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Total Synthesis of Nortopsentin D via a Late-Stage Pinacol-like Rearrangement

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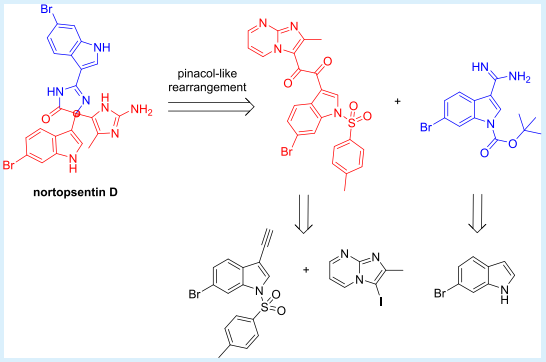
ABSTRACT: Nortopsentin D is part of a class of bis(indole) alkaloids known for their biological activity, including inhibitory activity in tumoral cells and antifungal activity. Herein we describe the first total synthesis of nortopsentin D, in which amidine and dione undergo a pivotal condensation and subsequent cyclization via a pinacol-like rearrangement. This synthesis represents a unique strategy for the formation of 5,5-disubstituted (4*H*)-imidazol-4-one containing natural products, many of which have yet to succumb to total synthesis.



Nortopsentin D (Figure 1) was originally isolated in 1996 from the axinellid sponge *Dragmacidon* sp. in deep waters south of New Caledonia[1] and later from the sponge *Agelas dendromorpha*.[2] This is a fascinating structural variant of the nortopsentin family, whose methylated derivative was shown to have high cytotoxicity toward tumoral cells (CC_{50} 18 nM) as well as antifungal activity against yeast.[1] Over the years, the nortopsentin family and its synthetic analogues have displayed a large range of biological activities in the areas of cytotoxicity, antiplasmodial, antibacterial, antifungal, and insecticidal activities.[3] Catalytic hydrogenation of nortopsentins A–C was previously reported to render the synthetic analogue D (Figure 1), which is unfortunately also sometimes referred to in the literature as nortopsentin D.[4]

Structurally, nortopsentin D is composed of a complex central trisubstituted (4*H*)-imidazol-4-one, with a 6-bromoindole at the C2 position and a 4-methyl-1*H*-imidazol-2-amine and 6-bromoindole at C5. Nortopsentin D is one of several known 5,5-disubstituted (4*H*)-imidazol-4-one containing natural products.[5] Of the products highlighted in Figure 1, only four have been previously synthesized. The indole alkaloid isolated from *Dendrodoa grossularia* was synthesized by Hupp and Tepe in 2008,[6] where the tertiary carbon was formed through an oxazole rearrangement, producing a hydantoin that was later converted into a 2-amino-imidazole. Contrastingly, the tertiary carbon of (+)-calcaridine A was formed through a *N*-sulfonylaziridine driven oxidative rearrangement of imidazole, as reported by Koswatta et al. in 2008.[7] Lastly, dictazole B was first synthesized in 2014 by Skiredj et al. through a [2 + 2] cycloaddition of aplysinopsin monomors, and a dictazole B-type skeleton was later used to form (±)-tubastrindole B via ring expansion.[8] The aforementioned methods for the formation of the 5,5-disubstituted (4*H*)-imidazol-4-one ring require substrate specific, linear paths. It is evident there is a lack of robust, convergent strategies for the formation of (4*H*)-imidazol-4-one's complex tertiary carbon that can be applied to the synthesis of these natural products.

Herein, we describe the first total synthesis of the natural product, nortopsentin D. The key step of this synthesis involves a condensation of novel dione and amidine intermediates followed by a subsequent rearrangement to produce the core (4*H*)-imidazol-4-one. This convergent method for the formation of the (4*H*)-imidazol-4-one's tertiary center is envisioned as a possible method to attain the total syntheses of several other 5,5-disubstituted imidazol-4-one containing natural products.

The proposed retrosynthetic plan is shown in Scheme 1. Due to the highly substituted imidazol-4-one ring, a late-stage cyclization via condensation of dione (3) and amidine (4) was proposed. This cyclization involves a pinacol-like rearrangement and is an effective way of forming 5,5-disubstituted imidazol-4-ones.[9] The dione (3) contains a protected version of the 4-methyl-1*H*-imidazol-2-amine and the 6-bromoindole found at C5 of nortopsentin D, whereas the amidine (4) contains nortopsentin D's C2 6-bromoindole. This proposed route is an opportunity to test the robustness of the cyclization,

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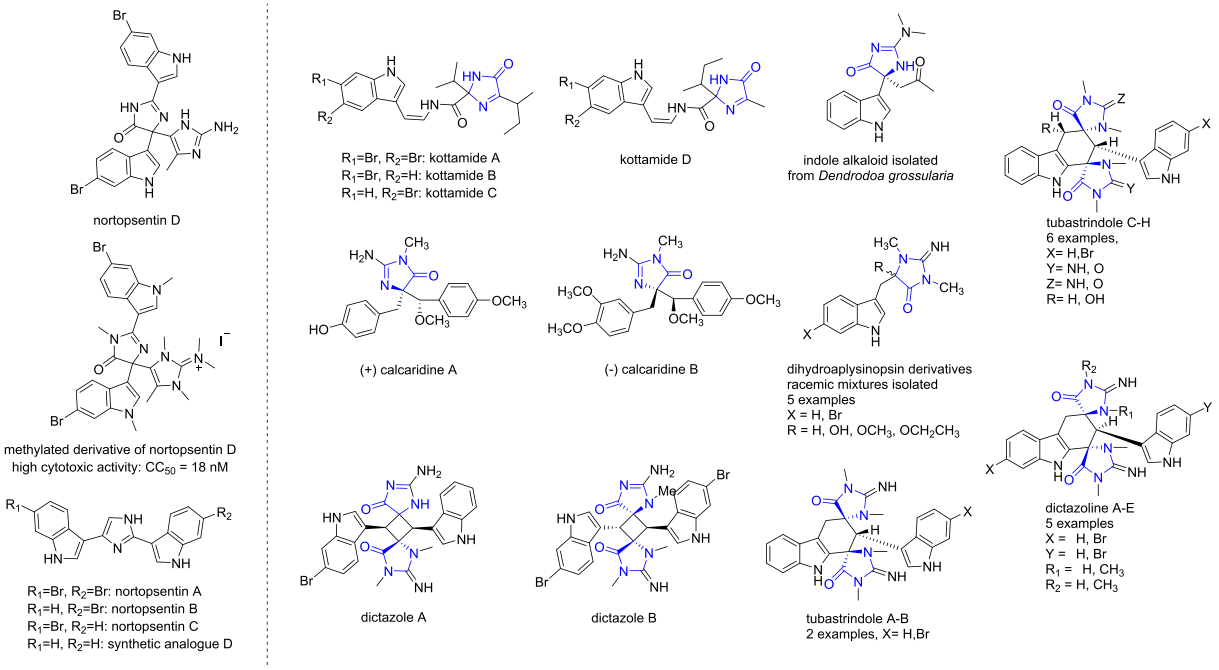
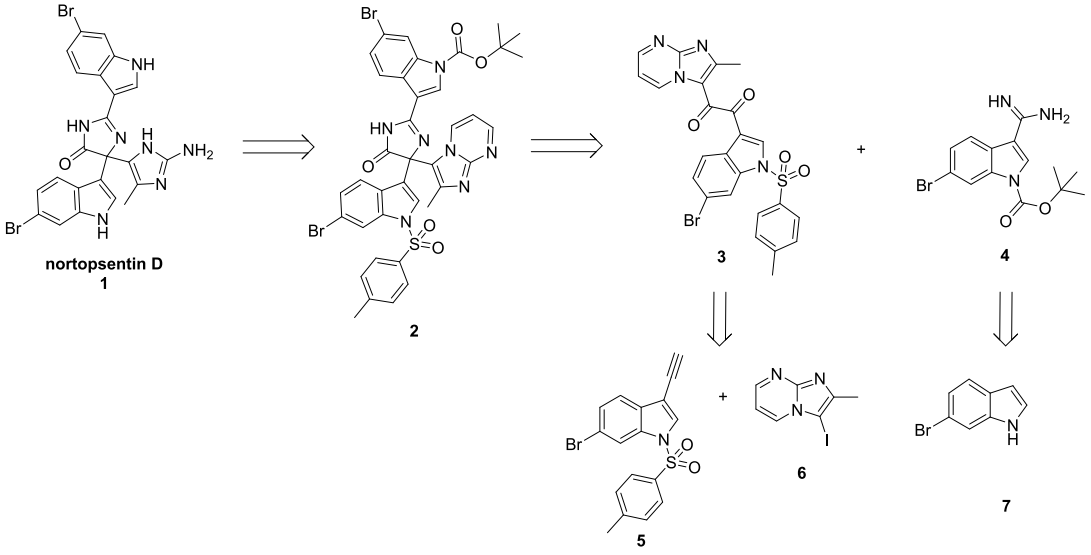


Figure 1. Natural products within the nortopsentin family and other 5,5-disubstituted (4*H*)-imidazol-4-one containing natural products.

Scheme 1. Retrosynthetic Analysis for Nortopsentin D (1)



highlighting its capacity to be exploited for the synthetic efforts toward other 5,5-disubstituted (4*H*)-imidazol-4-one containing natural products.

The synthesis of dione **3** is shown in Scheme 2. It began by synthesizing terminal alkyne **5**. Starting with 6-bromoindole (**7**), intermediate **8** was produced via iodination and subsequent *N*-tosylation, under the influence of triethylamine (TEA) and 4-dimethylaminopyridine (DMAP) and upon the addition of 4-toluenesulfonlyl chloride (TsCl). This was followed by a Sonogashira coupling of trimethylsilylethyne under standard conditions, with a subsequent protodesilylation of trimethylsilane using tetrabutylammonium fluoride (TBAF), which produced terminal alkyne **5** in 76% yield.[10] It should be noted that when the Sonogashira coupling was run at 60 °C,[10] yields were considerably lower, due to poor chemoselective coupling at the C3-iodo versus C6-bromo positions. Reduction of the temperature to room temperature led to better control over the coupling's chemoselectivity, significantly favoring the desired C3 position.

The other half of the dione intermediate began via the condensation of 1-chloroacetone (**9**) and 2-aminopyrimidine (**10**) upon addition of heat, to produce 3-methylimidazo[1,2-*a*]pyrimidine **11** in 58% yield. This bicycle represents a protected form of the 4-methyl-1*H*-imidazol-2-amine observed on C5 of nortopsentin D. Iodination of **11** with *N*-iodosuccinimide (NIS) led to the desired aryl iodide **6** in two steps with an overall yield of 50%.

Once intermediates **5** and **6** were in hand, a Sonogashira coupling led to the desired internal alkyne **12** in 85% yield. Compound **12** went through extensive experimentation to identify the best conditions for the oxidation of the internal alkyne to a dione, as the alkyne proved to be unstable under

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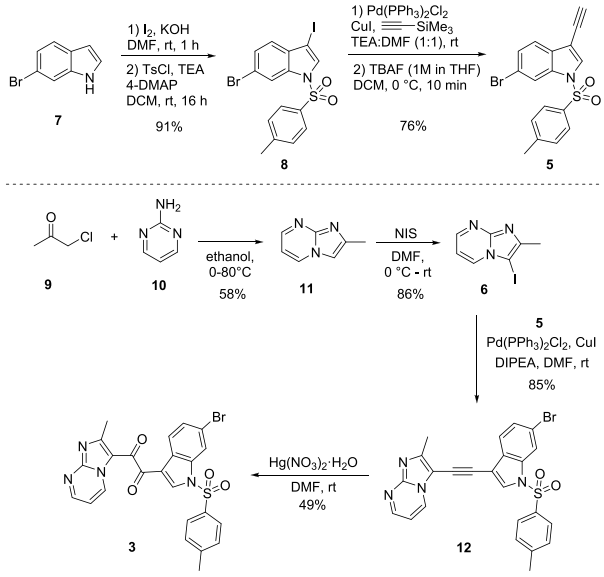
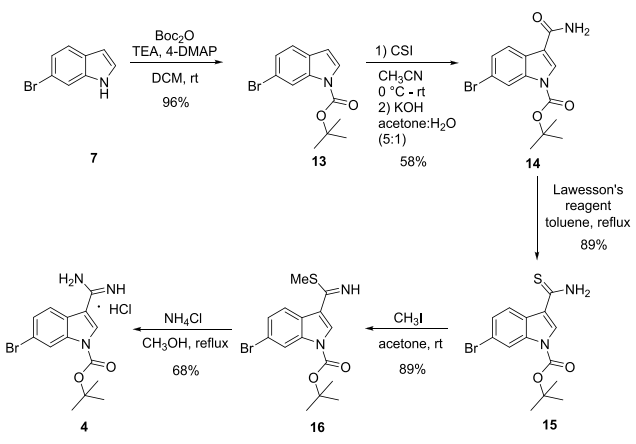
Scheme 2. Synthesis of Dione 3



harsh oxidative conditions and high temperatures. Exposure of **12** to a range of conditions (e.g., $KMnO_4$/TBAB,[11] ICl/$AgNO_3$,[12] $Pd(OAc)_2/AlCl_3$/DMSO/70−110 °C,[13] $PdCl_2$/DMSO/140 °C,[14] $RuCl_3/PhI(OAc)_2$,[15] 2-chloropyridine-*N*-oxide/$Ph_3PAuNTf_2$/75−85 °C[16]) led to low yields and a variety of complications, including decomposition of the starting material, loss of the tosyl protecting group, and, in some cases, oxidation of the 3-methylimidazo[1,2-*a*]-pyrimidine. The limitations of high temperature and harsh oxidation conditions were successfully overcome by use of mercuric nitrate monohydrate as an oxidation source. Within 8 h at room temperature under air, a 49% yield of the desired dione **3** was produced. Additionally, the reaction could go for up to 16 h without any change in yield or evidence of overoxidation.[17] Overall, dione **3** was synthesized in 4 linear steps in 14% yield.

With dione **3** in hand, the amidine intermediate **4** was prepared following a similar pathway as previously described in the synthesis of nortopsentin B and synthetic analogue D (Scheme 3).[18] The synthesis began with 6-bromoindole (**7**), a common building block available in multigram quantities. Di-*tert*-butyl dicarbonate was used to protect the indole's nitrogen, affording **13** in 96% yield. Functionalization of the C3 position

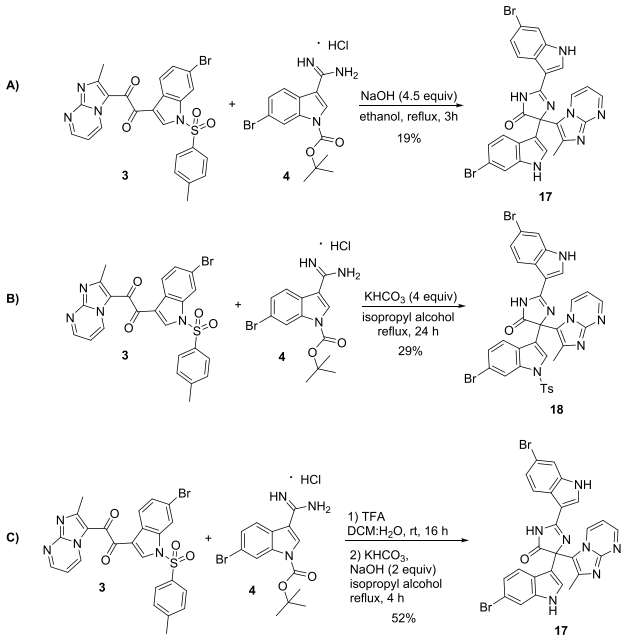
Scheme 3. Synthesis of Amidine 4



of indole with an amide was performed using chlorosulfonyl isocyanate (CSI), followed by potassium hydroxide in aqueous acetone to produce **14** (58%). Lawesson's reagent was used to convert the amide to a thioamide in 89% yield. The resultant compound **15** was then converted to a methyl thiol imine using methyl iodide, giving compound **16** in 89% yield. The last step in the preparation of key intermediate **4** was the substitution of methyl thiol with an amine using ammonium chloride in methanol. Overall, this pathway furnished the desired amidine **4** in 5 steps with an overall yield of 30%.

Once both key intermediates **3** and **4** were produced through a reliable and multigram scalable route, the formation of the core (4*H*)-imidazol-4-one was performed. Efforts in this cyclization are summarized in Scheme 4. First, following

Scheme 4. Optimization of the Cyclization of Intermediates 3 and 4



standard conditions reported for this condensation, intermediates **3** and **4** were reacted under basic conditions, using excess sodium hydroxide and refluxing in ethanol over the period of 3 h.[9] The procedure provided a 19% yield of the desired imidazol-4-one product **17** (Scheme 4A), where both the *N*-boc and *N*-tosyl protecting groups were deprotected during the reaction. Interestingly, the main side product from this reaction was detosylated dione, which remained uncondensed even upon heating over an extended period. It was theorized that the presence of indole's *N*-tosyl, and correlatively the added electrophilicity, may be necessary for condensation with amidine **4**. This theory was tested by using a weaker, less nucleophilic base (potassium bicarbonate) and less nucleophilic solvent (isopropanol) to avoid *N*-tosyl deprotection (Scheme 4B). After refluxing for 24 h, a 29% yield of cyclized product **18** was collected, where the indole's *N*-tosyl remained intact, supporting this theory.

Curiously, it was observed that the only cyclized product formed in Scheme 4A and 4B had lost the amidine's *N*-boc protecting group. This prompted a new theory regarding the nucleophilic nature of **4**: *N*-boc deprotection of the indole must occur before the amidine will condense with dione **3**.

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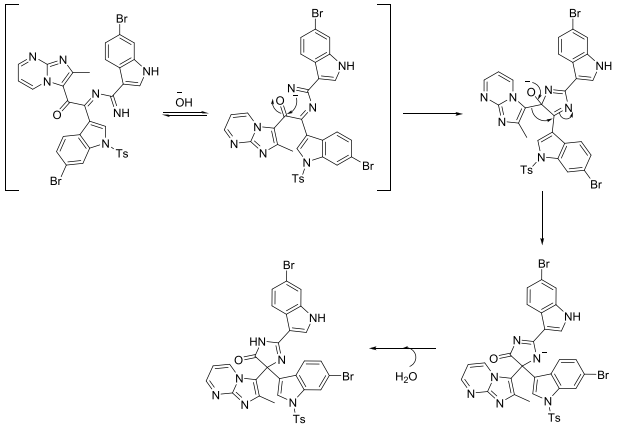
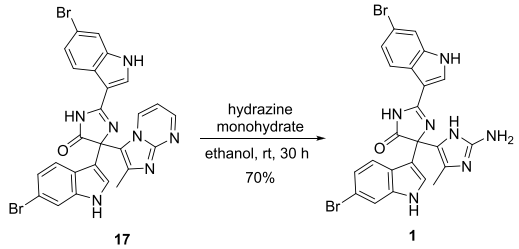
Scheme 4C describes how this theory was tested. First, *N*-boc deprotection of amidine **4** was performed, using trifluoroacetic acid (TFA). After reacting for 16 h, volatiles were removed, and the reaction was basified (pH = 8) in isopropanol using an excess of potassium bicarbonate and minimal amount of sodium hydroxide. Upon introduction of dione **3**, the reaction was heated until cyclization was complete. To simplify the isolation of this reaction, *N*-detosylation was performed in one pot, upon the addition of excess sodium hydroxide and heat. Overall, this modified procedure produced 52% yield of the desired (4*H*)-imidazol-4-one product. Through this optimization process, we determined the condensation of amidine and dione is susceptible to changes in electron densities and can be manipulated to improve the conversion to product. A proposed mechanism for this cyclization is shown in Scheme 5.[9]

Scheme 5. Proposed Mechanism for Imidazol-4-one Formation via Pinacol-like Rearrangement



Once the cyclization was optimized, we moved onto the last step of this total synthesis. Here, the 3-methylimidazo[1,2-*a*]pyrimidine of **17** was deprotected using hydrazine monohydrate, affording the title compound, nortopsentin D, in 70% yield (Scheme 6).

Scheme 6. Final Step in the Total Synthesis of Nortopsentin D



Spectroscopic data obtained from **1** is in full agreement with the original isolation paper (for a direct comparison, see Table S1 in the Supporting Information).[1] Interestingly, and as Pietra and co-workers reported, several carbon peaks associated with the (4*H*)-imidazol-4-one ring were very broad and only made visible through enhanced apodization (exponential = 8 Hz). To further confirm the presence of the central heterocyclic ring, X-ray crystallography was used to determine the crystal structure of cyclized product **17** (Figure 2). The X-ray crystallographic data confirms the presence of a central (4*H*)-imidazol-4-one ring.

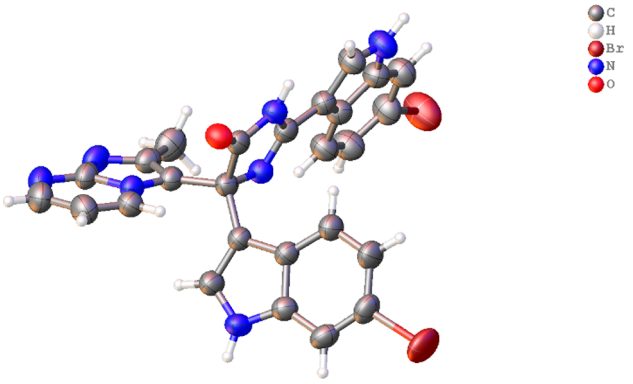


Figure 2. X-ray crystal structure of cyclized imidazol-4-one containing product **17**; thermal ellipsoids shown with 50% probability.

In conclusion, we have accomplished the first total synthesis of nortopsentin D. This highly convergent synthesis only included 7 linear steps with an overall yield of 1.6%. The structure described in Mancini et al.'s original isolation report[1] has been confirmed through both NMR and X-ray crystallography. This pathway features a unique method for the formation of the 5,5-disubstituted (4*H*)-imidazol-4-one ring, which can be envisioned for use in multiple other total syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01681.

Experimental procedures, characterization data, X-ray crystal data and experimental, and NMR spectra (PDF)

Accession Codes

CCDC 2081971 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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