Natural Product Synthesis

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Bioinspired Total Synthesis of Sespenine**

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Dedicated to Professor Chengye Yuan on the occasion of his 90th birthday

Abstract: *The first total synthesis of sespenine, a rare indole sesquiterpenoid from a mangrove endophyte, has been accomplished. A bioinspired aza-Prins/Friedel–Crafts/retro Friedel–Crafts cascade reaction assembles the bridged tetrahydroquinoline core. Further investigations on the aza-Prins cyclization imply that the C3 configuration of the hydroxyindolenine intermediate is crucial to the biosynthesis of sespenine and its congener xiamycin A.*

Indole terpenoids have been of growing interest from the chemical, biological, and biosynthetic perspectives.[1] Sespenine (**1**; Figure 1) is an indolosesquiterpenoid derivative which was isolated from an endophytic *Streptomyces* in 2011.[2] It displays a spiro-tetrahydroquinoline[3,4] scaffold attached to a cyclic ketone bridge, which is strikingly similar to the fungal (*Aspergillus*) metabolite aspernomine (**2**).[5] Biosynthetically, **1** and **2** may originate from indosespene (**3**) and anominine (**4**),[6,7] respectively, through a cationic cascade reaction.[2,8] Scheme 1 illustrates such a reaction from **3** to **1**. Oxidation at the indole C3-position may give the hydroxyindolenine **5**,[9] which, upon the activation of the imine by an acid, could undergo an aza-Prins cyclization[10] to form the cationic species **6**. It is noteworthy that a similar aza-Prins reaction was observed during our synthesis of indotertine A.[11] A Friedel–Crafts annulation and subsequent retro Friedel–Crafts fragmentation would then deliver **1**, presumably through the intermediacy of the dearomatized **7**. The driving force of this cascade may be attributable to the steric proximity of the positive charges and the electron-rich functionalities, as well as the re-aromatization of **7**. However, the above hypothesis has only been examined in a simple model system.[8a] The details of this intriguing process, for instance, the fate of the C3-*epi*-**5** and the interruptive or competitive pathways of the cascade, remain unresolved. Herein, we report the first total synthesis of **1** and provide the experimental evidence to address these questions.

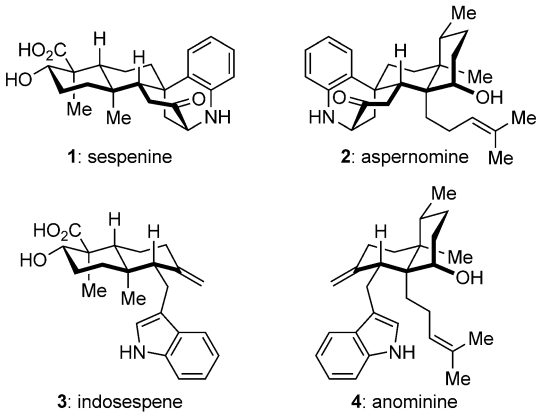
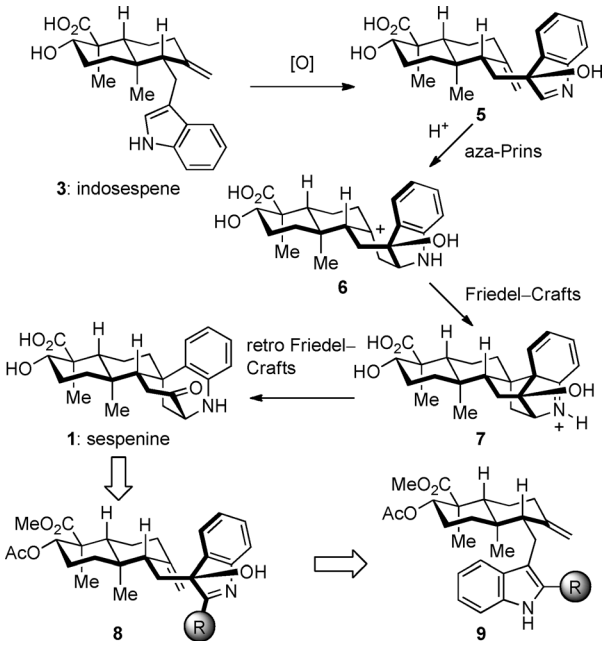


Figure 1. Sespenine and aspernomine, and their plausible biosynthetic precursors indosespene and anominine, respectively.



Scheme 1. Retrosynthetic analysis of sespenine based on its postulated biosynthetic model.

Our retrosynthetic analysis of sespenine (Scheme 1) is based on the biosynthetic model. The hydroxyindolenine **8** is

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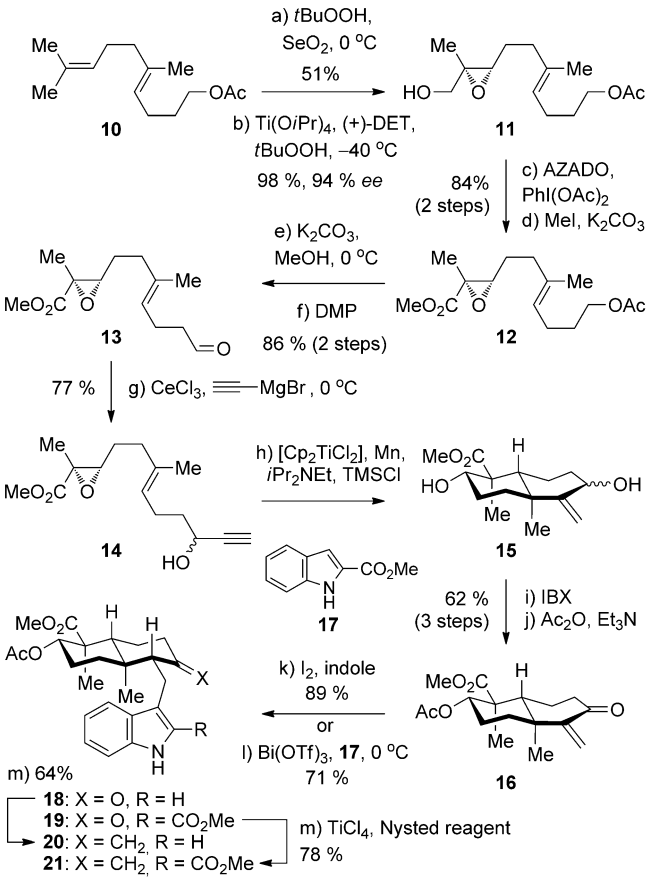
considered to be the substrate for the cascade reaction. The substituent at the indole C2-position would be crucial to the success of this transformation. To our knowledge, C2-non-substituted hydroxyindolenines (e.g. **5**) have not been isolated and characterized, presumably because of their instability. When it bears a substituent, **8** could be more easily handled.[12,13] Thus, besides the straightforward biomimetic approach, we devised a more practical alternative involving the C2-substituted **8** as the substrate for the cascade. The hydroxyindolenines are traced back to the corresponding indole precursors (e.g. **9**). Efficient access to these compounds with the flexibility of varying the C2 substituents through conjugate addition/methylenation is preferential.

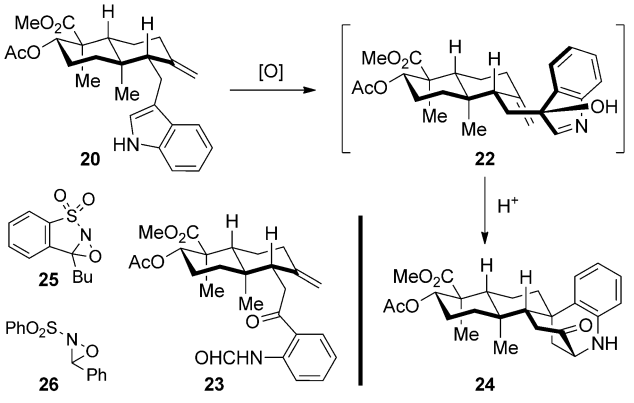
Scheme 2 depicts a general approach toward the synthesis of the indosespene-type intermediates, featuring a titanium-(III)-catalyzed radical cyclization[14] and an acid-promoted indole conjugate addition. Allylic oxidation of the known compound **10**[15] and subsequent Sharpless epoxidation gave the epoxy alcohol **11** (50% overall yield, 94% *ee*), which was converted into the ester **12** by oxidation [2-azaadamantane *N*-oxyl (AZADO), $PhI(OAc)_2$][16] and methylation (K_2CO_3, MeI) in 84% yield over the two steps. The compound **12** was deacetylated, and DMP oxidation of the resultant alcohol formed the aldehyde **13** (86% overall yield). Treatment with ethynylcerium reagent, prepared in situ from ethynylmagnesium bromide and anhydrous $CeCl_3$,[17] afforded the alcohol **14** (77% yield) as an inconsequential diastereomeric mixture. Reduction of $[Cp_2TiCl_2]$ (20 mol%) with manganese generated a titanium(III) species in situ, which initiated epoxide opening and radical cyclizations to furnish the *trans*-decalin **15**.[18] Selective oxidation of the allylic hydroxy group with IBX, followed by acetylation of the unreacted alcohol provided the enone **16** (62% yield for the 3 steps), thus setting the stage for the conjugate addition. I_2 was found to be a mild yet efficient promoter for the addition of indole,[19] thus leading to the ketone **18** in 89% yield as a single diastereomer. $Bi(OTf)_3$ smoothly effected the addition of the C2-substituted **17** to give the ketone **19** as the major diastereomer (71% yield).[20,21] The next olefination (Nysted reagent, $TiCl_4$) furnished the indosespene-type products **20** and **21** with good efficiency.[22]



Scheme 2. General access to the indosespene-type intermediates. Cp = cyclopentadienyl, DET = diethyl tartrate, TMS = trimethylsilyl.

We investigated the oxidation of the C2-nonsubstituted substrate **20** extensively, to form the desired hydroxyindolenine intermediate **22**. Some informative results are summarized in Table 1. In each case, a complex mixture of products was obtained, and we characterized the major one after careful purification. Notably, **22** or its aminal version has not been successfully isolated, as we suspected at the retrosynthetic analysis stage. Treatment with oxone/acetone gave the cleavage product **23** in 16% yield (Table 1, entry 1). *m*CPBA rapidly reacted with the indole moiety as well as the exocyclic C=C bond of **20**, and **23** and its epoxy derivative were both detected (entry 2).[13b,c] Mechanistically, **23** may arise from over-oxidation (Baeyer–Villiger-type reaction or oxaziridination-fragmentation) of **20**. To our delight, oxidation with PIFA in wet MeCN afforded minute amounts of a new compound, which turned characteristically pink with Hanessian's stain and later proved to be the final product of the devised cascade, **24** (entry 3). About 5% of **23** was also isolated under these conditions. However, further attempts to

Table 1: Oxidation of the C2-nonsubstituted indosespene-type precursor.



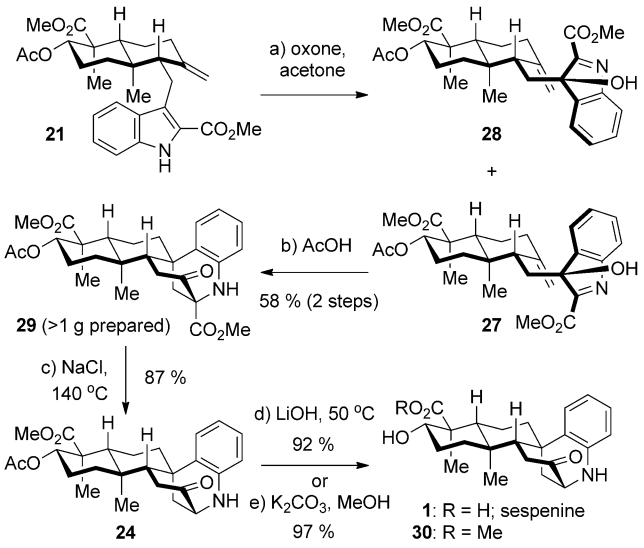
Entry	Conditions[a]	Major product (Yield [%])
1	oxone, acetone	**23** (16%)
2	*m*CPBA	**23** (15%)
3	$PhI(OCOCF_3)_2$, water	**24** (ca. 5%); **23** (ca. 5%)
4	OsO_4, NMO, AcOH	**24** (ca. 5%)
5	oxaziridine **25**, AcOH	**24** (10%)
6	oxaziridine **26**, AcOH	**24** (21%)

[a] See the Supporting Information for details. *m*CPBA = *m*-chloroperbenzoic acid, NMO = *N*-methylmorpholine.

optimize the above reaction conditions were fruitless. In the presence of AcOH (2.0 equiv), exposure of **20** to OsO_4/NMO also provided **24**, albeit in low yield (entry 4). We then examined the oxaziridine **25**,[23] which was successfully used for the indole C3 hydroxylation.[13e–i] Similarly, mildly acidic conditions were required for generating **24** (10% yield, entry 5). The yield was improved to 21% by using the oxaziridine **26** (entry 6).[13j,23]

The above results imply that **22** or its aminal version readily enters undesired reaction channels such as over-oxidation (e.g. Table 1, entries 1 and 2). Rearrangement to the indoxyl or oxindole[8a,13e–l] may also compete with the cascade reaction, although we did not isolate the corresponding by-products. This seemingly straightforward biomimetic process suffers from poor efficiency, limited scale, and tedious purification. More importantly, the details of the cascade reaction cannot be properly studied because of the instability of the hydroxyindolenine intermediate.

We turned our attention to the alternative precursor **21** which bears a methoxycarbonyl substituent at C2 (Scheme 3). Exposure of **21** to oxone/acetone cleanly gave a pair of C3 epimers (**27** and **28**, ca. 2.7:1 ratio), and no over-oxidation



Scheme 3. Synthesis of sespenine from the C2-substituted precursor.

products were detected. This chromatographically inseparable mixture was directly subjected to AcOH at 22 °C, and the anticipated cascade reaction of **27** was completed in 1 hour to furnish the aniline **29** in 58% overall yield from **21**. This two-step sequence was amplified on multiple hundred milligram scale with consistent efficiency, thus providing more than 1 g of **29** in total. Krapcho demethoxycarbonylation[24] afforded **24** in 87% yield. Then global hydrolysis furnished sespenine (**1**), which displays identical spectral and physical properties with those of an authentic sample (see the Supporting Information). Deacetylation of **24** with K_2CO_3/MeOH yielded the sespenine methyl ester **30**, the structure of which was secured by X-ray crystallographic analysis (Figure 2).[25]

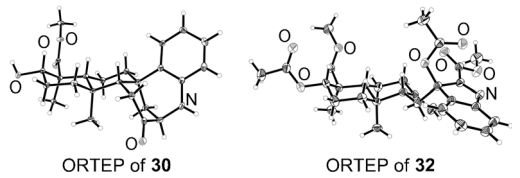
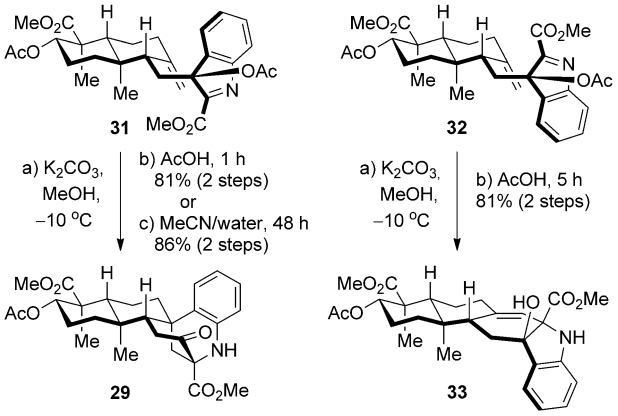


Figure 2. ORTEP drawings of **30** and **32**. Thermal ellipsoids shown at 30% probability.

During the large-scale preparation of **29**, a small portion of an aza-Prins-type product was isolated, together with the partially recovered **28**. Thus, the details of the cyclization reactions of **27** and **28** were further investigated individually. We converted the crude mixture of **27** and **28** into the corresponding acetates **31** and **32** (Scheme 4), respectively and separated them by HPLC. The structure of **32** was confirmed by X- ray crystallographic analysis (Figure 2).[25]

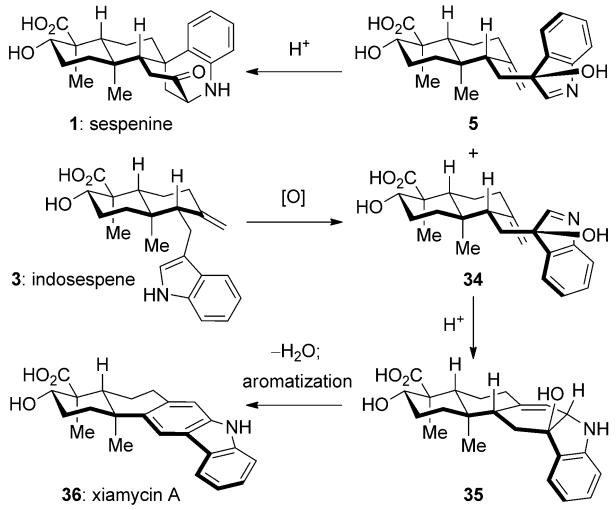


Scheme 4. The different reaction modes of the two hydroxyindolenine epimers.

With the both C3 diastereomers in pure form, we observed different reaction modes and rates, as shown in Scheme 4. Selective deacetylation of **31** followed by treatment with AcOH (22 °C, 1 h) gave **29** in 81% overall yield (with 15% of recovered **31**). No indoxyl or oxindole rearrangement or cascade interruption products were detected. Interestingly, upon prolonged reaction times (48 h) at 22 °C, the cascade reaction was effected smoothly in wet MeCN without an acid promoter (Scheme 4). In parallel, **32** was subjected to a similar sequence to afford a cyclization product **33** as a single diastereomer in 84% overall yield.[26] This aza-Prins cyclization (AcOH, 22 °C, 5 h) is significantly slower than the above cascade reaction. No other by-products were observed except for the recovered **32** (7%). Notably, **31** and **32** were inert under the mild acidic conditions described above. This reaction is similar to the bioinspired transformation from drimentine F into indotertine A reported by us previously,[11] in which the postulated cationic intermediate undergoes a regiospecific proton elimination to form the trisubstituted C=C bond. We then repeated the oxidation/cyclization sequence from **21** and prolonged the times of acid treatment.

Satisfactory overall yields of **29** (58%) and **33** (19%) were achieved.

The above experiments indicate that the facial selectivity of the indole C3 oxidation determines the modes of the following cyclizations, which result in the products with markedly different scaffolds. Our results strongly support the biosynthetic model of the formation of sespenine and xiamycin A from indosespene and, more importantly, corroborate the C3 configuration of the hydroxyindolenine intermediate (e.g. **5**, Scheme 1) as a major determinant for the course of the reactions (Scheme 5). As shown, the enzymatic oxidation at C3 of indosespene, mediated by XiaF,[6c] may generate the two epimers **5** and **34**, each of which would enter a specific track to sespenine or a xiamycin A precursor **35**. The latter could undergo dehydration and oxidative aromatization to yield thermodynamically stable xiamycin A (**36**).[6]



Scheme 5. A biosynthetic model of the formation of sespenine and xiamycin A from indosespene with the stereochemical details.

In summary, we have accomplished the first total synthesis of sespenine. Taking advantage of the indosespene-type precursor bearing a C2-methoxycarbonyl substituent, we developed a scalable aza-Prins/Friedel–Crafts/retro Friedel–Crafts reaction cascade, for assembling the core of sespenine. Further studies on the aza-Prins cyclization reveal the importance of the C3 configuration of the hydroxyindolenine intermediate, which complement and support the biosynthetic proposal of sespenine and xiamycin A.

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[26] The compound **33** is identical with the minor product isolated during the large scale preparation of **29**.