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A New Modular Indole Synthesis. Construction of the Highly Strained CDEF Parent Tetracycle of Nodulisporic Acids A and B

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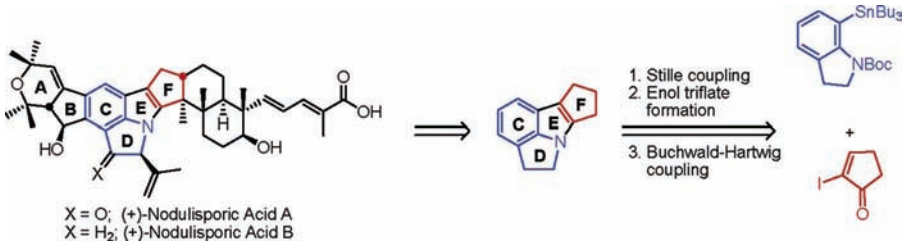
ABSTRACT



Construction of the highly strained CDEF parent tetracycle, a structural motif found only in the potent ectoparasiticidal agents (+)-nodulisporic acids A and B and related congeners, has been achieved via a new modular indole synthesis, exploiting a sequential Stille cross-coupling/ Buchwald–Hartwig union/cyclization tactic. The new indole synthesis holds the promise of rapid assembly of diverse, highly substituted indoles possessing uncommon substitution patterns.

The nodulisporanes, a novel class of indole diterpene alkaloids, display potent insecticidal properties, particularly effective against flea and tick infestations in dogs and cats.[1] Their mode of action, modulation of the invertebrate-specific glutamate-gated chloride ion channels, ensures little or no mammalian toxicity.[2] Nodulisporic acid A [(+)-**1**] was first reported by the Merck Research Laboratories in 1997 (Figure 1).[3] Although exhibiting good in vitro and in vivo activity against fleas, the potency, stability, and pharmacokinetic profile were not optimal; Merck and Co. therefore launched a medicinal chemistry campaign to optimize the profile of this lead compound. A chemical mutagenesis program was also initiated to prepare a large number (>1000) of analogues.[4] To date, however, none of the reported analogues exhibit more potency than (+)-**1**, although some improvement in pharmacokinetic properties has been achieved.

Intrigued by the architectural complexity, in conjunction with the remarkable antiparasitic activity, we initiated a synthetic program to devise a modular strategy that would

(1) Sings, H.; Singh, S. *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier Academic Press: San Diego, CA, 2003; Vol. 60, pp 51−163.

(2) Ludmerer, S. W.; Warren, V. A.; Williams, B. S.; Zheng, Y.; Hunt, D. C.; Ayer, M. B.; Wallace, M. A.; Chaudhary, A. G.; Egan, M. A.; Meinke, P. T.; Dean, D. C.; Garcia, M. L.; Cully, D. F.; Smith, M. M. *Biochemistry* **2002**, *41*, 6548−6560.

(3) Ondeyka, J. G.; Helms, G. L.; Hensens, O. D.; Goetz, M. A.; Zink, D. L.; Tsipouras, A.; Shoop, W. L.; Slayton, L.; Dombrowski, A. W.; Polishook, J. D.; Ostlind, D. A.; Tsou, N. N.; Ball, R. G.; Singh, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 8809−8816.

(4) Chakravarty, P. K.; Shih, T. L.; Colletti, S. L.; Ayer, M. B.; Snedden, C.; Kuo, H.; Tyagarajan, S.; Gregory, L.; Zakson-Aiken, M.; Shoop, W. L.; Schmatz, D. M.; Wyvratt, M.; Fisher, M. H.; Meinke, P. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 147−150.

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permit construction of not only the naturally occurring nodulisporic acids but also, importantly, congeners not readily available from the natural products.

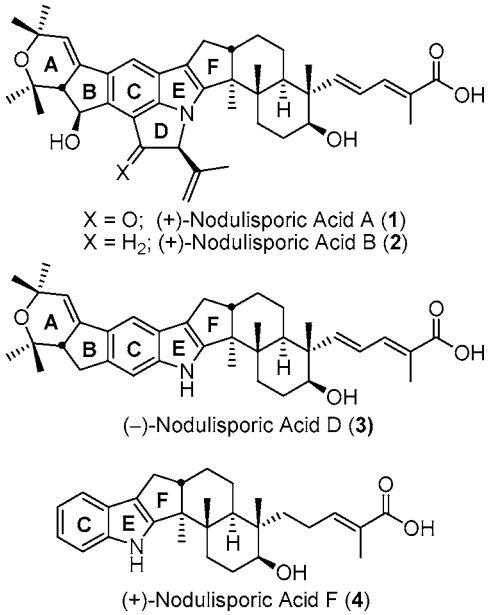


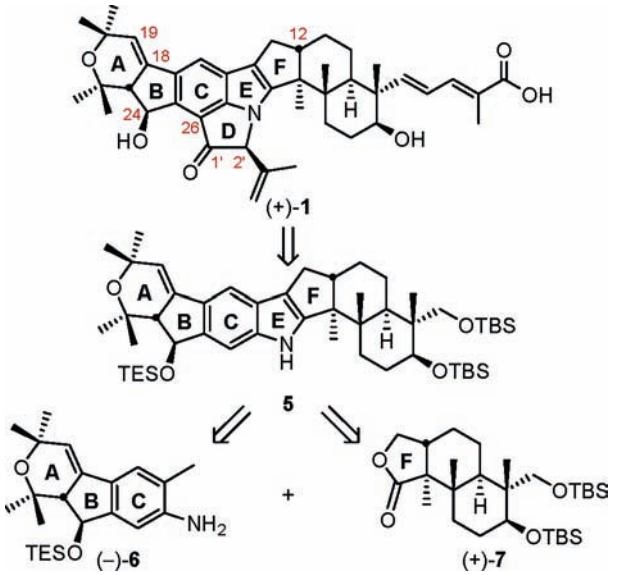
Figure 1. Representative nodulisporic acid congeners.

From the outset, we recognized the challenge of the inherent strain of the central CDEF core of **1** and **2**. To accommodate this structural feature, we envisioned a late-stage construction of the D-ring employing advanced heptacycle **5** (Scheme 1), the latter expected to arise via union of western hemisphere (−)-**6**[5] with eastern hemisphere (+)-**7**,[6] exploiting the indole synthetic protocol developed and employed for related indole diterpene syntheses in our laboratory.[7]

However, en route to both (−)-nodulisporic acid D (**3**) and heptacycle **5**, the considerable instability of the C(24) hydroxyl group, in conjunction with both the propensity of the C(18)−C(19) olefin to migration and the C(2′) center to epimerization, became apparent. Successful elaboration of ring D would thus demand extremely mild conditions.

Examination of the literature for viable tactics to elaborate the requisite CDE core of the nodulisporic acids revealed only two scenarios, one involving the addition of oxalyl chloride to a highly electron-rich indole (**8**; Figure 2)[8] and the second being a classic Fischer indole synthesis employing hydrazone **10**.[9]

Scheme 1. First-Generation Retrosynthetic Analysis



Although we were able to extend the Fischer indole sequence to tetracyclic indole **16** (Scheme 2), possessing the requisite 2-isopropenyl substituent[10] found in nodulisporic acids A and B, all attempts to employ hydrazones derived from five-membered ketones such as 1,3-cyclopentanedione or cyclopentanone (**17** or **18**, respectively) furnished none of the desired tetracycles (**19** or **20**).

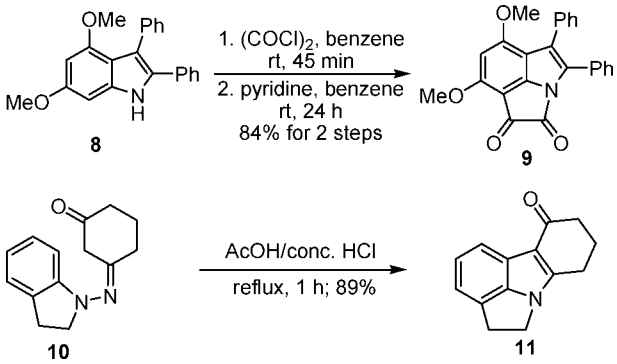


Figure 2. Reported approaches to the CDE tricycle.

That the corresponding five-membered systems (**19** and **20**) would possess significant bond angle distortion (i.e., ring strain) was clearly apparent upon examination of the single-crystal X-ray structure of **16**.

(5) Smith, A. B., III.; Ishiyama, H.; Cho, Y. S.; Ohmoto, K. *Org. Lett.* **2001**, *3*, 3967−3970.

(6) Smith, A. B., III.; Cho, Y. S.; Ishiyama, H. *Org. Lett.* **2001**, *3*, 3971−3974.

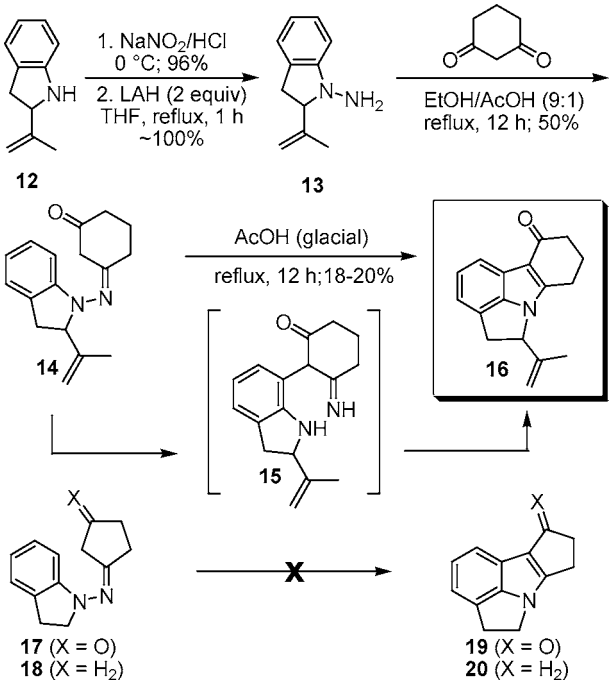
(7) (a) Smith, A. B., III.; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957−2969. (b) Smith, A. B., III.; Cui, H. *Org. Lett.* **2003**, *5*, 587−590. (c) Smith, A. B., III.; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255.

(8) Black, D. S. C.; Bowyer, M. C.; Catalano, M. M.; Ivory, A. J.; Keller, P. A.; Kumar, N.; Nugent, S. J. *Tetrahedron* **1994**, *50*, 10497−10508.

(9) van Wijngaarden, I.; Hamminga, D.; van Hes, R.; Standaar, P. J.; Tipker, J.; Tulp, M. T. M.; Mol, F.; Olivier, B.; de Jonge, A. *J. Med. Chem.* **1993**, *36*, 3693−3699.

(10) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807−809.

Scheme 2. Application of the Fischer Indole Synthesis



Undaunted, we explored a number of alternative protocols to introduce ring D, employing model systems **21**−**24** (Figure 3); the approaches included: (a) metal carbene N−H insertion (**21**); (b) intramolecular nucleophilic displacement (**22**); (c) Dieckmann condensation (**23**); and (d) intramolecular Heck carbonylation (**24**). None of these tactics proved successful, thus providing additional testimony to the inherent ring strain of the CDE tricyclic core of the nodulisporic acids.

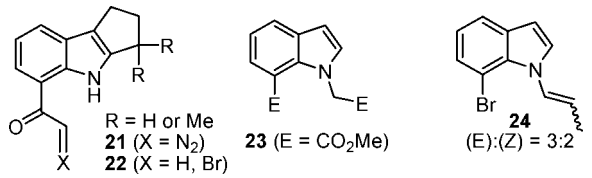
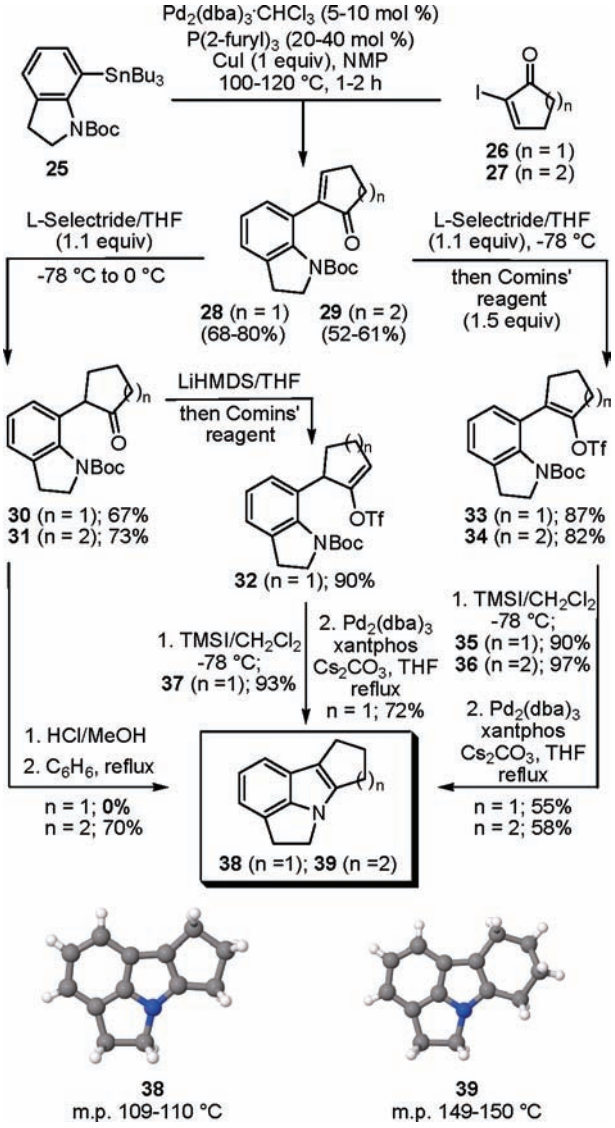


Figure 3. Prospective tactics for CDE tricycle construction.

We turned next to a transition-metal-catalyzed approach (e.g., ketone arylation[11] or Stille cross-coupling) envisioning intermediates such as **15**. We of course recognized that conversion to the indole would, at best, be difficult employing thermodynamic conditions. To this end, reaction of 2-iodo-cycloalkenones[12] (**26** and **27**) with indoline **25**[13] furnished the corresponding cycloalkenones **28** and **29** in good yield, which in turn were readily reduced with L-Selectride to cycloalkanones **30** and **31**, respectively (Scheme 3). Exposure of **31** to methanolic HCl afforded the corresponding tetracyclic indole **39** in good yield.

Scheme 3. Stille Cross-Coupling/Buchwald−Hartwig Union/Cyclization Tactic[a]



[a] The X-ray crystal structure images above, **38** and **39**, were generated from the PDB files using Jmol Viewer Version 10.

However, similar treatment of the five-membered congener **30** proved ineffective even upon extended exposure to a variety of acids, solvents, and temperature regiments; only decomposition occurred.

Fully convinced that **38** could not be generated employing thermodynamic conditions, we converted enones **28** and **29** to the corresponding enol triflates **33** and **34**, respectively; removal of the Boc group set the stage for an intramolecular Buchwald−Hartwig cyclization between an enol triflate and a secondary amine (**35** and **36**).[14] Initial efforts to achieve the requisite C−N bond formation employing $Pd_2(dba)_3$/

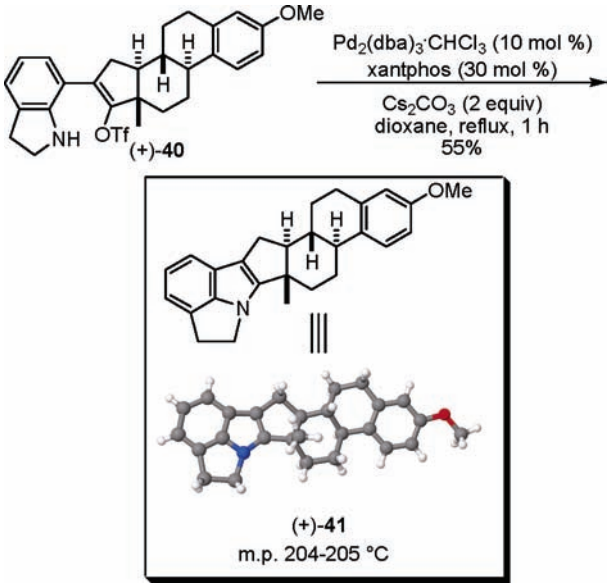
(11) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.
(12) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 917−918.
(13) Diep, V.; Dannenberg, J. J.; Franck, R. W. *J. Org. Chem.* **2003**, *68*, 7907−7910.

xantphos in toluene proved disappointing. Presumably strong bases (e.g., LiHMDS, NaO*t*-Bu) are not compatible with the enol triflate moiety.

After considerable experimentation, conversion of **36** to **39** was achieved via treatment with 2.5 mol % of $Pd_2(dba)_3$ and 7.5 mol % of xantphos in THF at reflux, employing Cs_2CO_3 as a mild base (Scheme 3). These conditions, however, did not yield **38** when employed with **35**. On the other hand, when the kinetically derived enol triflate **37** was prepared from **30** and reacted, tetracycle **38** was obtained in high yield. Alternatively, increasing both the catalyst and the ligand loading 4-fold [10 mol % of $Pd_2(dba)_3$ and 30 mol % of xantphos] furnished **38** from **35** in 55% yield. The structures of both tetracycles **38** and **39** were secured by single-crystal X-ray crystallography (Scheme 3). Not surprisingly, considerable bond angle distortion was observed in **38** (see Supporting Information).

To demonstrate that the new modular indole synthesis would prove suitable for construction of highly strained indoles, as found in the CDEF core of nodulisporic acids (+)-**1** and (+)-**2**, (+)-estrone was converted to enol triflate (+)-**40** (see Supporting Information) and subjected to the Buchwald−Hartwig conditions; heptacycle (+)-**41** was isolated in 55% yield (Scheme 4).

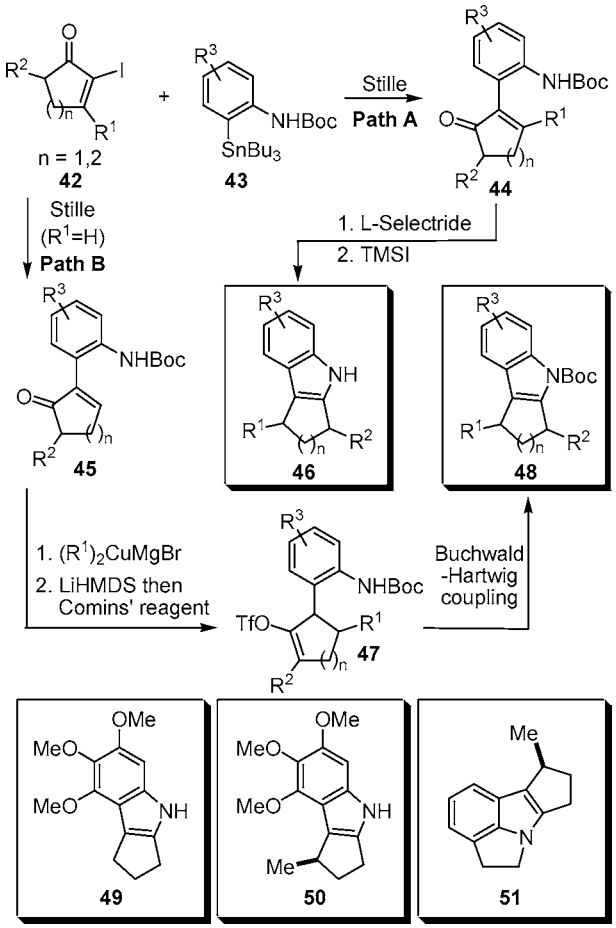
Scheme 4. Preparation of a Highly Substituted and Strained Indole Derived from (+)-Estrone



An overview of the modular indole protocol is presented in Scheme 5; indoles **49** and **50** were prepared via path A, and indole **51** was prepared via path B. Particularly noteworthy is the regiochemical outcome for **50** and **51**.

(14) To the best of our knowledge, there has been no report of a Pd-catalyzed intramolecular C−N bond forming reaction between an enol triflate and a secondary amine.

Scheme 5. General Scheme for Construction of Diverse Indoles



In summary, a new, modular synthesis of indoles has been developed exploiting a Stille cross-coupling/Buchwald−Hartwig union/cyclization tactic. The reaction conditions are mild, and as such, the new synthesis holds great promise for the ready access of structurally diverse indoles.

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Supporting Information Available: Spectroscopic and analytical data for all new compounds, as well as selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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