Prayogik Rasayan

Synthetic Approaches to Anominine: A Key Indole Diterpenoid from *Aspergillus spp.*

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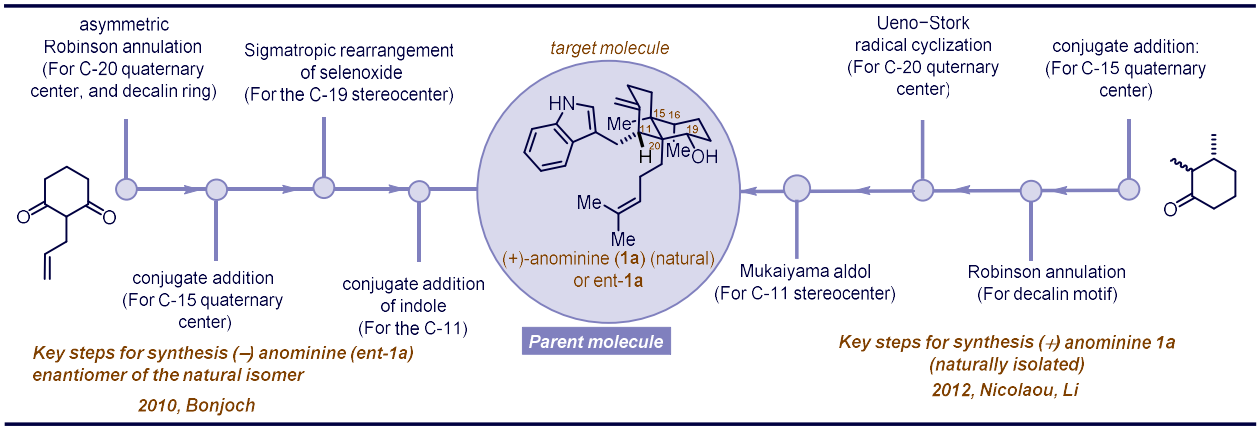
Abstract

Indole-based diterpenoids are a specific class of naturally occurring bioactive molecules that have garnered significant interest from synthetic organic chemists. These compounds exhibit diverse and fascinating biological activities, including anticancer, antifungal, and anti-inflammatory properties. Moreover, the molecular architectures of these indole-based diterpenoids are highly complex, presenting significant synthetic challenges. This complexity, combined with their biological relevance, makes them ideal targets for total synthesis. In this review, we focus on anominine, an indole-based diterpenoid, and summarize recent advances in its total synthesis. Anominine is notable for its biological activity and serves as the parent compound for several other congeners isolated from the fungal sclerotia of the genus *Aspergillus*. Spp. Various research groups have developed diverse synthetic routes to access anominine. By highlighting those notable syntheses, we aim to showcase the progress in this area and provide insights into future directions for the synthesis of related natural products.



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1. Introduction

Total synthesis is a dynamic and ever-evolving branch of organic chemistry dedicated to the construction of complex molecules from simpler chemical building blocks. Its main goal is to develop efficient, reproducible, and often novel methods to assemble molecules, many of which have significant biological or pharmaceutical importance. Developing a synthetic protocol for them leads to the advancement of organic chemistry and provides a crucial source of potential drug molecules. Many pharmaceuticals and bioactive compounds are either from natural products or directly derived from or inspired by naturally occurring molecules.[1] Various living organisms produce chemical compounds known as natural products. These compounds often have complex structures, making them challenging but highly desirable. The complexity of these molecules often reflects their biological importance, as they frequently interact with biological systems in unique ways, leading to interesting therapeutic properties.

The secondary metabolites, which are not directly involved in the growth or development of the producing organism, often play a critical role in its defense mechanisms, and several of them show various important bioactivities. A study of fungal sclerotia from the genus *Aspergillus* led to the isolation of several biologically active secondary metabolites, including complex indole- and tetrahydroquinoline-based diterpenoids.[2,3] Anominine (**1a**)[3b] is a structurally representative member of an ever-growing family of naturally occurring secondary metabolites which includes tubingensin A (**1b**),[3b] aspernomine (**1c**),[4] 10,23-dihydro-24,25-dehydroaflavinine (**1d**),[5] and aflavinine (**1e**),[6] (Figure 1). Structurally, they feature challenging tetra-, penta-, or hexacyclic ring scaffolds with a *cis*-fused decalin unit. These frameworks contain four to eight contiguous stereogenic centers, including two to three quaternary centers. These intricate molecular architectures exhibit noteworthy biological properties, including anti-insecticidal activity, significant cytotoxicity against three human solid tumor cell lines, and in vitro antiviral activity against herpes simplex virus type 1. Owing to their pharmacological potential and structurally diverse, complex nature, these natural products have emerged as key targets for total synthesis in the last two decades. In this review, we summarize the synthesis of anominine **1a** to date. Compound **1a** was first isolated in 1989 by Gloer's group and initially named nominine. However, since the same name

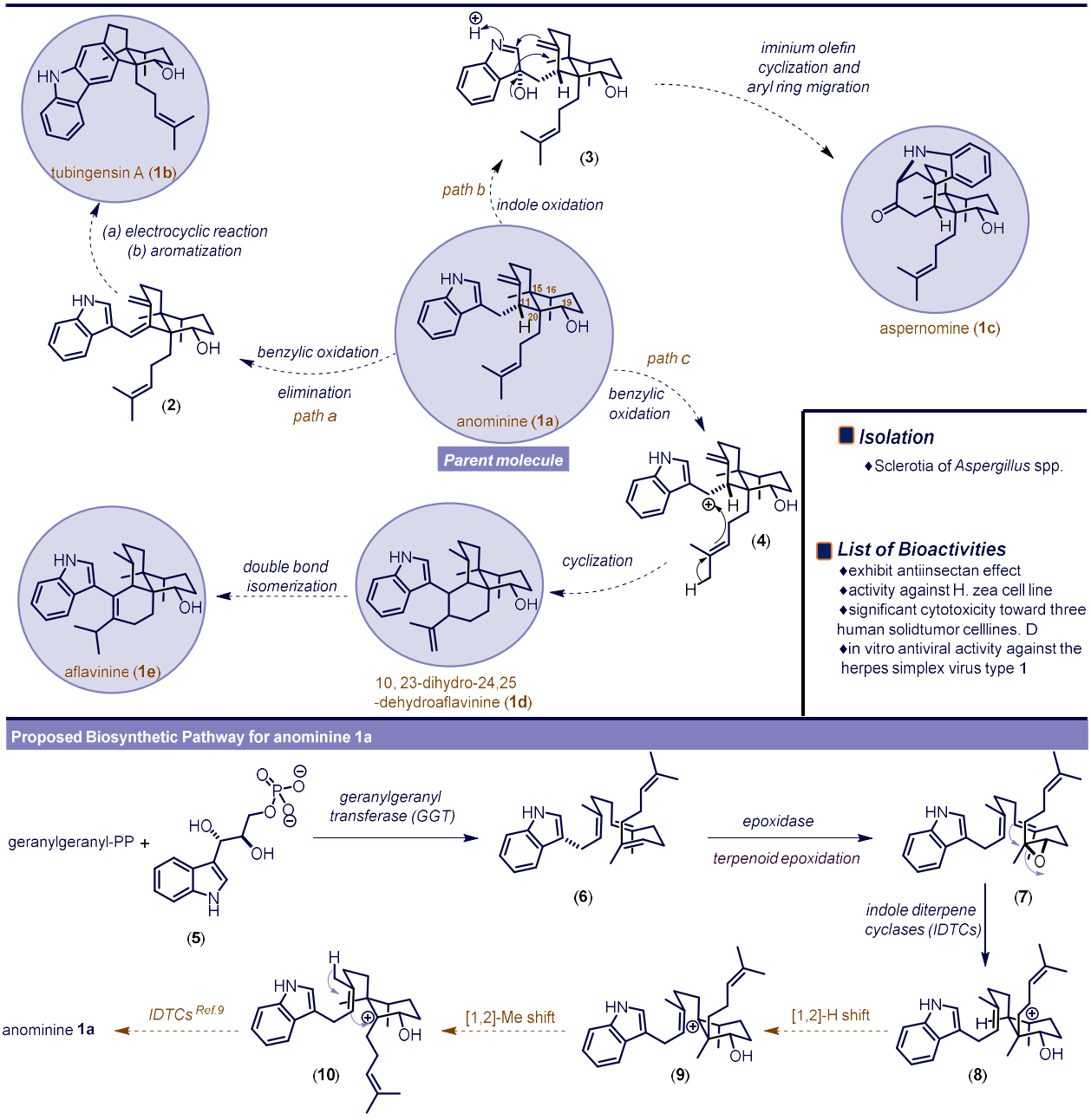


Figure 1: (A) Representative members of the anominine family and their hypothetical biosynthetic relation, natural source, and bioactivity (B) Proposed biosynthesis for anominine **1a**

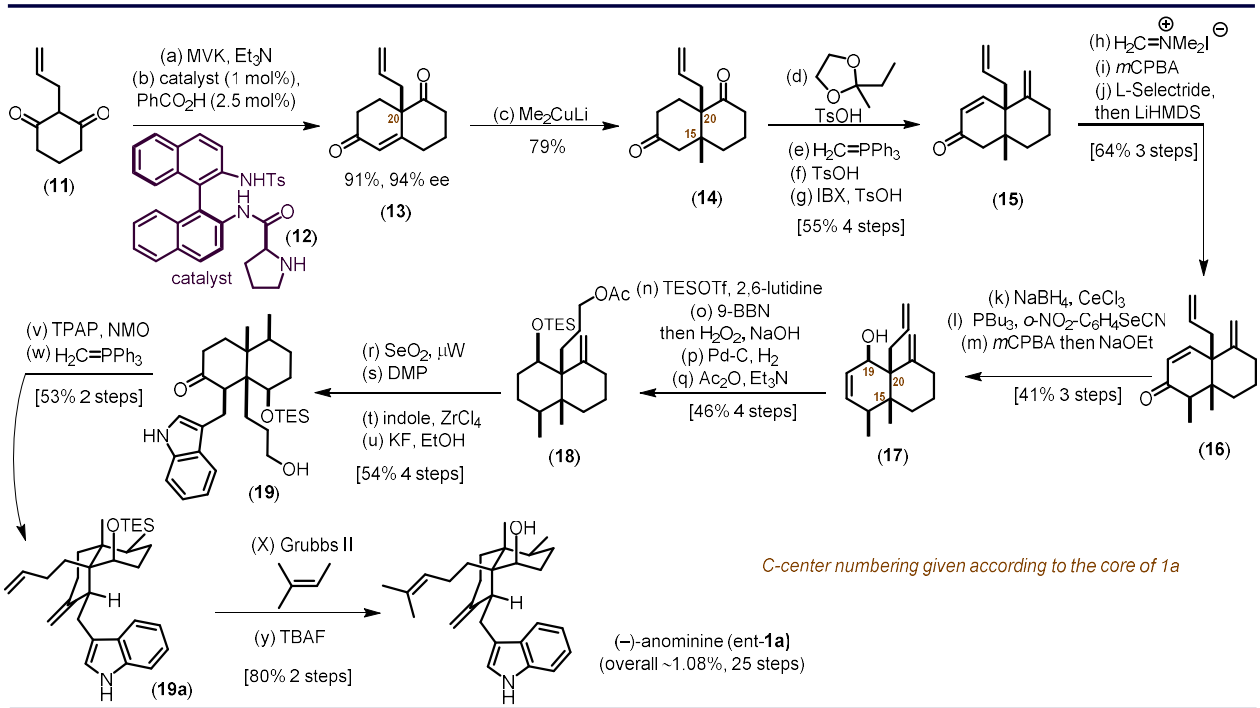
had already been assigned to a hetisine-type aconite alkaloid in 1982; they subsequently renamed it anominine. [7a,b]

In 2012, Nicolaou, Li, and their coworkers elegantly proposed a biosynthetic network based on intriguing structural relationships that link the molecules above to the parent compound, anominine **1a** (Figure 1A).[8] As described in Figure 1, following path a, benzylic oxidation of **1a**, followed by the elimination of the C-11 hydrogen, generates intermediate **2**. This intermediate could then undergo a 6π-electrocyclization/aromatization sequence to produce **1b**. Alternatively, along path b, oxidation at the indole 3-position would yield intermediate **3**, which, upon protonation of the indolic nitrogen, sets the stage for nucleophilic attack by the exocyclic alkene. This is followed by a pinacol-pinacolone rearrangement-like migration of the aryl ring, which would result in the synthesis of **1c**. In path c, benzylic oxidation leads to the formation of a carbocationic intermediate **4**. A nucleophilic attack by the side chain double bond followed by the elimination of proton from the isopropelynic methyl group would produce the fused tricyclic structure **1d**, which may then undergo double bond isomerization to yield **1e**. However, no such biochemical evidence is present in the literature.

Since all members of the anominine family contain a C28 unit, this suggests a mixed-origin biosynthetic pathway, where an indole heterocycle participates in a condensation reaction with a diterpene. Tang and coworkers mentioned in their article that the proposed biosynthesis of **1a** originates from 3-geranylgeranyl indole **6** (Figure 1B).[9] The key enzymes involved in this biosynthetic pathway include GGPP synthase (GGPPS), which synthesizes geranylgeranyl pyrophosphate (GGPP), and geranylgeranyl transferase (GGT), which couples GGPP with indole-3-glycerol phosphate to form **6**. Later, a flavin-dependent epoxidase generates the regioselective epoxide **7**, initiating a cationic reaction cascade. Nucleophilic attack by the neighboring double bond produces the first cationic intermediate **8**. Subsequently, a 1,2-hydride shift, followed by a 1,2-methyl shift and cyclization through nucleophilic attack of the nearest alkene, forms the *cis*-fused decalin structure. The elimination of an exocyclic proton ultimately yields **1a**. Tang group identified indole diterpene cyclases (IDTCs) responsible for converting compound **8** to **1a** (Figure 1). Using IDTCs homologs from various fungal hosts, they combinatorially assembled IDT pathways and discovered the genetically standalone IDTCs involved in the cyclization pathway for **1a**.[9]

2. *Bonjoch's Total Synthesis of (–)-Anominine ent-1a*

In 2010, Bonjoch and coworkers reported the first asymmetric total synthesis of *ent*-anominine ent-**1a (Scheme 1)**.[7] Their successful route to ent-**1a** began with the generation of the two vicinal quaternary stereogenic centers, starting with the one at C20, which was established through an asymmetric Robinson annulation of 1,3-dione **11** (Scheme 1). They showcased the efficient synthesis of Wieland-Miescher ketone-type compounds in high enantioselectivity utilizing the organocatalysts. Using their established process, they achieved up to 98.5:1.5 er, 91% yield of diketone **13** using 2.5% *N*-Ts-(*Sa*)-binam-L-Pro **12** as the catalyst under the solvent-free conditions starting from 2-allylated vinylogous acid **11**. The second quaternary center at C15 was then established through a subsequent conjugate addition reaction using a Gilman reagent, which yielded compound **14**. Next, selective protection of the less hindered ketone, methylenation of the other keto functionality utilizing standard Wittig reaction condition followed by deprotection, and oxidation with IBX obtained the enone **15**. Due to the angular quaternary centers on **15**, the molecule became congested; hence, several attempts for direct alkylation of **15** led mainly to O-methylation. They overcome such a problem by reacting the enone **15** with Eschenmoser salt, followed by N-oxide formation, elimination, and a selective reduction by the Ganem protocol, followed by equilibration, completed the net methylation, and generated the correct stereoisomer **16**. C-19 OH group was then installed by Sigmatropic rearrangement of the allyl selenoxide in the presence of water, followed by the treatment of NaOEt. According to their observation, water is helping to do the epimerization at the selenium center, which is required to obtain the right stereocenters.



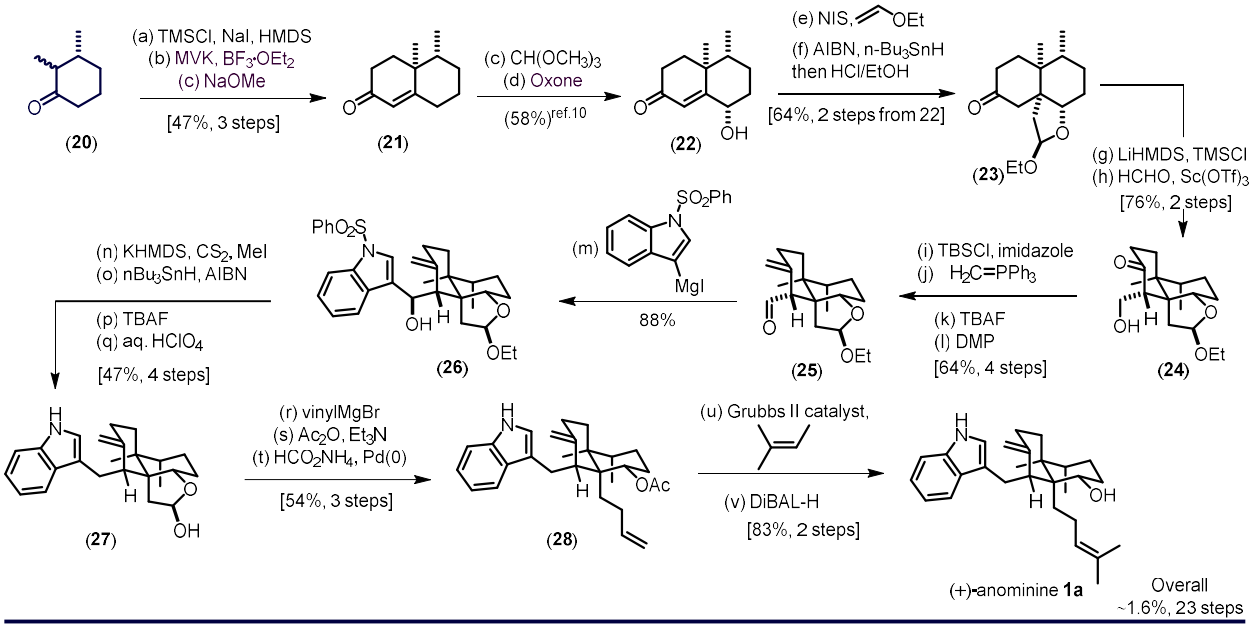
Scheme1: Bonjoch synthesis of (–) anominine ent-**1a** in 25 steps starting from diketone **11**

Subsequently, alcohol protection and hydroboration-oxidation of the terminal monosubstituted olefin, followed by regioselective hydrogenation of the double bond and acetate formation, yielded compound **18**. Allylic oxidation of **18** produced an enone, which, upon conjugate addition with indole and removal of acetate, generated intermediate **19**. Next, oxidation of primary alcohol and bis-methylenation generated the advanced intermediate **19a**. Finally, selective Ru-mediated cross-metathesis with compound **19a**, followed by deprotection of the TES group, completed the synthesis of (–)-anominine ent-**1a**.

3. *Nicolaou, and Li's Total Synthesis of (+)-Anominine 1a*

In 2012, Nicolaou, Li, and their coworkers accomplished another total synthesis of parent anominine **1a**.[8] The

synthesis began with the readily available, enantiomerically pure, though diastereomerically impure, ketone **20** (Scheme 2). The first quaternary center was constructed through regioselective formation of the trimethylsilyl (TMS) enol ether, followed by $BF_3{\cdot}OEt_2$-promoted diastereoselective 1,4-addition and subsequent Robinson annulation with methyl vinyl ketone, yielded the bicyclic enone **21** in 47% overall yield. A secondary hydroxyl group was introduced at the γ-position of the enone following the literature protocol,[10] using oxone as the oxidant and completed the synthesis of **22**. Later, sequential Iodoetherification, Ueno–Stork radical cyclization followed by acidification generated angular quaternary stereocenter, and the corresponding tricyclic compound **23** was obtained as a single diastereomer. Subsequently, the regioselective silyl enol ether formation, followed by a $Sc(OTf)_3$-mediated aqueous Mukaiyama aldol reaction with formaldehyde, yielded the hydroxyl ketone **24**. Then **24** underwent four additional steps, including silylation, Wittig olefination, desilylation, and oxidation, afforded compound **25**. Afterward, an indole-based Grignard reagent addition to aldehyde **25**, generated a secondary alcohol **26**. Compound **26** was transformed to lactol intermediate **27** *via* xanthene formation, radical deoxygenation, desulfonylation, and acid hydrolysis. The lactol **27** proved highly resistant to nucleophilic attack, requiring heating to 60°C for vinyl-MgBr addition, which resulted in the desired ring-opening diol product. The diol was directly subjected to bisacetylation (Ac_2O/Et_3N) and Tsuji reduction [$Pd(PPh_3)_4$ (cat.), HCO_2NH_4], yielded mono deoxygenated product **28**. Finally, cross-metathesis between **28** and freshly distilled 2-methyl-2-butene using the Hoveyda−Grubbs II catalyst, followed by removal of the acetyl group with DIBAL-H, resulted in the synthesis of naturally occurring (+)-**1a**.



Scheme 2: Nicolaou, Li approach to (+) anominine **1a** in 23 steps starting from

4. Conclusions

The promising biological profile of indole-based diterpenoids has generated significant interest in the development of efficient and divergent synthetic strategies for their synthesis. (+)-anominine is proposed as a key intermediate for other congeners in the family of indole-based diterpenoids produced by *Aspergillus* species. The first synthesis of the unnatural (−)-anominine was accomplished by the Bonjoch group in ~1.08% overall yield and in 25 steps, starting from a readily available 1,3-diketone. In contrast, Nicolaou and Li reported a 23-steps total synthesis of the natural (+)-anominine in ~1.6% overall yield, starting from a commercially available ketone. Their synthetic strategies help to access the other related natural products from *Aspergillus spp.,* that are not included in this manuscript. Nonetheless, more step-economic and diversified approaches remain to be developed.

5. Acknowledgements

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