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Total Syntheses of Naucleamides A–C and E, Geissoschizine, Geissoschizol, (*E*)-Isositsirikine, and 16-*epi*-(*E*)-Isositsirikine

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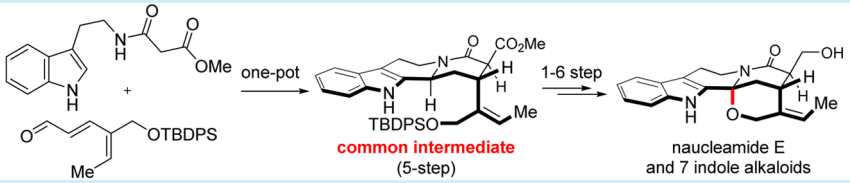
Supporting Information



ABSTRACT: A divergent approach for the enantioselective total synthesis of eight monoterpenoid indole alkaloids was developed. The approach allows the first total syntheses of naucleamides A–C and E in only 6–8 steps and also enables the efficient synthesis of geissoschizine, geissoschizol, (*E*)-isositsirikine, and 16-*epi*-(*E*)-isositsirikine in 10–11 steps from commercially available crotonic aldehyde. The synthesis features a one-pot organocatalyzed asymmetric Michael addition/Pictet–Spengler reaction. Notably, biomimetic synthesis of naucleamide E was achieved by oxidative cyclization of naucleamide A.

The plants of the *Nauclea* species are widely used in folk medicine in the tropical regions of Africa and Asia for treating a variety of illnesses, such as malaria, pain, colds, and fever. To date, more than 60 monoterpene indole alkaloids have been isolated from this genus, and some of them have antiproliferative, antiparasitic, and antimicrobial activities.[1] In 2003, the search for structurally unique constituents from the bark and wood of *Nauclea latifolia* by Kobayashi and co-workers led to the isolation of five novel biogenetically related alkaloids, which were named naucleamides A–E (**1**–**5**, Figure 1).[2] Structurally, **1**–**3** share the common 6/5/6/6 tetracyclic skeleton with the trans H(3)/H(15) configuration. Notably, naucleamide E (**5**) possesses an unprecedented 6/5/6/6/6 pentacyclic ring system with an amino acetal bridge that is rarely encountered in natural product. Biosynthetically, **5** could be formed in vitro through enzymatic selective C–H oxidation of naucleamide A (**1**). Surprisingly, 16-*epi*-naucleamide E (**6**) was not isolated from the same plant, which could be theoretically derived from enzymatic oxidation of naucleamide B (**2**). In addition, naucleamides A–E were isolated from nature in only 0.8–1.6 mg. The scarce availability from natural sources has limited their medicinal evaluation. Moreover, no total synthesis of any of these specific compounds has been reported to date.[3]

Geissoschizine (**7**) and a number of congeners (**8**–**10**) also have a common 6/5/6/6 tetracyclic skeleton with the cis H(3)/H(15) configuration but are related by N(4)–C(22) bond opening, ring chain tautomerization, and N(4)–C(21) bond formation to naucleamides **1**–**5** (Figure 1).[4−8] Importantly, **7**, isolated from a variety of plant species, occupies a unique place among alkaloids by serving as the early biogenetic precursor to

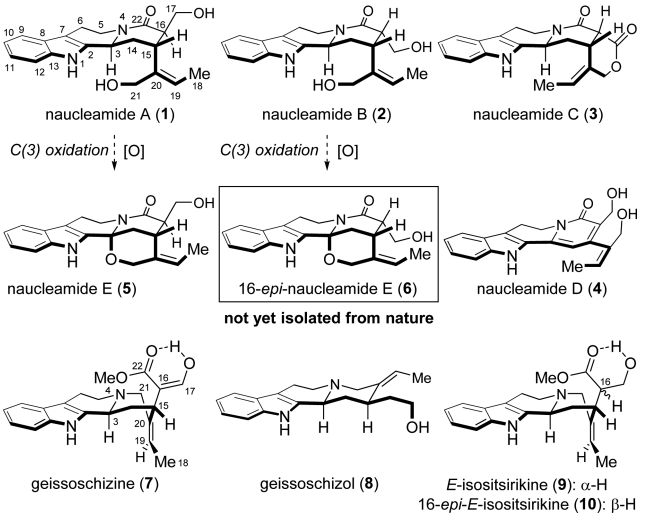


Figure 1. Structures of the monoterpenoid indole alkaloids.

virtually all other families of monoterpenoid indole alkaloids. Although numerous total syntheses of geissoschizine have been reported,[6] only the groups of Winterfeldt, Overman, Martin, and Cook have achieved the asymmetric synthesis.[7] The catalytic asymmetric synthesis of 7 has not yet been reported.

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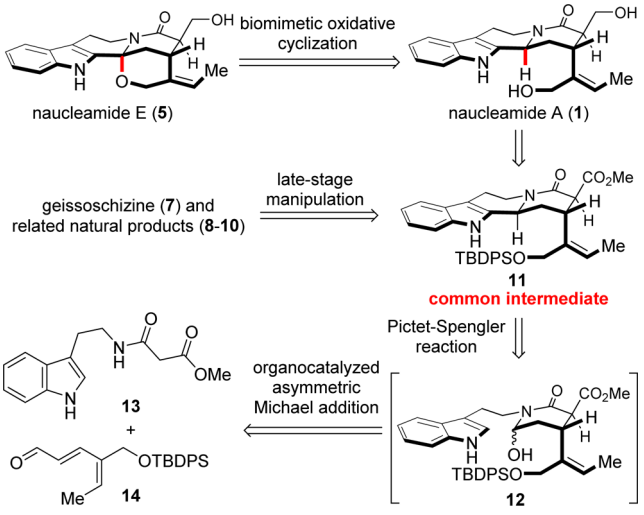
We sought to develop a novel asymmetric approach to these alkaloids based on the nature-inspired divergent concept.[9−11] More importantly, inspired by the biogenetic relationship between **1** and **5**, we envisioned that **5** could be obtained from **1** through a final-stage biomimetic selective C−H oxidation strategy. As C−H oxidative coupling can directly construct carbon−carbon and carbon−heteroatom bonds in a single step without prefunctionalization, it has been a powerful strategy in the total syntheses of natural products in recent years.[12−14] Despite these advances, the synthesis of such a bridged-ring system through direct C−H oxidation of *N*-carbamoyl derivatives has rarely been reported.[15] In addition, the non-enzymatic oxidation of unprotected **1** is more challenging due to the sensitivity of the electron-rich indole to oxidation, the site-selectivity between C(3) and C(6), as well as the difficulty in accessing the amino acetal bridged-ring versus β-hydrogen elimination to form naucleamide D (**4**). Here, we report the efficient and divergent total syntheses of naucleamides A−C (**1**−**3**) and E (**5**), geissoschizine (**7**), geissoschizol (**8**), (*E*)-isositsirikine (**9**), and 16-*epi*-(*E*)-isositsirikine (**10**) in only 6−11 steps. In these syntheses, the challenging stereochemical problems of the relative and absolute configuration at C(3) and C(15) were effectively controlled.[9,16] Among them, the total syntheses of target molecules **1**−**3** and **5** were achieved for the first time. The total synthesis of naucleamide E was achieved via biomimetic oxidative cyclization of **1**.

Retrosynthetically, we envisioned **1**−**3**, **5**−**10**, and other related indole alkaloids could be prepared from the common intermediate **11** by late-stage manipulation (Scheme 1).

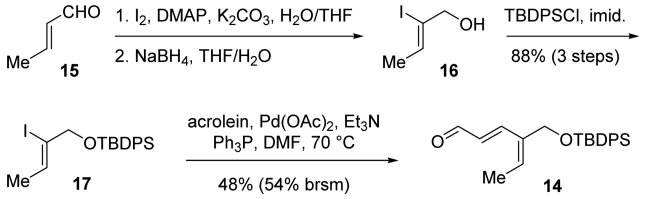
Scheme 1. Retrosynthetic Analysis



Naucleamide E could be prepared from **1** by a final-stage selective C−H oxidation.[17−19] In turn, the tetracyclic indole **11** with all carbon and functional groups might be convergently prepared from the known amidomalonate **13** and 2,4-dienal **14** via organocatalyzed asymmetric Michael addition followed by a Pictet−Spengler reaction.[20,21] Although the catalytic asymmetric conjugate addition of amidomalonates to cinnamic aldehyde derivatives has been independently developed by Franzen's and Rios' groups, 2,4-dienal has never been employed in such a reaction. Several challenging issues have to be addressed. First, 2,4-dienal was usually employed as nucleophile but not electrophile.[22,23] Second, the competition between 1,4- versus 1,2-addition and 1,6-addition of the first nucleophilic attack is crucial.

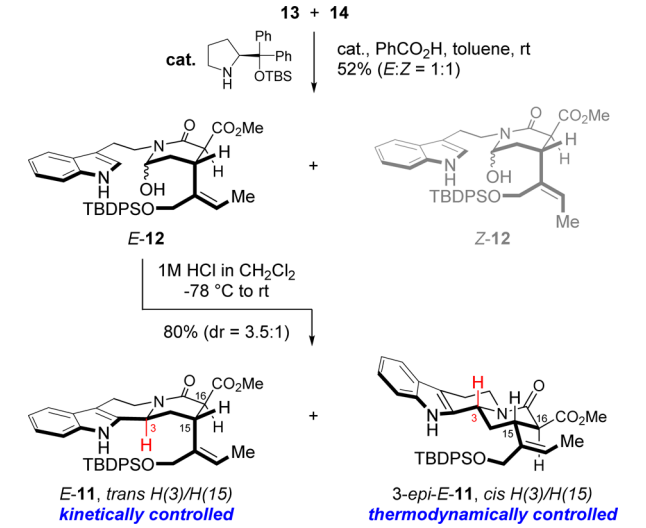
2,4-Dienal **14** was not reported before, so we devised a short route for its synthesis from the known alcohol **16**, which could be readily prepared from commercially available crotonic aldehyde **15** by iodination and reduction (Scheme 2).[24] Protection of alcohol **16** with TBDPSCl gave product **17**. Heck reaction of vinyl iodide **17** and acrolein afforded the desired 2,4-dienal **14**.

Scheme 2. Four-Step Synthesis of 2,4-Dienal 14



With the dienal **14** in hand, the organocatalyzed asymmetric Michael addition between **13** and **14** was investigated (Scheme 3). Initial attempts under Franzen's and Rios' optimized reaction

Scheme 3. Concise Synthesis of Intermediate 11



conditions revealed that no reaction occurred. Gratifyingly, when the reaction was run in toluene at 40 °C for 8 days, the desired hemiaminal (*E*)-**12** accompanied by unexpected (*Z*)-**12** was obtained in 8% yield in a 1:1 ratio. Following extensive reaction optimization (catalyst, additive, solvent, temperature; for detailed information, see Supporting Information), we finally found that the addition of an acid additive is essential for high yields, and benzoic acid was the best. Under the optimized reaction conditions, **12** could be obtained in 52% yield (*E*/*Z* = 1:1), which could be readily separated by flash column chromatography.

The acid-catalyzed cyclization of **12** was then investigated (Scheme 3). Inspired by the elegant studies by Sarpong group during their synthesis of the yohimbinoid alkaloids,[16a] we found that treatment of (*E*)-**12** with HCl in Et_2O at −78 °C afforded (*E*)-**11** and 3-*epi*-(*E*)-**11** in 80% yield (dr 3.5:1), in favor of our desired product (*E*)-**11**. Both (*E*)-**11** and 3-*epi*-(*E*)-**11** were subjected to the aforementioned acid-catalyzed cyclization conditions. However, the interconversion of (*E*)-**11** and 3-*epi*-(*E*)-**11** was not observed. These results indicated that (*E*)-**11** is a

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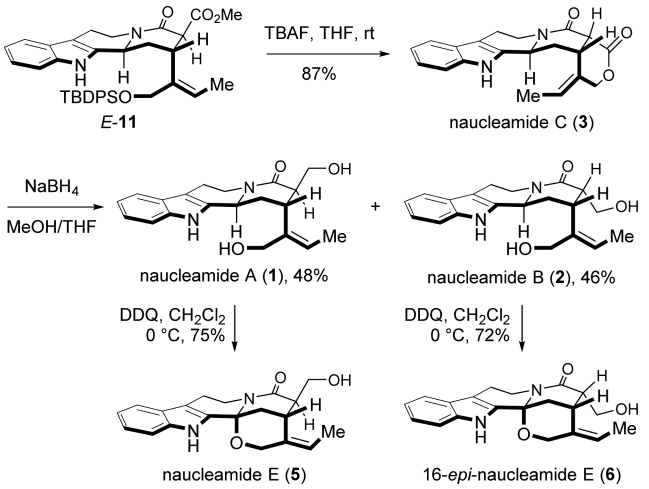
kinetically controlled product and 3-*epi*-(*E*)-**11** is a thermodynamically controlled product, and this process was determined by a transition state.[20] The enantioselectivity of (*E*)-**11** could be easily determined at this stage, with an enantiomeric excess value of 96% (see Supporting Information). The stereochemistry at C-16 is assigned by following the literature reported by the group of Franzén,[20b] and the H−H coupling constants between H-15 and H-16 (for (*E*)-**11**, J = 11.6 Hz; for 3-*epi*-(*E*)-**11**, J = 12.4 Hz). It is worthy to note that the conjugate addition and the acid-catalyzed cyclization could be performed in a one-pot process with the same diastereoselectivity. Thus, we have successfully established a five-step route to **11**, which needed only three flash column chromatography purifications.

With the tetracyclic intermediate **11** in hand, we turned our attention to the synthesis of **1**−**3** and **5** (Scheme 4). Thus,

Scheme 4. Synthesis of Naucleamides A−C (1−3) and E (5)

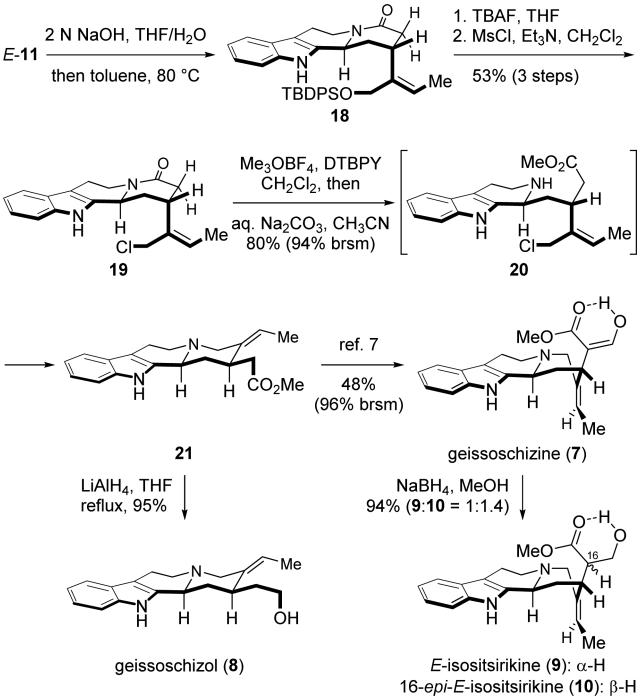


deprotection of the TBDPS group of compound (*E*)-**11** with anhydrous TBAF in THF accompanied by spontaneous cyclization furnished **3** in 87% yield.[2] We observed that the solubility of **3** was not very good in CD_3OD. When recorded in DMSO-d_6, the NMR spectra of **3** indicated the presence of a keto-form at C(16) instead of an enol-form reported in literature.[2] Reduction of lactone **3** with $NaBH_4$ in MeOH and THF gave **1** and **2** in 48 and 46% yield, respectively.[2]

With **1** in hand, we performed the direct conversion of **1** to **5** through a selective C−H oxidation (Scheme 4). The initial attempt to oxidation of **1** with iodine failed to give the desired product **5**.[17] Oxidation of **1** with iodosobenzene diacetate yielded complex product, and no desired product was obtained.[18] Aerobic oxidation of **1** was further investigated.[19] However, no reaction occurred. This result also proved that **5** is not an artificial product in the laboratory. Oxidation of **1** with DDQ proceeded smoothly and successfully afforded **5** in 75% yield.[2S] Interestingly, oxidation of **2** with DDQ readily yielded **6** in 72% yield, which has not been isolated from nature. Thus, we have achieved the first total synthesis of **1**−**3** and **5**, which required only 6−8 steps from commercially available crotonic aldehyde **15**. The first asymmetric total syntheses of these four alkaloids demonstrated that our strategy offered an efficient route to a broad range of indole alkaloids.

We next turned to the synthesis of **7**, **8**, and **9** and **10** (Scheme 5).[4−8] Removal of the methyl ester followed by deprotection of the silicon group on (*E*)-**11** yielded the corresponding alcohol, which was subsequently treated with MsCl and Et_3N to provide

Scheme 5. Syntheses of Geissoschizine, Geissoschizol, (*E*)-Isositsirikine, and 16-*epi*-(*E*)-Isositsirikine



the allylic chloride **19** in 53% yield over three steps. At this stage, methanolysis of amide **19** via the corresponding imidate salts successfully afforded amino ester **20** in good yield, which was prone to cyclization to generate the known deformyl geissoschizine **21** in 80% yield, together with 15% of the starting lactam **19**.[7] Finally, according to the protocol reported in the literature, compound **21** was readily converted to **7**,[7] **8**,[7d] **9**, and **10**.[8] Thus, we have achieved the catalytic asymmetric syntheses of **7**−**10** for the first time, and our total syntheses of these natural products required only 10−11 steps from **15**.

In summary, we have developed a unified strategy for the enantioselective synthesis of monoterpene indole alkaloids. The pivotal common intermediate (*E*)-**11** was synthesized in only five steps from commercially available **15**, which featured a one-pot organocatalyzed asymmetric Michael addition/Pictet−Spengler reaction. The approach allows the first total syntheses of naucleamide A (7 steps, 3.2% overall yield), naucleamide B (7 steps, 3.0% overall yield), naucleamide C (6 steps, 6.6% overall yield), and naucleamide E (8 steps, 2.4% overall yield), as well as the catalytic asymmetric total syntheses of geissoschizine (10 steps, 3.5% overall yield), geissoschizol (10 steps, 3.5% overall yield), (*E*)-isositsirikine (11 steps, 1.4% overall yield), and 16-*epi*-(*E*)-isositsirikine (11 steps, 1.9% overall yield). Notably, the total synthesis of **5** was achieved by a final-stage biomimetic selective C−H oxidation strategy. The synthesis and biological studies of the other members of the related indole alkaloids and analogues are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00983.

Full experimental procedures and ^1H and ^{13}C NMR spectra of compounds **1**−**3**, **5**−**12**, **14**, and **17**−**21** (PDF)

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Notes

The authors declare no competing financial interest.

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