Natural Product Synthesis

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2-Thioindoles as Precursors to Spiro-Fused Indolines: Synthesis of (±)-Dehaloperophoramidine**

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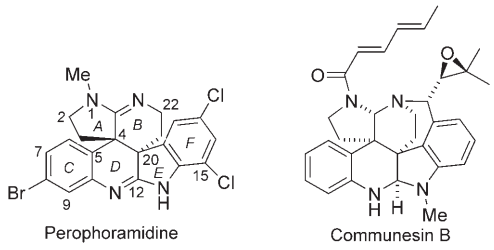
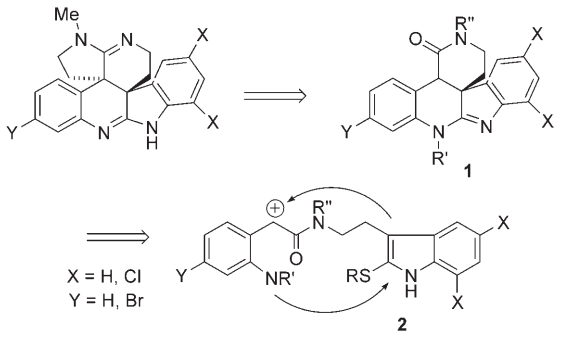
A large number of complex indole- and indoline-containing alkaloids have been isolated from the marine environment over the past decade.[1] Among these compounds is perophoramidine, which was isolated from the colonial ascidian *Perophora namei* by Ireland and co-workers.[2] The hexacyclic bisamidine skeleton of perophoramidine (see Scheme 1), which contains vicinal quaternary centers, was established with the help of extensive 2D NMR experiments and was later validated by the total synthesis developed by Fuchs and Funk.[3] Preliminary biological data indicated that perophoramidine is cytotoxic to HMT 116 colon carcinoma cells and is able to induce apoptosis by poly(adenosine-5′-diphosphate-ribose)polymerase (PARP) cleavage.[4]



Scheme 1. Structures of perophoramidine and communesin B.

Our interest in the synthetic chemistry of 2-thioindoles,[5–7] combined with the novel structural features of perophoramidine and its preliminary biological data, induced us to initiate a program to target its synthesis. Described herein are our preliminary results in this area and the synthesis of (±)-dehaloperophoramidine.

We considered several synthetic routes to the perophoramidine skeleton, but ultimately settled upon the approach illustrated in Scheme 2.[8] We envisioned that the intramolecular coupling between the 3-position of a 2-thioindole with a pendant electrophile would serve to generate one of the perophoramidine spiro-fused rings; the resulting thioimidate

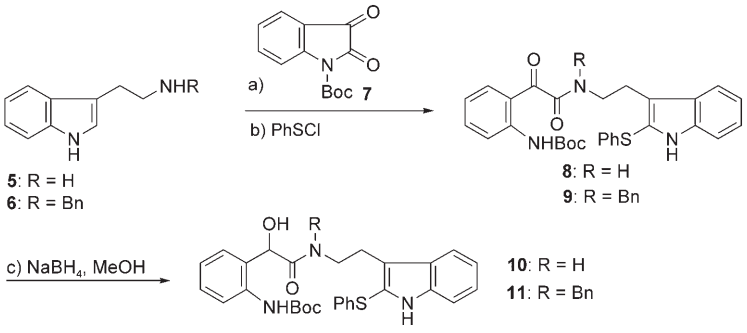


Scheme 2. Retrosynthetic analysis of perophoramidine.

would be nicely set up to undergo a subsequent cyclization with the pendant amine. The result of this cascade would be the generation of two rings, five of perophoramidine's six rings, and **1**. Incorporation of the remaining quaternary center and the A ring would provide perophoramidine. If successful, we were confident that the strategy outlined in Scheme 2 would not only enable us to efficiently synthesize perophoramidine but would also allow us to target other members of this family (namely, communesin B)[9] along with analogues for biological evaluation.

Clearly, the success of the strategy outlined in Scheme 2 depended upon the nucleophilicity of 2-thioindoles. As an indication of their reactivity, we had previously demonstrated that 2-thioindoles undergo "interrupted" Pictet–Spengler cyclizations to spiro-fused indolines (namely, **4**) when treated with the appropriate aldehyde in the presence of 4-Å molecular sieves (MS) at room temperature [Eq. (1)].[10] It is noteworthy that these conditions are milder than those used for related reactions of indoles that lack the thioether at the 2-position.[11]

With this in mind, we set out to investigate whether reactions related to that outlined in Equation (1) could be carried out to generate the dehaloperophoramidine skeleton. The synthesis of the requisite cyclization precursor is illustrated in Scheme 3. The coupling of tryptamine or benzyl-



Scheme 3. Synthesis of cyclization precursors **10** and **11**: a) *N*-Boc-isatin (**7**), THF, RT, 7 h (70%); b) PhSCl, CH_2Cl_2, 0°C→RT, 12 h (97%); c) $NaBH_4$, MeOH, 0°C, 0.5 h.

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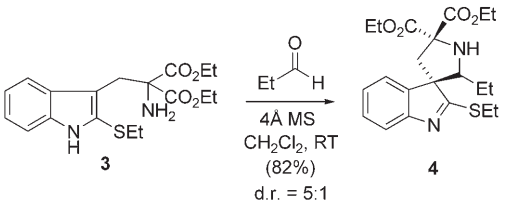
protected tryptamine with *N-tert*-butyloxycarbonyl (*N*-Boc)-protected isatin followed by thioether incorporation and reduction with $NaBH_4$ provided cyclization precursors **10** and **11**, respectively.[12]

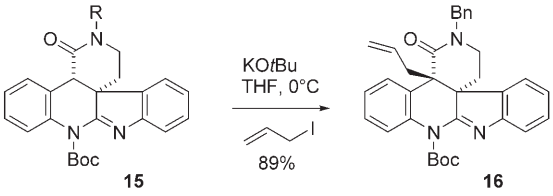


(1)

With a facile route to their synthesis in hand, we were prepared to examine the ability of **10** and **11** to undergo the key cyclization reaction. As a further indication of the nucleophilicity of 2-thioindoles, the desired cyclization occurred under the conditions used for the generation of the mesylate from **11** to give spirocycle **13** as a 1:1 mixture of C4 diastereomers. In contrast to the results with **11**, unprotected amide **10** did not undergo the desired cyclization but instead underwent competitive decomposition upon extended exposure to the reaction conditions. Presumably, this latter result is due to the inability of **10** to overcome the propensity of the amide to exist as its *s-trans* rotamer.[13]

The fact that **13** existed as a mixture of C4 diastereomers was inconsequential; treatment of the mixture with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to equilibration at C4, and only one of the two diastereomers underwent a subsequent cyclization to give the C12 amidine **15** in 79% overall yield from **9**. Following optimization studies, we found it best to carry out both transformations in a single flask by concentrating the reaction mixture containing **13**, dissolving the resulting residue in CH_2Cl_2, and subjecting the resulting solution to DBU (Scheme 4).

With pentacycle **15** in hand, we examined the generation of the C4 quaternary center as a precursor to the A ring [Eq. (2)]. To achieve this goal, we ultimately settled upon an N,O-ketene acetal allylation reaction similar to that employed by Artman and Weinreb in their perophoramidine studies;[14] although they had used NaH, we found it best to employ KO*t*Bu as the base. Quenching the resulting ketene acetal with allyl iodide led to **16** as a single diastereomer in 89% yield.



(2)

Pentacycle **16** proved to be amenable to single-crystal X-ray analysis, thus firmly establishing that the reaction of **15** had resulted in the desired C4 and C20 diastereomer needed for the synthesis of perophoramidine (Figure 1).

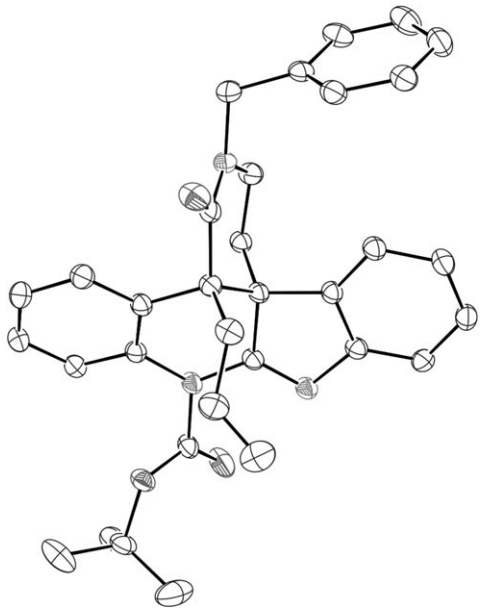
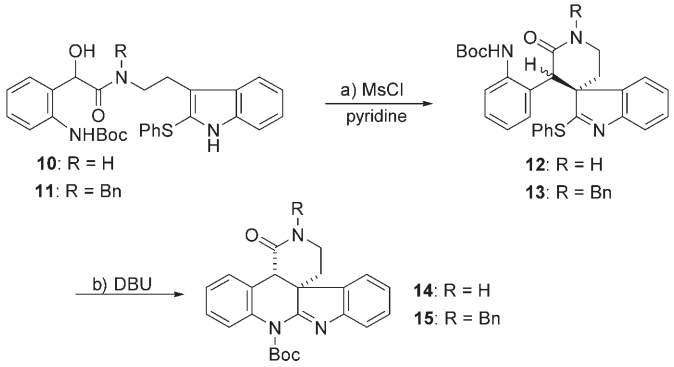


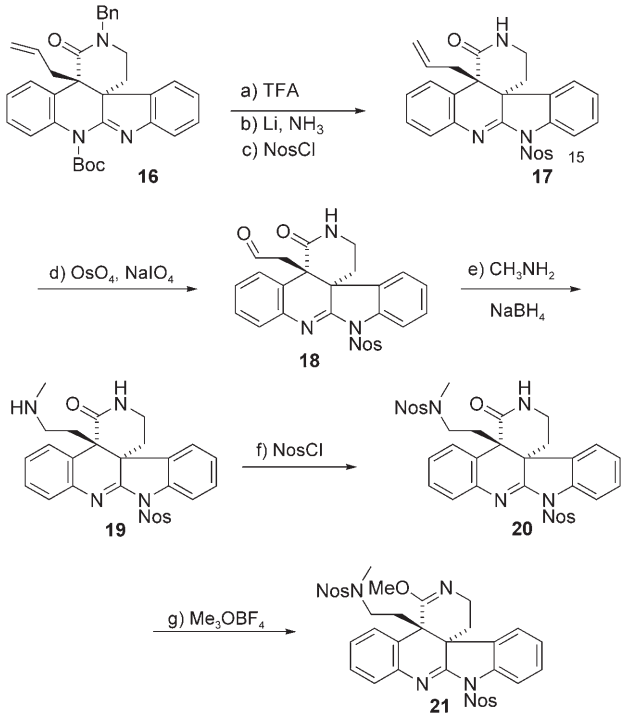
Figure 1. ORTEP drawing of **16** from X-ray crystallographic analysis.

With ready access to **16**, all that remained to complete the synthesis of dehaloperophoramidine was the generation of the A ring (Scheme 1). We anticipated accomplishing this aim by converting the olefin in **16** into the corresponding amine, activating the lactam, and carrying out the requisite cyclization reaction to the C24 amidine. To accomplish these goals, we first needed to remove the benzyl group on the lactam. Although **16** decomposed when subjected to dissolving-metal conditions, we were able to affect the removal of the benzyl group when the N11 Boc group was absent. Thus, removal of the Boc group from **16** and subjecting the resulting compound to dissolving-metal conditions gave **17** after the selective formation of the *o*-nitrobenzensulfonyl (nosyl)-protected amidine. Interestingly, as evidenced by the downfield shift of the C15 proton in **17** relative to **16**, this latter reaction resulted in the selective formation of the N13 nosyl derivative. Oxidative cleavage of the alkene and reductive amination gave **19**. Conversion of the secondary amine into the



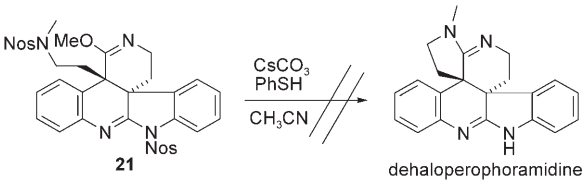
Scheme 4. Cyclization to the perophoramidine pentacycle: a) MsCl, pyridine, 0°C, 4 h; b) DBU, CH_2Cl_2, 0°C→RT (R = Bn: 79%, 3 steps; R = H: 0%). Ms = methanesulfonyl chloride.

corresponding nosyl derivative gave **21** after activation of the lactam through its conversion into the corresponding methyl imidate (Scheme 5).



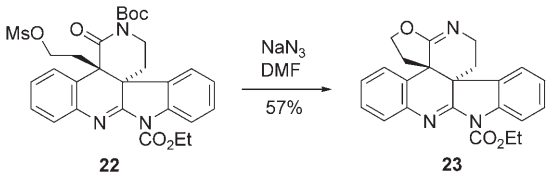
Scheme 5. Generation of the perophoramidine A-ring precursor: a) TFA, 0 °C→RT, 12 h; b) Li, NH_3, THF, −78 °C, 10 min; c) Boc_2O, NEt_3, THF, 0 °C→RT, 8 h (69 %, 3 steps); d) OsO_4, $NaIO_4$, NaOAc, THF, H_2O, 0 °C, 3 h; e) CH_3NH_2·HCl, NaOAc, MeOH, RT, 7 h; $NaBH_4$, 0 °C, 1 h; f) NosCl, NEt_3, THF, 0 °C→RT, 12 h (42 %, 3 steps); g) Me_3OBF_4, iPr_2NEt, CH_2Cl_2, 0 °C, 1 h (44 %). Nos = nosyl.

In the last critical transformation to dehaloperophoramidine, attempts to form the A ring under the conditions developed by Fuchs and Funk were completely unsuccessful in our hands.[15] As an indication of its lack of reactivity, we also were unable to convert the methyl imidate (or the corresponding imido triflate) in **21** into the corresponding amidine [Eq. (3)] through its intermolecular coupling with methyl amine or ammonia.



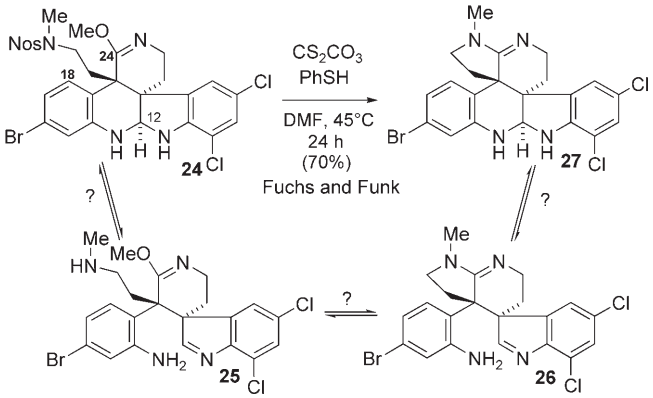
(3)

Interestingly, when we attempted to generate the azido substrate that corresponded to **22** as a precursor to a C24 amidine from an aza-Wittig reaction, we isolated *O*-alkylated adduct **23** [Eq. (4)]. Our attempts to use a similar reaction to form an acyclic amidine were unsuccessful as a result of our aforementioned inability to generate the requisite acyclic amidine precursor.



(4)

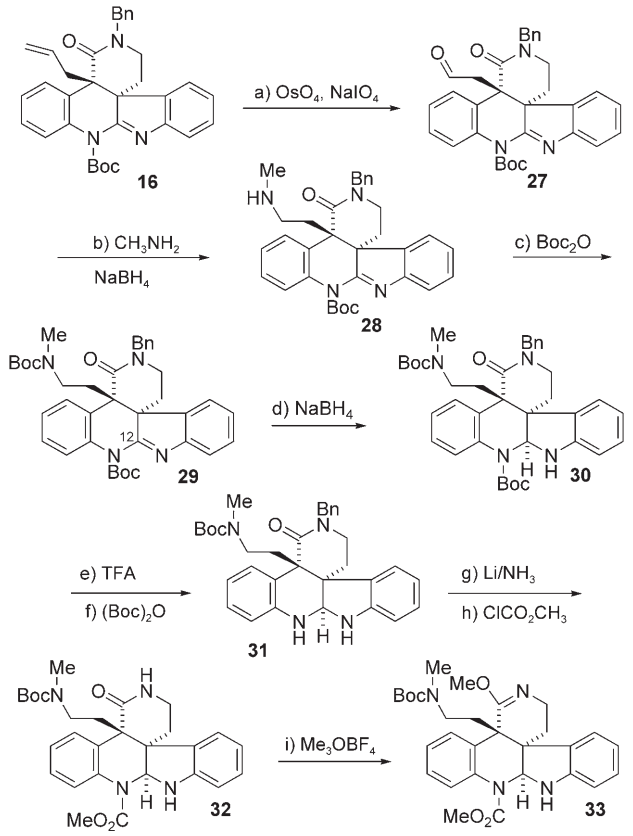
The significant difference between the successful substrate prepared by Fuchs and Funk (namely, **24**) and ours was the oxidation state of C12; they had employed a C12 aminal to our amidine. As we believe steric congestion at C24 to be the problem with imidate **21**, we suspected that the success of Fuchs and Funk with **24** might be related to its ability to undergo a reversible ring-opening reaction to temporarily relieve some of the congestion about C24 in the course of its conversion into **27** (Scheme 6).[16]



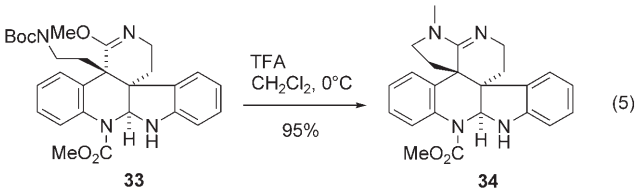
Scheme 6. Proposed mechanism for the cyclization to amidine **27** developed by Fuchs and Funk. DMF = dimethylformamide.

With this hypothesis driving our efforts, we synthesized the C12 aminal cyclization precursor from the allyl alkylation adduct **16** (Scheme 7). Oxidative cleavage and reductive amination gave **28**. Incorporation of the Boc group onto the secondary amine and reduction of the C12 amidine gave **30**. Note that reduction of the amidine did not occur during the reductive amination reaction. Aminal generation at C12 and global removal of the Boc groups gave **31** after reintroduction of the Boc moiety onto the secondary amine. Reductive removal of the benzyl group and selective incorporation of the methyl carbamate at N11 gave **32**.[17] Finally, conversion of the amide into the corresponding methyl imidate with trimethyloxonium tetrafluoroborate gave the targeted cyclization precursor **33**.

With **33** in hand, it remained to remove the Boc group and induce cyclization. We were pleased to find that exposure of **33** to trifluoroacetic acid (TFA) not only resulted in the removal of the Boc group but also led to the generation of the desired C24 amidine in 95 % yield [Eq. (5)].



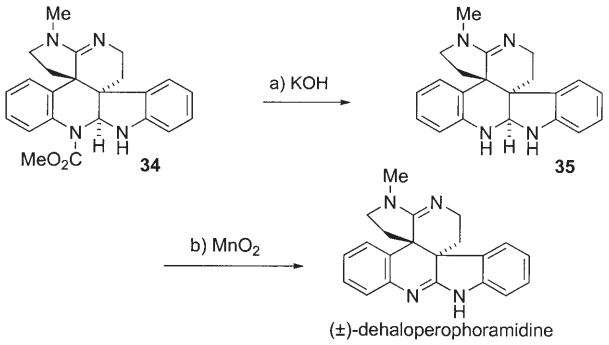
Scheme 7. Conversion of pentacycle **16** into imidate cyclization precursor **33**: a) OsO_4, $NaIO_4$, NaOAc, THF, H_2O, 0 °C, 3 h (72%); b) CH_3NH_2·HCl, NaOAc, MeOH, RT, 7 h; $NaBH_4$, 0 °C, 1 h; c) Boc_2O, NEt_3, THF, 0 °C→RT, 12 h (82%, 2 steps); d) $NaBH_4$, EtOH, 0 °C→RT, 18 h (89%); e) TFA, CH_2Cl_2, 0 °C→RT, 8 h; f) Boc_2O, NEt_3, THF (97%, 2 steps); g) Li, NH_3, THF, NH_4Cl, −78 °C; h) $ClCO_2CH_3$, pyridine, CH_2Cl_2, temp, time (88%, 2 steps); i) Me_3OBF_4, $NaHCO_3$, CH_2Cl_2, 0 °C, 1 h (81%).



(5)

To complete the synthesis of dehaloperophoramidine, it remained to remove the methyl carbamate and oxidize the aminal to the corresponding amidine. This occurred uneventfully; exposure of **34** to KOH and MeOH followed by oxidation with MnO_2 under the conditions developed by Fuchs and Funk gave (±)-dehaloperophoramidine, whose spectral data matched the data reported by Ireland and coworkers (Scheme 8).[2]

In conclusion, we have successfully generated (±)-dehaloperophoramidine from a highly efficient spirocyclization reaction of a readily available 2-thiotryptamine derivative. We are currently examining this reaction in the synthesis of other interesting alkaloids, including members of the communesin family. These efforts will be reported in due course.



Scheme 8. Completion of the preparation of (±)-dehaloperophoramidine: a) KOH, MeOH, H_2O, 100 °C, 6 h (71%); MnO_2, CH_2Cl_2, RT, 0.5 h (64%).

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[15] We also explored a number of other basic and acidic conditions without success.
[16] An examination of molecular models of **21** and **24** indicates that approach of the amine onto the C24 imidate carbon is blocked by the C18 proton; the formation of **25** allows the aromatic ring to rotate, thus alleviating this problem.
[17] When the aminal was protected with a Boc group, reductive removal of the benzyl group resulted in the decomposition of the perophoramidine ring system.

