

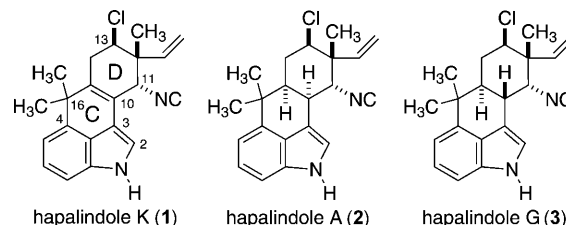
Total Synthesis of the Chlorine-Containing Hapalindoles K, A, and G**

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Indole alkaloids of the terrestrial blue-green algae^[1] are structurally diverse natural products and have elicited a broad response in the form of new chemical methods and preparations. This enterprise is driven, in part, by the diverse biological activity that is often associated with metabolites of cyanobacteria resident in these algae.^[2] Beginning with the syntheses of (non-chlorine-containing) hapalindoles J and M by Muratake and Natsume,^[3] fischerindole,^[4] hapalindole,^[3,5] welwitindolinone,^[4,6] and ambiguine^[7] natural products have been accessed by total synthesis.^[8] The chlorine-containing congeners further increase the functional and stereochemical diversity of this natural product class, but solutions for their synthesis are few in number. Fukuyama and Chen reported the first synthesis of a hapalindole that contains a chiral secondary alkyl chloride (hapalindole G, **3**).^[5g] The *syn* relationship between the chlorine and the methyl groups was established by a cyclopropane-ring-opening reaction with lithium chloride. In 2005, Baran and co-workers reported the syntheses of fischerindoles I and G.^[4] The configuration at C13 of these linear tetracycles is diastereomeric to that in **3**, and was also constructed through a series of stereospecific transformations, including an epoxide-ring-opening reaction.^[4] The same neopentyl chloride is contained within welwitindolinone A, and the solution reported by Wood and co-workers involved a chloronium-induced [1,2]-methyl shift to establish the *anti* relationship between methyl and chlorine.^[6a,b] Equally elegant was the preparation of (+)-welwitindolinone A from (–)-fischerindole I by Baran and co-workers.^[4,7]

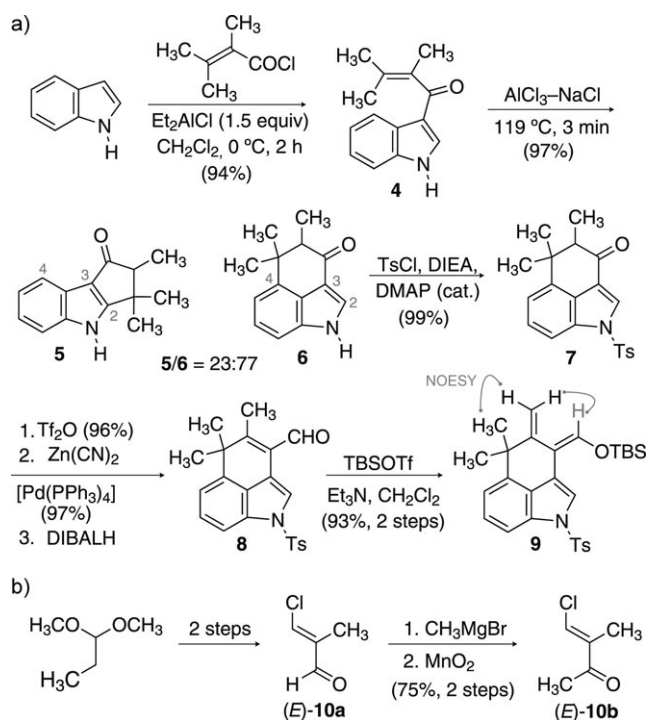
We report herein the first total synthesis of hapalindoles K (**1**) and A (**2**), and a formal synthesis of hapalindole G (**3**; Scheme 1). We used 1) a twofold electrophilic aromatic substitution (EAS) reaction of indole with α -methyl tiglic acid chloride, 2) a demanding intermolecular [4+2] cycloaddition, and 3) a late-stage Ritter reaction. These key steps provided the convergency and functional group installation needed to deliver each target in 15 steps or less.

In an earlier report, we applied a rhodium(II)-catalyzed cyclohexannulation to construct the ABC ring system of ambiguine G, which bears a substituent at C1.^[9] The require-



Scheme 1. Structures of hapalindoles K, A, and G.

ments for accessing hapalindoles **1–3** are more directly addressed by construction of the tricyclic ring system through an acylation/alkylation protocol in two steps (Scheme 2a). The Et_2AlCl -mediated Friedel–Crafts acylation of indole with α -methyl tiglic acid chloride provided adduct **4** in excellent yield.^[10] An extensive screening of Lewis acids to effect the desired C4–C16 bond formation was unsuccessful, as a retro-Friedel–Crafts acylation that returned indole was predominant in most cases. However, we discovered that the desired tricyclic ketone **6** could be obtained by the treatment of **4** with



Scheme 2. Diene and dienophile synthesis. NOESY correlations are shown for compound **9**. DIBALH = diisobutylaluminum hydride, DIEA = *N,N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethylsulfonyl, Ts = toluene-4-sulfonyl.

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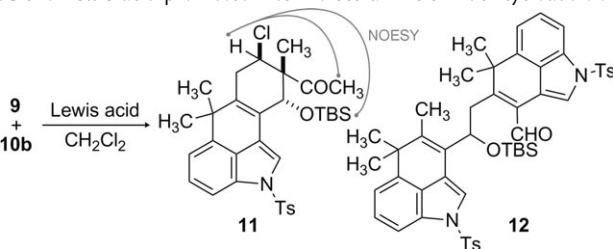
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a molten $\text{AlCl}_3\text{--NaCl}$ solution.^[11] The temperature was very critical to the regioselective outcome of this cyclization step, since optimal temperatures (117–120 °C) provided **6** as the major product, but elevated temperatures led predominantly to the corresponding regioisomer **5**. On a larger scale, purification was reserved until after the sulfonamide formation, since the undesired compound **5** (containing a fischer-indole backbone) was unreactive under these conditions. Ketone **7** was subsequently converted to its enol triflate^[12] and treated with $\text{Zn}(\text{CN})_2$ and $[\text{Pd}(\text{PPh}_3)_4]$ to give the α,β -unsaturated nitrile in excellent yield.^[13] Nitrile reduction with DIBALH was followed by treatment of the resulting enal **8** with TBSOTf and Et_3N . This sequence furnished the requisite diene **9** with the desired geometry.

With diene **9** and dienophile **10a** (Scheme 2b) in hand, different strategies were evaluated to effect the desired intermolecular Diels–Alder cycloaddition.^[14] Attempts to carry out the cycloaddition under thermal conditions led to a slow desilylation of **9** to form the corresponding enal **8**, as well as the decomposition of the dienophile through an undefined pathway. The Lewis acid promoted Diels–Alder cycloaddition between diene **9** and β -chloromethacrolein **10a**^[15] was also investigated, but the Mukaiyama aldol product predominated in all attempts.

In order to slow down the 1,2-addition pathway, we evaluated dienophile **10b** as a substitute for β -chloro- α -methyl acrolein (Scheme 2b). A range of Lewis acids were examined to promote the cycloaddition, as partially outlined in Table 1.

Table 1: Lewis acid promoted intermolecular Diels–Alder cycloaddition.



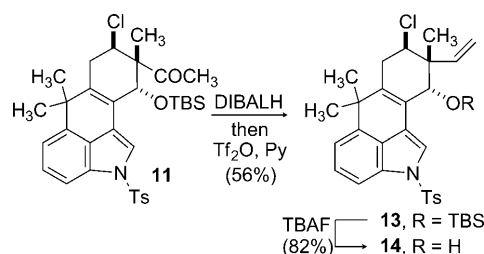
Entry	Lewis acid	T [°C]	t [h]	Ratio of 11/12/8 ^[a]	Yield of 11 [%] ^[b]
1	TMSOTf	−78	2	1:0:1	18
2	TiCl_4	−20	0.5	1:3:1	24
3	$\text{Ti}(\text{iOPr})_4$	0	12	0:0:1	–
4	Et_2AlCl	0	12	0:0:1	–
5	Me_3Al	0	12	0:0:1	–
6	EtAlCl_2	−20	1	3:1:0	36
7	EtAlCl_2 ^[c]	−78 → −20	3	13:1:1	59

[a] Determined by analysis of the crude reaction mixture by ^1H NMR spectroscopy. [b] Yield of isolated product. [c] Use of toluene instead of CH_2Cl_2 as the solvent led to **11** in 54% yield.

The use of trimethylsilyl triflate provided the first evidence of cycloaddition, but the reaction suffered from low conversion and formation of enal **8** (Table 1, entry 1). However, it appeared that a single regio- and diastereomer of the desired Diels–Alder adduct **11** was formed. The use of titanium tetrachloride improved the conversion to products

that resulted from C–C bond formation, but the Mukaiyama aldol product **12** was formed as the major product. It should be noted that **12** could be recycled to enal **8** upon treatment with TiCl_4 with little overall loss of material. Many titanium and aluminum Lewis acids favored the formation of enal **8** (Table 1, entries 3–5). However, use of ethyl aluminum dichloride successfully improved selectivity and conversion to **11** (Table 1, entry 6), and these conditions could be further optimized to obtain the Diels–Alder cycloadduct in 59% yield of isolated product (Table 1, entry 7). The yield, combined with the analysis of the crude reaction mixture by ^1H NMR spectroscopy, suggests a high degree of regio- and diastereoselectivity, and an additional amount (15%) of **8** and **12** could be isolated.

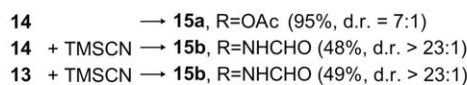
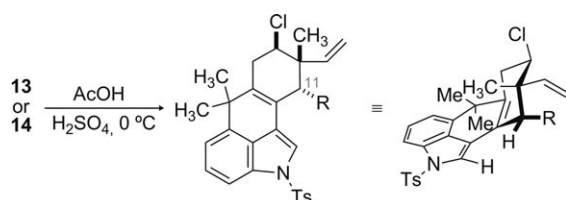
With the tetracyclic core of the hapalindoles in place, our attention focused on elaboration of the cyclohexene ring. Reduction of the ketone, and in situ treatment of the alcohol with triflic anhydride and pyridine provided alkene **13** in 56% yield (Scheme 3). When using the purified alcohol, evidence



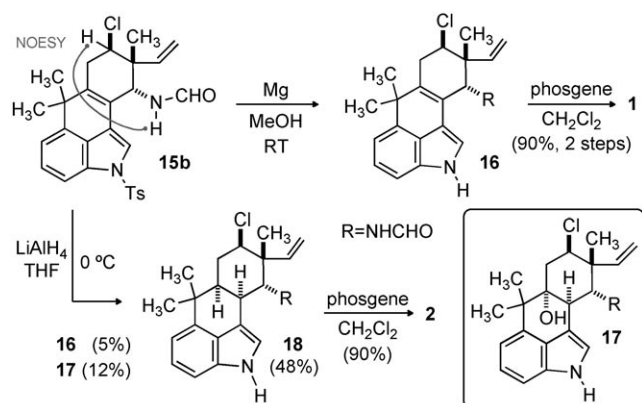
Scheme 3. Completion of the neopentyl chloride subunit. Py = pyridine, TBAF = tetrabutylammonium fluoride.

for the production of a Grob fragmentation product was found, which may have contributed to the slightly reduced yield. Desilylation using TBAF led to allylic alcohol **14**.

At this stage, efforts to construct the C11–N bond using an established five-step protocol were unsuccessful.^[4,5g] Decomposition of the starting material was observed, perhaps influenced by the presence of the chloride and C10–C15 unsaturation. However, exposure of **14** to $\text{H}_2\text{SO}_4\text{--AcOH}$ provided acetate **15a** in excellent yield and good diastereoselectivity (d.r. = 7:1; Scheme 4). The relative stereochemistry was assigned by chemical correlation of **15a** to alcohol **14**. Furthermore, the high degree of retention of configuration is consistent with the approach of acetic acid to the intermediate allylic cation along an axial trajectory. The coupling constants associated with the chloro-substituted axial methine ($J = 9$ and 5.4 Hz) support the assignment of the acetate to an axial position. Application of a Ritter reaction to **14** using TMSCN as a nitrogen source provided formamide **15b** as a single diastereomer.^[16] The formation of an allylic cation and an axial approach of the nucleophile again rationalize the diastereoselectivity, which was further confirmed by the observation of a NOESY cross-peak (in Scheme 5). A second possible source of stereocontrol is the proximity of the equatorial position to C2 of the indole ring, as an unfavorable steric interaction occurs. Further investigation revealed that silyl ether **13** was a suitable Ritter substrate,



Scheme 4. The Ritter reaction as the key to set the C11–N bond. TMS = trimethylsilyl.



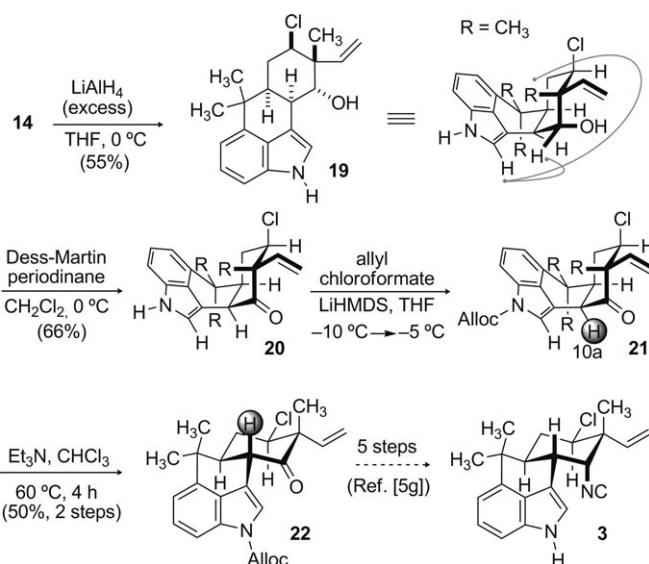
Scheme 5. Preparation of **1** and **2**. NOESY correlations are shown for compound **15b**.

which provided **15b** in a comparable yield. Subsequently, the synthesis of **1** could be accomplished in two straightforward synthetic operations which included deprotection of the tosyl group and isonitrile formation (Scheme 5).

Compound **2** exhibits two additional chiral centers at C10 and C15 in the *cis*-decalin ring system (rings C and D), which is possibly of higher energy than the corresponding ring system in hapalindole G (**3**). The potential complication of the neopentyl chloride notwithstanding, we chose to examine the reductive approach of Muratake and Natsume in this context.^[17] Exposure of formamide **15b** to lithium aluminum hydride provided the desired *cis*-fused ring system as formamide **18** (Scheme 5). Additionally, alcohol **17** and detosylated indole **16** could be isolated. Treatment of formamide **18** with phosgene then provided **2**.

Modification of this sequence can also provide access to the *trans*-fused hapalindoles such as compound **3**. Reduction of allylic alcohol **14**, again using the protocol of Muratake and Natsume, afforded alcohol **19** (Scheme 6). Dess–Martin periodinane mediated oxidation^[18] of alcohol **19** was followed by protection of the indole nitrogen as allyl carbamate **21**. Epimerization at C10 was effected by triethylamine to lead to *trans*-decalin **22**. This intermediate was prepared by Fukuyama and Chen in the total synthesis of (–)-hapalindole G.^[5g]

In summary, we have described a twelve-step total synthesis of hapalindoles A and K and a formal synthesis of hapalindole G. Each case highlights the value of the key



Scheme 6. Preparation of **3**. Alloc = allyloxycarbonyl, LiHMDS = lithium hexamethyl disilazide, THF = tetrahydrofuran.

precursor—neopentyl chloride **11**—by using a convergent, stereocontrolled approach. A second new development in this overall approach is the use of the Ritter reaction to establish the C10–N bond stereoselectively. This aspect was key to the brevity of each synthesis.

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