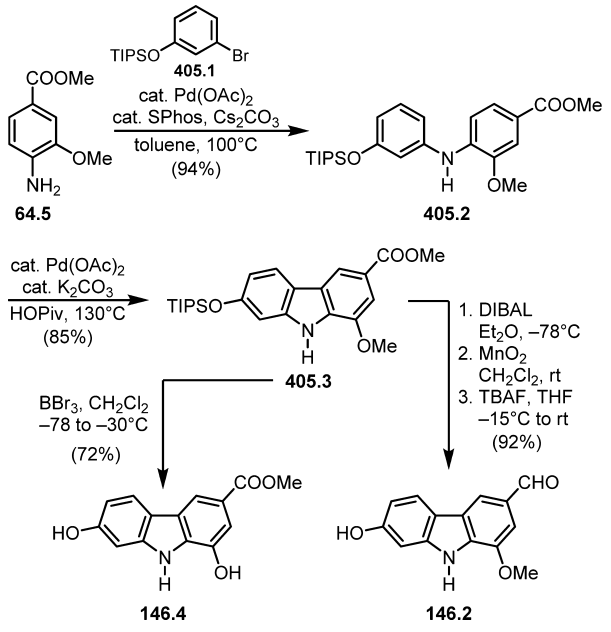
16.3. Total Synthesis of Clausine Q and Clausine R

Knölker and co-workers described the first total synthesis of the 1,7-dioxygenated carbazoles clausine Q (**146.2**) and clausine R (**146.4**) using a palladium(II)-catalyzed oxidative cyclization of a diarylamine as key step (Scheme 405).[375] Buchwald–Hartwig amination of the triisopropylsilyl protected 3-bromophenol **405.1** with the methyl 4-aminobenzoate **64.5** provided the diarylamine **405.2**. Oxidative cyclization of **405.2** was induced by heating with catalytic amounts of palladium(II) acetate and potassium carbonate in pivalic acid. The silyl-protected 1,7-dioxygenated carbazole **405.3** was obtained in up to 85% yield. Treatment with an excess of boron tribromide led to cleavage of both protecting groups and provided directly clausine R (**146.4**) in 3 steps and 58% overall yield based on the arylamine **64.5**. Clausine Q (**146.2**) was obtained from the protected carbazole-3-carboxylate **405.3** by a three-step sequence of reduction of the ester group, oxidation of the resulting hydroxymethylene to a formyl group, and, finally, chemoselective cleavage of the silyl-protecting group with TBAF. This approach led to clausine Q (**146.2**) in 5 steps and 74% overall yield based on the arylamine **64.5**.

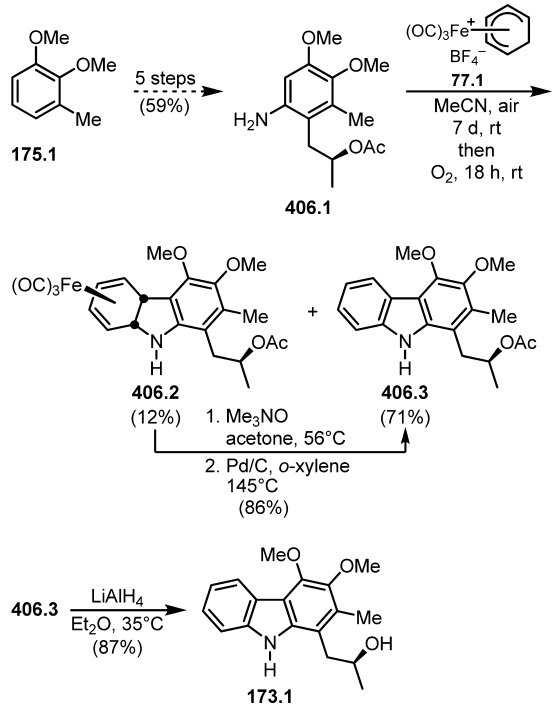
16.4. Synthesis of Streptoverticillin

In 2011, Knölker and co-workers described the enantioselective total synthesis of both natural (*S*)-streptoverticillin (**173.1**) and non-natural (*R*)-streptoverticillin [(*R*)-**173.1**], using an iron-mediated construction of the carbazole framework (Scheme 406).[412] The (*S*)-arylamine **406.1** was synthesized in 5 steps

Scheme 405



Scheme 406



and 59% overall yield from 3-methylveratrole (**175.1**) and (*S*)-propene oxide following the route described by Knölker et al. for the corresponding (*R*)-enantiomer.[893,894] The (*R*)-arylamine (*R*)- **406.1** has been used as an intermediate in Knölker's enantioselective synthesis of carquinostatin A (**183.1**) and lavanduquinocin (**204.2**). For the synthesis of the carbazole framework, a solution of the (*S*)-arylamine **406.1** and the iron complex salt **77.1** in acetonitrile was stirred in the dark at room temperature for 7 days in air and then for 18 h under an oxygen atmosphere. Under these conditions, the carbazole **406.3** was obtained in 71% along with the dihydrocarbazole–tricarbonyliron complex **406.2** (12% yield). The complex **406.2** could

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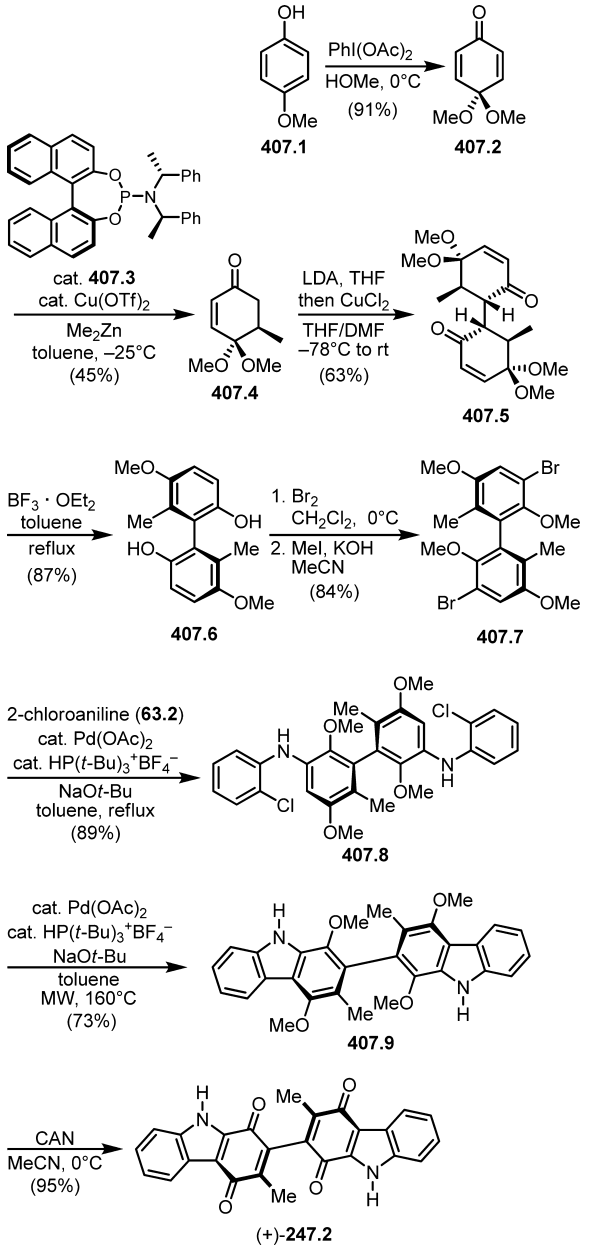
also be transformed into the carbazole **406.3** in a two-step procedure by sequential treatment with trimethylamine *N*-oxide and palladium on activated carbon. Reductive cleavage of the acetyl protecting group with lithium aluminum hydride provided streptoverticillin (**173.1**) in 3 steps and 71% overall yield based on the iron complex salt **77.1**. The absolute configuration of synthetic (*S*)-streptoverticillin (**173.1**) has been confirmed by an X-ray analysis of the crystalline 6-bromo derivative. Synthetic (*S*)-streptoverticillin (**173.1**) displayed the same sign for the optical rotation as the natural product. Non-natural (*R*)-streptoverticillin [(*R*)-**173.1**] was prepared from (*R*)-**406.1** following the same route.

16.5. Total Synthesis of (+)-Bismurrayaquinone A

In 2011, Thomson and co-workers reported the enantioselective synthesis of axially chiral (+)-bismurrayaquinone A [(+)-**247.2**] (Scheme 407).[535] The optical properties of bismurrayaquinone A (**247.2**) were not determined during isolation.[203] Thus, it is not known whether bismurrayaquinone A (**247.2**) occurs in nature as a single enantiomer. Hydroquinone monomethyl ether (**407.1**) was first oxidized to quinone dimethyl ketal (**407.2**) with (bisacetoxyiodo)benzene in methanol. Enantioselective methylation was then achieved following Feringa's protocol.[895] Thus, conjugate addition of dimethylzinc in the presence of catalytic amounts of copper(II) triflate and chiral ligand **407.3** led to the chiral cyclohexenone **407.4** in excellent enantioselectivity (99% ee). Oxidative dimerization of the enolate of **407.4** using copper(II) chloride led to the dimer **407.5**.[896] The chiral axis was then established by boron trifluoride–diethyl ether-complex-induced elimination of methanol to give the axially chiral phenol **407.6** in 99% ee. Bromination and methyl ether formation provided the axially chiral biphenyl **407.7**. Double Buchwald–Hartwig amination of **407.7** with 2-chloroaniline (**63.2**) and subsequent palladium(0)-catalyzed cyclization afforded the 2,2′-biscarbazole **407.9** without any racemization of the chiral axis (99% ee). Finally, oxidation of **407.9** with ceric ammonium nitrate provided (+)-bismurrayaquinone A [(+)-**247.2**] (99% ee, $[\alpha]_D^{20}$ = +6.53, c 0.12, $CHCl_3$) in 9 steps and 12% overall yield. (+)-Bismurrayaquinone A [(+)-**247.2**] has been proven to be configurationally stable at room temperature. Upon heating at 110 °C, racemization occurred within 51 h.

Scheme 407



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Notes

The authors declare no competing financial interest.

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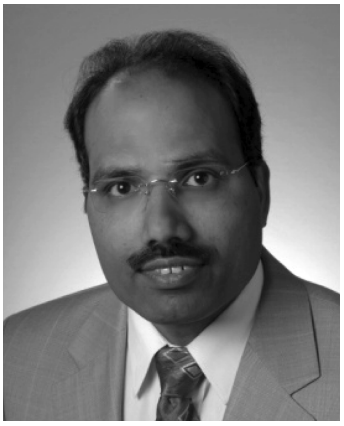

Kethiri Raghava Reddy was born in Garimilla Pally, Andhra Pradesh, India, in 1963. He studied chemistry at Kakatiya University in Warangal, where he received his B.Sc. in 1984 and his M.Sc. in 1987. After qualifying for the National Educational Test, he joined the group of Professor H. Ila at the North-Eastern Hill University in Shillong for a Ph.D., which he completed in 1995. He continued in the same research 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 Universität Karlsruhe, Germany. He continued as a postdoctoral fellow at the Universität Karlsruhe for two further years. In 2001, he followed the Knölker research group to the Technische Universität Dresden, where he worked as a staff scientist until 2009, when he joined Jubilant Biosys in Bangalore, India, as a Sr. Principal Scientist.

Hans-Joachim Knölker was born in Rehren, Germany, in 1958. He studied chemistry at the Universities of Göttingen and Hannover (1978−1983). He received his Ph.D. in the research group of Professor E. Winterfeldt at the University of Hannover (1983−1985). Following his postdoctoral studies with Professor K. P. C. Vollhardt at the University of California in Berkeley (1986), he returned to the University of Hannover for his habilitation (1987−1990). He was Full Professor of Organic Chemistry at the University of Karlsruhe (1991−2001) and Chairman of the Chemistry Department at the University of Karlsruhe (1995−1997). In 2000, he was a visiting scientist in India invited by the Indian National Science Academy (INSA). Since 2001, he is Professor of Organic Chemistry at the Technische Universität Dresden. He is cofounder of the biotech company JADO Technologies in Dresden. He is a fellow of the Japan Society for the Promotion of Science (JSPS) and of the Royal Society of Chemistry. In 2006, he was elected as an Ordinary Member of the Saxon Academy of Sciences, and since 2008, he is a member of the presidium of this academy. In 2011, he became the editor of the series "The Alkaloids—Chemistry and Biology". His research interests include the development of novel synthetic methodologies, organometallic chemistry, natural product synthesis, biomolecular chemistry, and medicinal chemistry.

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