

RESEARCH ARTICLE

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Sespenine is a structurally unusual indole sesquiterpenoid isolated from endophytic *Streptomyces* sp. HKI0595. Herein, we report a ten-step (the longest linear sequence) synthesis of this molecule from commercially available materials, on the basis of our first generation synthesis. Sharpless asymmetric epoxidation and Stille–Miyata coupling were used to construct a functionalized epoxy ester, which underwent Ti(III) mediated reductive radical cyclization to give a *trans*-decalin intermediate with a 2-methoxycarbonylindole side chain. Oxidation of this compound afforded a pair of epimeric 3-hydroxyindolenines, and the major isomer entered a bioinspired cascade of Prins cyclization/Friedel–Crafts/retro Friedel–Crafts under acidic conditions, to furnish the polycyclic core of sespenine. Sespenine analogues bearing different C2 substituents were prepared with similar chemistry. Xiamycin A, a carbazole congener of sespenine, was synthesized from the minor hydroxyindolenine epimer as well.

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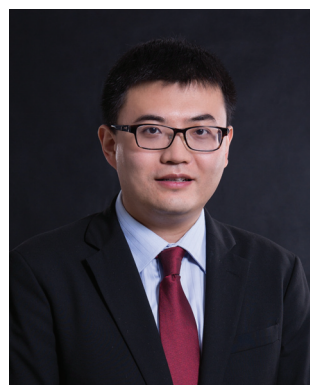
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Introduction

Indole terpenoids have been of increasing interest in the area of chemical synthesis^{1–3} and biosynthesis⁴ because of their fascinating structures and promising biological activities. Recently, we have accomplished total syntheses of a series of indole terpenoids such as those from the anominine, drimentine, mycoleptodiscin, and hapalindole families,⁵ during which some useful methods and strategies have been developed.⁶ In 2011, Ding *et al.* discovered sespenine (**1**, Fig. 1), a structurally unusual polycyclic molecule from *Streptomyces* sp. HKI0595,⁷ a bacterial endophyte of the



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Ang Li was born in Jilin, China, in 1982. In 2004, he received his B.Sc. degree at Peking University, where he worked with Prof. Zhen Yang. He earned his PhD under the supervision of Prof. K. C. Nicolaou at The Scripps Research Institute in 2009. After a brief stay as a research fellow at the Institute of Chemical and Engineering Sciences in Singapore, he joined Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, as

a professor in 2010. His current research is focused on the total synthesis of structurally and biologically interesting natural products.

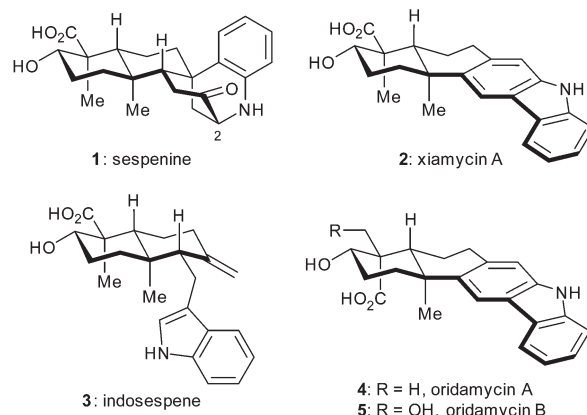


Fig. 1 The structures of sespenine and related indole sesquiterpenoids.



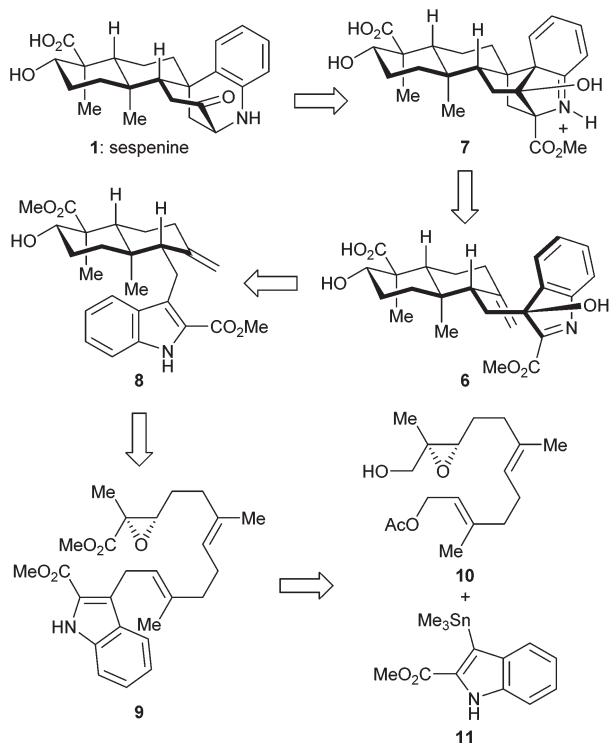
mangrove *Kandelia candel*, together with a number of biogenetically relevant indole sesquiterpenoids such as xiamycin A (2) and indosespene (3). Soon after, Zhang and coworkers independently isolated several xiamycin A related natural products.⁸ This indole terpenoid family quickly drew attention from the perspectives of biosynthesis and chemical synthesis.⁹ In 2014, we accomplished the first total synthesis of sespenine (1),¹⁰ which featured a Lewis acid promoted conjugate addition and a bioinspired cationic cascade reaction. The Baran group disclosed elegant syntheses of xiamycin A (2) and dixiamycin B; the latter possessing an N–N linkage was assembled through an electrochemical oxidative dimerization of the former.¹¹ We then reported syntheses of xiamycin A, indosespene, oridamycins A and B (2–5, Fig. 1), and dixiamycin C¹² using two parallel strategies of 6π electrocyclization/aromatization^{13–15} and indole C2 C–H bond activation/Heck annulation.¹⁶ Herein, we report the second generation syntheses of sespenine (1) and xiamycin A (2) as well as the preparation of sespenine analogues with various substituents at C2.

Results and discussion

The retrosynthetic analysis of sespenine (1) is illustrated in Scheme 1. The molecule is traced back to an advanced intermediate 6, which may undergo a cascade sequence of Prins cyclization/Friedel–Crafts/retro Friedel–Crafts to reach 1, *via* the intermediacy of the dearomatized compound 7. It is well precedented that an electron rich arene serves as a suitable

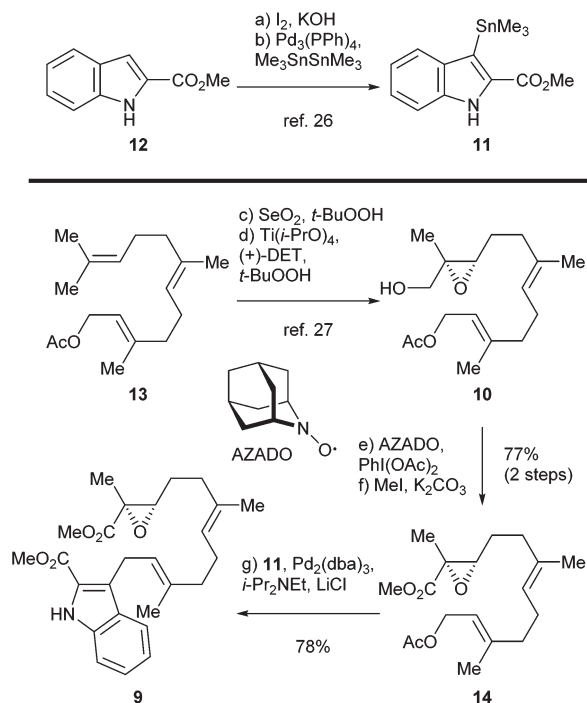
nucleophile to trap the carbocation generated through a Prins reaction.^{17,18} The retro Friedel–Crafts reaction from 7 to 1, which can also be viewed as a retro aldol reaction, would take advantage of the driving force of re-aromatization. Notably, Ding *et al.* hypothesized a similar reaction cascade in the biosynthetic pathway toward 1,⁷ and another relevant process was proposed for the biogenesis of aspernomine, a structurally more complex indole diterpenoid, by McWhorter and Tantillo, respectively.¹⁹ A subtle change in our plan of chemical synthesis of 1, compared with the above mentioned biosynthetic speculations, is the existence of a C2 substituent (a methoxy-carbonyl group in the case), which helps stabilizing the 3-hydroxyindolenine intermediate.^{20,21} Compound 6 is expected to arise from the precursor 8 *via* chemoselective oxidation of its indole moiety in the presence of an exocyclic C=C bond. *trans*-Decalin 8 is simplified to α,β -epoxy ester 9. Ti(III) induced epoxide opening radical reaction, which was pioneered by RajanBabu and Gansäuer,²² has been elegantly exploited by the groups of Barrero, Oltra, Fernández-Mateos, Cuerva, Roy, Reisman, *etc.* in complex molecule synthesis.²³ Borrowing from a precedent¹² in our synthesis of indosespene (3), we may rely on a reductive opening of the epoxide followed by radical cascade cyclization catalyzed by Ti(III) species *in situ* generated by Cp_2TiCl_2 and Mn, to prepare 8 from 9. The indole motif should be tolerated under such conditions. Compound 9 would be disassembled into readily available building blocks allyl acetate 10 and stannane 11, the recombination of which could be effected through allyl Stille–Miyata coupling.²⁴

The synthesis of sespenine (1) commenced with the construction of a functionalized epoxy ester 9, as shown in Scheme 2. We first explored the feasibility of Friedel–Crafts type allylation at the C3 position of commercially available methyl indole-2-carboxylate (12). However, these reactions proved to be inefficient under a variety of acidic or basic conditions,²⁵ presumably due to the electron-deficiency of 12. Stannane 11 was then prepared from 12 *via* a two step sequence reported by Routier *et al.*²⁶ Iodination under basic conditions afforded the corresponding C3 iodide, which was converted to 11 through a Pd-catalyzed stannylation [$\text{Pd}(\text{PPh}_3)_4$, Me_3SnMe_3]. We then synthesized allyl acetate 14, which later served as a coupling partner of 11. Farnesyl acetate (13) was subjected to a two step process of allylic oxidation (SeO_2 , *t*-BuOOH) and Sharpless asymmetric epoxidation [$\text{Ti}(\text{i-PrO})_4$, (+)-diethyl *L*-tartrate, *t*-BuOOH] to reach the epoxy alcohol 10, according to the known literature.²⁷ Although this compound could be oxidized stepwise to give the corresponding carboxylic acid with good overall efficiency, treatment with a catalytic amount of 2-azaadamantane *N*-oxyl (AZADO, Scheme 2) developed by Iwabuchi²⁸ and stoichiometric $\text{PhI}(\text{OAc})_2$ effected the transformation in one pot.²⁹ The resultant carboxylic acid was methylated by using MeI and K_2CO_3 to afford the ester 14 in 77% yield for the two steps. A variety of conditions for the allyl Stille–Miyata coupling between 14 and 11 were examined. The conditions [$\text{Pd}_2(\text{dba})_3$, *i*-Pr₂NEt, LiCl] modified from those described by Hegedus and coworkers proved to be optimal for delivering the coupling



Scheme 1 Retrosynthetic analysis of sespenine.

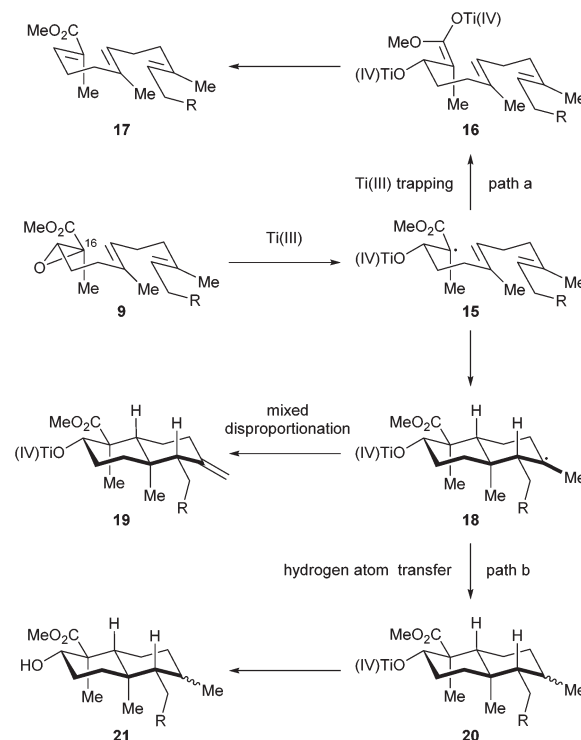




Scheme 2 Synthesis of functionalized α,β -epoxy ester **9**. Reagents and conditions: (e) AZADO (4 mol%), $\text{PhI}(\text{OAc})_2$ (3.0 equiv.), CH_2Cl_2 , 22 °C, 12 h; (f) MeI (2.0 equiv.), K_2CO_3 (1.5 equiv.), DMF, 22 °C, 30 min, 77% (2 steps); (g) **11** (1.2 equiv.), $\text{Pd}_2(\text{dba})_3$ (5 mol%), LiCl (3.0 equiv.), $i\text{-Pr}_2\text{NEt}$ (3.0 equiv.), DMF, 50 °C, 1 h, 78%.

product **9** (78% yield).²⁴ Notably, the quality of stannane **11** was crucial to this reaction; the freshly prepared stannane was required to ensure a good coupling efficiency.

We then directed our attention to the Ti(III) mediated radical cascade cyclization for synthesizing **8** from **9**. The conditions [Cp_2TiCl_2 , Mn, TMSCl, collidine] developed by Cuerva and coworkers were employed for the initial investigation.^{23c} The anticipated product **8** with an exocyclic C=C bond was obtained with an excellent level of stereochemical control, albeit in less than 20% yield. Over-reduction and deoxygenation, which are illustrated as reaction paths a and b in Scheme 3, respectively, turned out to be severe side reactions accompanied by the desired one. From a mechanistic perspective, the activated C16–O bond of α,β -epoxy ester **9** was cleaved by Ti(III) species generated *in situ* by Cp_2TiCl_2 and Mn, to initiate an electron deficient radical **15**, which then underwent cascade cyclization. However, this radical could also be trapped by an excess of Ti(III) species to form a Ti(IV) enolate **16**;³⁰ similar transformations are well-precedented in the context of SmI_2 chemistry.³¹ Further β elimination of OTi(IV) gave an α,β -unsaturated ester **17** as a byproduct. High concentration of Ti(III) in the reaction system increased the formation of **17**. On the other hand, a tertiary radical **18** generated from the tandem cyclization may enter a Ti(III) mediated mixed disproportionation pathway to reach the desired product **19**,^{30a} or unfortunately terminate *via* a hydrogen atom transfer to form

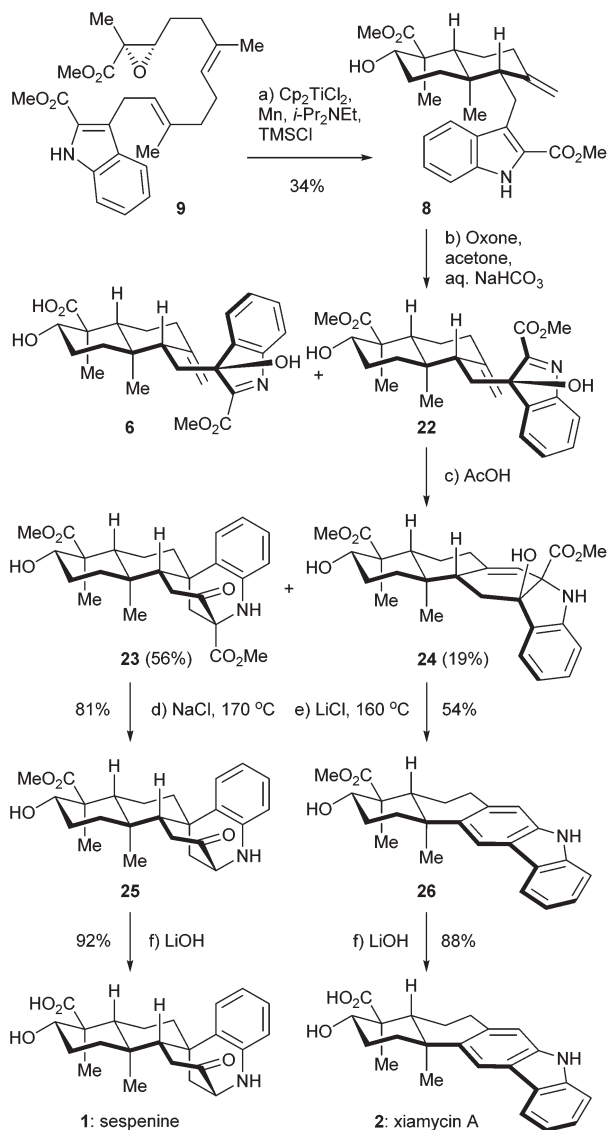


Scheme 3 Postulated pathways of the Ti(III) mediated radical reaction.

the byproduct **21**.³² Inspired by Cuerva's studies of the amine effect in Ti(III) chemistry,³³ we found that $i\text{-Pr}_2\text{NEt}$ was superior to collidine as an additive for suppressing the over-reduction, and strictly anhydrous conditions were critical to inhibit the hydrogen atom transfer. Under our optimized conditions [Cp_2TiCl_2 (20 mol%), Mn, TMSCl, $i\text{-Pr}_2\text{NEt}$], compound **8** was isolated in 34% yield (Scheme 4). A suitable initial concentration of Cp_2TiCl_2 (0.08 M) was important as well. Considering the stereochemistry and functionality outcome of this reaction, such efficiency was acceptable and thus allowed us to carry on the synthesis.

With compound **8** in hand, we completed the syntheses of sespenine (**1**) and xiamycin A (**2**) through a divergent approach, as depicted in Scheme 4. Treatment of **8** with Oxone in acetone in the presence of aq. NaHCO_3 buffer afforded a C3 epimeric mixture of hydroxyindolenine **6** and **22** in a *ca.* 2.8 : 1 ratio. The structure of **22** was indirectly verified by X-ray crystallographic analysis of its bis-acetylated derivative.³⁴ Exposure of this chromatographically inseparable mixture to AcOH for 5 h at ambient temperature provided compounds **23** and **24**, in 56% and 19% yields over the two steps, respectively. The former presumably arose from the devised cascade reaction, while the latter was possibly generated *via* a straightforward aza-Prins cyclization.^{5b} The Krapcho decarboxylation (NaCl , 170 °C) of **23** delivered sespenine methyl ester **25** in 81% yield,³⁵ the structure of which was confirmed by X-ray crystallographic analysis.³⁴ Under these conditions, the other methoxy-carbonyl of the molecule remained untouched. Hydrolysis of





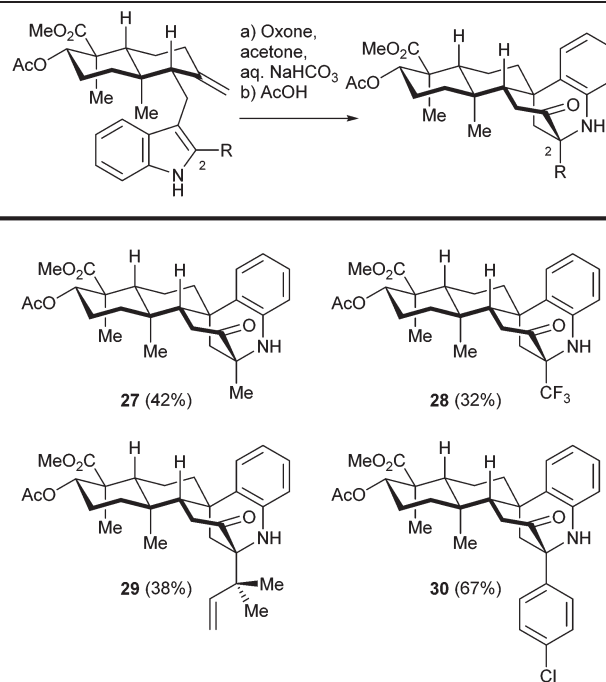
Scheme 4 Total syntheses of sespenine and xiamycin A. Reagents and conditions: (a) Cp_2TiCl_2 (20 mol%), Mn (8.0 equiv.), $i\text{-Pr}_2\text{NEt}$ (6.0 equiv.), TMSCl (5.0 equiv.), THF, 22 °C, 12 h, 34%; (b) Oxone (2.0 equiv.), acetone/saturated aq. NaHCO_3 (1:1), 22 °C, 15 min; (c) AcOH (5.0 equiv.), CH_2Cl_2 , 22 °C, 5 h, 56% for **23** (2 steps), 19% for **24** (2 steps); (d) NaCl (10 equiv.), DMSO/water, 170 °C, 2 h, 81%; (e) LiCl (10 equiv.), DMSO/water, 160 °C, 1 h, 51%; (f) aq. LiOH (2.0 M)/THF/MeOH, 50 °C, 10 h, 92% for **1**; 88% for **2**.

25 with aq. LiOH rendered sespenine (**1**) smoothly. Interestingly, under similar Krapcho conditions (LiCl, 160 °C), compound **24** was directly converted into xiamycin A methyl ester **26** in 54% yield. This one pot process may involve sequential ester hydrolysis, β -lactone formation, decarboxylation,³⁶ and dehydrogenative aromatization. The *cis* orientations of the hydroxyl and carboxylic acid functionalities set the geometric basis of β -lactone formation. Basic hydrolysis furnished xiamycin A (**2**) with good efficiency. The spectra and physical properties of the synthetic sespenine and xiamycin A were

consistent with those reported for the naturally occurring samples.

We then investigated the cationic cascade with indole substrates bearing various C2 substituents, as shown in Table 1. Sterically bulky (reverse prenyl) and electron deficient (trifluoromethyl) groups did not interfere with the tandem reaction, which indicates the wide range of stabilizing groups for 3-hydroxyindolenine intermediates. The overall yield of the two step sequence was mainly determined by the efficiency as well as the facial selectivity of the hydroxylation step, and the following cascade reaction was relatively efficient in general. Thus, a number of sespenine analogues (**27–30**) were readily obtained, setting the stage for further biological studies. Notably, the precursors of these compounds were synthesized through a modified version of our first generation approach (construction of an α,β -unsaturated enone, conjugate addition of indole derivatives, and methylenation; see the ESI† for details), instead of the second generation approach (Stille–Miyata coupling and Ti(III)-mediated cyclization) described in this paper. To assemble one specific indosespenine (**3**) type structure, the latter route was more efficient because of the shorter linear sequence. However, the former route was superior when a collection of such compounds needed to be synthesized for preliminary biological studies. A considerably large quantity of the enone was prepared first, and a variety of readily available indole derivatives were then added to it, to generate different analogues rapidly. In contrast, protocols for

Table 1 Preparation of sespenine analogues through the cationic cascade reaction



^a Oxone (2.0 equiv.), acetone/saturated aq. NaHCO_3 (1:1), 22 °C, 15 min. ^b AcOH (5.0 equiv.), CH_2Cl_2 , 22 °C, 1 h.



preparing 2-substituted-3-stannylindoles varied according to the electronic effect and functional group compatibility, which hampered the collective synthesis *via* the second generation strategy.

Conclusions

We developed a ten-step (the longest linear sequence) total synthesis of sespenine from commercially available materials based on our first generation synthesis. Stille–Miyata coupling was exploited to construct a functionalized α,β -epoxy ester, and Ti(III) mediated epoxide opening radical cyclization gave a *trans*-decalin intermediate bearing a 2-methoxycarbonylindole side chain. Indole C3 oxidation afforded a pair of epimeric 3-hydroxyindolenines, the major isomer of which then underwent a cascade of Prins cyclization/Friedel–Crafts/retro Friedel–Crafts to furnish the sespenine core. Xiamycin A was synthesized from the minor hydroxyindolenine epimer. Four analogues of sespenine with various C2 substituents were prepared. This work may facilitate the biosynthetic and biological studies of sespenine and related natural products.

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