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Diversity Oriented Convergent Access for Collective Total Synthesis of Bioactive Multifunctional Carbazole Alkaloids: Synthesis of Carbazomycin A, Carbazomycin B, Hyellazole, Chlorohyellazole, and Clausenaline D

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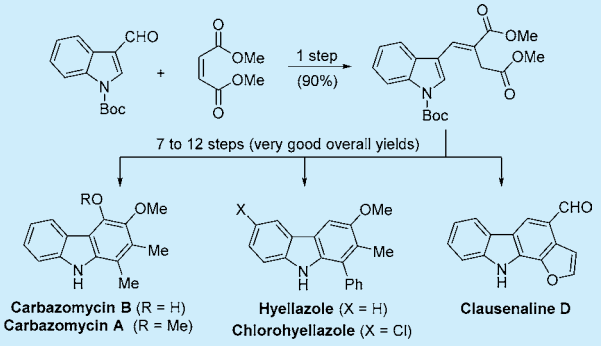
Supporting Information

ABSTRACT: Facile syntheses of imperative carbazole alkaloids carbazomycin A, carbazomycin B, hyellazole, chlorohyellazole, and clausenaline D have been demonstrated starting from readily available Boc-protected 3-formylindole and dimethyl maleate. The suitably substituted aromatic rings have been designed comprising three/four significant C−C bond forming reactions. The competent Wittig reaction, selective monoalkylations, one-pot regioselective Weinreb amide formation and Boc-deprotection, well designed Grignard reactions, dehydrative intramolecular cyclizations, and Baeyer−Villiger rearrangement of aromatic aldehydes were the main features.



Total synthesis of bioactive natural products leading to essential medicines is the priority area in science.[1] Development of new synthetic stratagems for the collective total synthesis of different classes of natural products is a challenging task of contemporary interest.[2] A large number of carbazole alkaloids have been isolated from plant, animal, microbial, and marine genesis (Figure 1).[3] They are an important

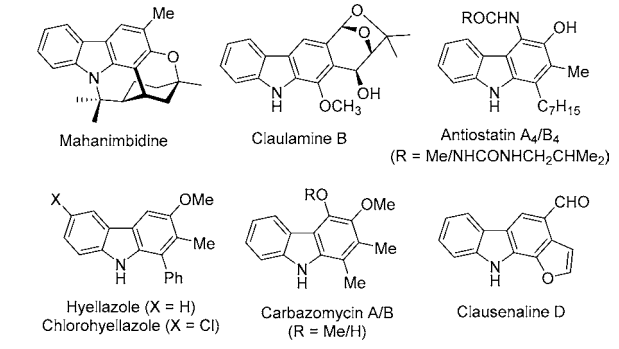


Figure 1. Diversely substituted carbazole alkaloids.

class of natural products from the point of view of novel structural topographies and major biological activities.[3−5] Carbazoles exhibit well proven antitumor, antibiotic, antiviral, anti-HIV, anti-inflammatory, antimalarial, psychotropic, antihistaminic, antioxidative, and significant antituberculosis activities. Moreover, carbazoles are used in the treatment of hypertension, ischemic heart disease, and congestive heart failure.[3−5] They have also been used in illustrious hole-transporting electroluminescent materials and are potential building blocks in functional materials owing to their electrical and thermal properties.[6] Therefore, carbazoles have been crucial target compounds and several elegant product specific syntheses of these have been reported during the past few decades.[3−5] The main steps involved in their synthesis were acid/base/metal/heat/light-catalyzed aryl−carbon/aryl−nitrogen/aryl−aryl couplings of two suitably substituted building blocks and the specific intramolecular cyclizations.[3−5] In the synthesis of carbazoles, construction of an appropriate fully functionalized aromatic ring system is the important assignment for steric and/or electronic factors and reactivity reasons.[7] Despite tremendous synthetic efforts to develop regioselective installation of appropriate substituents on these heterocyclic structures, general and efficient methods are still limited.[3−6] In the continuation of our studies on the total synthesis of bioactive natural products,[8] we reasoned that the readily available suitably substituted 3-formylindole derivatives and dimethyl maleate would constitute a diversity oriented new approach to this important class of compounds. In this context we herein report the robust route to essential carbazole alkaloids (Schemes 1−3).

A careful search of major carbazole alkaloid structures revealed that a pathway encompassing a completely open scope for introduction of a broad range of substituents at appropriate positions would provide a general approach to an array of fascinating bioactive natural and unnatural carbazole and fused carbazole architectures. A general representation and concise

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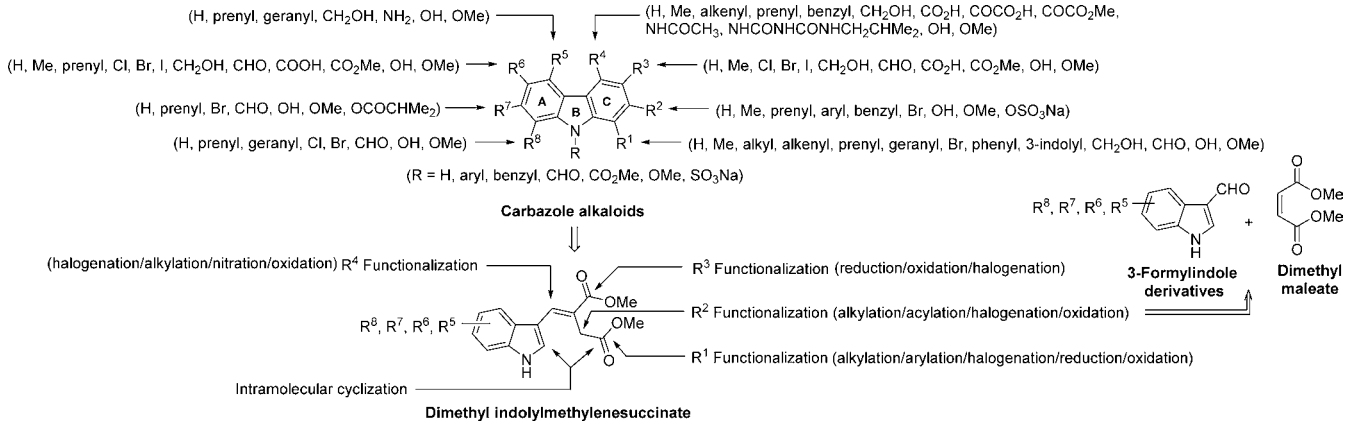
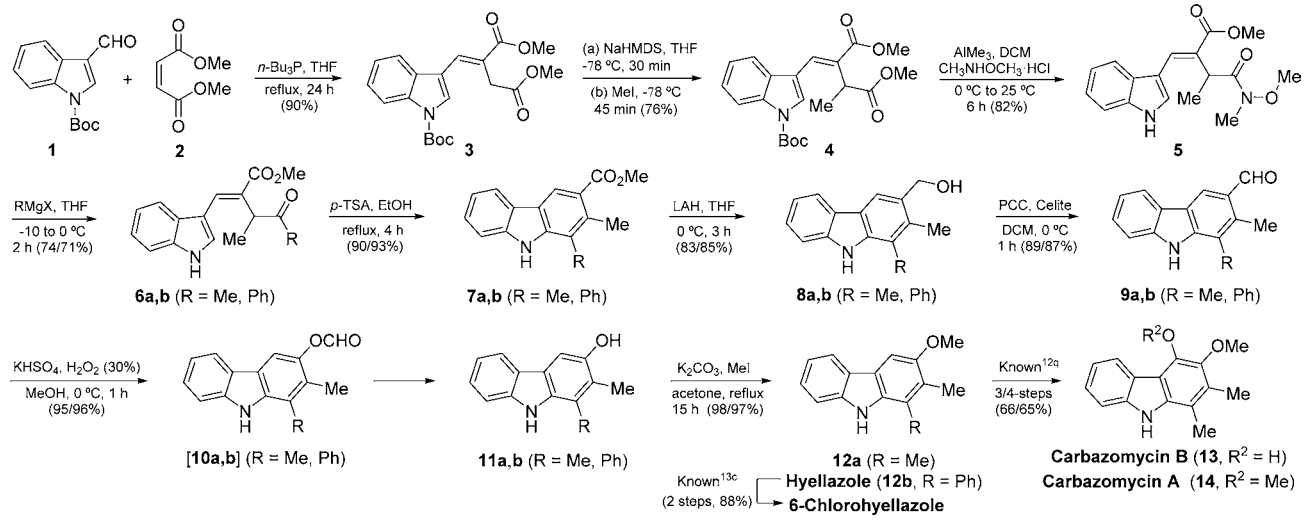
Scheme 1. General Representation of Known Major Carbazole Alkaloids and Their Retrosynthetic Analysis



Scheme 2. Synthesis of Carbazole Alkaloids from Boc-Protected 3-Formylindole and Dimethyl Maleate



retrosynthetic analysis of carbazole alkaloids has been depicted in Scheme 1. Retrosynthetically, the stepwise inter- and intramolecular coupling reactions of three carbon units from suitably substituted 3-formylindole derivatives with three carbon units from dimethyl maleate would constitute a general pathway to the majority of diversely substituted carbazole alkaloids. As represented in Scheme 1, multiple electro- and nucleophilic reactions would be possible on the potential antecedent dimethyl indolylmethylenesuccinate. Productively, it bears the correct number of electro- and nucleophilic C-atoms, accurately located, to introduce the appropriate substituents and/or functional groups along with a site for dehydrative intramolecular cyclization to form the desired aromatic ring structure. Accordingly, we prepared a synthetic plan to accomplish the collective synthesis of five carbazole alkaloids: carbazomycin A (antibiotic) and carbazomycin B (antibiotic and 5-lipoxygenase inhibitor) isolated from *Streptoverticillium ehimense*,[9] hyellazole and chlorohyellazole from *Hyella caespitosa*,[10] and clausenaline D from *Clausena lansium*.[11] Several syntheses of the first four target compounds and their closely related analogues have been known in the literature.[12−14] Several syntheses of structurally closely related furocarbazoles have also been known in the literature,[15] while the synthesis of the very recently isolated clausenaline D is awaited.

The initially studied reaction of 3-formylindole with an in situ generated Wittig reagent[16] from dimethyl maleate (**2**) and tributylphophine was not very efficient, and the required product was formed only in 33% yield. However, the alternatively performed reaction of Boc-protected 3-formylindole (**1**) with the same Wittig reagent stereoselectively furnished the desired potential precursor **3** in 90% yield, essentially under neutral reaction conditions (Scheme 2). The *E*-geometry of product **3** was confirmed on the basis of *peri* interaction of the vinylic proton with an ester carbonyl group.[8a,16] The conjugation of the 3-formyl unit with the lone pair of electrons on the indole N-atom is responsible for its decline in reactivity, and therefore the *N*-Boc protection activates it for the anticipated Wittig reaction. The NaHMDS induced chemo- and regioselective monomethylation of an activated allylic methyelene carbon in **3** with methyl iodide provided the necessary product **4** in 76% yield. Providentially, the formed carbanion did not endure the plausible intramolecular 1,6-addition course generating a 6−5−5 heterocyclic system. Trimethylaluminum prompted the regioselective coupling reaction of *N*,*O*-dimethylhydroxylamine hydrochloride with diester **4** to form the desired product **5** in 82% yield.[17] Conveniently, transformations of the more reactive unconjugated ester unit to a Weinreb amide and *N*-Boc-deprotection took place in the presence of trimethylaluminum/*N*,*O*-dimethylhydroxylamine hydrochloride. The well-organized chemoselective reactions of methylmagnesium bromide and phenylmagnesium bromide with Weinreb amide **5** cleanly delivered corresponding ketones **6a,b** in 74% and 71% yields, respectively.

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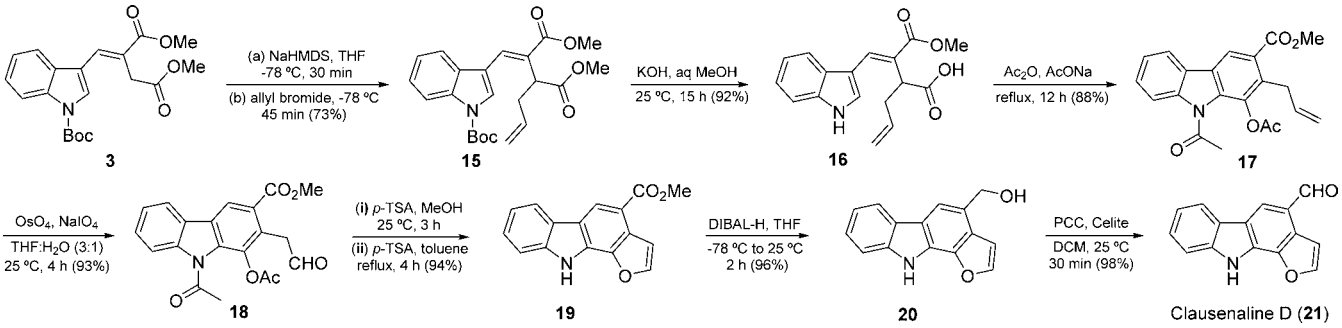
Scheme 3. First Total Synthesis of Clausenaline D



p-TSA catalyzed dehydrative intramolecular cyclization of ketones **6a,b**, providing the products **7a,b** in 90%/93% yields, efficiently constituting the rightly functionalized aromatic ring C. LAH-reduction of the ester function in **7a,b** followed by the PCC-oxidation of formed intermediate alcohols **8a,b** yielded corresponding aromatic aldehydes **9a,b** in very good overall yields in two steps. The Baeyer–Villiger oxidation of aromatic aldehydes **9a,b** formed the corresponding unisolable formate esters **10a,b** which, upon in situ hydrolysis, transformed to the known phenolic compounds **11a,b**[12p,q] in 95%/96% yields. The present Baeyer–Villiger oxidation reaction was highly temperature and time sensitive. Fortunately, we did not notice any oxidation of aldehyde to the corresponding carboxylic acid under the employed set of reaction conditions. The base-catalyzed chemoselective *O*-methylation of compound **11a** gave the corresponding known methyl ether intermediate **12a** in 98% yield from which the three-step synthesis of carbazomycin B (**13**) is known in the literature.[12q] Carbazomycin B (**13**) on simple *O*-methylation forms carbazomycin A (**14**) in high yield.[12q] Methylation of compound **11b** furnished the natural product hyellazole (**12b**) in 97% yield from which a two-step synthesis of yet another natural product, chlorohyellazole, is known in the literature.[13c] The analytical and spectral data obtained for both showed that the advanced intermediate **12a** of carbazomycins and hyellazole (**12b**) were in complete agreement with the reported data.[12,13]

In the next phase, the total synthesis of fused carbazole clausenaline D was planned by assigning the present protocol (Scheme 3). The NaHMDS induced regioselective introduction of an allyl group at an activated allylic methyelene carbon in **3** with allyl bromide provided the required product **15** in 73% yield. Controlled base-catalyzed regioselective hydrolysis of the more reactive unconjugated ester unit in **15** was feasible under ambient reaction conditions and directly formed the Boc-deprotected monoacid **16** in 92% yield. The Ac_2O–AcONa stimulated dehydrative intramolecular cyclization of product **16** directly delivered the corresponding *N*- and *O*-acylated carbazole derivative **17** in 88% yield. The transformation of the C–C double bond in compound **17** to the corresponding diol followed by an in situ oxidative cleavage using OsO_4 and $NaIO_4$ delivered the desired aliphatic aldehyde **18** in 93% yield. The use of diacyl protection in substrate **17** was essential, as the corresponding free phenolic compound on treatment with OsO_4/$NaIO_4$ resulted in a complex reaction mixture. A one-pot *p*-TSA/MeOH mediated double deacylation of **18** followed by dehydrative intramolecular cyclization in refluxing *p*-TSA/toluene yielded the furocarbazole **19** in 94% yield. The DIBAL-H reduction of the aromatic ester unit in **19** to the corresponding alcohol **20** followed by its PCC-oxidation delivered the desired natural product clausenaline D (**21**) in 94% yield over two steps. The analytical and spectral data obtained for clausenaline D were in complete agreement with the reported data.[11]

In summary, starting from easily available chemicals and reagents, we have demonstrated a diversity oriented convergent access for collective synthesis of five different carbazole alkaloids with very good overall yields. In the present approach, generation of a suitably substituted basic carbazole skeleton in just 4/5 steps utilizing three carbon fragments from each 3-formylindole and dimethyl maleate is remarkable. Furthermore, the generation of biaryl systems without the aryl–aryl coupling is also noteworthy. Syntheses of these alkaloids have been accomplished without involving any discrete protection–deprotection steps. For an appropriate functionalization of aromatic ring A, the synthesis itself can begin with suitably substituted indole derivatives; otherwise, the functionalization of aromatic ring A toward the end part of the total synthesis would also be feasible. Further studies on the total synthesis of a few selected carbazole alkaloids using different types of electro- and nucleophilic reactions on the pivotal intermediate dimethyl indolylmethylenesuccinate are in progress in our laboratory. The present approach is general in nature and can provide access to a large number of carbazole alkaloids and their congeners for SAR studies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for the preparation of all compounds and their tabulated analytical and spectral data. ^{1}H NMR, ^{13}C NMR, and DEPT spectra of compounds **3**–**9**, **11**, **12**, and **15**–**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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