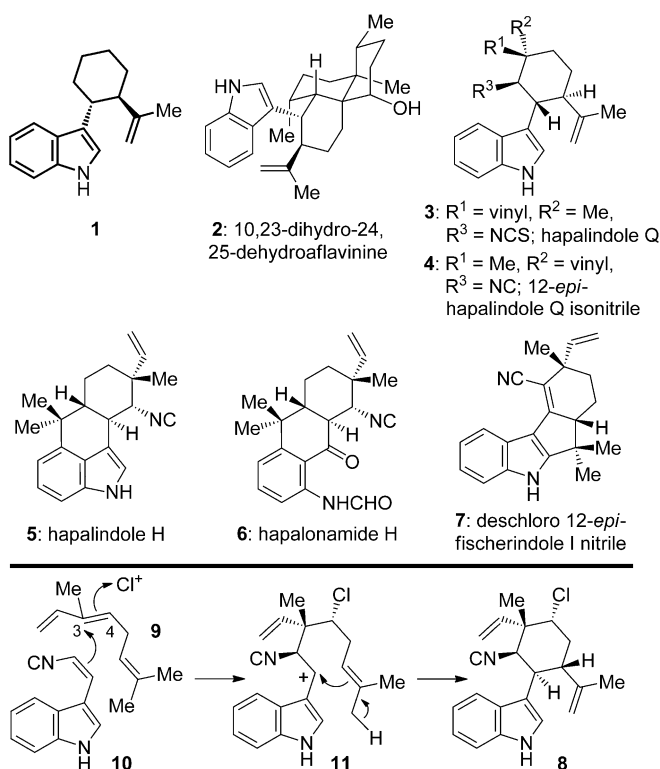


Total Synthesis of Hapalindole-Type Natural Products**

Zhaohong Lu, Ming Yang, Pengxi Chen, Xiaochun Xiong, and Ang Li*

Abstract: A unified and bioinspired oxidative cyclization strategy was used in the first total syntheses of naturally occurring 12-*epi*-hapalindole **Q** isonitrile, hapalonamide **H**, deschloro 12-*epi*-fischerindole **I** nitrile, and deschloro 12-*epi*-fischerindole **W** nitrile, as well as the structural revision of the latter. Hapalindoles **H** and **Q** were also synthesized.

During synthetic studies on indole terpenoids,^[1] we noticed a common structural motif (**1**, Scheme 1) appearing in 10,23-



Scheme 1. Some indole terpenoids containing 1-indolyl-2-propenyl-cyclohexane motif and a hypothesis of the biogenesis of such structures.

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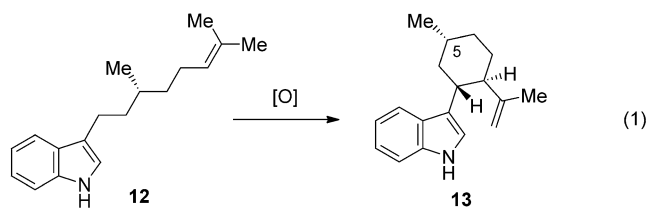
[+] These authors contributed equally to this work.

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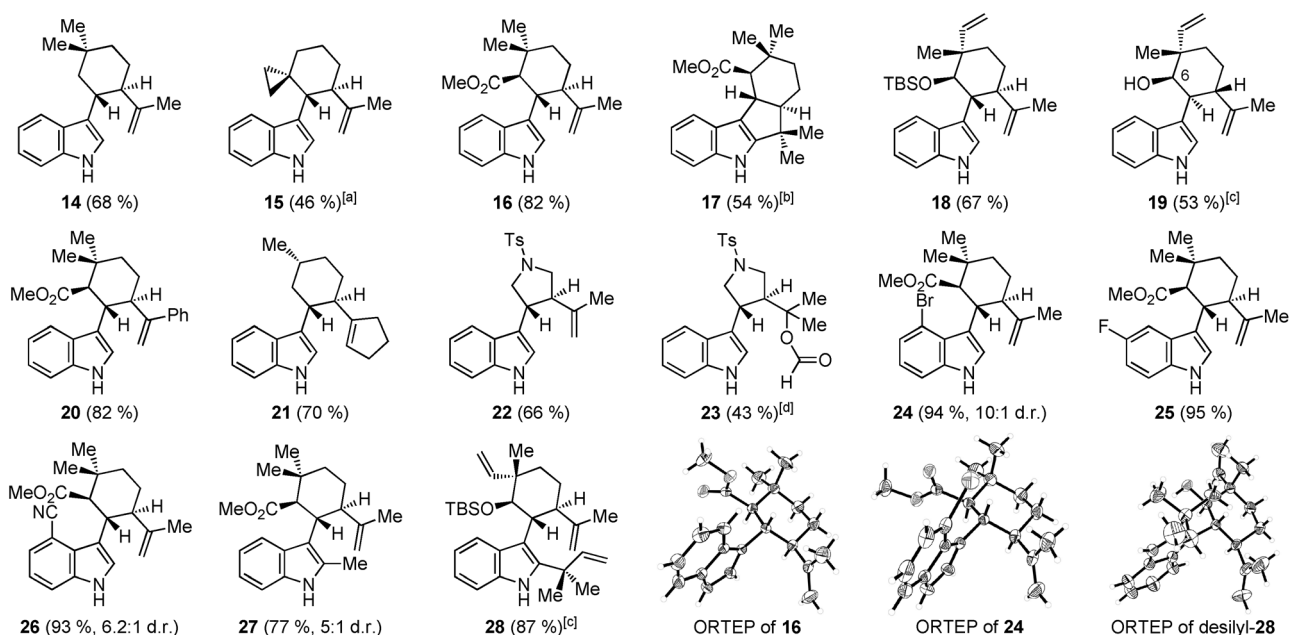
dihydro-24,25-dehydroflavinine^[2] (**2**) and the hapalindole-type natural products (e.g. **3–7**),^[3–7] and were intrigued by its biogenesis. Moore et al. proposed a biosynthetic route to 12-*epi*-hapalindole **E** (**8**; Scheme 1).^[3,7] Upon activation by Cl(I), the C3=C4 bond of β -ocimene (**9**) could be attacked by 3-vinylindole **10**, to generate a benzylic cation **11**. Prins-type cyclization would then proceed to give **8**. Inspired by this proposal, we envisioned a mechanistically similar transformation as a general access to the **1**-type structures; the benzylic oxidation of a linear indole precursor is more practical and flexible to generate the cation intermediate such as **11**, from a chemical perspective. Herein, we report the total synthesis of **3–7** and the revision of the originally assigned structure of deschloro 12-*epi*-fischerindole **W** nitrile,^[4d] based on the development of such a Prins-type oxidative cyclization reaction.

We first investigated the cyclization reaction using substrate **12** in combination with oxidants for benzylic oxidation [Eq. (1)]. SeO₂ or ceric ammonium nitrate (CAN) resulted in



complete decomposition. 2-Iodoxybenzoic acid (IBX) oxidation^[8] gave cyclization product **13** in roughly 10% yield, despite incomplete conversion and partial decomposition. Treatment with 2 equiv of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)^[9–12] in DMF at 80 °C improved the yield to 55%. Under these conditions, **13** was obtained as a single, *trans* diastereomer. This configuration may be explained by the reaction proceeding through an all-equatorial chairlike transition state. The major byproduct was the corresponding indolyl ketone.

The scope of the oxidative cyclization is summarized in Scheme 2. Products **14–28** were obtained in moderate to excellent yields. The structures of **16**, **24**, and desilyl-**28** were verified by X-ray crystallographic analysis.^[13] In all cases, the indolyl and alkenyl substituents kept a *trans* orientation. A radical-clock experiment gave smooth cyclization to furnish **15**.^[10] No cyclopropane-opening products were detected, which supports a cationic, rather than radical, pathway. Compounds **17** and **23** may originate from the intramolecular Friedel–Crafts and intermolecular DMF-trapping reactions,^[14] respectively, which corroborates the proposed cationic pathway. The nonpolar solvent 1,2-dichloroethane (DCE) and the relatively low reaction temperature play

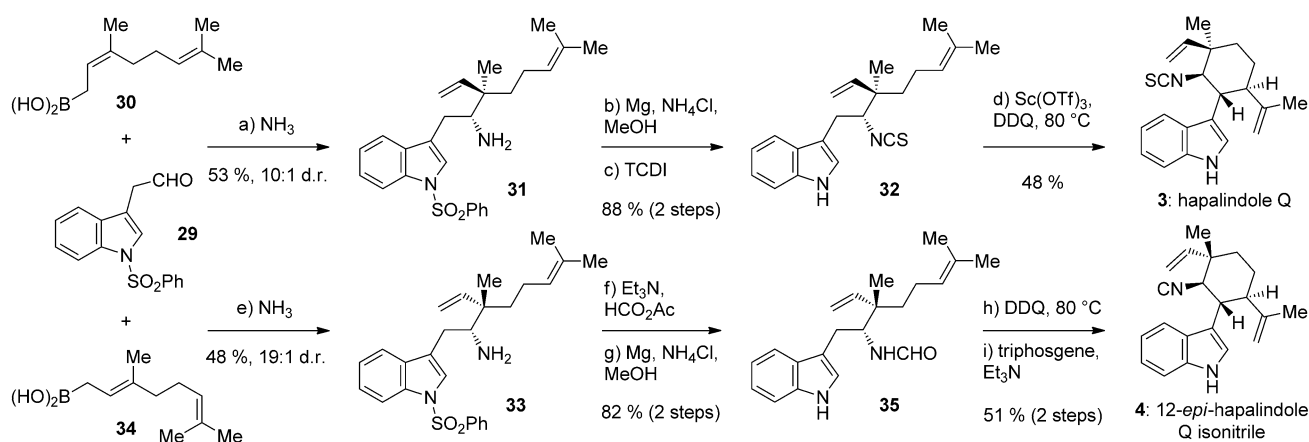


Scheme 2. Scope of the Prins-type oxidative cyclization reaction. General conditions: 2.0 equiv of DDQ, DMF, 80 °C. [a] 1.5 equiv of $\text{Sc}(\text{OTf})_3$. [b] 1.1 equiv of DDQ, DCE, 50 °C. [c] 22 °C. [d] 1.1 equiv of DDQ, 22 °C.

subtle roles to prevent the proton elimination and promote the Friedel–Crafts annulation. The configuration at the homobenzylic position significantly influenced the stereochemical outcome of the cyclization (compounds **16–20** and **24–28**), setting the basis of the stereocontrolled synthesis of hapalindoles (vide infra). The free alcohol (see compound **19**) displayed the opposite stereo-inducing effect as compared to other substituents, which provides for a stereodivergent approach to hapalindole-like molecules. Other alkenyl groups can be used as nucleophiles (see compounds **20** and **21**). Five-membered-ring formation proceeded well (see compounds **22** and **23**). Various indole substituents were tolerated (see compounds **24–28**), which makes this reaction attractive for the preparation of a wide range of hapalindole analogues. For products **24**, **26**, and **27**, a mixture of

atropisomers was obtained. Product **28** with a reverse-prenyl group at indole C2 is potentially useful for the ambiguous synthesis.^[5i] Notably, $\text{Sc}(\text{OTf})_3$ was found to be an important additive in some cases (see compound **15**), presumably through imine activation.^[10d]

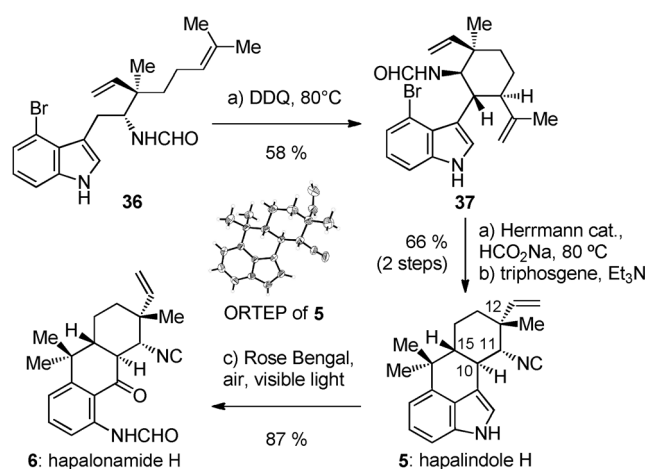
Having established the method, we directed our attention to the syntheses of hapalindole **Q**^[5f–h] and 12-*epi*-hapalindole **Q** isonitrile (Scheme 3). The synthesis of **4** has not been reported perhaps because the stereochemical variation between **3** and **4** at C12 made some of the previous strategies inapplicable to the synthesis of the latter. The oxidative cyclization strategy simplified this problem to the preparation of a pair of diastereomeric linear precursors and enabled a unified approach to both molecules (Scheme 3). Direct synthesis of the primary homoallylic amines proved challeng-



Scheme 3. Total syntheses of hapalindole **Q** and 12-*epi*-hapalindole **Q** isonitrile. TCDI = 1,1'-thiocarbonyldiimidazole.

ing: Kobayashi's protocol^[15] failed to give the desired amines due to the low reactivity of the allylic boronic esters used. We made recourse to the free boronic acids.^[16] Treatment of known aldehyde **29**^[17] with *cis* boronic acid **30**^[16] in liquid NH₃^[15] provided amine **31** (53 % yield, ca. 10:1 d.r.), which underwent desulfonation and thioisocyanate formation to afford compound **32** (88 % overall yield). Exposure of **32** to DDQ and Sc(OTf)₃ at 80 °C furnished racemic hapalindole Q (**3**) in 48 % yield. Similarly, amine **33**, which was obtained from **29** and *trans* boronic acid **34**,^[16] was further converted to formamide **35**. The oxidative cyclization followed by dehydration proceeded smoothly to give racemic 12-*epi*-hapalindole Q isonitrile (**4**) in 51 % yield (2 steps). These syntheses took advantage of the flexible access to the substrates and the functional group tolerance of the cyclization.

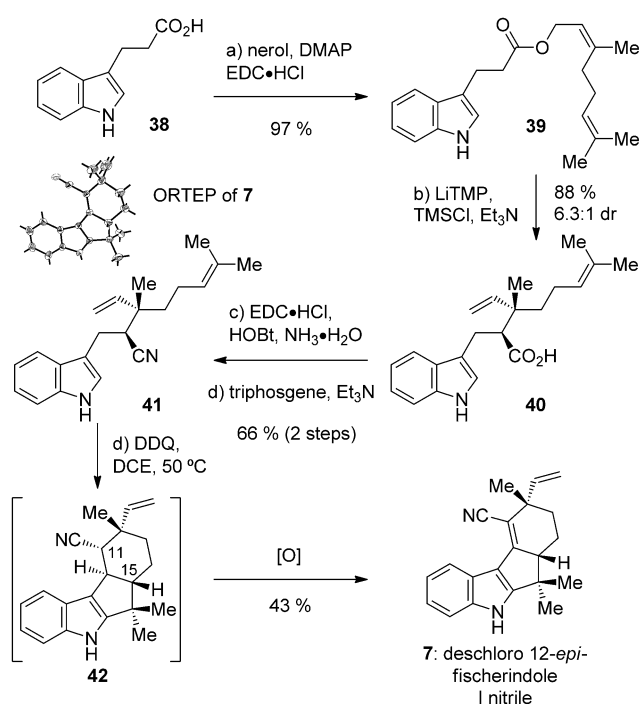
We applied the above strategy and method to the synthesis of racemic hapalindole H^[5b] and hapalonamide H (Scheme 4). Compound **36** was constructed from **30** and 4-Br-



Scheme 4. Total syntheses of hapalindole H and hapalonamide H.

29^[17,18] (39 % yield) in a similar fashion to that described above. The cyclization afforded compound **37** (58 % yield), which was subjected to Baran's conditions for reductive Heck annulation.^[5f] Dehydration of the resultant formamide provided hapalindole H (**5**, 66 % yield, 2 steps); its structure was confirmed by X-ray crystallographic analysis.^[13] In this synthesis, the stereocenters at C11 and C12 were pre-installed on the linear precursor, and those at C10 and C15 were secured by the oxidative cyclization. Thus, no additional redox process was required for the stereochemical adjustment.^[5b] Photosensitized oxidation of **5** (air, Rose Bengal, visible light) gave hapalonamide H (**6**) in 87 % yield^[19] presumably through an ¹O₂ cleavage mechanism, which represents the first synthesis of this natural product.

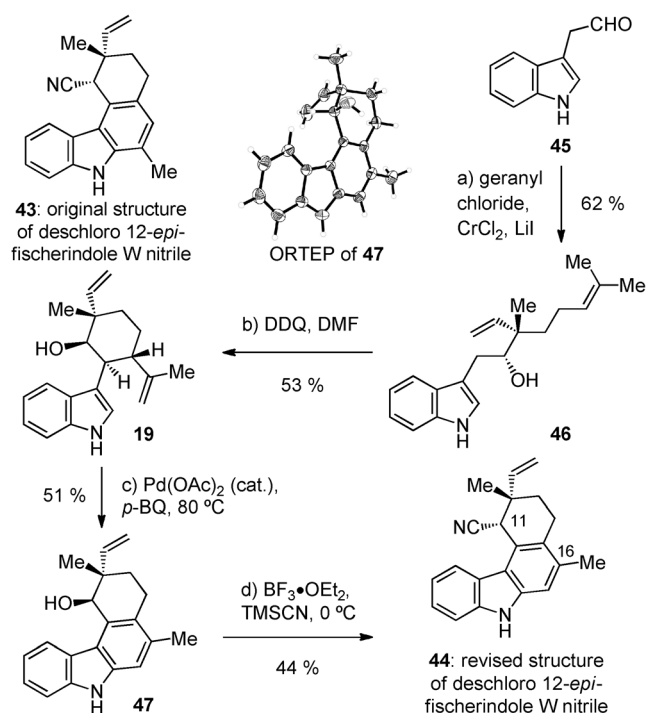
The first synthesis of deschloro 12-*epi*-fischerindole I nitrile (**7**) possessing a tetracyclic framework was accomplished (Scheme 5), based on the cyclization cascade observed leading to compound **17** (Scheme 2). Distinct from many other members of the hapalindole family, **7** contains a nitrile rather than an isonitrile or thioisocyanate function. Condensation of acid **38** with nerol ((*Z*)-3,7-dimethyl-2,6-



Scheme 5. Total synthesis of deschloro 12-*epi*-fischerindole I nitrile. EDC = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, TMP = 2,2,6,6-tetramethylpiperidine, TMS = trimethylsilyl, HOBT = 1-hydroxybenzotriazole.

octadien-1-ol) afforded ester **39**, which underwent an Ireland–Claisen rearrangement (LiTMP, TMSCl) to give acid **40** as a major diastereomer. This compound was converted to nitrile **41** (66 % overall yield) as the cyclization substrate. The C11 stereocenter was used transiently for directing the stereochemical outcome at C15 of the product and then vanished. Treatment of **41** with DDQ (3 equiv) in DCE at 50 °C furnished racemic deschloro 12-*epi*-fischerindole I nitrile (**7**) in 43 % yield in a one-pot reaction, presumably via intermediate **42** (see compound 17 in Scheme 2). The structure of **7** was verified by X-ray crystallographic analysis.^[13]

The structure of deschloro 12-*epi*-fischerindole W nitrile^[4d] (**43**, Scheme 6) seemed at odds with the presumed biosynthetic pathway, in which it would arise from an isopropenyl-containing precursor. On this basis, we proposed an alternative structure (**44**), in which the aryl methyl is moved to C16.^[20] Our total synthesis (Scheme 6) confirmed this to be the correct structure. CrCl₂-mediated allylation^[21] of unprotected aldehyde **45** furnished the cyclization substrate **46** (62 % yield), which was subjected to the oxidative cyclization conditions to give **19** (53 % yield, see Scheme 2). Exposure of **19** to Pd(OAc)₂ and *p*-benzoquinone at 80 °C provided carbazole **47** in 51 % yield through an oxidative Heck annulation;^[22] the structure of **47** was confirmed by X-ray crystallographic analysis.^[13] Treatment of **47** with BF₃·OEt₂/TMSCN gave the corresponding benzylnitrile (ca. 3:1 mixture of C11 diastereomers). The spectra of the major isomer **44** (44 % yield after purification) are identical to those reported for the natural sample. Thus, we revised the structure of the natural product from **43** to **44**.



Scheme 6. Total synthesis of revised deschloro 12-*epi*-fischerindole W nitrile. *p*-BQ = 1,4-benzoquinone.

In summary, we developed a Prins-type oxidative cyclization reaction and accomplished the total syntheses of a number of structurally diverse natural products of the hapalindole family. This strategically novel and flexible approach may facilitate biological studies of these natural products and their analogues.

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- [1] a) Y. Sun, R. Li, W. Zhang, A. Li, *Angew. Chem. Int. Ed.* **2013**, 52, 9201; *Angew. Chem.* **2013**, 125, 9371; b) Y. Sun, P. Chen, D. Zhang, M. Baunach, C. Hertweck, A. Li, *Angew. Chem. Int. Ed.* **2014**, 53, 9012; *Angew. Chem.* **2014**, 126, 9158; c) M. Bian, Z. Wang, X. Xiong, Y. Sun, C. Matera, K. C. Nicolaou, A. Li, *J. Am. Chem. Soc.* **2012**, 134, 8078.
- [2] M. R. TePaske, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *Tetrahedron* **1989**, 45, 4961.
- [3] J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio, P. S. Baran, *J. Am. Chem. Soc.* **2008**, 130, 17938, and references therein.
- [4] The isolation of 3–7: a) R. E. Moore, C. Cheuk, X.-Q. 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; b) R. E. Moore, X.-Q. G. Yang, G. M. L. Patterson, R. Bonjouklian, T. A. Smitka, *Phytochemistry* **1989**, 28, 1565; c) D. Klein, D. Daloze, J. C. Braekman, L. Hoffmann, V. Demoulin, *J. Nat. Prod.* **1995**, 58, 1781; d) H. Kim, A. Krunić, D. Lantvit, Q. Shen, D. J. Kroll, S. M. Swanson, J. Orjala, *Tetrahedron* **2012**, 68, 3205.
- [5] Elegant total syntheses of hapalindole-type natural products: a) H. Muratake, M. Natsume, *Tetrahedron* **1990**, 46, 6331; b) H. Muratake, H. Kumagami, M. Natsume, *Tetrahedron* **1990**, 46, 6351; c) V. Vaillancourt, K. F. Albizzati, *J. Am. Chem. Soc.* **1993**, 115, 3499; d) T. Fukuyama, X. Chen, *J. Am. Chem. Soc.* **1994**, 116, 3125; e) M. Sakagami, H. Muratake, M. Natsume, *Chem. Pharm. Bull.* **1994**, 42, 1393; f) A. C. Kinsman, M. A. Kerr, *Org. Lett.* **2001**, 3, 3189; g) A. C. Kinsman, M. A. Kerr, *J. Am. Chem. Soc.* **2003**, 125, 14120; h) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2004**, 126, 7450; i) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2005**, 127, 15394; j) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, 446, 404; k) A. Chandra, J. N. Johnston, *Angew. Chem. Int. Ed.* **2011**, 50, 7641; *Angew. Chem.* **2011**, 123, 7783; l) R. J. Rafferty, R. M. Williams, *J. Org. Chem.* **2012**, 77, 519. Also see Ref. [3].
- [6] Selected synthetic studies on hapalindole-type natural products: a) H. Muratake, M. Natsume, *Tetrahedron* **1990**, 46, 6343; b) P. Harrington, M. A. Kerr, *Synlett* **1996**, 1047; c) P. Harrington, M. A. Kerr, *Can. J. Chem.* **1998**, 76, 1256; d) A. C. Kinsman, M. A. Kerr, *Org. Lett.* **2000**, 2, 3517; e) M. A. Brown, M. A. Kerr, *Tetrahedron Lett.* **2001**, 42, 983; f) R. J. Rafferty, R. M. Williams, *Tetrahedron Lett.* **2011**, 52, 2037; g) R. J. Rafferty, R. M. Williams, *Heterocycles* **2012**, 86, 219; h) A. Chandra, R. Viswanathan, J. N. Johnston, *Org. Lett.* **2007**, 9, 5027; i) J. N. Johnston, M. A. Plotkin, R. Viswanathan, E. N. Prabhakaran, *Org. Lett.* **2001**, 3, 1009; j) R. Viswanathan, E. N. Prabhakaran, M. A. Plotkin, J. N. Johnston, *J. Am. Chem. Soc.* **2003**, 125, 163; k) R. Viswanathan, D. Mutnick, J. N. Johnston, *J. Am. Chem. Soc.* **2003**, 125, 7266.
- [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.
- [8] K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.* **2001**, 123, 3183.
- [9] DDQ for indole benzylic oxidation: a) Y. Oikawa, O. Yonemitsu, *J. Org. Chem.* **1977**, 42, 1213; b) S. Shimizu, K. Ohori, T. Arai, H. Sasai, M. Shibasaki, *J. Org. Chem.* **1998**, 63, 7547; c) T. Wang, Q. Xu, P. Yu, X. Liu, J. M. Cook, *Org. Lett.* **2001**, 3, 345; d) T. Ohshima, Y. Xu, R. Takita, M. Shibasaki, *Tetrahedron* **2004**, 60, 9569; e) C. Guo, J. Song, S.-W. Luo, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2010**, 49, 5558; *Angew. Chem.* **2010**, 122, 5690; f) S. Patir, E. Ertürk, *Org. Biomol. Chem.* **2013**, 11, 2804.
- [10] DDQ for more general C–H oxidation: a) W. Tu, L. Liu, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2008**, 47, 4184; *Angew. Chem.* **2008**, 120, 4252; b) W. Tu, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2009**, 48, 4567; *Angew. Chem.* **2009**, 121, 4637; c) L. Liu, P. E. Floreancig, *Org. Lett.* **2009**, 11, 3152; d) B. Yu, T. Jiang, J. Li, Y. Su, X. Pan, X. She, *Org. Lett.* **2009**, 11, 3442; e) L. Liu, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2010**, 49, 3069; *Angew. Chem.* **2010**, 122, 3133; f) L. Liu, P. E. Floreancig, *Angew. Chem. Int. Ed.* **2010**, 49, 5894; *Angew. Chem.* **2010**, 122, 6030; g) L. Liu, P. E. Floreancig, *Org. Lett.* **2010**, 12, 4686; h) G. J. Brizgys, H. H. Jung, P. E. Floreancig, *Chem. Sci.* **2012**, 3, 438; i) D. J. Clausen, P. E. Floreancig, *J. Org. Chem.* **2012**, 77, 6574; j) Y. Cui, P. E. Floreancig, *Org. Lett.* **2012**, 14, 1720; k) X. Han, P. E. Floreancig, *Org. Lett.* **2012**, 14, 3808; l) G. R. Peh, P. E. Floreancig, *Org. Lett.* **2012**, 14, 5614; m) X. Han, G. R. Peh, P. E. Floreancig, *Eur. J. Org. Chem.* **2013**, 1193; n) Z. Meng, S. Sun, H. Yuan, H. Lou, L. Liu, *Angew. Chem. Int. Ed.* **2014**, 53, 543; *Angew. Chem.* **2014**, 126, 553.
- [11] Electrochemical oxidative cyclization: a) K. D. Moeller, *Tetrahedron* **2000**, 56, 9527; b) J. B. Sperry, D. L. Wright, *Chem. Soc. Rev.* **2006**, 35, 605; c) K. D. Moeller, *Synlett* **2009**, 1208; d) S. Duan, K. D. Moeller, *J. Am. Chem. Soc.* **2002**, 124, 9368; e) J. Mihelcic, K. D. Moeller, *J. Am. Chem. Soc.* **2003**, 125, 36; f) A. K. Miller, C. C. Hughes, J. J. Kennedy-Smith, S. N. Gradd, D. Trauner, *J. Am. Chem. Soc.* **2006**, 128, 17057; g) H.-C. Xu, K. D. Moeller, *J. Am. Chem. Soc.* **2008**, 130, 13542; h) H.-C. Xu, K. D. Moeller, *Angew. Chem. Int. Ed.* **2010**, 49, 8004; *Angew.*

- Chem.* **2010**, *122*, 8176; i) A. Redden, R. J. Perkins, K. D. Moeller, *Angew. Chem. Int. Ed.* **2013**, *52*, 12865; *Angew. Chem.* **2013**, *125*, 13103; j) H.-C. Xu, J. Campbell, K. D. Moeller, *J. Org. Chem.* **2014**, *79*, 379.
- [12] Selected examples of non-oxidative generation of unsaturated indolenine: a) A. Palmieri, M. Petrini, R. R. Shaikh, *Org. Biomol. Chem.* **2010**, *8*, 1259; b) R. Ballini, A. Palmieri, M. Petrini, E. Torregiani, *Org. Lett.* **2006**, *8*, 4093; c) P. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem. Int. Ed.* **2009**, *48*, 1313; *Angew. Chem.* **2009**, *121*, 1339; d) M. C. Dobish, J. N. Johnston, *Org. Lett.* **2010**, *12*, 5744.
- [13] CCDC 991945 (**5**), 993629 (**7**), 991944 (**16**), 992001 (**24**), 993270 (desilyl-**28**), 993269 (**47**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [14] Under these optimized conditions, **16** and **22** were not detected.
- [15] M. Sugiura, K. Hirano, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 7182.
- [16] M. Raducan, R. Alam, K. J. Szabó, *Angew. Chem. Int. Ed.* **2012**, *51*, 13050; *Angew. Chem.* **2012**, *124*, 13227.
- [17] V. Chagnault, J. Lalot, P. V. Murphy, *ChemMedChem* **2008**, *3*, 1071.
- [18] J. Yang, H. Wu, L. Shen, Y. Qin, *J. Am. Chem. Soc.* **2007**, *129*, 13794.
- [19] a) R. Bonjouklian, L. A. Spangle, R. E. Moore, *J. Org. Chem.* **1989**, *54*, 719; b) R. E. Moore, X.-Q. G. Yang, G. M. L. Patterson, *J. Org. Chem.* **1987**, *52*, 3773. For a similar structure, see Ref. [1b].
- [20] A natural product bearing a similar carbazole motif: M. R. TePaske, J. B. Gloer, D. T. Wicklow, P. F. Dowd, *J. Org. Chem.* **1990**, *55*, 5299.
- [21] S. Nowotny, C. E. Tucker, C. Jubert, P. Knochel, *J. Org. Chem.* **1995**, *60*, 2762.
- [22] a) A. Kong, X. Han, X. Lu, *Org. Lett.* **2006**, *8*, 1339; b) A. Li, manuscript submitted.