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Total Synthesis of (−)-Nodulisporic Acids D, C, and B: Evolution of a Unified Synthetic Strategy

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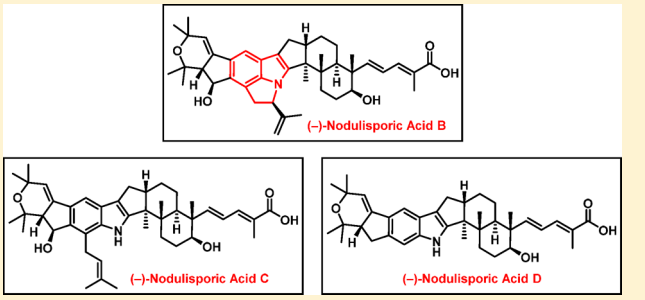
Supporting Information

ABSTRACT: A unified synthetic strategy leading to the total synthesis of (−)-nodulisporic acids D, C, and B is described. Key synthetic transformations include a nickel−chromium-mediated cyclization, an aromatic ring functionalization employing a novel copper-promoted alkylation, a palladium-catalyzed cross-coupling cascade/indole ring construction, and a palladium-mediated regio- and diastereoselective allylic substitution/cyclization reaction, the latter to construct ring D.



1. INTRODUCTION

Nodulisporic acids A−F (**1**−**6**)[1] (Scheme 1), reported by the Merck Research Laboratories, constitute an architecturally intriguing family of indole terpenes[2] that have been found to possess potent insecticidal activity.[3] Subsequent structure−activity relationship studies at Merck revealed that the highly substituted indole core and secondary C(24) hydroxyl group are the key structural elements required for the insecticidal activity.[4] These two functionalities, in conjugation with the dienoate side chain, also lead to significant instability both in vitro and in vivo;[1,4] for example, the C(24) hydroxyl group undergoes facile dehydration mediated by the carboxylic acid,[1] while exposure to air leads to oxidative ring opening of the indole core.[1a,c] This sensitivity pattern clearly conspires to add significant chemical challenge vis-à-vis structural modifications and/or synthetic strategies toward the nodulisporic acids.[5,6]

Shortly after the Merck structural/medicinal chemistry program,[4,5] we launched synthetic studies toward the total synthesis of members of the nodulisporic acid family. From the outset, this program had two major goals: (1) the construction of the highly strained CDE tricyclic indole−indoline scaffold found only in these natural products and (2) the development of a unified synthetic strategy to obtain not only the naturally occurring nodulisporic acids but also unnatural analogues. This effort initially culminated in the first synthesis of the simpler, more stable (+)-nodulisporic acid F (**6**), exploiting at the time a new two-component indole ring construction (Scheme 2A) developed in our laboratory.[7] To construct the more advanced nodulisporic acids (**1**−**4**), we developed a new union strategy exploiting a palladium-mediated cross-coupling/indole construction tactic based on the chemistry of Barluenga and coworkers.[8] (Scheme 2B).

The initial success of the new strategy was first demonstrated by the total synthesis of (−)-nodulisporic acid D (**4**),[9] again via union of two advanced intermediates. Evolution of that synthetic venture has now led to the first total synthesis of (−)-nodulisporic acid C (**3**) and (−)-nodulisporic acid B (**2**) along with generation of an unnatural analogue, 2′-*epi*-nodulisporic acid B, all as their sodium salts. Herein we report a full account of the development and evolution of this unified strategy for the synthesis of nodulisporic acids D (**4**), C (**3**), and B (**2**).

2. RESULTS AND DISCUSSION

For construction of (−)-nodulisporic acid D (**4**), the multisubstituted indole was dissected retrosynthetically into western hemisphere **7** and eastern hemisphere **8** (Scheme 3). While the former was envisioned to be constructed via an Enders alkylation[10]/Stille−Kelly cyclization[11] sequence employing hydrazone (+)-**9** and an iodide derived from commercially available benzoic acid **10**,[12] the latter was to arise via a difunctionalization/cyclization sequence utilizing advanced intermediate (+)-**11**. We note that we had developed a process-scale synthesis of (+)-**11** during our earlier total synthesis of (+)-nodulisporic acid F (**6**).[13]

The construction of western hemisphere **7** (Scheme 4) thus began with benzoic acid **10**. Borane reduction followed by iodination[14] led to benzyl iodide **12**. Hydrazone (+)-**9** was then employed for the Enders asymmetric alkylation[10] with **12** to furnish (+)-**13**, a single enantiomer with the requisite *S* stereogenicity (vide infra) at C(23). The chiral auxiliary was next removed via ozonolysis to produce ketone (+)-**14**, after

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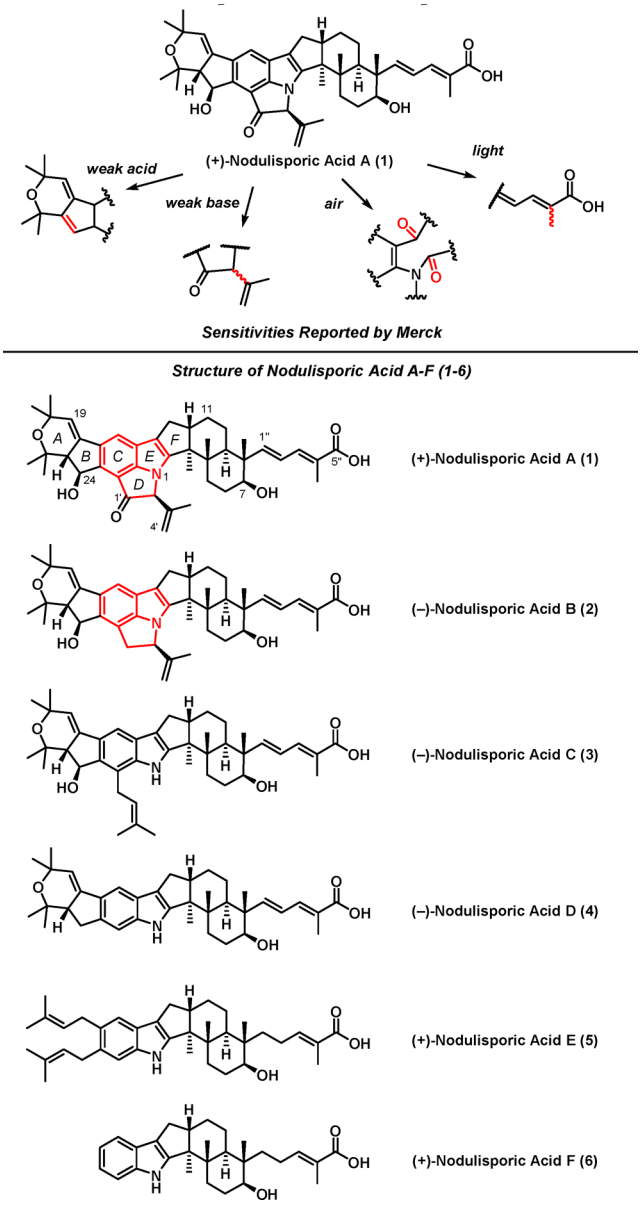
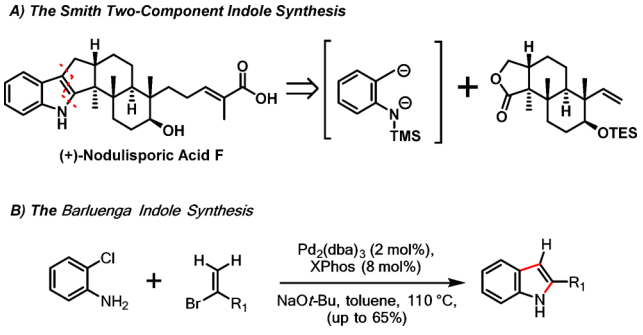
Scheme 1. Structures of the Indole Terpenes Nodulisporic Acids A–F

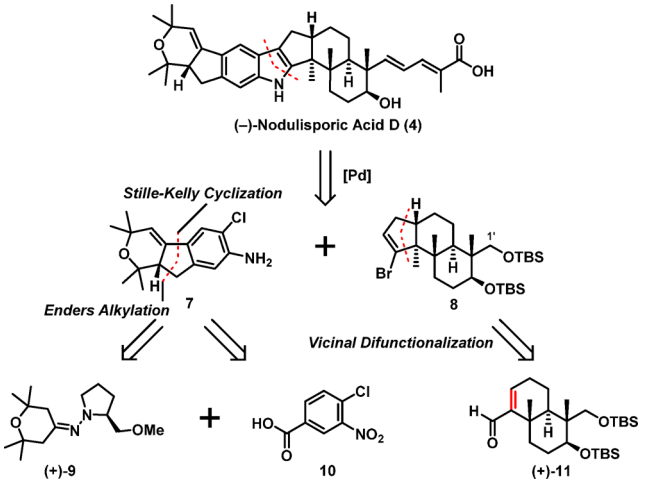


Scheme 2. Synthetic Strategy for the Nodulisporic Acids

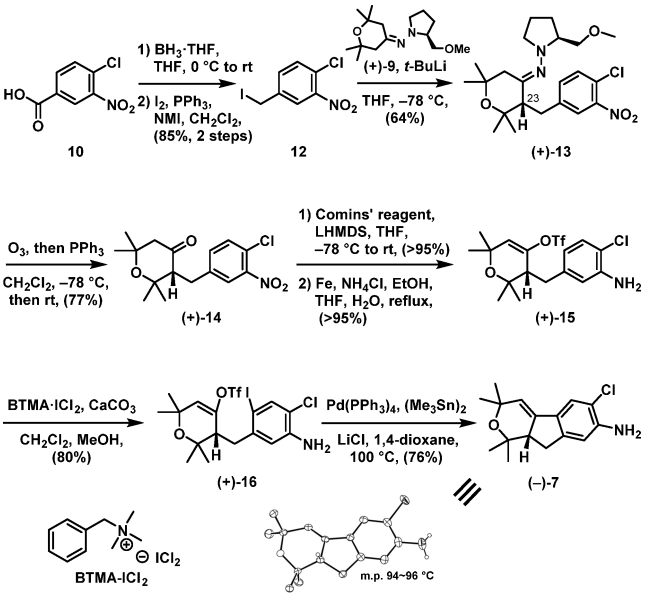


which a Comins triflation protocol[15] was employed to produce the corresponding vinyl triflate. In turn, reduction of the nitro group using iron/NH_4Cl[16] delivered aniline (+)-**15** in near-quantitative yield. A mild electrophilic iodination reagent

Scheme 3. Retrosynthetic Analysis of (–)-Nodulisporic Acid D (4)



Scheme 4. Synthesis of Western Hemisphere (–)-7



(BTMA-ICl_2)[17] was then applied to aniline (+)-**15** to furnish iodide (+)-**16** in 80% yield, which upon a Stille–Kelly reaction[11] completed construction of the western hemisphere, aniline (–)-7, the absolute configuration of which was confirmed by X-ray analysis. The overall yield for the eight-step sequence to (–)-7 was 25%.

The construction of eastern hemisphere **8** began with aldehyde (+)-**11** (Scheme 5). Stereoselective conjugate addition with in situ-generated vinyl cuprate[18] led to silyl enol ether (–)-**17** as a single diastereomer. Surprisingly, (–)-**17** could be purified via silica column chromatography, likely because the steric hindrance protects the silyl enol ether from hydrolysis. The stereoselectivity of this reaction presumably results from limited accessibility of the top face, which is blocked by the C(29) quaternary methyl group. On the basis of the same reasoning, alkylation of the enolate derived via treatment with MeLi was expected to produce the same facial selectivity. To this end, treatment with MeLi in THF followed by alkylation (condition 1) generated the quaternary stereocenter at C(3), albeit with unsatisfactory

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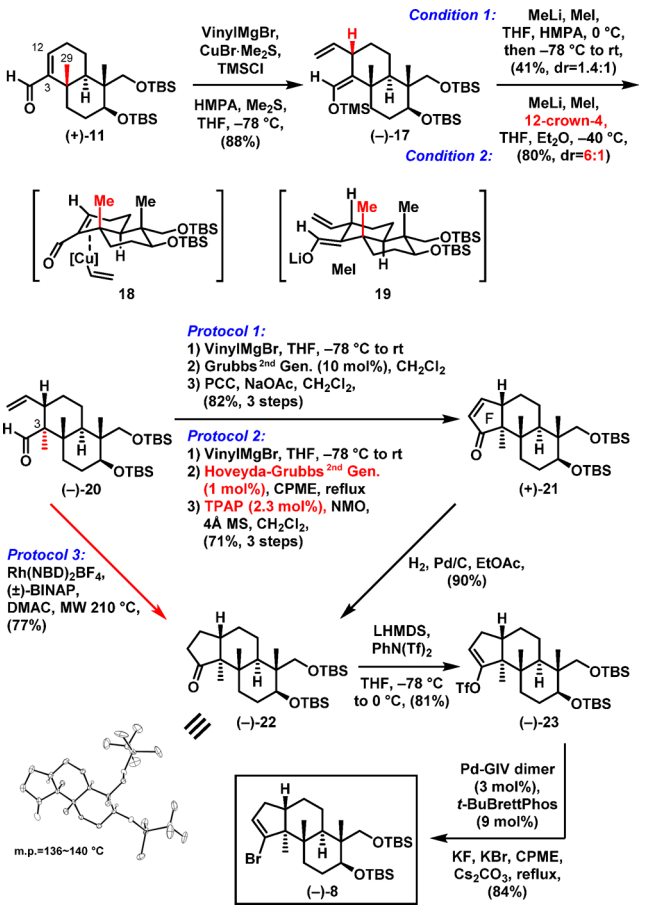
Scheme 5. Synthesis of Eastern Hemisphere (−)-8



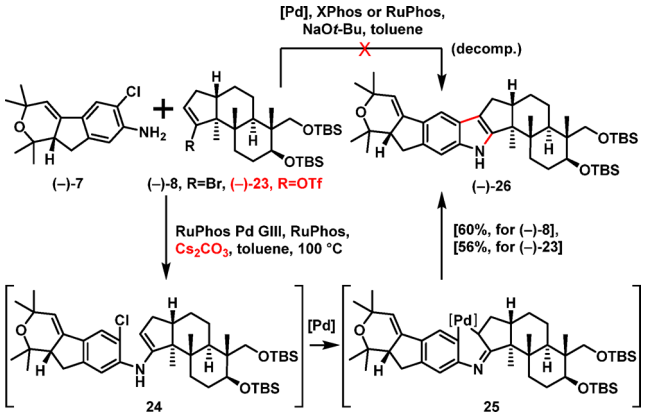
selectivity (dr = 1.4:1). We reasoned that a crown ether could chelate the lithium cation, thereby generating a more reactive anion species, which might allow the alkylation to take place at a lower temperature with improved diastereoselectivity.[19] In the presence of 12-crown-4 and a finely tuned solvent system (1:1 THF/Et_2O), alkylation at −40 °C provided a 6:1 diastereomer selectivity (condition 2). With aldehyde (−)-**20** in hand, we moved to the construction of ring F. Our initially established metathesis cyclization sequence (Scheme 5, protocol 1)[9] proved effective, although a 10 mol % loading of the second-generation Grubbs catalyst[20] was required, along with a large amount of toxic pyridinium chlorochromate (PCC) for the oxidation. Upon scale-up these issues could fortunately be addressed by utilizing the second-generation Hoveyda−Grubbs catalyst[21] (1 mol %) to effect the ring-closing metathesis and a Ley[22] oxidation (protocol 2). The solvent cyclopentyl methyl ether (CPME)[23] proved to be optimal for the metathesis, which permitted a higher reaction temperature. Enone (+)-**21** was thus produced in a comparable yield (71%) over the three steps. Hydrogenolysis of (+)-**21** then led to (−)-**22** in 90% yield. The structure of (−)-**22** was secured by X-ray analysis.

Upon further consideration, a possible one-step cyclization of aldehyde (−)-**20** to give its constitutional isomer ketone (−)-**22** (protocol 3) was explored, employing an intramolecular hydroacylation reaction[24] utilizing $Rh(NBD)_2BF_4$/(±)-BINAP.[25] Pleasingly, (−)-**22** was generated in 77% yield. Unfortunately, use of less than a stoichiometric amount of the [Rh] reagent and/or a lower reaction temperature led to a significant decrease in the reaction rate, likely due to the steric hindrance of neopentyl aldehyde (−)-**20**. Nevertheless, this cyclization is a rare example of a rhodium-mediated hydroacylation in a complex structural setting.

Continuing toward vinyl bromide (−)-**8**, triflation of (−)-**22** led to (−)-**23**, which upon bromination via a Buchwald protocol,[26] modified slightly by employing the Pd-GIV dimer precatalyst[27] in combination with CPME as the solvent, yielded (−)-**8** in excellent yield (84%).

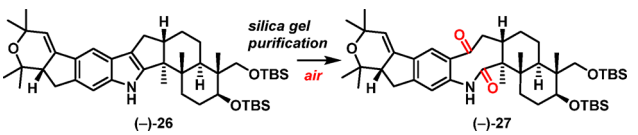
With both the western hemisphere, aniline (−)-**7**, and the eastern hemisphere, bromide (−)-**8**, in hand, we explored the proposed cascade cross-coupling union/indole construction tactic (Scheme 6). Initial attempts applying the Barluenga

Scheme 6. Development of the Barluenga Cross-Coupling Union



conditions[8] led to a complex mixture with no desired product. Reasoning that the strong basicity of NaO*t*-Bu may be detrimental to the reaction, we applied a weaker inorganic base (Cs_2CO_3) in combination with the Buchwald third-generation palladacycle RuPhos precatalyst.[28] Pleasingly, the desired indole product (−)-**26** was obtained not only using vinyl bromide (−)-**8** but also with the more readily available vinyl triflate (−)-**23** (available in one step from (−)-**22**; Scheme 5) in similar yields. Mechanistically, this union/cyclization cascade involves a Buchwald−Hartwig reaction via aniline (−)-**7** with (−)-**8** or (−)-**23** to afford enamine **24**, which then undergoes a palladium-mediated enamine cyclization[29] via **25** with tautomerization to generate the desired indole core (−)-**26**. However, isolation of indole (−)-**26** proved to be challenging! Significant decomposition (>50%) was observed after normal silica gel column purification. Analysis of the decomposition mixture identified amide (−)-**27** (Scheme 7) as the major component. Further experiments suggested that indole (−)-**26** undergoes slow (days) oxidation in air to form (−)-**27** even in the absence of silica gel. Similar stability issues were observed both during our previous synthetic venture leading to (−)-21-isopentenylpaxilline[30] and in the Merck reports.[1a,c] To resolve this purification

Scheme 7. Air Oxidation of the Nodulisporic Indole Core



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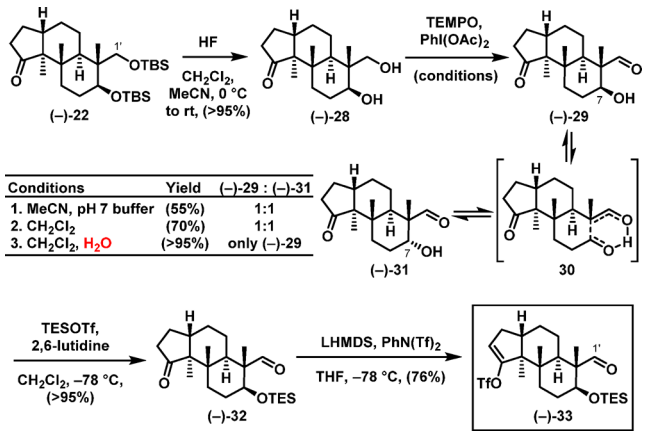
issue, we developed a *nitrogen-purged vacuum silica gel column chromatography* purification method (see the Supporting Information) to afford (−)-**26** in 60% and 56% yield from bromide (−)-**8** and triflate (−)-**23**, respectively.

At this stage of the synthesis, considering the significant oxygen sensitivity of the indole core, we revised our synthetic plan to avoid any late-stage oxidations. Specifically, the C(1′) position of the new eastern hemisphere (Scheme 8) was now

Scheme 8. Construction of the Revised Eastern Hemisphere (−)-33

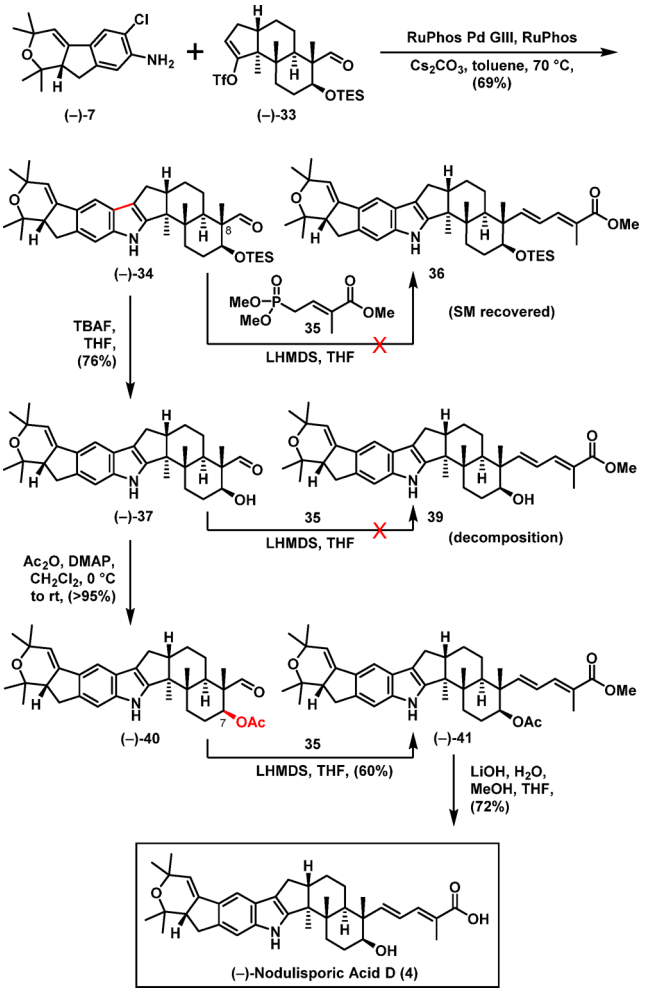


planned to be oxidized prior to construction of the indole core. Toward this end, removal of both TBS groups in ketone (−)-**22** led to diol (−)-**28**, which was oxidized chemoselectively to aldehyde (−)-**29** employing a 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)-mediated protocol.[31] The reported oxidation conditions led to an epimeric mixture at C(7), likely via an intramolecular aldol/retro-aldol process. This issue was resolved by employing a biphasic solvent system (1:1 CH_2Cl_2/H_2O). Protection of the secondary alcohol followed by triflation then furnished the new eastern hemisphere, aldehyde (−)-**33**. The refined four-step sequence to (−)-**33** proceeded in an overall yield of 65%.

Applying our union conditions to western hemisphere (−)-**7** and the revised eastern hemisphere (−)-**33** (Scheme 9), now at a lower temperature (70 °C) and higher concentration, led to the desired indole (−)-**34** in 69% yield, importantly with the aldehyde group tolerated. Surprisingly, however, the aldehyde functionality proved inert toward the envisioned Horner−Wadsworth−Emmons reaction[32] to install the dienoate side chain. We reasoned that this lack of reactivity was likely due to the steric hindrance of the C(8) neopentyl position. The triethylsilyl (TES) group was therefore removed to alleviate the steric constraint. The derived alcohol (−)-**37** again led only to a complex mixture with the same olefination protocol. This observation led us to envision that an acetyl group at C(7) might serve not only as a temporary protecting group but also as an electrophilic anion directing group. Alcohol (−)-**37** was therefore acetylated. Pleasingly, the Horner−Wadsworth−Emmons reaction with acetate (−)-**40** and phosphonate **35**[33] yielded the desired dienoate (−)-**41** in 60% yield. Hydrolysis of the latter (LiOH) completed the first total synthesis of (−)-nodulisporic acid D (**4**), for which the spectroscopic data were identical in all respects with the published data.[1e]

With the total synthesis of (−)-nodulisporic acid D (**4**) achieved, we were encouraged to continue our synthetic drive

Scheme 9. Endgame for (−)-Nodulisporic Acid D



to orchestrate a *unified strategy* to access the architecturally more complex nodulisporic acids C, B, and A (Scheme 10). It is noteworthy that in each of these there is a C(24) hydroxyl group that is known to undergo elimination readily, as well as a more complex indole core.[1] Nodulisporic acid C (**3**), for example, possesses a C(26) prenyl unit, while nodulisporic acids B (**2**) and A (**1**) contain a strained[1a,c,6b] CDE tricyclic indole−indoline motif, including a stereogenic center at C(2′) that is distal from the other stereogenicity. Finally, **1** presents a carbonyl group at C(1′)!

To access the more complex nodulisporic acids, we first required a protocol that would permit functionalization of western hemisphere **43** at C(26) with a prenyl unit (Scheme 10), followed by union with eastern hemisphere **44**, leading to advanced indole intermediate **42**. Depending on the specific prenyl unit selected, such a strategy would hold promise to access not only (−)-nodulisporic acid C (**3**) but potentially (−)-nodulisporic acid B (**2**) and eventually (+)-nodulisporic acid A (**1**) via late-stage cyclization/D-ring constructions.

Toward this end, the indole core (**45**, Scheme 11) of (−)-nodulisporic acid C (**3**) was disconnected retrosynthetically to yield western hemisphere **46** and now C(7)-acetate **47** as the eastern hemisphere to avoid a late-stage two-step protecting group interchange, as required in the synthesis of **4** (vide supra). While **47** would derive from advanced FGH intermediate (−)-**33**, which was employed in our (−)-nod-

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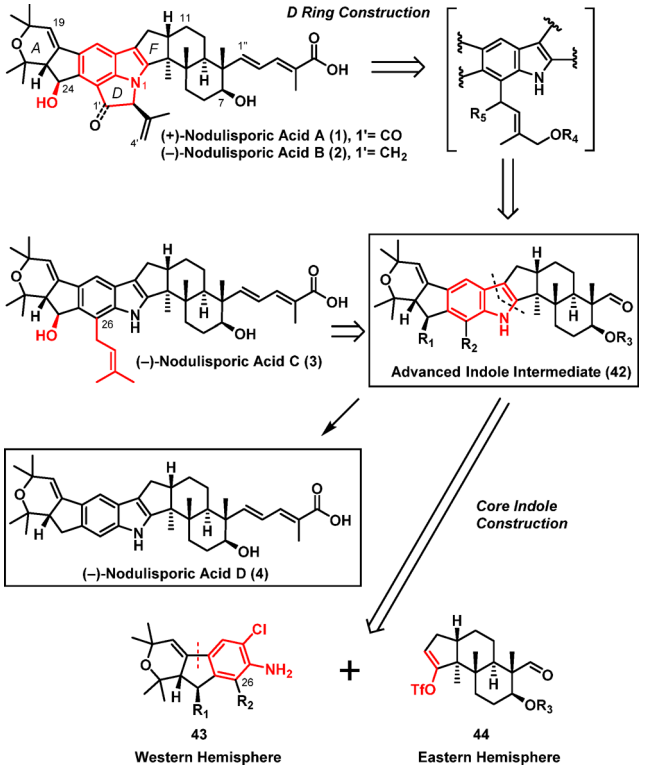
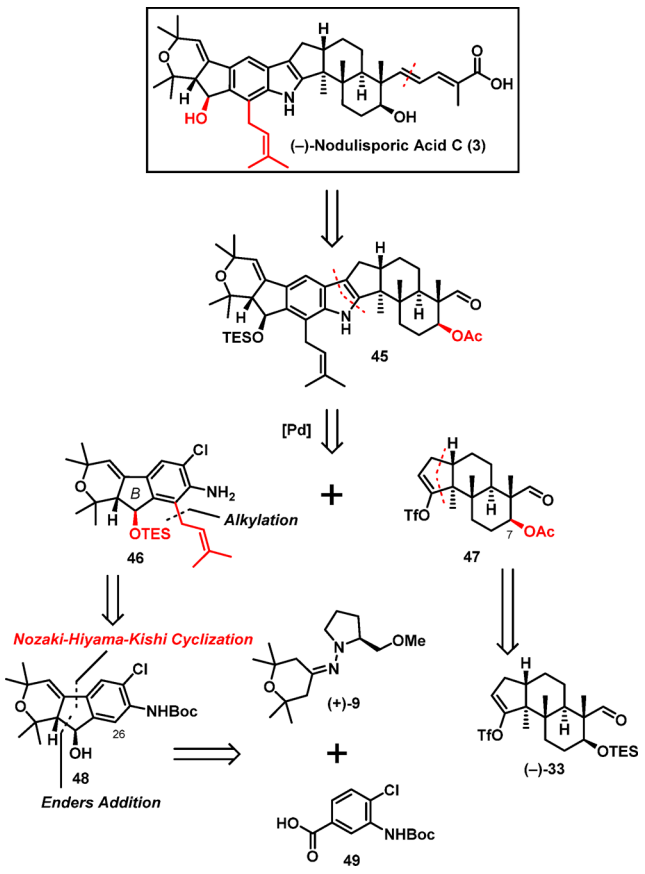
Scheme 10. Unified Synthetic Strategy To Access the Advanced Nodulisporic Acids



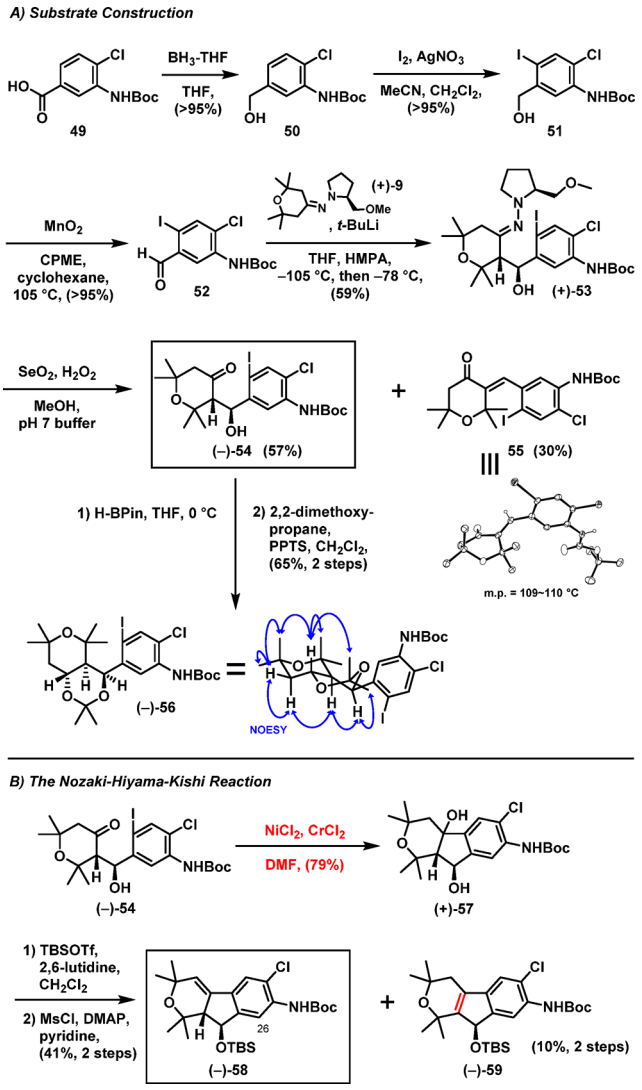
Scheme 11. Retrosynthetic Analysis of (−)-Nodulisporic Acid C (3)



ulisporic acid D synthesis (Scheme 9),[9] the critical C(26)-functionalized western hemisphere **46** was envisioned to be generated via an *N*-Boc-directed ortho-lithiation/alkylation[34] utilizing tricyclic intermediate **48**. Construction of **48** in turn would entail union of the aldehyde derived from commercially available benzoic acid **49** with hydrazone (+)-**9**, now via an Enders asymmetric addition[35] to establish both the relative and absolute configurations, as employed in our earlier nodulisporic acid synthetic ventures.[12] Then instead of the previously established Stille−Kelly cyclization protocol employed in the synthesis of **4** that required use of the toxic and volatile reagent hexamethylditin,[36] which could be a significant issue upon scale-up, a Nozaki−Hiyama−Kishi cyclization[37] was envisioned.

Toward this end (Scheme 12A), borane reduction of **49** followed by electrophilic iodination led to benzyl alcohol **51.**

Scheme 12. (A) Substrate Construction; (B) Nozaki−Hiyama−Kishi Reaction



Oxidation (MnO_2) then provided benzyl aldehyde **52**, which was submitted to the Enders asymmetric addition[35] with (+)-**9** to deliver hydrazone (+)-**53**, again as a single enantiomer. Next, by means of the oxidation protocol established previously in our laboratory,[6c] *β*-hydroxy ketone (−)-**54** was

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obtained, albeit with enone **55** as a significant side product lacking the benzylic hydroxyl group. The structure of **55** was assigned by X-ray analysis, while the relative configuration of (−)-**54** was confirmed by nuclear Overhauser effect spectroscopy (NOESY) analysis of (−)-**56**, which was derived from (−)-**54** via a reduction/acetalization sequence.

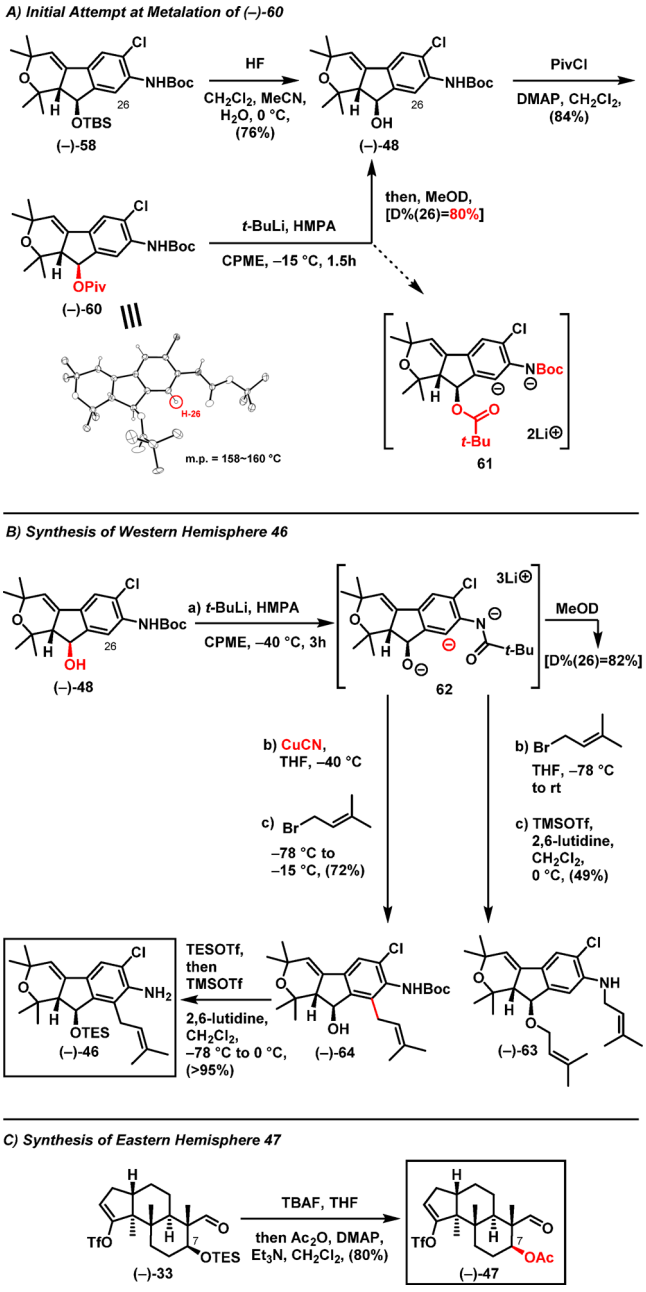
At this stage, given the previously cited toxicity issues related to the Stille−Kelly cyclization, we turned to the Nozaki−Hiyama−Kishi protocol[37] (Scheme 12B). Treatment of (−)-**54** with chromium(II) chloride in the presence of a catalytic amount of nickel(II) chloride smoothly led to tricyclic diol (+)-**57** in 79% yield. Notably, this transformation was carried out in the presence of a free benzylic hydroxyl group. After construction of the tricyclic system, the secondary hydroxyl of (+)-**57** was protected chemoselectively as the *tert*-butyldimethylsilyl (TBS) ether, and the tertiary hydroxyl group was eliminated to deliver olefin (−)-**58** along with a minor side product, (−)-**59**, wherein the double bond had migrated.

With (−)-**58** secure (ca. >1 g), we turned to an exploration of the critical ortho-lithiation/alkylation. Initial attempts at deprotonation at C(26) of (−)-**58** proved unrewarding (Scheme 13A), as only minimal lithiation was observed in commonly employed ethereal solvents (THF or Et_2O) with or without an additive (i.e., HMPA or TMEDA).[34] We postulated that the steric congestion of the TBS group at C(26) of (−)-**58** was the issue. We therefore turned to the use of a pivalate (Piv) group at C(24), introduced by a two-step deprotection/pivalation sequence (Scheme 13). Although the steric environment of pivalate derivative (−)-**60** may be similar to that of TBS ether (−)-**58**, as suggested by the X-ray structure of (−)-**60**, we reasoned that the pivalate group might facilitate deprotonation at C(26) as an additional directing group. Thus, (−)-**60** was subjected to direct lithiation employing *t*-BuLi/HMPA/CPME. Upon addition of MeOD, we observed considerable deuterium incorporation at C(26) (80% D by ^{1}H NMR), but the pivalate group was gone. Nevertheless, this observation encouraged us to explore alcohol (−)-**48** for the directed lithiation.

Pleasingly, successful deprotonation of (−)-**48** at C(26) was observed with *t*-BuLi (6 equiv)/HMPA/CPME (Scheme 13B). A MeOD quench experiment revealed 82% D incorporation at C(26). However, upon addition of prenyl bromide, C-alkylation did not occur; instead, only O- and N-alkylation took place, furnishing (−)-**63** in 49% yield after removal of the Boc group. Presumably, strong chelation from the neighboring alkoxide and/or carbamate groups reduces the desired reactivity of the aryl anion **62**. We reasoned that addition of a copper(I) salt might decrease the reactivity of the N and O anions while increasing the reactivity of the C anion, possibly via generation of a cuprate species.[38] After investigation of a number of different copper(I) salts (see the Supporting Information), we discovered that addition of CuCN permitted exclusive C-alkylation (72%). Protection of the derived alcohol (−)-**64** as the silyl ether and removal of the Boc group, both achieved in one pot, completed the construction of western hemisphere (−)-**46**. The requisite eastern hemisphere **47** (Scheme 13C) in turn was obtained via a single-flask deprotection/acetylation operation employing advanced intermediate (−)-**33** used in the synthesis of **4**.

With both hemispheres (−)-**46** and (−)-**47** in hand, we moved to the key union tactic exploited for nodulisporic acid D (**4**), but disappointingly, the conditions used in the synthesis of **4** (i.e., RuPhos, Pd_2dba_3, or the palladacycle precatalyst), as

Scheme 13. Synthesis of Western Hemisphere 46 and Eastern Hemisphere 47



well as the use of other biaryl phosphine ligands, solvents, and bases, led only to either recovery of both starting materials or complex mixtures.[39] It appeared that the desired cross-coupling was inhibited by the additional steric hindrance of the prenyl side chain now present in western hemisphere (−)-**46**. This lack of productive cross-coupling provides another example where palladium-mediated amination of two highly encumbered substrates is often challenging.[40]

Reasoning that different phosphine ligands may alter the behavior of the palladium catalyst, we turned to a screen to identify possible phosphine ligands (see the Supporting Information). Eventually we discovered that a combination of $Pd(OAc)_2$ and APhos[41] with triflate (−)-**47** (Scheme 14) delivered the desired union product (+)-**72** while tolerating the multiple sensitive functionalities, in particular the C(8)

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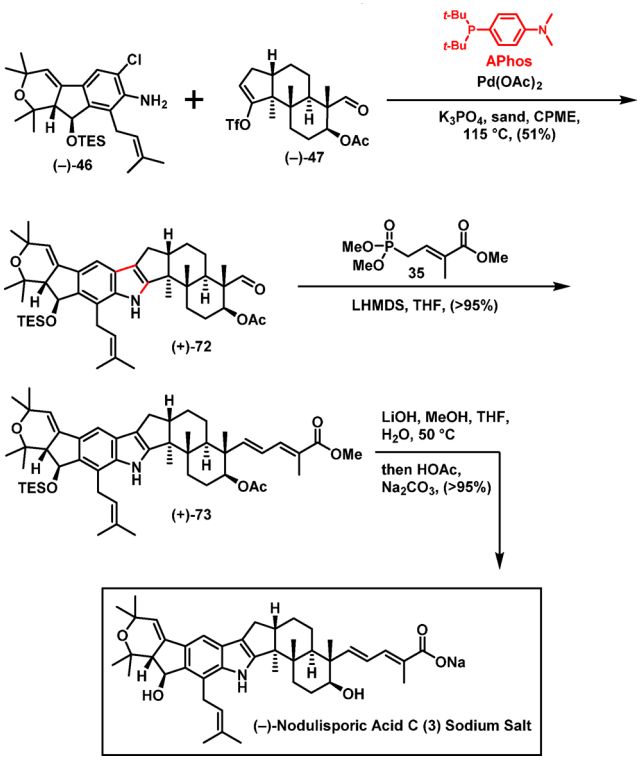
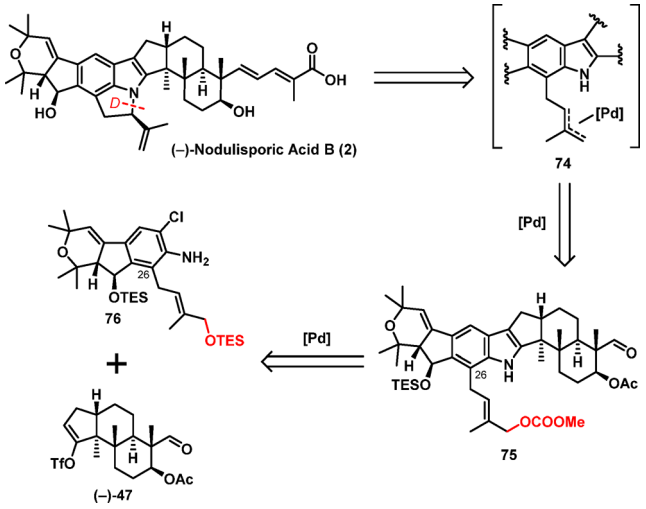
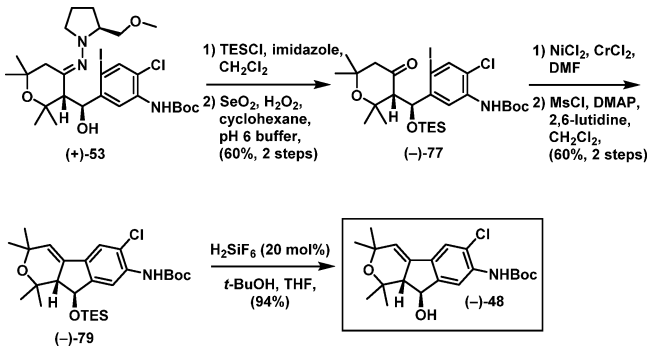
Scheme 14. Endgame for (−)-Nodulisporic Acid C (3)



Scheme 15. Retrosynthetic Analysis of (−)-Nodulisporic Acid B (2)



Scheme 16. Second-Generation Western Hemisphere Synthesis



aldehyde and the base-sensitive C(7) acetate. It is likely that the specific combination of steric and electronic effects of APhos facilitated the union sequence,[41b] as suggested by the superior reactivity of Aphos toward Suzuki−Miyaura coupling.[41]

Initially, however, the reproducibility and scalability of the union reaction proved to be troublesome. Experimentally, we observed that the employed base (K_3PO_4) was often deposited on the inner surface of the reaction flask as a thick residue, especially upon prolonged heating. As a result, either incomplete conversion or decomposition occurred. Pleasingly, the addition of sand (ca. 50 mg/1 mL of solvent) to the reaction mixture prevented deposition of the base via agitation, thereby furnishing a constant yield (51%) upon scale-up. With the critical union achieved, the Horner−Wadsworth−Emmons reaction[32] with phosphonate **35**[9] on aldehyde (+)-**72** installed the dienoate side chain in near-quantitative yield. Hydrolysis of the derived dienoate (+)-**73** with LiOH/MeOH/H_2O followed by salt exchange pleasingly completed the first total synthesis of (−)-nodulisporic acid C (**3**), stabilized as the sodium salt, for which the spectral data were identical in all respects with the published Merck data.[1d]

With the total synthesis of both (−)-nodulisporic acid D (**4**) and C (**3**) achieved, we proceeded to the construction of the highly strained tricyclic indole−indoline core with the embedded D-ring present in nodulisporic acid B (**2**) (Scheme 15). Here we envisioned a Tsuji−Trost palladium-promoted allylic cyclization reaction[42] employing **75** as the appropriately C(26)-functionalized advanced indole to construct ring D.

At the outset of this venture, and with a critical need for more overall efficacy for scale-up, we devised a second-generation route to advanced tricyclic intermediate (−)-**48** that was employed in the synthesis of **3** (Scheme 13). To this end, the hydroxyl group of hydrazone (+)-**53** (Scheme 16) was first protected as the TES ether, and the resulting intermediate was submitted to oxidation (SeO_2, H_2O_2), applying a biphasic solvent system (water/cyclohexane), to deliver ketone (−)-**77** in 60% yield over the two steps, thereby avoiding the previous issue of facile hydroxyl elimination. Next, application of the Nozaki−Hiyama−Kishi cyclization followed by elimination provided (−)-**79**, now without production of the double-bond isomer (see Scheme 12B). Removal of the TES group employing the refined conditions of H_2SiF_6/*t*-BuOH[43] completed the second-generation synthesis of (−)-**48** with an overall yield of 34% over the five steps from (+)-**53**, compared with 14% for the first-generation synthesis.

Application of our ortho-lithiation/alkylation tactic from the nodulisporic acid C synthesis, now employing iodide **80** (Scheme 17)[44] possessing the requisite allylic OTES substituent for generation of ring D, led to (−)-**81**, albeit in modest yield (45%), with 37% of the starting material (−)-**48** recovered, which fortunately could be recycled. Alcohol (−)-**81** was next converted in a single-flask operation to (−)-**76** in 77% yield via silylation and Boc group removal. Union with triflate (−)-**47** employed in the synthesis of **3** via our now established cross-coupling protocol then led to the corresponding indole (+)-**82** in 35% yield (vide infra), which in turn was converted to carbonate (−)-**75** via a two-step chemoselective deprotection/carbonation sequence.

With (−)-**75** in hand, we explored the proposed Tsuji−Trost cyclization. Initial attempts to generate ring D utilizing

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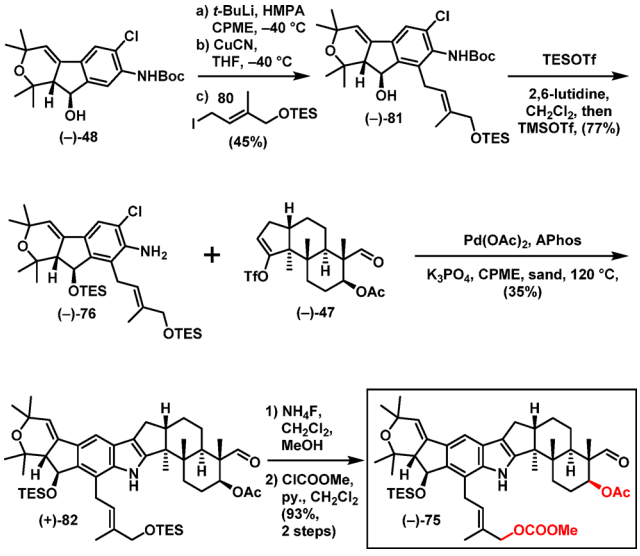
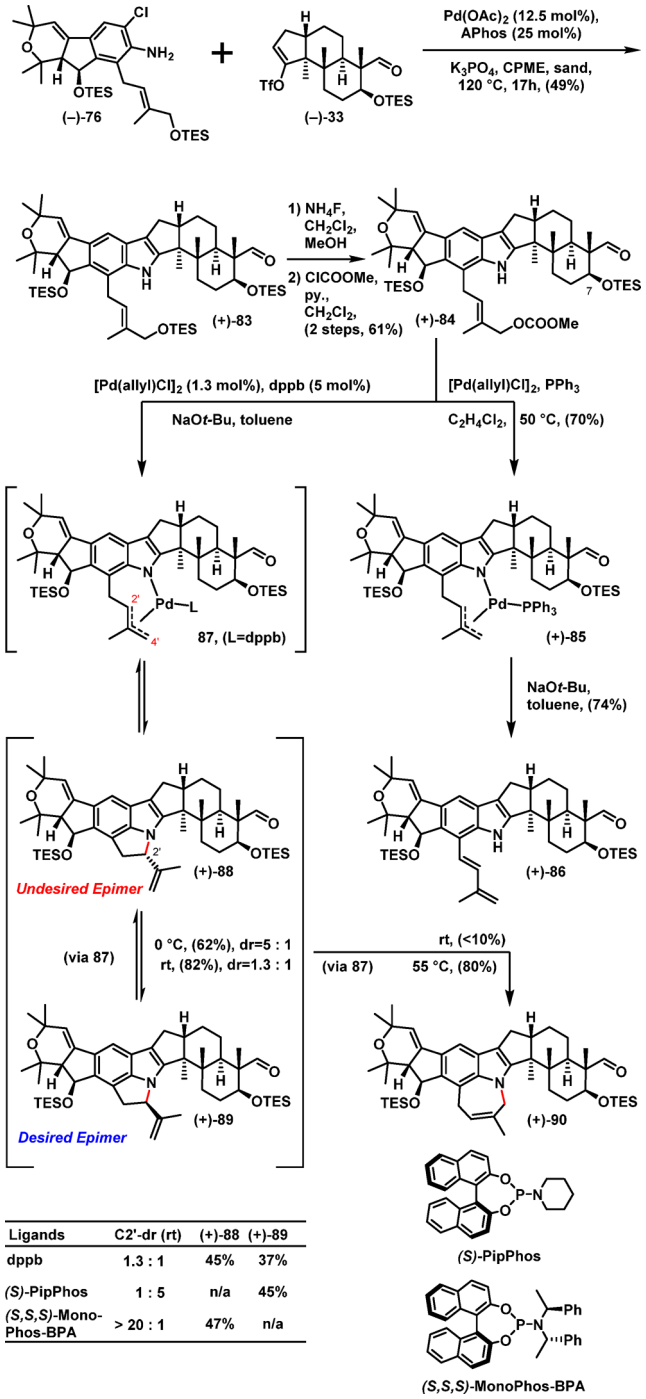
Scheme 17. Synthesis of the Cyclization Precursor



Scheme 18. The Key Cyclization Reaction



Ligands	C2'-dr (rt)	(+)-88	(+)-89
dppb	1.3 : 1	45%	37%
(S)-PipPhos	1 : 5	n/a	45%
(S,S,S)-Mono-Phos-BPA	> 20 : 1	47%	n/a

either a palladium or iridium catalytic system,[45] with or without an external base such as K_3PO_4 or DBU, in various solvents proved unrewarding; only recovery of starting materials was achieved. Employing a stronger base such as NaO*t*-Bu also led only to decomposition, likely because of the base sensitivity of the −OAc group. We therefore adjusted the synthetic scheme, revisiting the use of triflate (−)-**33** employed in the synthesis of **4** (Scheme 18).

To this end, the union of aniline (−)-**76** with triflate (−)-**33** led to the corresponding indole (+)-**83**, now in 49% yield. Next, by means of the same synthetic sequence as described in Scheme 17, carbonate (+)-**84** was acquired in 61% yield over two steps. With the hydroxyl group at C(7) now protected as the TES ether, the issue of the base sensitivity of the acetyl group had been eliminated.

Use of $[Pd(allyl)Cl]_2/PPh_3$ again, however, did not result in the desired cyclization but instead produced diene (+)-**86**, with the isolation of a small amount of the palladium species (+)-**85**. Complex **85** did not undergo the desired ring D cyclization under either neutral or basic conditions but instead provided diene (+)-**86** again, likely via *β*-hydride elimination. Reasoning that the *β*-hydride elimination might be suppressed by a specific ligand that could occupy the empty coordination site on palladium, we investigated different ligands (see the Supporting Information). After extensive optimization, we eventually discovered that employing the bidentate ligand 1,4-bis(diphenylphosphino)butane (dppb) at room temperature for 17 h resulted in an 82% combined yield of (+)-**88** and (+)-**89**, albeit with a dr of 1.3:1. However, when the reaction was conducted at 55 °C for 17 h, (+)-**90** containing a seven- instead of a five-membered ring was produced as the major product (80%). The ring expansion is likely driven by the high strain energy[1a] of (+)-**88** and (+)-**89** inherent in the nodulisporic tricyclic indole−indoline core. Fortunately (+)-**88** and (+)-**89** proved readily separable via silica gel chromatography, and importantly, the structures could be assigned by extensive NMR analysis.

From the mechanistic perspective, we envisioned that the initially formed *π*-allylpalladium species **87** undergoes cyclization at C(2′) to produce the kinetic product (+)-**88**. Importantly, this cyclization is reversible, specifically with dppb as the ligand;[46] at room temperature, a thermodynamic mixture [(+)-**88**/(+)-**89** = 1.3:1] is produced. Again, for the same reason, but now at 55 °C, the thermodynamically more stable product (+)-**90** dominates.[47]

At this stage, we reasoned that introduction of external stereogenicity might influence the cyclization transition state. We therefore turned to the chiral phosphoramidite ligands developed by Feringa.[48] Pleasingly, treatment of (−)-**84** as before, but now with the addition of (*S*)-PipPhos as the ligand (5 mol %) led predominantly to the desired epimer (+)-**89** (dr = 5:1), albeit in 45% yield, whereas the ligand (*S*,*S*,*S*)-MonoPhos-BPA[49] (4 mol %) gave almost exclusively (+)-**88**. Notwithstanding the modest yield of (+)-**89**, a regio- and

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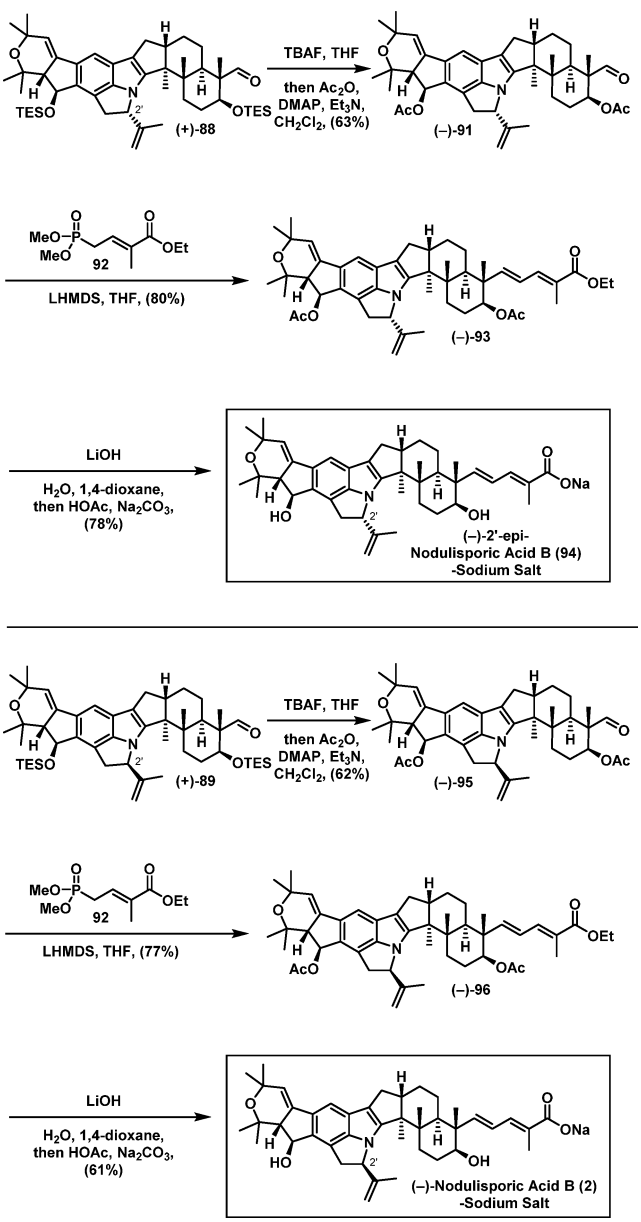
diastereoselective cyclization had been achieved that successfully led to the construction of the highly strained tricyclic indole−indoline core of (−)-nodulisporic acid B (**2**).

Having arrived at (−)-**89**, the tricyclic indole−indoline core of (−)-nodulisporic acid B, we found, not unexpectedly, that the acid and oxygen sensitivities of this advanced intermediate became an even greater issue;[1a,c] exposure to either air or standard silica gel chromatographic protocols led to significant decomposition. Notwithstanding the stability issues, careful elaboration of (+)-**89** and (+)-**88** individually in the absence of oxygen, followed by removal of the silyl groups, one-pot acetylation, exploiting our Horner−Wadsworth−Emmons directed olefination tactic developed earlier, and careful hydrolysis protocols, led to the first total synthesis of (−)-nodulisporic acid B (**2**) and the epimer (−)-2′-*epi*-nodulisporic acid B (**94**), both stabilized as their sodium salts (Scheme 19). The spectral data for the former were identical in all respects to the published Merck NMR data,[1c] and the structure of the latter was assigned on the basis of extensive NMR and HRMS analysis.

Scheme 19. Endgame for (−)-Nodulisporic Acid B (2)



3. CONCLUSION

In summary, the first total syntheses of (−)-nodulisporic acids D, C, and B as well as the unnatural analogue (−)-2′-*epi*-nodulisporic acid B, each stabilized and fully characterized as the sodium salt, have been achieved in a stereocontrolled fashion via a unified synthetic strategy. Synthetic studies toward the more complex nodulisporic acid A as well as analogues thereof continue in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b04053.

Experimental procedures and spectroscopic and analytical data for all new compounds (PDF)
X-ray crystallographic data for **7** (CIF)
X-ray crystallographic data for **22** (CIF)
X-ray crystallographic data for **55** (CIF)
X-ray crystallographic data for **60** (CIF)
X-ray crystallographic data for **67** (CIF)

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Notes

The authors declare no competing financial interest.

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