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Studies Toward Communesin F: A Diels–Alder Approach

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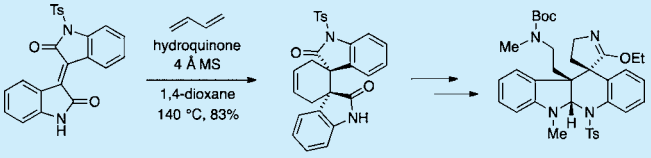
Supporting Information

ABSTRACT: A Diels–Alder reaction is used as a key step in a synthetic study toward communesin F, in order to simultaneously introduce both of the all-carbon quaternary stereocenters with complete control of relative stereochemistry. Further manipulations of the cycloadduct, toward the hexacyclic core-structure of communesin F, are also disclosed.



Communesin F (**1**, Figure 1) belongs to a group[1] of 8 architecturally unique and highly congested heptacyclic indole alkaloids of fungal origin. Members of this family have been shown to exhibit intriguing activities in biological assays, for example, cytotoxicity toward P-388 lymphocytic leukemia cell lines.[2] They also share a close structural resemblance with perophoramidine (**2**, Figure 1), a marine alkaloid isolated in 2002 from the colonial ascidian *Perophora namei*.[3]

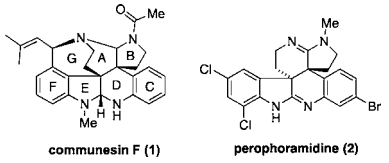


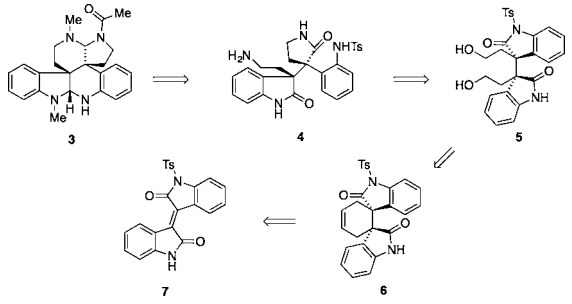
Figure 1. Structures of communesin F and perophoramidine.

Although the hexacyclic core structures of the communesins and perophoramidine are strikingly similar, they display notable differences. For example, perophoramidine is comprised of a bis-amidine functionality rather than the bis-aminal functionality of the communesins. Moreover, perophoramidine lacks the azepine ring (the G-ring in **1**, Figure 1) of the communesins, and instead features halogenated aromatic rings. But the most pivotal difference in terms of synthesis design is the opposite relative stereochemistry of the vicinal quaternary stereocenters, a notoriously challenging motif.[4] This disparity renders it a truly challenging task to develop a general strategy for accessing both the communesins and perophoramidine. Consequently, despite having received significant attention from organic chemists, which has resulted in several syntheses,[5−7] no general approach that can access both the communesins and perophoramidine has so far been disclosed. Furthermore, simultaneous installation of the quaternary stereocenters has to date only been realized for perophoramidine,[8] whereas the approaches to the communesins all rely on a stepwise introduction of the quaternary stereocenters, using enolate alkylations to install the second quaternary carbon. Such approach to the vicinal quaternary all-carbon stereocenters can, at best, access one diastereomer, but the inherent limitations in the methodology normally precludes access to the second diastereomer.

In light of their intriguing structures and the formidable challenge imposed by the quaternary stereocenters, we became interested in developing a strategy to the communesin alkaloids, which would rapidly and efficiency address the core problem of setting the vicinal quaternary stereocenters, and also allow access to the diastereomeric core-structure found in perophoramidine.

As a model system for the communesins, we decided to pursue hexacyclic bis-aminal **3**, which we envisioned obtaining from lactam **4** (Scheme 1). For this series of transformations (**4** → **3**), two ring-closing strategies were considered, differing by the order of the ring-closing events (Scheme 2). In the first strategy, the D-ring would be installed first, followed by the A-ring, whereas in the second strategy the order is reversed. Given the strong precedence from previous syntheses[9] for intermediates corresponding to **8**, and the complete absence of precedence for intermediates resembling **9**, it was initially decided to pursue the former strategy.

Scheme 1. Retrosynthetic Analysis of Model System 3



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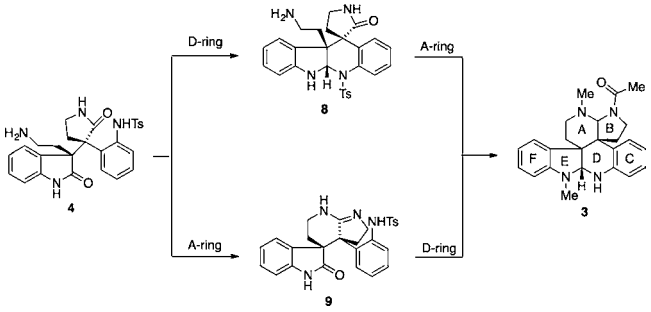
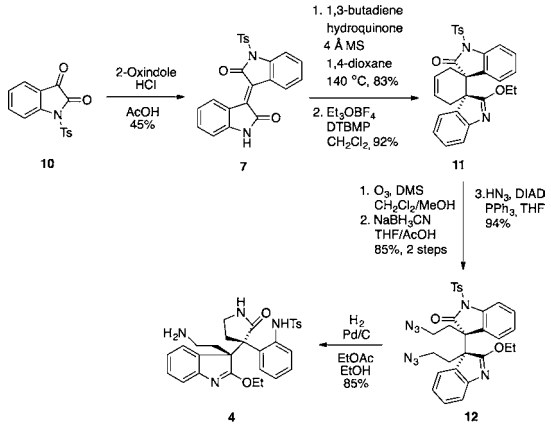
Scheme 2. Two Strategies for the Synthesis of 3 from 4



Lactam **4** was then to be derived from diol **5** by substitution of the hydroxyl moieties with azide,[10] followed by reduction and in situ lactamization. It was anticipated that the five-membered lactam would be kinetically favored in this reaction, which would allow for differentiation of the chemically similar hydroxy-ethyl chains in **5**. The diol **5**, in turn, could originate from cyclohexene **6** after oxidative cleavage of the double bond, followed by reduction of the resultant dialdehyde. A Diels–Alder reaction between readily available *N*-Ts isoindigo (**7**) and 1,3-butadiene was then planned for the formation of key intermediate cyclohexene **6**. Importantly, this transformation would not only install both quaternary stereocenters with full control of relative stereochemistry, but would also, because of the direct correlation of dienophile geometry and product stereochemistry, allow access to the opposite diastereomer of **6** by using the double bond isomer of **7**.

Our journey started from *N*-Ts isatin (**10**), which was condensed with oxindole to afford the dienophile, *N*-Ts isoindigo (**7**) (Scheme 3). We were pleased to find that

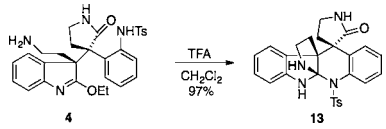
Scheme 3. Synthesis of Lactam 4



heating compound **7** in dioxane at 140 °C for 8 h in the presence of 1,3-butadiene afforded the desired cycloadduct **6** in high yield.[11] It was observed that the use of molecular sieves in this reaction boosted the yield by preventing water-induced cleavage of the *N*-tosyl protecting group. It is worth noting that at this early stage of the synthesis, the vicinal quaternary stereocenters have been installed with correct relative stereochemistry, as well as all C–C bonds present in the target compound **3**. The cycloadduct was then converted into imidate **11** by *O*-alkylation using Meerwein's salt. Somewhat surprisingly, the application of Hünig's base in this transformation resulted in almost exclusive *N*-alkylation, whereas the use of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) gave the desired *O*-alkylation product **11** in high yield.

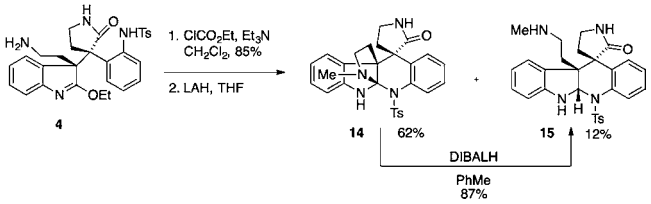
Ozonolytic cleavage of the double bond and reductive workup proceeded smoothly and furnished the dialdehyde, which was directly reduced using $NaBH_3CN$ to the corresponding diol, followed by conversion into diazide **12** using Mitsunobu conditions with hydrazoic acid as the azide source.[12] The stage was now set for the next critical step in the sequence, the differentiation of the 2-azidodethyl moieties in **12**. Gratifyingly, hydrogenation of the diazide **12** directly afforded the five-membered lactam **4** as the major isomer in high yield. At this point, the plan called for installation of the D-ring, which would ideally involve addition of the aniline nitrogen to the imidate, generating a sulfonyl amidine, which was then to be followed by reduction to the aminal oxidation state. However, achieving this transformation in the presence of the more nucleophilic primary amine proved difficult, as orthoamide **13** was the observed product under a variety of reaction conditions (Scheme 4).[13]

Scheme 4. Cyclization of 4 into Orthoamide 13



Unable to prevent the formation of orthoamide **13**, methods for converting **13** into the corresponding D/E-ring aminal was briefly investigated but proved unsuccessful. It was hypothesized that the N–H group of the 2-aminoethyl moiety may impede the disconnection and thus prevent the desired reaction. In order to evaluate this notion, **4** was protected as the ethyl-carbamate (Scheme 5), which was subsequently

Scheme 5. Synthesis of Aminal 15



reduced using LAH. Interestingly, in this reaction, a mixture of *N*-methyl orthoamide **14** and aminal **15**[14] was isolated in good yields. It was speculated that orthoamide **14** might be an intermediate in the formation of aminal **15**, and by resubjecting **14** to the reaction conditions this was shown to indeed be the case. However, DIBALH was found to be a superior reducing agent for this transformation and cleanly afforded the aminal **15** from orthoamide **14** (Scheme 5).

With all but the A-ring installed, we proceeded by Boc protecting the secondary amine in **15** followed by imidate formation using Meerwein's salt to give **16** (Scheme 6). On the basis of literature precedence, it was expected that removal of the Boc group would trigger an addition of the resultant secondary amine to the imidate, which would deliver the corresponding amidine.[5a,b] However, exposure of **16** to 5% TFA in CH_2Cl_2 initially furnished the amine **17**,[15] which did not spontaneously cyclize to the desired amidine, but instead isomerized into aminal **18** upon heating or standing in solution.

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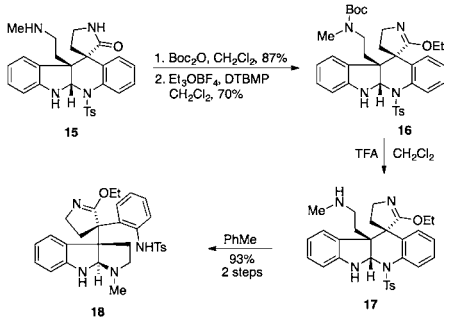
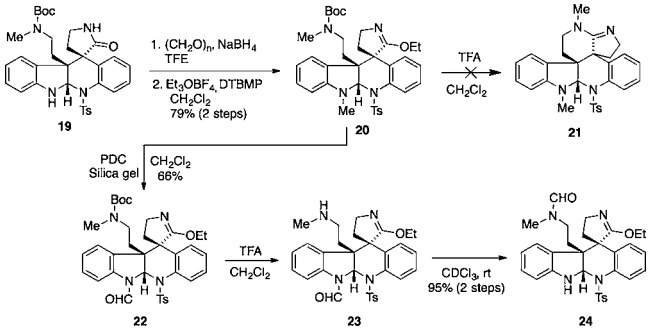
Scheme 6. Synthesis and Deprotection of Substrate 16 and Subsequent Isomerization



The mechanism of this isomerization may involve a base mediated elimination of the sulfonamide moiety followed by addition of the *N*-Me aminoethyl side-chain to the resulting imine. Accordingly, the proclivity of **17** to isomerize is dependent on the presence of the aniline *N*-H proton as well as the ability of the sulfonamide to act as a leaving group. In an effort to thwart this base-facilitated isomerization, compound **19** was subjected to reductive methylation with paraformaldehyde followed by treatment with triethyloxonium tetrafluoroborate to give imidate **20** in 79% over two steps (Scheme 7).

Scheme 7. Synthesis of Cyclization Substrates 20 and 22



Removal of the Boc group in **20** resulted in an inseparable mixture of two new compounds, both of which still contained the imidate moiety,[16] and none of the expected amidine **21**. It appeared that, once again, the D/E-ring aminal system is not stable to the reaction conditions, and in an effort to increase its stability it was decided to oxidize the indole *N*-Me group into an *N*-formyl. To this end, **20** was oxidized using PDC to *N*-formyl derivative **22**,[17] affording tentatively, compound **23** after removal of the Boc protecting group. To our dismay, secondary amine **23** failed to cyclize into the corresponding amidine, and instead slowly isomerized by formyl migration into compound **24**.

Evidently, for compounds **17** and **20** discussed above, isomerization of the D/E-ring aminal is more facile than the desired cyclization into the A/B amidine system, while for compound **23**, intramolecular migration of the *N*-formyl group appears to be more facile than addition of the secondary amine to the imidate moiety. It has been shown that similar approaches as those discussed above to the A/B-ring system are successful when the azepine moiety (G-ring) is already present.[5a,b] Although the dramatic influence exerted by the seven-membered ring is genuinely surprising, it appears to have the effect of impeding isomerization of the aminal functionality, and possibly also enforcing a conformation of the amino nitrogen, favorable for addition to the imidate and thus lowering the entropic barrier.

In summary, we have developed a rapid and highly efficient Diels–Alder approach to the vicinal quaternary stereocenters of the communesins. We successfully installed five of the six rings present in the target model system; however, the final ring closure was hampered by unforeseen aminal isomerization reactions. We are currently investigating the alternative ring-closing strategy outlined in Scheme 2.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for new compounds. 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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(11) The relative stereochemistry of **6** was established by NOESY analysis of compound **20**. See Supporting Information for details
(12) The use of DPPA as the azide source resulted exclusively in cyclization to a 7-membered ether.
(13) Basic reaction conditions also gave **13** but in significantly lower yield. TFA gave the highest yield of **13**.
(14) The stereochemistry of the aminal carbon was confirmed by NOESY analysis of compound **20**. See Supporting Information for details.
(15) Because of the isomerization of **17**, it could never be fully characterized, and its structure is therefore tentatively assigned.
(16) As judged from the ^{1}H NMR of the crude reaction mixture. Attempts to alter their ratio failed, and since we were unable separate the mixture, elucidation of their structures was not possible.
(17) Attempts to introduce methylcarbamate or tosyl failed, giving back only unreacted starting material.

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