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Total Synthesis of Epoxyeujindole A

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Supporting Information

ABSTRACT: The total synthesis of epoxyeujindole A, a structurally unusual indole diterpenoid isolated from *Eupenicillium javanicum*, has been accomplished for the first time. The synthesis features a late-stage cationic cyclization strategy, which took advantage of an electron-rich olefinic substrate. The CDE ring system was assembled via an enantioselective conjugate addition/alkylation, a Luche cyclization, and a Nozaki–Hiyama–Kishi reaction. The heavily substituted A ring was constructed through a Suzuki–Miyaura coupling and a cationic cyclization, and the bridged fused B ring was formed through a Prins reaction.

Indole terpenoids comprise a large number of biologically and biosynthetically interesting natural products.[1] Recently, we focused our attention to a class of indole diterpenoids first discovered by the Gloer group from *Asperigillus*, the parent molecule of which is anominine (**1**, Figure 1).[2] The syntheses

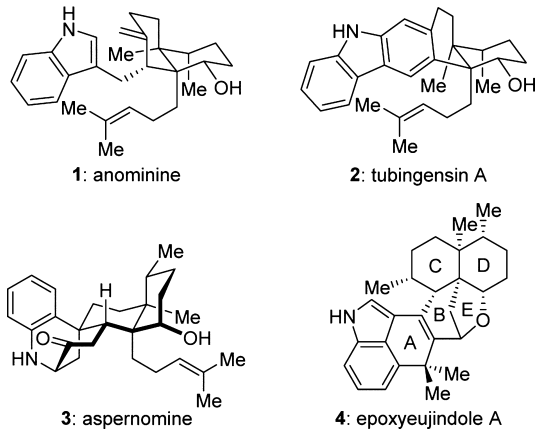
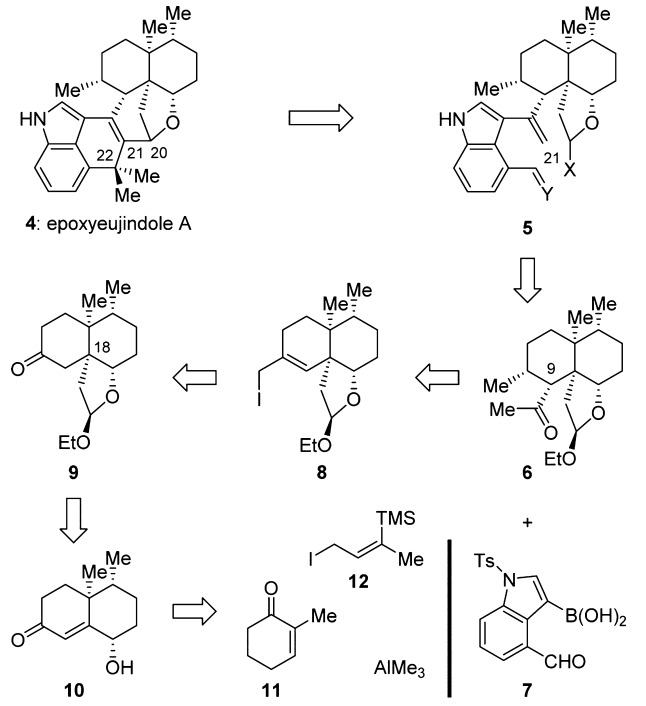


Figure 1. Selected indole terpenoids of the anominine family.

of **1** and its carbazole congener tubingensin A (**2**) were reported by Bonjoch, Garg, and us,[3−5] while other members such as aspernomine[2c] (**3**) have not been synthesized to our knowledge. In 2011, Nakadate et al. reported the isolation of structurally complex anominine-related compounds from *Eupenicillium javanicum*, including epoxyeujindole A (**4**), although its absolute configurations were not determined.[6] **4** possesses a heptacyclic scaffold that is nontrivial to access from **1** through a biomimetic synthesis.[4a] Its congested nature poses a considerable challenge for chemical synthesis. Here we report the first and asymmetric total synthesis of **4**.

As illustrated in Scheme 1, two key disconnections at C20–C21 and C21–C22 bonds are envisioned in our retrosynthetic

Scheme 1. Retrosynthetic Analysis of Epoxyeujindole A



analysis. We take advantage of the electron-rich nature of the exocyclic olefin of substrate **5**, for two sequential Prins cyclizations.[7] The strategy avoids functionalization at C21 of **5** and ensures a tetrasubstituted olefin in the product. The gem-dimethyl at C22 may be installed on a ketone precursor by using Reetz/Trauner's protocol (methyl addition followed by cationic methylation of the resultant tertiary alcohol).[8] **5** is then disassembled into ketone **6** and boronic acid **7**, and the former may arise from allyl iodide **8**. The two-carbon unit at C9 is expected to be introduced via a Nozaki–Hiyama–Kishi coupling with acetaldehyde. Further simplification of **8** results in tricycle **9**. The tetrahyrdofuran motif bearing quaternary C18 could be constructed by Luche cyclization.[9] Thus, **9** is traced back to enone **10**, which would be prepared from enone **11**, iodide **12**, and Me_3Al through a sequence of asymmetric conjugation and alkylation.[10]

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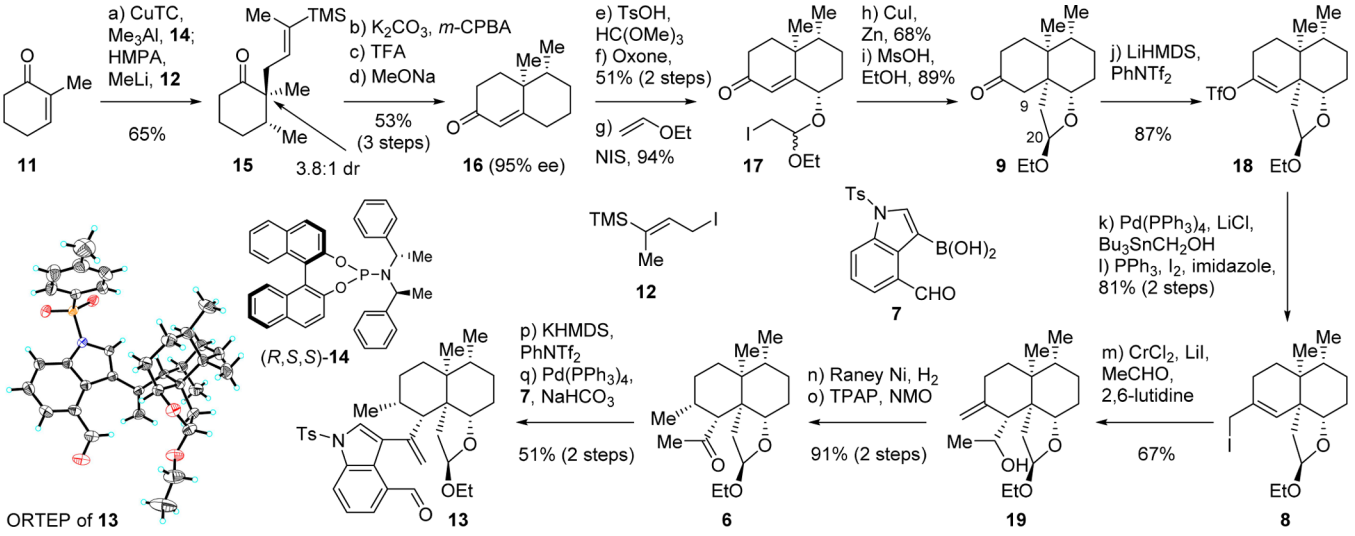
Scheme 2. Synthesis of Advanced Intermediate 13[a]



[a]Reagents and conditions: (a) Me_3Al (1.2 equiv), CuTC (2 mol %), **14** (4 mol %), Et_2O, −30 °C, 2.5 h; MeLi (1.0 equiv), HMPA (2.5 equiv), −30 °C, 20 min; **12** (1.3 equiv), THF, −30 °C, 24 h, −10 °C, 24 h, 0 °C, 48 h, 65%; (b) K_2CO_3 (2.0 equiv), *m*-CPBA (1.2 equiv), CH_2Cl_2, 0 °C, 1.5 h; (c) TFA/CH_2Cl_2, 0 °C, 15 min; (d) MeONa (3.0 equiv), MeOH, 22 °C, 2.5 h, 53% (3 steps); (e) $HC(OMe)_3$ (18 equiv), TsOH (15 mol %), DMF, 10 °C, 2 h; (f) Oxone (1.0 equiv), −5 °C, THF, 1.5 h, 51% (2 steps); (g) NIS (6.0 equiv), ethyl vinyl ether (8.0 equiv), CH_2Cl_2, 0 °C, 1.5 h, 94%; (h) Zn (9.0 equiv), CuI (2.7 equiv), pyridine/water (1:4), 22 °C, 2 h, 68%; (i) MsOH (20 mol %), EtOH, 22 °C, 1 h, 89%; (j) LiHMDS (2.3 equiv), $PhNTf_2$ (1.9 equiv), THF, −78 °C, 10 min, 87%; (k) $Pd(PPh_3)_4$ (10 mol %), Bu_3SnCH_2OH (2.0 equiv), LiCl (2.0 equiv), THF, 65 °C, 2 h; (l) PPh_3 (1.2 equiv), I_2 (1.2 equiv), imidazole (3.0 equiv), CH_2Cl_2, 0 °C, 30 min, 81% (2 steps); (m) $CrCl_2$ (5.0 equiv), LiI (1.2 equiv), 2,6-lutidine (10 equiv), MeCHO (21 equiv), 22 °C, 5 h, 67%; (n) Raney Ni, H_2 (60 bar), EtOH, 22 °C, 1 h; (o) TPAP (10 mol %), NMO (3.0 equiv), CH_2Cl_2, 22 °C, 30 min, 91% (2 steps); (p) KHMDS (1.1 equiv), $PhNTf_2$ (1.8 equiv), THF, −30 °C, 10 min; (q) $Pd(PPh_3)_4$ (10 mol %), $NaHCO_3$ (1.6 equiv), **20** (1.5 equiv), toluene/MeOH/water (4:1:1), 22 °C, 30 min, 51% (2 steps).

Based on the above analysis, we first synthesized an advanced intermediate **13** in an enantioselective manner (Scheme 2). Inspired by the work of Alexakis, Cramer, and Cook,[11] we carried out an asymmetric conjugate addition (**11**, CuTC, Me_3Al) with phosphoramidite ligand (*R,S,S*)-**14** to set the first stereocenter. The resultant enolate was activated *in situ* by adding MeLi and HMPA and then quenched by allyl iodide **12**,[12] providing ketone **15** with an excellent level of enantioselectivity (*vide infra*). The diastereoselectivity (ca. 3.8:1) and efficiency (65% yield) of the one-pot reaction are acceptable at this early stage. Notably, trapping the enolate with methyl vinyl ketone (MVK) was inefficient (<20% yield), presumably due to the severe polymerization of MVK under these conditions. Thus, **12** served as a suitable alternative of MVK. Epoxidation of the alkenyl silane with *m*-CPBA followed by TFA promoted rearrangement afforded the corresponding diketone,[13] which underwent aldol condensation (MeONa) to reach enone **16** in 53% overall yield. The enantiomeric excess of **16** was measured to be 95% by HPLC (see Supporting Information), and its absolute configurations were determined by comparing with chiral pool derived **16**.[4a,14] This compound was subjected to a known three-step sequence[4a] to afford iodide **17**. We examined reductive radical conditions for the next 5-*exo-trig* cyclization: treatment with SmI_2 resulted in a moderate yield of the tricycle along with a large portion of the reductive cleavage products, and modified Luche conditions[9] (Zn, CuI, pyridine/water) significantly suppressed such side reactions and improved the yield to 68%. The Luche protocol is more practical than conventional radical ones in terms of reaction scale and purification. This diastereomeric acetal mixture (ca. 1.4:1 at C20) was converted to thermodynamically more stable **9** smoothly by exposure to MsOH in EtOH.

Further elaborations of tricycle **9** at C9 led to compound **13**, as shown in Scheme 2. Regioselective deprotonation was effected by treatment with LiHMDS. Such selectivity was not observed on C20-*epi*-**9**, which indicates a directing effect by the ethoxy oxygen, presumably through chelation with Li/base aggregates. Notably, KHMDS gave no selectivity in this reaction. The Li enolate was trapped by $PhNTf_2$ to afford triflate **18** in 87% yield, which then underwent Stille−Migita coupling [$Pd(PPh_3)_4$, Bu_3SnCH_2OH, LiCl] followed by iodination (Ph_3P, I_2, imidazole) to furnish allyl iodide **8** (81% yield for the two steps). The introduction of the two-carbon unit at C9 was achieved by Nozaki−Hiyama−Kishi coupling ($CrCl_2$, LiI) with acetaldehyde,[4d,15] leading to alcohol **19** in 67% yield as a single detectable diastereomer. **19** tends to cyclize to generate a bridged acetal under the coupling conditions. Thus, 2,6-lutidine is crucial as a buffering additive. The observed facial selectivity may be attributable to the conformation of the D ring (see ORTEP of **13** as an indirect reference), and the configuration at C8 is inconsequential. Establishing the C10 stereochemistry turned out to be problematic. Crabtree catalyst directly caused bridged acetal formation because of its acidity. Pd/C resulted in C=C bond migration and poor diastereoselectivity for hydrogenation. Silylation of the secondary alcohol increased the steric hindrance and inhibited the hydrogenation under the Crabtree conditions. This issue was solved by Raney Ni-mediated hydrogenation under a pressure of 60 bar. TPAP oxidation gave methyl ketone **6** in 91% yield for the two steps. Triflation followed by Suzuki−Miyaura coupling with boronic acid **7** provided the key intermediate **13**, the racemic sample of which was readily crystallized from EtOAc/petroleum ether (1:1). The relative stereochemistry of **13** was thus confirmed by X-ray crystallographic analysis (Scheme 2). The triflate intermediate

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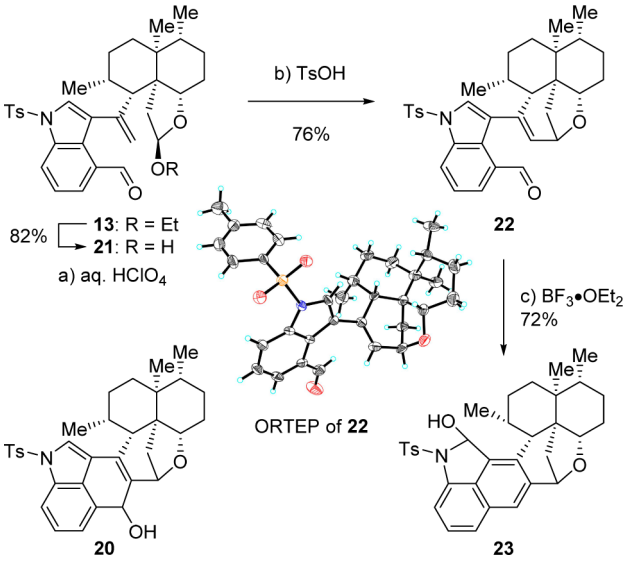
was sensitive to basic conditions at elevated temperature, and the acetylene byproduct was formed. Therefore, $NaHCO_3$ was used as a mild base for the cross coupling.[16]

We then explored the double Prins strategy toward the synthesis of heptacycle **20** (Scheme 3). Hydrolysis of **13** with

Scheme 3. Synthesis of Unexpected Heptacycle 23[a]

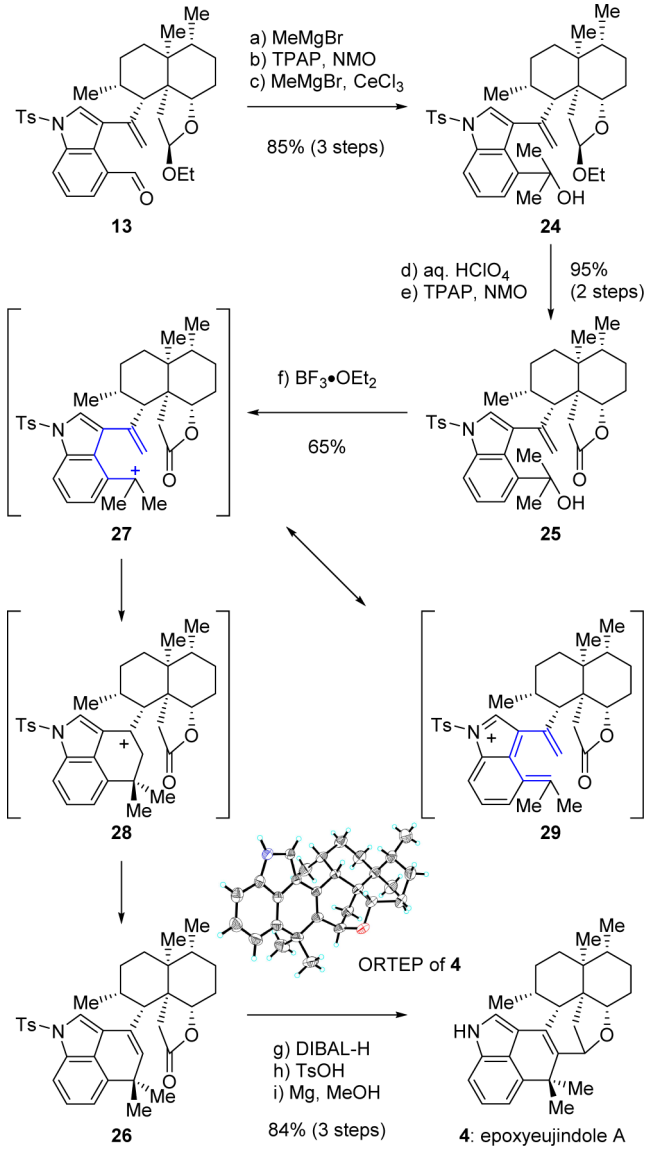


[a]Reagents and conditions: (a) aq. $HClO_4$ (0.50 M), THF, 22 °C, 8 h, 82%; (b) TsOH (1.0 equiv), CH_2Cl_2, 22 °C, 30 min, 76%; (c) BF_3·OEt_2 (2.7 equiv), CH_2Cl_2, 22 °C, 10 min, 72%.

aq. $HClO_4$ (0.50 M) furnished compound **21** (82% yield). The hemiacetal functionality was considered to be more reactive than the aldehyde in the following Prins reaction, because of the ease of oxonium formation. Exposure of **21** to TsOH rapidly afforded the bridged tetracycle **22** in 76% yield, which implies the steric proximity between C20 and C21. The structure of **22** was confirmed by X-ray crystallographic analysis of a racemic sample (Scheme 3). Further activation of the carbonyl of **22** with BF_3·OEt_2 gave a cyclization product (72% yield). However, spectroscopic analysis revealed that it is naphthalene derivative **23** rather than desired product **20**.[17] Although the formation of **23** may proceed through the intermediacy of **20**, we failed to halt the transformation at the stage of the latter, presumably due to the thermodynamic preference to the former. The installation the gem-dimethyl at C20 of the naphthalene scaffold is not straightforward. A tertiary alcohol was prepared from the aldehyde; however, a number of side reactions including dehydration occurred instead of the desired cyclization under acidic conditions.

Having encountered the above problems, we swapped the order of the two cyclizations, as depicted in Scheme 4. Aldehyde **13** was converted to tertiary alcohol **24** through a three-step sequence with good overall efficiency. The second methyl addition had to rely on a Ceric reagent[4b] due to the competitive deprotonation of the methyl ketone substrate. In order to form the A ring prior to the B ring, we transiently protect the acetal as a lactone. Acid hydrolysis followed by TPAP oxidation provided compound **25** in 95% yield for the two steps; the benzylic tertiary hydroxyl was tolerated under these conditions. Exposure of **25** to BF_3·OEt_2 effected a ring closure to give hexacycle **26** in 65% yield. This vinylogous Friedel–Crafts reaction may proceed through a pathway

Scheme 4. Completion of the Synthesis of Epoxyeujindole A[a]



[a]Reagents and conditions: (a) MeMgBr (2.3 equiv), THF, −78 °C, 10 min; (b) TPAP (10 mol %), NMO (6.1 equiv), CH_2Cl_2, 22 °C, 30 min; (c) MeMgBr (4.2 equiv), $CeCl_3$ (5.0 equiv), THF, 0 °C, 30 min, 85% (3 steps); (d) aq. $HClO_4$ (0.50 M), THF, 22 °C, 5 h; (e) TPAP (10 mol %), NMO (3.0 equiv), CH_2Cl_2, 22 °C, 30 min, 95% (2 steps); (f) BF_3·OEt_2 (1.5 equiv), $MeNO_2$, 75 °C, 5 min, 65%; (g) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 °C, 10 min; (h) TsOH (3.0 equiv), CH_2Cl_2, 22 °C, 30 min; (i) Mg (19 equiv), MeOH, 22 °C, 1 h, 84% (3 steps).

illustrated in Scheme 4, via the intermediacy of **27** and **28**. Interestingly, this reaction shares some features with a 6π electrocyclization process, as the postulated cation species **27** can be considered as a triene form (**29**). Thus, the ring closure may take advantage of the strong driving force of electrocyclization.[18,19] Reinstallation of the hemiacetal functionality by DIBAL-H reduction followed by treatment with TsOH built the heptacyclic skeleton of the natural product through a Prins cyclization. Reductive desulfonation with Mg in MeOH afforded epoxyeujindole A (**4**) in 84% yield for the three steps, the structure of which was verified by X-ray crystallographic analysis using a copper target. The spectra and physical

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properties of the synthetic sample are identical with those of the authentic sample. Thus, the synthesis clarifies the absolute configurations of naturally occurring **4**. Notably, we attempted to build the heptacyclic core of **4** directly from **24** through a cascade reaction, which would avoid the unfortunate redox manipulation. However, such endeavors were unsuccessful.

In summary, we have accomplished the first and asymmetric synthesis of epoxyeujindole A, a heptacyclic indole diterpenoid from the anominine family. The key C−C bond formations at an early stage include an enantioselective conjugate addition/alkylation, a Luche cyclization, a Nozaki−Hiyama−Kishi reaction, and a Suzuki−Miyaura coupling. The assembly of the highly substituted A and B rings relies on sequential cationic cyclizations. The synthesis provides an efficient access to epoxyeujindole A and potentially other relevant anominine congeners as well, which may facilitate the biological studies of these structurally intriguing molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09198.

Experimental procedures and compound characterization (PDF)
Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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