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Concise Total Synthesis of Dehaloperophoramidine

*Kirill Popov, Anita Hoang, and Peter Somfai**

Abstract: *Perophoramidine, dehaloperophoramidine, and communesin F are structurally related alkaloids having intriguing polycyclic structures. A strategy for the synthesis of dehaloperophoramidine has been developed. In this synthesis all skeletal atoms and all functional groups required to reach the target molecule are incorporated early in the sequence. This approach led to the discovery of two novel substrate-specific domino processes, one encompassing four steps and the other comprising five steps, thus resulting in an eight-step synthesis of dehaloperophoramidine.*

Total synthesis of complex organic molecules, and perhaps natural products in particular, has evolved dramatically, and increasingly more complex structures have succumbed to laboratory synthesis.[1] Much of the progress in this area can be ascribed to the development of new or improved methods for carbon–carbon and carbon–heteroatom bond construction, as well as to the concomitant evolutionary progress made in the design and planning of chemical syntheses of complex organic molecules. During the last two decades the focus in this area has shifted from assembling more complex structures to improving the overall efficiency of the process. Consequently, all aspects of efficiency, related to both individual steps and to complete reaction sequences, are of central importance, the goal being to reach the "ideal synthesis".[2]

Perophoramidine (**2**)[3] and Communesin F (**3**)[4] are structurally related indole alkaloids isolated from marine species *Perophora namei* and *Enteromorpha intestinalis*, respectively (Figure 1).[5] Perophoramidine (**2**) has demonstrated activity against the HCT116 colon carcinoma cell line with an IC_{50} of 60 μm, while communesin F (**3**) was shown to exhibit insecticidal activity against instar silkworm's larvae. Because of their intriguing structures and promising biological activities, this family of alkaloids has stimulated substantial interest from the scientific community and has resulted in a number of elegant syntheses.[6]

Dehaloperophoramidine (**1**) is the synthetic analogue of **2** lacking the aromatic halogens, and was first reported in the original isolation paper.[5b] Structural challenges, which need to be addressed during total synthesis of this molecule, are

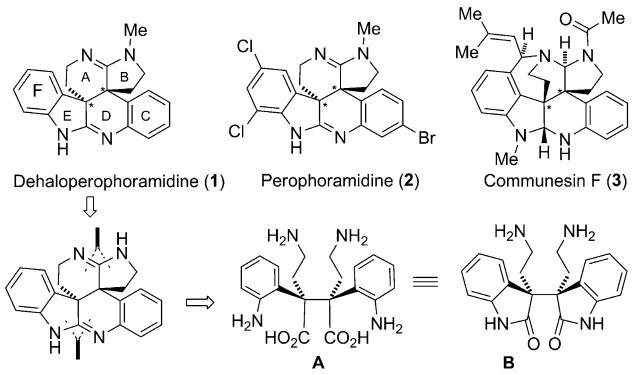

Figure 1. Indole alkaloids containing vicinal all-carbon quaternary stereocenters. Latent symmetry of dehaloperophoramidine (**1**) is revealed when all carbon-nitrogen bonds are disconnected.

mainly related to the vicinal all-carbon quaternary centers having *trans* relative stereochemistry (indicated with stars, Figure 1),[7] the complex polycyclic system, and the bis(amidine) functionalities. Compound **1** has previously been prepared in 18 and 17 steps, thus reflecting the current state of the art.[8]

Our analysis of **1** was guided by two considerations: 1) all skeletal carbon atoms required for **1**, including the vicinal all-carbon stereocenters, should be installed early in the reaction sequence, and 2) all necessary functional groups should be introduced at the beginning of the synthesis and in their correct oxidation state. With this in mind, disconnection of all carbon–heteroatom bonds in **1**, specifically four C–N bonds, reveals the latent symmetry in the target molecule and delivers the σ-symmetric synthon **A**,[9] or its obvious analogue bis(oxindole) **B**, which appeared to be an excellent platform on which to investigate novel domino processes.[10] In continuing the analysis, it was considered that **B**, or its synthetic equivalent, compound **5** (Figure 2), should be accessible from the commercially available isoindigo (**7**).

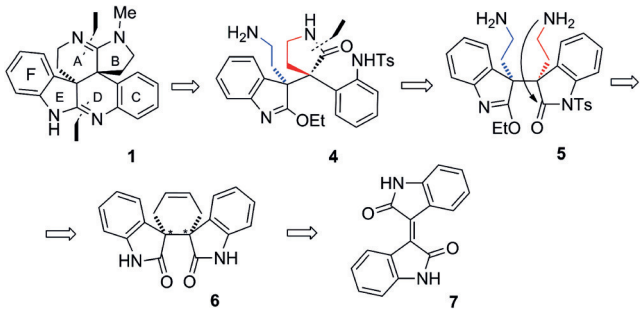

Figure 2. Retrosynthetic analysis of **1**. Ts = 4-toluenesulfonyl.

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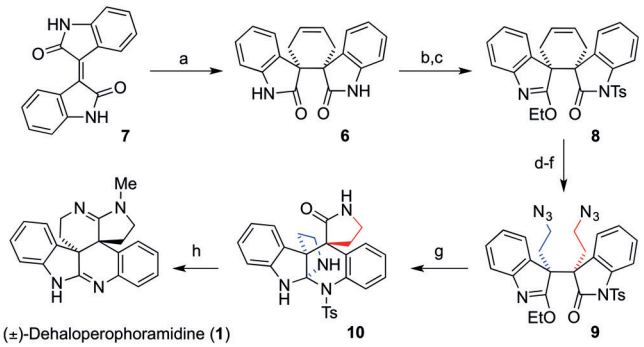
For **5** we planned to differentiate between the aminoethyl moieties by allowing a kinetically controlled formation of the B ring, thus affording the compound **4**. It was also appreciated that conversion of **5** into **4** might initiate a domino reaction with concomitant formation of the D ring, an opportunity that clearly had to be investigated. In any case, several routes from **4** to **1** can be envisioned and the final selection of reactions was to be made once **4**, or an equivalent, was secured. Of considerable concern was the selectivity issue related to the planned introduction of the N-methyl group at a late stage in the sequence, although this issue has been addressed previously.[11]

The underlying criteria behind our analysis outlined in Figure 2 was to allow intramolecular proximity effects which can set the stage for novel domino processes, and eventually result in an efficient synthesis of **1**. In the event, during our studies towards the synthesis of **1** a continuous exploration of possible proximity effects resulted in the discovery of two new powerful domino processes, one encompassing four discrete reactions steps and the other comprising five steps, thus significantly increasing the overall efficiency of the reaction sequence. Compared to the previous syntheses of **1** and **2**, the present approach differs in the efficient assembly of the trypthamine dimer analogue **5** and its rapid conversion into **1**.

Commercially available isoindigo (**7**) was subjected to a SmI_2-mediated reductive bis(alkyl)ation reaction with *cis*-1,4-dichlorobutene to afford the cyclohexene **6** as a single diastereomer and in high yield (Scheme 1).[12] To prepare for the subsequent differentiation of the aminoethyl side-chains, **6** was monotosylated and then converted into the corresponding imidate **8**. A one-pot ozonolysis/reduction of this material and subsequent Mitsunobu reaction[13] using HN_3 furnished the bis(azide) **9**.

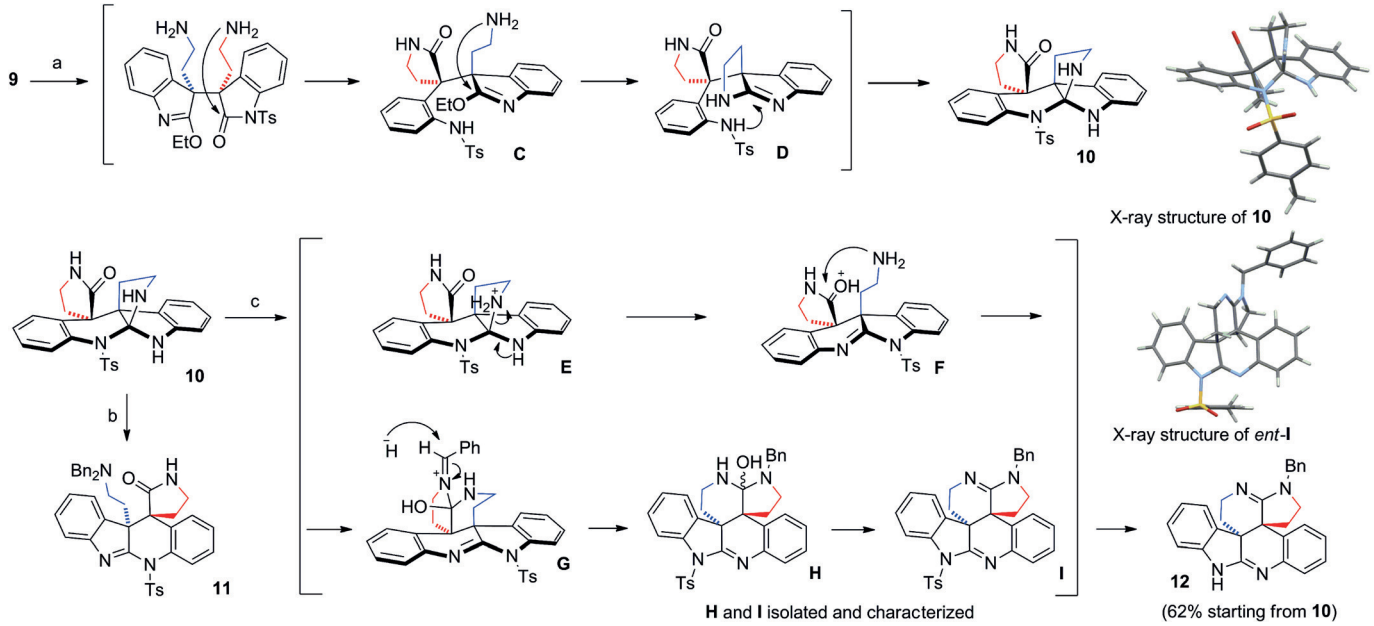
Hydrogenolysis of **9** (H_2, Pd/C, EtOAc) not only resulted in the expected formation of the B ring lactam, but also initiated a domino process ultimately resulting in the formation of the hexacyclic *ortho*-amide **10** in quantitative yield.[14] This domino reaction is believed to involve initial hydrogenolysis of **9** to furnish **5**, with a subsequent kinetically controlled ring-closure to form the desired five-membered lactam **C** (Scheme 2). Subsequent addition of the remaining 2-aminoethyl moiety to the imidate affords the corresponding amidine **D**, which, because of the inherent strain in the system, is trapped by the sulfonamide to give **10**. The structure of **10** was inferred by NMR spectroscopy and eventually proven by single-crystal X-ray crystallographic analysis. It appears that the careful selection of activating groups in **8**, that is, the imidate and sulfonimide, and proximity effects work in concert to promote the conversion of **9** into the **10**.



Scheme 1. Reaction conditions: a) *cis*-1,4-dichlorobutene, SmI_2, LiCl, THF 0 °C, 68% (single diastereomer); b) KH, TsCl, THF, 72% (brsm); c) Meerwein's reagent, TFA, DCM, 0 °C, 98%; d) O_3, DMS, DCM/MeOH (4:1), −78 °C; e) $NaBH_3CN$, THF/AcOH (5:1); f) HN_3, PPh_3, DIAD, THF, 0 °C, 90% over 3 steps; g) H_2 (1 atm), Pd/C 10 w%, EtOAc, 99%; h) $(CH_2O)_n$, $NaBH(OAc)_3$, 80 °C, 52%. DCM = dichloromethane, DIAD = diisopropyl azodicarboxylate, DMS = dimethylsulfate, TFA = trifluoroacetic acid, THF = tetrahydrofuran, Meerwein's reagent = Et_3OBF_4.

The formation of **10** secured our primary goal of differentiating between the aminoethyl side-chains, with the concomitant formation of the B and D rings of the final product, thus supplying us with an advanced intermediate. To transform **10** into **1**, we needed to selectively disconnect the aliphatic amine from the *ortho*-amide carbon atom while retaining the oxidation state at this position, construct the A ring, and selectively methylate the B ring nitrogen center.

Towards this end, a thorough investigation of the reactivity of the *ortho*-amide moiety in **10** revealed that treatment of this material with benzaldehyde under basic reductive amination conditions resulted in the formation of the N,N-dibenzylamino amidine **11** (Scheme 2). This result indeed demonstrated that the aminoethyl moiety could be disconnected from the *ortho*-amide carbon atom while retaining the oxidation state at this position. In addition, at some point during the conversion of **10** into **11** the N-Ts moiety participates in a 1,3-sulfur shift[15] with concomitant isomerization of the carbon–nitrogen double bond. Although this rearrangement is inconsequential for the overall outcome, it is believed that it reflects the thermodynamic preference between the two possible amidine isomers. Further experimentation showed that when **10** was subjected to reductive amination under acidic conditions (PhCHO, $NaBH(OAc)_3$, AcOH, CF_3CH_2OH)[16] the N-Bn bis(amidine) **12** was formed as a single regioisomer. It is noted that this domino process results in the conversion of the *ortho*-amide moiety into the corresponding amidine, formation of the A ring with simultaneous formation of the A/B amidine, regioselective N-benzylation of the A/B amidine, a 1,3-sulfur shift of the N-Ts group, and hydrolysis of the sulfonamide. The conversion of **10** into the fully functionalized A/B/C/D/E/F ring system **12** significantly increases the overall efficiency of our approach and also resolves the initial concern about the regioselective N-alkylation of the aliphatic amidine moiety. It is believed that the conversion of **10** into **12** proceeds by initial formation of the protonated lactam **F**, which then undergoes cyclization and reductive amination to afford the intermediate **H**. The remarkable regioselectivity in the N-benzylation is ascribed to the faster rate of formation of an iminium ion from pyrrolidine than from piperidine.[17] Under the acidic reaction conditions **H** is then dehydrated to furnish the intermediate **I** followed by hydrolysis of the sulfonamide to give **12**. It was also possible to isolate **H** (see the Supporting Information for spectroscopic details), in which the 1,3-sulfur shift has already occurred, and subjecting it to acidic reaction conditions (AcOH, CF_3CH_2OH) resulted in clean conversion into **I**



Scheme 2. Reaction conditions[18]: a) H_2 (1 atm), Pd/C 10 w%, EtOAc, 99%; b) PhCHO, $NaBH_4$, TFE, K_2CO_3, 80°C, 69%; c) PhCHO, $NaBH(OAc)_3$, AcOH, TFE, 80°C. TFE = 2,2,2-trifluoroethanol.

(characterized by single-crystal X-ray analysis, see Scheme 2). When **10** was subjected to the same reaction conditions it remained unaffected, thus indicating that reductive amination must precede amidine formation.

Applying this domino transformation to **10** (1.00 g scale) using paraformaldehyde yielded dehaloperophoramidine (**1**) in 52% yield (0.350 g, Scheme 1), and completed our eight-step synthesis of the target molecule starting from isoindigo (**7**) in 23% overall yield.

We have shown that when opportunities for domino processes are already provided in the design phase of a complex molecule synthesis, highly efficient routes can be obtained. As a result, **1** was obtained from **7** in eight steps and 23% overall yield. To realize this synthesis, the necessary functional groups having the correct oxidation states, as well as all skeletal carbon atoms were included early in the reaction sequence. The synthesis includes two powerful domino transformations, the conversion of **9**→**10** and **10**→**1**, encompassing four and five discrete reaction steps, respectively. It was also been demonstrated that both processes can be performed on the gram scale. Although the first domino reaction, or part of it, was already foreseen at the planning stage of the synthesis, the second was the result of a thorough investigation of the reactivity of **10**. It is assumed that the successful implementation of our synthesis design is a result of the thermodynamic preference for the formation of the hexacyclic ring system present in **1**.

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[18] CCDC 1432648 (**10**) and 1432649 (*ent*-**I**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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