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Asymmetric Total Synthesis of Neoxaline

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Supporting Information

ABSTRACT: A first asymmetric total synthesis and determination of the absolute configuration of neoxaline has been accomplished through the highly stereoselective introduction of a reverse prenyl group to create a quaternary carbon stereocenter using (−)-3a-hydroxyfuroindoline as a building block, construction of the indoline spiroaminal via cautious stepwise oxidations with cyclizations from the indoline, assembly of (*Z*)-dehydrohistidine, and photoisomerization of unnatural (*Z*)-neoxaline to the natural (*E*)-neoxaline as the key steps.

Oxaline (**1**) is a member of a novel class of biologically active prenylated indole alkaloids possessing a unique indoline spiroaminal framework, notably containing a 1,1-dimethylallyl ("reverse prenyl") group at the benzylic ring junction and an (*E*)-dehydrohistidine moiety (Figure 1).[1]

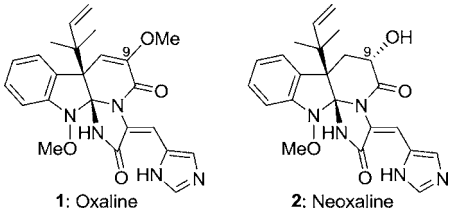
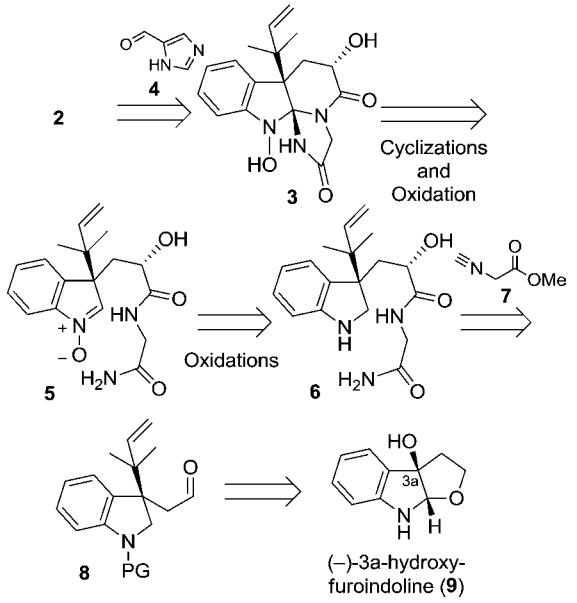


Figure 1. Oxaline family.

Because of their intriguing structures, the biosynthesis of the oxaline family has attracted significant study.[2] Typically, oxaline families have been isolated from *Penicillium* spp.[1,3] and found to exhibit moderate antibacterial, antifungal, and anticancer activities. In 1979, we reported the isolation of neoxaline (**2**) from a culture broth of *Aspergillus japonicus* Fg-551,[4] which is still the only example produced from an organism other than *Penicillium* spp. The absolute configuration of **2** was predicted by comparison to other oxaline family members of known absolute stereochemistry. Interestingly neoxaline inhibits cell proliferation and arrests the cell cycle during the M phase but does not exhibit antibacterial or antifungal activities.[5] Therefore, we embarked on a project to synthesize neoxaline and reported the construction of the indoline spiroaminal framework in 2005.[6] Although the oxaline family is an attractive synthetic target, no total synthesis of this family has been disclosed to date. Herein we report the first asymmetric total synthesis of **2** and the determination of its absolute configuration.

Our retrosynthetic analysis is described in Scheme 1. Neoxaline was envisioned to arise via an aldol reaction of

Scheme 1. Retrosynthetic Analysis of Neoxaline (2)



indoline spiroaminal **3** with aldehyde **4** followed by an elimination reaction to construct the dehydrohistidine. The indoline spiroaminal framework could be constructed through careful stepwise oxidations and cyclizations from indoline **6**, which was envisioned to arise via addition of isocyanoacetate **7** to aldehyde **8**. We previously reported the concise asymmetric synthesis of (−)-3a-hydroxyfuroindoline (**9**), and its applications in natural product synthesis were also reported by us[7] and other groups.[8] In the synthesis of physovenine (an acetylcholinesterase inhibitor), we reported that the radical allylation of the xanthate ester prepared from **9** took place from the convex face to the tetrahydrofuran moiety.[7c] Therefore, we expected the reverse prenyl group would be introduced in a stereoselective manner from **9**, with the leaving group at the C3a position.

Optically active **9** was prepared from commercially available tryptophol **10** under modified Katsuki−Sharpless asymmetric epoxidation conditions (Scheme 2).[7a] The protecting group of

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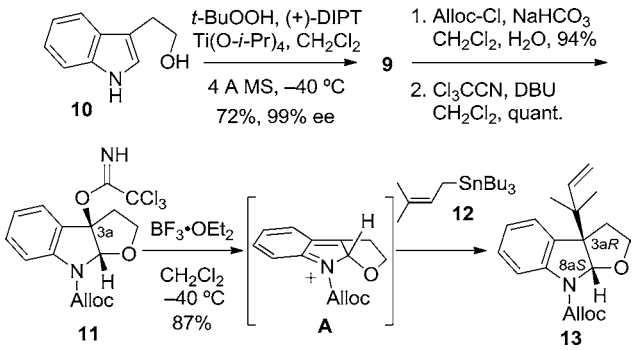
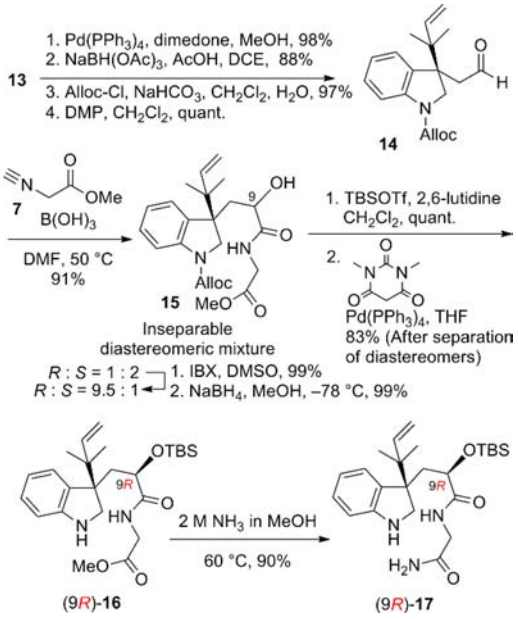
Scheme 2. Stereoselective Introduction of the Reverse Prenyl Group at the Benzylic Ring Junction



the secondary amine and the leaving group at the C3a position were required for the key allylation. We found via screening of substituents that allyloxycarbonyl (Alloc) and trichloroacetimidate were appropriate protective and leaving groups, respectively. After imidate **11** was obtained from **10**, the allylation took place via the expected intermediate **A** to give the (3a*R*,8a*S*)-**13** as a single diastereomer by treatment of **11** with prenyl tributylstannane (**12**) in the presence of $BF_3{\cdot}OEt_2$ at −40 °C. The stereochemistry was confirmed by nuclear Overhauser effect (NOE) spectroscopy and comparison with a known compound.[7c,9]

The cyclization precursor **17**, which has three nitrogen atoms at the appropriate positions, was synthesized as described in Scheme 3. For construction of the α-hydroxyamide moiety, we

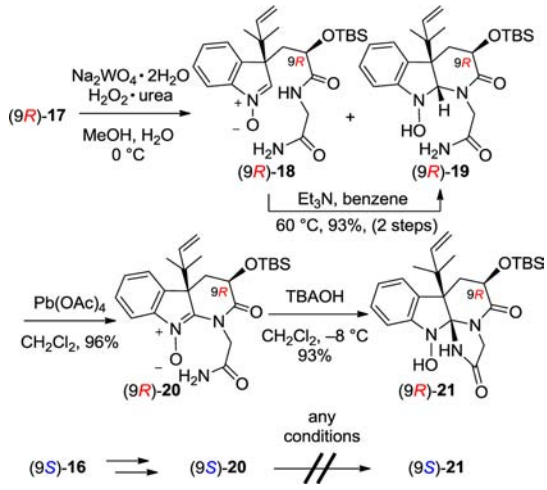
Scheme 3. Preparation of Cyclization Precursor 17



attempted to open the tetrahydrofuran ring of **13**. However, the tetrahydrofuran ring could not be opened without removing the amine protecting group. After removal of the Alloc group, reductive ring opening of the tetrahydrofuran was accomplished with $NaBH(OAc)_3$ under acidic conditions. The resulting secondary amine was reprotected with an Alloc group, and the hydroxyl group was oxidized to give the corresponding aldehyde **14** under Dess−Martin oxidation conditions.[10] Boric acid-mediated addition[11] of isocyanoacetate **7** to **14** afforded α-hydroxyamide **15** as an inseparable diastereomeric mixture (9*R*:9*S* = 1:2)[12] in excellent yield. As described later, the major isomer (9*S*)-**15** could not be converted to the corresponding indoline spiroaminal. The diastereomeric ratio of **15** could be changed to 9*R*:9*S* = 9.5:1 by oxidation of the hydroxyl group to the ketone followed by a reduction process. α-Hydroxyamide **15** could be separated from the mixture by silica gel column chromatography after conversion to the indolines (9*R*)-**16** and (9*S*)-**16** via *tert*-butyldimethylsilyl (TBS) protection of the hydroxyl group and subsequent removal of the Alloc group. Treatment of the resulting diastereomer (9*R*)-**16** with 2 M NH_3 in methanol at 60 °C afforded amide (9*R*)-**17**.

With the cyclization precursor in hand, we attempted to construct the indoline spiroaminal framework (Scheme 4).

Scheme 4. Construction of Indoline Spiroaminal (9*R*)-21



Oxidation of (9*R*)-**17** with $H_2O_2{\cdot}$urea in the presence of $NaWO_4{\cdot}2H_2O$[13] provided nitrone (9*R*)-**18** and diaminal (9*R*)-**19**. The crude mixture of (9*R*)-**18** and (9*R*)-**19** was treated with Et_3N in benzene at 60 °C to convert (9*R*)-**18** to (9*R*)-**19**, affording (9*R*)-**19** in excellent yield. The cyclic diaminal (9*R*)-**19** was oxidized with $Pb(OAc)_4$ to afford the *N*-oxoamidine (9*R*)-**20**. After screening of several sets of basic conditions for the cyclization of nitrone (9*R*)-**20**, we found that tetra-*n*-butylammonium hydroxide (TBAOH) was the most efficient reagent for generation of indoline spiroaminal (9*R*)-**21** in excellent yield as a single diastereomer. The nitrone (9*S*)-**20**, which was prepared from (9*S*)-**16** in a manner similar to that for the 9*R* isomer,[14] was not cyclized under any conditions.

Successful or unsuccessful cyclization was expected because of the conformational difference in cyclic nitrones (9*R*)-**20** and (9*S*)-**20** (Figure 2). In the case of the 9*R* isomer, the terminal amide could be accessed by the nitrone carbon on the upper face to provide the desired indoline spiroaminal (9*R*)-**21**. However, the amide group in nitrone (9*S*)-**20** is located under

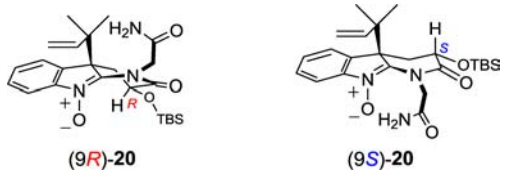


Figure 2. Predicted conformations of *N*-oxoamidine **20**.

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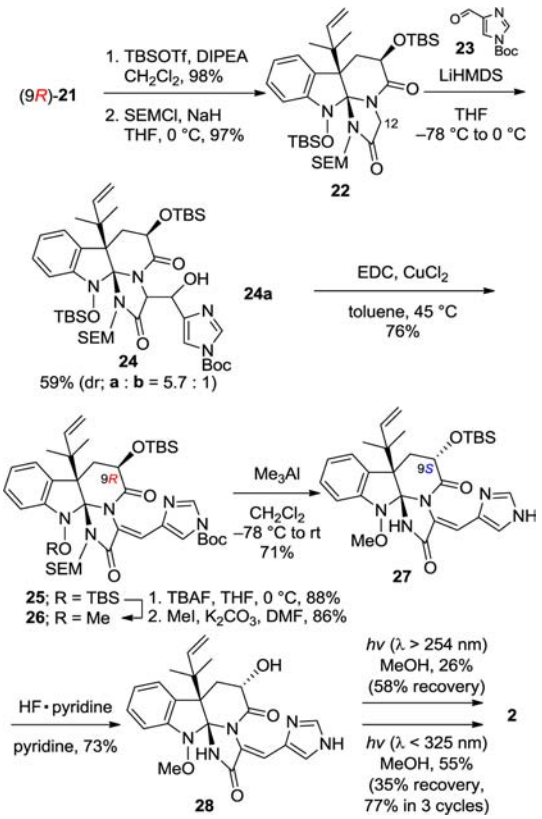
the nitrone face as a result of loss of steric repulsion between the reverse prenyl group and the TBS group and originally seemed more unlikely to assemble an indoline spiroaminal framework.

With the core framework assembled, the final issue was the introduction of the conjugated imidazole at C12 (Scheme 5).

Scheme 5. Total Synthesis of Neoxaline (2)



Selective methylation of the hydroxyl group resulted in low yield because of undesired methylation of the amide.[6] Therefore, the hydroxyl group and amide needed to be protected by TBS and 2-(trimethylsilyl)ethoxymethyl (SEM) groups, respectively,[15] to configure the desired enolate for the aldol reaction. The aldol reaction with **22** and imidazolyl aldehyde **23**[16] proceeded smoothly to give **24a** together with a minor diastereomer **24b** (**a**:**b** = 5.7:1), which could be separated by silica gel column chromatography. The elimination reaction of **24a** under Sai's conditions[17] provided (*Z*)-dehydrohistidine **25** as a single isomer in good yield. All attempts to obtain the (*E*)-dehydrohistidine from **24a** or **24b** failed. Therefore, we presumed that the olefin geometry could be isomerized by photoirradiation at a late stage of the synthesis. Selective deprotection of the *N*-hydroxide by TBAF followed by methylation provided methoxide **26**. Removal of all of the protecting groups generated **28**, the geometrical isomer of neoxaline, in two steps. Fortunately, in the treatment with Me_3Al to remove the SEM and Boc groups, the C9 stereogenic center was completely epimerized to the *S* configuration.[18] Scott and co-workers reported the isomerization of (*E*)-roquefortine by UV irradiation at 330 nm to provide the thermodynamically stable (*Z*)-roquefortine.[19] The photoisomerization of unnatural (*Z*)-neoxaline (**28**) upon mercury lamp irradiation (λ > 254 nm) provided natural (*E*)-neoxaline (**2**) in unsatisfactory yield (26% with 58% recovery of the *Z* isomer **28**). In the course of studying the isomerization, we found that the geometric isomers of neoxaline were at equilibrium under the photoirradiation conditions. Thus, to improve the efficiency of the isomerization, we attempted selective excitation of the unnatural *Z* isomer **28**. Since the maximum absorption wavelengths of the *Z* and *E* isomers were 314 and 330 nm, respectively, a short-pass filter that blocked light with λ > 325 nm was applied. As a result, the desired isomerization was efficiently induced, affording natural (*E*)-**2** in good yield (55% with 35% recovery of *Z* isomer **28**; 77% in three cycles).

All of the spectra data (^{1}H NMR, ^{13}C NMR, mass, IR) of synthetic **2** were identical with those of naturally occurring neoxaline (**2**).[14] However, the optical rotation could not be compared because of its flexible value in $CHCl_3$. We eventually determined that the optical rotation of synthetic **2** {$[\alpha]_D^{24}$ = +78.7 (*c* = 0.02, 1.0% $CH_3COOH/CHCl_3$)} and naturally occurring **2** {$[\alpha]_D^{26}$ = +78.3 (*c* = 0.02, 1.0% $CH_3COOH/CHCl_3$)} matched, as did both LC-CD spectra.[14] Therefore, the absolute configuration was determined.

In conclusion, we have reported the first asymmetric total synthesis of neoxaline (**2**) through the highly stereoselective introduction of a reverse prenyl group to create the quaternary carbon stereocenter, the construction of the indoline spiroaminal via three oxidations and two cyclizations from indoline (9*R*)-**17**, and photoisomerization of unnatural (*Z*)-neoxalilne (**28**) to natural (*E*)-neoxaline (**2**) as the crucial steps. This approach can facilitate the large-scale synthesis of **2**. Indeed, to date we have prepared more than 100 mg of **28**. Considering the highly scalable synthesis of **2** and the construction of the dehydrohistidine at the late stage, this synthesis could be applied to the preparation of neoxaline analogues, including related natural products. Total syntheses of the members of the neoxaline family and investigations of their structure–activity relationships are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Imidate **11** was treated with allyl tributylstannane instead of **12** to introduce an allyl group at C3a. Subsequently, removal of the Alloc group and protection of resulting secondary amine with a Cbz group afforded the known intermediate of physovenine.[7c]

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(12) (a) The carbons of **15** are numbered as in neoxaline. (b) After conversion toward amide **17** from **15**, the stereochemistry at C9 was confirmed by comparison with the compound derived from the stereochemically defined known material.[6,14] The NOE spectrum of **26** supported the C9 stereochemistry.[18]

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(18) The stereochemistry at C9 was confirmed by the NOE spectrum of **26** and the transformation of **27** toward (9*S*)-**26** via reprotection of two nitrogens.

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