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Total Synthesis of (±)-Cordypyridones A and B and Related Epimers

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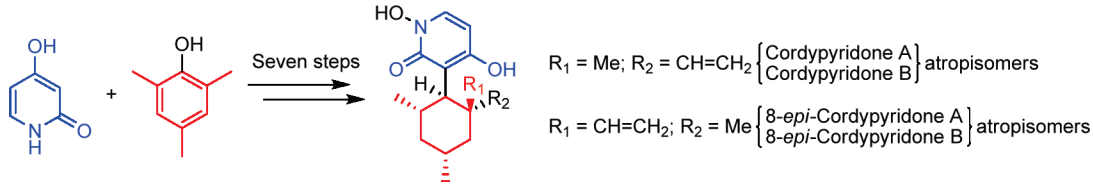
ABSTRACT



Efficient racemic synthesis of two antibacterial and antimalarial natural products, cordypyridones A and B, was achieved from inexpensive, commercially available starting materials in an overall yield of 15% (8% and 7%, respectively). This convergent synthesis utilizes a key coupling step of two fragments and the subsequent functional group transformations lead to the target compounds and their 8-*epi*-analogues.

The atropisomeric cordypyridones A (**1a**) and B (**1b**) are attractive targets for total synthesis due to their highly functionalized compact structures and interesting biological activities (Figure 1). Cordypyridone A was first isolated by Houck from the fungus culture OS-F61800 and was shown to induce erythropoietin in human cells.[1] Cordypyridones A and B were isolated by Isaka et al. in 2001 from a culture broth of the insect pathogenic fungus Cordyceps nipponica BCC 1389 and were shown to display potent in vitro antimalarial activity against *Plasmodium falciparum* (K1, multidrug resistant strain) with IC_{50} values of 66 and 37 ng/mL respectively, c.f. 160 ng/mL for chloroquine diphosphate.[2] In 2002, Clardy et al. reported the isolation of cordypyridones A and B from Akanthomycin gracilis ARS2910 and the cordypyridones were shown to exhibit antibacterial activity against *Staphylococcus aureus* producing a kill zone at 25 ng per application.[3]

The biological activities of *N*-hydroxypyridones have long been recognized and are thought to originate from their ability to bind to metal ions under physiological conditions.[4] Compounds of this type are widely considered to be siderophores, allowing microorganisms to sequester insoluble iron(III) salts.[5] To this end, the structurally related compound pyridoxatin (**2**) has been isolated as its Fe[L_3] complex (named terricolin) and the absolute configuration was elucidated by X-ray crystallographic methods.[6] It is noteworthy that the absolute stereochemistry of the 8-, 10-, and

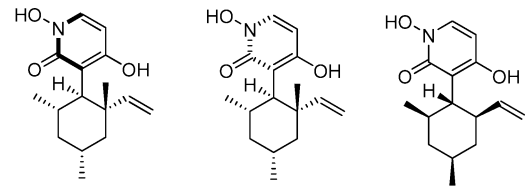


Figure 1. Cordypyridones A and B (atropisomers) and pyridoxatin.

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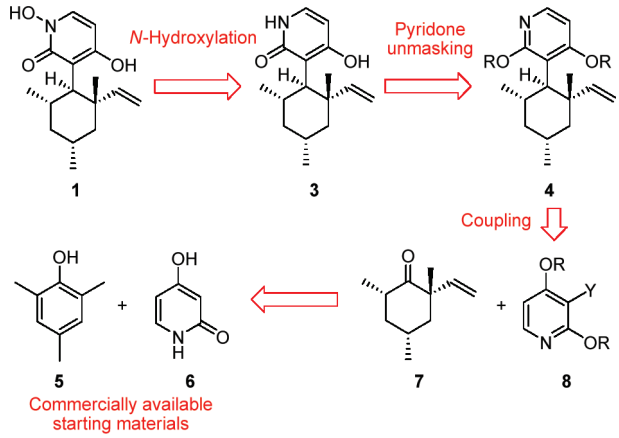
12-substituents of cordypyridones A and B have opposite stereochemistry to that reported in pyridoxatin.

Although the total synthesis of (±)-pyridoxatin (**2**) has been reported by Snider and Lu in as early as 1994,[7] the approach cannot be readily applied to the synthesis of the cordypyridones. In addition, although the methodology as reported was elegant in design, the reported synthetic route is not amenable to the rapid synthesis of related compound libraries of related structures. To this end, the objective of our work reported here is to develop a convergent synthetic route to the cordypyridones A and B, structuring the route for maximum flexibility for future forays into analogue synthesis. Our study also constitutes the first reported total synthesis of cordypyridones A and B.

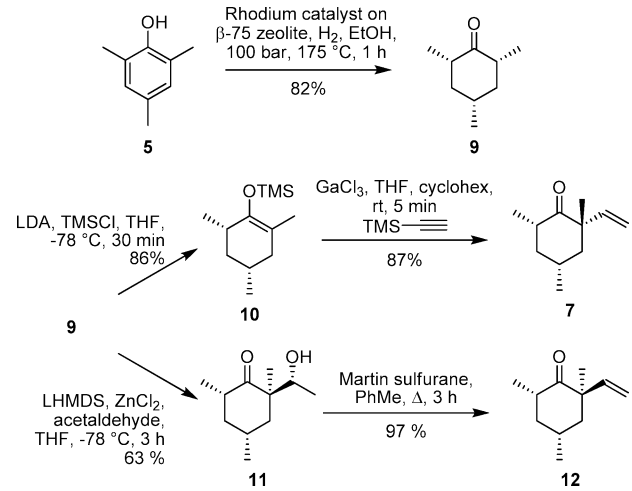
Our retrosynthetic analysis of cordypyridones A and B is shown in Scheme 1. The key step in the synthesis would utilize the nucleophilic attack of a pyridyl anion **8** onto the appropriately functionalized cyclohexanone **7**, with removal of the superfluous hydroxyl group being effected diastereoselectivity. The brevity of this analysis along with the structural simplicity of the precursors makes this route attractive for implementation.

Scheme 1. Retrosynthetic Analysis of Cordypyridones A and B



The total synthesis of (±)-cordypyridones A and B commenced with the preparation of 2,4,6-trimethylcyclohexanone (**9**). This *meso*-ketone had been synthesized previously by Mori et al. in two steps by hydrogenation of the commercially available phenol **5** with Raney nickel and subsequent oxidation of the cyclohexanol with Jones' reagent.[8] In our laboratories, we had previously developed a zeolite-supported rhodium catalyst for applications in hydrogenation reactions.[9] To our delight, the use of this heterogeneous catalyst in the reduction of **5** gave the *meso*-cyclohexanone **9** directly in 82% yield. This presumably arises from the "controlled" reduction (as opposed to the over-reduction) of **5** to the cyclohexenol, which then

Scheme 2. Racemic Synthesis of the Cyclic Vinyl Ketones



spontaneously tautomerises to form the *meso*-ketone **9** as a single diastereoisomer (Scheme 2). With the *meso*-ketone in hand, the installation of the vinyl substituent at the α-position to the ketone functionality can be easily achieved. By using methodology that has been established for cyclohexanones,[10] the vinyl substituent can be installed *syn* to the methyl substituents on the cyclohexane ring by coupling the corresponding silyl enol ether **10** with ethynyltrimethylsilane in the presence of gallium trichloride. In his paper, Yamaguchi describes the mechanism of such systems in which gallium, after migration to α-carbon, favors an equatorial position with insertion of the vinyl substituent proceeding with retention of configuration.[10] This gave a mixture of diastereomers (>9:1) in favor of the desired vinyl ketone **7**.

The epimeric vinyl compound can also be synthesized from the meso ketone **9** and hence this provides access to 8-*epi*-cordypyridones A and B. Aldol reaction of **9** with acetaldehyde led to the alcohol **11** with the new carbon−carbon bond installed *anti* to the methyl substituents on the cyclohexanone ring. The relative stereochemistry observed in **11** occurs due to the steric effect of the 4,6-dimethyl groups, which directs the attack of the chelated acetaldehyde to occur from the less sterically hindered face. This stereochemistry was confirmed through single crystal structural analysis as shown in Figure 2. Elimination of the hydroxyl group in **11** can be effected efficiently with both Martin's sulfurane as well as under basic conditions via the corresponding mesylate or tosylate.

With the cyclohexanone fragment in hand, we turned our attention to the synthesis of the pyridine **13**. This was readily

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(9) **Synthesis of the Rhodium Catalyst.** Rhodium trichloride (0.38 g) in ultrapure water (4.0 mL) was added to β-H 75 zeolite (5.00 g) suspended in ultrapure water (8 mL). The resulting slurry was stirred at room temperature for 10 h to achieve a uniform dispersion after which the water was removed under reduced pressure. The solid residue was calcinated in a Carbolite Furnace (CWF-1200), using the following temperature program with a temperature rate increase of 2 °deg/min: (a) hold at 200 °C for 2 h; (b) hold at 400 °C for 2 h; (c) hold at 500 °C for 8 h. The calcinated material was powdered and further dried in an oven at 90 °C for 5 h.
(10) Arisawa, M.; Miyagawa, C.; Yamaguchi, M. *Synthesis* **2002**, 138.

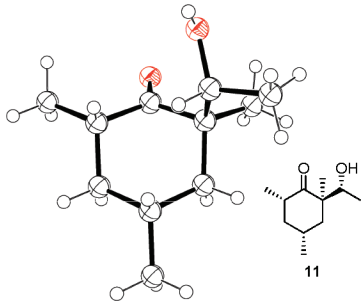


Figure 2. X-ray crystallographic analysis of 2-(1-hydroxyethyl)-2,4,6-trimethylcyclohexanone **11** was employed to prove the relative stereochemistry of the α-quaternary carbon center. Displacement ellipsoids show 50% probability levels. Hydrogen atoms are drawn as circles with small radii. The crystal structure has three molecules in the asymmetric unit with only one enantiomer shown for clarity.

accessed in a one-pot two-step process from commercially available 2,4-dihydroxypyridine **6** by regioselective bromination and subsequent *O*-methylation (Scheme 3).

The assembly of the core structure of the cordypyridones constitutes the key step in the synthetic route. This was achieved via a lithium−halogen exchange of **13**, followed by nucleophilic attack of the pyridyl anion on the vinyl ketone **7** (Scheme 4). Quenching of the intermediate oxyanion with methyl chlorooxoacetate gave the desired oxalate **14** directly in an isolated yield of 61% and as a 3:1 mixture of atropisomers.

The Dolan−MacMillan deoxygenation protocol was employed to remove the superfluous tertiary hydroxyl group in **14**.[11] In this sequence, a planar radical on C-7 is generated and quenching of the radical with tributyltin hydride occurs, as expected, from the least hindered face leading to **15**. This stereochemical outcome is supported by C-7 and C-12 proton coupling constants of 11 Hz, indicating the diaxial arrangement.

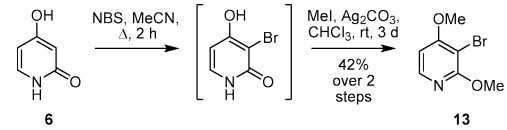
Standard methoxy-deprotection conditions (BBr_3, TMSI, NaSEt) failed to give the desired pyridone **3** and complex mixtures of products were obtained. Interestingly, we observed that under acidic conditions the 4-hydroxy group of the pyridone moiety reacts in an intramolecular fashion onto the vinyl group to give a fused tricyclic system, reminiscent of the structural skeletons of cordypyridones C and D (Scheme 5).

Gratifyingly, the use of a neat Grignard reagent at 165 °C afforded the desired atropisomeric pyridones of **3**.[12] Isaka, in his original isolation paper, reported the formation of 1-dehydroxycordypyridone A (**3**) through the *N*-dehydroxylation of cordypyridone A with $LiAlH_4$.[2] Comparison of our spectroscopic data with the published data confirmed our successful synthesis of 1-dehydroxycordypyridone A.

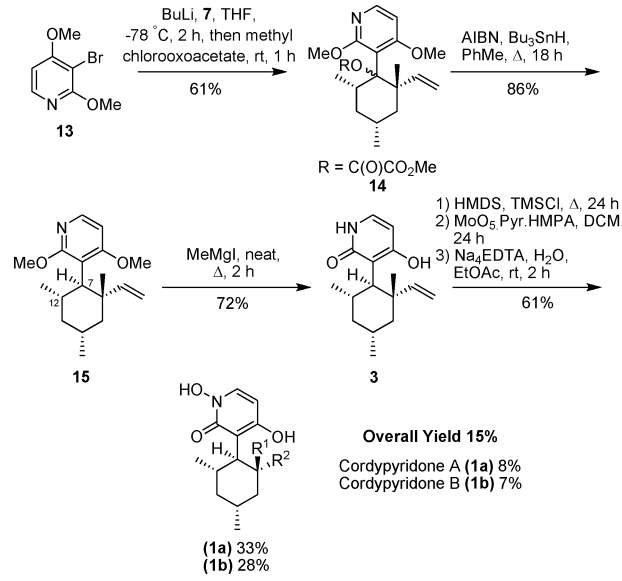
N-Hydroxylation of the pyridone **3** was undertaken according to the literature method of Sammes.[13] Silylation of **3** with HMDS and TMSCl caused racemization of the atropisomeric mixture at elevated temperatures and afforded the crude bis((trimethylsilyl)oxy)pyridine, which was then oxidized with Vedejs reagent (MoO_5·Pyr·HMPA) at room temperature. Extraction of the molybdenum with tetrasodium EDTA gave cordypyridones A and B as a mixture of atropisomers, which were separable by preparative HPLC, in a combined yield of 61% (33% and 28%, respectively). With this, the total synthesis of cordypyridones A and B was completed in an overall yield of 15%. This constitutes the first reported total synthesis of (±)-cordypyridones A and B.

This methodology was also applied to the synthesis of 8-*epi*-cordypyridone A and B, via the oxalate **16**, in an

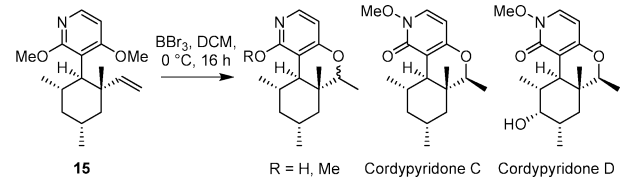
Scheme 3. Synthesis of the Pyridyl Fragment



Scheme 4. Coupling and Elaboration to **1a** and **1b**



Scheme 5. Formation of the Fused Tricyclic Skeleton



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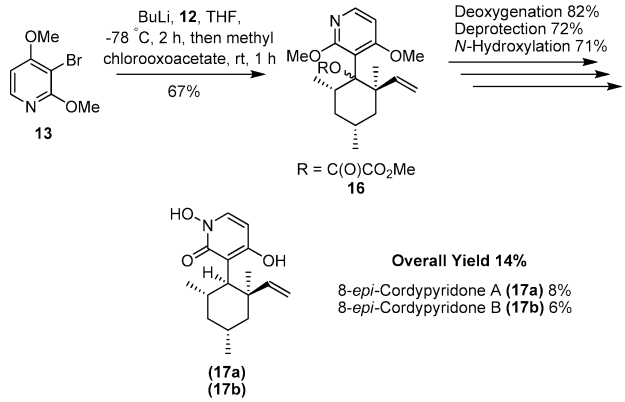
Scheme 6. Application of Methodology to the Synthesis of **17a** and **17b**



overall yield of 14% (Scheme 6). As the structures of the atropisomers 8-*epi*-cordypyridones A and B have not been reported previously, assignments of the atropisomers were by analogy to the ^{1}H NMR chemical shifts as well as HPLC retention times observed for cordypyridones A and B.

The methodology above demonstrates the versatility of the synthetic route to cordypyridones and related compounds. Current work is focused on the synthesis of analogues for biological testing and this will be reported in due course.

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Supporting Information Available: Full experimental procedures and accompanying spectroscopic data of all compounds including the CIF file for the β-hydroxy ketone **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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