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Indole Diterpenoid Synthetic Studies. Construction of the Heptacyclic Core of (−)-Nodulisporic Acid D

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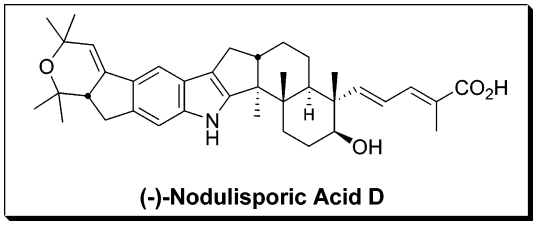
ABSTRACT



(-)-Nodulisporic Acid D

Construction of the heptacyclic core of (−)-nodulisporic acid D, a representative member of a recently discovered class of architecturally complex, ectoparasiticidal indole alkaloids, has been achieved. The modular synthetic strategy comprises an expedient, stereocontrolled synthesis of a tricyclic western hemisphere, in conjunction with union of an eastern hemisphere, exploiting the 2-substituted indole synthetic protocol introduced and developed in our laboratory.

The nodulisporanes comprise an important class of indole diterpene alkaloids, reported by the Merck Research Laboratories, that are of contemporary interest due to their potent insecticidal properties, particularly for the treatment of flea and tick infestations in dogs and cats.[1] The first member of this class, (+)-nodulisporic acid A (**1**, Figure 1),[2] a product of the endophytic fungus *Nodulisporium* sp. (MF5954), was found to be an effective systemic ectoparasiticidal agent,[3] devoid of mammalian toxicity, resulting from the mode of action which entails modulation of invertebrate-specific glutamate-gated chloride ion channels. Interruption of the chloride channel results in insect paralysis and ultimate death. Although nodulisporic acid A (**1**) exhibited good in vitro and in vivo activity against fleas, the potency and pharmacokinetic profile were not optimal. A medicinal chemistry campaign was therefore undertaken. In parallel with traditional medicinal chemistry efforts, Merck scientists also sought analogues and/or natural congeners of the parent compound, both from the original producer as well as variants derived by chemical mutagenesis. Nodulisporic acid D [(−)-**2**], a diminutive form of nodulisporic acid A (**1**), was isolated from the mutant strain *Nodulisporium* ATCC74473. Structural assignment entailed comparison of the ^{1}H and ^{13}C NMR data with that of (+)-nodulisporic acid A and related analogues.[4] Particularly noteworthy was the absence of the isoprene unit that bridges the C26−N1 positions of the more complex nodulisporanes, as well as the absence of the C24 hydroxyl group. The structural assignment of **2** was fully corroborated by HMBC experiments. From the biological perspective, nodulisporic acid D

(1) Sings, H.; Singh, S. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier Academic Press: New York, 2003; Vol. 60, p 51.

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(3) Ludmerer, S. W.; Warren, V. A.; Williams, B. S.; Zheng, Y. C.; 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.

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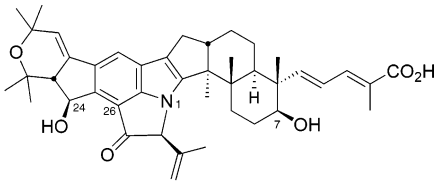
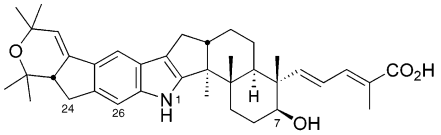




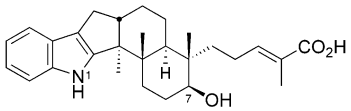


Figure 1. Nodulisporic acids A (**1**), D (**2**), and F (**3**); nodulisporic acid numbering.

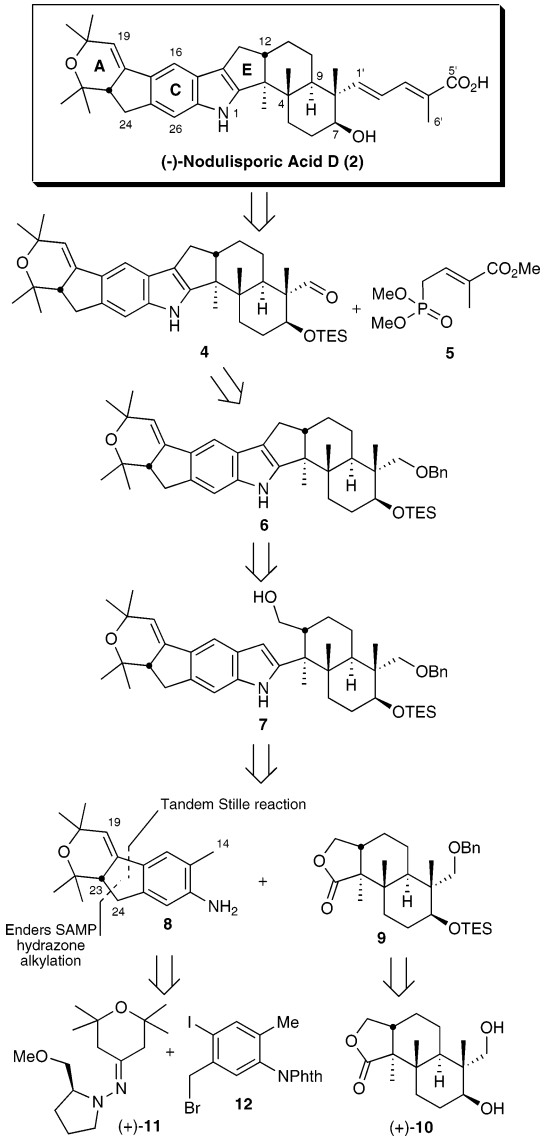
(**2**) proved to be 62-fold *less* active than nodulisporic acid A (**1**) in an ex vivo flea assay (LD_{90} = 92.6 and 1.5 μM, respectively) and >4000-fold lower in potency in an in vitro competitive binding assay (IC_{50} > 1.0 μM). Biosynthetically, **2** is significant as the gateway intermediate for the genesis of advanced nodulisporic acids (D → A).[4]

Intrigued by the architectural complexities and the biological activities of the nodulisporanes, in conjunction with our long-standing interest in the indole diterpenoid class of natural products,[5] we recently embarked on a program aimed at the total synthesis of key members of this class. Our ultimate goal is to devise a convergent, *modular* synthetic strategy that will permit access not only to the nodulisporic acids but also to an array of unnatural analogues not easily accessible by chemical modification of the naturally produced congeners.

The cornerstone of our initial synthetic strategy was anticipated to entail the 2-substituted indole synthesis that we introduced in 1986 and subsequently developed.[6] The successful application of this tactic for the total synthesis of (+)-nodulisporic acid F (**3**), the simplest and first member of the nodulisporic acid family of alkaloids to succumb to synthesis, was disclosed in the preceding Letter.[7] Herein, we present a synthetic strategy for (−)-nodulisporic acid D (**2**), in conjunction with recent progress that has led to the synthesis of the heptacyclic core (vide infra).

From the retrosynthetic perspective, late-stage Horner−Wadsworth−Emmons reaction between heptacyclic aldehyde **4** and known phosphonate **5**[8] would install the requisite dienoate side chain (Scheme 1). Advanced aldehyde **4** in turn was expected to arise from **6** via hydrogenolytic removal of the benzyl group, followed by oxidation of the resulting primary alcohol. The corresponding heptacyclic indole **6** would then arise via regioselective intramolecular carbon alkylation of **7**, as exploited to great advantage first in our total synthesis of (−)-21-isopentenylpaxilline,[9] and later for (+)-nodulisporic acid F.[7] Union of the western and eastern hemispheres, the cornerstone of the synthetic strategy, would

Scheme 1. Retrosynthetic Analysis for Nodulisporic Acid D



(5) For representative studies, see: (a) Smith, A. B., III; Mewshaw, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 1796. (b) Mewshaw, R. E.; Taylor, M. D.; Smith, A. B., III. *J. Org. Chem.* **1989**, *54*, 3449. (c) Smith, A. B., III; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197. (d) Smith, A. B., III; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G., Jr.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438. (e) Smith, A. B., III; Kanoh, N.; Minakawa, N.; Rainier, J. D.; Blase, F. R.; Hartz, R. A. *Org. Lett.* **1999**, *1*, 1263. (f) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *114*, 1438.

(6) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengler, P. A. *Tetrahedron* **1986**, *42*, 2957.

(7) Smith, A. B., III; Davulcu, A. H.; Kürti, L. *Org. Lett.* **2006**, *8*, 1665.

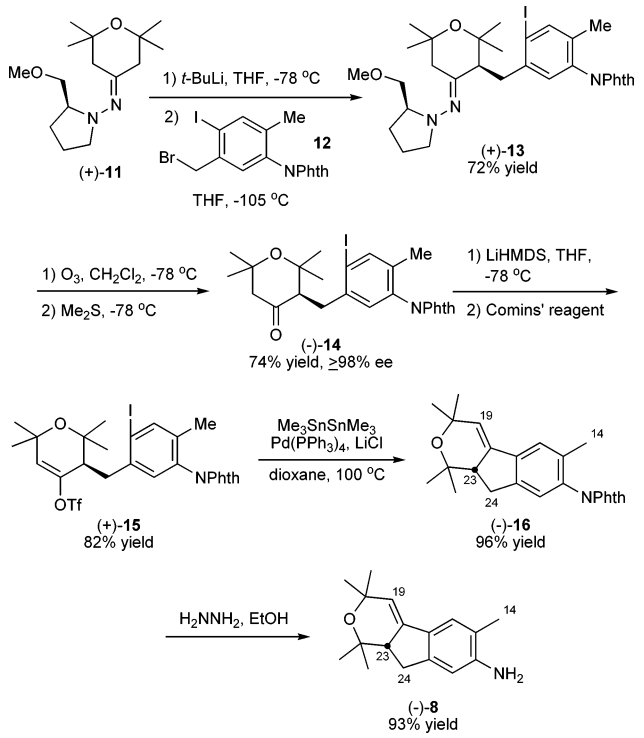
(8) Evans, D. A.; Miller, S. J.; Ennis, M. D. *J. Org. Chem.* **1993**, *58*, 471.

(9) Smith, A. B., III; Cui, H. *Org. Lett.* **2003**, *5*, 587.

then entail reaction of **9**, available from known lactone (+)-**10**, with the N-silylated dianion derived from aniline **8**. To construct aniline **8**, we envisioned a reaction sequence involving an Enders SAMP hydrazone protocol[10] to secure the stereogenicity at C23, followed by a tandem Stille cross-coupling/cyclization[11] sequence to generate the tricycle (i.e., the C17−C18 σ-bond).[12]

We initiated the synthetic venture with construction of western hemisphere **8** (Scheme 2), beginning with the metalation of known SAMP hydrazone (+)-**11**[12] (*t*-BuLi, THF, −78 °C), followed by alkylation with benzylic bromide **12** at −105 °C, to deliver adduct (+)-**13** as a single diastereomer in 72% yield, after thermal equilibration of the initially formed mixture of (*E*)- and (*Z*)-hydrazone adducts [ca. predominantly (*Z*)-hydrazone by ^{1}H NMR]. Exposure of (+)-**13** to ozone, followed by reductive workup, effected oxidative removal of the SAMP auxiliary to furnish ketone (−)-**14** in 74% yield and with ≥98% enantiomeric excess (ee).[13] Subsequent kinetic enolization (LiHMDS, THF, −78 °C) and, in turn, reaction with the Comins' reagent [*N*-(5-chloro-2-pyridyl)triflimide] effected conversion to enol triflate (+)-**15** in 82% yield.

Scheme 2. Preparation of the Western Hemisphere Subtarget



We turned next to the critical tandem Stille ring closure. After extensive experimentation, the conditions first put forth by Kelly[14] for intramolecular biaryl cross-couplings [e.g., $Pd(PPh_3)_4$, $Me_3SnSnMe_3$, LiCl, 1,4-dioxane] achieved the envisioned tandem sequence (i.e., conversion to the aryl stannane followed by ring closure); tricycle (−)-**16** was obtained in 96% yield. Removal of the phthalimide protecting group (H_2NNH_2, EtOH; 93% yield) completed the construction of aniline (−)-**8** in five steps and 40% overall yield from bromide **12**.

To secure the absolute configuration of (−)-**8**, the corresponding 3-bromophthalimide derivative (−)-**17** was prepared (see Supporting Information). X-ray crystallographic analysis, exploiting the anomalous dispersion tactic, confirmed both the connectivity and the absolute stereochemistry (Figure 2), thereby demonstrating that the C23 configuration, was in accord with that predicted by the Enders SAMP hydrazone model.[10]

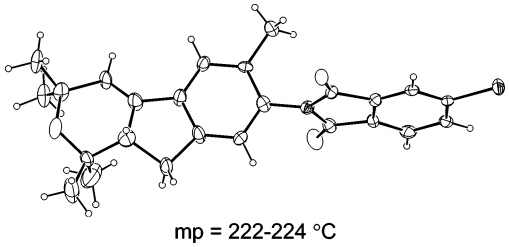


Figure 2. ORTEP representation of phthalimide (−)-**17**.

Union of (−)-**8** with lactone (−)-**9** next entailed treatment of the N-silylated dianion derived from the in situ generated *N*-trimethylsilyl-(−)-**8** with (−)-**9** [available in two steps from known lactone (+)-**10** (Scheme 3)]; ketoaniline (+)-**18** was produced in 94% yield.

From the perspective of the scope of our 2-substituted indole synthetic protocol, construction of (+)-**18** represents an interesting example, given the three potential sites for deprotonation (e.g., the allylic hydrogen at C23 and the benzylic hydrogens at C14 and C24) present in (−)-**8**. Aniline (−)-**8** also contains an embedded styryl motif, which holds the potential for anionic polymerization under the reaction conditions.[15] Not surprisingly, our first attempts to generate the N-silylated dianion derived from (−)-**8** proved difficult. However, careful purification of (−)-**8**, preferably via recrystallization of phthalimide (−)-**16**, in conjunction with rigorous exclusion of O_2 during dianion generation, led successfully to ketoaniline (+)-**18** upon exposure to (−)-**9**.

The failure of ketoaniline (+)-**18** to undergo the anticipated indolization (as observed in simpler systems)[5] was again attributed to steric effects exerted by the adjacent C3

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(11) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *The Stille Reaction*; John Wiley and Sons: New York, 1998; p 20.

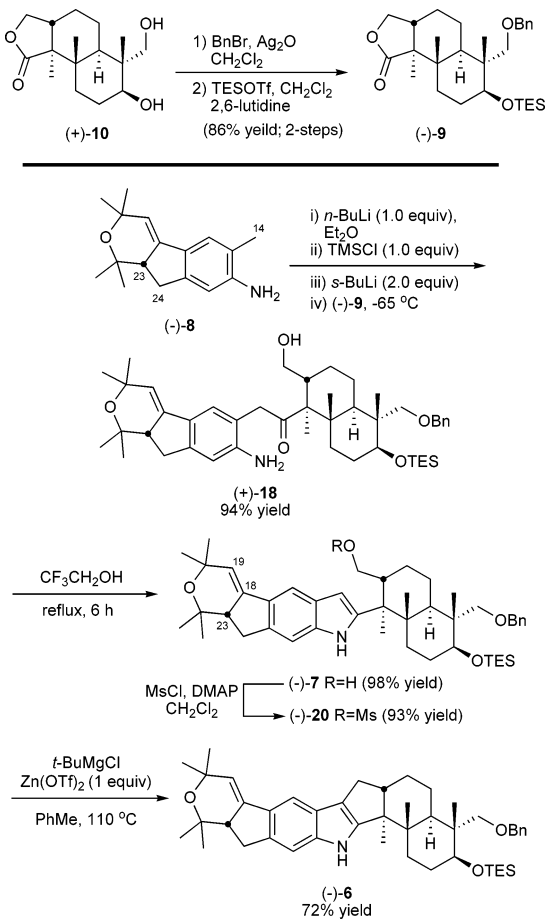
(12) For a similar sequence see: Smith, A. B., III; Ishiyama, H.; Cho, Y. S.; Ohmoto, K. *Org. Lett.* **2001**, *3*, 3967.

(13) The enantiomeric excess was determined by reverse-phase HPLC employing a chiral column. See Supporting Information.

(14) Kelly, T. R.; Li, Q.; Bhushan, A. *Tetrahedron Lett.* **1990**, *31*, 161.

(15) The alkyllithium-initiated anionic polymerization of styrenes is well-known; see: Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. Indeed, 5-vinyl-2-methylaniline undergoes facile anionic polymerization upon exposure to *s*-BuLi.

Scheme 3. Fragment Coupling; Access to the Heptacycle (−)-**6**



quaternary center (nodulisporic acid numbering), which presumably attenuates the rate of heteroatom−Peterson olefination relative to thermodynamically driven intramolecular N → O silyl migration. This result was not a major issue, as early work in our laboratory demonstrated that such ketoanilines readily undergo acid-promoted cyclodehydration to the corresponding indole.[7] In the case at hand, however, all attempts to achieve the acid-promoted cyclodehydration of ketoaniline (+)-**18** (e.g., PhH, PPTS, reflux; $CHCl_3$, SiO_2, 23 °C) led not only to indolization but also to concomitant migration of the trisubstituted $\Delta^{18,19}$ olefin to furnish the isomeric tetrasubstituted $\Delta^{18,23}$ olefin. This propensity for acid-induced bond migration was not completely surprising. In the original isolation paper, exposure to TFA led to a similar outcome. The exceptional sensitivity, however, to extremely mild acids was unexpected. Similar attempts to effect the requisite indolization without olefin isomerization employing Lewis acids [e.g., $Sc(OTf)_3$, TMSOTf, $MgBr_2 \cdot Et_2O$] or dehydrating agents [e.g., $TiCl_4$, $MgSO_4$, Burgess reagent] also met with failure. Success was eventually achieved upon treatment with 1,1,1-trifluoroethanol at reflux (6 h); the yield of (−)-**7** was 98%! Selection of this reaction protocol was based upon the conjecture that the weakly acidic ($pK_a \approx 13$), highly polar ($\epsilon = 26.5$) nature of 1,1,1-trifluoroethanol might drive the dehydration without olefin isomerization. To secure the structure of (−)-**7**, C(7,13) diol (−)-**19**, a highly crystalline compound, was prepared and subjected to single-crystal X-ray analysis (Figure 3).

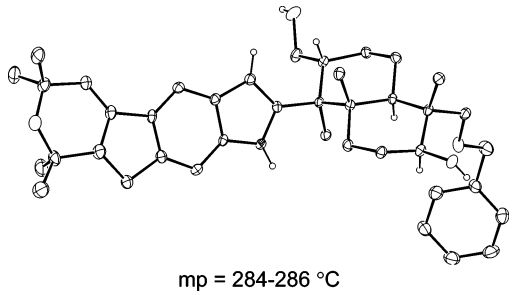


Figure 3. ORTEP representation of diol (−)-**19**.

To complete construction of the heptacyclic core of nodulisporic acid D (**2**), methanesulfonate (−)-**20** was prepared [MsCl, DMAP]. Execution of the annulation conditions developed and optimized in conjunction with our total synthesis of (+)-nodulisporic acid F [e.g., *t*-BuMgCl, PhMe, $Zn(OTf)_2$ (10 equiv), 110 °C] proceeded with high regioselectivity, albeit at first furnishing the heptacyclic core (−)-**6** in only modest yield (<30%). Pleasingly, decreasing the amount of $Zn(OTf)_2$ to 1.0 equiv delivered (−)-**6** in 72% yield, with ≥20:1 regioselectivity favoring the desired C3 isomer. That the heptacyclic core of nodulisporic acid D [(−)-**6**] was in hand was secured by detailed ^1H NMR and ^{13}C NMR analysis, with particular emphasis directed toward the correspondence of the chemical shifts and *J* values observed for the C13 methylene of (−)-**6**, compared to the values reported for nodulisporic acid D.

In summary, we have implemented a convergent synthetic approach, culminating in an expedient preparation of (−)-**6**, the heptacyclic core of (−)-nodulisporic acid D (**2**). Current efforts are focused on completion of the total synthesis of (−)-nodulisporic acid D and related congeners.

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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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