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A Concise Approach to Paxilline Indole Diterpenes

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Supporting Information

ABSTRACT: A synthetic approach to paxilline indole diterpenes is described. The route to the pentacyclic core relies on a new regioselective alkenylation of ketones and a tandem radical addition−aldol reaction sequence to access vicinal quaternary stereocenters. Emindole SB, the simplest member of the family, is synthesized in 11 steps from commercially available material to demonstrate the application of this approach.

Paxilline indole diterpenes comprise a family of fungal metabolites with a diverse set of biological activities. Notable examples include inhibition of potassium channels by paspalinine, penitrem A, and aflatrem;[1] alteration of cellular lipid balance by terpendoles C and D;[2] insecticidal activity of nodulisporic acids;[3] and inhibition of mitosis by terpendole E and 11-ketopaspaline.[4] Other reports detail antimicrobial[5] and antiviral[6] activities of paxilline indole diterpenes, further broadening the scope of potentially useful biological effects exerted by these natural products. Over 80 congeners identified to date (e.g., **1**, **2**, and **3**, Figure 1) share a common polycyclic

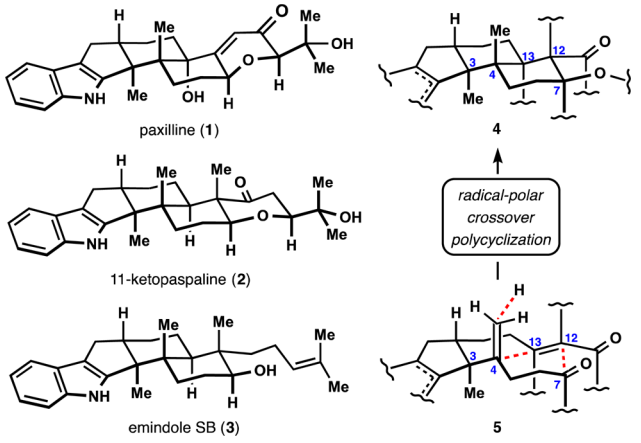

Figure 1. Representative paxilline indole diterpenes.

core that is believed to arise from an unusual polycyclization of a prenylated indole precursor.[7] The resulting structural complexity of paxilline indole diterpenes attracted considerable attention from synthetic organic chemists. In 1985, Smith and Mewshaw reported a pioneering synthesis of paspaline, with over a dozen more syntheses of this and other related natural products appearing in the following years.[8] A notable hallmark of many of those investigations has been the challenge associated with the direct assembly of an embedded *trans*-hexahydroindene fragment including vicinal quaternary stereocenters.[9] Here we demonstrate a solution to this problem that allows an 8-step stereocontrolled assembly of a functionalized pentacyclic core of paxilline indole diterpenes. As a proof of concept, we also report a synthesis of emindole SB (**3**),[6,10] a key biosynthetic precursor to more complex congeners, in 11 steps from commercially available material.

We believed that rapid access to a functionalized polycyclic terpenoid core (such as **4**, Figure 1) would allow the concise assembly of various paxilline indole terpenes. The aldol motif of **4** was expected to provide a convenient handle for diversification of the terpenoid scaffold, and a carbonyl or related functionality of the five-membered ring would serve for installation of the indole moiety. We sought to set the stereochemistry of the crucial *trans*-juncture of the hexahydroindene motif early in the synthesis and envisioned a direct assembly of the tricyclic core bearing vicinal quaternary stereocenters (at C3 and C4) via a radical−polar crossover polycyclization of a cyclopentanone derivative **5** initiated by chemoselective hydrogen atom transfer (HAT) to the 1,1-disubstituted alkene at C4.[11−13] In this process, the key carbon−carbon bond formations would result from intramolecular radical conjugate addition[12,14] (C4−C13 bond) and aldol (C12−C7 bond) reactions.[15]

We reasoned that the brevity of the proposed route would depend in part on efficient installation of the C3 quaternary stereocenter of **5** and we identified alkenylation of the corresponding cyclopentanone derivative as the most direct approach. A literature survey revealed that regioselective intermolecular alkenylation of unsymmetrical ketones bearing two unactivated enolizable positions finds little precedent,[16] with examples of formation of quaternary stereocenters being particularly scarce.[17] After extensive experimentation, we chose to employ terminal alkynes as electrophiles in the reaction with silyl enol ethers serving as enol surrogates.[18,19] The desired alkenylation was eventually achieved by treating enol ether **6** with *O*-TBS-protected 4-pentyn-1-ol in the presence of indium(III) bromide[19,20] (Scheme 1). Subsequent mild acidic workup afforded alcohol **7** in a highly regio- and stereoselective manner. This reaction likely proceeds via the intermediacy of corresponding vinylindium species and requires utilization of substoichiometric amounts of indium(III) bromide.[19] Subsequent chemoselective Sharpless allylic oxidation[21] of **7** followed by double oxidation of the resulting diol completed the assembly of dialdehyde **8**.

Our initial attempts to perform radical−polar crossover polycyclization of dialdehyde **8** resulted in successful formation

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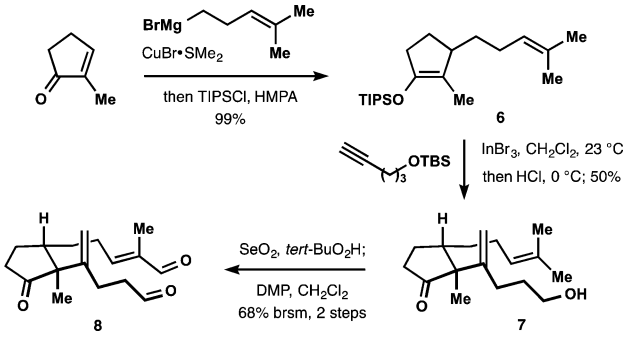
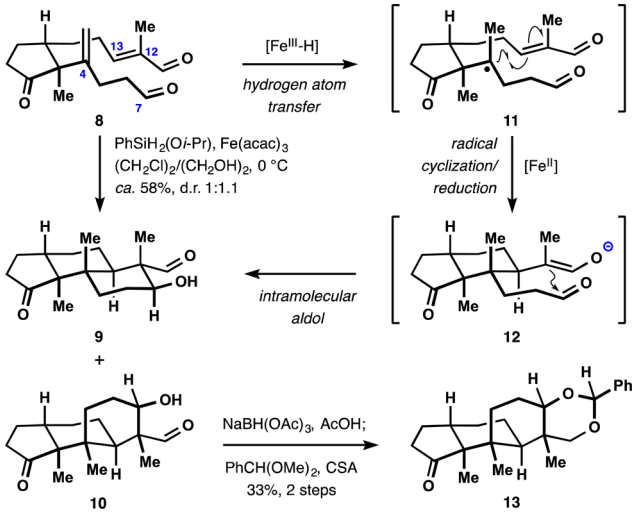
Scheme 1. Synthesis of the Polycyclization Precursor



of the desired C4−C13 and C12−C7 bonds, but favored the undesired diastereomer and exhibited overall low efficiency of the transformation. Extensive screening of catalysts and reductants revealed that application of iron(III) acetylacetonate[12] and (isopropoxy)phenylsilane[22] led to substantial increase in the yield of tricyclic products (Scheme 2). Thus,

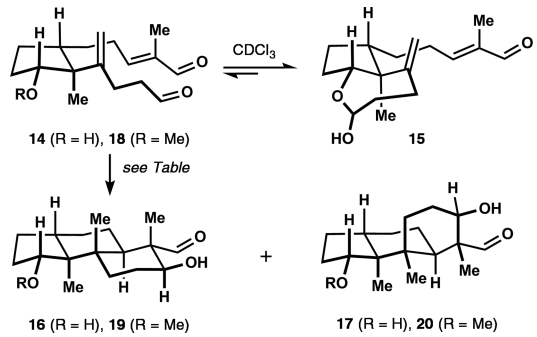
Scheme 2. Polycyclization En Route to the Tricyclic Core



treatment of **8** with (isopropoxy)phenylsilane in a mixture of 1,2-dichloroethane and ethylene glycol at 0 °C in the presence of iron(III) acetylacetonate afforded a nearly equimolar mixture of **9** and **10** in ca. 58% yield (24% isolated yield of **9**).[23] This transformation likely involves HAT to the 1,1-disubstituted alkene, followed by the conjugate addition of the intermediate *tert*-alkyl radical **11**, reduction to the corresponding enolate **12** (or its diastereomer en route to **10**), and subsequent aldol reaction with the aliphatic aldehyde functionality. The structures of **9** and **10** (after conversion to dioxane **13**) were confirmed by X-ray crystallographic analysis. It should be noted that in both cases the β-hydroxyaldehyde motif was formed in a highly diastereoselective manner. Surprisingly, changing the nature of the solvent and performing the reaction at lower temperatures led only to the increase in content of the undesired diastereomer, with ratios as high as 2.5:1 favoring ketone **10** being obtained. Application of other iron(III), cobalt(III), and manganese(III)-based catalysts did not favorably affect the ratio of diastereomers **9** and **10**, but instead led to increased formation of byproducts resulting from the conjugate reduction of α,β-unsaturated aldehyde **8**.

During our studies, we observed that aldehyde **8** existed predominantly in the form of the corresponding hemiacetals at C7 in the presence of alcoholic solvents such as deuterated methanol. We reasoned that introduction of a hydroxy group in place of the ketone functionality of **8** could allow for reversible formation of cyclic hemiacetal intermediates. Indeed, secondary alcohol **14** was found to exist as an approximately 1:2 mixture with the corresponding cyclic hemiacetal **15** in a solution of deuterated chloroform (Table 1). We speculated that this

Table 1. Tether-Controlled Polycyclization



entry	conditions	ratio[a]
1	**14**, $Fe(acac)_3$, $PhSiH_2(Oi\text{-}Pr)$, $(CH_2Cl)_2$/ $(CH_2OH)_2$, 0 °C	5.0 (**16**) : 1.0 (**17**)
2	**14**, $Fe(acac)_3$, $PhSiH_2(Oi\text{-}Pr)$, $(CH_2Cl)_2$/ $(CH_2OH)_2$, -20 °C	7.1 (**16**) : 1.0 (**17**)
3	**14**, $Fe(acac)_3$, $PhSiH_2(Oi\text{-}Pr)$, $(CH_2Cl)_2$/ $(CH_2OH)_2$, 23 °C	3.1 (**16**) : 1.0 (**17**)
4	**14**, $Fe(acac)_3$, $PhSiH_2(Oi\text{-}Pr)$, EtOH, 0 °C	1.5 (**16**) : 1.0 (**17**)
5	**18**, $Fe(acac)_3$, $PhSiH_2(Oi\text{-}Pr)$, $(CH_2Cl)_2$/ $(CH_2OH)_2$, 0 °C	1.6 (**19**) : 1.0 (**20**)
6	**18**, $Fe(acac)_3$, $PhSiH_2(Oi\text{-}Pr)$, $(CH_2Cl)_2$/ $(CH_2OH)_2$, 23 °C	1.9 (**19**) : 1.0 (**20**)
7	**18**, $Fe(acac)_3$, $PhSiH_2(Oi\text{-}Pr)$, EtOH, 0 °C	1.0 (**19**) : 1.4 (**20**)

[a]According to integration of aldehyde peaks in ^{1}H NMR spectra of crude reaction mixtures.

transient tether could allow for the desired stereocontrol over the initial radical cyclization. In accord with our predictions, subjection of **14** to the standard polycyclization conditions (see Scheme 2) afforded a 5:1 mixture of diols **16** and **17** (entry 1, Table 1),[24] effectively reversing the selectivity exhibited by the parent substrate **8**. The ratio of products was temperature dependent with lower temperatures favoring the desired scaffold **16** (entries 2 and 3), thereby reversing the trend observed for the parent substrate **8** (see discussion above). When the solvent was replaced with ethanol, the ratio of **16** to **17** deteriorated (entry 4).[25] Methylation of the secondary hydroxy group led to similar deterioration of diastereomeric ratios with ether **18** affording a 1.6:1 mixture of tricycles **19** and **20** (entry 5).[26] Effects of solvent and temperature on polycyclization of substrate **18** were similar to those for the parent compound **8** (entries 6 and 7).

Guided by the aforementioned logic, we proposed that an indole N−H in place of a hydroxy group could serve as an anchor to control the stereoselectivity of polycyclization in a similar fashion. Corresponding cyclic hemiaminal motifs have been previously identified in a number of indole-containing alkaloids,[27] suggesting viability of similar intermediates. To test our hypothesis, we began with the Fischer synthesis of indole **22** from ketone **21** (Scheme 3). Conversion of the *N*-phenylhydrazone of **21** into **22** was best achieved by heating with an excess of anhydrous zinc chloride in toluene.[28] Parikh−Doering conditions[29] proved optimal for oxidation of diol **22** and secured access to hemiaminal **23** after mild basic workup.

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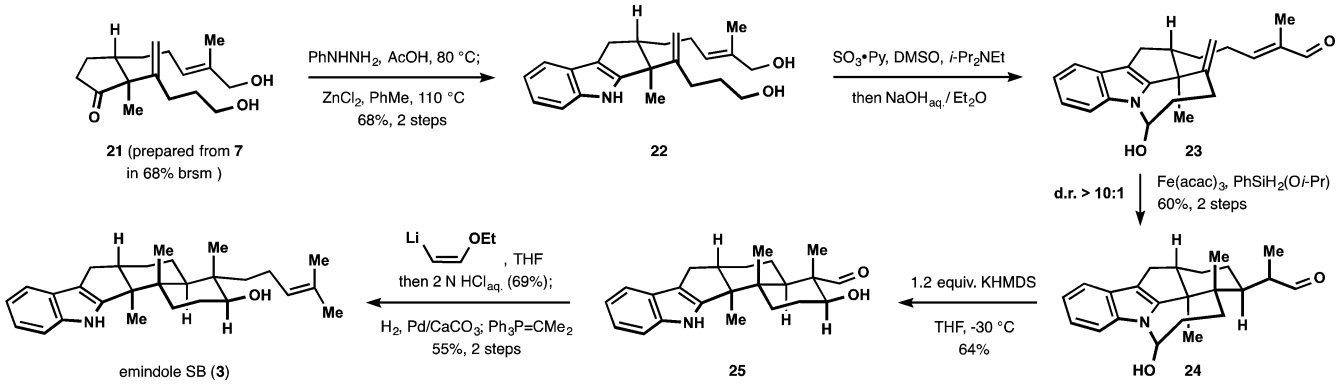
Scheme 3. Synthesis of (±)-Emindole SB (3)



Hemiaminal **23** was produced as a single diastereomer (stereochemistry of the hemiaminal was not determined) and underwent facile dehydration to the corresponding enamine upon prolonged exposure to acid. Subjection of **23** to the cyclization conditions ((isopropoxy)phenylsilane and iron(III) acetylacetonate in ethanol at 0 °C) triggered facile radical cyclization to pentacyclic intermediate **24**.[30] However, the stability of the hemiaminal fragment[31] required subsequent treatment with strong base in order to complete construction of the desired pentacyclic core, concluding the assembly of four new stereocenters with excellent selectivity. The radical cyclization required rigorous exclusion of oxygen from the reaction mixture due to facile oxidation of intermediates. Hemiaminal **24** proved unstable in the presence of acid, undergoing dehydration to the corresponding enamine. In the end, the key functionalized pentacycle **25** was prepared in a total of eight steps from commercially available 2-methyl-2-cyclopenten-1-one. To demonstrate the application of our strategy, we synthesized (±)-emindole SB (**3**) in three steps from hydroxyaldehyde **25**. Thus, treatment of **25** with a large excess of (*Z*)-2-ethoxyvinyllithium followed by acidic workup,[32] subsequent hydrogenation of the corresponding unsaturated aldehyde, and Wittig olefination of the resulting mixture of lactols afforded emindole SB (**3**) in 11 steps from the commercially available precursor.

In summary, we disclose a concise approach to the functionalized pentacyclic core of paxilline indole diterpenes featuring a new and potentially useful alkenylation of ketones to construct quaternary stereocenters and a tandem radical addition−aldol reaction sequence to access challenging vicinal quaternary stereocenters in a highly stereoselective manner. We also demonstrate a short synthesis of (±)-emindole SB, which serves as a proof of concept for our approach. We anticipate that the strategy reported herein will be applicable to the asymmetric synthesis of a wide variety of paxilline indole diterpenes as well as their unnatural analogues,[33] the implementation of which is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11129.

Experimental procedures and spectroscopic data for new compounds (PDF)

X-ray crystallographic data for **9** (CIF)

X-ray crystallographic data for **13** (CIF)

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Notes

The authors declare no competing financial interest.

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(23) An elegant 19-step synthesis of hydroxyaldehyde (−)-**9** from 2-methyl-1,3-cyclohexadione was recently reported. See ref 8q.

(24) Relative configuration of the decalin fragment of **16** was confirmed by reduction to the corresponding triol, which proved identical by ^{1}H and ^{13}C NMR analysis to the product of double reduction of compound **9**. Relative configuration of the cyclopentanol fragment of **16** was established by NOE experiments.

(25) Ethylene glycol and 1,2-dichloroethane are immiscible; therefore, the concentration of alcohols in the 1,2-dichloroethane phase is expected to be significantly lower than in ethanol, decreasing the extent of intermolecular hemiacetalization. The reagents appear to dissolve preferentially in the 1,2-dichloroethane phase.

(26) Relative configurations of compounds **19** and **20** were established by NOE experiments.

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