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Directed Orthometalation and the Asymmetric Total Synthesis of *N*-Deoxymilitarinone A and Torrubiellone B

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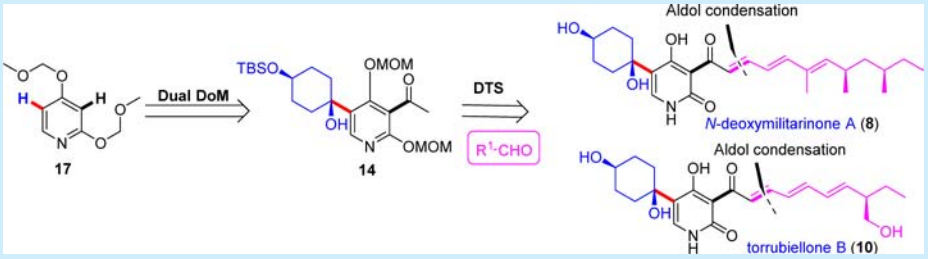
Supporting Information



ABSTRACT: A diverted total synthesis (DTS) approach to the total synthesis of pyridone alkaloids *N*-deoxymilitarinone A (**8**) and torrubiellone B (**10**) has been developed. The common intermediate **14** was first assembled by a dual directed orthometalation process using a methoxymethyl group as directed metalation group. Other crucial steps include the assembly of polyenes under aldol condensation for DTS using general and concise strategy and diastereoselective synthesis of the *syn*-dimethyl array by an Evans aldol reaction.

Pyridone alkaloids, which comprise a small group of fungal metabolites, possess an expansive repertoire of biological activities intimately mirroring their structural diversity, ranging from antifungal, antibacterial, insecticidal, and cytotoxic activity to the induction of neurite outgrowth in different cell assays.[1] From a general point of view, pyridone alkaloids are attractive targets for total syntheses because of their unique 3,5-disubstituted 4-hydroxypyridone structure, their various biological and chemical properties, and the difficulties in obtaining them in pure forms from natural sources. More than 50 pyridone alkaloids with related structures are known, and synthetic pathways to these molecules have been investigated extensively.[2] Previous targets in this class of natural products, including tenellin (**1**),[3a] bassianin (**2**),[3b] farinosone A and B (**3** and **4**),[3c] militarinone D (**5**),[3d] and pyridovericin (**6**)[3e] (Figure 1), have focused on the construction of 4-hydroxy-5-phenyl-2-pyridone skeletons via palladium-mediated C−C bond formation at the C5-position. Based on the intriguing structural relationships, several proposed biogenetic relationships connecting the above-mentioned militarinones were revealed in some detail, showing how the biosynthetic sequence likely proceeds.[4] Few examples focused on 4-hydroxy-5-alkyl-2-pyridone skeletons such as those present in *N*-deoxymilitarinone A (**8**),[5a] militarinone A (**9**),[5b] torrubiellones A and B (**11** and **10**),[5c] militarinones E and F (**12** and **13**)[5d] (Figure 1), and thus synthesis to this subclass of natural products remains a challenge. Notably, the only example of total synthesis of 4-hydroxy-5-alkyl-2-pyridones including apiosporamide and YM-215343 to date was accomplished by Williams and co-workers in 2005.[6]

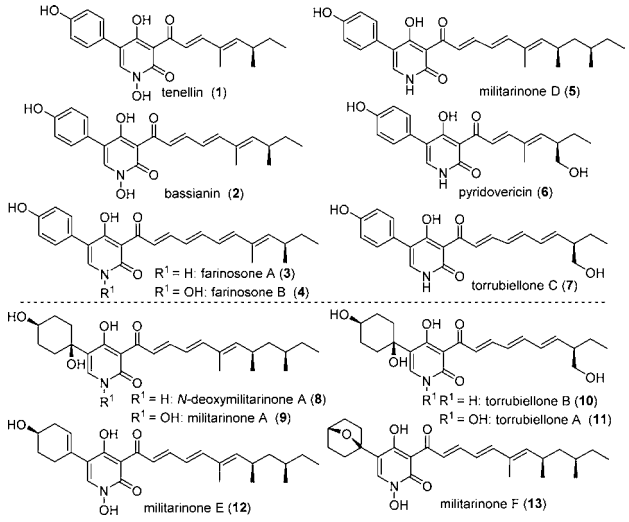


Figure 1. Selected members of the pyridone alkaloids family.

N-Deoxymilitarinone A, a new pyridone alkaloid member of the militarinone family, was initially isolated by bioassay-guided fractionation from the mycelium of the entomogenous fungus *Paecilomyces farinosus* RCEF 0097 by Hamburger and co-workers in 2006. It displayed neurite sprouting in PC 12 cells when tested at 33 and 100 μM concentrations while a cytotoxic effect was observed in human neurons (IMR-32) at a

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concentration of 100 μM.[5a] Torrubiellones A and B (**11** and **10**), which are new pyridone alkaloids, were recently isolated from the spider pathogenic fungus Torrubiella sp. BCC 2165 by Isaka and co-workers. Torrubiellone A (**11**) exhibited antimalarial activity with an IC_{50} value of 8.1 μM, while very weak cytotoxic activity was shown.[5c] To date, no total synthesis or synthetic approach to pyridone alkaloids **8**–**13** has been reported.

Since pyridone alkaloids possess a similar core structure and differ only in their polyene chain structure and substitution pattern, we implement a strategy that exploits diverted total synthesis to focus on increasing structural and library diversity in a more efficient manner, constructing future pyridone analogue syntheses for biological studies. Indeed, these targets are perfect for application of a unified approach as recently demonstrated by Gademann and co-workers via a Horner–Wadsworth–Emmons (HWE) reaction on a densely functionalized pyridone β-ketophosphonate.[7] Herein we report the successful development of a strategy that has enabled completion of the first asymmetric total synthesis of *N*-deoxymilitarinone A (**8**) and torrubiellone B (**10**), devising the route for maximum flexibility of future forays into analogue synthesis. The general concept and synthetic strategy for this total synthesis is illustrated in Figure 2. With regard to the final

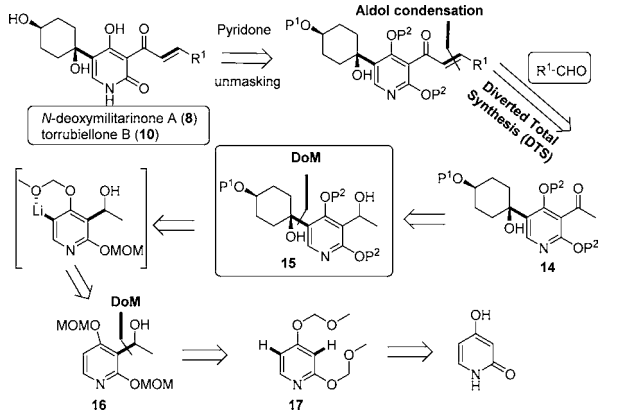
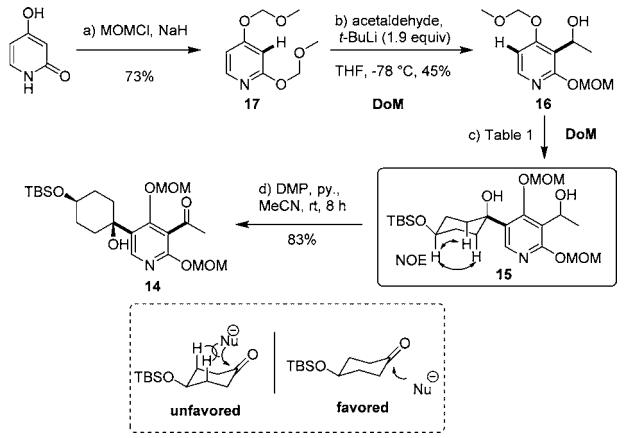


Figure 2. Retrosynthetic strategy for 4-hydroxy-5-alkyl-2-pyridone alkaloids.

construction of target molecules, the key step in this synthesis involves aldol condensation of the key advanced intermediate **14** with appropriately functionalized conjugated aldehydes, which is expected to give the desired *E* isomers in high yields.[8] Importantly, an additional challenge is the stereoselective construction of the core skeleton of 4-hydroxy-5-alkyl-2-pyridone. We envisioned that the key advanced intermediate would be constructed by a stereoselective alkylation at the 5-position of the pyridone via a directed orthometalation (DoM) process using methoxymethyl groups (MOM) as directed metalation groups (DMGs).[9] To the best of our knowledge, such an approach has never been applied in the numerous reported total syntheses of pyridone alkaloids. Retrosynthetic simplification of alcohol **16** based on a secondary DoM reaction process for regioselective alkylation leads to precursor **17**, which is in turn obtainable by the protection of 4-hydroxy-2-pyridone. The brevity of this synthetic approach coupled with the simplicity of the precursors in terms of structure compelled us to embark on its implementation.

In our synthesis, the first challenge was the choice of the appropriate protecting group along with the DMGs for the hydroxy group on the pyridone ring (Scheme 1). Standard silyl

Scheme 1. Synthesis of the Key Advanced Intermediate Pyridone Unit 14



protecting groups, such as TBS, as well as alkyl-containing groups, such as Me, Bn, or PMB, tertiary amide, and carbamate DMGs such as OPiv or $OCONEt_3$, led to decomposition during isolation or on their removal. Finally, we found that the methoxymethyl group proved ideal for our purposes. Ultimately, we were able to achieve regioselective ortho-lithiation at the C3-position without affecting the C5-position of 2,4-protected pyridone in the presence of MOM as directing group followed by addition to acetaldehyde. We are pleased to find that only C3-substituted alcohol **16** was observed with 45% yield when the reaction mixture was treated with 1.9 equiv of *t*-BuLi.[10] The corresponding alcohol **16** provided another challenge for stereoselective C–C bond formation at the C5-position of 2,4-protected pyridone. Reaction with 4-(*tert*-butyldimethylsilyloxy)cyclohexanone via secondary DoM strategy and using MOM as DMGs is probably the most difficult part in this proposed total synthesis protocol. First, we tried to utilize the same strategy of DoM reaction using MOM as the directing group for the C–C formation on C3 that we have successfully developed in the initial DoM reactions. Not surprisingly, only trace amount of the desired product **15** was detected by treating with different lithium reagents such as *n*-BuLi, *s*-BuLi, *t*-BuLi, PhLi, and MESLi, as well as organomagnesium reagents such as *i*-PrMgCl. To enhance the reactivity and stereoselectivity of this reaction, TMEDA was added as ligand in the presence of 4 equiv of *n*-BuLi. However, the reaction proceeded to give poor yield (23%) of the desired product. Further optimization revealed that 4 equiv of ligand TMEDA coordinated with 4 equiv of *s*-BuLi at −60 °C as the ideal condition for this transformation, giving a moderate yield (44%) and good stereoselectivity (*syn*/*anti* = 10:1) as determined by 2D NMR spectroscopy studies (Table 1).[11] Notably, around 40% of the starting material was recovered from the reaction, which was subjected to the same reaction again. The stereoselectivity can be explained by the steric hindrance due to 1,3-diaxial interactions caused by the bulky incoming nucleophile, resulting in a more preferable attack from the equatorial position rather than axial position. Subsequently, a final oxidation of the alcohol **15** provided the desired key intermediate ketone **14**.

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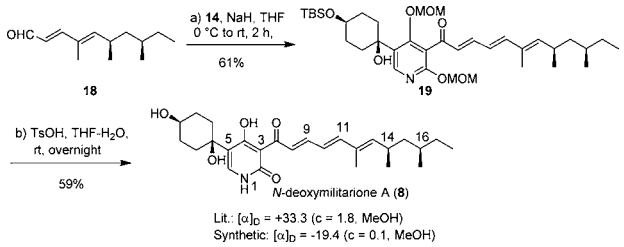
Table 1. Optimization of the DoM Reaction with 16 and (*tert*-Butyldimethylsilyloxy)cyclohexanone

reagents	T (°C)	yield[a] (%)	*syn*/*anti*[b]
n-BuLi or *s*-BuLi	−78 to rt	trace	nd
s-BuLi or *t*-BuLi	−78 to rt	trace	nd
MESLi or *i*-PrMgCl	−78 to rt	trace	nd
n-BuLi + TMEDA	−78 to rt	23	6:1
n-BuLi + HMPA	−78 to rt	11	5:1
s-BuLi + TMEDA	−78 to rt	34	9:1
t-BuLi + TMEDA	−78 to rt	18	10:1
s-BuLi + TMEDA	−30 to rt	complex	nd
s-BuLi + TMEDA	−60 to rt	44	10:1

[a]Isolated yield. [b]Ratio was determined by crude ^{1}H NMR.

Next, we focused on the synthesis of aldehyde **18** with all-*trans* polyene backbones via an efficient reaction sequence of an Evans aldol reaction, Wittig olefination, ester reduction, and Swern oxidation according to the reported procedures (Scheme 2).[12] The described protocols provided the required *R*-configured all-*E* unsaturated aldehyde efficiently and stereoselectively and were very reproducible on different scales.

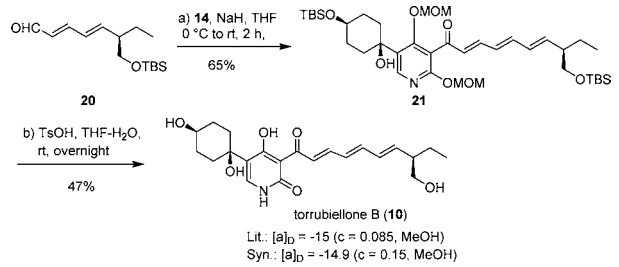
Scheme 2. Completion of the Total Synthesis of *N*-Deoxymilitarinone A (8)



With the key advanced intermediate pyridone unit **14** and all corresponding aldehyde side chains **18** and **20** successfully prepared, the first step in the late stage of the synthesis focused on the construction of the C═C via aldol condensation of the pyridone core structures with a polyene aldehyde chain, which constitutes the key step in the synthetic route (Scheme 2). We found that the aldol condensation step is prone to a range of side reactions. After careful optimization of the reaction parameters, the formation of byproducts is almost completely suppressed. The optimum condition required the use of 3 equiv of NaH in degassed THF at 0 °C with a 1:1.2 ratio of ketone **14** to aldehyde. The targeted protected natural product **20** was finally obtained after a few hours with moderate yield and good *E*/*Z* selectivity (10:1). Notably, this pyridone intermediate has the provision to react with other side chain aldehydes to access 4-hydroxy-5-alkyl-2-pyridone analogues under a similar protocol. Finally, subsequent cleavage of protecting groups was effected using TsOH to generate the synthetic product *N*-deoxymilitarinone A (**8**). The analytical data of the synthetic material were found to be identical in all respects in comparison with the published values,[5a] except for the inverted $[\alpha]_D$ value. The absolute configuration of the side chain portion therefore could not be confirmed unambiguously. However, we assumed the absolute configuration of *N*-deoxymilitarinone A to be (14*S*,16*S*), considering the proposed *syn* relative configuration of C14 and C16.[5a]

The synthesis established for *N*-deoxymilitarinone A, but using a different side chain aldehyde **20**, was also utilized for the synthesis of torrubiellone B. The same approach (diastereoselective alkylation, Wittig olefination, ester reduction, and Swern oxidation) was applied to prepare aldehyde **20**,[13] which was subjected to aldol condensation. Coupling the side chain with MOM-protected pyridone **14** delivered, after deprotection, the expected natural product torrubiellone B (**10**) (Scheme 3). All spectroscopic data were in good agreement with those obtained from the authentic sample.[5c]

Scheme 3. Completion of the Total Synthesis of Torrubiellone B (10)



In conclusion, we have reported a modular assembly for the efficient synthesis of a family of sensitive polyene pyridone alkaloids *N*-deoxymilitarinone A (**8**) and torrubiellone B (**10**). Notable elements in this divergent synthetic route include the following: (1) common intermediate **14** assembled by a dual directed orthometalation process using MOM as directed metalation groups, (2) assembly of the polyenes under aldol condensation for DTS in a few general steps, and (3) diastereoselectctive synthesis of the *syn*-dimethyl array in **18** by an Evans aldol reaction. With this synthetic approach in hand, future work will concentrate on an extension toward the total synthesis of other structurally similar natural products such as militarinone E and militarinone F.[5d] We believe that this work could be used to generate a library of pyridone alkaloid analogues and set the stage for in-depth structure−activity relationship studies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. 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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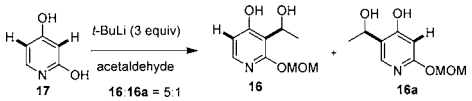
(10) C5-substituted alcohol **16a** was observed when the reaction was treated with 3.0 equiv of *t*-BuLi.



(11) We also performed the DoM reaction with **16** using $CeCl_3$ protocol during the optimization stage for this reaction under various conditions. Unfortunately, only a trace amount of desired product was obtained and the deprotection of one of the MOM groups resulted in the formation of major side product. (a) Yamashita, S.; Iso, K.; Kitajima, K.; Himuro, M.; Hirama, M. *Tetrahedron Lett.* **2009**, *50*, 3277−3279. (b) Yamashita, S.; Kitajima, K.; Iso, K.; Hirama, M. *J. Org. Chem.* **2011**, *76*, 2408−2425.

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