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Concise Enantiospecific Total Synthesis of Tubingensin A

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S Supporting Information

ABSTRACT: We report the enantiospecific total synthesis of (+)-tubingensin A. Our synthesis features an aryne cyclization to efficiently introduce the vicinal quaternary stereocenters of the natural product and proceeds in only nine steps (longest linear sequence) from known compounds.

Carbazole-containing natural products have long provided a fruitful area for scientific discovery.¹ The complex alkaloid tubingensin A (**1**)² and its structural isomer tubingensin B (**2**)³ are members of this class that were isolated from the fungus *Aspergillus tubingensis* by Gloer and co-workers in 1989 (Figure 1). Compounds **1** and **2** are both postulated to arise

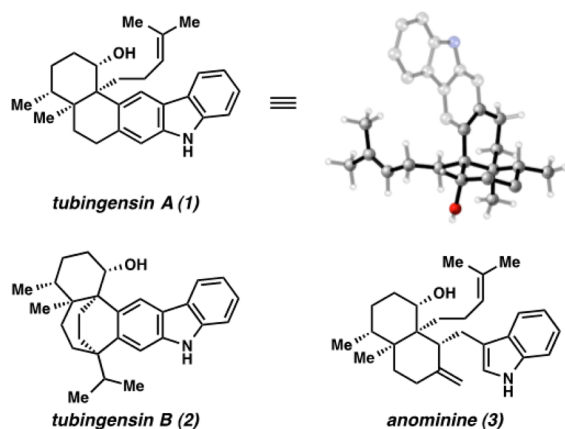


Figure 1. Tubingensin A (**1**) and related family members **2** and **3**.

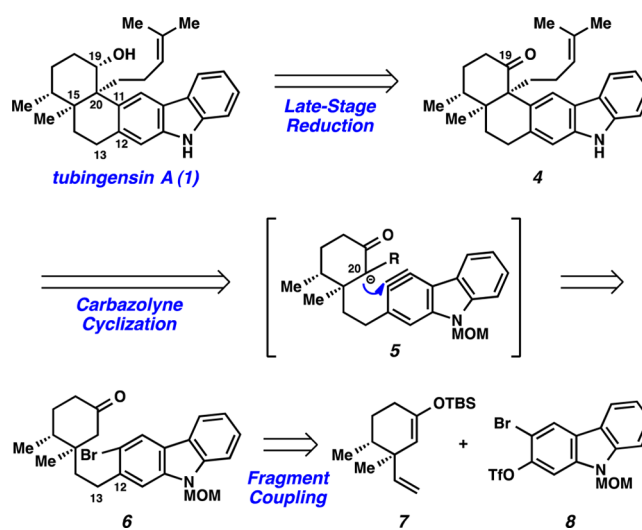
biosynthetically from the indole diterpenoid anominine (**3**)⁴ and have been shown to display antiviral, anticancer, and insecticidal activity.^{2,3} Structurally, tubingensin A (**1**) possesses a disubstituted carbazole that is fused to a densely functionalized *cis*-decalin framework.⁵ Moreover, the decalin core contains four contiguous stereocenters, two of which are vicinal quaternary centers. With regard to synthetic efforts toward tubingensin A (**1**), Bonjoch and co-workers reported an approach to assemble the natural product's scaffold,⁶ and Li and Nicolaou recently completed an elegant bio-inspired total synthesis of **1** that proceeds in 23 linear steps from a cyclohexyl precursor.^{4a}

Given our interest in assembling congested scaffolds using heterocyclic aryne intermediates,^{7,8} we questioned if the vicinal quaternary stereocenters of tubingensin A (**1**) could be introduced using aryne cyclization methodology. Although arynes have been used in an array of interesting trapping

experiments,⁹ their use in the assembly of sterically congested linkages is limited.¹⁰ Furthermore, to our knowledge, arynes have not previously been employed for the introduction of vicinal quaternary stereocenters. In this Communication, we report the use of a late-stage carbazolyne cyclization to efficiently construct the tubingensin A framework. Our approach not only demonstrates that arynes can be used for the assembly of challenging molecular scaffolds but also provides (+)-**1** in just nine steps (longest linear sequence) from known compounds.

Our retrosynthetic analysis for the synthesis of tubingensin A (**1**) is shown in Scheme 1. It was envisioned that the natural

Scheme 1



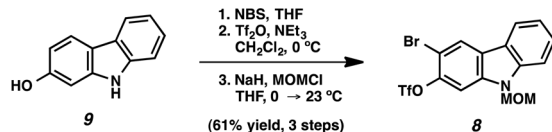
product would arise by late-stage reduction of ketone **4**. This intermediate could be constructed through a key carbazolyne¹¹ cyclization (see transition structure **5**). If successful, this transformation would fashion the challenging vicinal quaternary stereocenters and provide the *cis*-decalin framework of the natural product. Ketone **6**, the precursor to potential carbazolyne cyclization substrates, would ultimately arise from the coupling of two simple fragments, cyclohexyl derivative **7** and carbazole triflate **8**.

The key coupling partners were prepared in a straightforward manner (Figure 2). Commercially available hydroxycarbazole **9** was brominated using a known procedure.¹² Subsequent *O*-triflation and *N*-protection afforded **8** in 61% yield over three

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Synthesis of Carbazole Fragment



Synthesis of Cyclohexyl Fragment

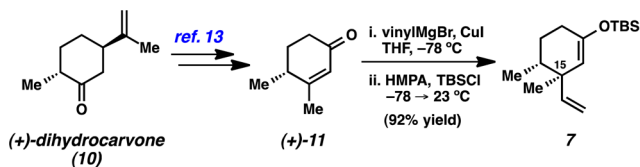
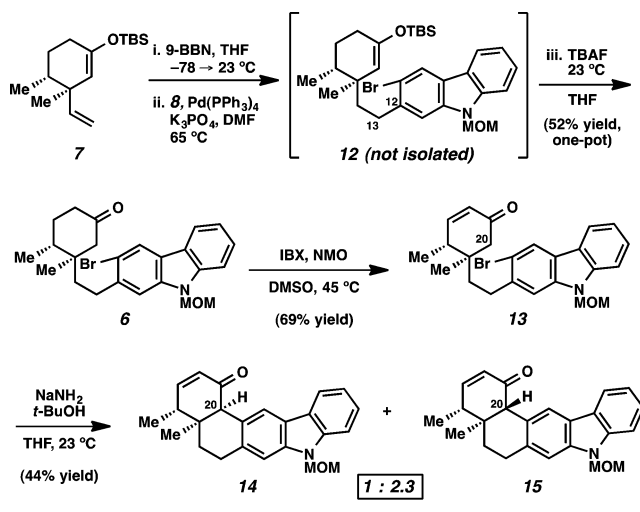


Figure 2. Synthesis of carbazole and cyclohexyl fragments.

steps. The synthesis of cyclohexyl fragment 7 began from commercially available (+)-dihydrocarvone (10), which was elaborated to enone 11 using a known three-step procedure.¹³ Vinyl cuprate addition and trapping of the resulting enolate furnished silyl enol ether 7 as a single diastereomer.¹⁴

With cyclohexyl fragment 7 and carbazole triflate 8 in hand, we pursued their coupling and the ensuing carbazolyne cyclization (Scheme 2). Treatment of 7 with 9-BBN¹⁵ led to

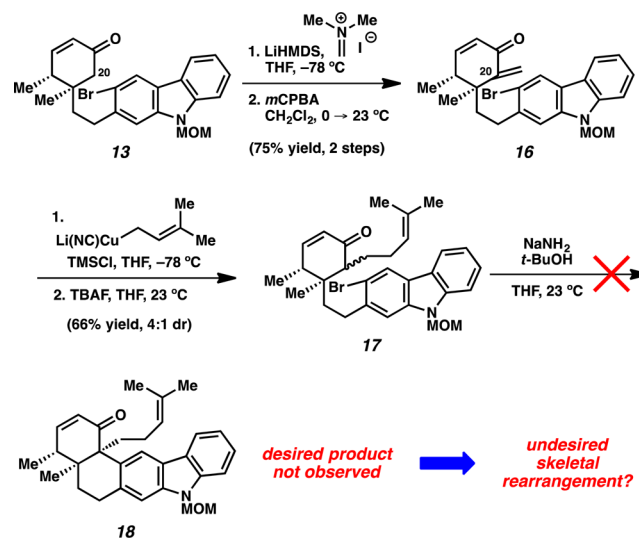
Scheme 2



chemoselective hydroboration of the terminal olefin. Subsequent Pd-catalyzed cross-coupling¹⁶ with 8 proceeded smoothly to generate coupled product 12. Addition of TBAF to the reaction mixture then delivered ketone 6. The highly optimized conversion of 7 and 8 to 6 in one pot¹⁷ provides a rare example of a silyl enol ether being employed as a ketone protecting group in a complex setting.^{14,18} To control regioselectivity of enolate formation in the forthcoming carbazolyne cyclization,¹⁹ ketone 6 was oxidized to enone 13 using IBX and NMO.²⁰ To our delight, exposure of enone 13 to NaNH₂ and *t*-BuOH in THF^{8c,21} facilitated the desired cyclization and afforded C20-epimeric products 14 and 15 in 44% combined yield (1:2.3 ratio). We hypothesize that 14 forms kinetically as the major product but is prone to epimerization under the reaction conditions.²²

Having demonstrated the feasibility of the carbazolyne cyclization, we next prepared a C20-substituted substrate to test if the method could be used to forge the critical vicinal quaternary stereocenters (Scheme 3). Sequential treatment of

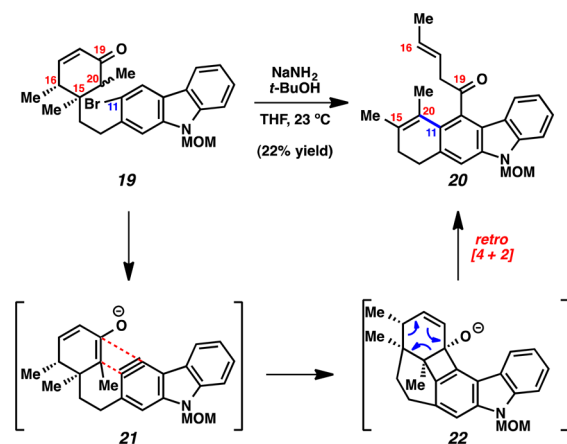
Scheme 3



enone 13 with LiHMDS and Eschenmoser's salt led to C20 alkylation.²³ Exposure of the crude adduct to *m*CPBA furnished enone 16.²⁴ Addition of prenylcuprate²³ provided 17 as an inconsequential mixture of diastereomers. Unfortunately, attempts to effect the carbazolyne cyclization of substrate 17 were unsuccessful. Analysis of the major product suggested that a skeletal rearrangement had occurred, rather than the desired formation of 18.

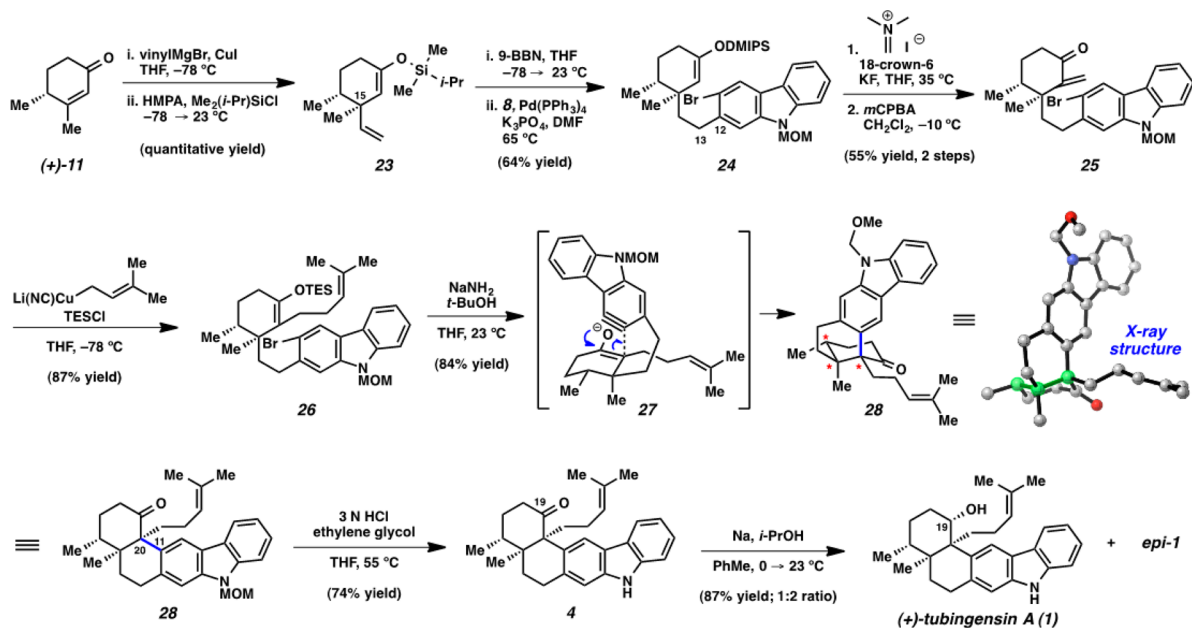
To identify the skeletal rearrangement product, we prepared the simpler C20 methylated substrate 19 and exposed it to aryne cyclization conditions (Scheme 4). The major product

Scheme 4



obtained was analogous to that formed in the attempted cyclization of 17. Interestingly, although the desired C11–C20 linkage was intact, a bond was unexpectedly formed between the carbazole and C19. In addition, the C15–C16 and C19–C20 linkages had been severed. 2D NMR analysis eventually revealed the rearranged structure to be compound 20. We propose that the desired enolate–carbazolyne intermediate indeed undergoes cyclization, but the resulting anion cyclizes onto C19, analogous to C–C aryne insertion reactions of 1,3-dicarbonyls (see transition structure 21).^{10e,25} A subsequent retro-Diels–Alder reaction, as shown in transition structure 22, and protonation yield 20.

Scheme 5



As the attempted cyclization indeed led to the desired C11–C20 bond formation, we postulated that a modified substrate might be more likely to undergo the desired transformation without rearrangement. Specifically, we envisioned that a substrate lacking the alkene in the six-membered ring could not suffer from the retro [4+2] cycloaddition and would thus not be prone to cyclohexyl ring fragmentation.²⁶ Therefore, we elected to prepare enol ether **26** (Scheme 5). In contrast to enone substrates **13** and **17**, the selectivity for C20 enolate formation for the critical carbazolyne cyclization would be dictated by the controlled formation of **26** as a single enol ether isomer.

The design and synthesis of substrate **26** ultimately proved fruitful and enabled an efficient enantiospecific total synthesis of tubingensin A (**1**), which is summarized in Scheme 5.²⁷ Vinyl cuprate addition to enone **11**, followed by trapping with Me₂(*i*-Pr)SiCl (DMIPSCl), gave enol ether **23**. Next, a one-pot hydroboration/Suzuki coupling (analogous to that described previously) afforded the desired coupled product **24** in 64% yield. Using the labile DMIPS enol ether, enone **25** was generated via a two-step sequence.²⁸ Subsequent cuprate addition and trapping with TESCl supplied arynes cyclization precursor **26**. Fortuitously, in the key step, arynes cyclization delivered the desired product **28** in 84% yield and established the vicinal quaternary centers with complete diastereoselectivity. The structure of **28** was verified by X-ray crystallography. Only two steps remained to complete the total synthesis: *N*-deprotection and ketone reduction. The removal of the MOM group of **28** provided ketone **4** smoothly. However, reduction proved more challenging. An array of reducing agents were examined, all of which gave the undesired C19 epimer as the major product.²⁹ The best conditions using Na/*i*-PrOH delivered a 1:2 ratio of tubingensin A (**1**) and its C19 epimer. It should be noted that oxidation of *epi*-**1** gives **4**, so the undesired epimer can be readily recycled.³⁰ Nonetheless, synthetic (+)-**1** was found to be identical to an authentic sample in all respects.

In summary, we have achieved a concise enantiospecific total synthesis of tubingensin A (**1**). Our synthesis features an arynes

cyclization to efficiently introduce the vicinal quaternary stereocenters of the natural product and proceeds in only nine steps (longest linear sequence) from known compounds. Further efforts to probe the use of arynes for the assembly of challenging molecular scaffolds are currently underway in our laboratory.

■ ASSOCIATED CONTENT

📄 Supporting Information

Detailed experimental procedures, compound characterization, and crystallographic data (CIF). 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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- (26) Although this strategy would not preclude the corresponding cyclobutyl ring formation, it was plausible that such an intermediate would fragment to give the desired carbazolyne cyclization product.
- (27) Alternatively, **26** could be derived from **17**; see the SI for details.
- (28) Analogous attempts to employ TBS ether **12** were unsuccessful.
- (29) Reduction of **4** with LiAlH₄ provided a ~1:7.7 mixture favoring *epi-1*. Attempts to reduce **28** with sodium naphthalenide gave a ~1:5 ratio favoring the undesired epimer, while borohydride reducing agents (e.g., L-Selectride, NaBH₄) were found to be unreactive. Meerwein–Ponndorf–Verley reduction was also unsuccessful.
- (30) Dess–Martin oxidation of *epi-1* gives **4** (60% yield, unoptimized). Exhaustive efforts to effect Mitsunobu inversion of *epi-1* failed.