ARTICLES

Total synthesis of marine natural products without using protecting groups

Phil S. Baran[1], Thomas J. Maimone[1] & Jeremy M. Richter[1]

The field of organic synthesis has made phenomenal advances in the past fifty years, yet chemists still struggle to design synthetic routes that will enable them to obtain sufficient quantities of complex molecules for biological and medical studies. Total synthesis is therefore increasingly focused on preparing natural products in the most efficient manner possible. Here we describe the preparative-scale, enantioselective, total syntheses of members of the hapalindole, fischerindole, welwitindolinone and ambiguine families, each constructed without the need for protecting groups—the use of such groups adds considerably to the cost and complexity of syntheses. As a consequence, molecules that have previously required twenty or more steps to synthesize racemically in milligram amounts can now be obtained as single enantiomers in significant quantities in ten steps or less. Through the extension of the general principles demonstrated here, it should be possible to access other complex molecular architectures without using protecting groups.

Although the field of total synthesis[1,2] has made great advances since 1828 (ref. 3), it is still far from being a mature or applied science[4,5]. For example, precise control over the individual reactivity of functional groups within a complex molecular architecture (chemoselectivity) still remains a largely unanswered challenge. Historically, the use of protecting groups has been the standard solution to this problem because they allow functional groups to be dealt with on an individual basis. Indeed, these functionality masks have permeated organic chemistry to the extent that textbooks state that avoiding them is impossible[6,7]. Their use has become routine even on molecules of low complexity[8]. Ideally, protecting groups are easily appended, allow one to smoothly perform the initially intended transformation, and then gracefully depart without incident. In practice, however, these artificial devices add at least two steps each to a synthetic sequence and sometimes dramatically lower the efficiency of a synthesis owing to unforeseen difficulties encountered during their removal or unintended side reactions initiated by their presence[9]. Ironically, their presence can lead to an additional layer of chemoselectivity considerations that often take centre stage within a complex total synthesis endeavour[8]. The multitude of complications imparted by protecting-group manipulations contributes to the perception that natural products, despite their overwhelming utility in medicine, are too complex to be synthesized efficiently in a drug discovery setting[10,11].

Figure 1 summarizes three different approaches to chemical synthesis using the complex natural product ambiguine H (**1**) as an example. In a biological setting, where the goal of synthesis is to create function rather than a specific target molecule, simple feedstock chemicals are woven together without protecting groups by using exquisitely selective enzymes[12]. For instance, it has been proposed that the key C–C bonds of the ambiguines are forged from an enzymatic enantioselective cation-olefin cyclization of a simple hydrocarbon with a 3-substituted indole[13]. Indeed, emulating nature (biomimetic synthesis) can sometimes lead to extremely efficient synthetic routes[1,2,14–16]. In contrast, a standard approach to synthesis uses strategic disconnections that are often made in order to shield perceived functional group incompatibilities *en route* to a specific target. Here we describe syntheses, the inspiration for which comes partly from studying the biosynthetic pathway, strictly avoid the use of protecting groups, and harness the natural reactivity of specific functional groups within a complex setting. This approach has led to solutions that would not have been apparent had the natural tendencies of the reactive centres been masked.

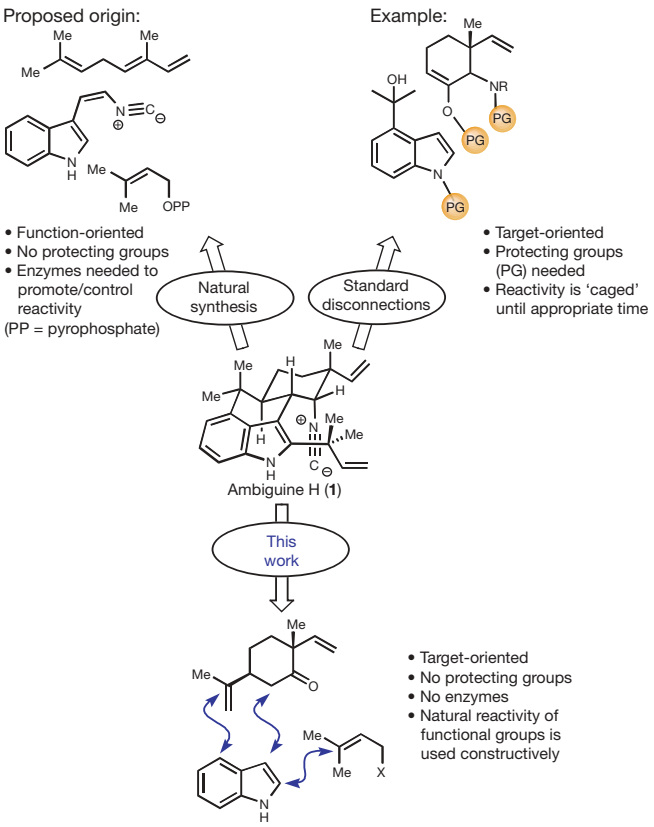

Figure 1 | Approaches to chemical synthesis. Here we show ambiguine H (**1**) as an example.

[1]Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, USA.

The Stigonemataceae family of cyanobacteria has produced a class of over 60 biogenetically related, architecturally complex, topologically unique, and functionally rich indole natural products that form the basis of the hapalindole[17,18], fischerindole[13], welwitindolinone[13], and ambiguine[19,20] alkaloids (Fig. 2). They exhibit a broad range of bioactivities including antifungal, antibacterial, antimycotic and anticancer properties, with some members having potencies comparable to clinical agents (streptomycin, puramycin and amphotericin)[13,17–20]. Further study of these potential medicinal agents is hampered by the fact that the cyanobacteria produce complex mixtures of these natural products in low yield. For instance, small quantities (about 5 mg) of **1**, **2**, **4** and **5** have been isolated in yields ranging from 0.00671% (for **2**) to 0.0213% (for **5**) following tedious purification and HPLC separation.

Total synthesis of hapalindole U (2) and ambiguine H (1)

Although there have been no published synthetic routes to the ambiguines, racemic hapalindole U (**2**, Fig. 2) has been constructed in 20 steps by a non-stereocontrolled sequence with multiple protecting groups[21]. Fig. 3 outlines a simple, enantioselective entry to the ambiguine alkaloid family, by way of **2**, facilitated by newly developed methodology for C–C bond formation and a deliberate effort to eliminate the use of protecting groups.

The synthesis commenced with readily available terpene **7**, which is synthesized in four steps by a route that closely parallels the strategy of ref. 22 (see Supplementary Information). The indole and terpene subunits were then merged without protecting groups using a direct indole coupling, a reaction that was invented specifically for forming this type of C–C bond[23]. This reaction has already been successfully employed in short syntheses of **3** and **6** (Fig. 2)[23] and furnished indole **8** as a single diastereomer in 61% isolated yield. An extensive screening of acids for the requisite site-selective (carbon C4) Friedel-Crafts annulation failed to furnish detectable quantities of **10**. Not surprisingly, cyclization at C2 rather than C4 of the indole was observed, along with decomposition. Rather than resorting to protecting groups to either shield the C2 position or as a means of tuning the electronic nature of the indole, a different strategy was pursued using an indole building block biased to react at the C4 position. The brominated indole **9** was therefore targeted as a potential precursor to **10** via a radical- or transition-metal-mediated cyclization. As a testament to the versatility of the direct indole coupling, 4-bromoindole merged with **7** reliably on a gram scale to produce **9** in 50% isolated yield. We note that this mode of C–C bond formation is orthogonal to other transition-metal-mediated processes in that coupling occurs selectively by C–H bond functionalization rather than by C–Br bond insertion. This reaction is reliant on the presence of a free N–H[24] and so we would not have discovered it had we resorted to protecting groups.

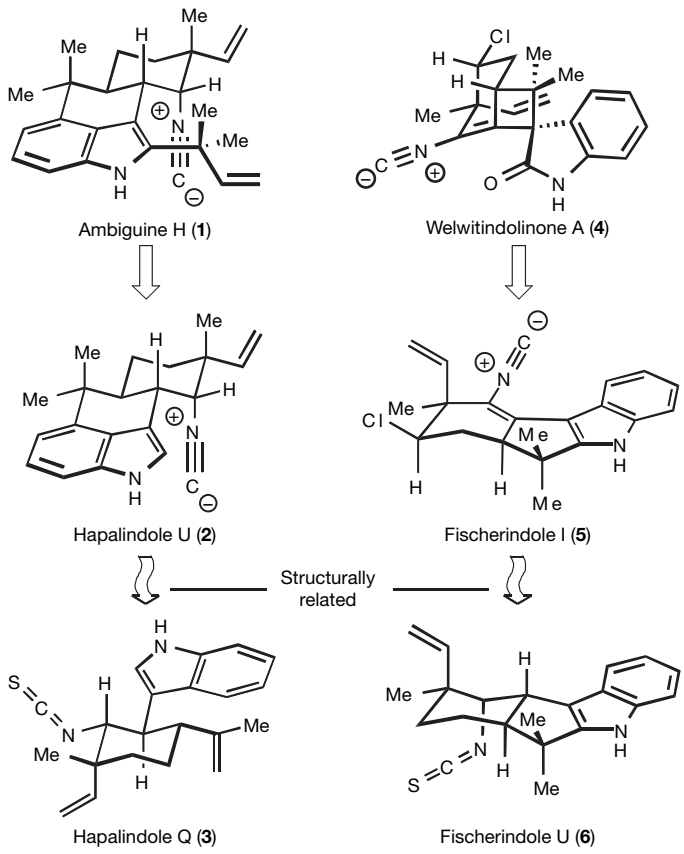

Figure 2 | Representative members of the ambiguine, fischerindole, hapalindole and welwitindolinone alkaloid families and proposed biosynthetic relationships.

To elicit the desired 6-*exo*-trig cyclization of **9** to **10**, radical- and palladium-mediated methods were explored. Although the former led mainly to the undesired 7-*endo*-trig and debrominated products, the reductive Heck[25] methods of Larock[26] and Grigg[27] showed some promise (18–39% isolated yield of **10** with significant amounts of **8**). Many conditions were screened to maximize the conversion of **9** to the annulation product **10** while suppressing the competing debromination pathway, leading to the formation of **8** as well as destruction of the catalyst in the highly reducing environment (see Supplementary Information for details). We discovered that the use of Herrmann's catalyst[28] as the Pd-source and its slow addition were necessary to reliably achieve a 65% isolated yield of **10**.

With the tetracyclic core of the ambiguines and hapalindoles in place, ketone **10** could be easily converted to hapalindole U (**2**) by stereocontrolled, microwave-assisted reductive amination, followed by formylation of the crude amine and dehydration of the resulting formamide. The overall isolated yield for the two-pot sequence was 60%. Synthetic **2**, prepared in four steps from ketone **7** (20% isolated yield, >1 g prepared), was spectroscopically identical to that reported by Moore[18] and was confirmed by X-ray crystallography: melting point 241 °C (decomposition, dec.), hexanes:Et_2O:MeOH, 10:5:1.

All that remained to bridge the gap between the hapalindole and ambiguine families (**2** → **1**) was the seemingly straightforward task of installing the *tert*-prenyl unit onto C2 of **2**. However, our attempts to achieve direct or indirect *tert*-prenylation onto **2**, as well as earlier intermediates, were unsuccessful owing to the incompatibility of the isonitrile with acids and transition metals, as well as the unusual reactivity of the indole nucleus within the tetracyclic ring system. For example, attempts to activate the indole for nucleophilic addition at carbon C2 (that is, C3 chloroindolenine formation) always led to either functionalization of C2 with the activating agent (via [1,2]-shift), attack at nitrogen N1 (with expulsion of the activating agent), or attack at the activating agent (returning starting material). On the basis of these empirical observations, and instead of resorting to protecting group chemistry to shield the fragile isonitrile and indole N–H, we devised a strategy to accommodate and exploit the natural reactivity of both functionalities.

Thus, exposure of **2** to *tert*-BuOCl, followed by prenyl 9-BBN, according to Danishefsky's protocol[29], produced the unusual crystalline pentacyclic chloroimidate **12** (structure confirmed by X-ray spectroscopy: melting point 244 °C (dec.), Et_2O). This product is presumably formed by a tandem sequence involving initial chlorination of the axial-configured isonitrile, nucleophilic attack of indole (C3), and addition of the prenyl reagent to the resulting imine **11**. The observed stereochemistry of the *tert*-prenyl unit at C2 probably stems from its addition to the less-hindered face of the folded architecture of imine **11**. The unorthodox nature of this transformation is consistent with the individual reactivity observed previously for the isonitrile and indole (see above). We reasoned that a Norrish-type cleavage[30] of the chloroimidate in **12** might initiate a fragmentation cascade to liberate the BBN functionality, the

extraneous chlorine atom, an unwanted C–C bond, and restore the indole and isocyanide moieties. Indeed, irradiation of **12** for five hours led to ambiguine H (**1**), accomplishing all five necessary tasks in a single step (63% yield based on recovered **12**). We suggest a mechanism for this transformation in Fig. 3. If the reactive functionalities of **2** were shielded with protecting groups, such chemical reactivity would not have been apparent (that is, the Norrish-like cleavage of a chloroimidate or the use of a sensitive isonitrile to assist in the activation of a free indole). Synthetic **1** exhibited identical spectroscopic data to that reported in ref. 20 and was confirmed by X-ray crystallography (melting point 228–231 °C (dec.), hexanes/Et_2O (1:1)), representing the first total synthesis of a member of the ambiguine natural product family. Because **1** is unstable on prolonged storage, we made gram quantities of **2** and converted it to **1** as needed; see Supplementary Information for details.

Total synthesis of welwitindolinone A (4) and fischerindole I (5)

The elimination of protecting groups and reduction of the number of steps in a total synthesis can also simplify the optimization of the overall yield of a sequence. Statistics dictate that because each step in a shorter sequence carries a greater impact on the overall efficiency of a synthesis, optimization is realized more rapidly than with the corresponding longer routes[31]. The recent total syntheses of fischerindole I (**4**) and welwitindolinone A (**5**)[32] are an illustration of this point. Although they represent some of the most complex natural products to be synthesized without protecting groups[8] and required only seven to eight chemical operations, their syntheses had overall yields of only 6.9% and 1.7%, respectively, from ketone **15** (Fig. 4). The synthesis also suffered from limited scalability owing to the technically demanding nature of the final two steps of the sequence. Figure 4 depicts revised syntheses of **4** and **5** that can be conducted on a much larger scale than that reported previously and in overall yields of 13.0% and 5.7%, respectively, from **15**—via optimization of individual steps, not an alteration in general strategy.

In five simple steps from carvone oxide[32], amine **17** is accessible in large quantities via the direct coupling of chloroketone **15** with indole (62% yield) followed by Friedel–Crafts cyclization and stereocontrolled reductive amination of **16** (see Supplementary Information for details). Amine **17** is then formylated, followed by immediate dehydration with phosgene to install the isonitrile functionality and furnish 11-*epi*-fischerindole G (**18**). In our previous route, **18** provided a scaffold on which to perform the requisite unsaturation to form **5** and an ensuing ring contraction to form **4**. We reasoned that the yield and selectivity problems in that route stemmed from the choice of a chlorine-based oxidant (*tert*-BuOCl) that was both inefficient and unselective. As shown in the synthesis of ambiguine H (see below), such oxidants react readily with isonitriles. To accomplish the conversion of **18** to **5**, an oxidant was chosen that was more suited to benzylic oxidations. By simply exposing **18** to DDQ[33] in the presence of water, fischerindole I (**5**) was produced in excellent overall yield (>2 g prepared), presumably through the intermediate α,β-unsaturated imine **19**. For the ensuing oxidative ring contraction, we reasoned that a hitherto-unknown fluorohydroxylation of indole rather than chlorohydroxylation should suppress isonitrile-derived side-product formation, owing to the increased hardness of fluorine over chlorine. A method for fluorohydroxylation of the indole moiety in **5** was developed using xenon difluoride[34] and water in acetonitrile, providing welwitindolinone A scaleably (>390 mg prepared), in 44% isolated yield, and as a single diastereomer. This cascade sequence can be envisioned to proceed through fluorination of the indole nucleus to give **20**, which is trapped with water to give **21**. Elimination of fluoride would give the azaorthoquinodimethane (**22**)[35], which undergoes a [1,5] sigmatropic rearrangement to furnish the spirocyclobutane of welwitindolinone A, as a single diastereomer. The observed chemoselectivity (in the presence of two other olefins and a reactive isonitrile) of this new reaction is worthy of further study. Because **4** and **5** are unstable on prolonged storage, gram quantities of **18** are made and converted to **4** and **5** as needed (see Supplementary

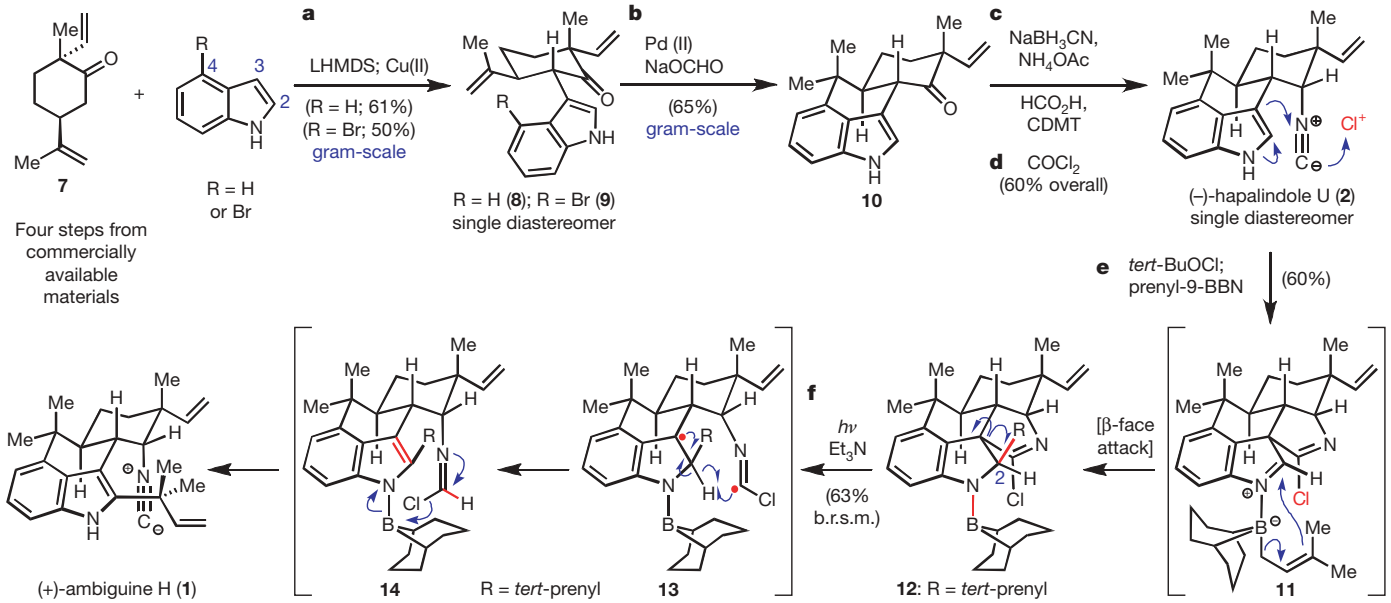

Figure 3 | Protecting-group-free synthesis of ambiguine H (1) and hapalindole U (2). Reagents and conditions as follows. **a**, Indole (1.9 equiv.), ketone **7** (1.0 equiv.), LHMDS (3.4 equiv.), Cu(II)-2-ethylhexanoate (1.5 equiv.), THF, starting temperature −78 °C, 5 min to 25 °C, yield is 61%; or 4-bromoindole (2.8 equiv.), ketone **7** (1.0 equiv.), LHMDS (4.4 equiv.), Cu(II)-2-ethylhexanoate (2.0 equiv.), THF, –78 °C, 5 min to 25 °C, 50%. **b**, $[Pd(P(o\text{-}tol)_3OAc]_2$ (0.05 equiv.), NaOCHO (1.25 equiv.), TBAB (2.0 equiv.), Et_3N (2.2 equiv.), DMF, 80 °C, slow addition of Pd over 5 h, 65%. **c**, NH_4OAc (40 equiv.), $NaCNBH_3$ (9.3 equiv.), MeOH/THF, microwave irradiation at 150 °C, 2.5 min; then HCO_2H (2.0 equiv.), CDMT (2.2 equiv.), DMAP (0.05 equiv.), NMM (2.2 equiv.), DCM, 2 h, 25 °C. **d**, $COCl_2$ (2.0 equiv.), Et_3N (17.5 equiv.), DCM, 0 °C, 60% over two steps. **e**, *tert*-BuOCl (1.15 equiv), DCM, –78 °C, 12 min; then prenyl-9-BBN (2.0 equiv), −78 °C, 30 min, 60%. **f**, Et_3N (5.0 equiv.), benzene, *hν*, 5 h, 63% b.r.s.m. (based on recovered starting material). LHMDS, lithium hexamethyldisilazide; THF, tetrahydrofuran; TBAB, *tetra-n*-butyl ammonium bromide; Et_3N, triethylamine; DMF, *N*,*N*-dimethylformamide; CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine; DMAP, 4-*N*-dimethylaminopyridine; NMM, *N*-methylmorpholine; DCM, dichloromethane; 9-BBN, 9-borabicyclo-nonane. For selected physical data for compounds **1**, **2**, **7**–**10** and **12**, see the Supplementary Information. Compounds **2**, **12** and **1** were verified by X-ray crystallography.

Information for details). The revised routes to **4** and **5** demonstrate how such mechanistically inspired reagent changes can greatly improve the overall efficiency of an extremely short synthesis. The only other reported total synthesis of **4** requires 25 steps and six protecting groups to deliver milligram quantities of racemic material[36].

Discussion

Taken together with the concepts of ''atom economy''[37] and ''step economy,''[38] we followed several general guidelines during the planning stage (retrosynthetic analysis)[39] of these syntheses: (1) redox reactions that do not form C–C bonds should be minimized[40], (2) the percentage of C–C bond-forming events within the total number of steps in a synthesis should be maximized[39,40], (3) disconnections should be made to maximize convergency[41], (4) the overall oxidation level of intermediates should linearly escalate during assembly of the molecular framework (except in cases where there is strategic benefit such as an asymmetric reduction)[42], (5) where possible, cascade (tandem) reactions should be designed and incorporated to elicit maximum structural change per step[43], (6) the innate reactivity of functional groups should be exploited so as to reduce the number of (or perhaps even eliminate) protecting groups[8,44], (7) effort should be spent on the invention of new methodology to facilitate the aforementioned criteria and to uncover new aspects of chemical reactivity[45], (8) if the target molecule is of natural origin, biomimetic pathways (either known or proposed) should be incorporated to the extent that they aid the above considerations[1,2,14–16,46]. Although these principles have existed conceptually and separately for several years[1,2,8,47], this series of total syntheses cohesively applies them as a whole.

Despite the demonstrated advantages, there are some limitations to deliberately excluding protecting groups from the synthesis of complex molecules. For instance, their inclusion within a synthetic plan may allow for a certain level of security, because perceived functional-group incompatibilities can be dealt with at the outset. Indeed, omitting protecting groups during the retrosynthetic planning stages of a complex molecule might involve a certain amount of risk and speculation, owing to the unpredictable reactivity that is inevitably encountered at the late stages of a total synthesis[48]. In some cases, the use of protecting groups may offer a more efficient or even the sole solution. For example, the total synthesis of certain classes of molecules, such as poly-ketides, -peptides, -saccharides, and -nucleotides, will perhaps always require some level of protection (not only owing to a lack of chemoselectivity but also the practical issues of purification and characterization).

In summary, representative members of a large class of natural products consisting of four different families have been constructed by adhering to the general principles outlined above. The enantioselective total syntheses of ambiguine H (**1**), hapalindole U (**2**), welwitindolinone A (**4**), and fischerindole I (**5**) require only seven to ten steps from commercially available materials and can easily be performed on a preparative scale using inexpensive reagents. Of those steps, approximately half involved C–C bond formation and aside from a stereoselective reductive amination, the oxidation states of intermediates gradually escalated from beginning to end. Certain aspects of these convergent syntheses also benefited from insights into their biosynthetic origins and the incorporation of designed cascade reactions. Finally, the deliberate exclusion of protecting groups from the overall synthetic design facilitated the development and discovery of new chemical reactions by harvesting the intrinsic reactivity within organic molecules.

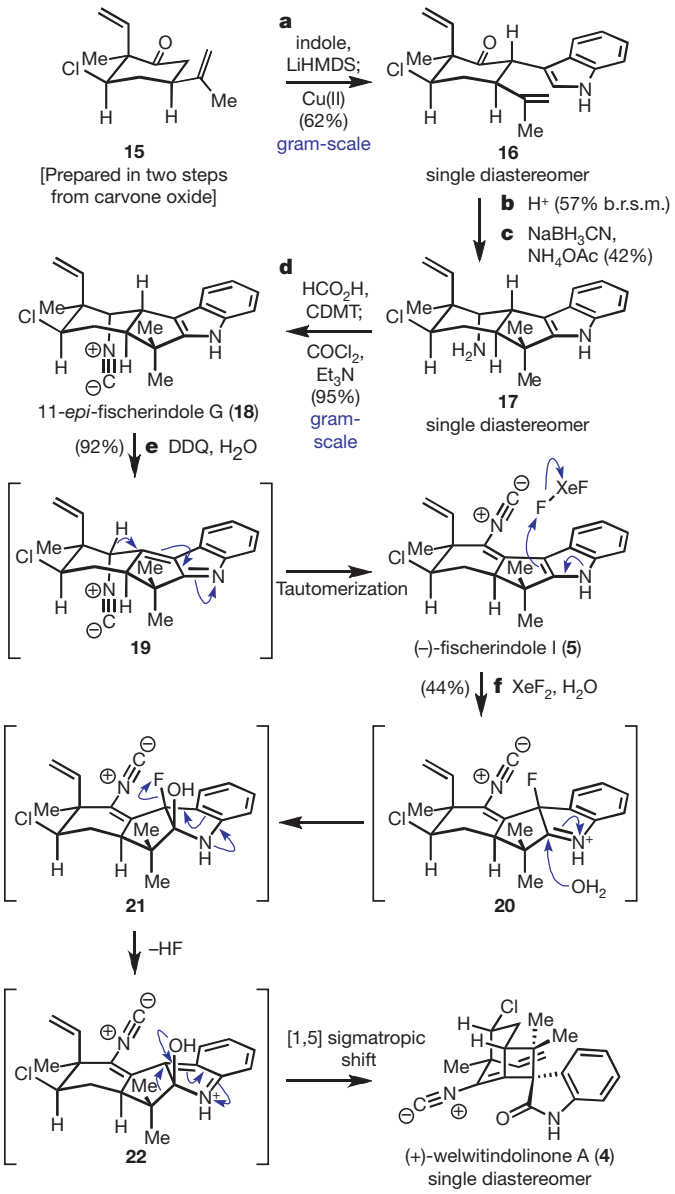

Figure 4 | Protecting-group-free total synthesis of fischerindole I (5) and welwitindolinone A (4). Reagents and conditions as follows. **a**, Indole (2.0 equiv.), LiHMDS (3.3 equiv.), THF, −78 °C, 30 min, copper(II)-2-ethylhexanoate (1.5 equiv.), −78 to 23 °C, 20 min, 62%. **b**, Montmorillonite K-10 clay, microwave irradiation at 120 °C, 6 min, 57% b.r.s.m. **c**, NH_4OAc (40 equiv.), $NaCNBH_3$ (7.5 equiv.), 3 Å molecular sieves, MeOH/THF, sonication, 18 h, 42%. **d**, HCO_2H (2.0 equiv.), CDMT (2.2 equiv.), DMAP (0.1 equiv.), NMM (2.2 equiv.), DCM, 23 °C, 30 min; Et_3N (17.5 equiv.), $COCl_2$ (2.0 equiv.), DCM, 0 °C, 10 min, 95%. **e**, DDQ (2.5 equiv.), H_2O, THF, 0 °C, 30 min, 92%. **f**, XeF_2, H_2O, MeCN, 23 °C, 5 min; 44%. DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; MeCN, acetonitrile. For selected physical data for compounds **18**, **5** and **4** see the Supplementary Information.

METHODS

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and spectroscopically homogenous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography. For full experimental details and procedures for all reactions performed and full characterization (^1H and ^{13}C nuclear magnetic resonance, high-resolution mass spectrometry, infrared, optical rotation, melting point, and R_f value) of all new compounds, see the Supplementary Information.

Received 11 October 2006; accepted 2 January 2007.

1. Nicolaou, K. C. & Sorensen, E. J. *Classics in Total Synthesis* (VCH, New York, 1996).
2. Nicolaou, K. C. & Snyder, S. A. *Classics in Total Synthesis II* (Wiley-VCH, Weinheim, 2003).
3. Wöhler, F. Ueber die Künstliche Bildung des Harnstoffe Poggendorfs. *Ann. Phys. Chem.* **12**, 253–256 (1828).
4. Service, R. F. Race for molecular summits. *Science* **285**, 184–187 (1999).

5. Seebach, D. Organic synthesis–where now? *Angew. Chem. Int. Edn Engl.* **29,** 1320–1367 (1990).
6. Kocienski, P. J. *Protecting Groups* 3rd edn (Thieme, New York, 2005).
7. Green, T. W. & Wuts, P. G. *Protective Groups in Organic Synthesis* 3rd edn (Wiley, Hoboken, 1999).
8. Hoffmann, R. W. Protecting group free synthesis. *Synthesis* 3531–3541 (2006).
9. Sierra, M. A. & de la Torre, M. C. *Dead Ends and Detours, Direct Ways to Successful Total Synthesis* (Wiley-VCH, Weinheim, 2004).
10. Butler, M. S. The role of natural product chemistry in drug discovery. *J. Nat. Prod.* **67,** 2141–2153 (2004).
11. Wilson, R. M. & Danishefsky, S. J. Small molecule natural products in the discovery of therapeutic agents: the synthesis connection. *J. Org. Chem.* **71,** 8329–8351 (2006).
12. Faber, K. *Biotransformations in Organic Chemistry* 3rd edn (Springer, New York, 1997).
13. Stratmann, K. *et al.* Welwitindolinones, unusual alkaloids from the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricate*. Relationship to fischerindoles and hapalindoles. *J. Am. Chem. Soc.* **116,** 9935–9942 (1994).
14. Scholz, U. & Winterfeldt, E. Biomimetic synthesis of alkaloids. *Nat. Prod. Rep.* **17,** 349–366 (2000).
15. Eschenmoser, A. Vitamin B_{12}: experiments concerning the origin of its molecular structure. *Angew. Chem. Int. Edn Engl.* **27,** 5–39 (1988).
16. Heathcock, C. H. The enchanting alkaloids of Yuzuriha. *Angew. Chem. Int. Edn Engl.* **31,** 665–681 (1992).
17. Moore, R. E., Cheuk, C. & Patterson, G. M. L. Hapalindoles: new alkaloids from the blue-green alga *Hapalosiphon fontinalis. J. Am. Chem. Soc.* **106,** 6456–6457 (1984).
18. Moore, R. E. *et al.* Hapalindoles, antibacterial and antimycotic alkaloids from the cyanophyte *Hapalosiphon fontinalis. J. Org. Chem.* **52,** 1036–1043 (1987).
19. Smitka, T. A. *et al.* Ambiguine isonitriles, fungicidal hapalindole-type alkaloids from three genera of blue-green algae belonging to the Stigonemataceae. *J. Org. Chem.* **57,** 857–861 (1992).
20. Raveh, A. & Carmeli, S. Antimicrobial ambiguines from the cyanobacterium *Fischerella* sp. collected in Israel. *J. Nat. Prod.* doi:10.1021/np060495r (in the press); published online 13 January 2007.
21. Muratake, H., Kumagami, H. & Natsume, M. Synthetic studies of marine alkaloids hapalindoles. Part 3. Total synthesis of (±)-hapalindoles H and U. *Tetrahedron* **46,** 6351–6360 (1990).
22. Mehta, G. & Acharyulu, P. V. R. Terpenes to terpenes. Stereo- and enantio-selective synthesis of (+)-α-elemene and a short route to a versatile diquinane chiron. *J. Chem. Soc. Chem. Commun.* 2759–2760 (1994).
23. Baran, P. S. & Richter, J. M. Direct coupling of indoles with carbonyl compounds: short, enantioselective, gram-scale synthetic entry into the hapalindole and fischerindole alkaloid families. *J. Am. Chem. Soc.* **126,** 7450–7451 (2004).
24. Baran, P. S., Richter, J. M. & Lin, D. W. Direct coupling of pyrroles with carbonyl compounds: short enantioselective synthesis of (*S*)-ketorolac. *Angew. Chem. Int. Edn Engl.* **44,** 609–612 (2005).
25. Nicolaou, K. C., Bulger, P. G. & Sarlah, D. Palladium-catalyzed cross-coupling reactions in total synthesis. *Angew. Chem. Int. Edn Engl.* **44,** 4442–4489 (2005).
26. Larock, R. C. & Babu, S. Synthesis of nitrogen heterocycles via palladium-catalyzed intramolecular cyclization. *Tetrahedr. Lett.* **28,** 5291–5294 (1987).
27. Burns, B. *et al.* Palladium catalysed tandem cyclisation-anion capture processes. Part 1: Background and hydride ion capture by alkyl- and π-allyl-palladium species. *Tetrahedr. Lett.* **29,** 4329–4332 (1988).
28. Herrmann, W. A. *et al.* Palladacycles as structurally defined catalysts for the Heck olefination of chloro- and bromoarenes. *Angew. Chem. Int. Edn Engl.* **34,** 1844–1848 (1995).
29. Schkeryantz, J. M., Woo, J. C. G., Siliphaivanth, P., Depew, K. M. & Danishefsky, S. J. Total synthesis of gypsetin, deoxybrevianamide E, brevianamide E, and tryprostatin B: Novel constructions of 2,3-disubstituted indoles. *J. Am. Chem. Soc.* **121,** 11964–11975 (1999).
30. Turro, N. J. *Modern Molecular Photochemistry* Ch. 13 (University Science Books, Sausalito, 1991).
31. Hudlicky, T. Design constraints in practical syntheses of complex molecules: current status, case studies with carbohydrates and alkaloids, and future perspectives. *Chem. Rev.* **96,** 3–30 (1996).
32. Baran, P. S. & Richter, J. M. Enantioselective total synthesis of welwitindolinone A and fischerindoles I and G. *J. Am. Chem. Soc.* **127,** 15394–15396 (2005).
33. Oikawa, Y. & Yonemitsu, O. Selective oxidation of the side chain at C–3 of indoles. *J. Org. Chem.* **42,** 1213–1216 (1977).
34. Shellhamer, D. F. *et al.* Reaction of xenon difluoride with indene in aqueous 1,2-dimethoxyethane and tetrahydrofuran. *J. Chem. Soc. Perkin Trans.* **II,** 401–403 (1991).
35. Baran, P. S. & Shenvi, R. A. Total synthesis of (±)-chartelline C. *J. Am. Chem. Soc.* **128,** 14028–14029 (2006).
36. Reisman, S. E., Ready, J. M., Hasuoka, A., Smith, C. J. & Wood, J. L. Total synthesis of (±)-welwitindolinone A isonitrile. *J. Am. Chem. Soc.* **128,** 1448–1449 (2006).
37. Trost, B. M. The atom economy—a search for synthetic efficiency. *Science* **254,** 1471–1477 (1991).
38. Wender, P. A. & Miller, B. L. in *Organic Synthesis: Theory and Applications* (ed. Hudlicky, T.) Vol. 2, 27–66 (JAI Press, Greenwich, Connecticut, 1993).
39. Corey, E. J. & Cheng, X.-M. *The Logic of Chemical Synthesis* (Wiley, New York, 1995).
40. Hendrickson, J. B. Systematic synthesis design. IV. Numerical codification of construction reactions. *J. Am. Chem. Soc.* **97,** 5784–5800 (1975).
41. Bertz, S. H. Convergence, molecular complexity, and synthetic analysis. *J. Am. Chem. Soc.* **104,** 5801–5803 (1982).
42. Evans, D. A. *Synthesis Design and the Oxidation State Issue* (Lecture at Scripps Research Institute, 12 February, 2004).
43. Nicolaou, K. C., Edmonds, D. J. & Bulger, P. G. Cascade reactions in total synthesis. *Angew. Chem. Int. Edn Engl.* **45,** 7134–7186 (2006).
44. Hoveyda, A. H., Evans, D. A. & Fu, G. C. Substrate-directable chemical reactions. *Chem. Rev.* **93,** 1307–1370 (1993).
45. Wender, P. A. (ed.) Frontiers in Organic Synthesis. *Chem. Rev.* **96** (special issue), 1–600 (1996).
46. Vanderwal, C. D., Vosburg, D. A., Weiler, S. & Sorensen, E. J. An enantioselective synthesis of FR182877 provides a chemical rationalization of its structure and affords multigram quantities of its direct precursor. *J. Am. Chem. Soc.* **125,** 5393–5407 (2003).
47. Nicolaou, K. C. & Snyder, S. A. The essence of total synthesis. *Proc. Natl Acad. Sci. USA* **101,** 11929–11936 (2004).
48. Dörwald, F. Z. *Side Reactions in Organic Synthesis* (Wiley-VCH, Weinheim, 2005).

Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

Acknowledgements We are grateful to M. R. Ghadiri for discussions and comments on the manuscript, P. Mariano for his comments on the mechanism of photocleavage, and B. Whitefield for his technical contributions. We thank S. Carmeli for a sample of natural ambiguine H (**1**). We also thank D.-H. Huang and L. Pasternack for NMR spectroscopic assistance, and G. Siuzdak and R. Chadha for mass spectrometric and X-ray crystallographic assistance, respectively. We also thank Biotage for a generous donation of process vials used extensively throughout these studies. Financial support for this work was provided by The Scripps Research Institute, Amgen, AstraZeneca, the Beckman Foundation, Bristol-Myers Squibb, DuPont, Eli Lilly, GlaxoSmithKline, Pfizer, Roche, the Searle Scholarship Fund, the Sloan Foundation, NSF (predoctoral fellowship to J.M.R.) and the NIH.

Author Information The X-ray crystallographic coordinates for the structures of compounds **1** (CCDC # 623052), **2** (CCDC # 623050), and **12** (CCDC # 623051) were deposited with the Cambridge Crystallographic Data Center. These data can be obtained free of charge at www.ccdc.cam.ac.uk/retrieving.html. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to P.S.B. (pbaran@scripps.edu).