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Total synthesis of hydroxystrobilurin A via Stille coupling

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This work is dedicated to the memory of the late Andrew J. Rea

Abstract

A six-step total synthesis of the fungicidal natural product hydroxystrobilurin A is described, utilising Stille chemistry for efficient access to the strobilurin (*E*,*Z*,*E*)-triene system.

The strobilurins are a family of 17 natural products produced by a variety of fungi in climate zones the world over, and the potent fungicidal activity they exhibit has been exploited in the development of several synthetic analogues as agrochemical fungicides.[1] This bioactivity is due to their (*E*)-β-methoxyacrylate subunit,[2] which enables binding to the ubiquinol oxidation centre of the cytochrome b–c_1 complex in the mitochondrial membrane, thus halting ATP generation.[3] Crucially, *Strobiluris* sp. are protected from the effects of their own products by a mutation in their ubiquinol binding sites, which prevents the binding of strobilurins.[4] Several total syntheses of natural strobilurins have been reported,[5] together with synthetic studies which led to the structural revision of several strobilurins.[6] Coleman and Lu's recent total synthesis of strobilurin B utilises palladium catalysis to assemble the triene system in a stereocontrolled manner,[7] the absence of which having been the *bête noire* of previous total synthetic efforts.[5]

We have also been investigating palladium-catalysed protocols for stereoselective strobilurin construction, and herein describe the first total synthesis of hydroxystrobilurin A (**1**).[8] Our approach to **1** was based upon the retrosynthesis in Figure 1; thus, a Stille coupling[9] of phenylethyne stannane **2**[10] and dibromoester **3**,[11] followed by reduction, should afford diene alcohol **4**, followed by a second Stille coupling of **4** with known stannyl acrylate **5**[12] to form **1**. This proposed strategy is both convergent and incorporates the required stereoselectivity in the formation of the strobilurin triene system. Investigation of this first approach to **1** began with the radical hydrostannylation of phenylethyne (**6**) to give phenylethenyl stannane **2** [94%, 12.4:1.0 (*E*):(*Z*) ratio] (Scheme 1).[10a] However, subsequent Stille coupling of **2** with dibromoester **3**[13] afforded a poor yield of diene ester **7** (<20%).[14]

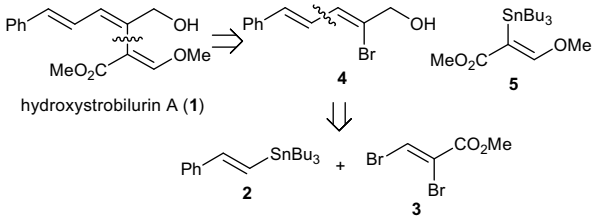

Fig. 1.

Thankfully, iodoester **8** (obtained by subjecting **3** to the Finkelstein conditions of Caddick et al.[15]) reacted efficiently[16] with **2** under Stille conditions[17] to give **7** (66%)

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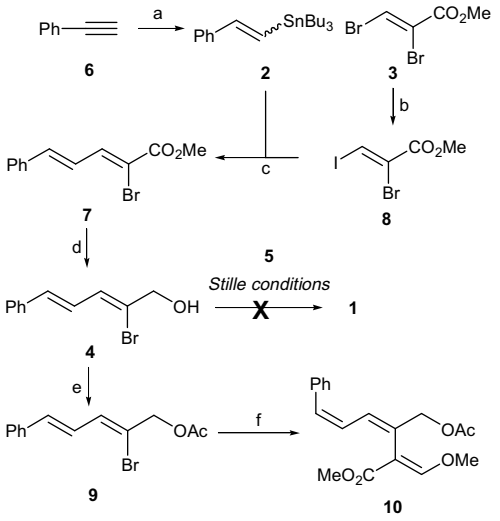


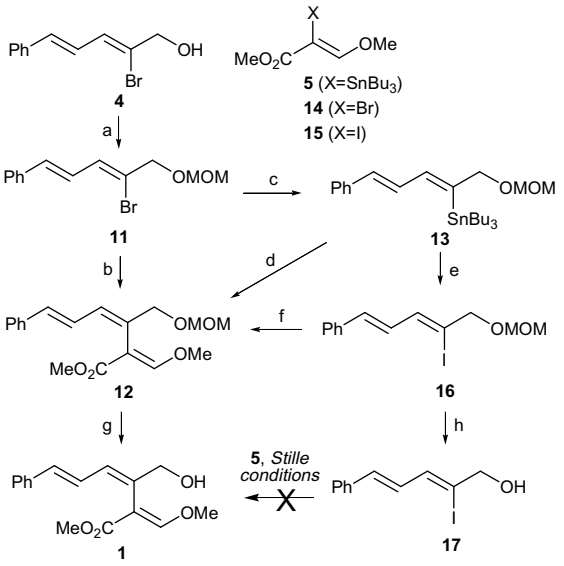
Scheme 1. Reagents and conditions: (a) Bu_3SnH, AIBN, 50 °C, 94%; (b) NaI, acetone, reflux, 67%; (c) Pd(dppf)Cl_2, DMF, 80 °C, 66%; (d) DIBAL-H, Et_2O, −78 to 0 °C, 89%; (e) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 0 °C→rt, 92%; (f) **5**, Pd_2dba_3, $AsPh_3$, CuI, NMP, 50 °C, 51%.

as a single stereoisomer. Subsequent DIBAL-H reduction of **7** to diene alcohol **4** proceeded without an incident (89%). Unfortunately, ensuing attempts to couple **4** and stannyl acrylate **5** under a variety of Stille conditions[18] were unsuccessful, with only unreacted or degraded starting materials isolated from reaction mixtures (Scheme 1).

Given that Hodgson et al. had successfully used **5** in several Stille couplings,[12b] and despite the fact that one of the usual strengths of the Stille coupling is its tolerance of a wide variety of functionalities, it seemed that the hydroxyl group of **4** was inhibiting the reaction. This hypothesis was confirmed when we examined the Stille coupling of acetate **9** (obtained by the reaction of **4** with acetic anhydride) with acrylate **5** and obtained triene **10** in 51% yield (Scheme 1). However, ^{1}H NMR spectroscopic analysis indicated that isomerisation had occurred[19] to give a triene acetate with (*Z*,*E*,*E*)-stereochemistry, presumably via a π-allyl palladium-catalysed process.

In a bid to prevent this isomerisation from occurring, the protecting group was changed to a MOM group (Scheme 2). Reaction of **4** with MOM–Cl gave the MOM ether **11**, which was reacted with stannane **5**, in the presence of Pd_2dba_3, $AsPh_3$ and CuI, in NMP, to afford the desired triene **12**, albeit in 18% yield. In an effort to improve the yield of this key step, the MOM ether **11** was converted to stannane **13** via a Pd-catalysed process. Unfortunately, **13** proved to be unreactive with both bromoacrylate **14**[11] (no reaction) and iodoacrylate **15**[11,12] (<10%) under Stille conditions.

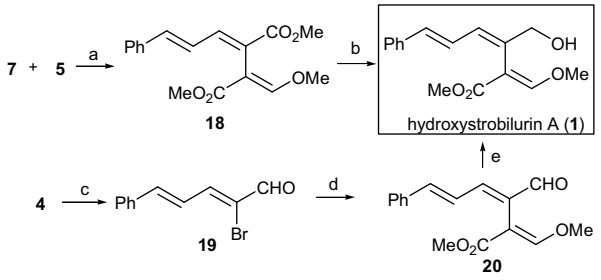
However, iodide **16**, obtained via iododestannylation of **13**, proved to be an efficient[20] coupling partner with **5** under Stille conditions, furnishing a 57% yield of **12** (91% pure by ^{1}H NMR analysis). The MOM ether of **12** proved to be immune to hydrolysis with catalytic acid,[21] but treatment with trimethylsilyl bromide as per Hanessian et al.[22]



Scheme 2. Reagents and conditions: (a) MOM–Cl, (*i*-Pr)$_2$NEt, CH_2Cl_2, 0 °C→rt, 57%; (b) **5**, Pd_2dba_3, $AsPh_3$, CuI, NMP, 50 °C, dark, 18%; (c) $(Bu_3Sn)_2$, Pd$(PPh_3)_2Cl_2$, PhMe, reflux, dark, 40%; (d) Pd(dppf)Cl_2, DMF, rt→50→100 °C, dark, <10%; (e) I_2, Et_2O, 0 °C, 66%; (f) **5**, Pd_2dba_3, $AsPh_3$, CuI, NMP, 50 °C, dark, 57%; (g) TMSBr, 4 Å molecular sieves, −30→0 °C, 11%; (h) TMSBr, 4 Å molecular sieves, −30 to 0 °C, 45%.

did afford a very low yield (11%) of **1** (Scheme 2). However, efforts to improve the efficiency of this process by scaling up the reaction resulted in even lower yields, with apparent triene isomerisation occurring subsequent to deprotection. Moreover, although MOM iodide **16** could also be hydrolysed to free-hydroxyl iodide **17**, it proved as unreactive as its bromo-analogue **4** as a Stille coupling partner for **5** en route **1**.

We now turned to exploring the potential of a functional group interconversion approach, whereby it was proposed that **1** might be accessible via selective reduction of an ester or aldehyde precursor. Reaction of bromide **7** and stannane **5** under Stille conditions furnished an excellent yield (86%) of triene ester **18**. Unfortunately, subsequent attempts to selectively reduce the non-vinylogous ester of **18** afforded a complex mixture of reduced products, from which only very low quantities of **1** could be recovered (Scheme 3).



Scheme 3. Reagents and conditions: (a) Pd_2dba_3, $AsPh_3$, CuI, NMP, dark, 50 °C, 86%; (b) DIBAl-H, CH_2Cl_2, −78 to 0 °C, 12%; (c) TPAP/NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 67% (79% based on recovered starting material); (d) **5**, Pd_2dba_3, $AsPh_3$, CuI, NMP, 50 °C, 74%; (e) $NaBH_4$, MeOH, 0 °C→rt, 9% (14% based on recovered starting material).

Reasoning that an aldehyde might prove more amenable to hydride reduction than an ester, alcohol **4** was oxidised[23] to diene aldehyde **19** (67%, 79% based on recovered starting material) with TPAP/NMO[24] (Scheme 3). Stille coupling of **19** and **5** furnished a pleasing 74% yield of triene aldehyde **20**. It was hoped that the aldehyde moiety of **20** might be more reactive to reduction by a hydride agent than the vinylogous ester group of **18**, however DIBAL-H treatment of **20** produced a complex mixture from which only a trace of **1** (<5%) was isolated.

Reduction of **20** with $NaBH_4$ was more successful, affording a low but improved yield of **1** (9%, 14% based on recovered starting material). Spectroscopic data for synthetic hydroxystrobilurin A (**1**) were in good agreement with those published.[8,25] However, further optimisation of this reaction was unsuccessful. Greater amounts of $NaBH_4$ drove the reaction to completion (2.0 equiv. led to the complete consumption of **20**), but this was concomitant with a proportional increase in the number of allylic proton signals in the ^1H NMR spectrum, presumably a result of 1,4-addition of hydride. The use of Luche's selective 1,2-hydride addition conditions[26] did seem to prevent this, but unfortunately also afforded only trace amounts of **1** and several new unidentified products.

This first total synthesis of hydroxystrobilurin A (**1**) comprises the longest linear sequence of six steps from phenyl ethyne (**6**). The use of Stille chemistry enabled efficient, stereocontrolled formation of the strobilurin triene system under relatively undemanding conditions.

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Supplementary data

Supplementary data (experimental procedures, characterisation data and copies of the NMR spectra of hydroxystrobilurin A) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.056.

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