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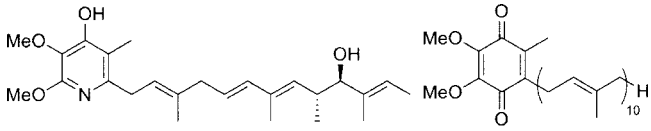
Total Synthesis of Piericidin A1. Application of a Modified Negishi Carboalumination-Nickel-Catalyzed Cross-Coupling

Bruce H. Lipshutz* and Benjamin Amorelli

Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106

Received December 11, 2008; E-mail: lipshutz@chem.ucsb.edu

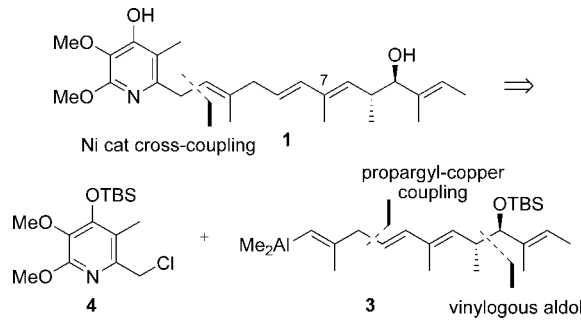
Piericidin A1 (**1**) is a metabolite of *Streptomyces mobaraensis* and *S. pactum*. It is a potent inhibitor of complex I ($K_i = 0.6-1.0$ μm)[1] in the mitochondrial electron transport chain sequence, where protein NADH:ubiquinone oxidoreductase (or NADH dehydrogenase) is responsible for the oxidation of NADH to NAD^+ using coenzyme Q_{10} (ubiquinone, **2**) as the hydride acceptor. Coenzyme Q_{10} (**2**) has also been reported to act as a potent endogenous antioxidant for the treatment of cancer and the relief of side effects caused by some cancer therapies.[2] Analogues of coenzyme Q_{10} have been shown to suppress cancer growth directly,[3] and therefore the competitive binding of piericidin A1 against complex I implicates its biological potential making it an attractive synthetic target.[4]



Our approach to a practical synthesis of piericidin A1[5] highlights a modified Negishi carboalumination followed by a Ni-catalyzed cross-coupling strategy recently introduced. This powerful strategy allows for couplings of benzylic chlorides and in situ generated vinylalanes, arrived at via stereoselective carboalumination of terminal alkynes.[6,7] Within the context of natural products total synthesis, however, the tolerance of multifunctionalized terminal alkynes had yet to be investigated. Moreover, notwithstanding the efficiency with which quinones and benzylic/heterobenzylic chlorides can be coupled to vinylalanes, piericidin A1 also features a fully fashioned, pentasubstituted pyridyl heterocyclic core.

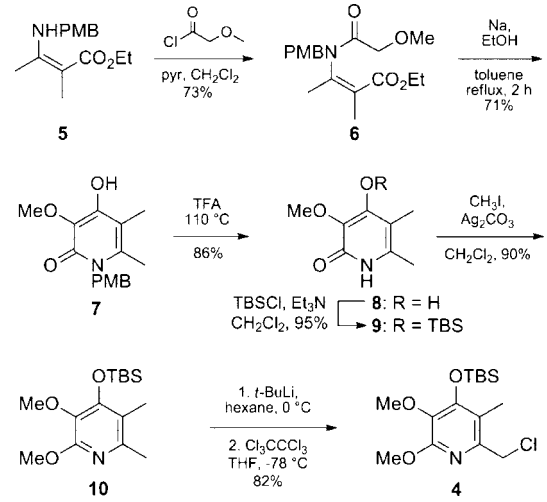
Retrosynthetically, the key disconnection (Scheme 1) features a penultimate one-pot Ni-catalyzed coupling of vinylalane **3**, generated in situ via a modified carboalumination,[6] to the chloromethylated pyridine **4**. The skipped enyne is anticipated by a propargyl selective (over allenyl) coupling of a corresponding vinyl iodide and TMS-propyne. A vinylogous Mukaiyama aldol reaction generates the eight carbon vicinal methyl/hydroxyl side chain framework.

Scheme 1. Restrosynthetic Analysis of Piericidin AI



The protected chloromethyl pyridinol **4** was prepared in seven steps from the *N*-*p*-methoxybenzyl-3-aminotiglate **5** (Scheme 2; see Supporting Information, SI). Acylation with methoxyacetyl chloride generated methoxyacetamido aminotiglate **6**, which underwent base promoted Dieckmann cyclization[8] to the corresponding 2-pyridone **7**. Attempted cyclizations with hexamethyldisilazane bases gave very low yields of the desired pyridone (**7**) at the expense of isomerization to the *E*-isomer of **6**. Treatment of **7** with TFA while heating in a sealed reaction flask followed by selective *O*-silylation gave 2-pyridone **9**. The heterocyclic chloride coupling partner **4** was obtained ultimately from an alkylative aromatization (CH_3I, Ag_2CO_3) followed by *ortho*-methyl chlorination with *tert*-butyllithium/hexachloroethane.

Scheme 2. Preparation of Chloromethylated Picoline **4**



The required acetylenic side chain precursor was assembled from an initial $TiCl_4$-promoted remote 1,6,7-asymmetric vinylogous Mukaiyama aldol reaction between D-valine derived *N*,*O*-silyl ketene acetal **11**[9] and tiglic aldehyde. This coupling provided the vicinal methyl/hydroxyl imide **12** in reasonable yield (Scheme 3).[10] Silylation with TBSCl in DMF, followed by removal of the chiral auxiliary with DIBAL in THF at −78 °C, gave enal **14**. The alternative two-step process via reduction to the corresponding allylic alcohol ($NaBH_4$, THF, H_2O) followed by oxidation (MnO_2, CH_2Cl_2, 88% overall) to **14** was employed in larger scale reactions due to the expected better stability profile for the allylic alcohol on storage relative to that of enal **14**. Direct Takai homologation[11] to vinyl iodide **16** consistently gave a mixture of the desired *trans*-iodide and an inseparable homologated *trans*-olefinic coproduct. Therefore, a two-step procedure was developed. Alkynylation of **14** with the Bestmann−Ohira diazophosphonate[12] gave reproducibly moderate yields of enyne **15** regardless of variations in the addition of reagent or reaction temperature. The mass balance, however,

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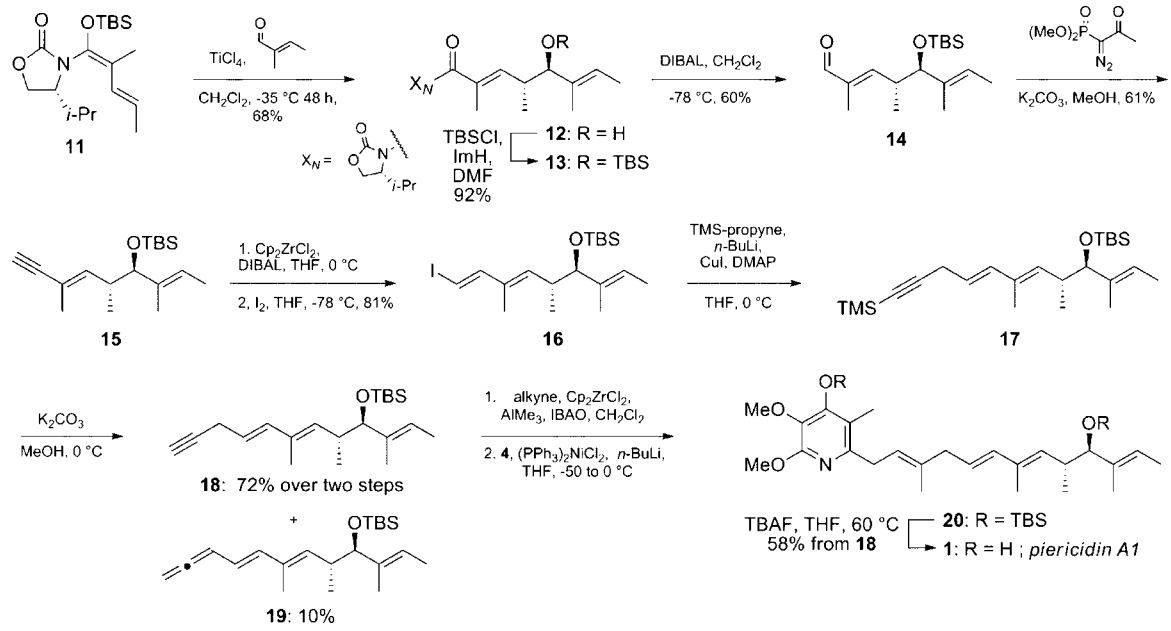
Scheme 3. Preparation of Alkyne Coupling Partner **18** and Completion of the Synthesis of Piericidin A1



was recovered as starting material. Attempts to apply the typical Corey−Fuchs and TMS-diazomethane promoted alkynylations were also unsuccessful, as each protocol gave products that were difficult to separate from the desired nonpolar alkyne. Hydrozirconation−iodination of enyne **15** with in situ prepared Schwartz's reagent followed by I_2 quench gave the vinyl iodide **16**.[13] The use of Schwartz's reagent was far superior to attempts at preparing vinyl iodide **16** with $Bu_3SnH/(PPh_3)_2PdCl_2$.[14] Propargyl coupling[15] of **16** with TMS-propyne gave unstable skipped enyne **17**, which was converted immediately with K_2CO_3 in MeOH to the desired terminal acetylene **18**, accompanied by the corresponding vinyl allene **19**. The extent of isomerization to allene **19** in the presence of excess K_2CO_3 at rt was minimized when protiodesilylation was conducted at 0 °C.

The crucial carboalumination of terminal alkyne **18** was effected with catalytic Cp_2ZrCl_2, trimethylaluminum, and isobutylalumi-noxane[6] in DCM. Once complete, the Ni(0) catalyst was added at −50 °C followed by the coupling partner **4**, after which the reaction was warmed to 0 °C. Without isolation, subsequent removal of the silyl protecting groups (TBAF, THF, 50 °C) afforded piericidin A1 in 58% yield from alkyne **18**. Comparison of spectral data of this material to that published,[5] including superimposable ^{1}H NMR spectra[16] as well as a ^{13}C NMR, HRMS, and specific rotation, confirm the assignment of our synthetic material as piericidin A1.

In summary, piericidin A1 (**1**) has been synthesized in a total of 18 steps from commercial material. The route involves a longest linear sequence of 11 steps (9 pots) from the *N,O*-silyl ketene acetal **11**, which overall compares very favorably with the previous synthesis of **1**.[5] A carboalumination/Ni-catalyzed cross-coupling applied to two complex partners highlights the potential of this technology in natural products total synthesis.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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