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Twelve-Step Asymmetric Synthesis of (–)-Nodulisporic Acid C

Nicole A. Godfrey[#], **Devon J. Schatz**[#], **Sergey V. Pronin**[*]

Department of Chemistry, University of California, Irvine, Irvine, California 92697-2025, United States

[#] These authors contributed equally to this work.

Abstract

A short, enantioselective synthesis of (–)-nodulisporic acid C is described. The route features two highly diastereoselective polycyclizations en route to the terpenoid core and the indenopyran fragment and a highly convergent assembly of a challenging indole moiety. Application of this chemistry allows for a 12-step synthesis of the target indoloterpenoid from commercially available material.

Nodulisporic acids (e.g., **1**, **2**, and **3**;Figure 1) comprise a group of secondary metabolites isolated from the endophytic fungus *Hypoxylon pulicicidum* (previously known as *Nodulisporium* sp.) that exhibit potent insecticidal activities.[1–6] These biological effects arise from the specific activation of a subset of ligand-gated chloride ion channels found in arthropods, but not in mammals, resulting in a potentially useful selectivity profile.[7] For example, the flagship congener, nodulisporic acid A (**1**), exhibits high efficacy against fleas while lacking overt toxicity in dogs.[5,8] The producing organism has proven difficult to culture.[9,10] Nevertheless, detailed investigations of nodulisporic acids as a starting point for the development of new antiflea medications for companion animals have been performed, resulting in identification of promising lead compounds.[11] As a part of broader efforts toward the paxilline indoloterpenoids,[12–14] multiple inquiries from organic chemists[15] recently culminated in the syntheses of nodulisporic acids B (**2**), C (**3**), and D.[16,17] In addition to the common indoloterpenoid core, these natural products contain an indenopyran motif found in other members of the paxilline family, such as the janthitrems and shearinines.[18,19] Here we demonstrate a 12-step asymmetric synthesis of (–)-nodulisporic

[*]**Corresponding Author** spronin@uci.edu.

ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectroscopic data for new compounds (PDF)

CIF file for compound **15** (CIF)

CIF file for compound **23** (CIF)

CIF file for compound **26** (CIF)

Notes

The authors declare no competing financial interest.

acid C (**3**) enabled by the development and implementation of new polycyclization-based strategies and a highly convergent assembly of a challenging indole moiety.

The key transforms in our retrosynthetic analysis of nodulisporic acid C (**3**) included a late-stage indole assembly to form the C14–C15 and N1–C2 bonds and two polycyclization events to access the terpenoid and indenopyran motifs. We envisioned a radical-polar crossover cascade initiated by a chemoselective[20,21] hydrogen atom transfer (HAT)[22–24] to construct the C4–C9 and C8–C7 bonds of the decalin fragment and a gold-catalyzed cycloisomerization[25] to construct the C18–C23 and O21–C22 bonds of the dihydropyran fragment. We previously discovered a diastereoselective polycyclization related to the proposed HAT-initiated cascade, which relied on a transient lactolization event to control the relative orientation of the C3–C4 vicinal quaternary stereocenters.[13] Implementation of this approach was expected to require multiple manipulations to accommodate both the assembly of the reactant and the late-stage installation of the indole moiety; therefore, an alternative solution was sought. The outcome of the polycyclization en route to the indenopyran motif was difficult to predict at the outset of our work.[26,27]

Our synthesis began with a copper-catalyzed asymmetric conjugate addition of alkylmagnesium bromide **5** to commercially available cyclopentenone **4** (Scheme 1). Extensive screening identified JosiPhos derivative SL-J015–1 as a suitable ligand for production of silyl enol ether **6** in excellent yield and with synthetically useful levels of enantioenrichment.[28] Alkenylation of enoxysilane **6** with pentynol derivative **7** was best performed in the presence of substoichiometric amounts of indium(III) bromide and acidic workup secured access to product **8**.[13,29] Cyclopentanone **8** was converted to the corresponding protected cyanohydrin, which underwent Sharpless allylic oxidation[30] and subsequent double oxidation of the resulting diol to deliver dialdehyde **9**.

Subjection of intermediate **9** to the conditions of ironmediated HAT[20,31] resulted in highly diastereoselective formation of the *trans*-decalin fragment and subsequent workup secured direct access to the cyclopentanone functionality of the desired tricyclic product **11**. The pronounced preference for the *trans*-decalin motif represents an unusual case of efficient differentiation between methyl and linear alkyl substituents and is in stark contrast to the lack of diastereoselectivity observed with the corresponding unprotected cyclopentanone derivative.[13] Presence of the pseudoaxial substituent at C2 proved crucial for obtaining high levels of diastereocontrol. Thus, only the *trans*-decalin is produced during the polycyclization to corresponding *tert*-alkyl ether **14** while low selectivity was previously observed in the case of the related *sec*-alkyl ether, which lacked the methyl substituent at C2.[13] Furthermore, undesired *cis*-decalin **15** is favored during the polycyclization of the corresponding dialdehyde, where C2 is sp^2 hybridized and the indole N–H group presumably exhibits unfavorable steric interactions en route to the *trans*-decalin product.

Protection of alcohol **11** delivered the corresponding pivalate, which could be obtained in a highly enantioenriched form (97% ee) upon recrystallization from hexanes. The pivalate was subjected to Horner–Wadsworth–Emmons olefination with phosphonate **12**,[32] providing access to ketone **13** in eight steps from commercially available material.

With the decalin-containing fragment of nodulisporic acid C in hand, we proceeded to assemble the indenopyran motif of the target natural product. We began with a three-step synthesis of arene **17** (Scheme 2), which included iodination of commercially available aniline **16**, formylation of the intermediate iodide, and nitration of the resulting arene. Addition of diorganozinc **18** to aldehyde **17** was accomplished in the presence of catalytic amounts of aminoalcohol **19** and efficiently delivered benzyl alcohol **20** with high enantioselectivity.[33] Sonogashira cross-coupling[34] of dibromide **20** with alkyne **21** proceeded chemoselectively and the intermediate diol was protected to yield cycloisomerization precursor **22**.

We discovered that treatment of enyne **22** with catalytic amounts of a gold(I) complex in the presence of a halide scavenger resulted in highly efficient and stereoselective formation of dihydropyran **23**. The process likely involves the initial nucleophilic attack on the alkyne-gold complex by the isobutenyl fragment and subsequent trapping of the resulting tertiary carbocation with the pendant hydroxyl group. This proposal is supported by the observation of allene **26**, which likely results from elimination of an alkenylgold intermediate[26] and accumulates in the reaction mixture under anhydrous conditions. Neither dihydropyran **23** nor allene **26** is observed upon treatment of alkyne **22** with acid, but these conditions are competent in converting intermediate **26** to the desired tricyclic product. The presence of the substituent at C26 proved to be crucial for obtaining high levels of stereocontrol during the reaction. Thus, products **23** and **27** are formed as single diastereomers in contrast to dihydropyran **28**. Allylic strain between the benzyl ether and the ortho substituent is expected to force rotation of the silyl group[35] toward the reaction center in the transition state of the initial cyclization, which can lead to the dramatic enhancement of the diastereoselectivity en route to products **23** and **27**. This proposal is consistent with the observed restricted rotation of the siloxy-bearing fragment in the ortho-substituted substrates.

Installation of the prenyl group into the aromatic moiety was best accomplished after the cycloisomerization. Thus, Stille cross-coupling[36] of bromide **23** with stannane **24** delivered chloroarene **25** in good yield, completing assembly of the indenopyran motif in eight steps from commercially available starting material and setting the stage for the fragment union.

After significant experimentation, we discovered that a trialkyltin enolate of ketone **13** could undergo a palladiumcatalyzed arylation with nearly stoichiometric quantities of chloroarene **25** (Scheme 3). A RuPhos-based palladium precatalyst[37] provided optimal performance and the arylketone was produced in a diastereoselective manner.[38] The stereochemical outcome of the reaction proved crucial for the successful completion of the synthesis. Treatment of arylation product **30** with zinc in the presence of acetic acid resulted in efficient formation of the desired indole under mild conditions. In this setting, diastereomer **29** returned the corresponding aminoketone and attempted cyclodehydration under forcing conditions led to elimination of the benzyl ether moiety. The sensitive nature of the indenopyran fragment was previously highlighted in the isolation and synthetic literature.[3,17] The facility of conversion of ketone **30** to the desired indole is in stark contrast to the previous reports of cyclodehydrations of relevant aminoketones[39] and can be instructive during synthetic

planning toward the other paxilline indoloterpenoids. Final manipulations in our synthesis of (–)-nodulisporic acid C (3) included deprotection of the silyl ether and saponification of the intermediate diester, which delivered the natural product in 12 steps from commercially available material (longest linear sequence).

In summary, we disclose an enantioselective synthesis of (–)-nodulisporic acid C that proceeds in a highly convergent manner. The relative brevity of our route was enabled by the development of two polycyclizations to rapidly assemble the decalin and indenopyran motifs and a ketone arylation protocol to unite the two complex fragments. In these processes, seemingly minor structural modifications within the crowded steric environments have a significant influence on the reactivity and have allowed for complete stereocontrol over the polycyclization events and facile construction of a sensitive indole fragment. The preponderance of these and related structural motifs among the paxilline indoloterpenoids suggests that lessons learned during our synthesis will find application in the assembly of other members of this fascinating family and simplify production of unnatural analogs for biological studies.

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(39). See references 12a–c, k, l.

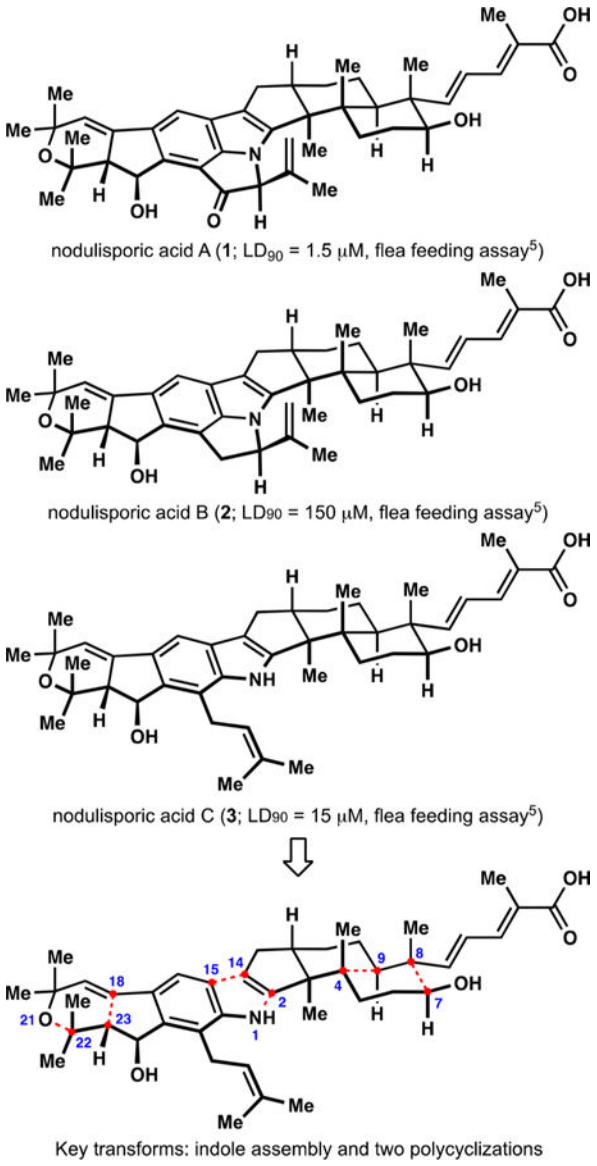
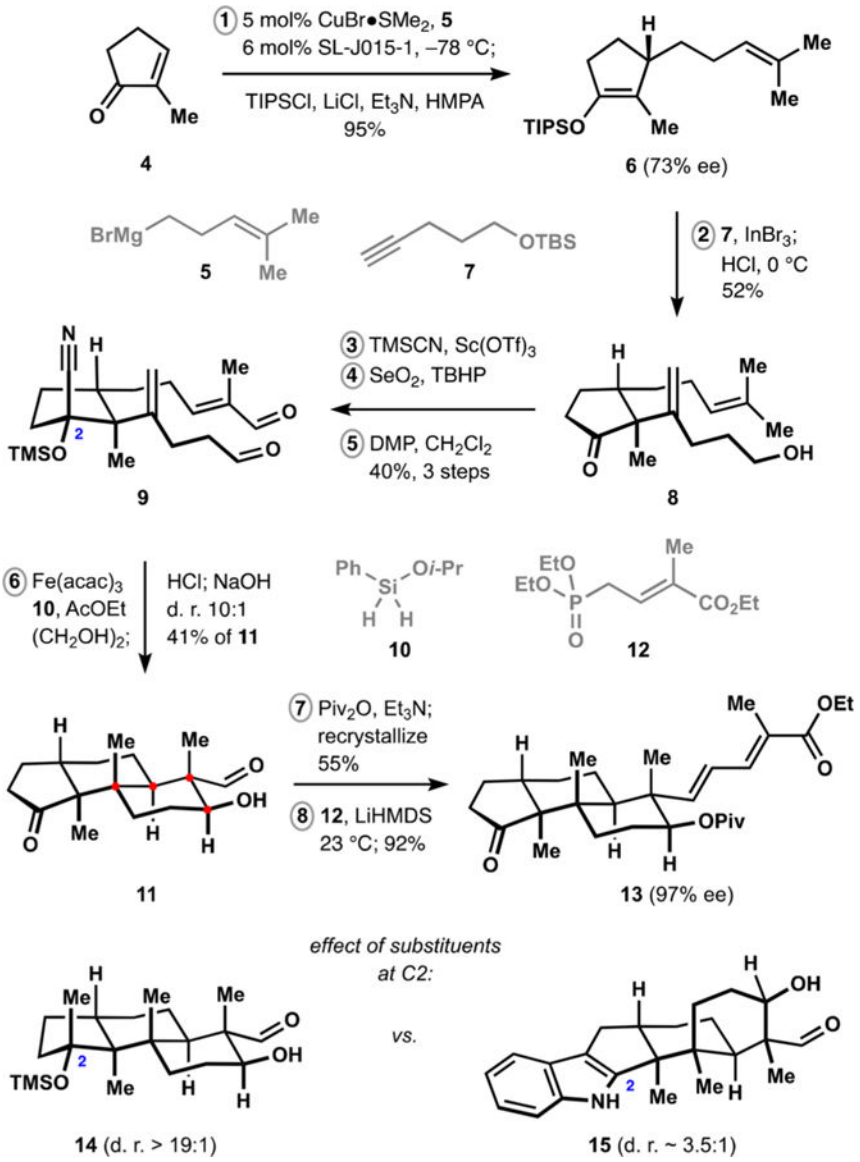
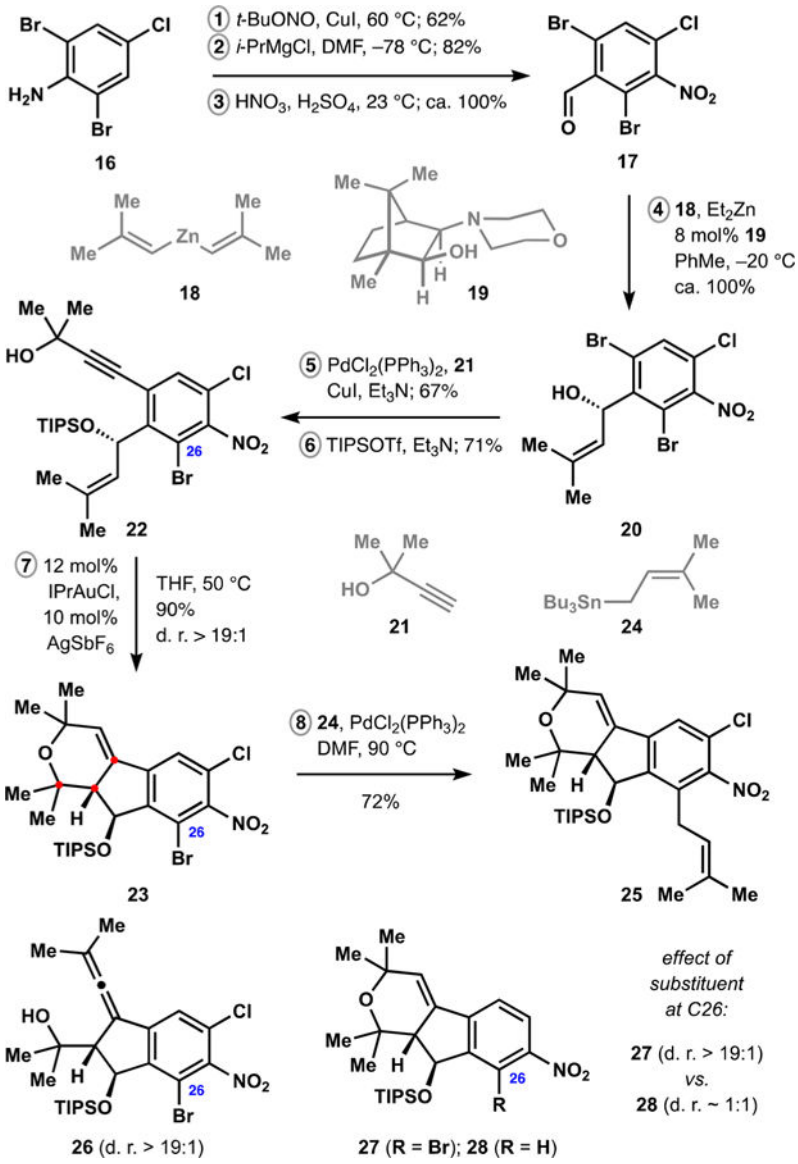


Figure 1.

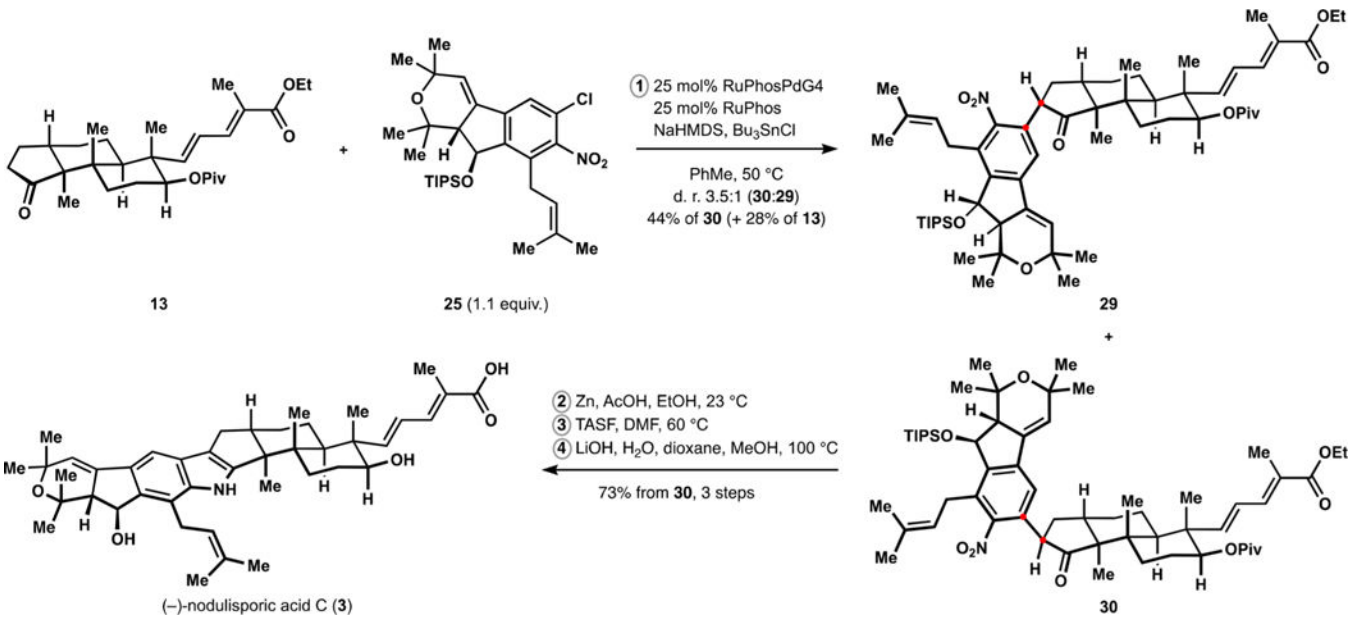
Representative nodulisporic acids and our analysis of nodulisporic acid C.



Scheme 1.
Synthesis of the Terpenoid Fragment



Scheme 2.
Synthesis of the Indenopyran Fragment



Scheme 3.
Synthesis of (–)-Nodulisporic acid C (3)