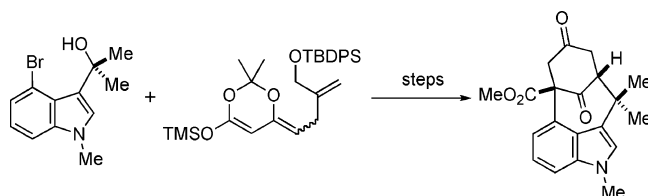


Approaches to *N*-Methylwelwitindolinone
C Isothiocyanate: Facile Synthesis of
the Tetracyclic CoreRichard W. Heidebrecht, Jr.,[†] Brian Gullledge,[§] and Stephen F. Martin^{*,§}Department of Chemistry and Biochemistry, The University of Texas at Austin,
Austin, Texas 78712

sfmartin@mail.utexas.edu

Received March 18, 2010

ABSTRACT



The synthesis of a functionalized, tetracyclic core of *N*-methylwelwitindolinone C isothiocyanate is reported. The approach features a convergent coupling between an indole iminium ion and a highly functionalized vinylogous silyl ketene acetal followed by an intramolecular palladium-catalyzed cyclization that proceeds via an enolate arylation.

A series of novel indole alkaloids were isolated in 1994 by Moore and co-workers from the extracts of blue-green cyanobacteria *Hapalosiphon wetwitschii* and *Westiella intracta*.¹ These compounds, which were collectively named welwitindolinones, possess a unique skeletal framework and were isolated along with the structurally related fischerindoles and hapalindoles. A putative biogenetic relationship among these alkaloids has been proposed.¹ These natural products exhibit diverse biological activities, perhaps the most exciting of which is the ability of some to reverse multiple drug resistance (MDR) during chemotherapeutic treatment of cancer.²

As a result of their novel structures and exciting biological activities, the various welwitindolinones have captured the attention of many groups, whose efforts have been chronicled in a number of accounts.³ Noteworthy are the elegant syntheses of welwitindolinone A isonitrile (**1**) independently

reported by Baran⁴ and Wood⁵ and of welwitindolinone A isothiocyanate (**2**) by Baran (Figure 1).⁶ Another important

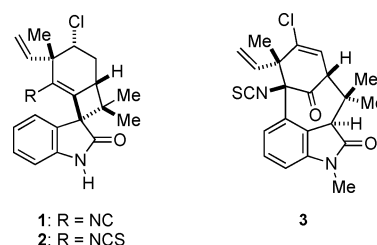


Figure 1. Structures of welwitindolinone A isocyanate (**1**), welwitindolinone A isothiocyanate (**2**), and *N*-methylwelwitindolinone C isothiocyanate (**3**).

member of this family is *N*-methylwelwitindolinone C isothiocyanate (**3**). Numerous efforts directed toward the synthesis of this challenging target have not yet reached fruition,⁷ but the tetracyclic core has been prepared by several groups.^{7b,g-k,m-o} We now report the details of some of our work in the area.

[†] The Broad Institute, 7 Cambridge Center, Cambridge, MA 02142.

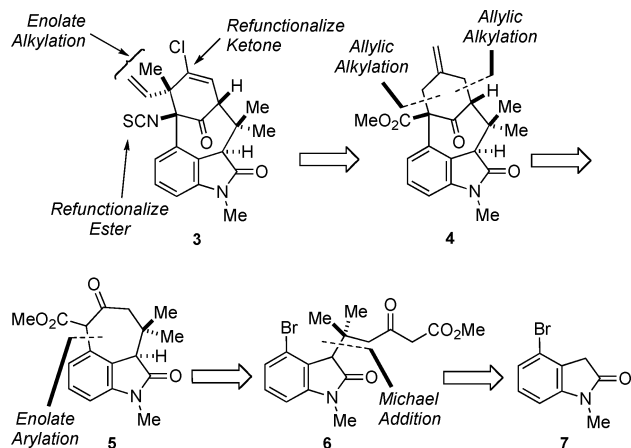
[§] The University of Texas at Austin.

(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) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241–247.

Our initial approach to *N*-methylwelwitindolinone C isothiocyanate (**3**) is outlined in retrosynthetic format in Scheme 1. We envisioned that the late-stage intermediate

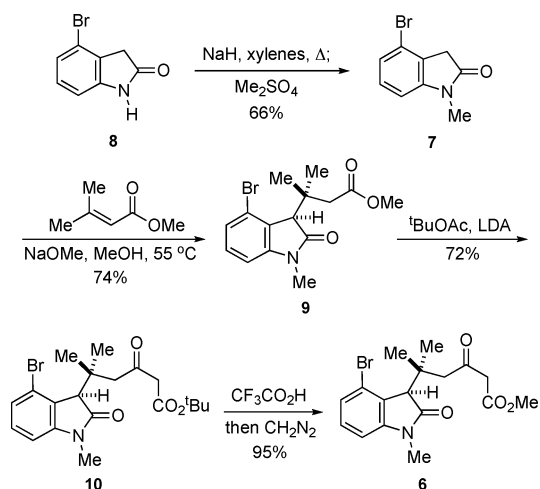
Scheme 1. Initial Retrosynthetic Proposal



4, which might be elaborated into **3** by a series of refunctionalizations and alkylations, might be accessible via a novel double allylic alkylation of the tricyclic ketoester **5**. The synthesis of **5** would then involve the cyclization of **6** via an enolate arylation, and compound **6** might be readily prepared by a Michael addition of *N*-methyl-4-bromooxindole (**7**).

In the event, 4-bromooxindole (**8**), prepared via a known procedure,⁸ was selectively *N*-methylated using a method developed by Bordwell (Scheme 2).⁹ Warming oxindole **7**

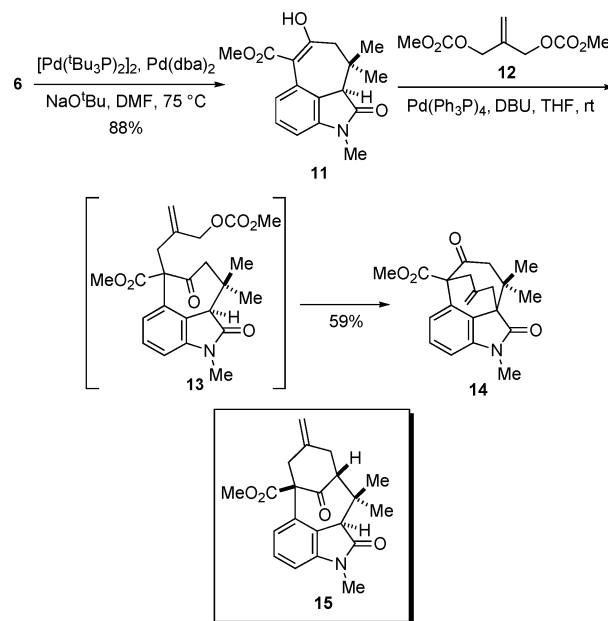
Scheme 2. Preparation of Ketoester **6**



in degassed sodium methoxide in methanol with excess methyl 3-methylcrotonate provided the adduct **9** in 74% yield. It was essential to rigorously exclude air in order to avoid extensive formation of the corresponding isatin deriva-

tive. The crossed Claisen condensation of **9** with the enolate of *tert*-butyl acetate afforded ketoester **10**. Because the *tert*-butyl ketoester group was prone to decarboxylation in subsequent reactions, it was converted to the methyl ester **6**. The overall yield of **6** from **9** via this two-step procedure was superior to that obtained using methyl acetate in the crossed Claisen condensation with **9**.

Scheme 3. Attempted Preparation of Tetracycle **15**



The next stage of the synthesis required the palladium-catalyzed cyclization of the enolate of the ketoester **6** (Scheme 3). Although use of bis-*tert*-butyl-2-biphenylphosphine as a ligand¹⁰ provided the cyclized β -keto ester, which existed in its enol form **11**, in 58% yield, significant amounts of unreacted **6** were invariably recovered; the structure of **11** was established by X-ray crystallography. On the other hand, use of a combination of commercially available tri-*tert*-butylphosphine palladium dimer¹¹ and either palladium bis-dibenzylideneacetone or chlorobisallylpalladium dimer in a ratio of 2:1 as suggested by Fu¹² gave the enol **11** in 88% yield. These reactions are sensitive to the presence of oxygen, and the best results were obtained with a freeze–pump–thaw protocol.

The synthetic plan then anticipated the conversion of **11** into the tetracyclic intermediate **15** via a palladium-catalyzed

(3) Reviews: (a) Avendanó, C.; Menéndez, J. C. *Curr. Org. Synth.* **2004**, *1*, 65–82. (b) Menendez, J. C. *Top. Heterocycl. Chem.* **2007**, *11*, 63–101. (c) Brown, L. E.; Konopelski, J. P. *Org. Prep. Proced. Int.* **2008**, *40*, 411–445.

(4) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394–15396.

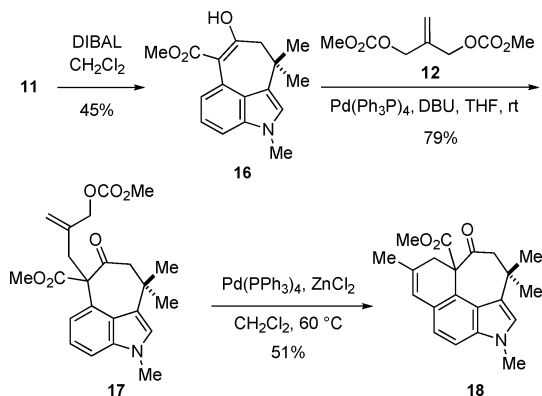
(5) (a) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448–1449. (b) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 2087–2100.

(6) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938–17954.

double allylic alkylation using the known bis-allylic carbonate **12**. However, when **11** was allowed to react with **12** in the presence of base and a number of Pd(0) catalysts, none of the desired **15** was obtained. Somewhat surprisingly, **14** was the only product isolated.¹³ This alternate mode of cyclization is presumably the consequence of the more acidic proton on the oxindole ring. A change of strategy that would obviate this deleterious cyclization was thus warranted.

Reasoning that the undesired cyclization mode would not be accessible to the indole analogue of **13**, **11** was transformed into **16**, which like **11** existed in its enolic form as confirmed via X-ray crystallography, in modest yield by reduction and dehydration (Scheme 4). Palladium-catalyzed alkylation of

Scheme 4. Attempted Preparation of an Indolic Tetracycle



16 with **12** afforded allylic carbonate **17**; however, all attempts using various bases to enolize the ketone function in **17** under the reaction conditions were unsuccessful.

(7) (a) Konopelski, J. P.; Deng, H.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105–1107. (b) 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. (c) Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001–3004. (d) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835–6838. (e) López-Alvarado, P.; García-Granda, S.; Álvarez-Rúa, C.; Avendaño, C. *Eur. J. Org. Chem.* **2002**, 1702–1707. (f) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. O.; Wood, J. L. *Ang. Chem. Int. Ed.* **2004**, *43*, 1270–1272. (g) MacKay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421–3424. (h) Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, *7*, 4087–4089. (i) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643–2645. (j) Lauchli, R.; Shea, K. J. *Org. Lett.* **2006**, *8*, 5287–5289. (k) Boissel, V.; Simpkins, N. S.; Bhalay, G. *Tetrahedron Lett.* **2009**, *50*, 3283–3286. (l) Boissel, V.; Simpkins, N. S. *Chem. Commun.* **2009**, 1398–1400. (m) Tian, X.; Hutters, A. D.; Douglas, C. J.; Garg, N. K. *Org. Lett.* **2009**, *11*, 2349–2351. (n) Trost, B. M.; McDougall, P. J. *Org. Lett.* **2009**, *11*, 3782–3785. (o) Brailsford, J. A.; Lauchli, R.; Shea, K. J. *Org. Lett.* **2009**, *11*, 5330–5333.

(8) Kosuge, T.; Ishida, H.; Inaba, A.; Nukaya, H. *Chem. Pharm. Bull.* **1985**, *33*, 1414–1418.

(9) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223.

(10) Fox, J. M.; Huang, S.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.

(11) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478.

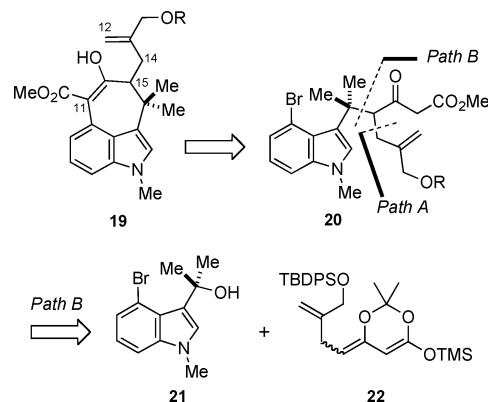
(12) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.

(13) The conversion of enol **11** into **14** under similar conditions has been previously reported. Holubec, A. A. Ph.D. Dissertation, 2000, Yale University. We thank a reviewer for calling this reference to our attention.

Interestingly, when **17** was treated with ZnCl₂ in the presence of a Pd(0) catalyst, **18** was formed in 51% yield.¹⁴ When this reaction was performed in the absence of the palladium catalyst, **18** was again isolated, albeit in only 28% yield.

Because the problem we encountered involved forming the C(14)–C(15) bond *after* forming the C(11)–C(12) bond, it occurred to us that reversing the order of these two bond constructions might be a viable alternative. This revised approach then dictated the intermediacy of a substrate such as **19**, which could be formed by cyclization of the β -keto ester **20** (Scheme 5). Our first attempts to prepare **20** involved

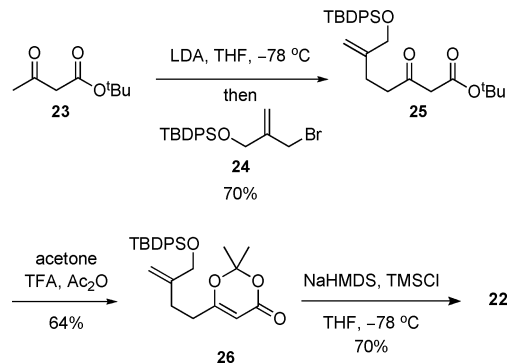
Scheme 5. Revised Retrosynthetic Analysis



the alkylation of the dianion of **10** with a suitably substituted allyl halide (path A), but these efforts were to no avail. We also envisioned that **20** might be accessed by path B, a process that would involve capture of the stabilized carbocation generated from **21** with a π -nucleophile such as **22**. At the time we conceived of this approach there was little precedent for such a construction.¹⁵ Shortly after we had conducted this reaction, Rawal reported a similar process using a *N*-protected indole in his work directed toward the welwitindolinones.^{7g,m} Since our original discovery, we have found this reaction to be more generally useful for preparing heteroaryl propanoic acid derivatives.¹⁶

In order to examine the feasibility of forming **20** via path B, the vinylogous silyl ketene acetal **22** was first prepared

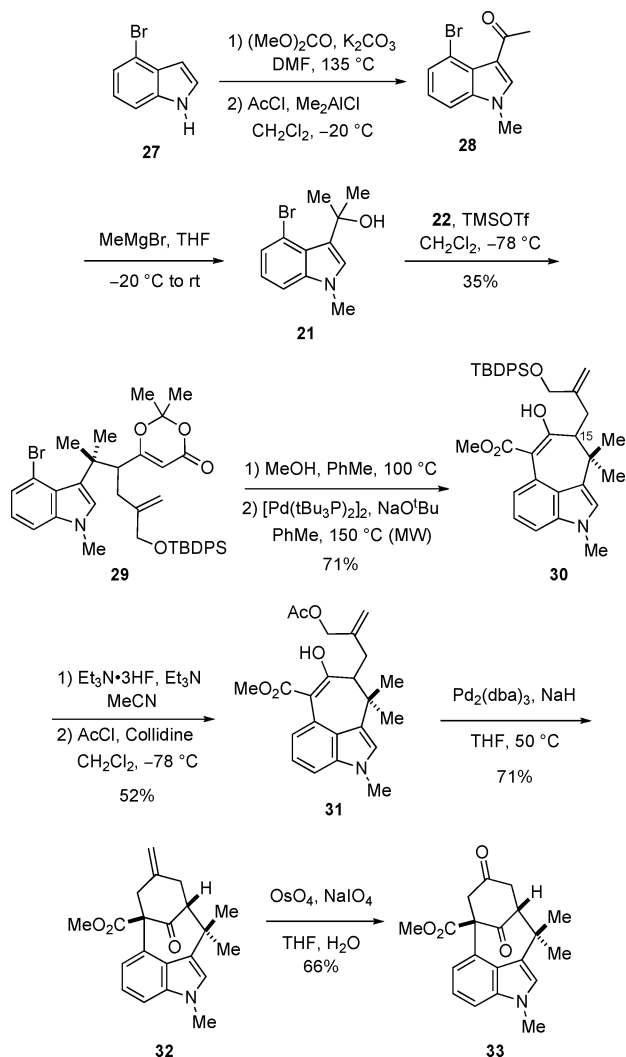
Scheme 6. Preparation of Vinylogous Silyl Ketene Acetal **22**



(Scheme 6). Accordingly, the bis-anion of *tert*-butyl acetoacetate (**23**) was alkylated with the allylic bromide **24**, which was easily prepared in two steps from the corresponding diol to furnish **25**. Dioxanone formation to give **26** and subsequent silylation of the dienolate derived from **26** gave **22**, which because of its instability was used without further purification as an inconsequential mixture (1.5:1) of isomeric olefins.

The requisite indole fragment **29** was then prepared from 4-bromoindole (**27**) by a procedure developed by Rapoport (Scheme 7).¹⁷ *N*-Methylation of **27** with dimethyl carbonate¹⁸

Scheme 7. Preparation of the Welwitindolinone C Skeleton



followed by acetylation at C(3) of **27** afforded ketone **28**.¹⁹ Reaction of **28** with methylmagnesium bromide provided the unstable tertiary alcohol **21**, which was immediately treated with the crude vinyllogous silyl ketene acetal **22** in the

presence of TMSOTf to form **29** in 35% yield over two steps. Heating **29** with methanol unveiled an intermediate ketoester **20** (*R* = TBDPS), which underwent palladium-catalyzed cyclization to give **30** in 71% yield from **29**. The silyl ether was cleaved with triethylamine hydrofluoride, but the subsequent acetylation of the resulting alcohol was complicated by competing reaction with the enolized ketone to give an enol acetate. After some experimentation, we discovered that selective acetylation of the alcohol could be achieved by the action of acetyl chloride in the presence of collidine at -78°C to furnish **31** in 52% overall yield from **30**. Cyclization of the sodium enolate derived from **31** was achieved by utilizing $\text{Pd}_2(\text{dba})_3$ to deliver the desired tetracycle **32** in 71% yield. Oxidative cleavage of the exocyclic olefin under Johnson–Lemieux conditions gave the dione **33**.

In preparing **33**, we have thus developed a facile entry to the tetracyclic scaffold found in *N*-methylwelwitindolinone C isothiocyanate (**3**). The synthesis features the coupling of an indole-stabilized carbocation with a vinyllogous silyl ketene acetal as a π -nucleophile together with a palladium-catalyzed enolate arylation and a palladium-catalyzed allylic alkylation. Efforts toward the application of this approach and variants thereof to the total synthesis of **3** are in progress and will be reported in due course.

Acknowledgment. We thank the National Institutes of Health (GM 25439), the Robert A. Welch Foundation, Pfizer, Inc., Merck Research Laboratories, and Boehringer Ingelheim Pharmaceuticals for their generous support of this research. We are also grateful to Vince Lynch (The University of Texas) for X-ray crystallography, Steve Sorey (The University of Texas) for NMR spectroscopy, and Bob Fu (The University of Texas) for helpful discussions and technical assistance.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds, plus X-ray coordinates for compounds **11** and **16** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL1006373

(14) For related cyclizations of 4-substituted indoles, see: Fillion, E.; Dumas, A. M. *J. Org. Chem.* **2008**, *73*, 2920–2923, and references therein.

(15) For examples, see: (a) Comins, D. L.; Stroud, E. D. *Tetrahedron Lett.* **1986**, *27*, 1869–1872. (b) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331–6342. (c) Grieco, P. A.; Handy, S. T. *Tetrahedron Lett.* **1997**, *38*, 2645–2648.

(16) Fu, T.-H.; Bonaparte, A.; Martin, S. F. *Tetrahedron Lett.* **2009**, *50*, 3253–3256.

(17) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106–5110. This material is also commercially available.

(18) Jiang, X.; Tiwari, A.; Thompson, M.; Chen, Z.; Cleary, T. P.; Lee, T. B. K. *Org. Process Res. Dev.* **2001**, *5*, 604–608.

(19) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485–1487.