Synthetic Methods

DOI: 10.1002/anie.200701881

Total Synthesis of Complex Cyanobacterial Alkaloids without Using Protecting Groups

Karl Gademann and Simone Bonazzi*

Keywords:
alkaloids · coupling reactions · natural products · synthetic methods · total synthesis

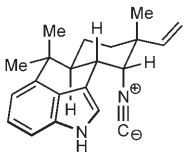
Protecting groups[1] are both a blessing and a curse for organic synthesis. The introduction of efficient blocking groups for reactive functional groups enabled the preparation of peptides, oligosaccharides, DNA, and most recently RNA using machines[2]. Protecting groups are thus directly responsible for the huge impact of this oligomer chemistry in biology and medicine. Also for nonoligomeric small molecules, protecting groups provided solutions in areas such as total synthesis or combinatorial chemistry.

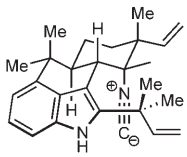
In many cases, however, protecting groups did not facilitate the synthetic project, but, to the dismay of the practitioner, introduced new problems.[3] The blocking groups could not be properly removed with a high yield, migration of these supposedly silent observers occurred, or, surprisingly, they introduced new, unwanted sites of reactivity. Further to these unpredictable events, the implicit fact that the attachment and the deprotection adds complexity and length to the synthetic endeavour further accentuates the problems associated with protecting groups. Chemists learned to accept these unavoidable problems with the stoicism of how some people accept "death and taxes". From all these points, avoiding protecting groups in general constitutes a necessity for "the ideal synthesis".[4]

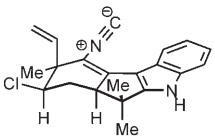
[*] Prof. Dr. K. Gademann, M. Sc. S. Bonazzi
Chemical Synthesis Laboratory
Swiss Federal Institute of Technology (EPFL)
1015 Lausanne (Switzerland)
Fax: (+41) 21-693-9700
E-mail: karl.gademann@epfl.ch
Homepage: http://isic.epfl.ch/lsync

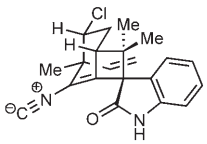
In a recent issue of the journal *Nature*,[5] Phil Baran, Thomas Maimone, and Jeremy Richter described new landmark total syntheses of several complex cyanobacterial alkaloids without resorting to using any protecting groups. In addition, their syntheses are characterized by brevity; the paper details the introduction of unusual strategies for bond disconnection and fascinating mechanistic hypotheses for other challenging problems.

Cyanobacteria are considered as a prime source for new bioactive compounds as a large diversity of isolated structures is known and they contain many gene clusters for metabolite production.[6] These prokaryotic photoautotrophs produce an intriguing set of indole natural products including the fischerindole, hapalindole, welwitindolinone, and ambiguine alkaloids.[7] All these structurally complex and densely functionalized compounds display a broad range of biological activities ranging from antibiotic, anticancer, and antifungal activities to insecticidal activities. In addition, the complex architecture inspired the imagination of chemists and established a proving ground for the development of new strategies and tactics in organic synthesis.[8]


(−)-hapalindole U


(+)-ambiguine H

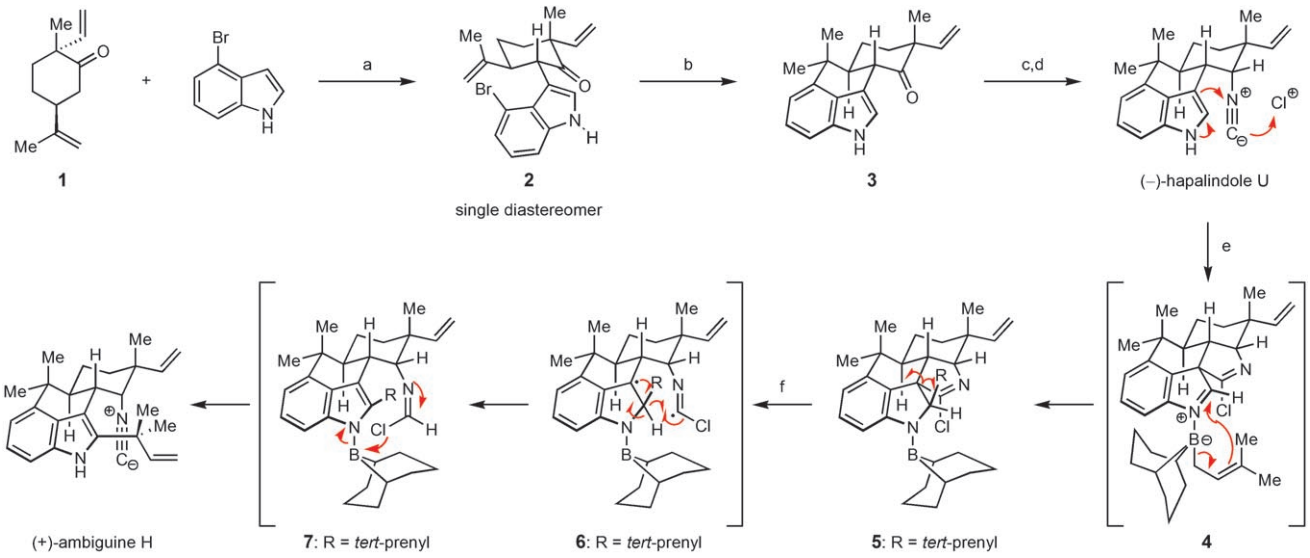

(−)-fischerindole I


(+)-welwitindolinone A

The structural challenges presented by hapalindole U, ambiguine H, fischerindole I, and welwitindolinone A include a densely functionalized cyclohexane ring fused to the indole nucleus forming cyclohexane, cyclopentane, and cyclobutane rings. All compounds contain at least one quaternary carbon atom attached to the indole ring and the latter two compounds are additionally halogenated. All four alkaloids contain the sensitive isonitrile functionality, which is only rarely found in natural products and also presents reactivity challenges to the synthetic design. The most appealing molecular architecture is displayed by welwitindolinone A with its cyclobutane spiro oxindole structure.

The synthesis started with the cyclohexanone derivative **1**, which can be obtained following established procedures, and 4-bromoindole (Scheme 1). The indole and terpene units were merged by a Cu-mediated coupling reaction, which was developed earlier by the same group.[8b] This fragment coupling reaction is very powerful in elaborating the key C–C bond in **2** in a very straightforward way, albeit in a moderate yield (50%, 5 mmol scale).

The next bond formation was carried out by a reductive Heck reaction. After careful experimentation, the authors discovered the beneficial role of Herrmann's catalyst as 5 mol% of this Pd source allowed for the formation of the hapalindole/ambiguine skeleton **3** in 61% yield. Reductive amination, formylation, and dehydration by using standard conditions resulted in the first



Scheme 1. Protecting-group-free synthesis of hapalindole U and ambiguine H. Reagents and conditions: a) LiHMDS, Cu^{II}-2-ethylhexanoate, THF, −78→25 °C (50%); b) $[Pd\{P(o\text{-tol})_3\}OAc]_2$ (5 mol%), NaOCHO, TBAB, Et_3N, DMF, 80 °C, slow addition of Pd over 5 h (65%); c) NH_4OAc, $NaCNBH_3$, MeOH/THF, microwave irradiation at 150 °C; then HCO_2H, CDMT, DMAP, NMM, DCM, 25 °C; d) $COCl_2$, Et_3N, DCM, 0 °C (60% over two steps); e) *t*BuOCl, DCM, −78 °C; then prenyl-9-BBN, −78 °C (60%); f) Et_3N, benzene, *hν*, (63%, based on recovered starting material). LiHMDS = lithium hexamethyldisilazide, TBAB = tetra-*n*-butyl ammonium bromide, DMF = *N*,*N*-dimethylformamide, CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine, DMAP = 4-*N*,*N*-dimethylaminopyridine, NMM = *N*-methylmorpholine, DCM = dichloromethane, 9-BBN = 9-borabicyclo-nonane.

target structure, (−)-hapalindole U. This straightforward synthetic sequence allowed for the preparation of significant amounts of this material, notably without the use of any protecting groups.

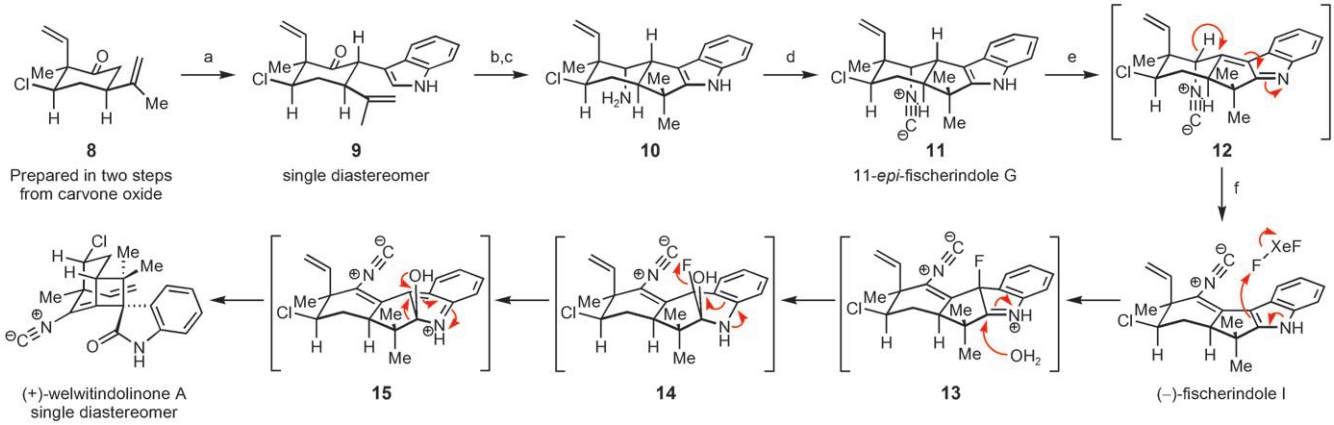
The link between the hapalindole and ambiguine families would be established by a prenylation at C2 on the indole ring. However, the presence of the sensitive isonitrile functionality prevented direct instalment of the side chain under standard conditions. To overcome these limitations, Baran et al.[5] elegantly utilized the reactivity presented both by the indole and the isonitrile group. Electrophilic chlorination of hapalindole U followed by treatment with prenyl-9-BBN resulted in the cyclic chloroimidate **4**. The transfer of the prenyl group is thought to occur after activation of the imine by the borane reagent. The observed configuration at the newly formed stereogenic center is probably a direct consequence of the molecular shape, with preferred attack from the less-hindered *Re* face.

Ambiguine H was obtained through a spectacular sequence: Irradiation of **5** led to homolytic cleavage to give postulated intermediate **6**. Subsequent hydrogen abstraction with concomitant elaboration of the indole ring (to give **7**) and simultaneous expulsion of both chloride and the BBN fragments in one single operation gave synthetic (+)-ambiguine H. The drawback of this photolysis strategy is the low yield, which is a direct consequence of product instability under the reaction conditions. Nonetheless, this elegant and straightforward route constitutes the first total synthesis of this natural product and enables the generation of large amounts of material for further biological studies.

Along the same lines, Baran et al.[5] demonstrated that other members of this class of natural products are obtained by applying the same principles: No protecting groups,[9] a straightforward synthetic route, and rapid assembly of molecular complexity. The synthesis started again with the Cu-mediated enolate indole coupling to link the terpene building block **8** (two steps from carvone oxide) to the indole (Scheme 2). Acid-catalyzed cyclization of **9** (montmorillonite K-10, microwave) gave the tetracyclic intermediate ketone (26% yield + 55% recovered **9**), which was then followed by a stereoselective reductive amination resulting in the precursor **10**. In contrast with an earlier approach to fischerindole I by the same group, Baran and et al.[5] chose this time to directly install the sensitive isonitrile functional group at this stage of the synthesis, preparing 11-*epi*-fischerindole G (**11**). Oxidation of the indole to the imine **12** allowed, after tautomerization, the isolation of (−)-fischerindole I in 92% yield.

The conversion of fischerindole I to welwitindoline A was achieved by a putative fluorohydroxylation of the indole ring (Scheme 2): Treatment of fischerindole I with XeF_2 first led to fluorination of the indole ring, followed by trapping of the intermediate iminium group in **13** with water. Elimination of fluoride in **14** could mechanistically lead to the iminoquinone methide **15**, which serves as a precursor for the rearrangement. Alternatively, a semipinacol rearrangement of **14** would be possible to furnish the target (+)-welwitindoline A as a single diastereoisomer.

The total syntheses of these four complex cyanobacterial alkaloids demonstrate the power of modern organic synthesis. Key features include: 1) protecting-group-free assembly, 2) high convergency, 3) cascade reactions are used to add molecular complexity, and 4) change of the oxidation state of the carbon skeleton is minimized.



Scheme 2. Protecting-group-free total synthesis of fischerindole I and welwitindolinone A. Reagents and conditions: a) LiHMDS, THF, −78 °C, copper(II)-2-ethylhexanoate, indole, −78 → 23 °C (62 %); b) Montmorillonite K-10 clay, microwave irradiation at 120 °C, (57 %, based on recovered starting material); c) NH_4OAc, $NaCNBH_3$, 3-Å molecular sieves, MeOH/THF, sonication, 18 h (42 %); d) HCO_2H, CDMT, DMAP, NMM, DCM, 23 °C, 30 min; Et_3N, $COCl_2$, DCM, 0 °C, 10 min (95 %); e) DDQ, H_2O, THF, 0 °C (92 %); f) XeF_2, H_2O, H_3CCN, 23 °C (44 %). DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.

Insight from biosynthetic considerations helped to design this elegant route, which relied on the intrinsic reactivity of the functional groups present. To exploit this, a protecting-group-free strategy was mandatory.

It should be pointed out that several protecting-group-free total syntheses have been performed over the last century. Early key examples include tropinone by Robinson,[10] usnic acid by Barton et al.,[11] or muscarine by Hardegger and Lohse.[12] The examples discussed herein, however, display much more complex molecular architectures and can thus be considered spectacular new landmarks in the vast arena of natural product total synthesis.

Published online: June 25, 2007

[1] For an overview, see: T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, Hoboken, **1999**.
[2] S. Pitsch, *Chimia* **2001**, *55*, 320.
[3] For an overview, see: M. A. Sierra, M. C. de la Torre, *Dead Ends and Detours. Direct Ways to Successful Total Synthesis*, Wiley, Weinheim, **2004**.
[4] R. W. Hoffmann, *Synthesis* **2006**, 3531.
[5] P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404; J. A. Porco, Jr. *Nature* **2007**, *446*, 383.
[6] A. M. Burja, B. Banaigs, E. Abou-Mansour, J. G. Burgess, P. C. Wright, *Tetrahedron* **2001**, *57*, 9347; K. Gademann, *Chimia* **2006**, *60*, 841.
[7] K. Stratmann, R. E. Moore, R. Bonjouklian, J. B. Deeter, G. M. L. Patterson, S. Shaffer, C. D. Smith, T. A. Smitka, *J. Am. Chem. Soc.* **1994**, *116*, 9935; R. E. Moore, C. Cheuk, G. M. L. Patterson, *J. Am. Chem. Soc.* **1984**, *106*, 6456; R. E. Moore, C. Cheuk, X. G. Yang, G. M. L. Patterson, R. Bonjouklian, T. A. Smitka, J. S. Mynderse, R. S. Foster, N. D. Jones, J. K. Swartzendruber, J. B. Deeter, *J. Org. Chem.* **1987**, *52*, 1036; T. A. Smitka, R. Bonjouklian, L. Doolin, N. D. Jones, J. B. Deeter, W. Y. Yoshida, M. R. Prinsep, R. E. Moore, G. M. L. Patterson, *J. Org. Chem.* **1992**, *57*, 857; A. Raveh, S. Carmeli, *J. Nat. Prod.* **2007**, *70*, 196.
[8] a) H. Muratake, H. Kumagami, M. Natsume, *Tetrahedron* **1990**, *46*, 6351; b) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2004**, *126*, 7450; c) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2005**, *127*, 15394; d) S. E. Reisman, J. M. Ready, A. Hasuoka, C. J. Smith, J. L. Wood, *J. Am. Chem. Soc.* **2006**, *128*, 1448; e) J. M. Ready, S. E. Reisman, M. Hirata, M. M. Weiss, K. Tamaki, T. V. Osaka, J. L. Wood, *Angew. Chem.* **2004**, *116*, 1290–1292; *Angew. Chem. Int. Ed.* **2004**, *43*, 1270.
[9] Hoffmann noted the protection in situ of the ketone in the synthesis of precursor **8**, see reference [4].
[10] R. Robinson, *J. Chem. Soc.* **1917**, *111*, 762.
[11] D. H. R. Barton, A. M. Deflorin, O. E. Edwards, *J. Chem. Soc.* **1956**, 530.
[12] E. Hardegger, F. Lohse, *Helv. Chim. Acta* **1957**, *40*, 2383.

