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Titanium(II)-Mediated Cyclizations of (Silyloxy)enynes: A Total Synthesis of (−)-7-Demethylpiericidin A_1

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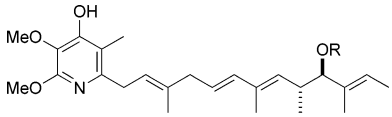
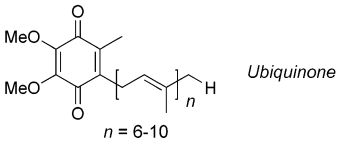
The piericidins[1] are a class of pyridine-containing antibiotics that display a broad range of biological effects, including cytotoxicity, anti-microbial and insecticidal activity. This activity has been ascribed to their structural homology to Coenzyme Q10 and concomitant effectiveness as inhibitors of mitochondrial electron transport.[2] Although the biological effects of the piericidins as inhibitors of electron transport have been well studied, they have not yet drawn the same level of synthetic attention as related compounds that also act via this mode, such as the annonaceous acetogenins. Apart from the recent paper from Boger and co-workers describing the total synthesis of piericidins A_1 and B_1,[3] there has been only a handful of reports describing efforts toward the synthesis of these valuable biological probes.[4]





Ubiquinone

In 1996, Kimura and co-workers described the isolation and structure elucidation of two further antibiotics of the piericidin class, 7-demethylpiericidin A_1 (SN-198D, **1**, Figure 1) and 7-demethyl-3′-rhamnopiericidin A_1 (SN-198B, **2**).[5] These two compounds inhibited the KB human nasopharyngeal cancer cell line with IC_{50} values of 11.0 and 4.5 μg mL^{-1}, respectively. In this Communication, we present a convergent total synthesis of 7-demethylpiericidin A_1 that is patterned on the strategy outlined in Figure 1 and features an application of our recently described Ti(II)-mediated cyclization of (silyloxy)enynes as the key reaction for the assembly of the polyene domain.[6,7]

The synthesis of the 2-stannylpyridine-containing component is shown in Scheme 1. Commercially available 2,3-dimethoxypyridine **3** was converted to pyridinol **4** in 70% yield by ortho-metalation with *n*-BuLi, quenching with $(MeO)_3B$, and oxidation with peracetic acid.[8] Subsequent protection as the SEM ether (Ag_2CO_3, SEMCl) provided **5** in 97% yield. Directed ortho-metalation and halogenation (*tert*-BuLi then $BrCl_2CCCl_2Br$, 79%, **5**→**6**), followed by LiTMP-mediated halogen dance[9,10] and alkylation with methyl iodide led to pyridine **7** in 85% yield. Lithium halogen exchange and quenching with chlorotributylstannane gave **8** in 96% yield and completed the synthesis of this fragment.

The polyene domain synthesis commenced with allylic alcohol **9**,[11] which was silylated with ethynyl(diisopropyl) bromosilane to give alkynylsilane **10** in 78% yield (Scheme 2). Subsequent

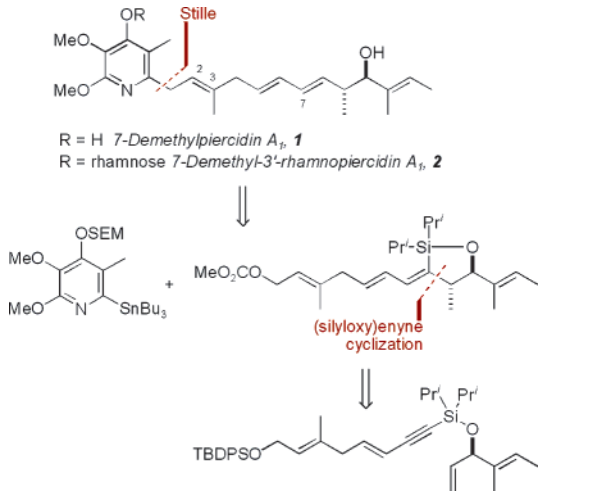
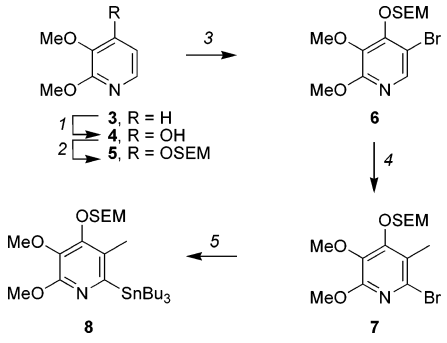


Figure 1. 7-Demethylpiericidins and an overview of synthesis strategy.

Scheme 1 [a]



[a] Reagents and conditions: (1) *n*-BuLi, THF, then $(MeO)_3B$ then aq. AcOOH, 70%; (2) SEMCl, Ag_2CO_3, 97%; (3) *t*-BuLi, THF, then 1,2-dibromotetrachloro ethane, 79%; (4) LiTMP, THF, −78 to −40 °C then MeI, −40 °C, 85%; (5) *t*-BuLi then Bu_3SnCl, 96%.

Sonogashira coupling with iodide **11**[12] provided (silyloxy)enyne **12** in 87% yield and set the stage for the key cyclization. Gratifyingly, subjecting **12** to the conditions employed in our earlier studies ($ClTi(OPr^i)_3$, *i*-PrMgCl, −40 °C) resulted in cyclization to produce the desired cyclic siloxane **13** in 52% yield.[13]

The final steps of the synthesis commenced with removal of the silyl ether (HF·pyr, 84%, **13**→**14**) and acylation (MeO_2CCl, pyridine, 97%) to give allylic carbonate **15**. Coupling of the polyene and pyridine-containing domains was achieved by a Stille coupling between **15** and pyridine **8** with $Pd_2(dba)_3$ in DMF to provide **16** in 55% yield.[14] Simultaneous removal of the SEM ether and cyclic siloxane was achieved by treatment with TBAF (75 °C, DMF) to produce 7-demethylpiericidin A_1 in 70% yield. Synthetic 7-demethylpiericidin A_1 was identical in all respects to natural **1**.[15]

In conclusion, we have described a synthesis of 7-demethylpiericidin A_1 that proceeds in nine steps from tiglic aldehyde via **9**

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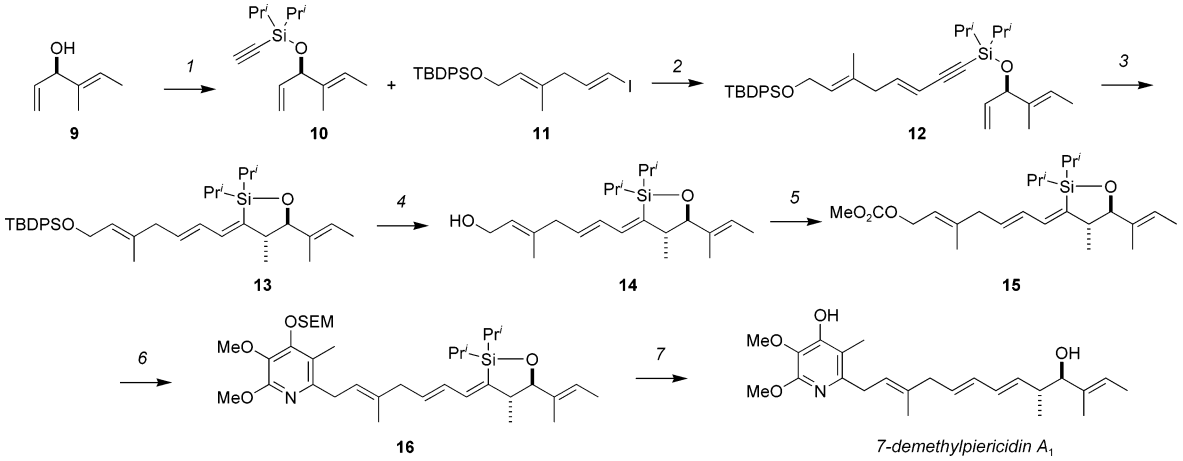
Scheme 2 [a]



[a] Reagents and conditions: (1) ethynyl(diisopropyl)bromosilane, Et_3N, DMAP, CH_2Cl_2, 78%; (2) $PdCl_2(PPh_3)_2$, CuI, Et_3N, 87%; (3) $ClTi(OPr^i)_3$, *i*-PrMgCl, 52%; (4) HF·pyr, 84%; (5) MeO_2CCl, pyr, CH_2Cl_2, 97%; (6) **8**, $Pd_2(dba)_3$, LiCl, DMF, 55%; (7) TBAF, DMF, 75 °C, 70%.

and highlights the utility of the titanium(II)-mediated cyclization of (silyloxy)enynes in the context of complex natural products synthesis.

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Supporting Information Available: Characterization data and spectra for new compounds (**6**−**8**, **10**−**16**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Alcohol **9** was synthesized by addition of vinylmagnesium bromide to tiglic aldehyde and then kinetic resolution employing Sharpless asymmetric epoxidation. See: Honda, T.; Mizutani, H.; Kanai, K. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1729.

(12) Synthesized from 4-iodo-3-methyl-3-buten-1-ol (Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445) by a sequence consisting of (a) silylation (TBSCl, imidazole, 86%); (b) conversion to the allylic alcohol (*t*-BuLi, paraformaldehyde, 82%), (c) protection of the allylic alcohol and removal of the TBS ether (TBDPSCl, imidazole then AcOH, 79%), (d) oxidation−olefination (Dess−Martin periodinane, CH_2Cl_2, then CHI_3, $CrCl_2$, THF−dioxane, 75% over two steps).

(13) To the limits of detection by ^{1}H NMR analysis of the crude reaction mixture, this reaction produces a single diastereoisomer (dr >95:5). In this instance, the major side reaction is simple reduction of the enyne.

(14) Under the conditions employed, this coupling provided a ∼2.5:1 ratio of *E*:*Z* diastereoisomers at the $\Delta^{2,3}$ olefin, from which the desired compound could be isolated by chromatography on $AgNO_3$-impregnated silica.

(15) See the Supporting Information for details.

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