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# Enantioselective Total Syntheses of Welwitindolinone A and Fischerindoles I and G

Phil S. Baran* and Jeremy M. Richter

*Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037*

Received September 8, 2005; E-mail: pbaran@scripps.edu

Moore and co-workers' discovery of the hapalindole, fischerindole, ambiguine, and welwitindolinone indole alkaloids from marine blue−green algae launched an exciting new chapter in natural products chemistry.[1] Missions aimed at their total syntheses are inspired by their array of promising bioactivities and unprecedented molecular architectures.[2] Welwitindolinone A (**1**, Figure 1) is a densely functionalized oxindole harboring three all-carbon quaternary centers, a neopentyl chlorine atom, and a striking spiro-fused cyclobutane that, upon cursory inspection, appears too strained to exist. Fischerindoles I (**2**) and G (**3**, Figure 1) represent the apex of molecular complexity within the fischerindole alkaloid class.[1] To date, no chlorinated members of the fischerindole alkaloid class have been prepared by total synthesis nor has any member of the welwitindolinones.[2,3a] This Communication describes enantioselective, protecting-group-free syntheses of **1**, **2**, and **3** in nine or fewer steps driven by a unique perspective on their biogenetic relationships and the development of powerfully simplifying transformations.

As illustrated in Figure 1, Moore and co-workers hypothesized[1] that **1** might arise from an unusual cationic cyclization of the hypothetical intermediate **4**. Unless there is enzymatic intervention, this transformation seems unlikely to occur based on thermodynamic considerations. In addition, despite the dozens of natural products isolated in this family, none contain architecture similar to the putative intermediate **4**. The planned synthesis of **1** was based on our proposition that **2** is the actual precursor to **1** by an oxidative ring contraction[4] despite the fact that such ring contractions to form four-membered carbocyclic rings are rare and, if successful, proceed under harsh conditions.[5,6] In principle, fischerindole I (**2**) could arise by dehydrogenation of the cyclohexane ring of fischerindole G (**3**) by way of indole oxidation followed by selective tautomerization to the $\Delta^{10,11}$ alkene isomer. The latter alkaloid should be accessible from **5** by a Friedel−Crafts alkylation and simple functional group manipulations. In turn, the union of chloroketone **6** and indole could lead to **5** in short order by the direct indole coupling recently developed in this lab.[3] The successful implementation of this plan is outlined in detail below.

It was clear from the outset that the C-12 (fischerindole numbering[1]) quaternary center with adjacent chlorine atom at C-13 would pose significant difficulties (Scheme 1). Indeed, the installation of such hindered chlorine atoms has historically been a great challenge.[7] After a multitude of strategies were evaluated, a simple solution emerged as detailed in Scheme 1. Enolization of (*R*)-carvone oxide with LiHMDS followed by addition of vinylmagnesium bromide furnished neopentyl alcohol **7** as a single isomer in 30% isolated yield.[8] In accord with Wender's studies,[8] the major byproduct of this reaction was derived from attack at the enolate-bearing carbon (C-10) via an $S_N2'$ pathway. To the best of our knowledge, this is the first example of such a reaction installing an all-carbon quaternary center. Chlorination using NCS/$Ph_3P$ provided key chloroketone **6** in 55% yield. Despite the modest overall yield of this two-step sequence, it can be used to easily prepare multigram quantities of **6** within 1 day. By comparison,

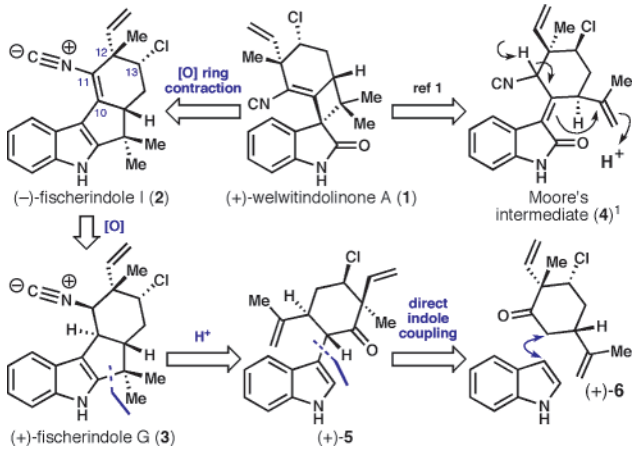



***Figure 1.*** Retrosynthetic analysis of welwitindolinone A (**1**) and fischerindoles I (**2**) and G (**3**).

the C-12 epimer of **6** was previously prepared from (*R*)-carvone oxide by a 10-step sequence in 10% overall yield.[9]

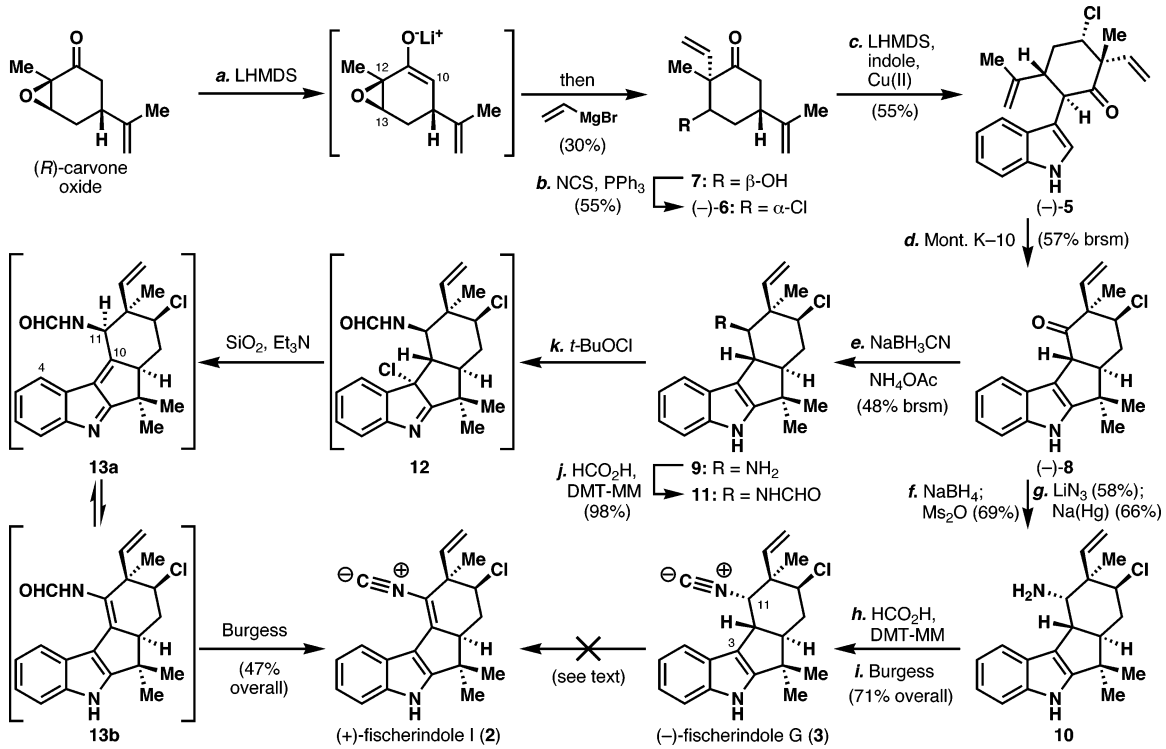
The crucial coupling of **6** with indole proceeded smoothly to furnish **5** in 55% isolated yield as a single diastereomer (colorless needles, mp 169−170 °C) despite the presence of an elimination-prone chlorine atom.[3] This effective method for direct C−C bond formation between $sp^2$ and $sp^3$ centers enables all the necessary carbon atoms of these complex natural products (**1**−**3**) to be procured in only three steps. Functional group manipulations are all that remained to complete the synthesis. Notably, this reaction was routinely carried out on a multigram scale. The stereochemical course of this reaction, and those preceding it, was verified by X-ray crystallographic analysis (Figure 2).

The observed reactivity of **5** and later intermediates differed significantly to that observed in the des-chloro fischerindole series.[3a] Several acid catalysts (see Supporting Information for a list) screened to elicit Friedel−Crafts cyclization of **5** to **8** routinely furnished ca. 20% isolated yield of **8** along with a number of side products (no recovered **5**). The use of Montmorillonite K-10 (DCE, 120 °C, microwave, 6 min) finally provided a workable solution, furnishing **8** in 40% isolated yield (57% brsm) after a single recycling of recovered starting material.[10] Attempted cyclizations of the amine or alcohol derived from ketone **5** were unsuccessful. Reductive amination[11] of **8** proceeded with complete diastereoselectivity (axial delivery) in the opposite sense[11,3a] to that obtained previously in systems lacking the C-13 chlorine atom to produce amine **9** in 26% isolated yield (48% brsm). Since the stereochemical outcome of the reduction prevented access to **3**, the reduction was left unoptimized and an alternative path was charted to access the correct amine (**10**, Scheme 1). Thus, ketone **8** was converted to amine **10** by following a sequence similar to that developed by Fukuyama:[9] (1) reduction from the α-face using $NaBH_4$, (2) mesylation using $Ms_2O$ in pyridine (69% over two steps), (3) displacement with $LiN_3$ (58% yield), and (4) reduction of the resulting azide using sodium−



**10.1021/ja056171r CCC: $30.25** 

***Scheme 1.*** Short, Enantioselective Total Syntheses of (+)-**2** and (−)-**3**[a]




[a] Reagents and conditions: (a) LHMDS (1.2 equiv), THF, − 78 °C, 30 min; −15 °C, $CH_2CHMgBr$ (2.0 equiv), 15 min, 30%; (b) THF, $PPh_3$ (1.0 equiv), NCS (1.0 equiv), 18 h, 55%; (c) indole (2.0 equiv), LHMDS (3.1 equiv), THF, −78 °C, 30 min, then Cu(II)2-ethylhexanoate (1.5 equiv), −78 to 23 °C, 15 min, 55%; (d) DCE, Montmorillonite K-10 clay (10 equiv), microwave irradiation, 120 °C, 6 min, filter, then repeat, 40% + 30% recovered **5**; (e) THF, MeOH, $NaCNBH_3$ (10 equiv), $NH_4OAc$ (40 equiv), 7 days, 26% **9** + 46% **8**; (f) MeOH, $NaBH_4$ (1.5 equiv), 0 °C, 5 min; then $Ms_2O$ (2.0 equiv), py, 23 °C, 30 min, 69% overall; (g) DMF, $LiN_3$ (3.0 equiv), 120 °C, 48 h; then EtOH, Na(Hg) (10 equiv), reflux, 4 h, 38% overall; (h) $HCO_2H$ (1.3 equiv), CDMT (1.4 equiv), DMAP (cat.), NMM (1.4 equiv), $CH_2Cl_2$, 23 °C, 30 min, 87%; (i) PhH, Burgess reagent (2.0 equiv), 23 °C, 30 min, 82%; (j) same as (h), 98%; (k) THF, TEA (1.0 equiv), *t*-BuOCl (1.5 equiv), 0 °C, 10 min, then $SiO_2/Et_3N$ (PTLC), then PhH, Burgess reagent (2.0 equiv), 23 °C, 30 min, 47% overall. CDMT = 2-Chloro-4,6-dimethoxy-1,3,5-triazine; DCE = 1,2-dichloroethane; DMF = *N*,*N*-dimethylformamide; DMAP = 4-(dimethylamino)pyridine; IBX = *o*-iodoxybenzoic acid; LHMDS = lithium hexamethyldisilazide; Ms = methanesulfonyl; NCS = *N*-chlorosuccinimide; NMM = *N*-methylmorpholine.

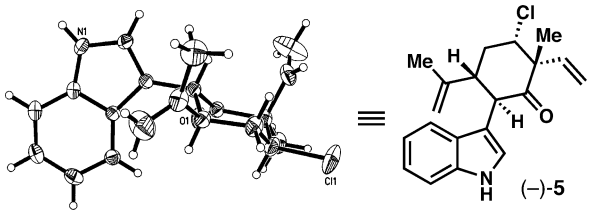



***Figure 2.*** X-ray crystal structure of **5**.

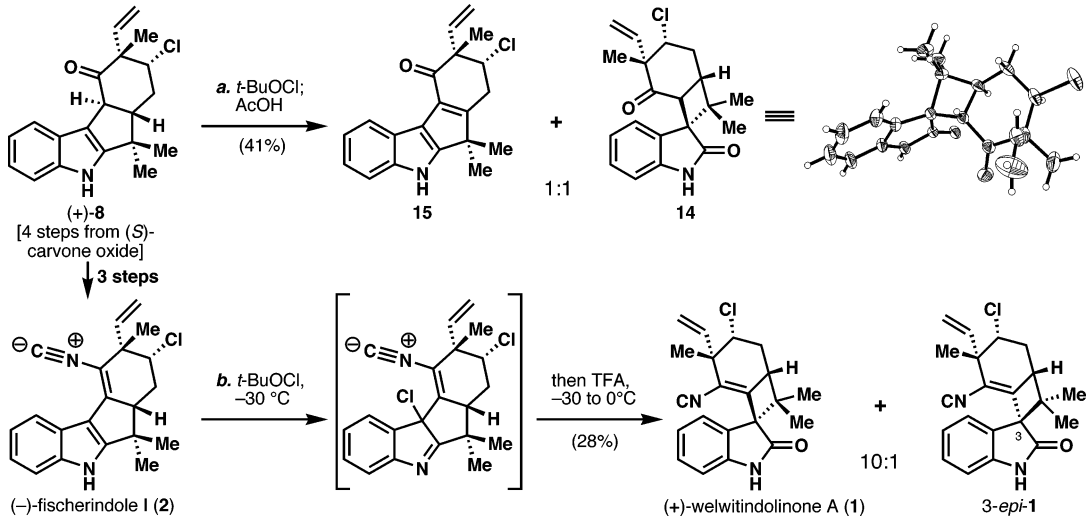
mercury amalgam (66% yield). Amine **10** was then formylated with formic acid/DMT-MM[12] and dehydrated using the Burgess reagent[13] to provide **3** in 71% yield over two steps. Synthetic (−)-**3** was spectroscopically identical to that reported with the exception of optical rotation [$[\alpha]_D$ −50 ($CH_2Cl_2$, *c* 0.02), nat. $[\alpha]_D$ +67 ($CH_2Cl_2$, *c* 0.09)]. In principle, the naturally occurring enantiomer of **3** could be prepared from (*S*)-carvone oxide (vide infra).

Despite a number of attempts, **3** and its formamide precursor could not be oxidized to **2** by either direct or indirect means. Exposure to various agents, such as DDQ, *p*-chloroanil, $MnO_2$, Pd/C, and IBX, led only to recovered starting material or decomposition as judged by TLC and $^1$H NMR. Treatment of **3** or the corresponding formamide with DMDO or *t*-BuOCl led to stable C(3)−OH or −Cl species, respectively, that were resistant to elimination/dehydration under a range of conditions. Electrophilic attack from the top face of **3**, away from the C-11 nitrogen functionality, would explain these failures since a difficult *syn* elimination would be required.

Attention was therefore returned to amine **9** in the hope that electrophilic attack would occur from the opposite face. Formylation[12] of amine **9** with DMT-MM/formic acid furnished **11** in 98% yield. Remarkably, **2** was produced in 47% overall yield when **11** was treated with *t*-BuOCl and $Et_3N$ at 0 °C followed by treatment with deactivated ($Et_3N$) silica gel and then exposure to the Burgess reagent. Synthetic (+)-**2** ($[\alpha]_D$ +24.4 ($CH_2Cl_2$, *c* 0.09), nat. value not given[1]) was spectroscopically identical to that reported. This compelling transformation likely occurs through 3-chloroindolenine **12**,[14] elimination to methyleneindolenine **13a**, tautomerization to **13b**, and dehydration to **2**. Dehydration of **13a** followed by tautomerization to **2** cannot be ruled out. The intermediate formamide **13a/b** could be isolated; however, it was unstable and therefore difficult to characterize. On the basis of the foregoing results and the stereochemical diversity present in this family of natural products, we propose that 11-*epi*-fischerindole G (not yet isolated) might be the actual biogenetic precursor to **2**.

With chemistry in place to access (+)-**2**, the *S* enantiomer of carvone oxide was employed to construct (−)-**2** ($[\alpha]_D$ −14.0 ($CH_2Cl_2$, *c* 0.05) in preparation for its conversion to (+)-**1** (absolute configuration not rigorously established by Moore[1]), as shown in Scheme 2. Although the proposed conversion of **2** to **1** might appear intuitive, practical difficulties were expected due to the sensitivity of both alkaloids to acidic media and the sheer ring strain of the resulting product. Our concerns were intensified by the knowledge that oxidative ring contractions to generate five- and six-membered rings typically require elevated temperatures, and hence, forming a strained four-membered ring should be even more difficult.[4] Preliminary studies on ketone (+)-**8** were conducted in order to determine the feasibility of the ring contraction. Thus, intermediate

***Scheme 2.*** Short, Enantioselective Total Syntheses of (+)-**1** and (−)-**2**[a]




[a] Reagents and conditions: (a) THF, TEA (1.0 equiv), *t*-BuOCl (1.7 equiv), 0 °C, 10 min; then 40:20:1 MeOH:$H_2O$:AcOH, 5 min, 41%, 1:1 mixture of **14** and **15**; (b) THF, TEA (1.0 equiv), *t*-BuOCl (1.5 equiv), −30 °C, 1 min; then 95:4:1 THF:$H_2O$:TFA, −30 to 0 °C, 5 min, 28%, 10:1 mixture of **1** and 3-*epi*-**1**. TFA = trifluoroacetic acid.

(+)-**8** was treated with *t*-BuOCl followed by dilute acid (gently heated in order to dissolve the substrate) to furnish spirooxindole **14** and enone **15** as a 1:1 mixture in 41% yield (unoptimized). The stereochemistry of **14** (colorless needles, mp 197−198 °C) was verified by X-ray crystallographic analysis (Scheme 2). Given the aforementioned considerations, it is remarkable that this reaction occurs at low temperature and within minutes. Although ketone **14** represents a potentially viable intermediate to complete the synthesis of **1**, attention was returned to fischerindole I in the hope that it could be directly converted to **1**. After much exploration, conditions were developed for the conversion of (−)-**2** to (+)-**1**. Exposure of (−)-**2** to 1.5 equiv of freshly prepared *t*-BuOCl in THF at −30 °C for 1 min followed by removal of solvent in vacuo, immediate dissolution in THF/$H_2O$/TFA (95:4:1),[15] and warming to 0 °C led to a 10:1 mixture of (+)-**1** and 3-*epi*-**1** (tentatively assigned) in 28% yield (unoptimized). Synthetic (+)-**1** was spectroscopically identical to that reported [$[\alpha]_D$ +160 ($CH_2Cl_2$, *c* 0.02), nat. $[\alpha]_D$ + 377 ($CH_2Cl_2$, *c* 0.078)], thus confirming its unusual structure and absolute configuration. The remarkable ease with which this ring contraction takes place suggests that Nature may be employing a similar strategy to access **1**.

Aside from the brevity (seven, eight, and nine steps to **2**, **1**, and **3**, respectively, from carvone oxide) and stereochemical control of the current syntheses, there are a number of prominent features: (a) application of the powerfully simplifying direct carbonyl−indole coupling reaction (**6** → **5**);[3] (b) two-step construction of the challenging quaternary center and adjacent chlorine atom common to this family of natural products from carvone oxide; (c) a position-selective tandem dehydrogenation/dehydration sequence (**11** → **2**); (d) an exceedingly facile oxidative ring contraction (**2** → **1**); (e) experimental evidence for an alternative biogenetic hypothesis for this family of alkaloids; and (f) absence of protecting groups and excessive oxidation state manipulations.

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**Supporting Information Available:** Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935−9942.
(2) Studies toward the welwitindolinones: (a) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326−6327. (b) Holubec, A. A. Ph.D. Thesis, Yale University, 2000. (c) Weiss, M. M. Ph.D. Thesis, Yale University, 2001. (d) Deng, H. Ph.D. Thesis, University of California, Santa Cruz, 2001. (e) Huang, S.-T. Ph.D. Thesis, Brandeis University, 2001. (f) Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001−3004. (g) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835−6838. (h) Alvarado, P. L.; García-Granda, S.; Álvarez-Rúa, C.; Avendaño, C. *Eur. J. Org. Chem.* **2002**, 1702−1707. (i) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1270−1272. (j) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421−3424. (k) Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, *7*, 4087−4089.
(3) (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450−7451. (b) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609−612.
(4) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1953**, *75*, 2572−2576.
(5) For the sole example of spirocyclobutane formation, see: Wenkert, E.; Moeller, P. D. R.; Piettre, S. R.; McPhail, A. T. *J. Org. Chem.* **1987**, *52*, 3404−3409.
(6) For a mechanistically related oxidative ring contraction that furnishes a strained $\beta$-lactam, see: Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714−3717.
(7) For example, see: (a) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4173−4182. (b) Albone, K. S.; Macmillan, J.; Pitt, A. R.; Willis, C. L. *Tetrahedron* **1986**, *42*, 3203−3214.
(8) (a) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114−2116. (b) Erhardt, J. M. Ph.D. Thesis, Harvard University, 1982.
(9) Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125−3126.
(10) Smyth, T. P.; Corby, B. W. *Org. Proc. Res. Dev.* **1997**, *1*, 264−267 and references therein.
(11) Vaillancourt, V.; Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499−3502.
(12) 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride: De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett* **2004**, *14*, 2570−2572.
(13) Creedon, S. M.; Crowley, H. K.; McCarthy, D. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1015−1017.
(14) The stereochemistry of the C-3 chlorine is inferred, as shown in Scheme 1, but has not been confirmed.
(15) Cushing, T. D.; Sanz-Cervera J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557−579.

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