JOC Article

Indole Diterpene Synthetic Studies. Total Synthesis of (+)-Nodulisporic Acid F and Construction of the Heptacyclic Cores of (+)-Nodulisporic Acids A and B and (−)-Nodulisporic Acid D

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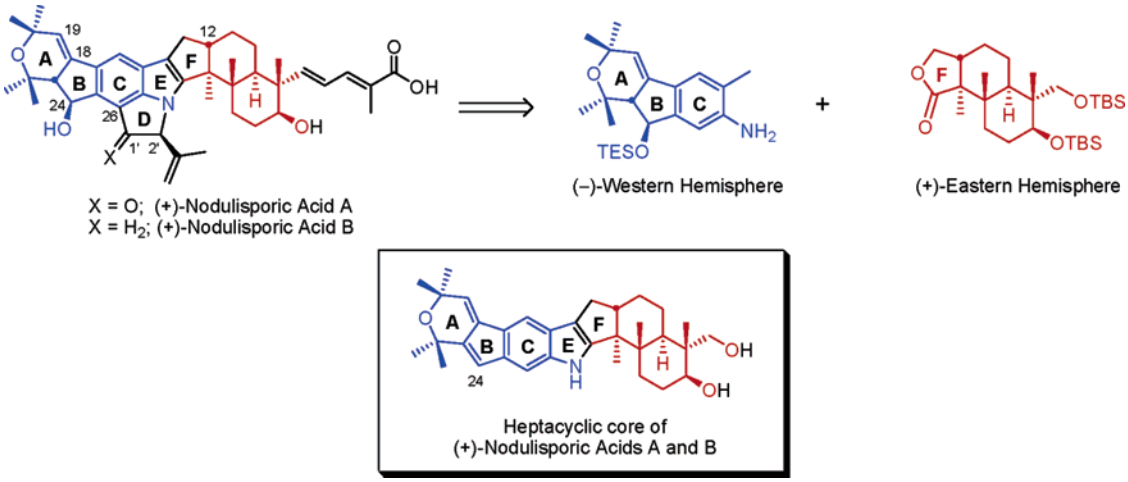
Received November 24, 2006



A first-generation strategy for construction of (+)-nodulisporic acids A (**1**) and B (**2**) is described. The strategy entails union of the eastern and western hemisphere subtargets via the indole synthesis protocol developed in our laboratory. Subsequent elaboration of rings E and F, however, revealed the considerable acid instability of the C(24) hydroxyl, thereby preventing further advancement. Nonetheless, preparation of the heptacyclic core of (+)-nodulisporic acids A and B, the total synthesis of (+)-nodulisporic acid F, the simplest member of the nodulisporic acid family, and elaboration of the heptacyclic core of (−)-nodulisporic acid D were achieved.

Introduction

In 1997, as part of an ongoing screening program to identify structurally unique, biologically active natural products having insecticidal activity, Ondeyka and co-workers at the Merck Research Laboratories reported the isolation of (+)-nodulisporic acid A (**1**, Figure 1), the most complex member of the nodulisporane class of indole diterpenoids.[1] Nodulisporic acid A (**1**) proved particularly effective against flea and tick infestations in dogs and cats.[2] Further in vitro and in vivo evaluation against the bedbug *Cimex lectularius* also revealed (+)-nodulisporic acid A, the most potent member of the nodulisporane family, to display a 10-fold greater systemic adulticidal efficacy (LD_{90} = 1 ppm) over the currently prescribed flea insecticide ivermectin (LD_{90} = 10 ppm).[3] Other members of the nodulisporic acid family proved to be 5- to >100-fold less active.[4] Importantly, (+)-nodulisporic acid A revealed no apparent toxicity to the host animal, while ef-

(1) 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.

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(3) Shoop, W. L.; Gregory, L. M.; Zakson-Aiken, M.; Michael, B. F.; Haines, H. W.; Ondeyka, J. G.; Meinke, P. T.; Schmatz, D. M. *J. Parasitol.* **2001**, *87*, 419−423.

10.1021/jo062422i CCC: $37.00
Published on Web 05/19/2007

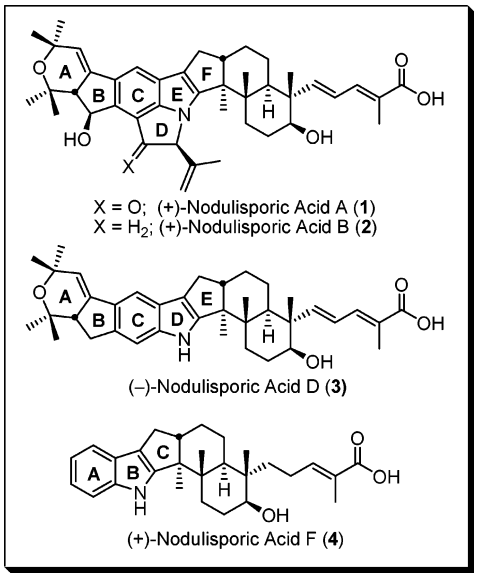
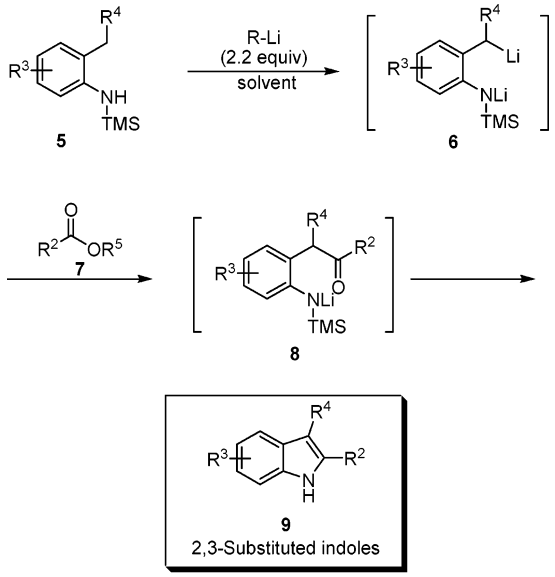


FIGURE 1. Representative nodulisporic acid congeners.

fectively killing the fleas subsequent to their ingestion of a blood meal. The lack of mammalian toxicity is ascribed to the observation that (+)-nodulisporic acid A is active only against glutamate-gated ion channels that are specific to invertebrates and not against glycine- and GABA-gated chloride ion channels common in mammals.[5,6] As a result, (+)-nodulisporic acid A is capable of selectively killing insects, while having no adverse effect on mammals.

Encouraged by the remarkable insecticidal activity against fleas, Merck & Co. undertook the development of (+)-nodulisporic acid A as a novel anti-flea agent for companion animals. Extensive biological evaluation revealed that, while nodulisporic acid A possessed good in vivo and in vitro activity, the stability and pharmacokinetic profiles were not optimal.[7] A medicinal chemistry campaign was therefore launched to optimize the profile of this lead compound. To date, more than 1000 analogues have been prepared using both chemical mutagenesis and traditional medicinal chemistry; none of the analogues, however, exhibit significantly greater potency than (+)-nodulisporic acid A, although some improvement in pharmacokinetic properties has been achieved.[7,8] Our longstanding interest in the total synthesis of indole diterpenoid natural products led us to initiate a synthetic program to devise a modular strategy that would permit the construction of not only the nodulisporic acids but also a number of congeners not easily accessed by direct chemical modification of the natural indoles.[9−14] The cornerstone of our modular synthetic strategy was envisioned to entail the indole synthetic protocol developed in our laboratory in the mid 1980s for the regiospecific construction of 2-substituted indoles (Scheme 1).[15,16] In simplest

SCHEME 1. The Modular Indole Synthesis Protocol Developed in Our Laboratory



R^2 = alkyl, aryl; R^{3-4} = alkyl, O-alkyl, O-aryl, Cl, F; R^5 = Me, Et;
R-Li: alkyllithium, aryllithium; solvent: hexanes, THF

form, this protocol calls for the union of an *N*-silylated dianion **6** with an ester or lactone **7** to afford an *N*-lithio keto amine **8** that subsequently undergoes an intramolecular heteroatom Peterson olefination[17] to furnish 2- or 2,3-substituted indoles **9**. Experience shows (vide infra) that in structurally complex esters and lactones the heteroatom Peterson olefination may not proceed. In such cases, the corresponding ketoaniline is produced upon protonation of intermediate **8**. Acid-promoted dehydration is then required to generate the indole nucleus. For construction of (+)-nodulisporic acids A and B, the requisite western and eastern hemispheres were envisaged to be **11** and **12**, respectively (Scheme 2).[18,19] After the union and subsequent elaboration of the advanced heptacyclic intermediate (Scheme 2, cf. **10**), we envisioned late-stage introduction of the highly strained D-ring via a Hendrickson annulation tactic.[20] The dienoic acid side chain would then be installed via a Stille

(4) Singh, S. B.; Ondeyka, J. G.; Jayasuriya, H.; Zink, D. L.; Ha, S. N.; Dahl-Roshak, A.; Greene, J.; Kim, J. A.; Smith, M. M.; Shoop, W.; Tkacz, J. S. *J. Nat. Prod.* **2004**, *67*, 1496−1506.

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(6) 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.

(7) 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.

(8) Ok, D.; Li, C.; Shih, T. L.; Salva, S.; Ayer, M. B.; Colletti, S. L.; Chakravarty, P. K.; Wyvratt, M. J.; Fisher, M. H.; Gregory, L.; Zakson-Aiken, M.; Shoop, W. L.; Schmatz, D. M.; Meinke, P. T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1751−1754.

(9) Smith, A. B., III; Davulcu, A. H.; Kürti, L. *Org. Lett.* **2006**, *8*, 1665−1668.

(10) Smith, A. B., III; Davulcu, A. H.; Kürti, L. *Org. Lett.* **2006**, *8*, 1669−1672.

(11) Smith, A. B., III; Cui, H. *Org. Lett.* **2003**, *5*, 587−590.

(12) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255.

(13) Smith, A. B., III; Sunazuka, T.; Leenay, T. L.; Kingerywood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197−8198.

(14) Smith, A. B., III; Mewshaw, R. *J. Am. Chem. Soc.* **1985**, *107*, 1769−1771.

(15) Smith, A. B., III; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757−3760.

(16) Smith, A. B., III; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957−2969.

(17) Krueger, C.; Rochow, E. G.; Wannagat, U. *Chem. Ber.* **1963**, *96*, 2132−2137.

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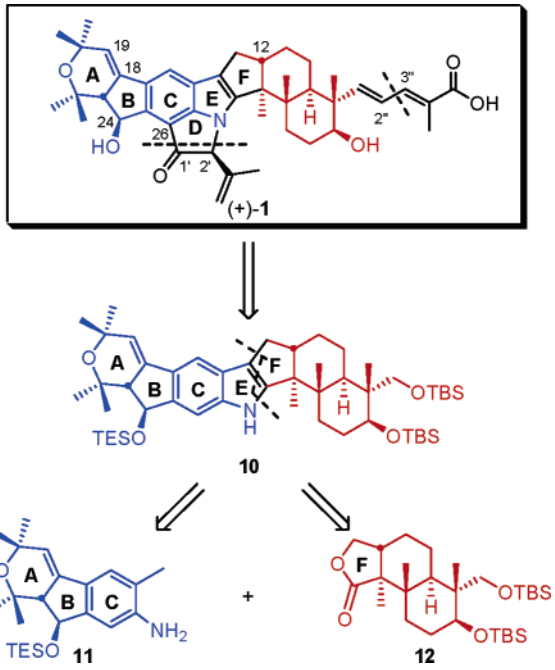
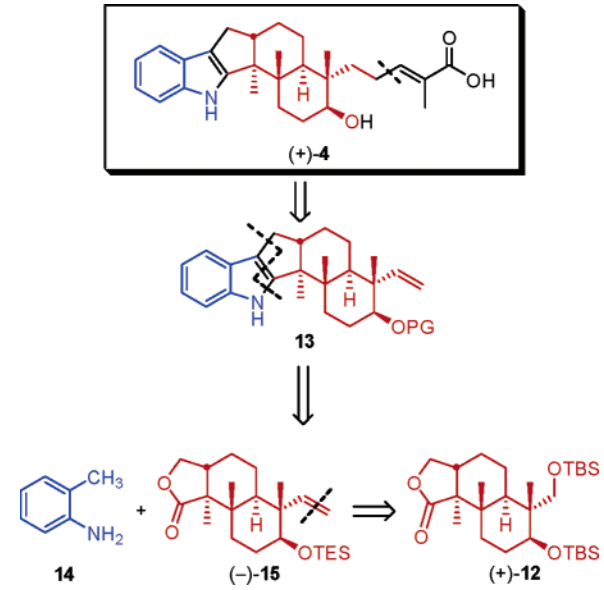
SCHEME 2. First-Generation Retrosynthetic Analysis of Nodulisporic Acid A (1)



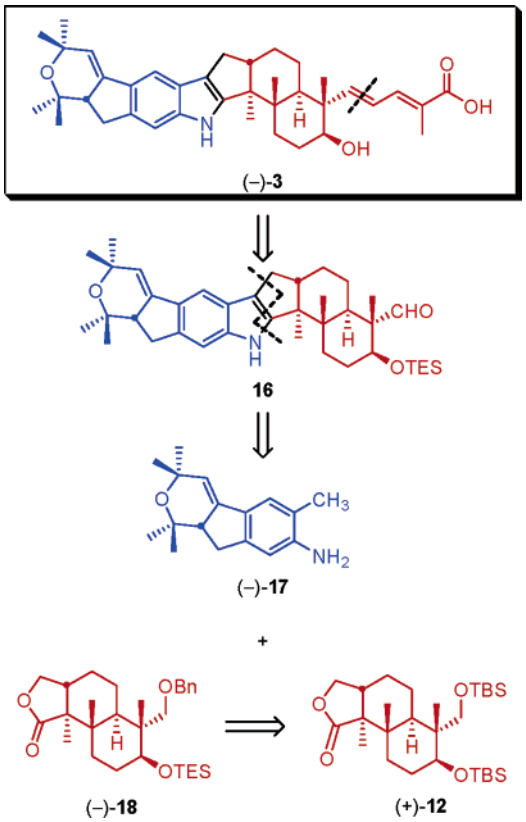
cross-coupling reaction as the last major synthetic operation.[21] As will be presented, the presence of several sensitive functionalities, including the C(24) benzylic hydroxyl group, the C(2′) epimerizable center, and the C(2)−C(14) electron-rich olefin, in conjunction with the highly strained *β*-ketodihydropyrrole moiety (i.e., D-ring), conspires to make the (+)-nodulisporic acids (**1** and **2**) most formidable synthetic targets.

Subsequent to the initiation of our nodulisporic acid A and B synthetic program, Merck and Co. disclosed a number of simpler nodulisporic acid congeners D and F (**3** and **4**).[4,22] We quickly recognized that the simpler congeners would serve as excellent early model systems to evaluate our nodulisporic acid A and B synthetic program. As with nodulisporic acids A and B, construction of D and F (Schemes 3 and 4) would again employ our indole synthetic tactic that has proven highly successful for the indole diterpenoids (−)-21-isopentenylpaxilline and (−)-penitrem D.[11,23] With this scenario in mind, tricyclic lactone (+)-**12** (or slightly modified congeners thereof) was envisioned to serve as a common eastern hemisphere coupling partner.[24] Our plan thus evolved to undertake first the total syntheses of the simpler nodulisporic acid congeners D (**3**) and F (**4**), and then to apply the lessons learned in these synthetic ventures to the construction of (+)-nodulisporic acids A and B (**1** and **2**).[25]

SCHEME 3. Retrosynthetic Analysis of (−)-Nodulisporic Acid F (4)



SCHEME 4. Retrosynthetic Analysis of (+)-Nodulisporic Acid D (3)



Results and Discussion

Synthesis of (+)-Nodulisporic Acid F: Union of the Eastern Hemisphere (+)-12 with *o*-Toluidine 14. Given that

(20) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1989**, *54*, 1144−1149.

(21) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652.

(22) Ondeyka, J. G.; Dahl-Roshak, A. M.; Tkacz, J. S.; Zink, D. L.; Zakson-Aiken, M.; Shoop, W. L.; Goetz, M. A.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2941−2944.

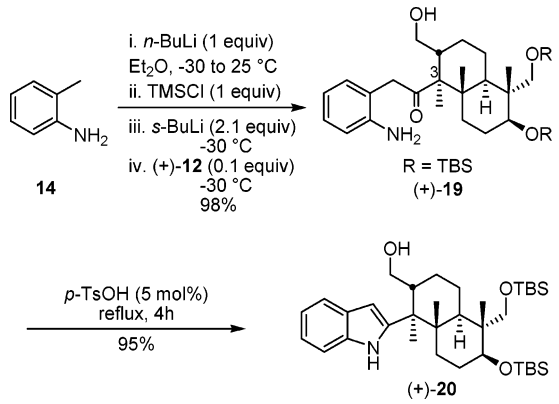
(23) (a) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254−11255. (b) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Minakawa, N.; Rainier, J. D.; Hartz, R. A.; Cho, Y. S.; Cui, H.; Moser, W. H. *J. Am. Chem. Soc.* **2003**, *125*, 8228−8237.

(24) (a) Smith, A. B., III; Cho, Y. S.; Ishiyama, H. *Org. Lett.* **2001**, *3*, 3971−3974. (b) For an improved scalable synthesis, see: Smith, A. B., III; Kürti, L.; Davulcu, A. H.; Cho, Y. S. *Org. Proc. Res. Dev.* **2007**, *11*, 19−24.

(25) For a preliminary account of this work, see: (a) Smith, A. B., III; Davulcu, A. H.; Kürti, L. *Org. Lett.* **2006**, *8*, 1665−1668. (b) Smith, A. B., III; Davulcu, A. H.; Kürti, L. *Org. Lett.* **2006**, *8*, 1669−1672.

the simplest member of the nodulisporane class of indole diterpenoids, nodulisporic acid F (**4**), does not possess substituents on the phenyl ring of the indole moiety, the commercially available *o*-toluidine **14** could serve as the western hemisphere coupling partner. To this end, *o*-toluidine **14** was converted to *N*-trimethylsilyl-*o*-toluidine and then treated with *s*-BuLi (2.1 equiv) to afford the corresponding dianion. Addition of eastern hemisphere lactone (+)-**12** furnished ketoaniline **19** in almost quantitative yield (Scheme 5). A large excess of the dianion was employed to ensure complete conversion of the more precious tricyclic lactone (+)-**12**. That the reaction failed to complete construction of the desired 2-substituted indole (+)-**20**, but rather terminated at the ketoaniline stage, was not completely unexpected given our experience in the total synthesis of (−)-21-isopentenylpaxilline[11] and (−)-penitrem D.[12] Presumably, the steric hindrance at the C(3) quaternary stereocenter adjacent to the carbonyl group prevents the heteroatom Peterson olefination from taking place. Pleasingly, acid-promoted cyclodehydration of (+)-**19** furnished the desired indole (+)-**20** in 95% yield.

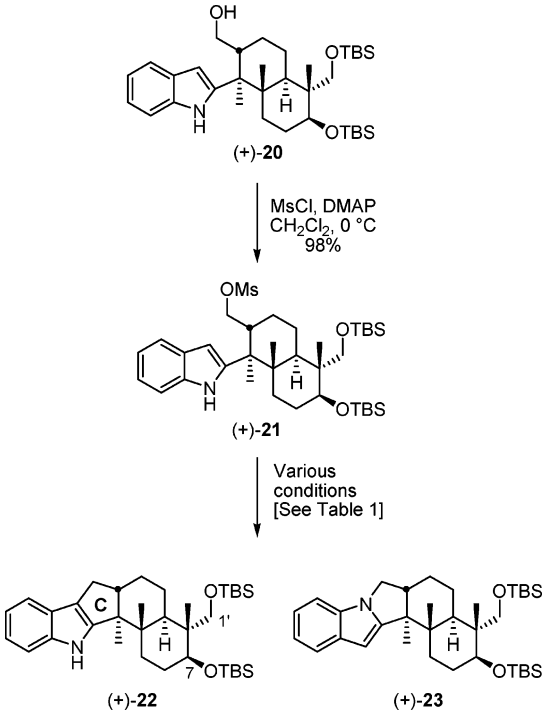
SCHEME 5. Coupling of *o*-Toluidine 14 with Lactone (+)-12



Elaboration of Ring C of Nodulisporic acid F (4). With indole (+)-**20** in hand, we turned to construction of ring C (Scheme 6), exploiting a tactic developed during the total synthesis of (−)-21-isopentenylpaxilline for this purpose.[11] Our expectation was that C(3)-alkylation of the indole would dominate over the undesired N-alkylation. The primary hydroxyl of (+)-**20** was therefore converted to the corresponding methanesulfonate (+)-**21** and in turn exposed to *t*-BuMgCl at reflux in toluene (entry 1, Table 1), conditions successfully employed in the total synthesis of (−)-21-isopentenylpaxilline.[11] A mixture of C- and N-alkylated products (+)-**22** and (+)-**23** (2.5:1.0, respectively) resulted. At room temperature, the undesired N-cyclized regioisomer (+)-**23** predominated (**22**/**23** = 1.0:8.2), consistent with the expected stereoelectronic bias favoring the formation of the N-cyclized product.[11] To increase both the regioselectivity and yield, optimization studies were carried out employing a number of different bases (Table 1). Inspired by the reported C3-arylation of unprotected indoles by Sames et al.,[26] we explored magnesium bis(hexamethyldisilazide) [Mg(HMDS)$_2$] as the base (entry 3, Table 1). High C3 regioselectivity is attributed by Sames to the steric bulk of the hexamethyldisilazide anion in the Mg coordination sphere. Unfortunately, when Mg(HMDS)$_2$ was employed, the undesired N-cyclized

(26) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050−8057.

SCHEME 6. Elaboration of the C-Ring



product (+)-**23** proved to be the major regioisomer. We also explored the use of MeMgI, as demonstrated by Danishefsky[27] in the total synthesis of staurosporine to furnish excellent C(3) indole selectivity (entry 4, Table 1). These conditions led to an improvement in the product ratio, albeit the observed modest yield precluded significant material advancement.

TABLE 1. Elaboration of the C-Ring of Nodulisporic Acid F

entry	conditions	ratio of **22**:**23**	yield (%)
1	*t*-BuMgCl, toluene, 110 °C	2.5:1.0	48
2	Bu_2Mg, toluene, 110 °C	2.8:1.0	42
3	$Mg(HMDS)_2$, toluene, 110 °C	1.0:1.8	21
4	MeMgI, toluene, 110 °C	7.7:1.0	41
5	*t*-BuMgCl, $Zn(OTf)_2$ (5 equiv), toluene, 110 °C	6.3:1.0	63
6	*t*-BuMgCl, $Zn(OTf)_2$ (10 equiv), toluene, 110 °C	9.0:1.0	72

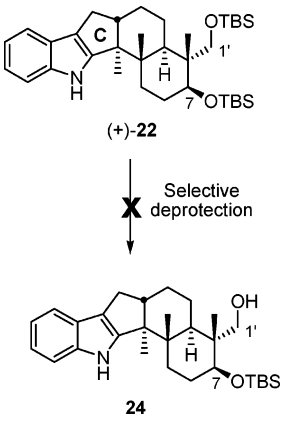
At this juncture, we reasoned that the generation of a more covalent indolyl nitrogen metal species (i.e., zinc) might favor C-cyclization over the undesired N-cyclization, known to predominate with metals that possess more ionic bonds (i.e., sodium, potassium, magnesium, etc.).[28] To this end, transmetalation of the initially formed indolyl *N*-magnesium species with zinc triflate [$Zn(OTf)_2$] furnished indole (+)-**22** in 72% isolated yield, with only 7% of the undesired (+)-**23** congener.

Selective Removal of the Primary TBS Protecting Group: A Difficult Transformation. With ample quantities of indole (+)-**22** in hand, we next attempted selective removal of the primary C(1′) TBS group in the presence of the C(7) secondary TBS ether. Subsequent elaboration of the side chain would then complete the synthesis of (+)-nodulisporic acid F (**4**). Despite extensive efforts employing a large number of

(27) Link, J. T.; Raghavan, S.; Gallant, M.; Danishefsky, S. J.; Chou, T. C.; Ballas, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 2825−2842.
(28) Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061−6066.

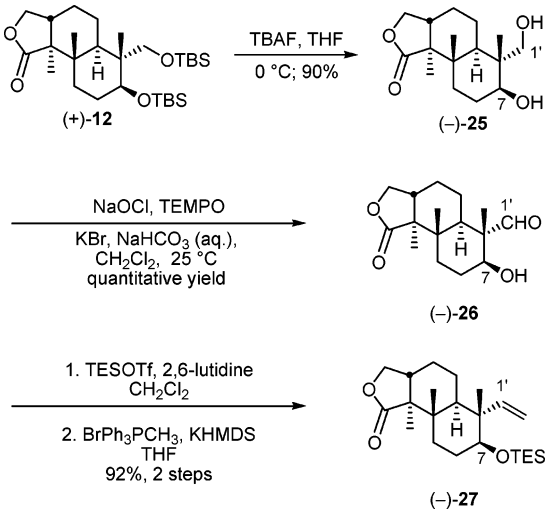
conditions, selective removal of the C(1′) TBS group could not be achieved (Scheme 7). We attribute this difficulty to the fact that, although the C(1′) carbon is primary, it is also neopentyl.

SCHEME 7. Failed Attempts to Selectively Remove the C(1′) TBS Ether



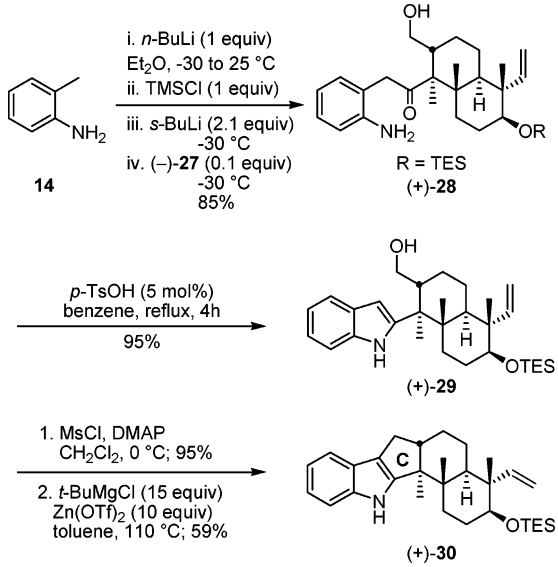
The failure to effect selective removal of the C(1′) TBS group had serious consequences, vis-à-vis our proposed endgame for the total synthesis of both nodulisporic acids F and D [(+)-**4** and (−)-**3**, respectively]. Specifically, modification of the C(1′) carbon would be required prior to union with the appropriate western hemisphere to avoid the selectivity issue. Accordingly, we constructed a new eastern hemisphere lactone [(−)-**27**] from (+)-**12** in 83% yield over four steps (Scheme 8). In this case, the TES group was selected to protect the secondary hydroxyl.

SCHEME 8. Preparation of a Modified Eastern Hemisphere Lactone (−)-27



In the event, both TBS groups were removed with tetrabutylammonium fluoride (TBAF) to furnish the corresponding diol (−)-**25**, which was then selectively oxidized at C(1′) employing the 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) under biphasic conditions to yield hydroxyaldehyde (−)-**26**.[29] Protection of the C(7) hydroxyl in (−)-**26** (97% yield) was followed by a one-carbon Wittig homologation[30] of the derived aldehyde to furnish the modified eastern hemisphere lactone (−)-**27**. We then turned to the coupling protocol employing the dianion derived from **14** (Scheme 9). Ketoaniline (+)-**28**, obtained in 85% yield, was subjected to cyclodehydration to furnish the desired 2-substituted indole (+)-**29**. Conversion to the corresponding mesylate was followed by closure of ring C

SCHEME 9. Coupling of Modified Eastern Hemisphere Lactone (−)-27 with Dianion Derived from 14



under the previously optimized conditions to complete construction of the pentacyclic indole (+)-**30** in 59% yield. A small amount of the undesired N-cyclized regioisomer (7.4:1.0) was also obtained. The relatively modest yield of (+)-**30** is attributed to a competitive E2 elimination of the primary mesylate to generate the corresponding exocyclic olefin. Completion of the total synthesis of (+)-**4** would now require a *B*-alkyl Suzuki−Miyaura cross-coupling to elaborate the side chain. Toward this end, hydroboration of the vinyl side chain of (+)-**30** employing the crystalline dimer of 9-BBN in toluene at 80 °C, according to the method described by Johnson et al.[31] (Scheme 10), furnished the corresponding alkylborane adduct. Other conditions resulted only in a low yield of the adduct, presumably due to the sterically encumbered olefin. The solvent was then exchanged for DMF, followed by the addition of the requisite vinyl bromide ester, $Pd(dppf)Cl_2$ (10 mol %), and powdered K_3PO_4 (2 equiv). Indole (+)-**31** was isolated in 69% yield. After a thorough optimization study we discovered that the morphology of the K_3PO_4 was critical to achieve high yields. Specifically, the K_3PO_4 must be finely powdered, otherwise the reaction is both slow and only furnishes (+)-**31** in low yield. Completion of the total synthesis of (+)-nodulisporic acid F (**4**) then proved straightforward; the methyl ester was saponified with LiOH (87% yield), followed by acid removal of the C(7) TES ether to furnish (+)-nodulisporic acid F (**4**) in 92% yield. The total synthesis thus proceeded with a longest linear sequence of 28 steps from Wieland−Miescher ketone and in an overall yield of 0.6%.

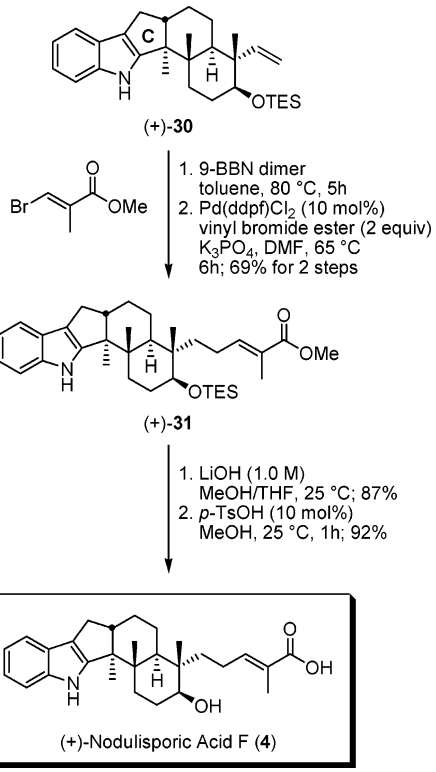
(−)-Nodulisporic Acid D: Preparation of the Western Hemisphere (−)-17. We turned next to the synthesis of (−)-nodulisporic acid D (**3**). Here a significantly more complex western hemisphere aniline **17** was required (Schemes 4 and 11). At the time (vide infra), we had already developed a synthetic route to the western hemisphere for nodulisporic acids

(29) De Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H. *Synthesis* **1996**, 1153−1174.

(30) Wittig, G.; Schollkopf, U. *Chem. Ber.* **1954**, *97*, 1318−1330.

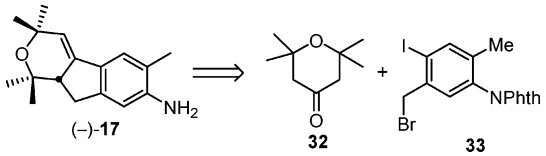
(31) Sabat, M.; Johnson, C. R. *Org. Lett.* **2000**, *2*, 1089−1092.

SCHEME 10. Completion of the Total Synthesis of (+)-Nodulisporic Acid F



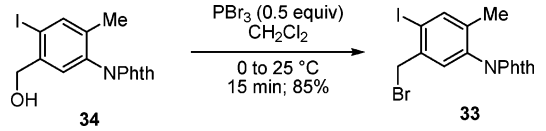
A and B, namely (−)-**11** (Scheme 2),[19] structurally similar to **17**, except incorporating the C(24) hydroxyl group (nodulisporic acid A numbering). An overview of the retrosynthetic analysis of **17** is illustrated in Scheme 11.

SCHEME 11. Retrosynthetic Analysis of Western Hemisphere (−)-17



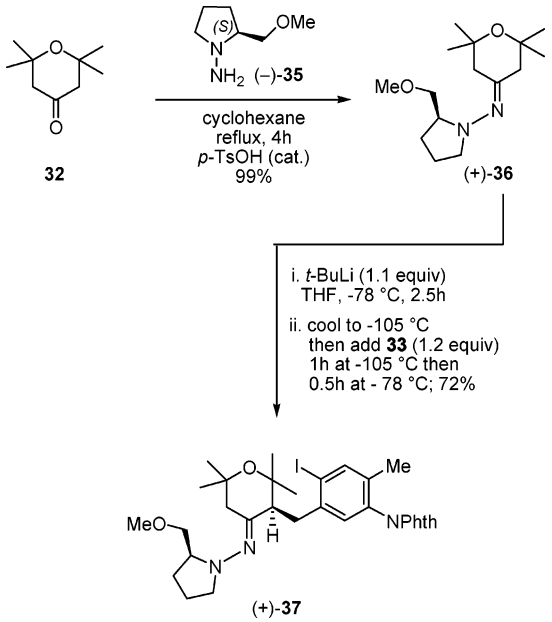
The synthesis of (−)-**17**, following the earlier developed route to (−)-**11**,[19] began with the preparation of benzylic bromide **33**, required as the alkylating agent for an Enders asymmetric SAMP hydrazone alkylation.[32] Accordingly, treatment of known benzylic alcohol **34**[19] with phosphorus tribromide furnished benzylic bromide **33** in 85% yield (Scheme 12). The Enders

SCHEME 12. Preparation of Benzylic Bromide 33



SAMP hydrazone/aldol protocol[32] was then executed to introduce the requisite stereocenter in (−)-**37**. Condensation of tetrahydro-γ-pyrone **32**[33] with the Enders SAMP hydrazine (-)-**35** furnished hydrazone (+)-**36** in near quantitative yield

SCHEME 13. Enders Asymmetric Alkylation of Hydrazone (+)-36



(Scheme 13), which could be conveniently purified by crystallization. Hydrazone (+)-**36** was then metalated with *t*-BuLi and the resulting anion alkylated with benzylic bromide **33**; adduct (+)-**37** was isolated in 72% yield as a single diastereomer, after thermal equilibration of the initially formed mixture of (*E*)- and (*Z*)-hydrazones. The requisite C(23) stereogenicity was confirmed by single-crystal X-ray analysis of the bromophthalimide analogue of **40** (vide infra), exploiting the anomalous dispersion tactic.[10] Ozonolysis of (+)-**37** next furnished ketone (−)-**38** in 75% yield (Scheme 14). The excellent enantiomeric excess (98%), determined by reverse-phase HPLC employing an enantiomerically enriched stationary phase, revealed little or no epimerization at C(23). Kinetic deprotonation of (−)-**38**, followed by capture of the resulting lithium enolate with the Comins reagent,[34] then furnished enol triflate (+)-**39** in 82% yield. The requisite Pd-catalyzed ring closure was next explored employing the conditions developed in the earlier synthesis of western hemisphere subtarget (−)-**11** (entry 1, Table 2).[19] After some optimization (entries 1−6, Table 2), the conditions of Kelly et al.[35] developed for intramolecular biaryl couplings (entry 6, Table 2) furnished (+)-**40** in near quantitative yield. Treatment of (+)-**40** with hydrazine revealed the aniline, completing construction of the tricyclic aniline coupling partner (−)-**17** in six steps from **32** (Scheme 14).

(−)-Nodulisporic Acid D: Assembly of the Heptacyclic Core. With ample quantities of the structurally complex tricyclic aniline (−)-**17** in hand, we turned to assembly of the heptacyclic core of (−)-nodulisporic acid D (**3**). The requisite tricyclic lactone (−)-**18** was prepared from known lactone (+)-**12** (Scheme 4).[24] Union was again achieved via generation of the dianion derived from (−)-**17**, followed by addition of tricyclic lactone (−)-**18**. Ketoaniline (+)-**43** was obtained in 94% yield (Scheme 15). Interestingly, despite the structural complexity of

(32) (a) Enders, D.; Whitehouse, D. L. *Synthesis* **1996**, 621−626. (b) Also see: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253−2329.

(33) Magnus, P.; Mansley, T. E. *Tetrahedron Lett.* **1999**, *40*, 6909−6912.

(34) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

(35) Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett.* **1990**, *31*, 161−164.

SCHEME 14. Preparation of Tricyclic Aniline (−)-17

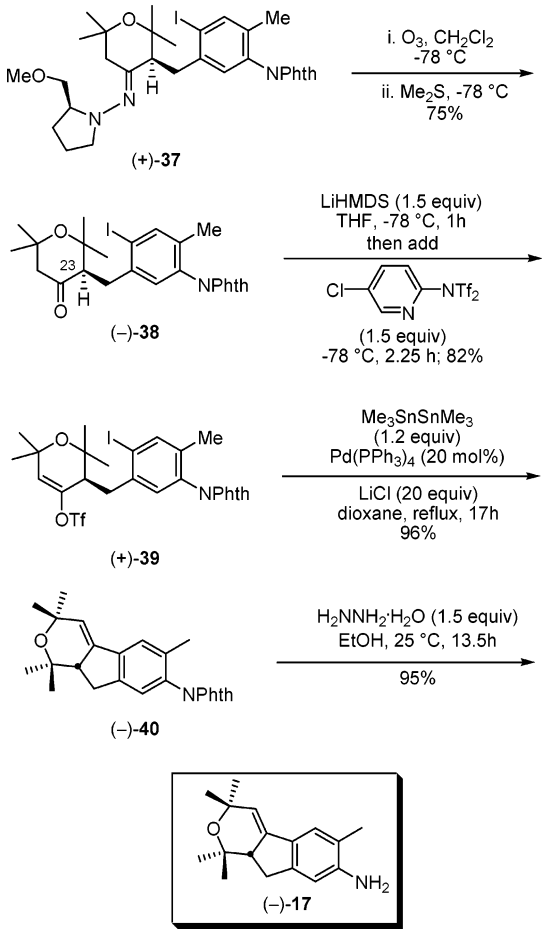
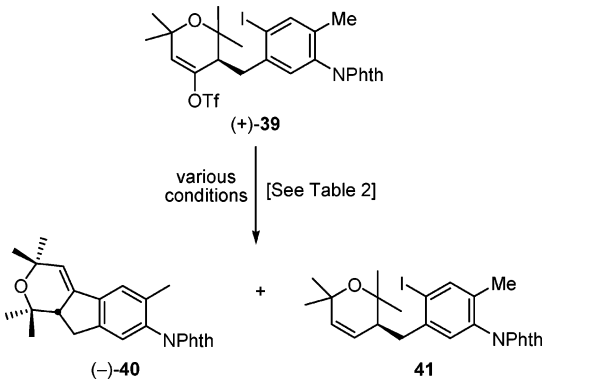


TABLE 2. Optimization of Stille−Kelly Coupling of Enol Triflate (+)-39



entry	conditions	ratio of **40**:**41**	yield (%)
1	$PdCl_2(PPh_3)_2$ (10 mol %), $TMSSnBu_3$ (3 equiv), Bu_4NBr (3 equiv), Li_2CO_3 (1 equiv) toluene, 110 °C	2.0:1.0	<50
2	$Pd(PPh_3)_4$ (20 mol %), $TMSSnBu_3$ (3 equiv), Bu_4NBr (3 equiv), Li_2CO_3 (1 equiv) xylenes, 140 °C	2.0:1.0	<50
3	$PdCl_2$(dppf) (5 mol %), bis(pinacolato)boron, Bu_4NBr (3 equiv), Li_2CO_3 (1 equiv), DMF, 75 °C	no rxn	
4	$Pd(PPh_3)_4$ (15 mol %), $Me_3SnSnMe_3$ (2 equiv), Bu_4NBr (3 equiv), Li_2CO_3 (1 equiv), xylenes, 140 °C	1.0:2.5	<50
5	$Pd(PPh_3)_4$ (10 mol %), $Me_3SnSnMe_3$ (2 equiv), LiCl (2 equiv), THF, 65 °C	no rxn	
6	$Pd(PPh_3)_4$ (20 mol %), $Me_3SnSnMe_3$ (1.2 equiv), LiCl (20 equiv), dioxane, 100 °C	only (+)-**40**	96

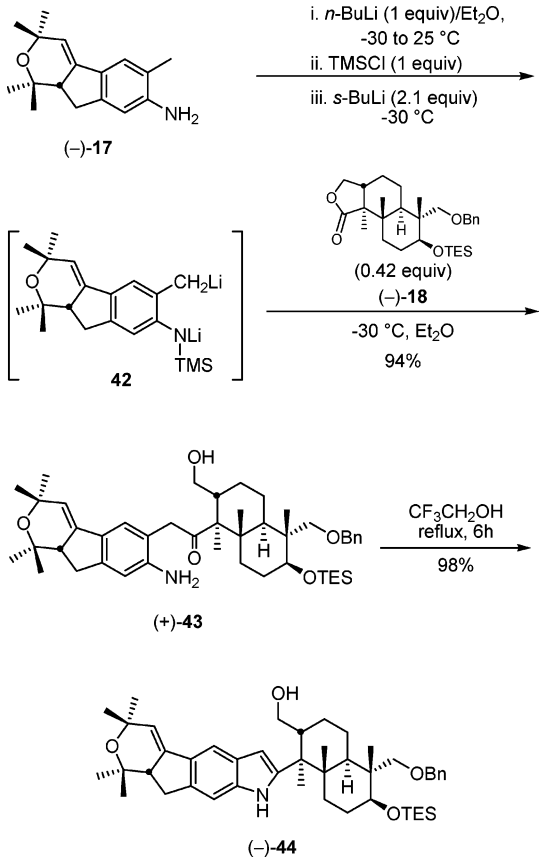
(−)-**17**, the resulting dianion **42** proved significantly more stable than the dianion derived from *o*-toluidine **14**. As a result, only slightly more than 2-fold excess (2.38 equiv) of dianion **42** was required for full conversion of tricyclic lactone (−)-**18** to ketoaniline (+)-**43**. Again, the union of (−)-**17** and (−)-**18** terminated at the ketoaniline stage. As before, indole formation was readily achieved in this case by exposing (+)-**43** to the very weak acid trifluoroethanol at reflux. Use of stronger acids such as *p*-toluenesulfonic acid for cyclodehydration led to facile migration of the trisubstituted $\Delta^{18,19}$ double bond to the isomeric tetrasubstituted $\Delta^{18,23}$ position. At this juncture, two additional steps were required to complete construction of ring F and thereby of the core of (−)-nodulisporic acid D (Scheme 16). The first step entailed conversion of the primary hydroxyl group to the corresponding mesylate (−)-**45**. Application of our now optimized annulation conditions [e.g., *t*-BuMgCl, $Zn(OTf)_2$ (10 equiv), toluene, reflux], developed during the total synthesis of (+)-nodulisporic acid F,[9] yielded (−)-**46**, albeit in modest yield (ca. 30%). Pleasingly, the reaction proceeded with high regioselectivity. Decreasing the amount of $Zn(OTf)_2$ to only 1 equiv improved the yield to 72%; the regioselectivity was now 20:1, favoring the C-alkylated heptacyclic core of (−)-nodulisporic acid D (**46**). In summary, the synthesis of the heptacyclic core of (−)-nodulisporic acid D (**46**) was achieved with a longest linear sequence of 10 steps beginning with (+)-**36**.

(+)-Nodulisporic Acids A and B: Development of a Scalable Synthesis of the Western Hemisphere [(−)-11]. The synthesis of the western hemisphere of nodulisporic acids A and B (−)-**11** was developed in our laboratory and reported in preliminary form in 2001.[19] As our synthetic program has progressed, we have engaged in the development of an improved, scalable synthesis to support the coupling studies. At issue was the number of required chromatographic purifications.

The sequence began with a five-step synthesis of aldehyde **49** from commercially available benzyl alcohol **47**; the overall yield was 70% (Scheme 17). The sequence proceeds with high efficiency and without resort to chromatography (100 g of **47** produced ca. 200 g of aldehyde **49**, the latter purified by crystallization). The Enders SAMP hydrazone/aldol tactic[32] was next employed to introduce the two requisite stereogenic centers in (−)-**11** (Scheme 18). To this end, treatment of hydrazone (+)-**36** with 1 equiv of *t*-BuLi at −78 °C was followed by stirring for 25 min, cooling to −100 °C, and addition of aldehyde **49**. The stability of the anion derived from (+)-**36** appeared to be poor above −100 °C, leading to substantial decomposition. A 2-fold excess of the nucleophile generated from (+)-**36** was therefore employed to maximize the yield of the corresponding *β*-hydroxyhydrazone (−)-**50**. As anticipated from the work of Enders,[32] the *syn* aldol adduct (−)-**50** proved to be the major product (71%; *syn:anti* = 5.5:1.0).

Removal of the chiral auxiliary via ozonolysis, followed by protection of the secondary alcohol as the TES ether, furnished (−)-**51**. Surprisingly, the ozonolysis step proved to be the most challenging step in this sequence. Numerous combinations of temperature, solvent, and reducing agents (e.g., PPh_3, Me_2S) were explored; yields ranged from 45 to 63%.[19] Analysis of the ozonolysis reaction mixture by NMR suggested that the initially formed product was not stable in the presence of ozone,

SCHEME 15. Coupling of Complex Aniline (−)-17 with Lactone (−)-18

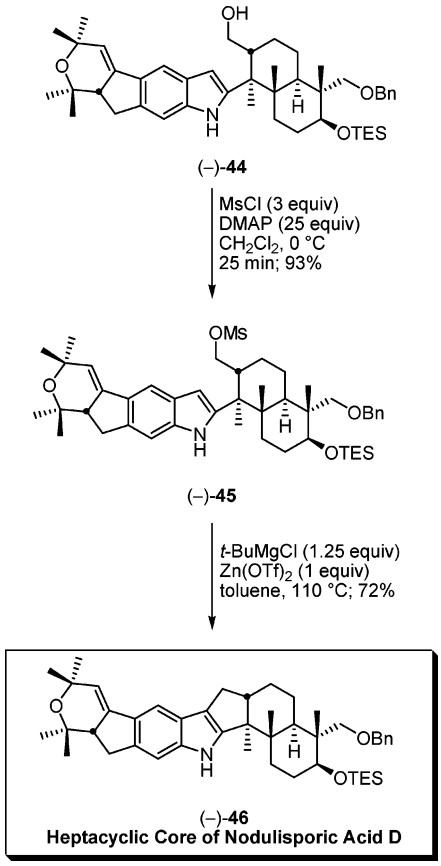


thus providing a possible explanation for the modest yield. Kinetic deprotonation of ketone (−)-**51**, followed by capture of the resulting lithium enolate with the Comins reagent,[34] furnished the requisite precursor (+)-**52** for the proposed tandem Stille cross-coupling event (Scheme 18). Initially, this two-step cyclization−deprotection sequence, employing the conditions developed by Shibasaki and Mori (Scheme 19),[36] was followed by removal of the phthalimide protecting group; only a modest yield (ca. 40−48%) resulted, due to reductive deiodination of (+)-**52**. We reasoned that deiodination was due to protonolysis of the incipient organometallic species. When the reaction mixture was rendered anhydrous prior to the addition of the Pd catalyst, by performing vacuum azeotropic removal of water with toluene, the yield of the two-step sequence was improved to 59%. The preparation of the western hemisphere (−)-**11** was thus achieved via a 14-step sequence (9 steps in the longest linear sequence); the overall yield was 21%.

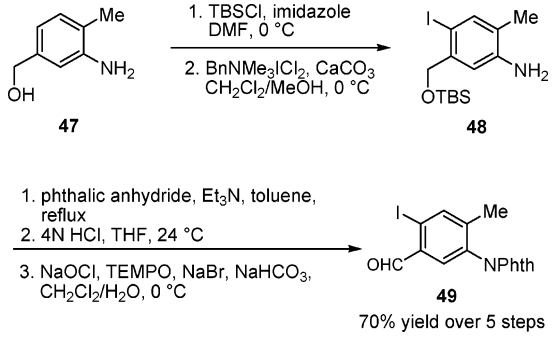
Elaboration of the Heptacyclic Core of Nodulisporic Acids A and B. Early on in our nodulisporic acid A and B synthetic program, we recognized that the dianion of (−)-**11** was not stable. That is, conversion of (−)-**11** to the *N*-trimethylsilyl derivative, followed by exposure to *sec*-butyllithium to generate dianion **53** at −78 °C (Scheme 20), led to rapid decomposition. A plausible pathway for the observed decomposition might comprise a 1,6-elimination of the OTES moiety resulting in the formation of **54**, capable of undergoing anionic polymerization. The net result was rapid consumption of aniline (−)-**11**. Thus, all attempts to couple dianion **53** with eastern hemisphere lactone

(36) Mori, M.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 3486−3493.

SCHEME 16. Preparation of the Heptacyclic Core of (−)-Nodulisporic Acid D

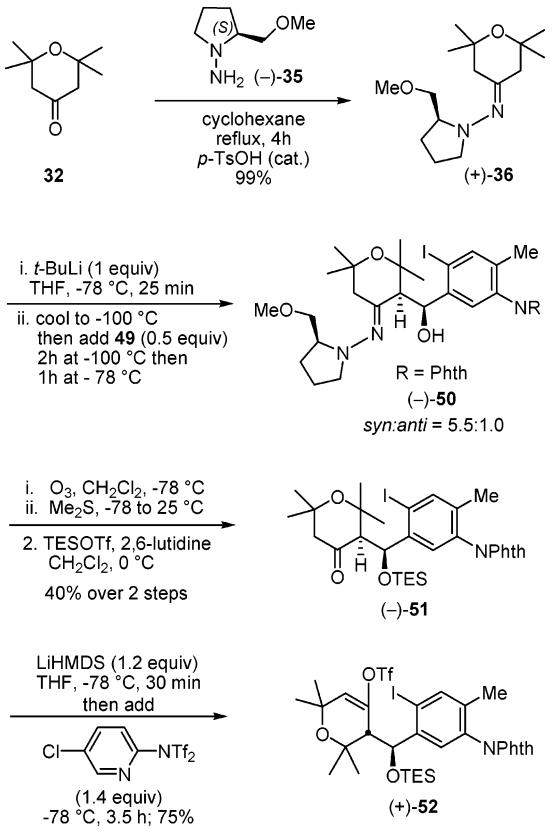


SCHEME 17. Preparation of Aldehyde 49 from Benzyl Alcohol 47

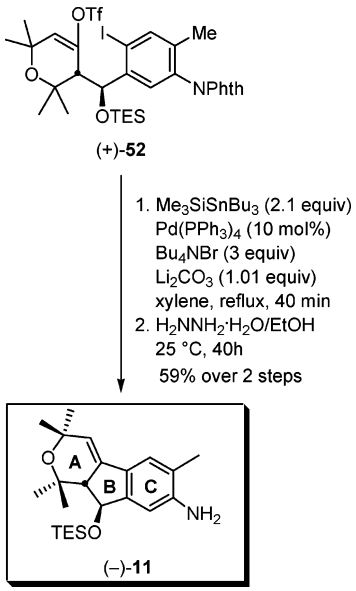


(+)-**12** proved unsuccessful. Undaunted, we reasoned that removal of the TES protecting group from the C(24) benzylic alcohol (nodulisporic acid A numbering) would lead to a more stable coupling partner, albeit a trianion. Also significant, the one-pot indole synthetic protocol involving N-silylation, followed by bismetalation would no longer be feasible. A new nitrogen protecting group would also be required. Screening a variety of aniline protecting groups revealed that the use of the *tert*-butoxycarbonyl (Boc) group led to the best coupling results (vide infra). To that end, protection of aniline (−)-**11** as the Boc derivative, followed by removal of the TES group (TBAF), furnished the modified western hemisphere (−)-**55** (Scheme 21). Treatment with a small excess of *tert*-butyllithium (ca. 3.3 equiv) at −78 °C led to what is presumed to be the corresponding trianion **56** (Scheme 21). Subsequent addition of an ethereal solution of lactone (+)-**12** containing 1 equiv of HMPA

SCHEME 18. Preparation of Coupling Precursor (+)-52

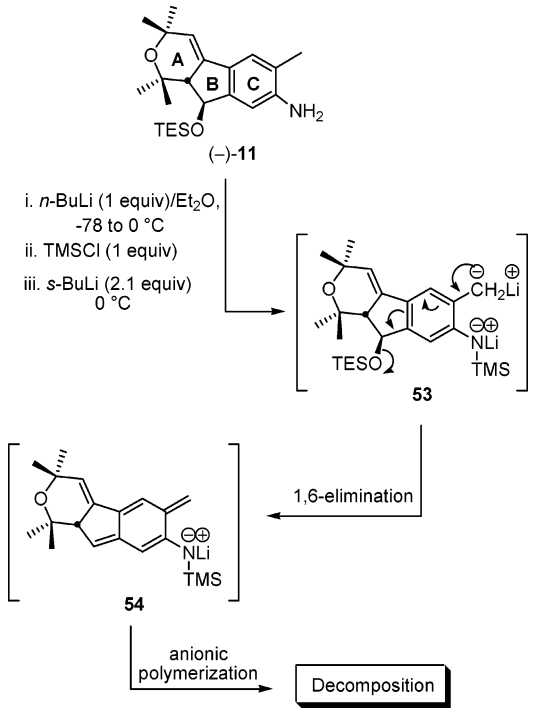


SCHEME 19. Preparation of Western Hemisphere Subtarget (−)-11

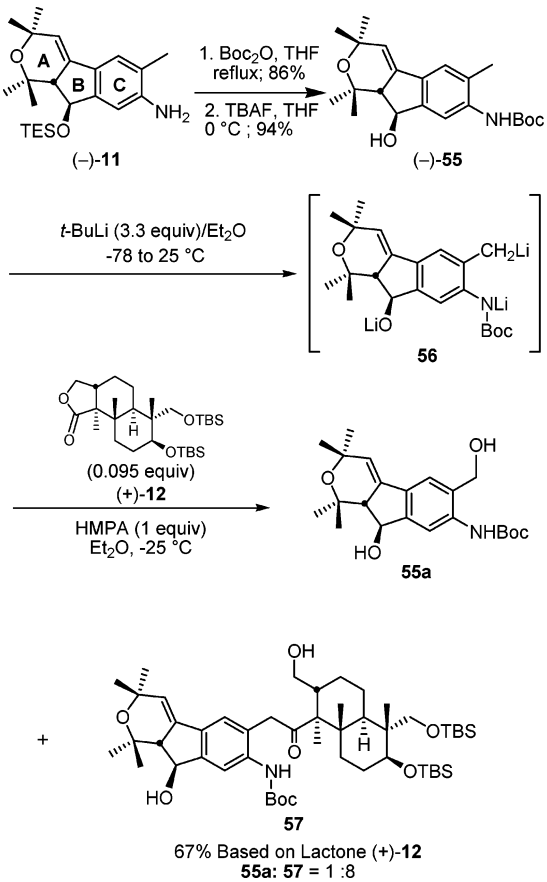


furnished ketoaniline **57** in 67% yield, in conjunction with oxidation product **55a** as a mixture (8:1, respectively). Again, a large excess of the western hemisphere aniline (−)-**55** was required to maximize the conversion of the eastern hemisphere lactone (+)-**12**. Careful chromatographic purification permitted recovery of nearly 84% of the valuable western hemisphere coupling partner (−)-**55**, which could be reused in subsequent coupling reactions. Mindful of the sensitivity of the C(24) hydroxyl group to acidic conditions, we next attempted to remove the Boc group under basic conditions (10% KOH/MeOH/at reflux), as prelude to formation of ring F. We had earlier demonstrated that these conditions removed the Boc

SCHEME 20. Conversion of Tricyclic Aniline (−)-11 to the Corresponding Dianion 53

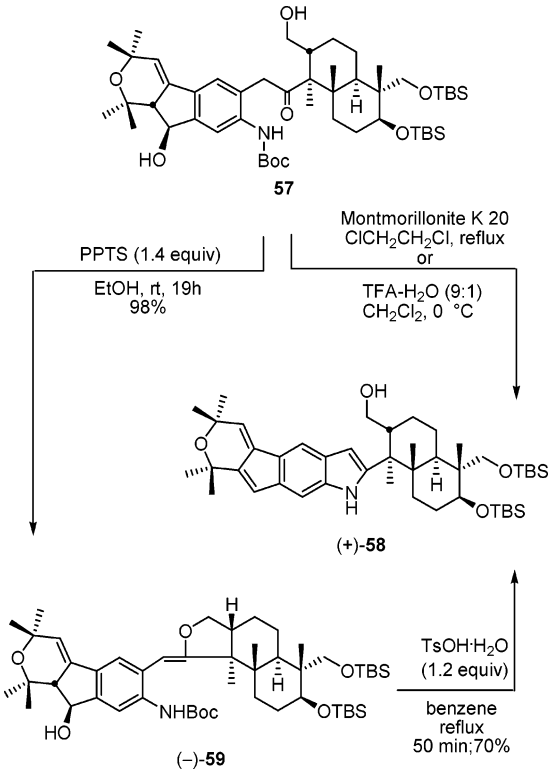


SCHEME 21. Preparation of a Modified Western Hemisphere Coupling Partner (−)-55 from (−)-11 and Coupling of Eastern Hemisphere (+)-12 with (−)-55



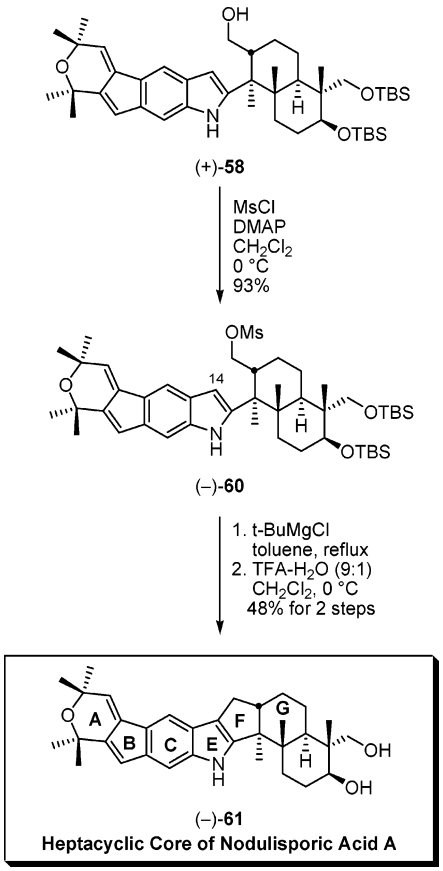
group from (−)-**55** in 94% yield. To our surprise, these conditions failed. Equally disappointing, various mild acidic conditions [e.g., montmorillonite K 20 in dichloroethane at reflux[37] or TFA/H_2O (9:1) in CH_2Cl_2 at 0 °C] led only to elimination of the C(24) hydroxyl, followed by indole formation (Scheme 22). However, upon exposure of **57** to PPTS (1.4 equiv), cyclic enol ether (−)-**59**, a single isomer (geometric isomerism unassigned), was produced in which both the Boc group and the C(24) hydroxyl remained intact. Further treatment of (−)-**59** with *p*-toluenesulfonic acid furnished the indole, but unfortunately loss of the C(24) hydroxyl also occurred. The yield of indole (+)-**58** was 70% (Scheme 22).

SCHEME 22. Indole Formation Studies



Elaboration of the F-Ring: Construction of the ABCEFGH Heptacyclic Skeleton of Nodulisporic Acids A and B. Despite the loss of the C(24) hydroxyl in (+)-**58**, we decided to explore the feasibility of F-ring construction to access the ABCEFGH core of the nodulisporic acids (Scheme 23). To this end, the primary hydroxyl was converted to the corresponding mesylate (−)-**60** and, again exposed to conditions developed during the total synthesis of (−)-isopentenylpaxilline (i.e., *t*-BuMgCl in toluene at reflux) to construct ring F.[11] In our previous synthetic studies (i.e., isopentenylpaxilline,[11] penitrem D,[12] nodulisporic acids D and F),[9,10] ring F construction proved to be one of the most challenging steps, due to competition between nucleophilic attack by the indole nitrogen. In the case of mesylate (−)-**60**, however, the desired C(14)-alkylated compound proved to be the major product (4:1). Initially, the undesired N-alkylation byproduct could not be separated from the desired C(14) alkylated product, but upon removal of the TBS protecting groups with trifluoroacetic acid (TFA), chromatographic separation proved possible; the heptacyclic indole (−)-**61** was obtained in 48% yield over two steps. Although lacking the C(24) hydroxyl group, indole (−)-**61** constitutes the heptacyclic ABCEFGH skeleton of (+)-nodulisporic acids A and B.

SCHEME 23. Elaboration of the F-Ring



In summary, the first total synthesis of (+)-nodulisporic acid F (**4**), as well as the heptacyclic core of nodulisporic acid D (−)-**46** has been achieved. In addition, we completed an effective union of the structurally complex western hemisphere aniline (−)-**55** with the eastern tricyclic lactone (+)-**12** employing a modified version our modular indole synthetic protocol. The *N*-Boc ketoaniline coupled product **57** was then converted to the corresponding indole (+)-**58**, albeit the acidic conditions led via dehydration to the loss of the C(24) hydroxyl group. Employing indole (+)-**58**, we were also able to elaborate ring F, thereby successfully achieving a synthesis of the ABCEFGH heptacyclic core skeleton (−)-**61** of nodulisporic acids A and B. In the following paper,[38] we describe a second-generation synthetic strategy, developed to circumvent the lability of the C(24) hydroxyl group.

Experimental Section

Preparation of Ketoaniline (+)-19. To a flame-dried 100 mL round-bottom flask equipped with a PTFE-coated stirbar were charged *o*-toluidine **14** (516 mg, 4.82 mmol, 1.0 equiv) and freshly distilled Et_2O (30 mL). The resulting clear, light yellow solution was cooled to −45 °C, treated with *n*-butyllithium (2.12 mL of a 2.5 M solution in hexanes, 5.29 mmol, 1.1 equiv) via syringe, and then warmed to 6 °C over 15 min. The resulting orange solution was cooled to −38 °C and treated with chlorotrimethylsilane (566.5

(37) Shaikh, N. S.; Gajare, A. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron Lett.* **2000**, *41*, 385−387.

(38) Smith, A. B., III; Kürti, L.; Davulcu, A. H.; Cho, Y. S.; Ohmoto, K. *J. Org. Chem.* **2007**, *72*, 4611−4620.

mg, 5.21 mmol, 1.05 equiv) via syringe, and then warmed to 5 °C over 15 min. The resulting off-white slurry was cooled to −40 °C, treated with *sec*-butyllithium (7.56 mL of a 1.4 M solution in cyclohexane, 10.59 mmol, 2.2 equiv), warmed to 4 °C, and aged at said temperature for 58 min to give a canary yellow slurry. This mixture was cooled to −35 °C and treated with a solution of lactone (+)-**12** (195 mg, 0.382 mmol, 0.079 equiv) in freshly distilled Et_2O (10 mL) via syringe, and the resulting mixture was warmed to 12 °C over 45 min. Upon quenching with saturated ammonium chloride (50 mL), the mixture was diluted with brine (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow oily residue. Flash column chromatography (11.0 cm × 5.0 cm SiO_2, hexanes/EtOAc 4:1 → 2:1) afforded ketoaniline (+)-**19** (234 mg, 98%) as an off-white foam: $[\alpha]_D^{25} = +8.33$ (*c* 0.54, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (dt, J = 1.5, 7.4 Hz, 1H), 6.89 (dd, J = 1.1, 7.4 Hz, 1H), 6.71 (dt, J = 1.1, 7.4 Hz, 1H), 6.68 (br d, J = 8.2 Hz, 1H), 3.88 (d, J = 16.8 Hz, 1H), 3.74 (dd, J = 5.2, 11.2 Hz, 1H), 3.59 (d, J = 16.8 Hz, 1H), 3.38 (d, J = 9.7 Hz, 1H), 3.27 (dd, J = 6.3, 10.8 Hz, 1H), 3.14 (dd, J = 7.4, 10.8 Hz, 1H), 3.13 (d, J = 9.7 Hz, 1H), 2.68 (m, 1H), 1.98 (dd, J = 3.7, 12.3 Hz, 1H), 1.90 (app dt, J = 4.1, 12.3 Hz, 1H), 1.58−1.72 (m, 4H), 1.30−1.40 (m, 5H), 1.22 (m, 2H), 1.00 (s, 3H), 0.99 (m, 2H), 0.95 (s, 9H), 0.88 (s, 9H), 0.64 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 146.1, 130.9, 127.9, 121.4, 118.7, 116.7, 71.1, 66.0, 64.2, 57.4, 46.2, 43.8, 40.3, 40.0, 35.8, 32.9, 27.2, 25.9, 25.8, 24.9, 20.6, 18.1, 17.9, 17.2, 12.8, 11.4, −3.7, −4.9, −5.4, −5.7; IR (neat) ν_{max} 3367 (br m), 2946 (s), 2862 (s), 1693 (m), 1632 (m), 1466 (m), 1389 (m), 1308 (w), 1254 (m), 1088 (s), 841 (s), 768 (s) cm^{-1}; HRMS (ESI-MS) calcd for $C_{35}H_{63}NO_4Si_2Na^+$ [(M + Na)$^+$] 640.4193, found 640.4187.

Preparation of Indole (+)-20. To a 100 mL round-bottom flask equipped with a water-cooled reflux condenser and PTFE-coated stirbar were charged ketoaniline (+)-**19** (220 mg, 0.356 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (4.8 mg, 0.025 mmol, 0.07 equiv), and HPLC-grade benzene (50 mL), and the resulting mixture was heated at reflux for 4 h. Upon cooling, the mixture was diluted with saturated $NaHCO_3$ (25 mL) and extracted with Et_2O (1 × 100, 2 × 50 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow foam. Flash column chromatography (11.5 cm × 4.5 cm SiO_2, hexanes/EtOAc 20:1 → 5:1) afforded indole (+)-**20** (202.5 mg, 95%) as a clear, colorless oil: $[\alpha]_D^{25} = +21.63$ (*c* 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.54 (br d, J = 7.5 Hz, 1H), 7.31 (br d, J = 7.3 Hz, 1H), 7.11 (br t, J = 6.9 Hz, 1H), 7.06 (br t, J = 7.2 Hz, 1H), 6.28 (s, 1H), 3.71 (dd, J = 5.7, 10.8 Hz, 1H), 3.55 (br d, J = 9.0 Hz, 1H), 3.38 (d, J = 9.6 Hz, 1H), 3.25 (br t, J = 9.7 Hz, 1H), 3.16 (d, J = 9.6 Hz, 1H), 2.42 (m, 1 H), 2.14 (br d, J = 12.5 Hz, 1H), 2.08 (br d, J = 11.6 Hz, 1H), 1.30−1.70 (m, 10H), 1.15 (br d, J = 11.7 Hz, 1H), 0.97 (s, 3H), 0.95 (s, 9H), 0.85 (s, 9H), 0.62 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 135.0, 128.3, 127.8, 120.9, 119.7, 119.5, 110.4, 102.5, 71.7, 66.4, 64.2, 46.7, 43.7, 41.8, 40.5, 36.8, 31.2, 27.3, 26.5, 25.9, 25.8, 21.0, 18.1, 18.0, 17.4, 12.9, −3.7, −4.9, −5.3, −5.6; IR (neat) ν_{max} 3359 (br s), 2947 (br s), 1462 (m), 1389 (m), 1244 (m), 1092 (s), 1003 (m), 845 (s), 775 (s), 671 (w) cm^{-1}; HRMS (ESI-MS) calcd for $C_{35}H_{62}NO_3Si_2^+$ [(M + H)$^+$] 600.4268, found 600.4293.

Preparation of Methanesulfonate (+)-21. To a 50 mL round-bottom flask equipped with a PTFE-coated stirbar were charged indole (+)-**20** (200 mg, 0.333 mmol, 1.0 equiv), 4-dimethylaminopyridine (1.02 g, 8.33 mmol, 25.0 equiv), and anhydrous CH_2Cl_2 (40 mL). The clear, colorless solution was cooled to 0 °C and then treated with methanesulfonyl chloride (381.8 mg, 3.33 mmol, 10.0 equiv) via syringe. The thin white slurry that resulted was aged at 0 °C for 40 min and then poured into a mixture of saturated ammonium chloride (75 mL) and brine (75 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow solid. Flash column chromatography (14.0 cm × 3.5 cm SiO_2, hexanes/EtOAc 9:1 → 5:1) afforded methanesulfonate (+)-**21** (225 mg, >99%) as a light yellow oil: $[\alpha]_D^{25} = +6.63$ (*c* 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (br s, 1H), 7.55 (br d, J = 7.8 Hz, 1H), 7.34 (br d, J = 7.4 Hz, 1H), 7.14 (br t, J = 7.1 Hz, 1H), 7.08 (br t, J = 7.1 Hz, 1H), 6.28 (s, 1H), 4.18 (br s, 1H), 3.81 (br t, J = 9.7 Hz, 1H), 3.71 (dd, J = 4.8, 10.8 Hz, 1H), 3.40 (d, J = 9.7 Hz, 1H), 3.17 (d, J = 9.7 Hz, 1H), 2.87 (s, 3H), 2.75 (br m, 1H), 2.20 (m, 1H), 2.08 (br d, J = 9.7 Hz, 1H), 1.42−1.66 (m, 7H), 1.34 (s, 3H), 0.96 (s, 6H), 0.86 (s, 9H), 0.63 (s, 3H), 0.08 (s 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 135.2, 127.7, 121.2, 119.7, 119.6, 110.5, 102.8, 74.6, 71.5, 65.8, 64.1, 46.5, 43.7, 40.6, 39.1, 37.0, 36.7, 30.9, 27.2, 25.9, 25.8, 20.6, 18.0, 17.9, 17.2, 15.2, 12.8, −3.7, −4.9, −5.4, −5.7; IR (neat) ν_{max} 3416 (br m), 2953 (s), 2856 (m), 1459 (m), 1352 (m), 1252 (m), 1175 (m), 1091 (m), 949 (m), 836 (m), 774 (m) cm^{-1}. HRMS (ESI-MS) calcd for $C_{36}H_{63}NO_5SSi_2Na^+$ [(M + Na)$^+$] 700.3863, found 700.3892.

Preparation of Pentacycle (+)-22. To a 100 mL round-bottom flask equipped with a water-cooled reflux condenser and PTFE-coated stirbar were charged mesylate (+)-**21** (50.0 mg, 0.074 mmol, 1.0 equiv), zinc triflate (270 mg, 0.740 mmol, 10.0 equiv), and anhydrous toluene (25 mL). The resulting mixture was heated to 110 °C and treated with *tert*-butylmagnesium chloride (555 μL of a 2.0 M solution in Et_2O, 1.11 mmol, 15.0 equiv) added dropwise via syringe. Upon cooling, the mixture was quenched with saturated ammonium chloride (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to an off-white solid. Flash column chromatography (12.0 cm × 4.5 cm SiO_2, hexanes/Et_2O 20:1) afforded pentacycle (+)-**22** (41.2 mg, 96%) as a waxy, white residue: $[\alpha]_D^{25} = +15.43$ (*c* 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (br s, 1H), 7.42 (m, 1H), 7.30 (m, 1H), 7.06 (m, 2H), 3.76 (dd, J = 5.2, 11.2 Hz, 1H), 3.44 (d, J = 10.1 Hz, 1H), 3.15 (d, J = 10.1 Hz, 1H), 2.76 (m, 1H), 2.66 (dd, J = 6.3, 13.0 Hz, 1H), 2.32 (dd, J = 10.8, 13.4 Hz, 1H), 2.02 (dd, J = 3.0, 12.7 Hz, 1H), 1.67−1.93 (m, 4H), 1.46−1.61 (m, 4H), 1.10 (s, 3H), 1.01 (s, 3H), 0.94 (s, 9H), 0.89 (s, 9H), 0.63 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 145.5, 130.8, 125.9, 125.1, 123.9, 123.8, 116.9, 77.4, 69.9, 58.5, 54.5, 49.3, 44.6, 42.6, 38.8, 33.4, 33.1, 31.5, 30.7, 28.3, 24.3, 23.7, 23.6, 20.0, 17.7, 2.1, 0.7, 0.4, −0.1; IR (neat) ν_{max} 3460 (br w), 2927 (s), 2855 (s), 1471 (m), 1385 (m), 1255 (m), 1084 (s), 835 (s), 773 (s), 739 (m) cm^{-1}; HRMS (ESI-MS) calcd for $C_{35}H_{60}NO_2Si_2^+$ [(M + H)$^+$] 582.4162, found 582.4148.

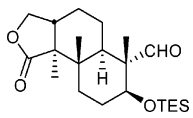
Physical Data for Undesired Cyclization Regioisomer (+)-23. Colorless needles; mp = 107−108.5 °C; $[\alpha]_D^{25} = +8.12$ (*c* 0.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (br d, J = 8.6 Hz, 1H), 7.19 (br d, J = 7.4 Hz, 1H), 7.09 (br t, J = 7.1 Hz, 1H), 7.03 (br t, J = 7.4 Hz, 1H), 6.04 (s, 1H), 4.00 (br t, J = 7.8 Hz, 1H), 3.77 (dd, J = 4.8, 10.1 Hz, 1H), 3.59 (br t, J = 10.1 Hz, 1H), 3.46 (d, J = 9.7 Hz, 1H), 3.15 (d, J = 9.7 Hz, 1H), 2.84 (m, 1H), 2.17 (dd, J = 2.6, 13.0 Hz, 1H), 1.00−1.75 (m, 8H), 1.27 (s, 3H), 1.14 (s, 3H), 0.94 (s, 9H), 0.90 (s, 9H), 0.64 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 132.1, 125.5, 120.4, 120.1, 118.8, 108.9, 91.5, 71.9, 64.3, 50.9, 46.8, 45.9, 43.7, 38.8, 36.8, 31.9, 30.4, 29.7, 27.7, 25.9 (2), 22.9, 21.9, 18.1, 15.7, 12.2, −3.5, −4.9, −5.2, −5.7; IR (neat) ν_{max} 2953 (s), 2928 (s), 2857 (m), 1458 (m), 1387 (w), 1251 (m), 1089 (s), 836 (s), 771 (s) cm^{-1}. HRMS (ESI-MS) calcd for $C_{35}H_{60}NO_2Si_2^+$ [(M + H)$^+$] 582.4163, found 582.4158.

Preparation of Diol (−)-25. To a 150 mL round-bottom flask equipped with a PTFE-coated stirbar were charged lactone (+)-**12** (968 mg, 1.89 mmol, 1.0 equiv) and freshly distilled THF (10 mL). The resulting clear, colorless solution was cooled to 0 °C and then

treated with a solution of tetrabutylammonium fluoride (5.87 mL of a 1.0 M solution in THF, 5.87 mmol, 3.1 equiv). The dark orange solution that resulted was warmed to 24 °C over the course of 35 min and then aged at 24 °C for 40 h. The reaction mixture was concentrated in vacuo to a dark orange residue. Flash column chromatography (16.0 cm × 5.0 cm SiO_2, EtOAc, 100% → EtOAc/MeOH, 9:1) afforded the diol (−)-**25** (482 mg, 90%) as a waxy, white residue: $[\alpha]_D^{25} = -11.38$ (*c* 0.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (dd, J = 7.1, 8.2 Hz, 1H), 3.91 (dd, J = 8.2, 11.2 Hz, 1H), 3.66 (br d, J = 10.4 Hz, 1H), 3.63 (dd, J = 5.9, 11.2 Hz, 1H), 3.37 (br d, J = 10.4 Hz, 1H), 2.62 (dddd, J = 3.4, 3.4, 7.1, 11.2 Hz, 1H), 2.47 (br s, 2H), 2.14 (ddd, J = 3.4, 3.4, 13.4 Hz, 1H), 1.65−1.76 (m, 3H), 1.54−1.64 (m, 3H), 1.34−1.47 (m, 2H), 1.17 (s, 3H), 1.13 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 75.3, 70.0, 69.2, 49.8, 42.4, 39.9, 39.7, 38.4, 29.7, 26.9, 21.8, 21.5, 18.1, 11.2, 11.1; IR (neat) ν_{max} 3394 (br s), 2942 (s), 1763 (s), 1454 (w), 1385 (w), 1238 (w), 1165 (w), 1045 (s), 984 (m) cm^{-1}. HRMS (CI-MS) calcd for $C_{16}H_{27}O_4^+$ [(M + H)$^+$] 283.1909, found 283.1909.

Preparation of Hydroxyaldehyde (−)-26. To a 150 mL round-bottom flask equipped with a PTFE-coated stirbar were charged diol (−)-**25** (479 mg, 1.89 mmol, 1.0 equiv), TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical, 2.3 mg, 0.015 mmol, 0.008 equiv), potassium bromide (3.5 mg, 0.029 mmol, 0.016 equiv), saturated $NaHCO_3$ solution (25 mL), and dichloromethane (50 mL). With vigorous stirring, the resulting biphasic mixture was cooled to 0 °C and then treated with sodium hypochlorite (commercial bleach, 2.47 mL of a ca. 0.72 M solution, 1.05 equiv) to give a vivid orange solution (the orange color is due to the persistent oxoammonium salt derived from TEMPO and serves as a visual indicator of the reaction endpoint). The resulting mixture was diluted with brine (50 mL) and saturated $NaHCO_3$ solution (50 mL) and subsequently extracted with EtOAc (3 × 75 mL). The combined organic extract was washed with brine (100 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to give analytically pure hydroxyaldehyde (−)-**26** (480 mg, quantitative yield) as a white solid: mp 106−108 °C; $[\alpha]_D^{25} = -10.35$ (*c* 0.77, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 4.18 (dd, J = 7.4, 8.6 Hz, 1H), 3.93 (dd, J = 8.6, 11.2 Hz, 1H), 3.76 (dd, J = 4.8, 11.2 Hz, 1H), 2.62 (m, 1H), 2.19 (ddd, J = 3.4, 3.4, 13.4 Hz, 1H), 1.89 (m, 1H), 1.11−1.86 (m, 8H), 1.22 (s, 3H), 1.14 (s, 3H), 1.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 179.1, 72.4, 69.1, 54.8, 49.5, 39.9, 39.3, 37.7, 29.6, 26.4, 24.0, 21.3, 17.9, 11.1, 8.6; IR (neat) ν_{max} 3402 (br s), 2943 (m), 1728 (s), 1446 (w), 1354 (w), 1254 (w), 1061 (w), 968 (w), 733 (w) cm^{-1}. HRMS (CI-MS) calcd for $C_{16}H_{24}O_4^+$ [(M)$^+$] 280.1674, found 280.1671.

Preparation of TES Ether (−)-S1.



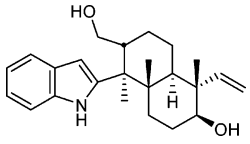
To a 200 mL round-bottom flask equipped with a PTFE-coated stirbar were charged hydroxyaldehyde (−)-**26** (170 mg, 0.606 mmol, 1.0 equiv), 2,6-lutidine (162 mg, 1.52 mmol, 2.5 equiv), and anhydrous dichloromethane (25 mL). The resulting clear, colorless solution was cooled to 0 °C, treated with triethylsilyl triflate (168 mg, 0.636 mmol, 1.05 equiv), warmed to 24 °C over 35 min, and then aged at 24 °C for 30 min. The reaction was then quenched with saturated ammonium chloride solution (20 mL) and subsequently extracted with dichloromethane (3 × 25 mL). The combined organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow solid residue. Flash column chromatography (13.0 cm × 3.5 cm SiO_2, hexanes/EtOAc 4:1 → 2:1) afforded the TES ether (−)-**S1** (231 mg, 97%) as a waxy white residue: mp = 101−103 °C; $[\alpha]_D^{25} = -14.77$ (*c* 0.68, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 4.13 (dd, J = 8.2, 10.4 Hz, 1H), 3.87 (dd, J = 8.2, 11.2 Hz, 1H), 3.72 (dd, J = 4.8, 11.2 Hz, 1H), 2.56 (m, 1H), 2.09 (ddd, J = 3.3, 3.3, 13.5 Hz, 1H), 1.82 (m, 1H), 1.50−1.75 (m, 5H), 1.28−1.41 (m, 2H), 1.17 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 0.87 (t, J = 8.6 Hz, 9H), 0.48 (q, J = 8.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 179.1, 73.7, 69.0, 55.4, 49.4, 39.8, 38.9, 37.5, 29.5, 26.9, 23.8, 21.2, 17.8, 10.9, 9.0, 6.6, 4.9; IR (neat) ν_{max} 2952 (s), 2876 (m), 2345 (w), 1769 (s), 1724 (s), 1453 (m), 1384 (m), 1241 (m), 1106 (s), 1050 (w), 1009 (w) cm^{-1}. HRMS (CI-MS) calcd for $C_{22}H_{39}O_4Si^+$ [(M + H)$^+$] 395.2618, found 395.2615.

Preparation of Revised Eastern Hemisphere Subtarget (−)-27. To a flame-dried 50 mL round-bottom flask equipped with a PTFE-coated stirbar were charged methyltriphenylphosphonium bromide (597.5 mg, 1.67 mmol, 3.0 equiv) and freshly distilled THF (20 mL). The resulting mixture was cooled to 0 °C, treated with potassium hexamethyldisilazide (3.34 mL of a 0.5 M solution in toluene, 1.67 mmol, 3.0 equiv) via syringe, and warmed to 24 °C over 30 min to give a lemon yellow slurry. The reaction mixture was then cooled to 0 °C and treated with a solution of aldehyde (−)-**S1** (220 mg, 0.557 mmol, 1.0 equiv) in freshly distilled THF (15 mL) via syringe, and the resulting mixture was again warmed to 24 °C over 30 min. Upon quenching with saturated ammonium chloride (25 mL), the mixture was diluted with brine (50 mL) and extracted with Et_2O (1 × 100, 2 × 50 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to an orange oily residue. Flash column chromatography (15.0 cm × 3.5 cm SiO_2, hexanes/EtOAc 18:1 → 9:1) afforded compound (−)-**27** (208.5 mg, 95%) as a colorless oil that crystallizes on standing: mp 74−76 °C; $[\alpha]_D^{25} = -16.28°$ (*c* 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (dd, J = 10.4, 17.1 Hz, 1H), 5.04 (d, J = 10.4 Hz, 1H), 4.91 (d, J = 17.1 Hz, 1H), 4.12 (dd, J = 7.7, 8.2 Hz, 1H), 3.87 (dd, J = 8.6, 11.7 Hz, 1H), 3.28 (dd, J = 4.8, 11.7 Hz, 1H), 2.58 (dddd, J = 4.2, 4.2, 8.7, 11.9 Hz, 1H), 2.09 (ddd, J = 3.3, 3.3, 13.4 Hz, 1H), 1.76−1.66 (m, 1H), 1.64−1.48 (m, 4H), 1.39−1.25 (m, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 0.91 (s, 3H), 0.90 (t, J = 7.8 Hz, 9H), 0.51 (q, J = 7.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 148.9, 113.7, 77.6, 69.2, 49.9, 46.5, 43.7, 40.2, 37.9, 29.7, 27.6, 22.9, 21.5, 18.2, 11.0, 10.9, 6.8, 5.1; IR (neat) ν_{max} 2949 (s), 2877 (s), 1774 (s), 1637 (w), 1456 (m), 1412 (m), 1235 (m), 1107 (s), 1072 (s), 1049 (s), 1003 (s), 914 (m), 877 (m), 826 (m), 737 (s) cm^{-1}. HRMS (CI) calcd for $C_{23}H_{41}O_3Si^+$ [(M + H)$^+$] 393.2825, found 393.2816.

Preparation of Ketoaniline (+)-28. To a flame-dried 100 mL round-bottom flask equipped with a PTFE-coated stirbar were charged *o*-toluidine **14** (532.2 mg, 4.96 mmol, 1.0 equiv) and freshly distilled Et_2O (40 mL). The resulting clear, light yellow solution was cooled to −30 °C, treated with *n*-butyllithium (2.18 mL of a 2.5 M solution in hexanes, 5.46 mmol, 1.1 equiv) via syringe, and then warmed to 24 °C over 10 min and aged at said temperature for an additional 5 min. The resulting orange solution was cooled to −10 °C and treated with chlorotrimethylsilane (566.5 mg, 5.21 mmol, 1.05 equiv) via syringe and then warmed to 24 °C over 10 min. The resulting white slurry was cooled to −30 °C, treated with *sec*-butyllithium (7.8 mL of a 1.4 M solution in cyclohexane, 10.92 mmol, 2.2 equiv), warmed to 0 °C and aged at said temperature for 50 min to give a canary yellow slurry. This mixture was cooled to −50 °C and treated with a solution of lactone (−)-**27** (170 mg, 0.433 mmol, 0.10 equiv) in freshly distilled Et_2O (10 mL) via syringe, and the resulting mixture was warmed to 8 °C over 90 min. Upon quenching with saturated ammonium chloride (10 mL), the mixture was diluted with brine (25 mL) and extracted with Et_2O (4 × 30 mL). The combined organic extract was dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow oily residue. Flash column chromatography (14.0 cm × 3.5 cm SiO_2, hexanes/EtOAc 4:1 → 1:3) afforded ketoaniline (+)-**28** (184 mg, 85%) as a colorless oil: $[\alpha]_D^{25} = +64.2$ (*c* 2.12, $CHCl_3$); ^{1}H

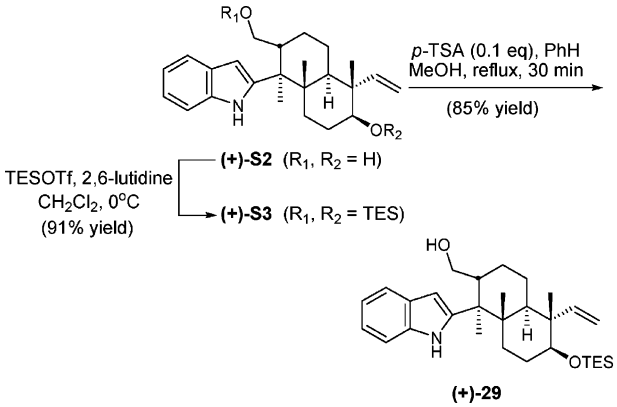
NMR (500 MHz, $CDCl_3$) δ 7.06 (dt, J = 1.1, 7.8 Hz, 1H), 6.88 (br d, J = 7.4 Hz, 1H), 6.71 (dt, J = 1.1, 7.4 Hz, 1H), 6.67 (br d, J = 7.8 Hz, 1H), 5.49 (dd, J = 10.8, 17.4 Hz, 1H), 5.07 (d, J = 10.8 Hz, 1H), 4.94 (d, J = 17.4 Hz, 1H), 3.88 (d, J = 16.7 Hz, 1H), 3.58 (d, J = 16.8 Hz, 1H), 3.34 (dd, J = 4.5, 11.5 Hz, 1H), 3.24 (dd, J = 6.3, 10.6 Hz, 1H), 3.11 (dd, J = 7.1, 10.6 Hz, 1H), 3.6−3.0 (br s, 2H), 2.65 (m, 1H), 1.93 (m, 1H), 1.78−1.58 (m, 3H), 1.47−1.22 (m, 9H), 1.01 (s, 3H), 0.97 (s, 3H), 0.95 (t, J = 7.7 Hz, 9H), 0.56 (q, J = 7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6, 149.2, 146.0, 130.8, 127.9, 121.4, 118.6, 116.7, 113.7, 77.3, 65.8, 57.2, 46.6, 46.1, 46.0, 42.7, 40.1, 33.1, 27.6, 24.9, 21.4, 16.9, 11.8, 11.4, 6.9, 5.1; IR (neat) ν_{max} 3366 (br s), 2950 (s), 2876 (s), 1691 (m), 1631 (m), 1459 (m), 1384 (m), 1303 (m), 1237 (m), 1112 (s), 1007 (s), 912 (w), 827 (w), 742 (m) cm^{-1}. HRMS (ESI-MS) calcd for $C_{30}H_{49}NO_3NaSi^+$ [(M + Na)$^+$] 522.3379, found 522.3377.

Preparation of Indole (+)-29. To a 100 mL round-bottom flask equipped with a water-cooled reflux condenser and PTFE-coated stirbar were charged ketoaniline (+)-**28** (240 mg, 0.481 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (6.04 mg, 0.024 mmol, 0.05 equiv), and HPLC-grade benzene (50 mL), and the resulting mixture was heated at reflux for 4 h. Upon cooling, the mixture was diluted with saturated $NaHCO_3$ (25 mL) and extracted with Et_2O (1 × 100, 2 × 50 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow oil. Flash column chromatography (11.5 cm × 4.5 cm SiO_2, hexanes/EtOAc 20:1 → 5:1) afforded indole (+)-**29** (220 mg, 95%) as a clear, colorless oil and diol (+)-**S2** (11.6 mg, 5%) as a white solid. **Physical data for indole:** $[\alpha]_D^{25}$ +10.8 (*c* 1.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.54 (app d, J = 7.4 Hz, 1H), 7.32 (app d, J = 7.8 Hz, 1H), 7.12 (dt, J = 1.5, 7.8 Hz, 1H), 7.07 (dt, J = 1.1, 7.5 Hz, 1H), 6.29 (s, 1H), 5.53 (dd, J = 10.8, 17.1 Hz, 1H), 5.08 (dd, J = 1.5, 10.8 Hz, 1H), 4.96 (dd, J = 1.5, 17.1 Hz, 1H), 3.56 (br d, J = 9.3 Hz, 1H), 3.33 (dd, J = 5.2, 10.8 Hz, 1H), 3.24 (dd, J = 8.2, 10.4 Hz, 1H), 2.41 (m, 1H), 2.11 (m, 1H), 1.12−1.65 (m, 9H), 1.32 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H), 0.91 (t, J = 8.2 Hz, 9H), 0.53 (q, J = 8.2 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 142.5, 135.0, 127.8, 121.0, 119.8, 119.5, 113.7, 110.4, 102.6, 77.9, 66.4, 46.8, 46.7, 43.7, 41.9, 40.4, 31.6, 27.7, 26.6, 21.9, 17.2, 14.8, 11.9, 6.9, 5.2; IR (neat) ν_{max} 3431 (br s), 2950 (s), 2877 (s), 1723 (w), 1636 (w), 1525 (w), 1457 (m), 1411 (m), 1379 (m), 1344 (m), 1291 (m), 1238 (m), 1109 (s), 1004 (s), 909 (m), 825 (m), 735 (s) cm^{-1}. HRMS (ESI-MS) calcd for $C_{30}H_{48}NO_2Si^+$ [(M + H)$^+$] 482.3454, found 482.3431. **Physical Data for Diol (+)-S2:**

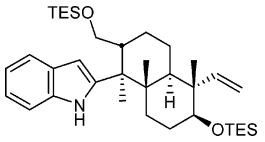


Colorless needles, mp 208 − 209 °C; $[\alpha]_D^{25}$ +63.6 (*c* 0.50, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.48 (br d, J = 7.8 Hz, 1H), 7.36 (br d, J = 7.8 Hz, 1H), 7.05 (dt, J = 1.1, 7.4 Hz, 1H), 6.98 (dt, J = 1.1, 7.4 Hz, 1H), 6.28 (s, 1H), 5.69 (dd, J = 10.8, 17.5 Hz, 1H), 5.19 (d, J = 10.8 Hz, 1H), 5.07 (d, J = 17.5 Hz, 1H), 3.57 (br s, 1H), 3.38 (dd, J = 4.8, 11.2 Hz, 1H), 3.15 (br t, J = 8.9 Hz, 1H), 2.49 (br m, 1H), 2.21 (br d, J = 11.9 Hz, 1H), 1.17 (br m, 1H), 1.37 (s, 3H), 1.3−1.7 (m, 8H), 1.17 (br s, 1H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 143.7, 137.2, 129.2, 121.5, 120.5, 119.8, 114.6, 111.7, 102.9, 79.6, 78.2, 66.8, 48.1, 47.5, 45.2, 42.9, 41.6, 33.2, 27.6 (2), 23.2, 17.9, 12.3; IR (neat) ν_{max} 3300 (br m), 2932 (br m), 1455 (m), 1005 (m), 750 (m) cm^{-1}. HRMS (ESI-MS) calcd for $C_{24}H_{34}NO_2^+$ [(M + H)$^+$] 368.2589, found 368.2583.

Protocol for Recycling of Diol (+)-S2.



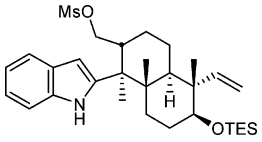
Preparation of Bis-TES Ether (+)-S3.



To a 100 mL round-bottom flask equipped with a PTFE-coated stirbar were charged diol (+)-**S2** (40 mg, 0.108 mmol, 1.0 equiv), 2,6-lutidine (58.4 mg, 0.545 mmol, 5.0 equiv), and anhydrous dichloromethane (50 mL). The clear, colorless solution was cooled to 0 °C, treated with triethylsilyl triflate (63.3 mg, 0.239 mmol, 2.20 equiv), and subsequently warmed to 24 °C over 30 min. The reaction was then quenched with saturated ammonium chloride solution (20 mL) and subsequently extracted with dichloromethane (3 × 25 mL). The combined organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow oily residue. Flash column chromatography (17.5 cm × 3.5 cm SiO_2, hexanes) afforded (+)-**S3** (59.2 mg, 91%) as a light yellow oil: $[\alpha]_D^{25}$ = −0.71 (*c* 1.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.57 (br d, J = 7.4 Hz, 1H), 7.32 (br d, J = 7.8 Hz, 1H), 7.14 (br t, J = 7.1 Hz, 1H), 7.09 (br t, J = 7.4 Hz, 1H), 6.31 (s, 1H), 5.56 (dd, J = 10.8, 17.5 Hz, 1H), 5.11 (d, J = 10.8 Hz, 1H), 4.98 (d, J = 17.5 Hz, 1H), 3.53 (br d, J = 8.9 Hz, 1H), 3.37 (dd, J = 5.6, 10.4 Hz, 1H), 3.18 (dd, J = 7.3, 9.7 Hz, 1H), 2.39 (m, 1H), 2.18 (br d, J = 13.8 Hz, 1H), 1.32 (s, 3H), 1.28−1.70 (m, 8H), 0.98 (s, 3H), 0.97 (s, 3H), 0.95 (t, J = 7.8 Hz, 9H), 0.92 (t, J = 7.8 Hz, 9H), 0.56 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 142.8, 134.9, 127.9, 120.9, 119.7, 119.4, 113.6, 110.3, 102.6, 77.9, 66.2, 46.8, 46.7, 43.8, 42.3, 40.4, 31.5, 27.8, 26.8, 22.1, 17.1, 15.1, 11.8, 6.9, 6.7, 5.2, 4.3; IR (neat) ν_{max} 3488 (br w), 3440 (br w), 2952 (br s), 2875 (s), 1636 (w), 1526 (w), 1457 (m), 1411 (m), 1289 (m), 1236 (m), 1094 (s), 1004 (s), 811 (m), 734 (s) cm^{-1}. HRMS (ESI-MS) calcd for $C_{36}H_{62}NO_2Si_2^+$ [(M + H)$^+$] 596.4319, found 596.4335.

Preparation of Indole (+)-29 from Bis-TES Ether (+)-S3. To a 50 mL round-bottom flask equipped with a water-cooled reflux condenser and PTFE-coated stirbar were charged bis-TES ether (+)-**S3** (50.0 mg, 0.084 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (2.11 mg, 0.0084 mmol, 0.1 equiv), methanol (10 μL), and HPLC-grade benzene (10 mL), and the resulting mixture was heated at reflux for 30 min. Upon cooling, the mixture was diluted with saturated $NaHCO_3$ (25 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow oil. Flash column chromatography (11.0 cm × 5.0 cm SiO_2, hexanes/EtOAc 9:1 → 2:1) afforded indole (+)-**29** (34.4 mg, 85% (98% BORSM)) as a clear, colorless oil: $[\alpha]_D^{25}$ +10.8 (*c* 1.6, $CHCl_3$). Spectral data were identical to that reported previously (vide supra).

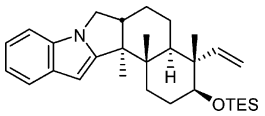
Preparation of Methanesulfonate (−)-S4.



To a 100 mL round-bottom flask equipped with a PTFE-coated stirbar were charged indole (+)-**29** (200 mg, 0.416 mmol, 1.0 equiv), 4-dimethylaminopyridine (1.26 g, 10.38 mmol, 25.0 equiv), and anhydrous CH_2Cl_2 (40 mL). The clear, colorless solution was cooled to 0 °C and then treated with methanesulfonyl chloride (476 mg, 3.33 mmol, 10.0 equiv) added dropwise via syringe. The thin white slurry that resulted was aged at 0 °C for 60 min and then poured into a mixture of saturated ammonium chloride (25 mL) and brine (25 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow oil. Flash column chromatography (14.0 cm × 5.0 cm SiO_2, hexanes/EtOAc 9:1 → 4:1) afforded methanesulfonate (−)-**S4** (230 mg, >99%) as a light yellow oil: $[\alpha]_D^{25}$ −13.10 (*c* 1.31, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (br s, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.30 (s, 1H), 5.54 (dd, J = 10.7, 17.4 Hz, 1H), 5.12 (d, J = 10.8 Hz, 1H), 4.99 (d, J = 17.3 Hz, 1H), 4.16 (br m, 1H), 3.82 (dd, J = 9.7, 9.7 Hz, 1H), 3.36 (dd, J = 6.1, 9.4 Hz, 1H), 2.87 (s, 3H), 2.74 (br m, 1H), 2.17 (br m, 1H), 1.70−1.39 (m, 8H), 1.37 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.92 (t, J = 7.9 Hz, 9H), 0.53 (q, J = 7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 141.0, 135.2, 127.6, 121.3, 119.8, 119.6, 113.9, 110.6, 102.5, 77.7, 74.5, 46.6, 46.5, 43.5, 40.5, 39.2, 37.1, 31.5, 30.3, 27.6, 25.8, 21.4, 16.9, 11.8, 6.9, 5.2; IR (neat) ν_{max} 3412 (br m), 2951 (br s), 2874 (m), 1717 (w), 1457 (m), 1348 (s), 1236 (m), 1174 (s), 1110 (s), 1002 (m), 948 (s), 824 (m), 744 (m) cm^{-1}. HRMS (ESI-MS) calcd for $C_{31}H_{49}NO_4SSiNa^+$ [(M + Na)$^+$] 582.3049, found 582.3045.

Preparation of Pentacycle (+)-30. To a 50 mL round-bottom flask equipped with a water-cooled reflux condenser and PTFE-coated stirbar were charged mesylate (50.0 mg, 0.089 mmol, 1.0 equiv), zinc triflate (324.6 mg, 0.893 mmol, 10.0 equiv), and anhydrous toluene (25 mL). The resulting mixture was heated to 110 °C and treated with *tert*-butylmagnesium chloride (670 μL of a 2.0 M solution in Et_2O, 1.34 mmol, 15.0 equiv) added dropwise via syringe. Upon cooling, the mixture was quenched with saturated ammonium chloride (50 mL) and extracted with Et_2O (3 × 25 mL). The combined organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a yellow oil. Flash column chromatography (12.0 cm × 3.5 cm SiO_2, hexanes/Et_2O 100:1 → 75:1) afforded pentacycle (+)-**30** (24.4 mg, 59%) as a light yellow oil: $[\alpha]_D^{25}$ +2.38 (*c* 0.81, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.40 (br d, J = 7.7 Hz, 1H), 7.30 (br d, J = 7.7 Hz, 1H), 7.00−7.08 (m, 2H), 5.56 (dd, J = 10.8, 17.3 Hz, 1H), 5.10 (dd, J = 1.5, 10.8 Hz, 1H), 4.97 (dd, J = 1.5, 17.3 Hz, 1H), 3.43 (dd, J = 4.5, 11.2 Hz, 1H), 2.76 (m, 1H), 2.67 (dd, J = 6.3, 13.4 Hz, 1H), 2.33 (dd, J = 10.8, 13.4 Hz, 1H), 1.84−1.99 (m, 2H), 1.68−1.77 (m, 2H), 1.52−1.66 (m, 4H), 1.33−1.46 (m, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 0.99 (t, J = 8.0 Hz, 9H), 0.98 (s, 3H), 0.60 (q, J = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 149.9, 140.5, 125.6, 120.6, 119.8, 118.6, 118.6, 113.7, 111.7, 78.1, 53.5, 49.6, 47.1, 44.3, 39.2, 33.7, 28.5, 27.8, 25.7, 24.6, 19.2, 14.6, 11.1, 7.2, 5.6; IR (neat) ν_{max} 3433 (br m), 2948 (br s), 1456 (s), 1299 (m), 1099 (s), 1002 (m), 826 (m), 739 (s) cm^{-1}. HRMS (ESI-MS) calcd for $C_{30}H_{46}NOSi^+$ [(M + H)$^+$] 464.3349, found 464.3351.

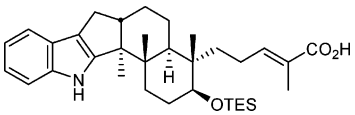
Physical Data for Undesired Cyclization Regioisomer (+)-S5.



Yield 3.31 mg (8.0% yield), light yellow oil: $[\alpha]_D^{25}$ +6.32 (*c* 0.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (br d, J = 7.4 Hz, 1H), 7.21 (br d, J = 7.2 Hz, 1H), 7.11 (app br t, J = 7.8 Hz, 1H), 7.04 (app br t, J = 7.4 Hz, 1H), 6.06 (s, 1H), 5.54 (dd, J = 10.4, 17.5 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 4.98 (d, J = 17.5 Hz, 1H), 4.01 (dd, J = 7.1, 9.7 Hz, 1H), 3.59 (dd, J = 9.7, 10.8 Hz, 1H), 3.40 (dd, J = 4.1, 10.1 Hz, 1H), 2.82 (m, 1H), 1.20−1.80 (m, 9H), 1.17 (s, 3H), 1.16 (s, 3H), 0.98 (s, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.58 (q, J = 7.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 149.6, 132.8, 132.0, 120.5, 120.1, 118.8, 113.6, 108.9, 91.6, 77.8, 51.1, 46.9, 46.7, 45.9, 43.7, 38.7, 32.1, 28.0, 23.3, 22.9, 17.8, 15.8, 10.9, 6.9, 5.2; IR (neat) ν_{max} 2949 (br s), 2874 (s), 1456 (s), 1261 (m), 1095 (br s), 1017 (br s), 876 (m), 799 (m), 743 (s) cm^{-1}. HRMS (ESI-MS) calcd for $C_{30}H_{46}NOSi^+$ [(M + H)$^+$] 464.3348, found 464.3353.

Preparation of Coupled Adduct (+)-31. To a 50 mL round-bottom flask equipped with a water-cooled reflux condenser and PTFE-coated stirbar were charged pentacycle (+)-**30** (50.0 mg, 0.108 mmol, 1.0 equiv), 9-BBN dimer (72.3 mg, 0.296 mmol, 2.75 equiv), and anhydrous toluene (8.0 mL). The resulting mixture was heated at 80 °C for 5 h. Upon cooling, volatiles were removed by vacuum transfer, and the resulting off-white solid residue was taken up in anhydrous *N*,*N*-dimethylformamide (8.0 mL). Upon treatment with $PdCl_2$(dppf) (8.8 mg, 0.011 mmol, 0.10 equiv), methyl-(*E*)-3-bromo-2-methylpropenoate **16** (38.6 mg, 0.216 mmol, 2.0 equiv), and powdered potassium phosphate (45.8 mg, 0.216 mmol, 2.0 equiv), the resulting magenta solution was heated at 65 °C for 6 h to yield a dark orange mixture. This was diluted with brine (150 mL) and extracted with Et_2O (3 × 50 mL). The combined organic extract was washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to an orange oil. Flash column chromatography (16.0 cm × 3.5 cm SiO_2, hexanes/Et_2O 30:1 → 15:1) afforded adduct (+)-**31** (41.9 mg, 69%) as a clear, colorless oil: $[\alpha]_D^{25}$ +19.1 (*c* 0.33, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.39 (dd, J = 1.9, 6.3 Hz, 1H), 7.31 (dd, J = 1.9, 6.7 Hz, 1H), 7.06 (app dt, J = 1.5, 6.7 Hz, 1H), 7.03 (app dt, J = 1.5, 6.3 Hz, 1H), 6.75 (app br t, J = 7.2 Hz, 1H), 3.73 (s, 3H), 3.61 (dd, J = 4.8, 9.7 Hz, 1H), 2.78 (m, 1H), 2.68 (dd, J = 6.3, 13.2 Hz, 1H), 2.34 (dd, J = 10.8, 13.2 Hz, 1H), 2.12 (m, 2H), 1.89 (m, 1H), 1.88 (br s, 3H), 1.38−1.82 (m, 7H), 1.28 (m, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 1.01 (t, J = 8.2 Hz, 9H), 0.84 (s, 3H), 0.65 (br q, J = 8.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 151.6, 143.2, 140.6, 127.7, 125.8, 120.8, 119.9, 118.8, 111.9, 74.5, 53.7, 52.1, 49.5, 42.4, 40.5, 39.8, 36.4, 33.9, 30.3, 28.6, 27.9, 25.7, 23.6, 23.1, 19.5, 17.3, 14.9, 12.8, 7.4, 6.0; IR (neat) ν_{max} 3391 (br m), 2949 (br s), 2874 (m), 1698 (s), 1646 (m), 1455 (m), 1385 (w), 1283 (m), 1099 (s), 1010 (m), 824 (m), 739 (s) cm^{-1}. HRMS (ESI-MS) calcd for $C_{35}H_{53}NO_3SiNa^+$ [(M + Na)$^+$] 586.3692, found 586.3687.

Preparation of Acid (+)-S6.



To a 50 mL round-bottom flask equipped with a PTFE-coated stirbar were charged ester (+)-**31** (30.2 mg, 0.054 mmol, 1.0 equiv), aqueous LiOH (6.0 mL of a 1.0 M solution), methanol (12 mL), and THF (HPLC grade, 6.0 mL), and the resulting mixture was vigorously stirred at 25 °C for 48 h. The resulting mixture was

subjected to rotary evaporation to remove volatiles and then adjusted to pH 2 with saturated citric acid solution. The resulting heterogeneous mixture was extracted with EtOAc (3 × 25 mL), and the combined organic extract was washed with brine (3 × 50 mL), dried over $MgSO_4$, filtered through a coarse frit, and concentrated in vacuo to a light yellow oil. Flash column chromatography (12.0 cm × 3.5 cm SiO_2, hexanes/EtOAc 4:1 → 1:1) afforded adduct (+)-**S6** (25.5 mg, 86.7%) as a waxy, white solid: $[\alpha]_D^{25}$ +20.20 (*c* 0.27, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ ca. 9 ppm (br s, 1H), 7.79 (br s, 1H), 7.38 (br d, J = 6.3 Hz, 1H), 7.29 (br dd, J = 1.8, 6.7 Hz, 1H), 7.05 (br dd, J = 1.5, 7.1 Hz, 1H), 7.02 (br dd, J = 1.5, 7.4 Hz, 1H), 6.90 (br t, J = 7.4 Hz, 1H), 3.60 (dd, J = 4.8, 10.1 Hz, 1H), 2.77 (m, 1H), 2.67 (dd, J = 6.7, 13.4 Hz, 1H), 2.33 (dd, J = 10.8, 13.4 Hz, 1H), 2.15 (m, 2H), 1.89 (br s, 3H), 1.40−1.91 (m, 8H), 1.21−1.38 (m, 3H), 1.13 (s, 3H), 1.04 (s, 3H), 1.00 (t, J = 8.2 Hz, 9H), 0.84 (s, 3H), 0.64 (br q, J = 8.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 151.6, 146.1, 140.6, 127.1, 125.8, 120.8, 119.9, 118.8, 118.7, 111.9, 74.5, 53.7, 49.5, 42.5, 40.5, 39.8, 36.3, 33.8, 28.6, 27.9, 25.7, 23.6, 23.4, 19.5, 17.3, 14.9, 12.5, 7.4, 6.0; IR (neat) ν_{max} 3426 (br m), 2933 (br s), 2874 (s), 1683 (s), 1455 (m), 1299 (m), 1098 (s), 1012 (m), 824 (m), 740 (s) cm^{-1}. HRMS (ESI-MS) calcd for $C_{34}H_{52}NO_3Si^+$ [(M + H)$^+$] 550.3716, found 550.3709.

Preparation of Synthetic (+)-Nodulisporic Acid F (4). To a 25 mL round-bottom flask equipped with a PTFE-coated stirbar were charged acid (+)-**S6** (25.0 mg, 0.046 mmol, 1.0 equiv), *p*-toluenesulfonic acid monohydrate (0.87 mg, 0.005 mmol, 0.10 equiv), and methanol (HPLC grade, 10 mL). The resulting mixture was stirred at 25 °C for 1 h and then subjected to rotary evaporation to yield a light yellow residue. Flash column chromatography (12.5 cm × 3.5 cm SiO_2, EtOAc/MeOH 20:1 → 10:1) afforded (+)-nodulisporic acid F (**4**) (22.0 mg, 92.4%) as a waxy, off-white residue: $[\alpha]_D^{25}$ +7.31 (*c* 1.70, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (br d, J = 7.8 Hz, 2H), 6.99 (dt, J = 1.5, 7.1 Hz, 1H), 6.96 (dt, J = 1.5, 7.4 Hz, 1H), 6.88 (br t, J = 7.4 Hz, 1H), 3.59 (dd, J = 4.5, 10.4 Hz, 1H), 2.82 (m, 1H), 2.66 (dd, J = 6.3, 13.0 Hz, 1H), 2.34 (dd, J = 10.8, 13.4 Hz, 1H), 2.26 (m, 1H), 2.19 (m, 1H), 1.91 (s, 3H), 1.66−1.88 (m, 9H), 1.54 (m, 1H), 1.42 (m, 1H), 1.17 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 152.4, 144.7, 142.2, 128.6, 126.4, 120.8, 119.8, 118.8, 118.2, 112.8, 74.2, 54.5, 50.4, 42.7, 41.6, 40.6, 37.2, 33.9, 28.5, 28.4, 26.5, 24.2, 23.6, 19.6, 17.4, 15.0, 12.6; IR (neat) ν_{max} 3424 (br s), 2939 (br s), 1685 (s), 1642 (m), 1455 (m), 1385 (m), 1299 (m), 1221 (m), 1095 (w), 1072 (m), 1024 (m), 918 (w), 754 (s) cm^{-1}; UV−vis λ_{max} = 230, 282 nm (MeOH). HRMS (ESI-MS) calcd for $C_{28}H_{37}NO_3Na^+$ [(M + Na)$^+$] 458.2671, found 458.2661.

Physical Data for Natural (+)-Nodulisporic Acid F. Amorphous off-white powder: $[\alpha]_D^{25}$ +7.20 (*c* 1.70, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (br d, J = 7.8 Hz, 2H), 6.99 (dt, J = 1.5, 7.1 Hz, 1H), 6.96 (dt, J = 1.5, 7.4 Hz, 1H), 6.88 (br t, J = 7.4 Hz, 1H), 3.59 (dd, J = 4.5, 10.4 Hz, 1H), 2.82 (m, 1H), 2.66 (dd, J = 6.3, 13.0 Hz, 1H), 2.34 (dd, J = 10.8, 13.4 Hz, 1H), 2.26 (m, 1H), 2.19 (m, 1H), 1.91 (s, 3H), 1.66−1.88 (m, 9H), 1.54 (m, 1H), 1.42 (m, 1H), 1.17 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 152.4, 144.7, 142.2, 128.6, 126.4, 120.9, 119.9, 118.8, 118.2, 112.8, 74.2, 54.5, 50.4, 42.7, 41.6, 40.6, 37.2, 33.9, 28.5, 28.4, 26.5, 24.2, 23.6, 19.6, 17.4, 15.0, 12.6; UV−vis λ_{max} = 230, 282 nm (MeOH).

Acknowledgment. Financial support was provided by the National Institutes of Health (National Institute of General Medical Sciences) through Grant GM-29028 and by the Bristol-Myers Squibb Pharmaceutical Research Institute (for stipend support of A.H.D.). We are also grateful to Eli Lilly and Company for the graduate fellowship to L.K., the Merck Research Laboratories for generous financial support of this research program, and to Dr. P.T. Meinke for providing generous samples of natural (+)-nodulisporic acid F and (−)-nodulisporic acid D. Finally, we thank Dr. G. Furst, Dr. R.K. Kohli, and Dr. P. Carroll for assistance in obtaining NMR spectra, high-resolution mass spectra, and X-ray crystallographic data, respectively.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all other new compounds. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062422I