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REVIEW ARTICLE

Total synthesis of architecturally complex indole terpenoids: strategic and tactical evolution

Yike Zou and Amos B. Smith, III

Indole terpenes have attracted the interests of synthetic chemists due to their complex architectures and potent biological activities. Examples of total syntheses of several indole terpenes were reviewed in this article to honor Professor KC Nicolaou.
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INTRODUCTION

The indole diterpenoids constitute a large family natural products which possess interesting architectures and diverse biological activities.[1–3] Among these, the paspaline subclass features a common multi-substituted indole core in conjunction with a tricyclic terpene moiety that features a signature trans-anti-trans 5,6,6-fused ring system (Figure 1).[4–6] This subclass displays a wide variety of biological activities including tremorgenic, antibacterial, antitumor, antiviral and insecticidal activity.[7–13] In the early 1980s we initiated a synthetic program involving the paspaline indole diterpenoids and have over the years achieved a number of total syntheses (Figure 1). In this review, we will present the strategic and tactical evolution of this long-term program, focusing on the construction of the multi-substituted indole cores and the trans-anti-trans 5,6,6-fused ring systems. Of equal importance, we will review two recent total syntheses of indole terpenoids which are structurally related to the systems in which we have engaged. The latter is included, not inappropriately, given the purpose of this review is to honor Professor KC Nicolaou, a friend and previous colleague in the Chemistry Department at the University of Pennsylvania, Philadelphia, PA.

DISCUSSION

The beginning

This synthetic venture began with (−)-paspaline (Figure 1), an architecturally complex indole diterpenoid that was initially disclosed by the Arigoni and co-workers[14–16] in the mid 1960s (Figure 1).

Our synthetic interests concerned not only the disubstituted indole core but equally the trans-fused 5/6 ring system, both of which were challenging structural features from the synthetic perspective. No syntheses of the paspaline-type indole diterpenoids had been achieved at that time. At the outset, we decided to take advantage of a reductive alkylation protocol (**1**→**3**),[17] that was developed early in our laboratory, to construct the fused pyran moiety (Scheme 1).

The synthesis thus began with bicyclic ketone **4** (Scheme 2), which was derived from enone **1** via a reductive alkylation.[17] Nazarov cyclization of the generated diene (**5**) then led to tricyclic enone **6** which was set up for a key vicinal bifunctional reaction. Exploiting the Trost alkylation protocol from their aphidicolin synthesis,[18] the critical trans-fused 5/6 ring system was generated albeit with disfavored diastereoselectivity (trans:cis = 0.5:1), the latter likely due to conformational constraints. Notwithstanding this shortcoming, side chain elongation of the trans isomer **7** led to olefin **8**. Following an epoxidation-cyclization cascade, the fused pyran ring F of **9** was established, which was further converted to the indolization precursor **10**. Optimization of the Gassman indole synthesis[19] at this late stage proved challenging due to the substrate structural complexity; nonetheless the first total synthesis of (−)-paspaline was achieved, in a total of 23 steps.[20,21]

Strategy evolution: a second-generation formal synthesis

The critical unmet issue in our first generation paspaline synthesis comprised introduction of the vicinal quaternary stereocenters in **7** in a stereocontrolled fashion. Recognizing that the trans-fused 5/6 ring system is higher in strain energy than the cis counterpart, and that the computed trans-fused 6/6 ring system would constitute a thermodynamically more favorable situation, the strategic decision was made on the basis of a 6/6 to 5/6 ring contraction. To this end, a second generation strategy was initiated with the Robinson annulation of (+)-Wieland–Miescher ketone **12** (Scheme 3). The resulting enone **13** was then subjected to Luche conjugate addition[22,23] to establish the C/D trans 6/6 geometry of **14**. With the desired trans configuration in hand, a ring contraction sequence successfully led to the desired 5/6 trans ring system (**15**) as a single diastereomer. Encouraged by this result, we further expanded the reductive alkylation protocol on the late stage intermediate **16**. The last two stereocenters were then introduced in a highly stereoselective manner to lead eventually to common advanced olefin intermediate **7,** cumulating in a second generation, now formal total synthesis of (−)-paspaline that proceeded with full stereocontrol.[24,25]

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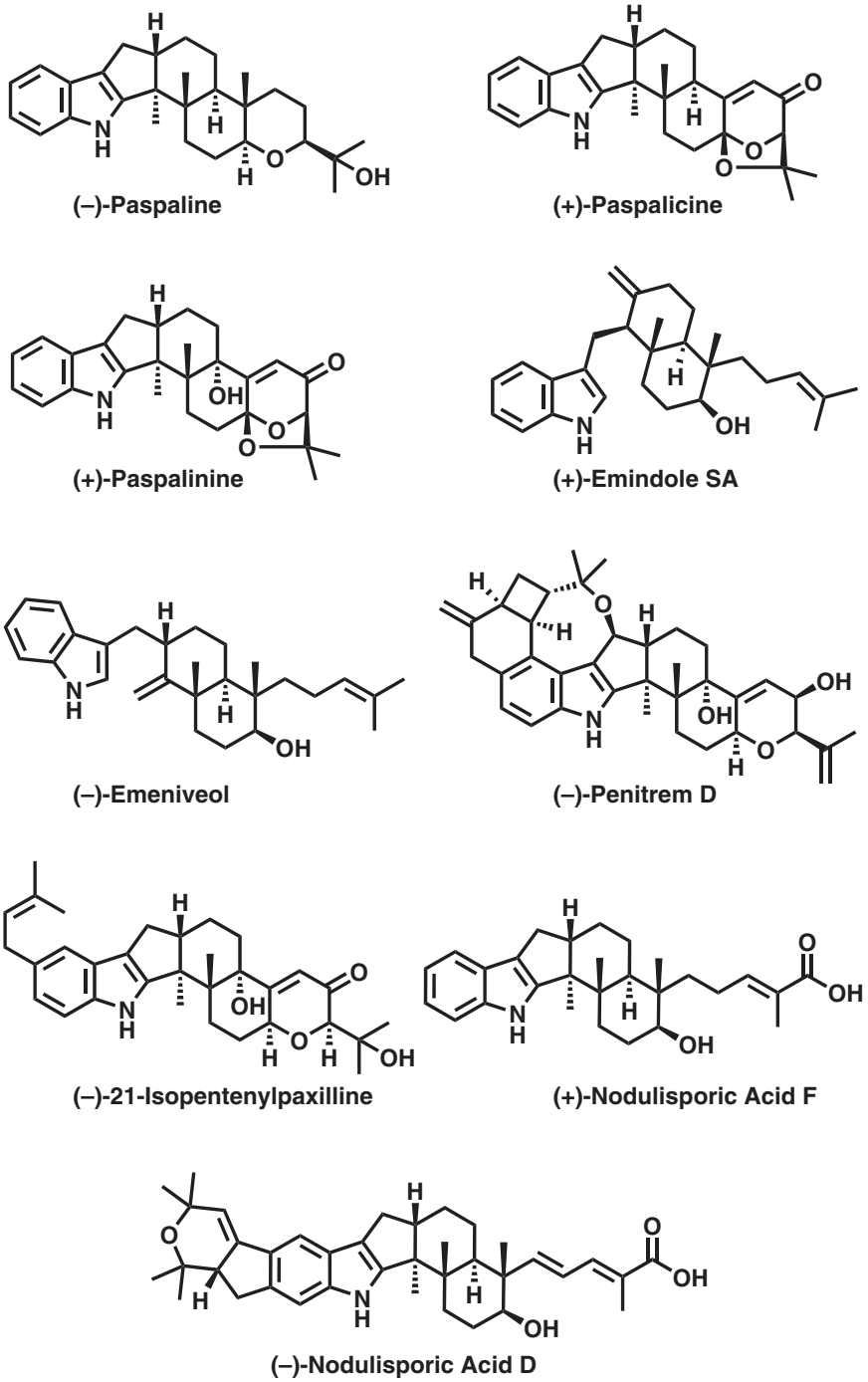
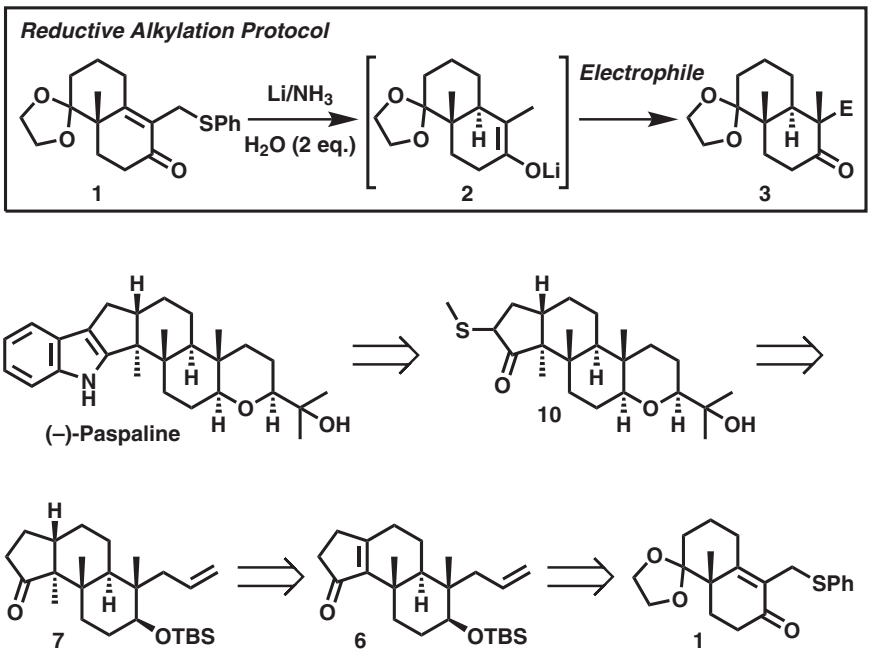


Figure 1 Representative indole terpenes that have been synthetically achieved.

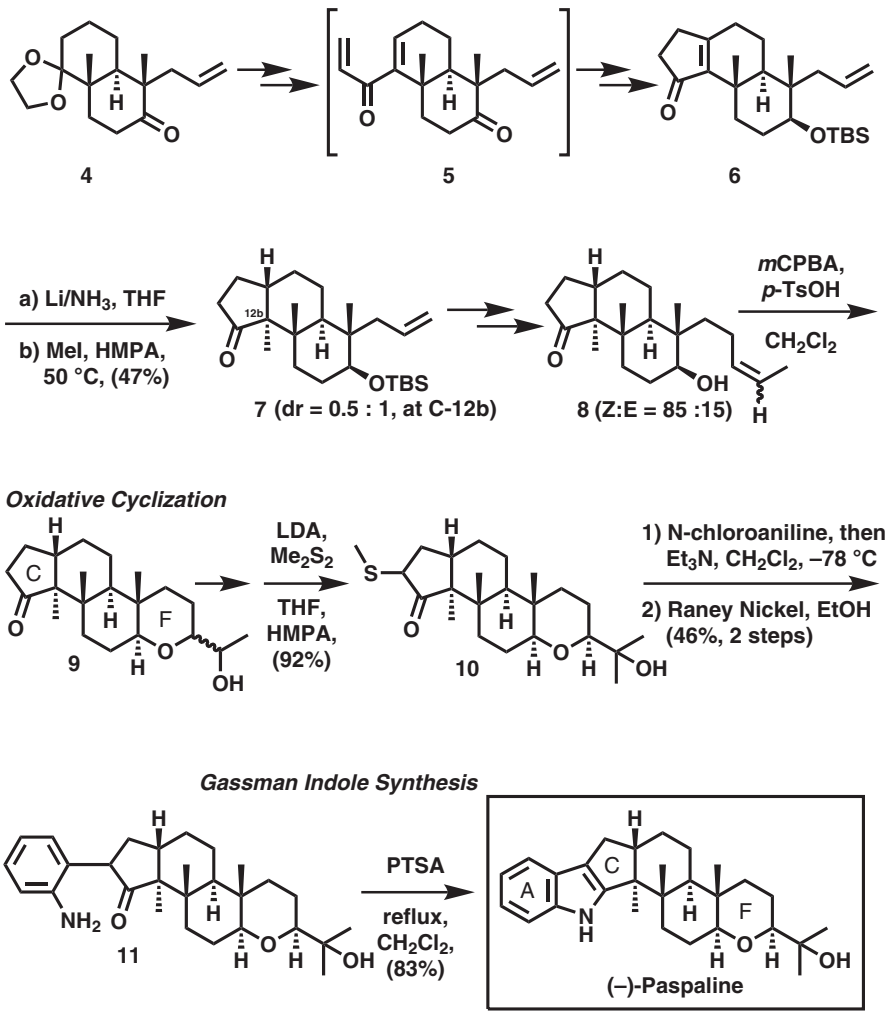
Development of a unified strategy

Gaining access to the advanced intermediate **15** (Scheme 3) via a second generation strategy not only improved efficiency but also led to a unified strategy to construct the structurally more complex members of the indole diterpenoid family (Scheme 4).

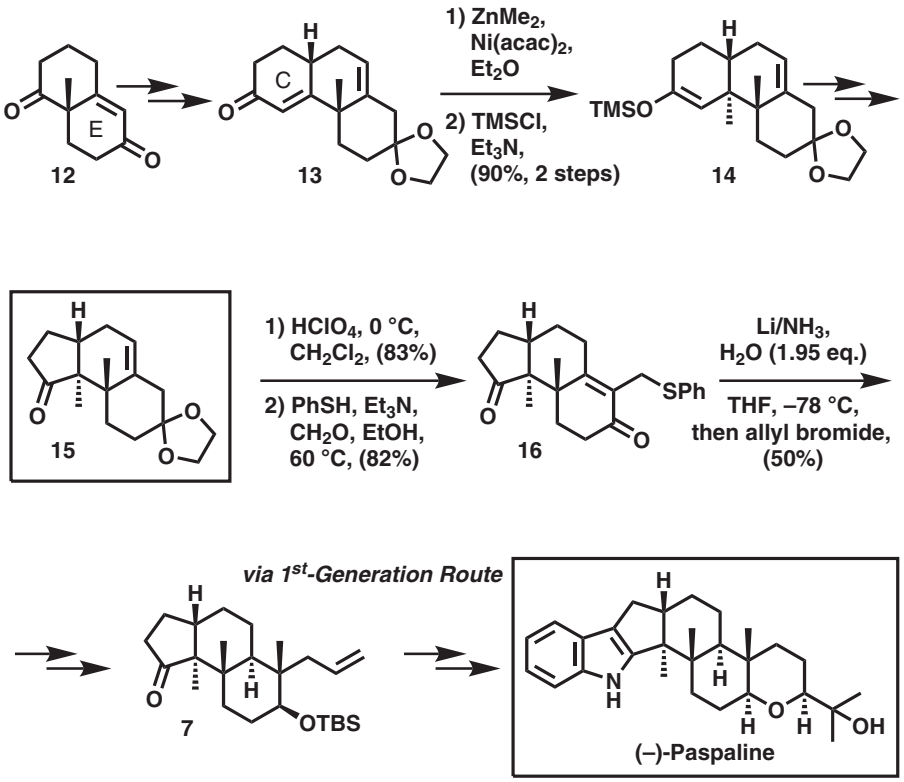
For the syntheses of (+)-paspalicine and (+)-paspalinine (Scheme 5), the latter being a naturally occurring tremorgen that features a tertiary hydroxyl groups at C(13), we began with the earlier stage construction of the indole system via a Gassman indole protocol to provide common indole **16a** (Scheme 5). A Stork hydrazone alkylation[26] with advanced intermediate **17** and epoxide **18** proved unexpectantly challenging due to the substrate complexity and the harsh reaction conditions required; pleasingly, conditions were eventually discovered that led to key advanced union intermediate **19**, that embodied the full carbon elements of the targeted natural products. Acylation of **19** followed by hydrazone hydrolysis provided enone **20**, which in turn was treated with acid to promote an intramolecular trans ketalization that precisely set up the cis pyran geometry of ketal **21**. The acetyl group in **21** was then removed by hydrolysis and the derived product subjected to Moffatt oxidation[27] to generate



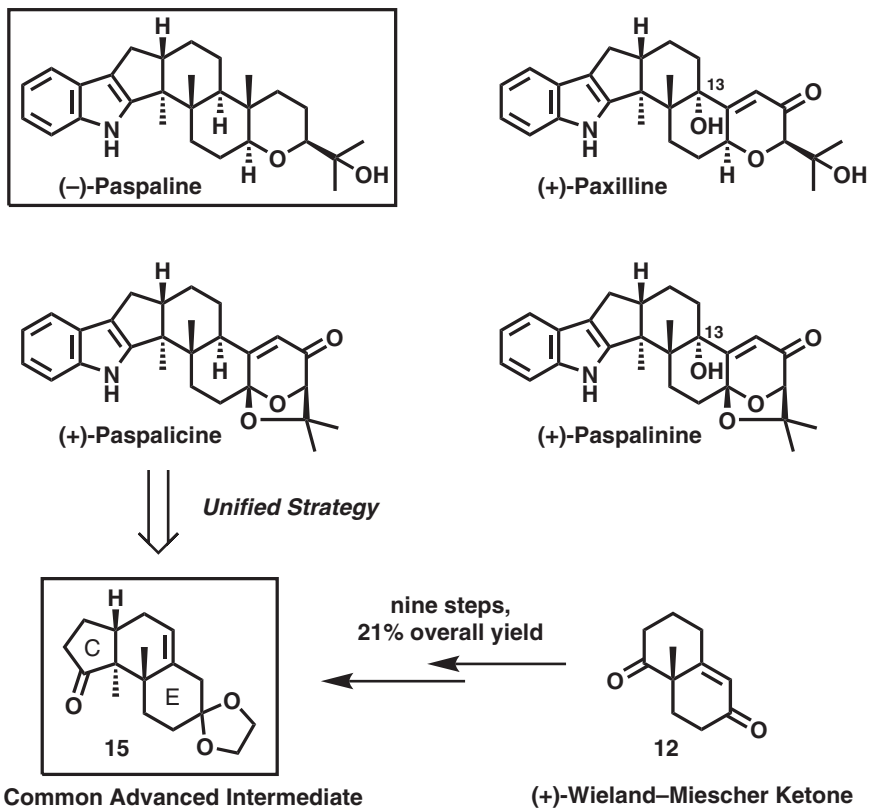
Scheme 1 Retrosynthetic analysis of (–)-paspaline.



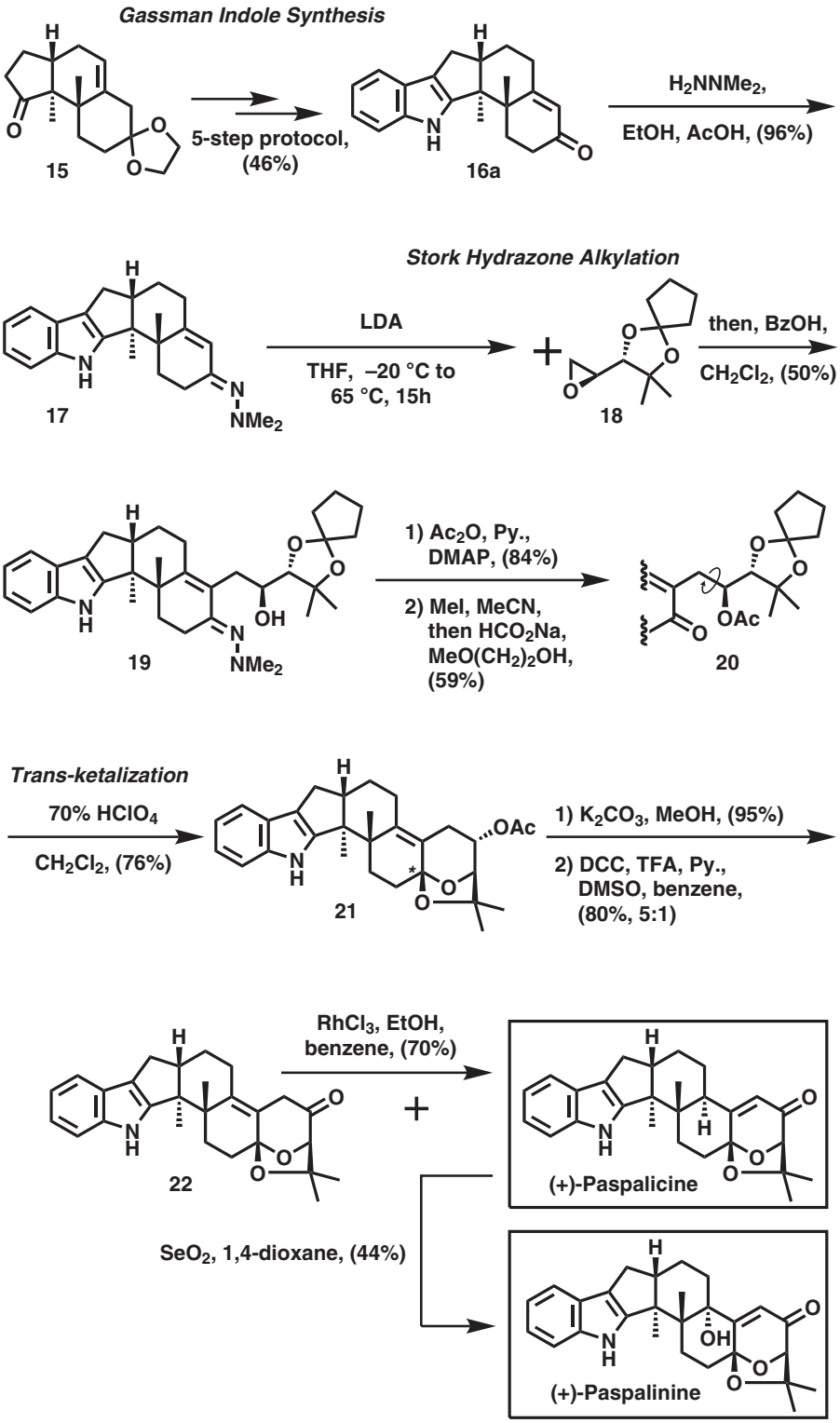
Scheme 2 First generation total synthesis of (–)-paspaline.



Scheme 3 Second generation synthesis of (−)-paspaline.



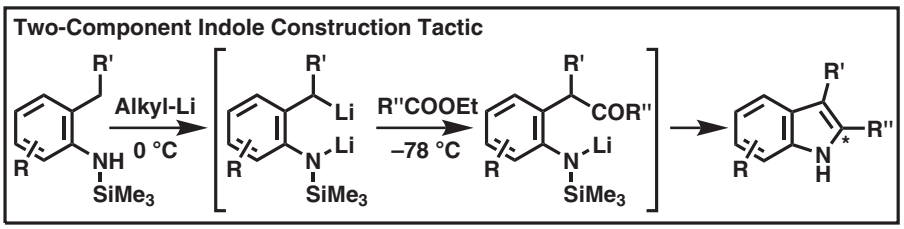
Scheme 4 Development of a unified strategy.



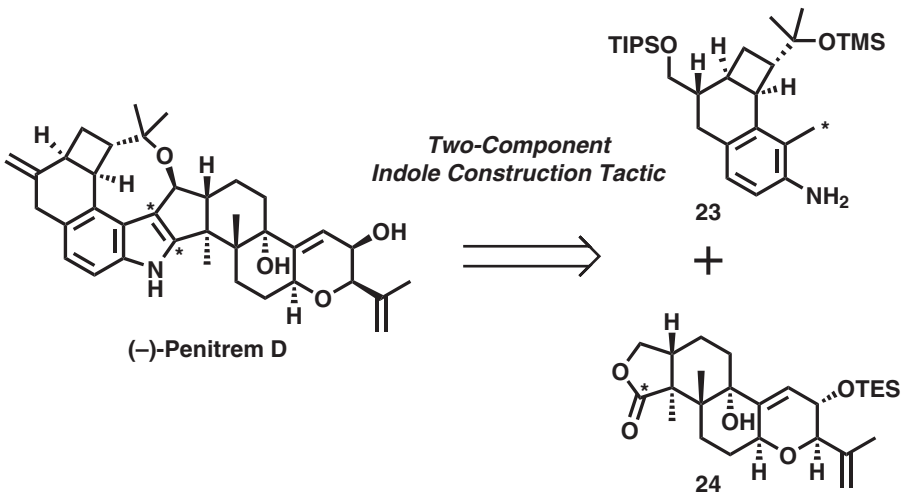
Scheme 5 Total syntheses of (+)-paspalicine and (+)-paspalinine.

ketone **22**, wherein the isolated double bond underwent smooth isomerization into the requisite conjugated position upon applying the conditions of Grieco[28,29] to complete the first total synthesis of (+)-paspalicine.[30] After extensive experimentation, we were successful in converting (+)-paspalicine to (+)-paspalinine by treatment with selenium dioxide.[31]

With two additional indole terpenes constructed, we reviewed the overall synthetic program and recognized that the frequently employed Gassman indole synthesis protocol, although playing a major role in the construction of the multi-substituted indole skeletons, the sequence often required at best four to five steps that proceeded in only moderate yield (40–50%). We thus faced the dilemma of



Scheme 6 Two-component indole construction tactic.



Scheme 7 Retrosynthetic analysis of (–)-penitrem D.

employing an early stage coupling to construct a substituted indole core which then had to be carried through the synthetic sequence with considerable care, and then introduced via a late-stage elaboration utilizing complex fragments, at best in moderate to low yield. We thereafter sought to develop a more general strategy that would permit efficient construction (that is, single step) of a multi-substituted indole system that would employ large, late stage union fragments.

Development and validation of a new indole synthetic protocol

Our accumulation of interests and efforts in anion chemistry[17,20,32–34] led to the discovery and validation of a two-component indole construction tactic (Scheme 6) which was initiated by bis-metalation of an N-silyl-*o*-toluidine.[35] The resulting dianion was then added to an ester to generate the corresponding ketone, which in turn would undergo an intramolecular aza-Peterson olefination/tautomerization to yield the disubstituted indole in a 'single flask'.[36] With this protocol established, and in conjugation with our previous successful syntheses of (−)-paspaline, (+)-paspalicine and (+)-paspalinine, we devised a blueprint for expanding the two-component 'one-flask' indole construction tactic for the considerably more complex indole terpene (−)-penitrem D (Scheme 7). Toward this end we envisioned the use of *o*-toluidine **23** and lactone **24**.

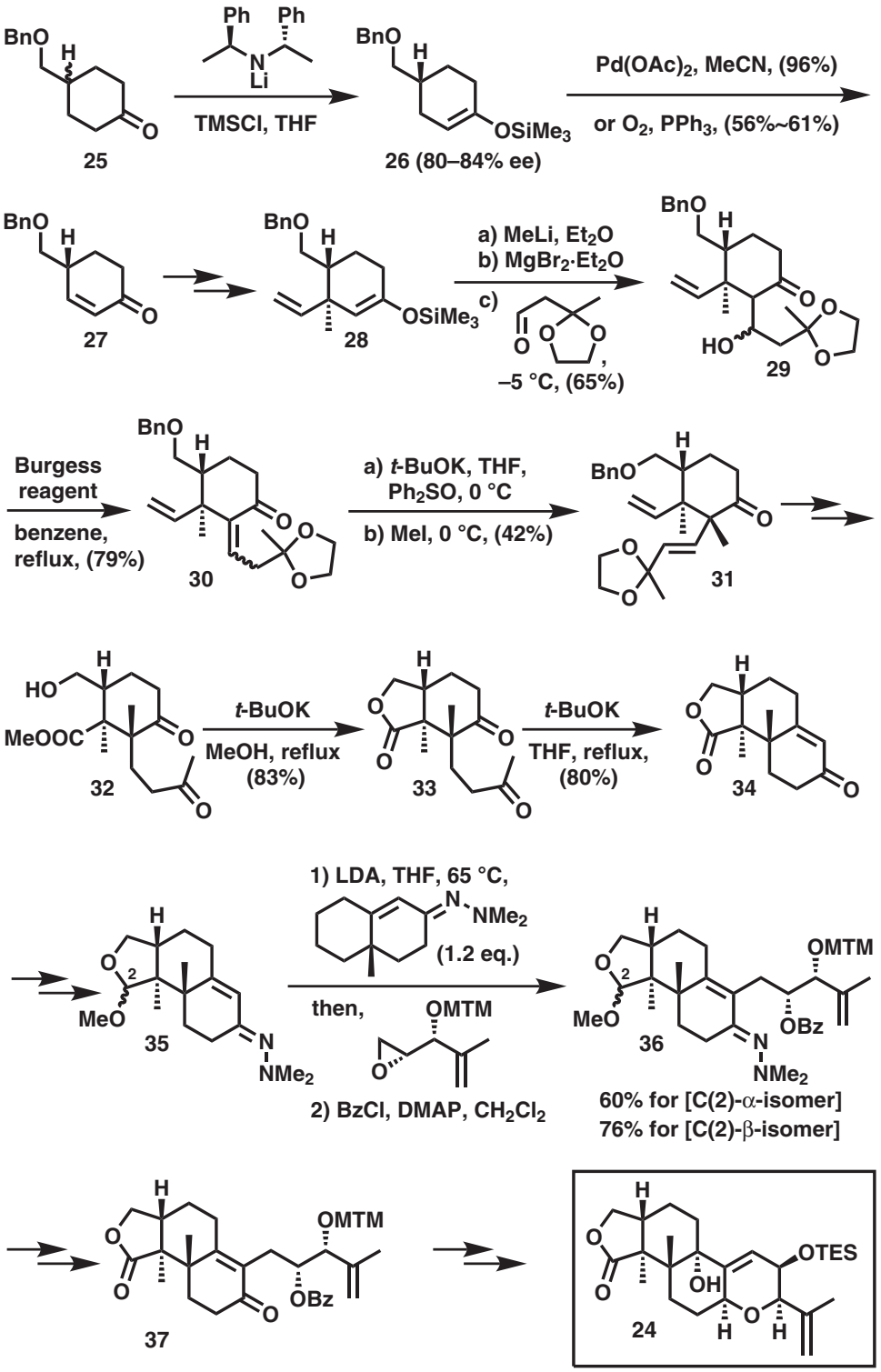
Lactone fragment **24** (Scheme 8) was constructed beginning with the kinetic deprotonation of ketone **25** employing the Whitesell reagent.[37] The resulting enol silyl ether **26** was then carried forward via a series of transformations (**27**→**28**), including a conjugate addition/oxidation/conjugate addition sequence, that eventually led to the tricyclic lactone **34**. In similar fashion to that of the (+)-paspalinine and (+)-paspalicine synthetic ventures, a late-stage Stork hydrazone alkylation protocol was applied on **35** to install the side chain, which in turn was fashioned into the desired cis pyran that eventually permitted elaboration of the highly functionalized tetracyclic core of lactone **24**.

To access the required advanced *o*-toluidine cyclobutane fragment **23**, we began with enone **27a** (Scheme 9), the enantiomer of an early stage intermediate (**27**) in the synthesis of lactone **24**. A [2+2] photocycloaddition of **27a** with methyl acrylate led to **38** with the requisite 6/4 cis ring geometry. A Woodward-Wilds modification of the Robinson annulation[38,39] followed by Semmler-Wolff aromatization[40,41] eventually afforded advanced *o*-toluidine **23**.

With both fragments in hand, we turned to the two-component indole construction (Scheme 10). *In situ* generation of dianion **41** permitted attack of the carbon-anion on the lactone carbonyl of **24**. The resulting union intermediate (**42**) then underwent an intramolecular aza-Peterson olefination/tautomerization in a finely-tuned binary solvent system that eventually landed the system at the desired multi-substituted indole **43**, which comprised the fully elaborated carbon skeleton of penitrem D, remarkably in 81% yield.

With the two-component indole synthesis tactic now demonstrated on highly elaborated late stage substrates, the end game of (−)-penitrem D was at hand. Parikh–Doering oxidation followed by acid treatment permitted equilibration between **44** and **45**. Pleasingly, a single treatment with scandium triflate converted the equilibrium mixture to macrocyclic ether **46** via a cascade cyclization in a highly stereoselective fashion (dr > 95:5). After an elimination sequence to introduce the exomethylene moiety, the first and to date only total synthesis of architecturally complex indole diterpenoid (−)-penitrem D was achieved in a highly convergent and fully stereocontrolled manner.[42,43]

During the (−)-penitrem D synthetic venture, a new indole diterpenoid, (−)-21-isopentenylpaxilline (Scheme 11) appeared in the literature.[44] A unified synthetic strategy was thus proposed exploiting



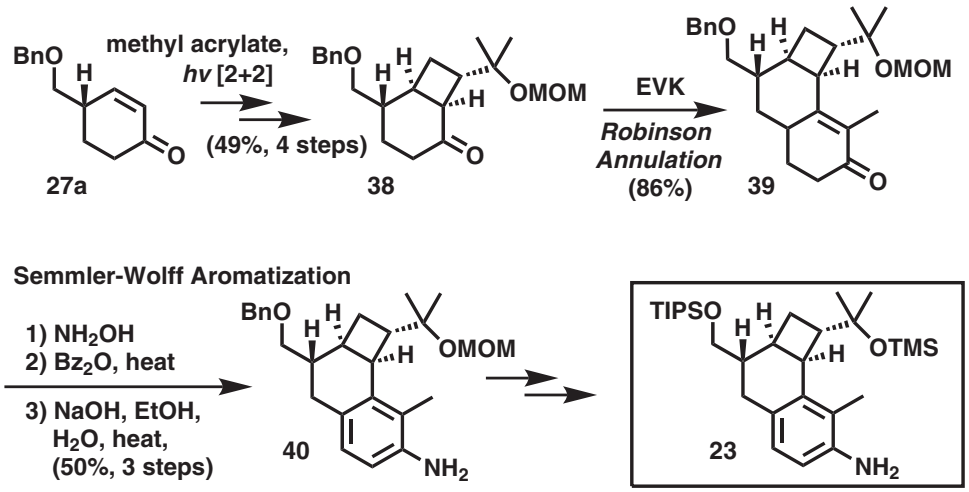
Scheme 8 Synthesis of lactone **24** fragment.

our two-component indole construction tactic. Beginning with advanced intermediate **49** employed in the (−)-penitrem D synthesis, a similar side chain introduction sequence led to the highly elaborated lactone **50**, which in this case was alkylated with dianion **48**.

Pleasingly, the second example of our two-component indole construction tactic could be altered slightly to form indole **52**. Negishi cycloalkylation[45] followed by late stage elaboration then led to the first total synthesis of (−)-21-isopentenylpaxilline.[46,47]

The nodulisporic acids

In the late 1990s to the early 2000s, a series of indole terpenoids with a novel scaffold, namely the nodulisporic acids A−F (Figure 2), were



Scheme 9 Synthesis of aniline **23** fragment.

discovered at the Merck Research Laboratory and found to possess potent insecticidal activities.[48–52] These novel indole diterpenes embodied a highly strained, electron-rich indole or indoline ring system, the latter of which proved air sensitive, and in several cases the benzylic-homoallylic secondary hydroxyl group at C-24 was found to be extremely labile to very mild acid (that is, even unstable to the inherent dienoic acid moiety!).[51] Continuing with our long-standing interest in the indole diterpenes, we initiated a synthetic campaign towards the nodulisporic acid family of molecules.

Total synthesis of (+)-nodulisporic acid F and (−)-nodulisporic acid D

At the outset we selected the structurally less complex member, (+)-nodulisporic acid F (Scheme 12), to employ our two-component indole construction tactic with aniline **55** and lactone **56**.

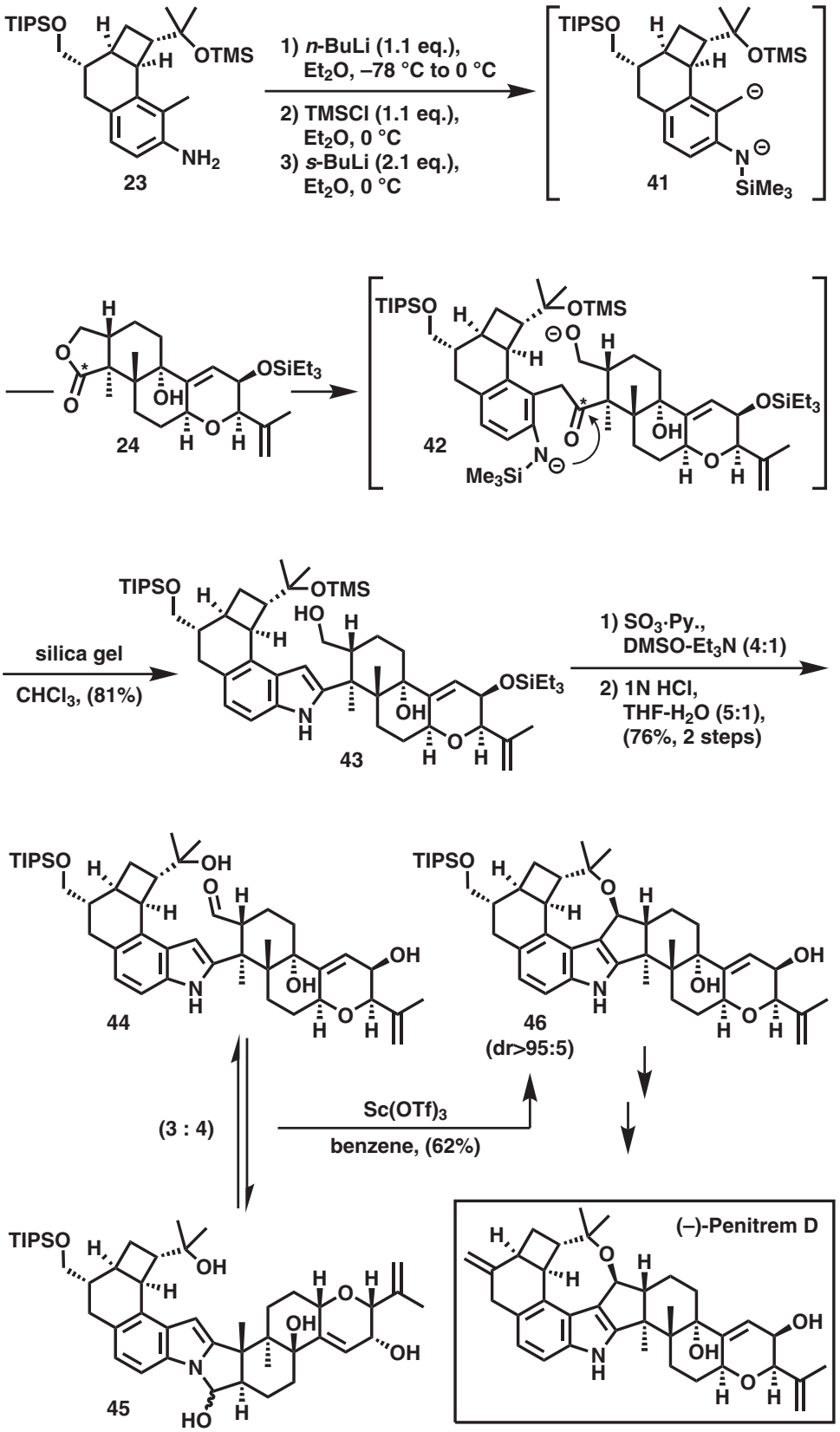
The lactone fragment (for example, **56**) not surprisingly required significant synthetic effort, the major obstacle being construction of the vicinal stereocenters, in a highly efficient manner, that are embedded in the 5/6 trans ring system. A new synthetic route to such systems was thus envisioned again beginning with (+)-Wieland–Miescher ketone (Scheme 13). Dissolving metal reduction of **57** followed by capture of the resulting enolate employing trimethylsilyl chloride (TMSCl)/Et_3N led to **59**, which was then subjected to an aldol reaction taking advantage of the remarkable 'aqueous formalin' protocol introduced by Kobayashi[53,54] to result in β-hydroxyl ketone **60** in 70% yield! We note this effective transformation was employed by Nicolaou and Li in their synthesis of (−)-anominine and (+)-tubingensin A (vide infra). Next a Gribble-Saksena-Evans reduction[55–57] was used to achieve the requisite stereoselective introduction of the C-7 hydroxyl in ketone **61** after some minor modifications including acid hydrolysis of the ketal and TBS protection of the diol. Subsequent triflation and Stille carbonylation[58] then provided enal **63**. Application of a Koga alkylation[59,60] intended to establish the requisite stereochemical relationship of the vicinal quaternary centers surprisingly led unexpectantly with reversal of the predicted stereogenicity at C-4. To correct the stereochemistry, an epimerization/lactonization sequence of **65** was required, initiated with a Pinnick oxidation.[61] The resulting acid was then transformed to methyl ester **65a** with TMS-CHN_2. Upon ozonolysis, the terminal double bond of **65a** was cleaved to an aldehyde which in turn was treated with DBU to establish the correct stereogenicity at C-4. Sodium borohydride reduction of aldehyde **65b** followed by lactonization completed the construction of the key advanced lactone **67.** Notably, the synthetic route to lactone **67** was developed into a scalable synthetic route starting from (+)-Wieland–Miescher ketone.[62]

With **56** now in hand, another example of our two-component indole construction tactic was successfully executed employing **56** and *o*-toluidine **55** (Scheme 14). Following a cyclization sequence involving **69** via mesylation/cyclization, we arrived at the desired indole core **70**. A late stage Suzuki-Miyaura cross coupling[63] and deprotection then completed the first total synthesis of (+)-nodulisporic acid F.[64,65]

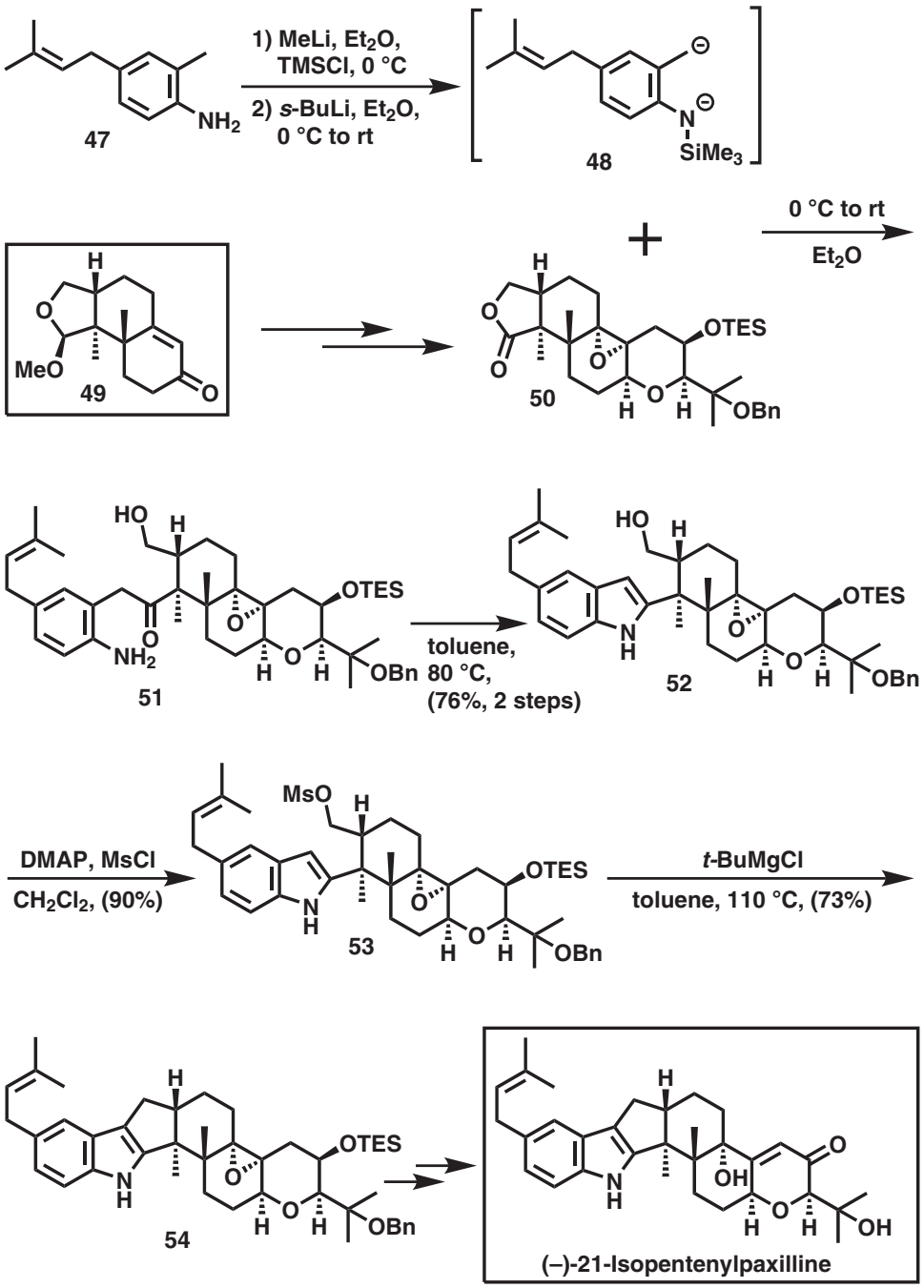
Advancing to (−)-nodulisporic acid D, a second representative member of the nodulisporic acid family of indole diterpenes alkaloids, we recognized that the harsh anionic conditions of the two-component indole construction tactic would likely lead to decomposition regardless of attempts at optimizations (Scheme 15).

We therefore committed to an alternative tactic to construct the indole core of the nodulisporic acids, while retaining the strategy of a late-stage large-fragment union. With our increasing involvement in transition metal mediated transformations,[64,66–71] we turned attention to the elegant indole synthetic protocol developed by Barluenga[72,73] (Scheme 16). Considering our complex substrate setting including the functional group sensitives, we reasoned that this adventure could provide an excellent opportunity to develop further the Barluenga indole construction method. To this end, (−)-nodulisporic acid D was dissected from the retrosynthetic perspective to chloroaniline **72** and vinyl triflate **73**.

The requisite tertiary stereocenter residing on chloroaniline **72** was envisioned to be introduced via an Enders asymmetric alkylation[74] employing hydrazone **75** (Scheme 17). Further structural modification followed by a Stille-Kelly cyclization[75–77] provided access to the requisite advanced chloroaniline **72**, pleasingly with high enantiopurity due to the Enders protocol. Of equally importance, our previous designed synthetic sequence to intermediate enal **63** (employed in the nodulisporic acid F synthetic venture) permitted major progress in overcoming our long-standing difficulty in constructing the 5/6 trans-fused ring system in **65c** (Scheme 18). The key new tactic here was twofold. A fine-tuned vinyl cuprate 1,4-addition with excellent facial selectivity generated enolate



Scheme 10 Key union transformation and late stage elaboration of (−)-penitrem D.



Scheme 11 Total synthesis of (−)-21-isopentenylpaxilline.

intermediate **63a**. Release of the enolate with methyllithium permitted a kinetic controlled alkylation from the bottom face to provide the desired stereoselectivity, thus setting the critical trans stereochemical relationship in an efficient manner. Upon minor modification involving ring closing metathesis,[78–81] neopentyl aldehyde **64a** was then smoothly converted to tricyclic ketone **65c**, that now comprised the core trans-anti-trans 5,6,6-fused ring system. Subsequent modifications led to advanced vinyl triflate **73**.

With both fragments **72** and **73** for (−)-nodulisporic acid D in hand, we were in position to explore their union. Pleasingly a combination of the Buchwald third generation RuPhos precatalyst[82–84] in the presence of cesium carbonate (Scheme 19) permitted the palladium mediated cascade involving amination/enamine cyclization to deliver indole nucleus **76** in 69% yield, with the sensitive aldehyde group intact! With core structure **77** in hand, Horner–Wadsworth–Emmons olefination[85,86] successfully led to side chain installation. Here we believed the neighboring acetate group participates in delivering the Horner–Wadsworth–Emmons reagent via an intramolecular fashion. Subsequent treatment of **78** with LiOH in H_2O/THF/methanol then led to the first total synthesis of (−)-nodulisporic acid D.[87] Currently, we are progressing on the total synthesis of the structurally more complex members in the nodulisporic acids family, including acids C and A; progress with this venture will be reported in due course.

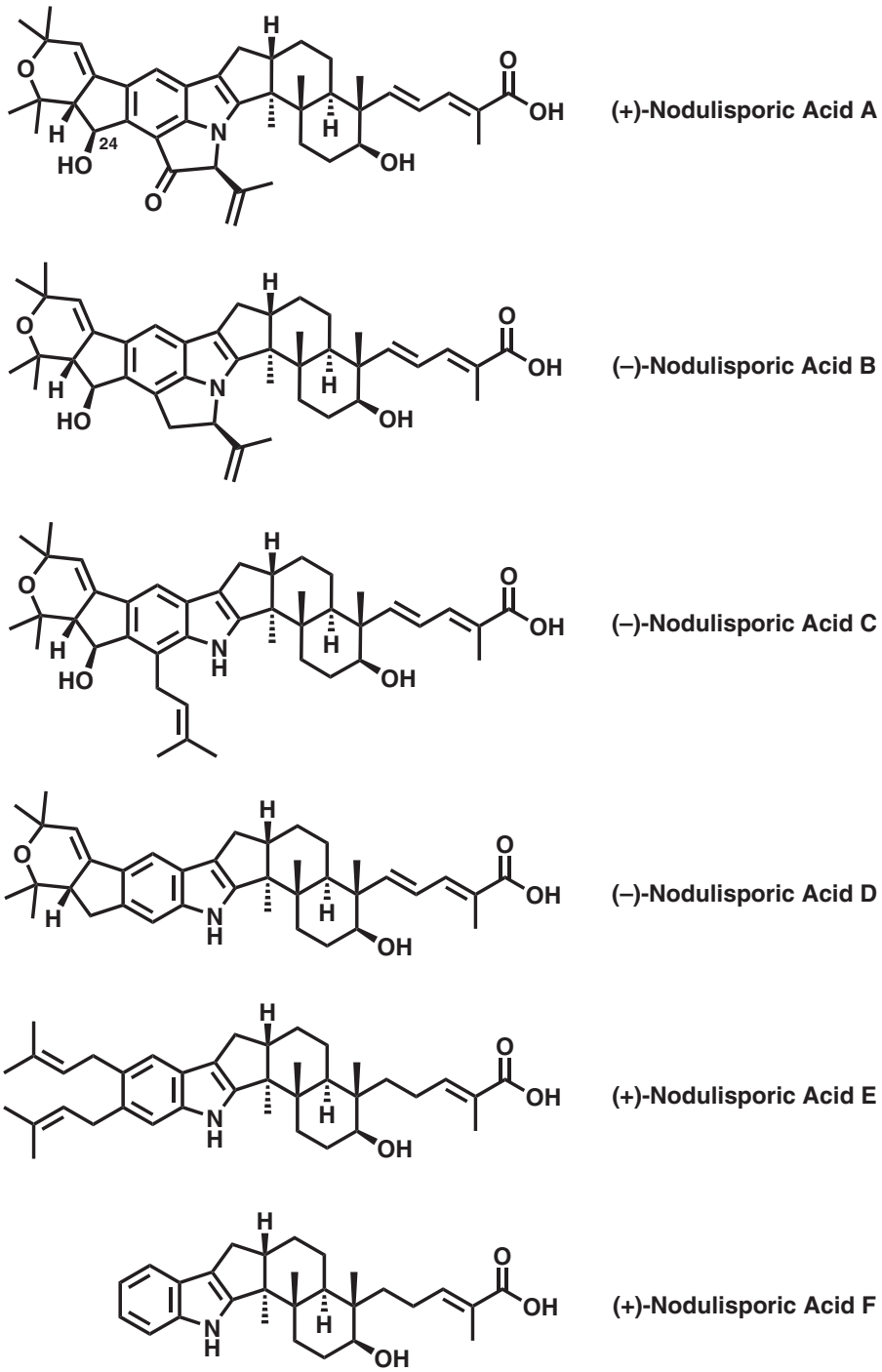
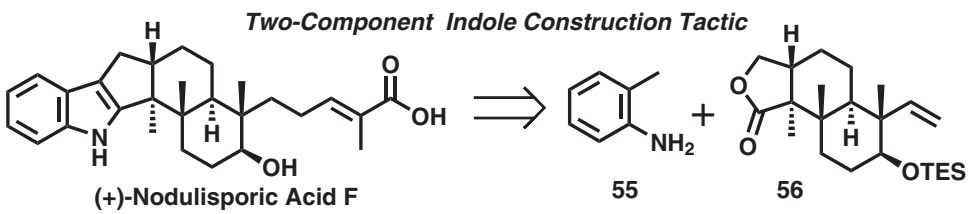
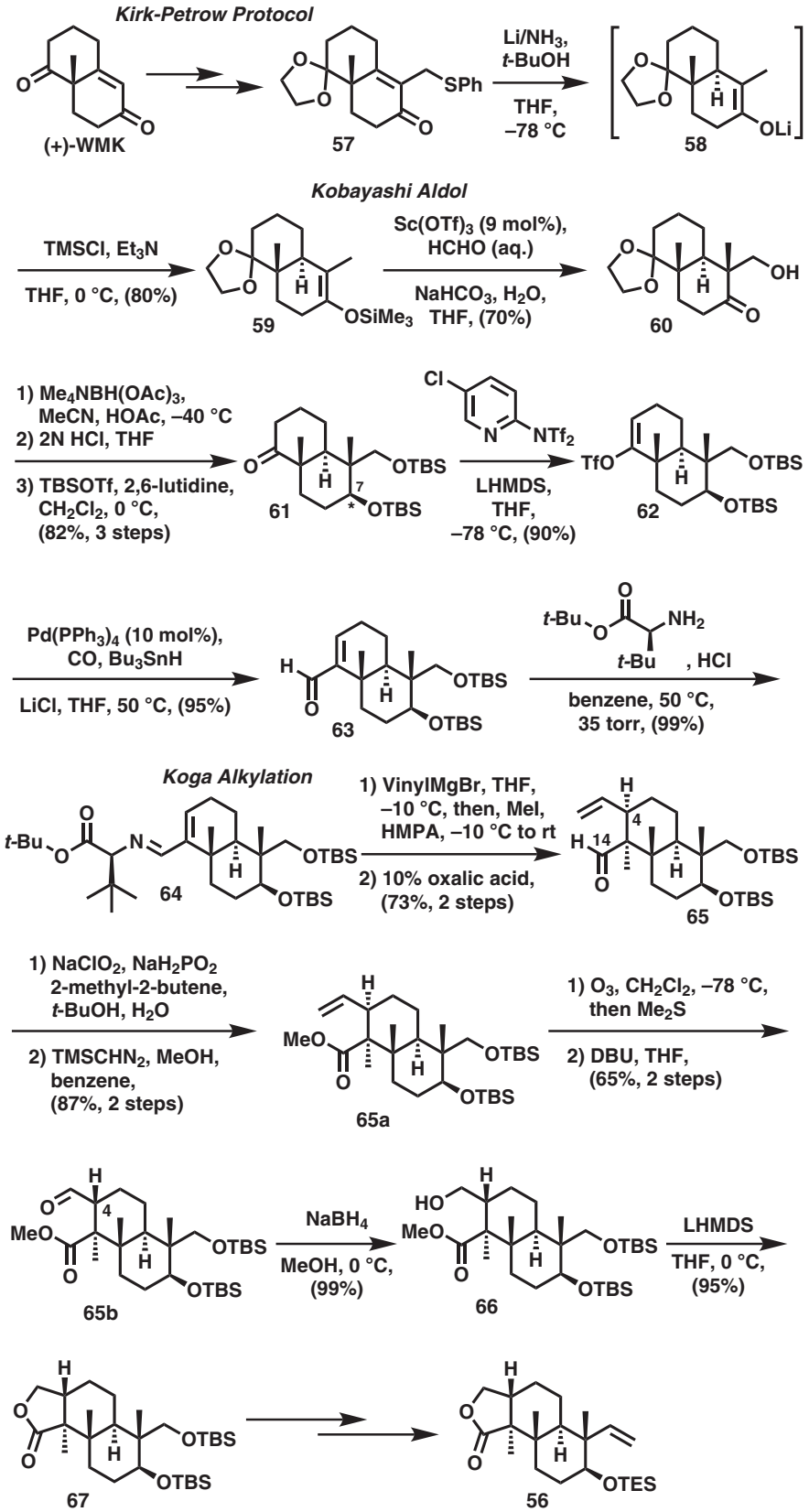


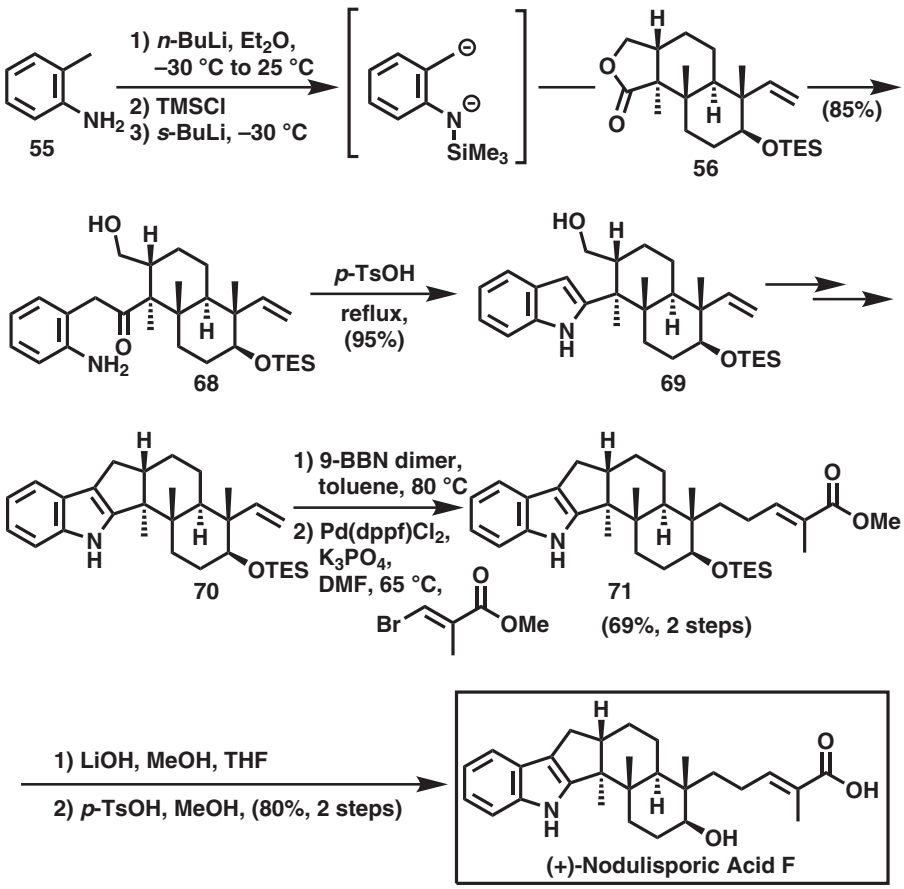
Figure 2 Representative structures of nodulisporic acids.



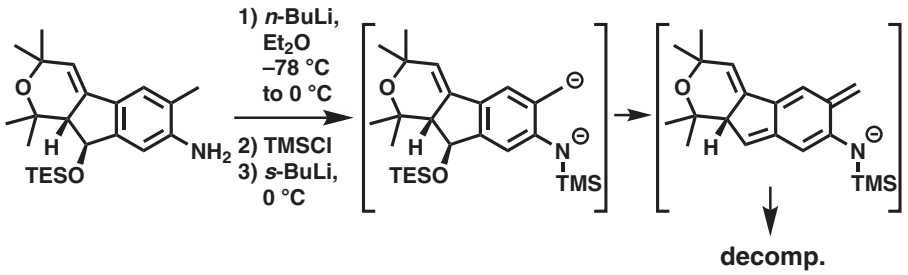
Scheme 12 Retrosynthetic analysis of (+)-nodulisporic acid F.



Scheme 13 Synthesis of lactone **56** fragment.



Scheme 14 Key union transformation and late stage elaboration of (+)-nodulisporic acid F.

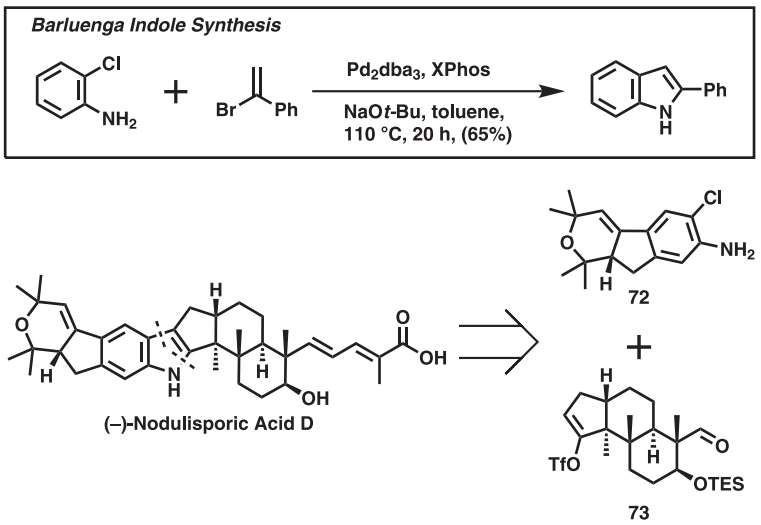


Scheme 15 Potential decomposition pathway of the dianion.

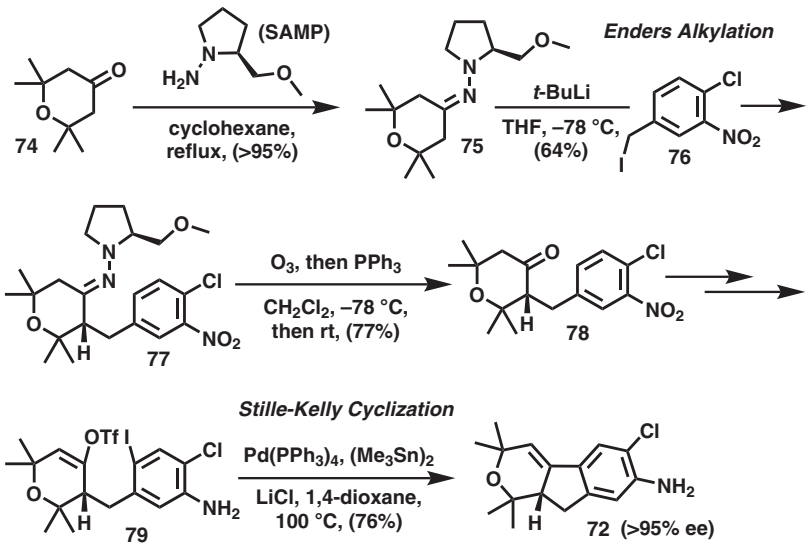
Two recent elegant total syntheses of indole diterpenoids

In 2012, Kuwahara from Tohoku University achieved a remarkable total synthesis of (+)-paspalinine (Scheme 20).[88] Strategically, the critical stereochemical relationship of the vicinal quaternary stereocenters of **80** was beautifully secured via the Simmons – Smith cyclopropanation of **81**, with the substituted indole core **79** constructed via a Corey – Stille union and oxidative cyclization tactic.

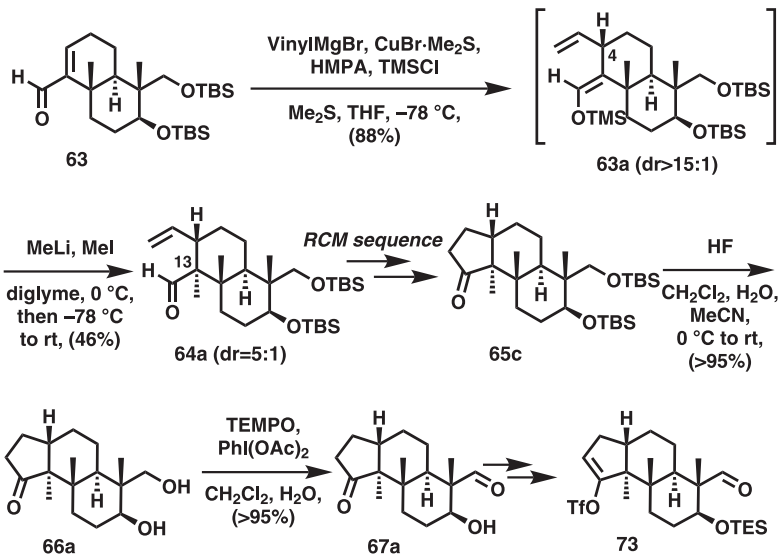
Beginning with (+)-Wieland–Miescher ketone, sequential transformations led to phosphonate **83** (Scheme 21), which in turn was transformed via an intramolecular Horner–Wadsworth–Emmons olefination to enone **81**. A substrate controlled stereoselective reduction with L-Selectride then furnished alcohol **84**, the hydroxyl group of which directed a Simmons – Smith cyclopropanation that after oxidation led to **85** as a single diastereomer. Regioselective cyclopropane ring opening, followed by triflation next set up the angular methyl and the vinyl triflate groups in **80**, which was subjected to cross coupling with aryl stannane **87** exploiting the Corey modified Stille coupling protocol[89] to provide union fragment **88**. A highly interesting oxidative cyclization mediated by palladium (II) trifluoroacetate then permitted construction of the indole core in **79**. Installation of the allyl carbonate group by deprotonation of **79** under thermodynamic conditions in turn permitted a Tsuji's palladium-catalyzed allylation[90] that provided enone **90**. Subsequent modifications, including cross metathesis with 1,1-dimethylallyl alcohol, followed by Sharpless asymmetric dihydroxylation, furnished triol **91,** which was subjected to an acid promoted cyclization and then oxidized to ketal **93** following deprotection to complete a formal synthesis of (+)-paspalicine. Interestingly, treatment of **93** under selenolation/oxidation



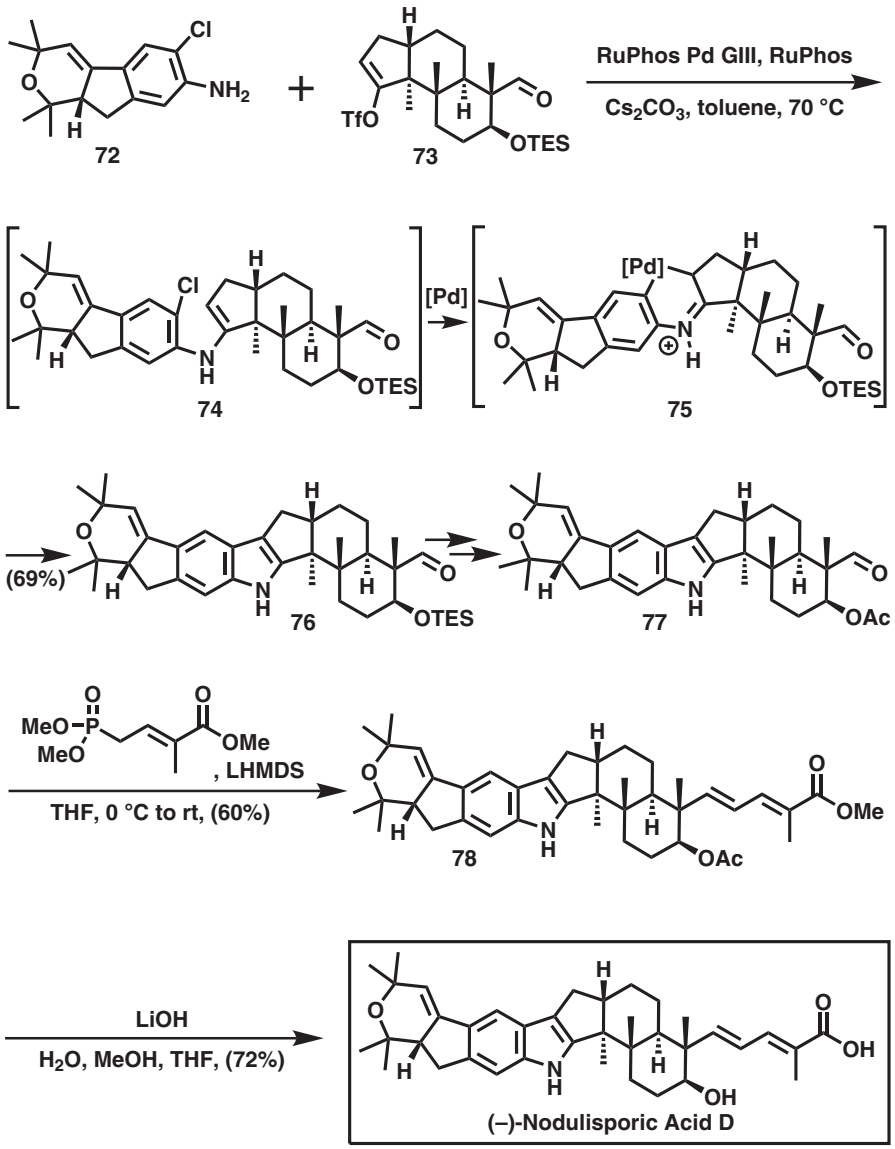
Scheme 16 Retrosynthetic analysis of (–)-nodulisporic acid D.



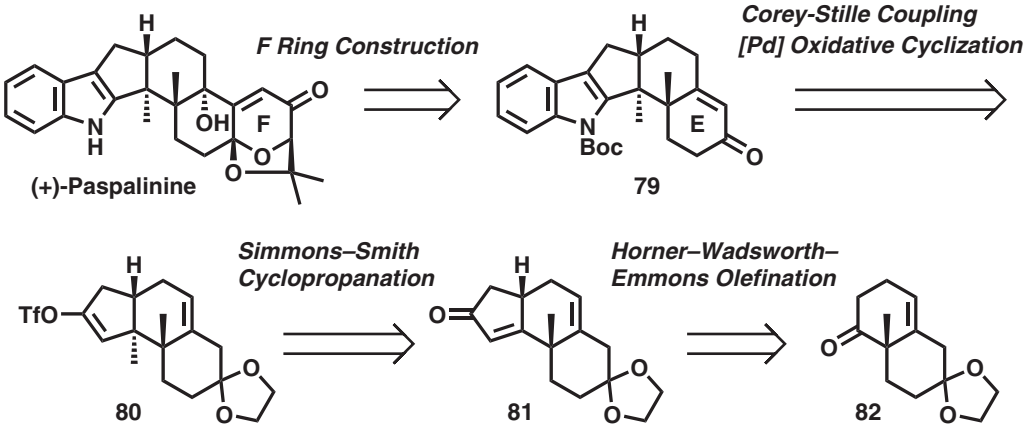
Scheme 17 Synthesis of western hemisphere **72**.



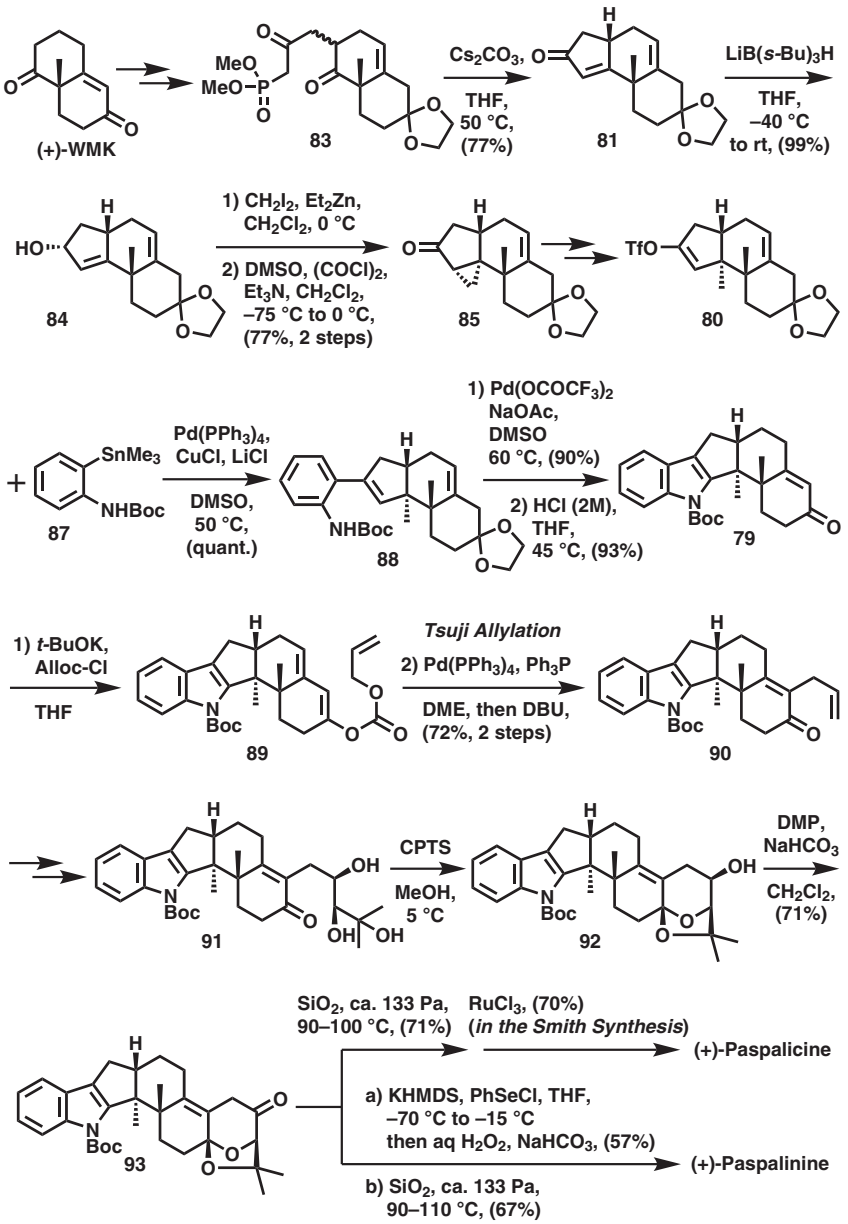
Scheme 18 Synthesis of eastern hemisphere **73**.



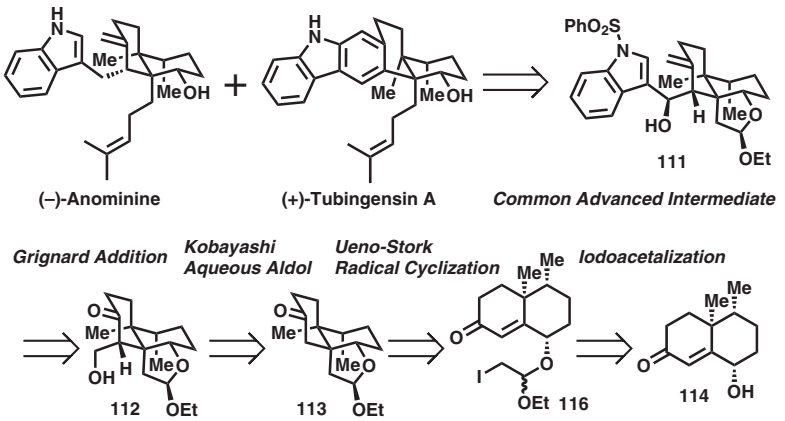
Scheme 19 Key union transformation and late stage elaboration of (−)-nodulisporic acid D.



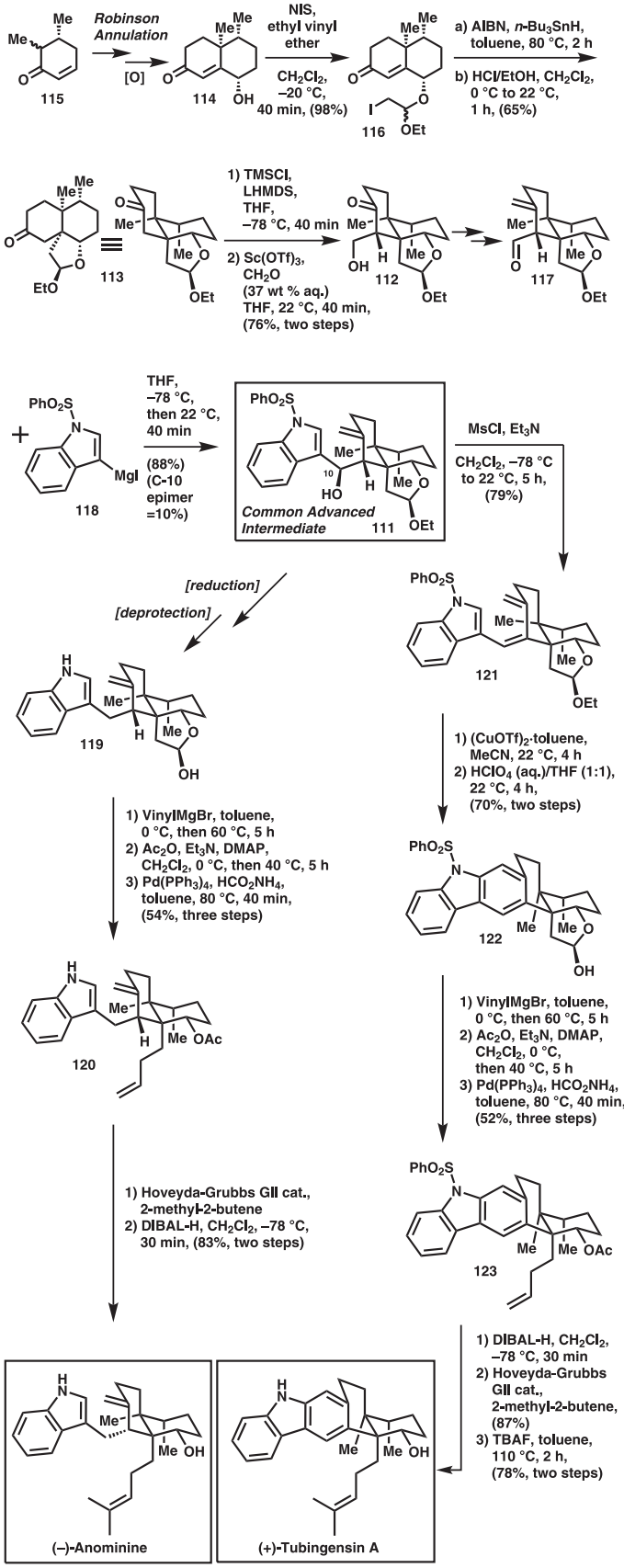
Scheme 20 Retrosynthetic analysis of (+)-paspalinine.



Scheme 21 Total synthesis of (+)-paspalinine and formal synthesis of (+)-paspalicine.



Scheme 22 Retrosynthetic analyses of (−)-anominine and (+)-tubingensin A.



Scheme 23 Total syntheses of (–)-anominine and (+)-tubingensin A.

conditions (unprecedented in our synthesis of (+)-paspalinine) provided the critical tertiary hydroxyl group and, after deprotection, led to the total synthesis of (+)-paspalinine.

We turn next to the elegant synthetic venture of the total syntheses of (−)-anominine and (+)-tubingensin A by Nicolaou and Li in 2012 (Scheme 22).[91] These two indole diterpenes, isolated from *Aspergillus* sp., possess significant biologic activities including anticancer, antiviral and antiinsectant.[92–95] Strategically, tricyclic ketone **113** served as the cornerstone of this synthetic venture, constructed from enone **114** via a stereoselective cyclization of **116**. A convergent approach would then permit Grignard addition to the aldehyde derived from **112** to furnish **111** that would nicely serve as a common advanced intermediate for both (−)-anominine and (+)-tubingensin A.

Beginning with enantiomerically enriched enone **115** (Scheme 23), a Robinson annulation/oxidation sequence led to bicyclic enone **114**, which was then converted to iodide **116**. Following a strategic cyclization via facial selective radical addition (for example, a Ueno-Stork radical cyclization)[96–98] led to tricyclic ketone **113** as a single diastereomer after treatment with HCl in ethanol. Generation of the kinetic enol silyl ether, followed by the previously described remarkable Kobayashi aldol reaction with 'aqueous' formaldehyde, provided alcohol **112** which was converted to aldehyde **117**. Subsequent Grignard addition led to the union fragment **111** in both excellent yield and diastereoselectivity considering the complex structural setting. Continuing with common advanced intermediate **111**, minor modifications yielded indole **119** which in turn was transformed to diene **120** via a Grignard addition/acetylation/Tsuji reduction[99] sequence. Cross metathesis employing the Hoveyda-Grubbs II catalyst with 2-methyl-2-butene followed by DIBAL reduction completed the total synthesis of (−)-anominine in a highly concise manner. In conjugation with this venture, the secondary hydroxyl group of common advanced intermediate **111** was eliminated to provide diene **121**, which was then subjected to CuOTf that led to a remarkable intramolecular 6π-electrocyclization/aromatization sequence to provide the multi-substituted carbazole core (**122**) of (+)-tubingensin A. Employing a similar Grignard addition/acetylation/Tsuji reduction sequence as employed for (−)-anominine, the derived olefin **123** was subjected to cross metathesis and deprotection to complete the total synthesis of (+)-tubingensin A.

SUMMARY

The total synthesis of architecturally complex indole containing natural products clearly remains an attractive venue for the practitioners of complex molecule synthesis. Strategic and tactical evolution will continue to be influenced by the development of new synthetic methods. Although there will never be an absolute finish line in the race to more concise synthetic strategies, a worthy total synthesis will be reached either by unique insight into the architectural structural features leading to the target or by the imaginative development of new synthetic methods and tactics involving novel chemistry. Congratulations to Professor KC Nicolaou in this regard!

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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