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Total Synthesis of Swinholide A: An Exposition in Hydrogen-Mediated C-C Bond Formation

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Abstract

Diverse hydrogen-mediated C-C couplings enable construction of the actin-binding marine polyketide swinholide A in only 15 steps (LLS); roughly half the steps required in two prior total syntheses. The redox-economy, chemo- and stereoselectivity embodied by this new class of C-C couplings are shown to evoke a step-change in efficiency.

Natural products that modulate microtubule dynamics in the course of cell division have emerged as an important class of anti-cancer compounds.¹ Taxol (paclitaxel), docetaxel (taxotere), ixabepilone (ixempra), eribulin mesylate (halaven) represent FDA approved members of this compound class. Consequently, the prospect of utilizing actin-binding marine polyketides in cancer therapy has garnered increasing interest.² Swinholide A, first isolated from the Okinawan marine sponge *Theonella swinhoei* in 1985,^{3,4} dimerizes actin ($K_d \sim 50$ nM).^{5a} A highly resolved X-ray crystal structure of swinholide A affixed to two actin molecules has been acquired.^{5c} The ability of swinholide A to disrupt the carefully regulated assembly of actin cytoskeletal constructs⁵ confers cytotoxicity in the ng/mL range against diverse tumor cell lines,⁶ making it the most potent member of its class (Figure 1).^{7,8,9} Due to its well understood mode of binding and potency, simplified functional analogues of swinholide A might serve as molecular probes or as starting points for the design of clinical candidates.² However, while analogues of other actin-binding natural products have been prepared,¹⁰ synthetic congeners of swinholide A have not – a fact that may be attributed to the daunting structural complexity of swinholide A and that high levels of potency require preservation of the symmetric 44-membered macrodiolide ring.¹¹ Indeed, despite numerous synthetic studies,¹² to date, only two total syntheses of swinholide A have been accomplished in the laboratories of Paterson (1994)¹³ and Nicolaou (1996).^{14,15} Additionally, a total synthesis of preswinholide A was reported by Nakata (1996).¹⁶

The original paradigm for polyketide construction, which encompasses prior syntheses of swinholide A, relies largely on C-C bond formations mediated by preformed organometallic C-nucleophiles. We have developed a broad, new family of catalytic carbonyl reductive couplings induced *via* hydrogenation or hydrogen auto-transfer.^{17a,b} These processes bypass

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

premetalated reagents and streamline the synthesis of polyketide natural products by merging redox and C-C bond construction events (redox-economy).^{17c,18} Additionally, by virtue of their highly chemo- and stereoselective nature, enantioselective C-C coupling can be achieved in the absence of protecting groups.¹⁹ Collectively, these attributes contribute to a step-change in efficiency.^{17b,c} Here, using multiple hydrogen-mediated C-C couplings, we report a 15-step (LLS) total synthesis of swinholide A – a route roughly half the length of the two preexisting total syntheses.

Retrosynthetically, we envisioned access to swinholide A through a direct macrodiolide formation *via* successive cross-metathesis-ring-closing metathesis of fragment **C** or a protected congener thereof.²⁰ The two prior syntheses of swinholide A install the macrodiolide ring through step-wise formation of ester/lactone linkages. The possibility that fragment **C** would engage in RCM (without initial CM) leading to formation of hemiswinholide rendered the outcome of this approach uncertain. The planned synthesis of fragment **C** is highly convergent and involves the use of methyl vinyl ketone serves as a doubly nucleophilic aldol lynchpin for the union of fragments **A** and **B**. Specifically, hydrogen-mediated reductive aldol reaction²¹ of methyl vinyl ketone with fragment **A** is followed by Mukaiyama aldol reaction²² of the resulting methyl ketone with fragment **B**. This strategy requires exceptional chemoselectivity, as rhodium catalyzed hydrogenation of MVK in the presence of fragment **A** must induce reductive coupling rather than conventional hydrogenation of the C2-C5 diene and C10-C11 olefin. Fragment **A** is prepared using one transfer hydrogenative alcohol C-H allylation²³ to form the C12-C13 carbon-carbon bond. As established in preliminary studies on the synthesis of the C19-C32 substructure of swinholide A,²⁴ Fragment **B** is accessible through cross-metathesis of the vinyl pyran **11** with iodo ether **15**. Vinyl pyran **11** is prepared through stereo- and site-selective allylation of commercially available (*S*)-1,3-butane diol **8**.²⁵ The iodo ether **14** is prepared from the *pseudo*-C₂-symmetric diol **13**, which, in turn, is obtained directly from 2-methyl-1,3-propane diol **12** *via* double diastereo- and enantioselective diol C-H *anti*-crotylation.²⁶

The synthesis of fragment **A** begins with enantioselective iridium-catalyzed alcohol *C*-allylation²³ of the commercially available alcohol **1** (Scheme 1). The homoallylic alcohol **2** is formed in 83% yield and 93% enantiomeric excess. The iridium catalyst is readily recovered and recycled in a second round of allylation to provide additional quantities of alcohol **2**. Cross-metathesis with acrolein followed by treatment of the resulting enal with allyltrimethylsilane results allylation of a transient cyclic oxacarbenium ion to provide the *trans*-2,6-disubstituted pyran **3** with good levels of diastereocontrol.²⁷ Chemoselective oxidative cleavage²⁸ of the terminal olefin of pyran **3** delivers aldehyde **4**. In close analogy to the work of Paterson,^{13c} exposure of aldehyde **4** to BF₃-etherate in the presence of silyl dienol ether **5**²⁹ triggers vinylogous Mukaiyama aldol addition to provide enal **6**. As predicted by the Cram-Reetz model,³⁰ good levels of 1,3-stereoiduction are observed. Protection of the alcohol as the TBS ether with subsequent addition of DDQ provides enal **7**. The resulting enal **7** was subjected to Wittig methylenation to form the C2-C5 diene. This sequence avoids problematic PMB-deprotection in the presence of the diene. Finally, Dess-Martin oxidation of the C15 alcohol delivers fragment **A** in 8 steps (LLS).

The synthesis of fragment **B** begins with catalyst-directed diastereo- and site-selective allylation of commercially available (*S*)-1,3-butane diol **8** (Scheme 3).^{24,25} The homoallylic alcohol **9**, which is formed as a single diastereomer, is then subjected to cross-metathesis with *cis*-1,4-diacetoxy-2-butene to form **10** as a 5:1 (*E:Z*)-mixture of olefin stereoisomers.

Exposure of **10** to the indicated chiral palladium catalyst results in Tsuji-Trost cyclization to form 2,6-*trans*-disubstituted pyran in 90% yield as a 4:1 mixture of diastereomers. Diastereoselectivity is independent of the olefin geometry of **10**. Subsequent *O*-methylation provides **11**. Cross-metathesis of **11** with iodoether **14**, previously prepared in our laboratory (Scheme 4),²⁶ was challenging due to competing alkene isomerization of **14**. Using the second-generation Grubbs-Hoveyda catalyst with 1,4-benzoquinone,³¹ the desired metathesis product **15** was obtained in 52% yield. Diimide reduction³² of the C25-C26 double bond, Bernet-Vasella cleavage³³ of the iodoether followed by TBS protection of the alcohol with subsequent oxidative removal of the PMB-ether provides **16**. Alkene oxidative cleavage and acryloylation of the β -hydroxy aldehyde converts **16** to fragment **B** in 10 steps (LLS).

The union of fragments **A** and **B** using methyl vinyl ketone (MVK) as a double nucleophilic aldol lynchpin begins with the hydrogen-mediated reductive aldol coupling²¹ of fragment **A**. Tolerance of multiple olefinic functional groups, including a terminal diene, to the conditions of rhodium catalyzed hydrogenation could not be assumed. Hence, the reaction of model aldehydes **17** and **19** was initially explored (Scheme 5). To our delight, the respective adducts **18** and **20** were formed in good yields without competing hydrogenation of the alkene functional groups. Good levels of selectivity were associated with discrimination of diastereotopic aldehyde π -faces and *syn*-diastereoselectivity in the aldol formation was complete. Encouraged by these results, fragment **A** was exposed to conditions for hydrogen-mediated reductive aldol coupling. The requisite aldol **21** was formed in 68% yield.

To complete the synthesis of swinholide A, aldol **21** was methylated to form **22**, which was converted to the enol silane and treated with fragment **B** in the presence of BF₃-etherate (Scheme 6). The product of Mukaiyama aldol addition **23** is formed in 72% yield as a single diastereomer, as predicted by the Cram-Reetz model.³⁰ Hydroxy-directed reduction of the ketone³⁴ followed by removal of silyl-protecting groups provides the acrylic ester **24**. Exposure of **24** to the second-generation Grubbs-Hoveyda catalyst provides the product of successive CM-RCM, swinholide A, in 25% yield along with the product of RCM, hemiswinholide, in 43% yield. The CM-RCM pathway appears critically dependent on preorganization derived from the internal network of hydroxyl hydrogen-bonds, as the silyl-protected precursors to **24** exclusively form RCM products under metathesis conditions.

In summary, by merging the characteristics of hydrogenation and carbonyl addition, we have unlocked a broad, new family catalytic C-C couplings that streamline chemical synthesis by virtue of their redox-economy, chemo- and stereoselectivity. As illustrated in the present synthesis of swinholide A, wherein 10 C-C bonds are formed by hydrogenative coupling, the target compound is made in 15 steps (LLS); roughly half the steps required in two prior total syntheses. A comparable step-change in efficiency is evident in other polyketide total

syntheses utilizing our methods.^{17c} Future work will focus on expanding the lexicon of hydrogen-mediated C-C bond formation, including the use of α -olefins as pronucleophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Structure of swinholide A, related secondary metabolites and analysis of prior total syntheses of swinholide A.^a

^aFor graphical summaries of prior total syntheses, see Supporting Information. Longest Linear Sequence (LLS); Total Steps (TS). Only transformations in the longest linear sequence (LLS) are considered in the analysis of reaction type.

Scheme 1.

Retrosynthetic analysis of swinholide A *via* C-C bond forming hydrogenation and transfer hydrogenation.

^aEnantioselectivity was determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Scheme 3.

Synthesis of fragment **B** via catalyst-directed diastereo- and site-selective allylation of diol **8**.^a

^a(*R,R*)-ligand = (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N,N'*-bis(2-diphenylphosphinobenzoyl). See Supporting Information for further experimental details.

Scheme 4.

Synthesis of iodoether **14** *via* diastereo- and enantioselective double *anti*-crotylation of diol **12**.^a

^aEnantioselectivity was determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Scheme 5. Hydrogen-mediated reductive aldol couplings of methyl vinyl ketone.^a^aSee Supporting Information for further experimental details.

Scheme 6.

Total synthesis of swinholide A *via* successive cross-metathesis-ring-closing metathesis (CM-RCM).^a

^aSee Supporting Information for further experimental details.