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

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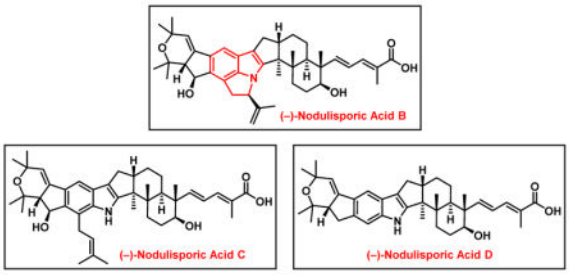
Abstract

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.

Graphical Abstract



The nodulisporic acids A-F (**1**-**6**)[1] (Scheme 1), reported by the Merck Research Laboratories, comprise an architecturally intriguing family of indole terpenes,[2] found to possess potent insecticidal activity.[3] Subsequent SAR 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-a-vis structural modifications and/or synthetic strategies towards the nodulisporic acids.[5,6]

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Supporting Information
The Supporting Information is available free of charge on the ACS Publication website at DOI:
Experimental procedures, as well as spectroscopic and analytical data for all new compounds (PDF)

Shortly after the Merck structural/medicinal chemistry program,[4,5] we launched synthetic studies towards the total synthesis of members of the nodulisporic acid family. From the outset, this program had two major goals: 1) construct the highly strained CDE tricyclic indole-indoline scaffold found only in these natural products; and 2) develop a unified synthetic strategy not only to the naturally occurring nodulisporic acids, but also to unnatural analogues. This effort initially cumulated in the first synthesis of the simpler, more stable nodulisporic acid (+)-F 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 base on the chemistry of Barluenga and coworkers[8] (Scheme 2B).

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 acids D (**4**), C (**3**), and B (**2**).

For construction of (−)-nodulisporic acid D (**4**), the multisubstituted indole was dissected retrosynthetically into the western and eastern hemispheres **7** and **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 (**8**) 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]

Construction of the 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** with a Comins triflation protocol[15] 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 (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 8-step sequence to (−)-**7** was 25%.

Construction of the 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 due to the steric hindrance which protects the silyl enol ether from hydrolysis. The stereoselectivity of this reaction presumably results from limited accessibility of the top face that is blocked by the C(29) quaternary methyl group. Given 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 generated the quaternary stereocenter at C(3), albeit with unsatisfactory selectivity (Condition 1; dr=1.4:1). Reasoning that use of a crown ether could chelate the lithium cation thereby generating a more reactive anion species, the alkylation might take place at a lower temperature with improved diastereoselectivity.[19] As such, in the presence of 12-crown-4 and a finely-tuned solvent system (THF: Et_2O=1:1), alkylation at −40 °C provided a 6:1 diastereomer selectivity (Condition 2). With aldehyde (−)-**20** in hand, we moved to construct ring F. Our initially established metathesis cyclization sequence (Scheme 5, Protocol 1)[9] proved effective; albeit, 10 mol% of the 2nd generation Grubbs catalyst[20] was required, with a large amount of toxic PCC for the oxidation. Upon scale- up these issues could fortunately be addressed by utilizing the 2nd 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 with 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 ketone (−)-**22** (Protocol 3), which comprise constitutional isomers, 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 reaction rate, likely due to the steric hindrance of the neopentyl aldehyde (−)-**20**. Nevertheless, this cyclization comprises 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 solvent, yielded (−)-**8** in excellent yield (84%).

With both western hemisphere aniline (−)-**7** and eastern hemisphere bromide (−)-**8** in hand, we explored the proposed cascade cross coupling union/indole construction tactic (Scheme 6). Initial attempts applying the Barluenga 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, a weaker inorganic base (Cs_2CO_3) was applied in combination with the Buchwald 3rd 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** [Scheme 5; one step from (−)-**22**] both in similar yields. Mechanistically, this union/cyclization cascade involves a Buchwald-Hartwig reaction via aniline (−)-**7** with (−)-**8** or (−)-**23** to enamine **24**, which then undergoes a palladium-mediated enamine cyclization[29] via **25** with tautomerization to generate the desired indole core (−)-**26**. Isolation of indole (−)-**26** however proved challenging! Significant decomposition (>50%) was observed after normal silica gel column purification. Analysis of the decomposition mixture led to amide (−)-**27** (Scheme 7), as the major component. Further experiments suggested that indole (−)-**26** undergoes slow oxidation to (−)-**27** in air (days)

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 Merck reports.[1a,c] To resolve this purification issue, we developed a *nitrogen-purged vacuum silica gel column chromatography* purification method (see Supporting Information) to afforded (−)-**26** in 60% and 56% yield respectively from bromide (−)-**8** and triflate (−)-**23**.

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 planned to be oxidized prior to construction of the indole core. Towards this end, removal of both TBS groups in ketone (−)-**22** led to diol (−)-**28**, which was oxidized chemoselectively to aldehyde (−)-**29** employing a 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 (CH_2Cl_2/H_2O, 1:1). Protection of the secondary alcohol followed by triflation then furnished the new eastern hemisphere aldehyde (−)-**33**. The refined 4-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 this lack of reactivity was likely due to the steric hindrance of the C(8) neopentyl position. The TES group was therefore removed to alleviate the steric constraint. The derived alcohol (−)-**37** again only led 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**), identical in all respects with the published spectroscopic data.[1e]

With the total synthesis of (−)-nodulisporic acid D (**4**) achieved, we were encouraged to continue our synthetic drive to orchestrate **a unified strategy** to access the architecturally more complex nodulisporic acids (C, B, and A; Scheme 10). Noteworthy here in each is a C(24) hydroxy group known to undergo readily elimination, as well as more complex indole cores.[1] Nodulisporic acid C (**3**) for example possesses a C(26) prenyl unit, while for nodulisporic acids B (**2**) and A (**1**) a strained[1a,1c,6b] CDE tricyclic indole-indoline motif, including a stereogenic center at C(2′) in B(**2**) and A(**1**), distal form the other stereogenicity. Finally A(**1**) presents a carbonyl at C(1′)!

To access the more complex nodulisporic acids, we first required a protocol that would permit functionalization of the western hemisphere **43** at C(26) with a prenyl unit (Scheme 10), followed by union with eastern hemisphere fragment **44**, leading to an advanced indole intermediate (**42**). Depending on the specific prenyl unit selected, such a strategy would hold

the promise not only to access (−)-nodulisporic acid C (**3**), but potentially to (−)-B (**2**) and eventually (+)-A (**1**) via a late-stage cyclization/D-ring constructions.

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

Towards this end (Scheme 12A), borane reduction of **49** followed by electrophilic iodination led to benzyl alcohol **51.** 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, employing the oxidation protocol established previously in our laboratory,[6c] β-hydroxyl ketone (−)-**54** was obtained, albeit with enone **55** as a significant side product lacking the benzylic hydroxy group. The structure of **55** was assigned by X-ray analysis, while the relative configuration of (−)-**54** was confirmed by NOESY analysis of (−)-**56**, 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] Treatment of (−)-**54** (Scheme 12B) 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. Having constructed the tricyclic system, the secondary hydroxyl of (+)-**57** was protected chemoselectively as the TBS ether and the tertiary hydroxyl group eliminated to deliver olefin (−)-**58**, along with a minor side product (−)-**59**, wherein the double bond had migrated.

With (−)-**58** secure (ca. > 1g), we turned to explore the critical ortho-lithiation/alkylation. Initial attempts at deprotonation of the C(26) position of (−)-**58** proved unrewarding (Scheme 13A), 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 the C(26) of (−)-**58** was the issue. We therefore turned to the use of a -OPiv group at C(24), introduced by a two-step deprotection/pivalation sequence (Scheme 13). Although the steric environment of the derivative pivalate (−)-**60** may be similar to 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. As such, (−)-**60** was subjected to direct lithiation

employing *t*-BuLi/HMPA/CPME. Upon addition of MeOD, we observed considerable deuterium incorporation at C(26) (D% = 80%, by ^{1}H-NMR), however the pivalate group was gone. Nevertheless, this observation encouraged us to explore the alcohol (−)-**48** for the directed lithiation.

Pleasingly, successful deprotonation of (−)-**48** at C(26) was observed with *t*-BuLi (6 eq.)/ 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, only O- and N-alkylation to furnish (−)-**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 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 construction of western hemisphere (−)-**46**. The requisite eastern hemisphere **47** in turn was obtained via a single flask deprotection/acetylation operation employing the advanced intermediate (−)-**33** used in the acid D (**4**) synthetic venture.

With both hemispheres (−)-**46** and (−)-**47** in hand, we moved to the key union tactic exploited for nodulisporic acid D (**4**). Disappointedly, conditions used in the (−)-nodulisporic acid D (**4**) synthesis (i.e., RuPhos, Pd_2dba_3 or the palladacycle precatalyst), as 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 due to the additional steric hindrance of the prenyl side chain now present in the 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 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) aldehyde and the base sensitive C(7) acetate. It is likely that the specific combination of both steric and electronic effects of APhos facilitated the union sequence,[41b] as suggested by the superior reactivity of Aphos towards Suzuki-Miyaura Coupling.[41]

Initially however the reproducibility and scalability of the union reaction proved troublesome. Experimentally, we observed that the employed base (K_3PO_4) often deposited on the inner surface of the reaction flask as a thick residual, especially on prolonged heating. As a result, either incomplete conversion or decomposition occurred. Pleasingly addition of sand (ca. 50 mg/1 mL 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, identical in all respects upon spectral comparison with the published Merck data.[1d]

With the total synthesis of both (−)-nodulisporic acid D (**4**) and C (**3**) achieved, we proceeded to 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 the advanced tricyclic intermediate (−)-**48** that was employed in the nodulisporic acid C (**3**) synthesis (Scheme 13). To this end, the hydroxy group of hydrazone (+)-**53** (Scheme 16) was first protected as TES ether, and then 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 step, thereby avoiding the previous issue of facile hydroxy elimination. Next, application of the Nozaki-Hiyama-Kishi cyclization followed by elimination provided (−)-**79**, now without producing the double bond isomer (see Scheme 12B). Removal of the TES group employing the refined conditions of H_2SiF_6/*t*-BuOH[43] completed a second-generation synthesis of (−)-**48** with an overall yield of 34%, compared to 14% of the first-generation, over the five steps from (+)-**53**.

Application of our ortho lithiation/alkylation tactic from the nodulisporic acid C synthesis with iodide **80** (Scheme 17),[44] now possessing the requisite allylic OTES substituent for ring-D generation led to (−)-**81**, albeit in modest yield (45%), with 37% starting material (−)-**48** recovered, that 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 acid C (**3**) synthesis 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 at generating ring-D utilizing either a palladium or iridium catalytic system,[45] with or without an external base such as K_3PO_4 or DBU in various solvent, proved unrewarding; only recovery of starting materials was achieved. Employing a stronger base such as NaO*t*-Bu also only led to decomposition, likely due to the base sensitivity of the -OAc group. We therefore adjusted the synthetic scheme revisiting the use of triflate (−)-**33** employed in nodulisporic acid D (**4**) synthesis (Scheme 18).

To this end, union of aniline (−)-**76** with triflate (−)-**33** led to the corresponding indole (+)-**83** now in 49% yield. Next employing the same synthetic sequence as describe in Scheme 17, carbonate (+)-**84** was acquired in 61% over the 2 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 resulted in none of the desired cyclization, but now producing diene (+)-**86**, with isolation of a small amount of the palladium species (+)-**85**, which did not undergo the desired ring-D cyclization under either neutral or basic conditions, but instead provided diene (+)-**86** again, likely via beta-hydride elimination. Reasoning that the beta-hydride elimination might be suppressed by a specific ligand that could occupy the empty coordination site on palladium, we investigated different ligands (see Supporting Information). After extensive optimization, we eventually discovered that employing the bidentate ligand 1,4-bis(diphenylphosphino)butane (dppb) at room temperature for 17 hours resulted in 82% combined yield of (+)-**88** and (+)-**89**, albeit with a dr of 1.3:1. However, if the reaction was conducted at 55 °C for 17 hours, (+)-**90** containing a seven- instead of a five-membered ring, was produced as a 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 palladium **π**-allyl species **87** undergoes cyclization at the C(2′) position 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 addition of (*S*)-PipPhos as the ligand (5 mol%) led predominately to the desired epimer (+)-**89** (dr=5:1) albeit in 45% yield, whereas the (*S,S,S*)-MonoPhos-BPA[49] ligand (4 mol%) gave almost exclusively (+)-**88**. Notwithstanding the modest yield of (+)-**89**, a regio- and 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 the tricyclic indole-indoline core (−)-**89** for (−)-nodulisporic acid B, not unexpectedly the acid and oxygen sensitivities of such advanced intermediates became an even greater issue;[1a,c] exposure to either air or to 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 and “one-pot” acetylation, exploiting our earlier developed Horner–Wadsworth–Emmons directed olefination tactic (Scheme 19) led, after careful hydrolysis protocols, 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; the former identical in all respects to the published Merck NMR date,[1c] the latter assigned upon extensive NMR and HRMS analysis.

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

their sodium salts, have been achieved in a stereocontrolled fashion via a unified synthetic strategy. Synthetic studies towards the more complex nodulisporic acid A, as well as analogs thereof continue in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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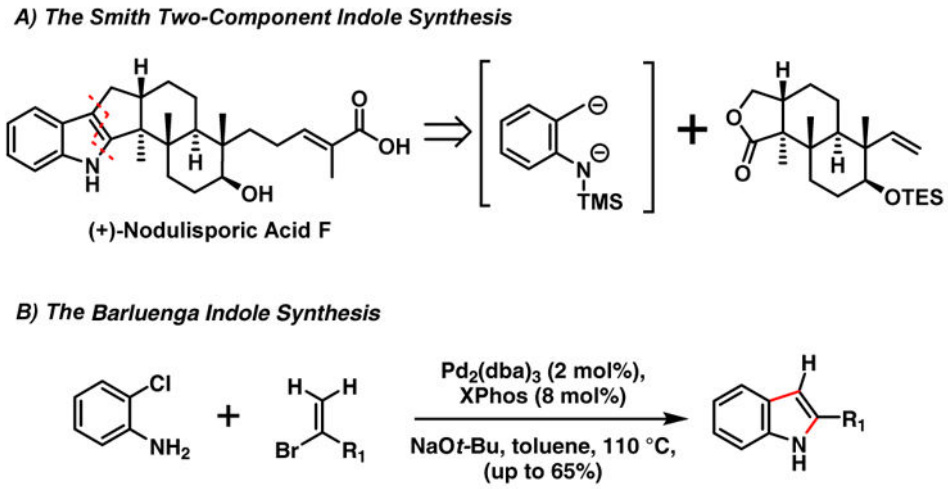
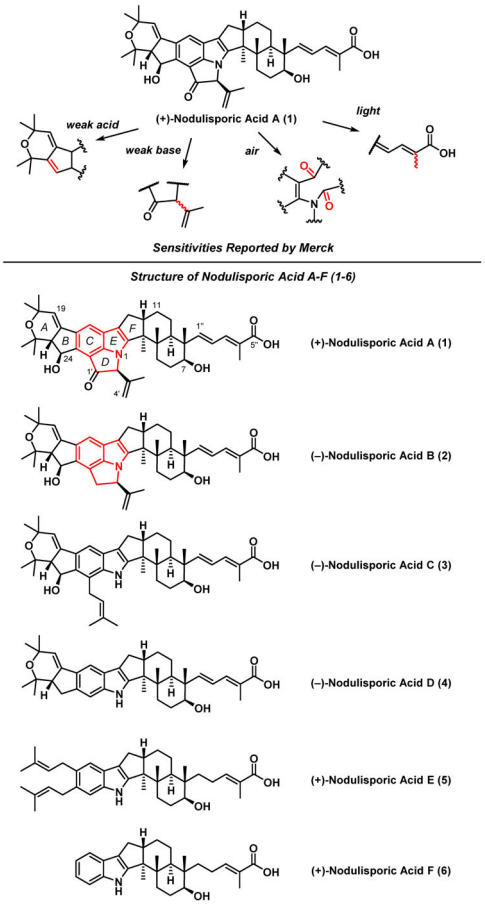
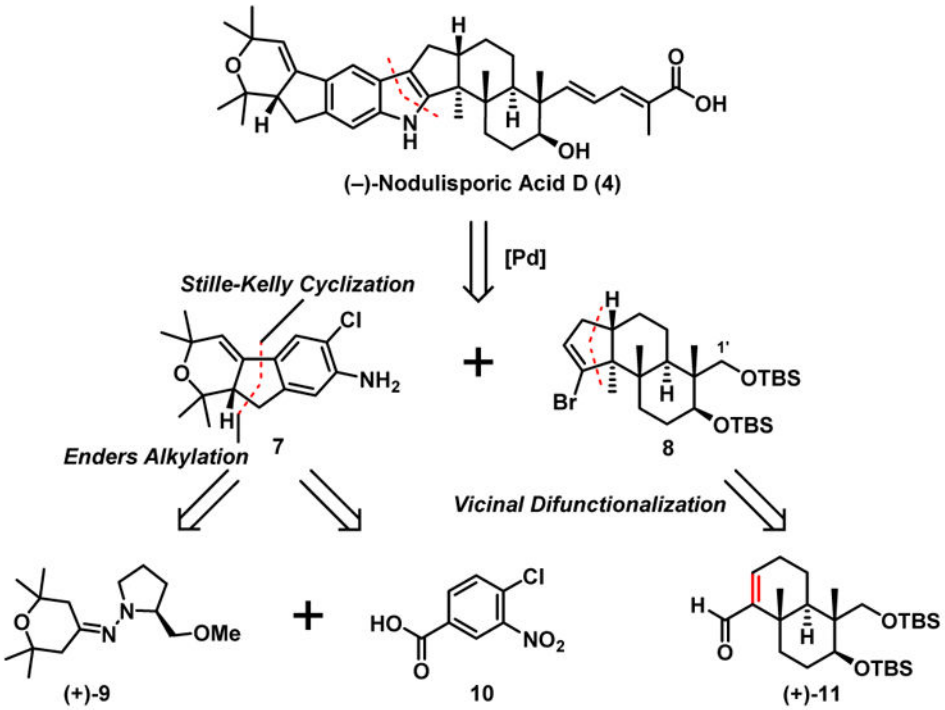
49. (*S*,*S*,*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta[2,1-a:3,4-a′]dinaphthalen-4-yl)bis(1-phenylethyl)amine



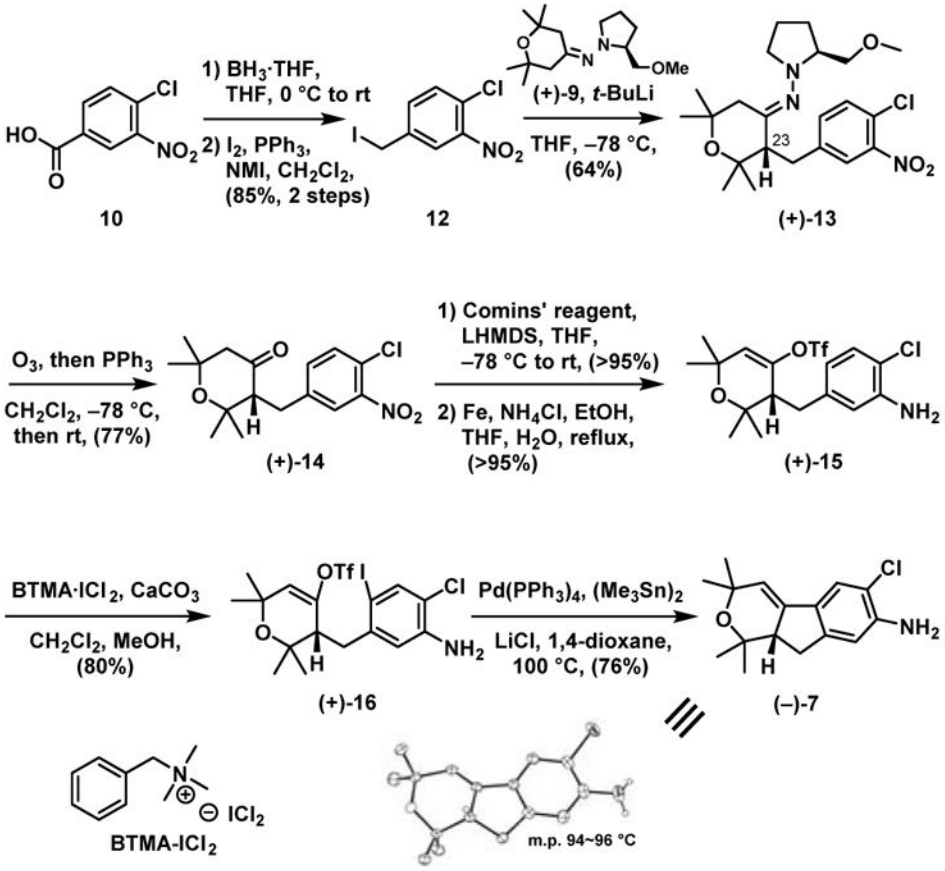
Scheme 1.
The Nodulisporic Acids Indole Terpenes (A-F)



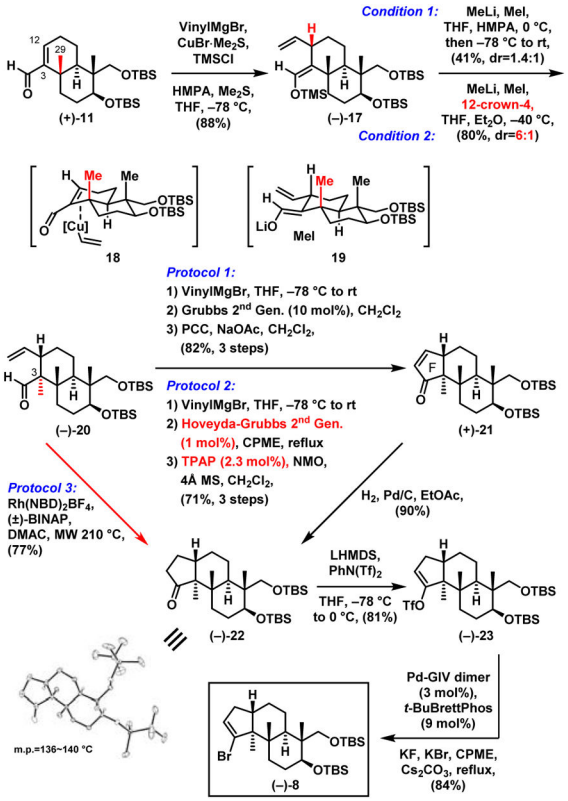
Scheme 2.
Synthetic Strategy for the Nodulisporic Acids



Scheme 3.
Synthetic Analysis of (−)-Nodulisporic Acid D (**4**)

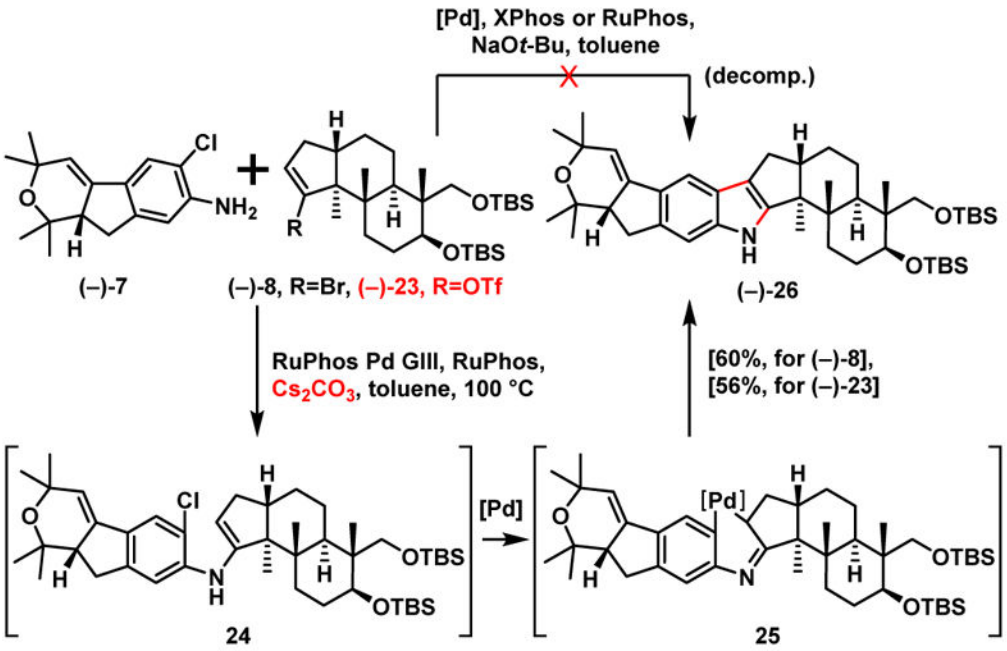


Scheme 4.
Synthesis of Western Hemisphere (−)-**7**

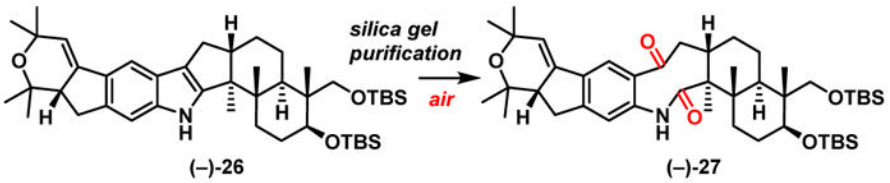


Scheme 5.

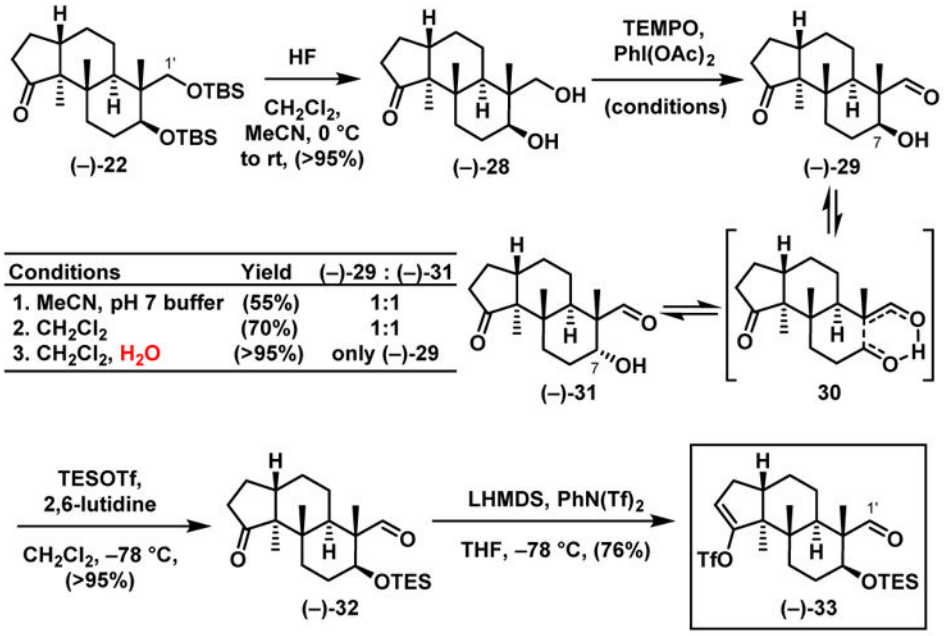
Synthesis of the Eastern Hemisphere (−)-**8**



Scheme 6.
Development of a Barluenga Cross Coupling Union

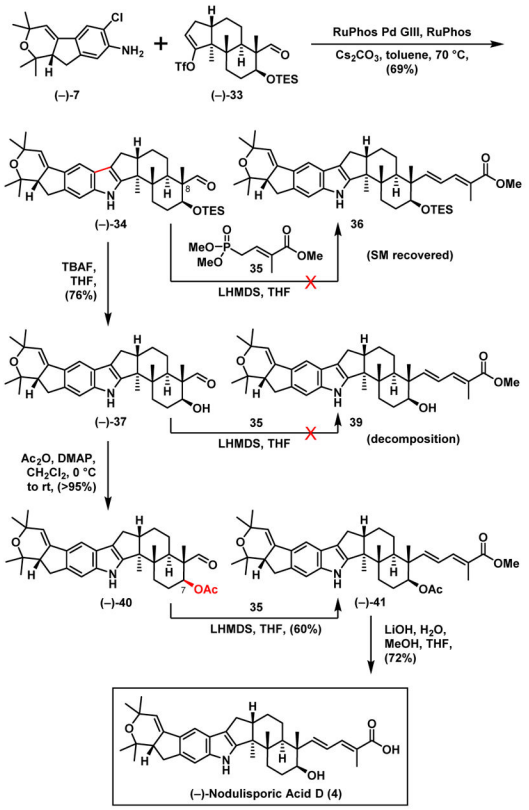


Scheme 7.
Air Oxidation of the Nodulisporic Indole Core

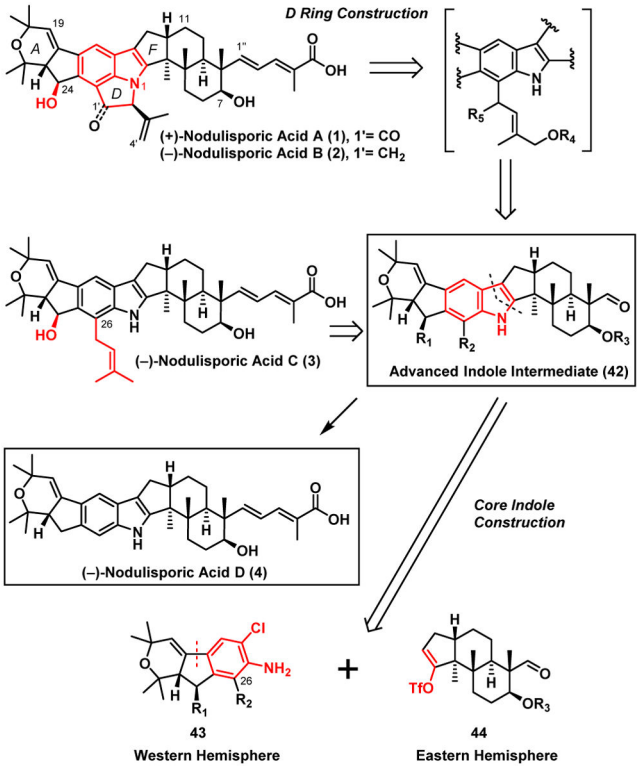


Scheme 8.

Construction of the Revised Eastern Hemisphere (−)-**33**

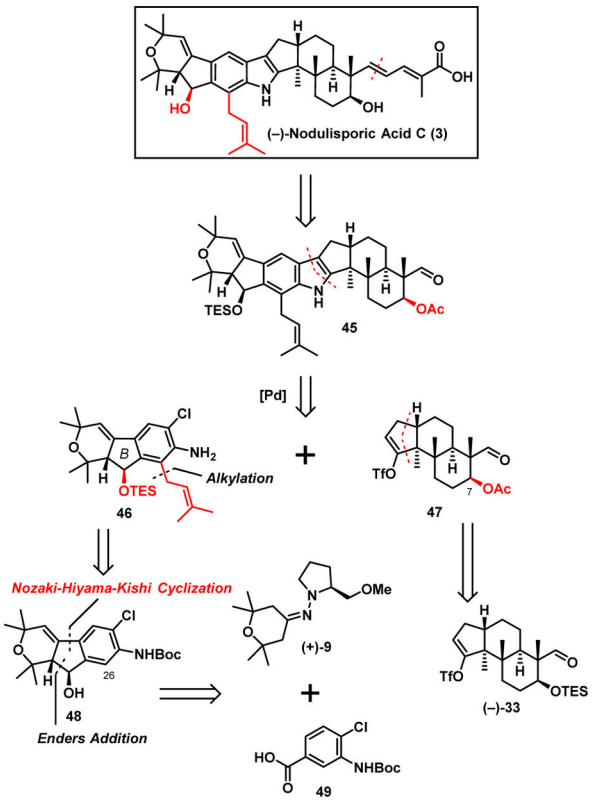


Scheme 9.
End Game of (−)-Nodulisporic Acid D

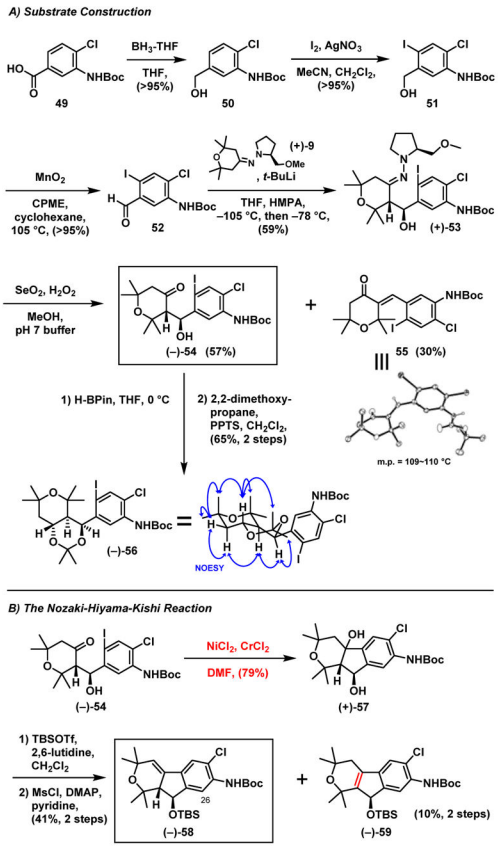


Scheme 10.

A Unified Synthetic Strategy to the Advanced Nodulisporic Acids

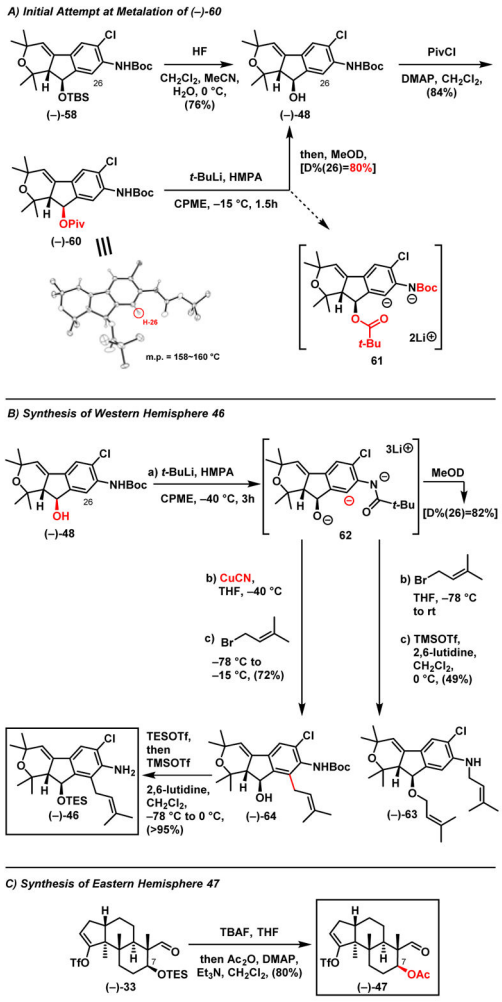


Scheme 11.
Synthetic Analysis of (−)-Nodulisporic Acid C (**3**)



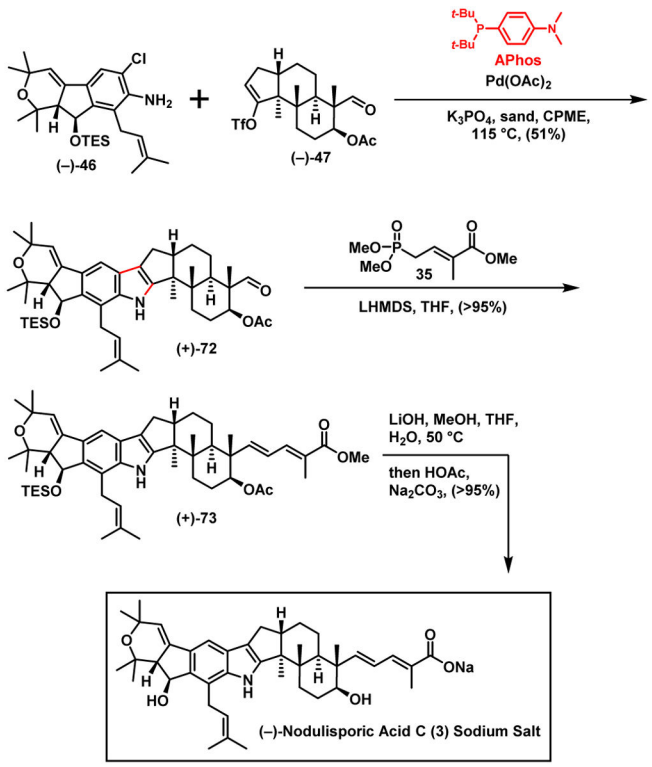
Scheme 12.

A) Substrate Construction; and B) The Nozaki-Hiyama-Kishi Reaction

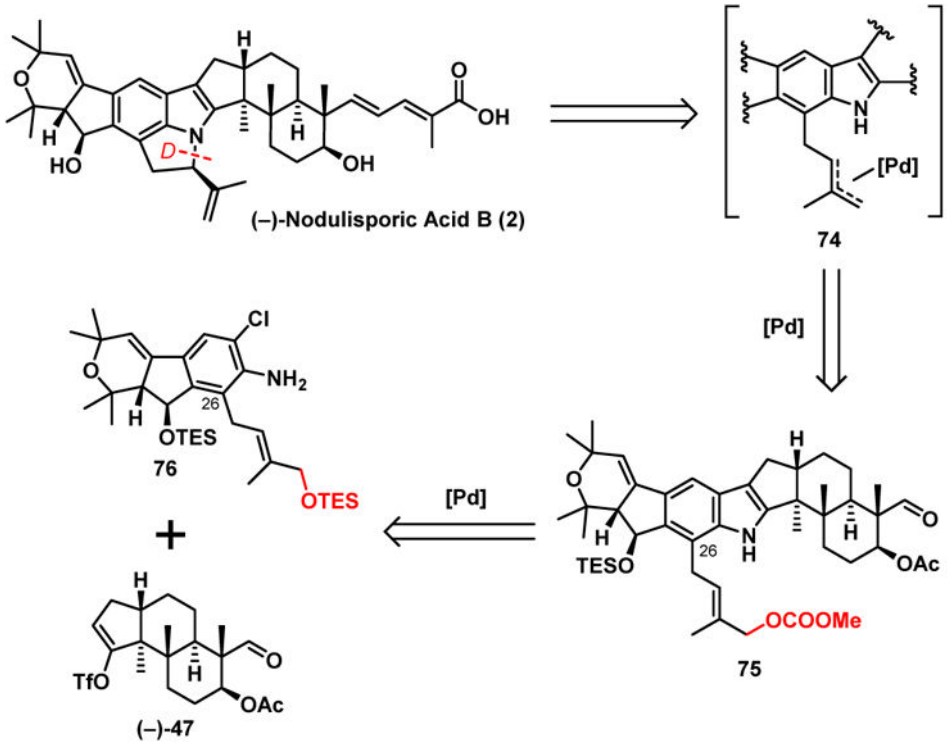


Scheme 13.

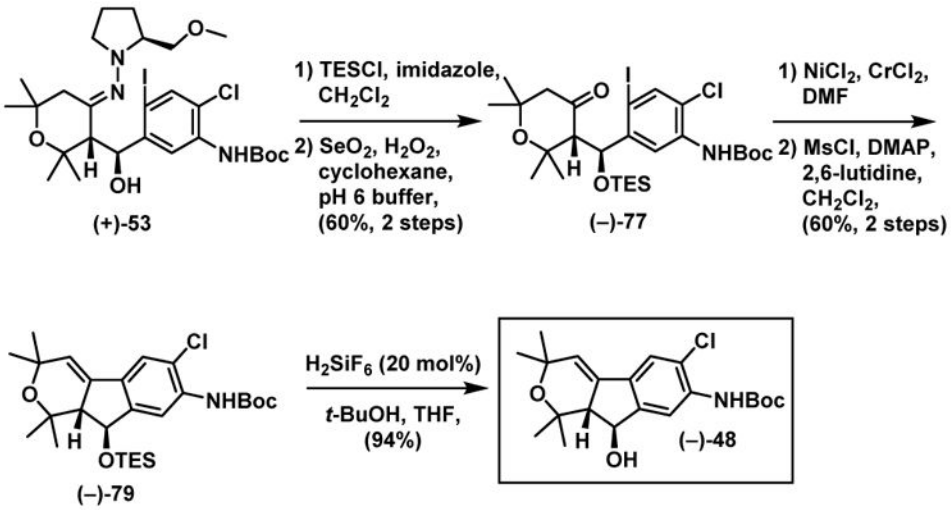
Synthesis of Western Hemisphere **46** and Eastern Hemisphere **47**



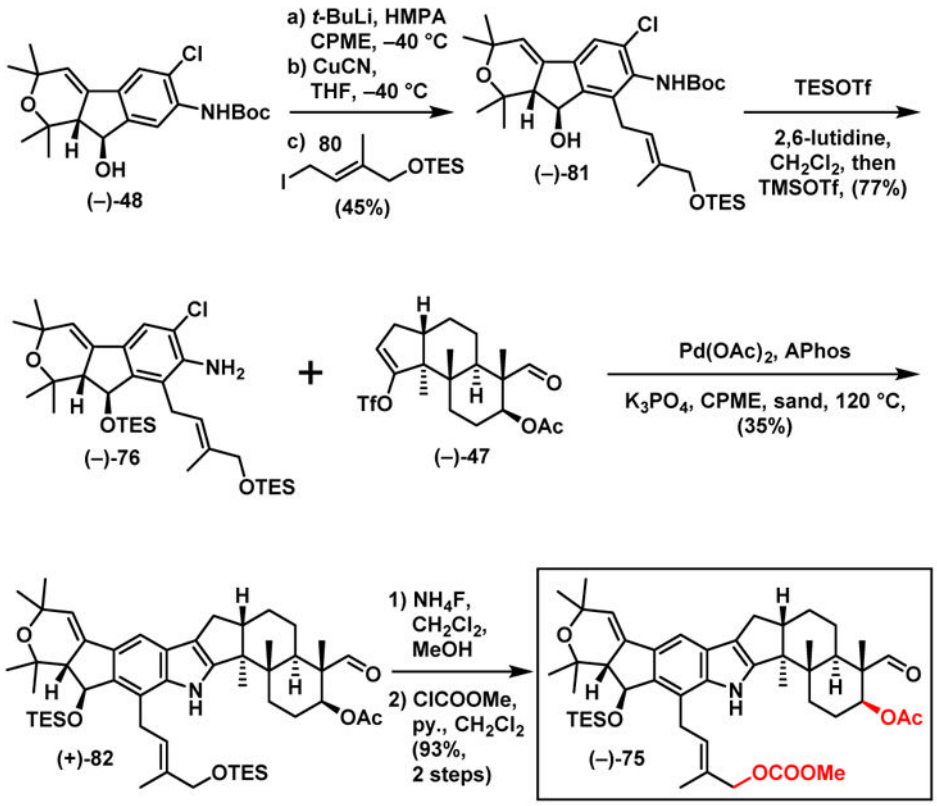
Scheme 14.
End Game for (−)-Nodulisporic Acid C (**3**)



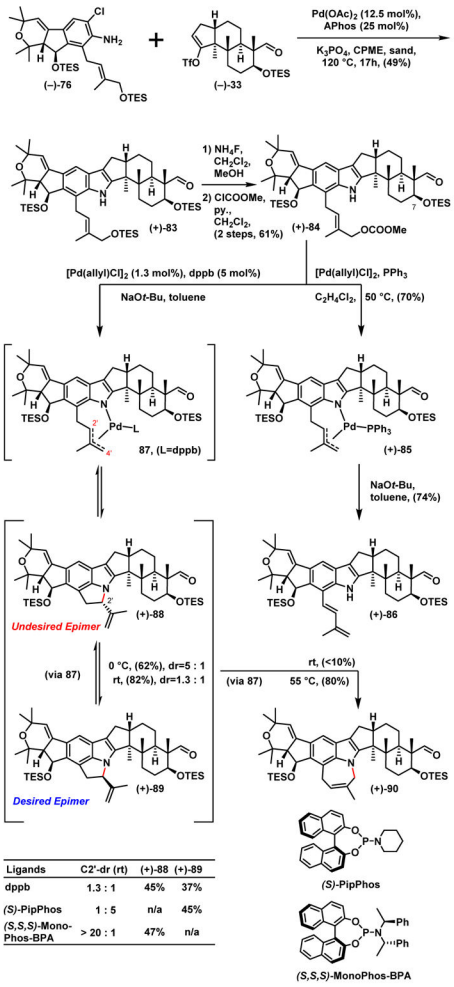
Scheme 15.
Synthetic Analysis of (−)-Nodulisporic Acid B (**2**)



Scheme 16.
Second-Generation Western Hemisphere Synthesis

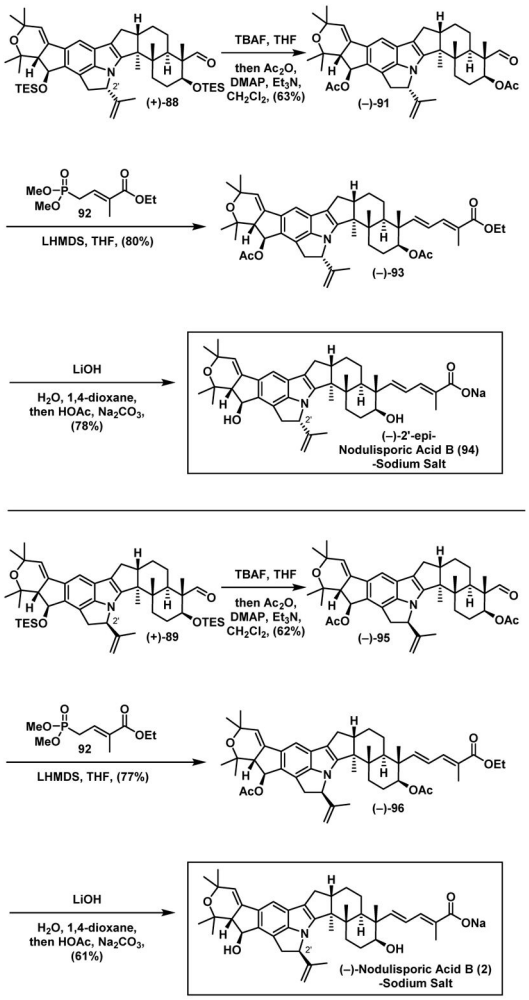


Scheme 17.
Synthesis of the Cyclization Precursor



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

Scheme 18.
The Key Cyclization Reaction



Scheme 19.
The End Game