Communication

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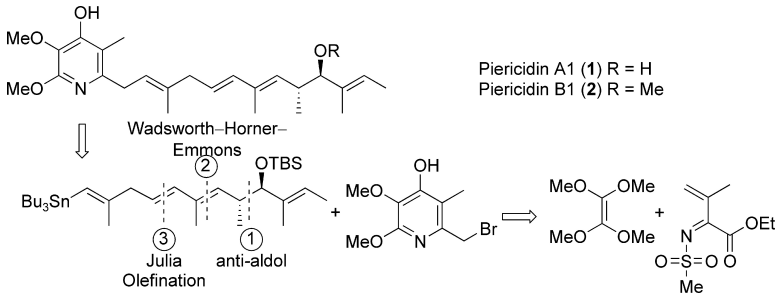

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Total Synthesis of Piericidin A1 and B1

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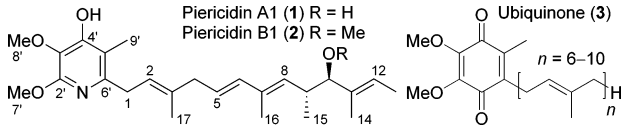
The piericidins are an important class of biologically active natural products isolated from *Streptomyces mobaraensis* and *S. pactam* of which piericidin A1 (**1**) is the prototypical member.[1] Piericidin A1 is one of the most potent inhibitors of the mitochondrial electron transport chain protein NADH-ubiquinone reductase (complex I, $K_i = 0.6-1.0$ nM) defined to date and has contributed extensively to the elucidation of the enzyme properties.[1] It has been suggested that the 4-hydroxypyridine of **1** (as the pyridone tautomer) mimics the quinone of ubiquinone (coenzyme Q, **3**) with the side chain of **1** mimicking the prenyl chain, and this apparent structural relationship was confirmed through their competitive binding against complex I.[2−4]

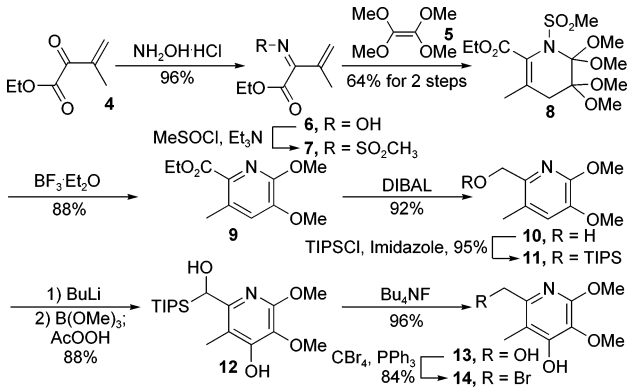


Despite an array of additional important biological activity, no total synthesis of a member of this now large class of natural products has been disclosed. In efforts directed at this family, the preparation of the fully elaborated pyridine ring system substituted with simplified side chains has been reported,[5] as well as an asymmetric synthesis of the C6−C13 segment of the side chain bearing the most recent stereochemical assignment (9*R*,10*R*).[6] Notably, the originally assigned absolute stereochemistry[7] of the side chain substituents of **1** has been challenged, reassigned, and remained to be determined.[8,9]

Herein we detail the first total synthesis of piericidin A1 and B1 by an approach that establishes the absolute stereochemistry of the natural products and will facilitate the synthesis of a series of key analogues. Central to the approach is an inverse electron demand Diels−Alder reaction between a *N*-sulfonyl-1-aza-1,3-butadiene[10] and tetramethoxyethene[11] followed by Lewis acid-promoted aromatization used to assemble the functionalized pyridine core.[12] Additional key elements in the convergent approach include the use of an asymmetric *anti*-aldol reaction to install the C9 and C10 relative and absolute stereochemistry, a modified Julia olefination for formation of the C5−C6 trans double bond with convergent assemblage of the side chain, and a penultimate heterobenzylic Stille cross-coupling reaction of the pyridyl core with the fully elaborated side chain.

The key *N*-sulfonyl-1-aza-1,3-butadiene **7** was accessed through a two-step sequence initiated by oxime formation of the ketone **4**[13] ($NH_2OH-HCl$, EtOH, 25 °C, 18 h, 96%) (Scheme 1). Treatment of the oxime **6** with Et_3N and methylsulfinyl chloride led to formation of the *O*-methanesulfinate and in situ homolytic rearrangement to give sulfonylimine **7** (CH_3SOCl, Et_3N, CH_2Cl_2, 0 °C, 20 min).[14] Treatment of **7** with tetramethoxyethene[11] (**5**, 18 h, toluene, 50 °C, 64% for two steps from **6**) smoothly afforded the [4 + 2] cycloadduct **8**. Characteristic of the unusual reactivity of

Scheme 1. Synthesis of the Pyridine Core



such electron-deficient *N*-sulfonylazadienes substituted with an additional C2 electron-withdrawing substituent,[12a,b] the Diels−Alder reaction of **7** with the electron-rich dienophile **5** was found to proceed at or near room temperature, even though **5** is tetrasubstituted and sterically demanding. Efforts to induce aromatization of **8** under a variety of basic conditions were not successful, whereas the use of the Lewis acid $BF_3{\cdot}OEt_2$ cleanly affected this transformation (CH_2Cl_2, 0 °C, 1 h, 88%). Reduction of the ethyl ester **9** with DIBAL (CH_2Cl_2, 0 °C, 1 h, 92%) followed by protection of the resulting alcohol **10** as its TIPS ether provided **11** (TIPSCl, imidazole, DMF, 25 °C, 18 h, 95%). It was envisioned that directed lithiation of the remaining site on the pyridine ring followed by a borylation/oxidation sequence would permit incorporation of the remaining oxygen substituent at C4′.[15] Thus, treatment of **11** with excess base followed by trimethylborate (5 equiv of BuLi, 6 equiv of $B(OMe)_3$, −78 °C, 1 h, 88%) and oxidative cleavage of the resulting aryl boronate ester unexpectedly provided the *C*-silylated species **12**, resulting from both the desired C4′ hydroxylation and a competitive reverse Brook rearrangement of the benzylic TIPS ether under the strongly basic conditions.[16] The use of fewer equivalents of base results in the migrated, non-oxidized product, and the use of alternative silyl ether protecting groups (TBS and TBPDS) or the free alcohol **10** itself resulted in lower yields of the diol **13**. The deprotection of **12** proceeded cleanly and, interestingly, through the *O*-silylated intermediate **S1**[16] (Bu_4NF, THF, 30 min, 25 °C, 80%) resulting from a Brook rearrangement, to give **13** (Bu_4NF, THF, 36 h, 25 °C, 96% overall). Conversion of **13** to the heterobenzylic bromide **14** (CBr_4, PPh_3, CH_2Cl_2, 25 °C, 84%) provided a surprisingly stable partner for the Stille cross-coupling.

Synthesis of the side chain C2−C5 segment consisted of the preparation of the vinyl iodide **17** appropriately substituted for Julia−Kocienski olefination[17] coupling with the C6−C13 side chain aldehyde **21**, accessible from the known alcohol **20**.[6] This was accomplished through the reaction of alcohol **15**[18] with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) under Mitsunobu conditions (DEAD,

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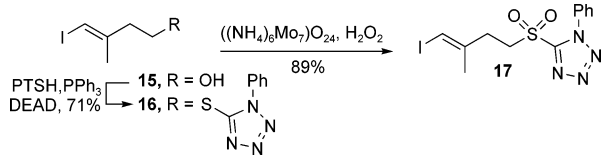
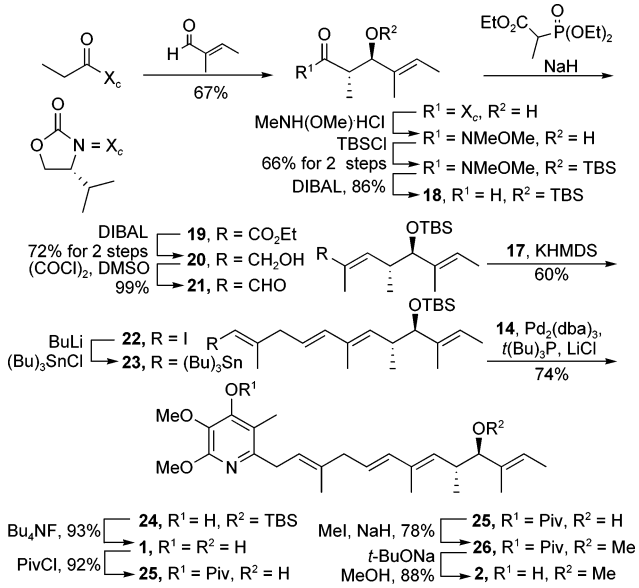
Scheme 2. Synthesis of **17**



Scheme 3. Synthesis of Piericidin A1 and B1



PPh_3, THF, 0 °C, 30 min, 71%) to provide thioether **16**, which was cleanly oxidized to the sulfone **17** with ammonium molybdate (H_2O_2, EtOH−THF, 25 °C, 6 h, 89%) (Scheme 2).[19] To address limitations in the reported synthesis of **18** (diastereomer separation),[6] a recently disclosed and more effective asymmetric *anti*-aldol reaction was employed to access aldehyde **18**,[20] which was converted to alcohol **20** as described[6] and oxidized under Swern conditions to give **21** ($(COCl)_2$, DMSO, −78 °C, 99%) (Scheme 3). A modified Julia coupling between **17** and **21** cleanly provided **22** (KHMDS, DME, −78 °C, 18 h, 60%) with the trans alkene isomer as the only detected product. Lithium−halogen exchange of the vinyl iodide **22** upon treatment with *n*-BuLi followed by treatment of the vinyllithium with tribuyltin chloride provided the vinyl stannane **23** for the Stille coupling with **14**.

Coupling of **14** with **23** was found to require elevated temperatures, high loadings of the $Pd_2(dba)_3/(tBu)_3P$ catalyst system employed by Fu,[21] and LiCl as an additive to achieve good conversions, and when applied to the coupling, provided **24** in superb conversions ($Pd_2(dba)_3$, $(tBu)_3P$, LiCl, dioxane, 70 °C, 18 h, 74%) without protection of the pyridyl phenol. A final deprotection of the TBS ether **24** (Bu_4NF, THF, 50 °C, 12 h, 93%) provided piericidin A1 identical in all respects with properties reported for the natural product (Scheme 3). This included the sign and magnitude of the reported optical rotation for **1** ($[\alpha]_D^{25}$ +1.8 (*c* 0.1, MeOH) vs lit[22] $[\alpha]_D^{25}$ +1.0 (*c* 0.1, MeOH)). However, the magnitude of this rotation value was viewed as insufficient to assign the absolute configuration of **1**. To more confidently address this assignment, the conversion to **1** of piericidin B1 (**2**), which exhibits a larger optical rotation value, was also conducted.[23] Thus, selective protection of the pyridine hydroxyl of **1** as its pivolate ester **25** (PivCl, HSO_4NBu_4, aqueous 5 N NaOH−CH_2Cl_2, 25 °C, 92%), followed by *O*-methylation of the secondary alcohol **25** (NaH, MeI, DMF, 25 °C, 1 h, 78%), and finally pivolate hydrolysis of **26** (*t*-BuONa, MeOH, 60 °C, 3 h, 88%) provided **2**. Synthetic piericidin B1 proved to be identical in all respects with properties reported for natural **2**, including its optical rotation ($[\alpha]_D^{25}$ −7.3 (*c* 0.2, MeOH) vs lit[23] $[\alpha]_D^{18}$ −6.5 (*c* 3.2, MeOH)), thereby further confirming the absolute configuration assignment for **1** and **2**.

Throughout these studies and the handling of **1**, **2**, **12**, **13**, **14**, and **24**, only the 4-hydroxypyridine tautomer, and not the 4-pyridone tautomer, was observed even in protic solvents. Provocatively, this suggests that the ability of **1** to bind and inhibit NADH-ubiquinone reductase (complex I) may result from mimicry of reduced coenzyme Q (hydroquinone) and rather than **3** itself. The synthesis of a series of analogues based on the natural products are underway and will probe such questions.

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Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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