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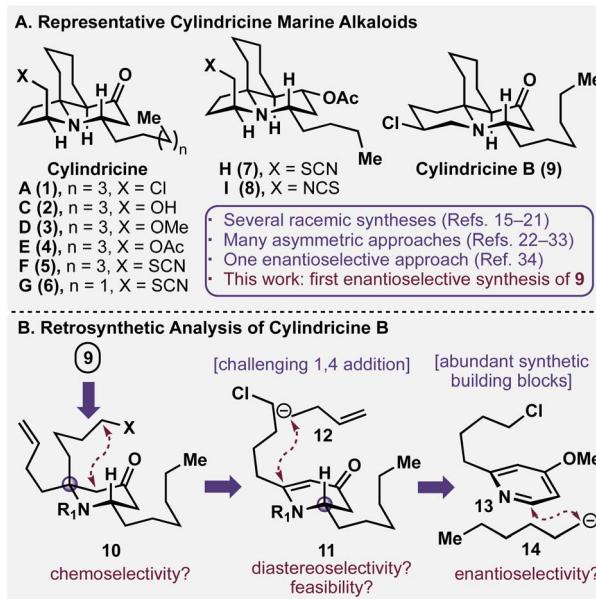
## Introduction

Marine natural products have been a unique source of leads for small molecule therapeutics for the past half-century.<sup>1,2</sup> Despite their therapeutic promise, however, it can often be challenging to source these bioactive molecules in large quantities due to their relative paucity and/or arduous isolation. As a result, synthetic chemistry plays an elevated role in elucidating the medicinal indices of these natural products, as their necessity demands strategically and tactically practical designs for laboratory preparation.<sup>3</sup> In particular, the total synthesis of marine alkaloids has benefitted the clinical advancement of several unique chemotypes, including tetrodotoxin,<sup>4,5</sup> lirubinectedin (Zepzelca®),<sup>6,7</sup> and salinosporamide A (Marizomib).<sup>8–10</sup>

Isolated off the coast of Tasmania in southern Australia, the cylindricine natural product family is constituted of several structurally intricate and stereochemically dense marine alkaloids (see Fig. 1A). Topologically, they are characterized by a tricyclic scaffold with four stereogenic centres, a piperidone core, and most family members bear a C14 heteroatomic functionality that varies between a chloride (1, 9),<sup>11</sup> alcohol (2), ether (3), acetate (4),<sup>12</sup> thiocyanate (5–7), and isothiocyanate (8).<sup>13</sup> Additionally, each family member has a chiral alpha-tertiary amine moiety that constitutes the primary synthetic hurdle, as these congested centres have been cited for being historically challenging for construction.<sup>14</sup> Intriguingly, while many racemic<sup>15–21</sup> and enantiospecific preparations of these alkaloids have been reported in the literature,<sup>22–33</sup> only one approach towards cylindricine C (2) is enantioselective in nature.<sup>34</sup> Herein, we report the inaugural enantioselective

preparation of (+)-cylindricine B (9), a flagship isomer of this marine alkaloid family.

A retrosynthetic analysis of cylindricine B (9) is depicted in Fig. 1B. It was envisioned that the chlorinated piperidine moiety could be forged at a late stage in the synthesis between the piperidine nitrogen and the adventitious butenyl side chain (see 10).<sup>15</sup> Furthermore, intramolecular enolate trapping *via* nucleophilic substitution of a pendant halide would enable the generation of the *cis*-azadecalolinone ring system.<sup>35</sup> The planned introduction of the butenyl group in 10 would require the addition of a four-carbon nucleophile (12) in conjugate fashion to vinyllogous amide 11. This prospective transformation is



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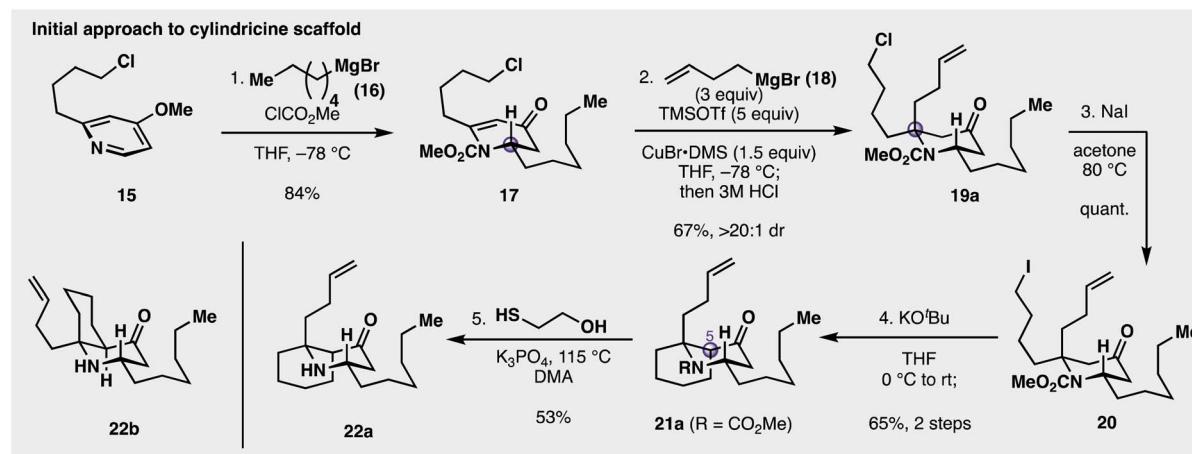


Fig. 2 Original synthetic approach to the cylindricines. This approach resulted in the synthesis of **22a**, which, based on comparison to past literature, is the 5,10-bis-epimeric diastereomer of the desired intermediate (structure is as depicted above).

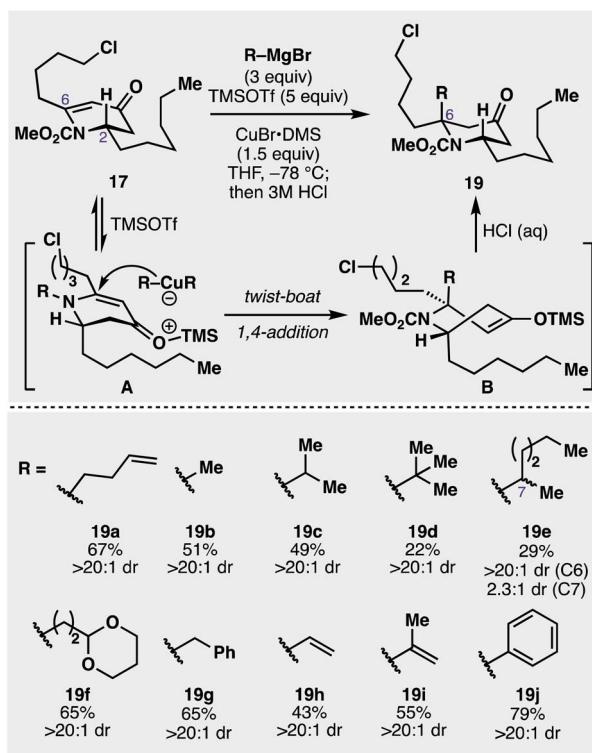


Fig. 3 Investigation of the scope for the 1,4 addition to vinylogous amide **17** to furnish multiply substituted piperidinones of structure **19**.

deceptively challenging, and while this type of addition is common for unsubstituted variants,<sup>36</sup> the establishment of this fully substituted centre has little precedent in the chemical literature.<sup>37–39</sup> However, we envisioned that its realization in this synthetic context would enable a direct access to the appropriately functionalized piperidone core. Vinylogous amide **11** was envisioned to arise from *in situ* activation and dearomatization of commercial pyridine **13** with anion **14** following formation of an intermediate pyridinium. It should be noted that Donohoe<sup>19</sup>

and Comins<sup>37</sup> have described dearomatic strategies towards the cylindricines. But, as articulated in their work, the establishment of the desired alpha tertiary amine either required circuitous downstream functional group interconversion or resulted in an undesired and/or unresolvable stereochemical outcome. By solving this difficult tactical requirement (*i.e.* conversion of **11** to **10**), concise synthetic access would be realized through the leveraging of a feedstock pyridine and simple organometallic nucleophilic coupling partners as starting materials.

## Results and discussion

The initial synthetic approach towards the cylindricines is depicted in Fig. 2. At the outset, a racemic construction of **9** was evaluated to assess the feasibility and selectivity of each step in the intended sequence. Commercially available pyridine **15** was selected as the starting point, and was treated with methyl chloroformate followed by *n*-hexylmagnesium bromide (**16**) at -78 °C to give piperidinone **17** in 84% yield. Next, the key construction of the fully substituted centre was evaluated. While many reaction parameters (*e.g.*, metal salts, Lewis acids) and substrates (differing carbamoyl groups) were evaluated, it was determined that the use of superstoichiometric amounts of organocuprate in the presence of excess trimethylsilyl triflate (TMSOTf) resulted in a 67% yield of desired product **19a** (see ESI†), following acidic hydrolysis of the intermediate silyl enol ether. Catalytic amounts (20 mol%) of Cu can be employed, but with lower yields and longer reaction times. At this stage of the synthesis, however, it was unknown whether this addition gave the desired diastereoselectivity needed to complete the synthesis of **9**. Thus, as 2D NMR spectroscopic analysis was inconclusive as to the facial preference of the addition, it was decided to validate this through the synthesis of a more elaborated and putative precursor. In this vein, it was seen that targeting **22b** (see Fig. 2) was operative, as its structure, if correct, had been previously reported by Snider and co-workers.<sup>15</sup> With this goal in mind, chloropiperidine **19a** was

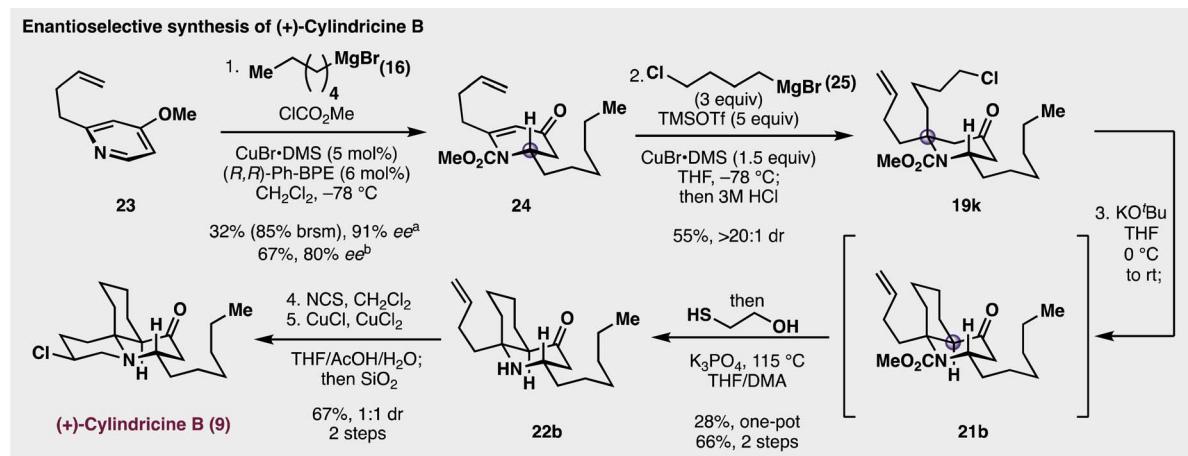


Fig. 4 Modified and successful synthetic approach to cylindricine B. <sup>a</sup>Reaction performed with 2 equiv. of  $C_6H_{13}MgBr$  and 2 equiv. of  $ClCO_2Me$ . <sup>b</sup>Reaction performed with 3 equiv. of  $C_6H_{13}MgBr$  and 3 equiv. of  $ClCO_2Me$ .

converted to its corresponding iodide (**20**) with  $NaI$ , and then treated with  $KO'Bu$  in THF to promote cyclization to the *cis* azadecalineone **21a**, while establishing the third stereocentre at C5 in 65% over the two steps. Cleavage of the methyl carbamate was accomplished with 2-mercaptopropanol in the presence of potassium phosphate at elevated temperature to cleanly deliver aminoketone **22a** in 53% yield. This compound did not spectroscopically (<sup>1</sup>H NMR) match Snider's reported intermediate (**22b**), likely indicating that the conversion of **17** to **19a** occurred in an anti fashion with respect to the established C2 stereocentre. This anti diastereoselectivity was significant because it provided evidence that conjugate additions to 2,6-disubstituted 4-piperidinones can proceed with the opposite facial preference compared with their 2-monosubstituted counterparts.<sup>36</sup> As many alkaloid structures contain these alpha-tertiary amine substructures,<sup>14</sup> this understanding of the feasibility and stereoselectivity will enable this transformation's use in downstream synthetic applications.

Given the success of this diastereoselective 1,4 addition to **17**, we wanted to further evaluate the scope of nucleophiles competent for addition to this prochiral centre (see Fig. 3). In addition to butenylmagnesium bromide (**16**), other alkyl Grignard reagents added diastereoselectively to the 4-piperidinone including methyl (**19b**), isopropyl (**19c**), and even *t*-butylmagnesium bromide (**19d**) added in with moderate efficiency (22% yield). Utilization of a prochiral Grignard reagent derived from 2-bromohexane resulted in the formation of two new stereocentres with a 2.3 : 1 diastereomeric ratio about the C7 stereocentre and >20 : 1 about the C6 stereocentre (see **19e**). Another Grignard bearing an acetal functionality (**19f**), potentially useful for downstream manipulation, was diastereoselectively appended in 65% yield. Benzylmagnesium bromide (**19g**), vinylmagnesium bromide (**19h**), and isopropenylmagnesium bromide (**19i**) were also successfully added onto the piperidone scaffold in 65%, 43%, and 55% yields respectively. Furthermore, product **19j** was synthesized in 79% from the addition of the corresponding phenyl Grignard reagent. While A<sup>1,3</sup> strain between the 2-substituent and the

carbamoyl group has proven a driving force for the diastereoselectivity of these additions in the past, we hypothesized the additional C6 alkyl chain complicated the traditionally accepted pathway for these additions (see Fig. 3). As Comins' has alluded to in prior work,<sup>37</sup> the additional C6 substituent provided a complex stereoelectronic conundrum in which the axially disposed conformation of the C2 group in the substrate (**A**), in concert with the carbamoyl group and the C6 substituent, likely drives the observed addition to proceed through an initial twist-boat conformation (**B**) that results in the observed anti diastereoselectivity, that, upon hydrolysis, give the observed products (**19a–k**). Importantly, all these additions proceeded with complete diastereorecontrol (>20 : 1) and provide a facile avenue for a diverse array of highly substituted 4-piperidone congeners.

Having understood the diastereoselective nature for synthesizing this fully substituted centre, a modified approach to the synthesis of cylindricine B (**9**) was undertaken (Fig. 4). In addition to a strategic change in the starting material, it was also surmised that the synthesis could be rendered enantioselective. To this end, butenylpyridine **23** was employed as the starting material for the enantioselective generation of piperidinone **24**. Based on precedent from Harutyunyan and co-workers,<sup>40</sup> treatment of **23** with 3 equivalents of methyl chloroformate and Grignard **16** (3 equiv.) in the presence of the  $CuBr$  complexed with (*R,R*)-Ph-BPE in  $CH_2Cl_2$  gave **24** in 67% yield and with 80.3% ee. Notably, a higher asymmetric induction was observed when only 2 equivalents of the chloroformate and the nucleophile (**16**) were employed, but the yield of **24** decreased to only 32%, but with higher enantioselectivity (91.4% ee). We attribute the lower enantiomeric excess in the first iteration was due to a slightly higher rate for the racemic background reaction of the Grignard reagent adding the pyridinium electrophile. Additionally, the preparation of **16** in ether was essential for the enantioselectivity as utilizing THF as a cosolvent resulted in poor asymmetric induction (17% ee). With **24** in hand, diastereoselective addition of chlorobutyl Grignard **25** in the presence of  $CuBr(DMS)$  generated piperidone **19k** in good yield

and with high diastereoselectivity. Next, deprotonation of **19k** with excess KO<sup>t</sup>Bu facilitated the intramolecular displacement of the pendant chloride to synthesize the azadecaline **21b**,<sup>35</sup> which, upon further treatment with 2-mercaptoethanol and base gave a modest yield (28%) of amine **22b**.<sup>41</sup> Conveniently, separating the cyclization and carbamate cleavage events resulted in a much higher two-step yield of 66% percent (72% and 91% for each step, respectively). Finally, chlorination of the amine was cleanly accomplished with NCS, and subsequent treatment with a CuCl/CuCl<sub>2</sub> mixture promoted amino chlorination of the butenyl side chain. Initially, this reaction formed a mixture of cylindricine A, cylindricine B, and their corresponding epimers. As precedented by Snider<sup>15</sup> and Heathcock,<sup>16</sup> this atom-transfer reaction was not diastereoselective, to which, following chromatographic separation of the reaction mixture, rendered pure samples of (+)-cylindricine B (**9**) and a 9:1 mixture of 13-*epi*-cylindricine B and 13-*epi*-cylindricine A. The successful synthesis of the natural product further confirmed the diastereoselectivity of the key 1,4-addition to establish the chiral alpha-tertiary amine centre. Lastly, it is worth noting that while earlier reports claimed that carbamate cleavage for substrates such as **21b** were not feasible,<sup>16</sup> the syntheses above disprove any previous claims of inertness about these protected, multiply substituted piperidone scaffolds.

## Conclusion

In conclusion, we have accomplished the first reported enantioselective synthesis of (+)-cylindricine B (**9**) in 5 or 6 steps from commercially available starting materials. This also constitutes only the second enantioselective route to the cylindricine family of marine alkaloids for which, to date, asymmetric syntheses have mainly hinged on using the chiral pool as synthetic starting points. A rare, but tactically important 1,4-addition to a 4-piperidinone (e.g., **24**) was utilized and further evaluated for its broader synthetic utility. This new protocol for the synthesis of (+)-**9** proceeds with a maximum 16% overall yield constituting one of the most concise routes reported for this synthetic target. Overall, the brevity of the approach was enabled by overcoming tactical challenges associated with the construction of multiply substituted piperidines in addition to the strategic leveraging of robust heteroaromatic starting materials. As dearomatic retrosynthetic logic continues to inspire efficient access to numerous alkaloid scaffolds, it is contended that the future is bright for its ability to inspire novel tactical and strategic disconnections in heterocyclic synthesis.

## Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

## Author contributions

This project included a joint conceptualization (JMS and DMD) while its experimental implementation was also carried out jointly (DMD and VKA). The original draft of the manuscript was

composed by the corresponding author (JMS), and all authors were involved in its review and editing.

## Conflicts of interest

There are no conflicts to declare.

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