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Total Synthesis of (−)-Anominine

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Many fungi produce specially adapted morphological structures called sclerotia that are critical to the long-term survival and propagation of the species. A systematic study of the sclerotia of *Aspergillus* spp. by Gloer's group several years ago led to the isolation of many unique, biologically active secondary metabolites.[1] Among these, our interests have focused on diterpenoids with novel ring structures characterized by two quaternary carbons at the decalin ring junction[2] and up to six contiguous stereocenters all arranged in a cis configuration (Figure 1). To date, none of these highly congested and structurally challenging diterpenoids have been synthesized,[3] nor have their absolute configurations been established.

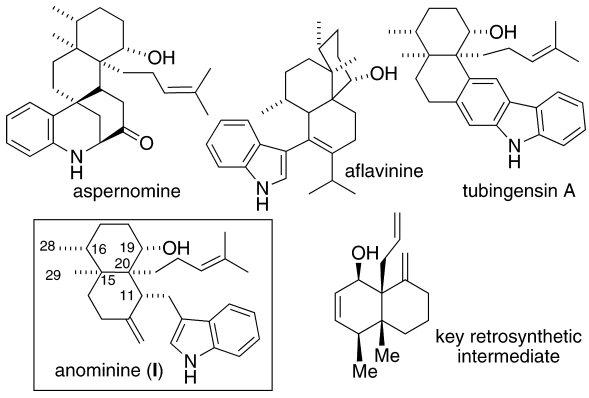
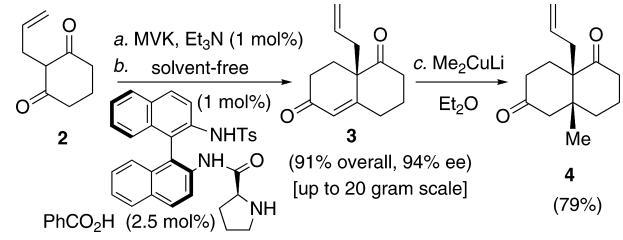


Figure 1. Representative diterpenoids with a common structural motif.

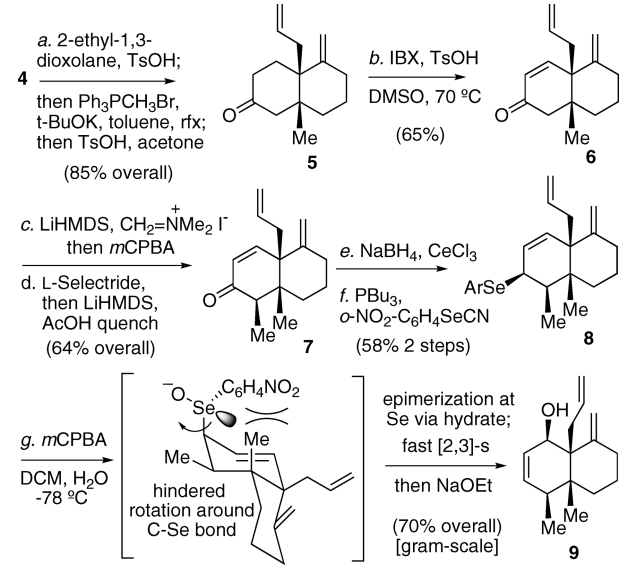
Focusing our attention on the synthesis of anominine (**1**),[4] most likely the parent structure from which the other metabolites are biogenetically derived,[5] we envisaged a retrosynthetic intermediate (depicted in Figure 1) embodying the four contiguous stereocenters of the terpene core and various double bonds that could be used as flexible handles to introduce further structural complexity. The final successful route to anominine began with the generation of the two quaternary stereogenic centers, the one at C20 being set up first by an asymmetric Robinson annulation of dione **2** (Scheme 1). A longstanding and unresolved problem in organic synthesis is the efficient preparation of Wieland−Miescher ketone-type compounds in high enantioselectivity, thus avoiding multiple purifications and recrystallizations. In an attempt to address this issue, we carried out an extensive survey of reaction conditions and organocatalysts. Starting from **2**, we found that **3** could be prepared in highly enantioenriched form (97% ee) using 2.5% *N*-Ts-(S_a)-binam-L-Pro as the catalyst under solvent-free conditions. Furthermore, we found that this method was general and could be applied to a wide range of substrates.[6] In the most optimized version, in which the catalyst loading was reduced to just 1%,[7] large quantities of the enantioenriched building block **3** (96% yield, 94% ee) could be secured. The high purity of **3** meant that it could be used without purification in the subsequent conjugated addition reaction to give **4** and set up the second quaternary center.

Scheme 1. Organocatalyzed Asymmetric Synthesis of **3**



A second relay procedure introduced the double bond at C11 by chemoselective protection of the less hindered carbonyl group of **4** followed by a Wittig methylenation and acid quench of the initially formed acetal (Scheme 2). Oxidation of ketone **5** with IBX in the presence of TsOH[8] formed the endocyclic enone **6**, which not only ensured the regioselectivity for the next alkylation step but also provided the necessary functionality for the rearrangement required to install the oxygen atom at C19. With the contiguous quaternary carbons in place, we then found that many attempted transformations failed, particularly when the reactive site was adjacent to one of the quaternary centers. For example, alkylation to introduce the C28 methyl with LiHMDS/MeI/HMPA was precluded by the predominance of O-alkylation, and plans to move the oxygen from C17 to C19 by a Wharton transposition were also thwarted by the unreactive nature of the internal double bond toward epoxidation. However, reaction of the lithium enolate of **6** with Eschenmoser's salt followed by *m*-CPBA oxidation of the resulting

Scheme 2. Synthesis of Key Intermediate **9**



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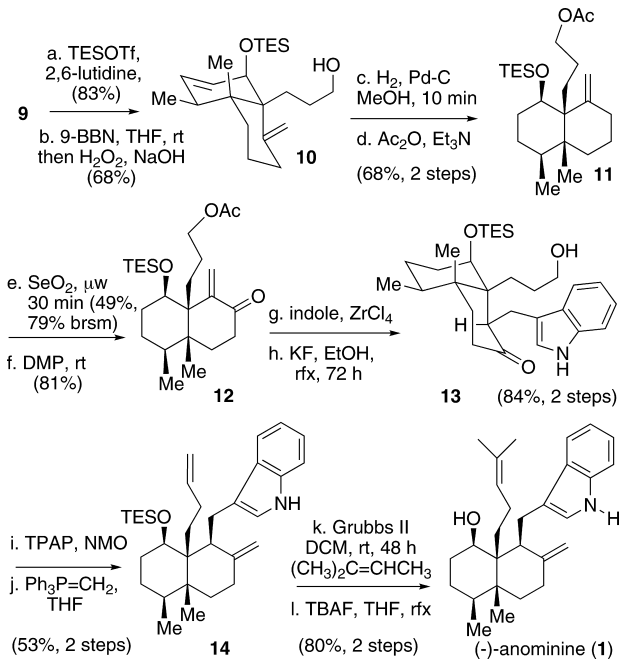
Scheme 3. Completion of the Synthesis of (−)-Anominine



β-aminoketone led to the exocyclic enone, which after chemoselective reduction and equilibration yielded stereochemically pure **7**. Diastereoselective reduction of ketone **7** under low-temperature Luche conditions afforded the required alcohol, which under Grieco conditions gave the allylic selenide **8** set up to undergo a sigmatropic rearrangement. Once again, the *cis*-decalin quaternary centers had a great effect on the outcome of the reaction by not allowing the **8** → **9** rearrangement when the initial oxidation was carried out under dry conditions. In sharp contrast, the rearrangement in a wet medium proved to be very effective, giving a stable selenenate that was readily converted to the key intermediate **9**. Presumably, the (*S*)-selenoxide depicted in Scheme 2 cannot adopt the required conformation for the rearrangement process because of steric hindrance around the C17−Se bond, which is due to the bulkiness of the *o*-nitrophenyl group and the methyl group at C15. However, water-induced epimerization at the Se stereogenic center[9] led to the (*R*)-selenoxide, which could evolve to **9** through the [2,3]-sigmatropic rearrangement.

After causing so many setbacks, the steric hindrance of the molecule now worked to our advantage, as we could chemoselectively transform the triene **9** (Scheme 3). Thus, after its protection as a TES ether, selective hydroboration at the allyl side chain to give alcohol **10** and a selective hydrogenation at the internal double bond followed by acetylation gave **11**. Allylic oxidation followed by Dess−Martin oxidation afforded the exocyclic enone **12**. Although efficient conditions (bismuth triflate, CH_3CN) were developed for the coupling of the indole using model systems,[10] attempts to apply them to the sterically demanding enone **12** were unsuccessful.[11] After a systematic screen of Lewis acid catalysts, only zirconium tetrachloride[12] was able to smoothly generate the coupled product, which after treatment with KF in refluxing EtOH provided the all-cis diastereomer in which the acetate was simultaneously cleaved to give **13** in 84% overall yield. Oxidation with Ley's perruthenate followed by Wittig bishomologation of the keto aldehyde gave **14**. Selective olefin cross-metathesis[13] upon the methylene in the side chain and cleavage of the TES group delivered **1**, which showed NMR spectroscopic data identical to those reported for the natural product. The data obtained for **1**, $[\alpha]_D = -21.0$ (*c* 0.3, MeOH), resulted in the assignment of **1** as *ent*-anominine and the absolute configuration depicted in Figure 1 for the natural (+)-anominine (**I**) {lit[4] $[\alpha]_D$ +23.6 (*c* 0.85, MeOH)}.

In summary, the first synthesis of anominine has been achieved. Keys to its success were the use of several chemoselective transformations controlled by the structurally congested nature of the bicyclic core and the development of a new, highly efficient method for the synthesis of Wieland−Miescher ketone compounds that should find wide application in natural product synthesis. This synthesis opens the way to access other related natural products from *Aspergillus* spp. via biomimetic processes, and work in this direction is now in progress.

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Supporting Information Available: Full experimental details and NMR spectral reproductions for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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