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Formal Synthesis of Premisakinolide A and C(19)−C(32) of Swinholide A via Site-Selective C−H Allylation and Crotylation of Unprotected Diols

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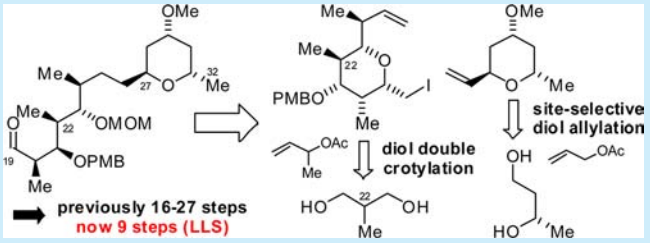
Supporting Information

ABSTRACT: Using stereo- and site-selective C−H allylation and crotylation of unprotected diols, an intermediate in the synthesis of premisakinolide A (bistheonellic acid B) that was previously made in 16−27 (LLS) steps is now prepared in only nine steps. This fragment also represents a synthesis of C(19)−C(32) of the actin-binding macrodiolide swinholide A.



The efficacy of anticancer agents that perturb microtubule dynamics (e.g., paclitaxel, docetaxel, ixabepilone, eribulin mesylate)[1] suggests actin-binding agents hold promise for cancer therapy.[2] Swinholide A, an actin-binding marine polyketide isolated in 1985 from the Okinawan marine sponge *Theonella swinhoei*,[3a] was first assumed to be secreted by symbiotic cyanobacteria[3c] but was later shown using Palauan specimens of the sponge to be linked to the presence of heterotrophic unicellular bacteria.[4] Swinholide A was initially mistaken for the monomeric macrolide hemiswinholide A[2a] until subsequent work[3b−e] revealed it to be a 44-membered macrodiolide (Figure 1). Other members of this class have been isolated (swinholides B−K, ankaraholides A and B),[5] including isoswinholide[5a] and their presumed biogenic precursor preswinholide (swinholide A seco acid).[6] Many marine natural products, the miskinolides (bistheonellides)[7] and scytophycin C,[8] have structural features in common with swinholide A (Figure 1).

Swinholide A is the most potent member of its class, with cytotoxicity against diverse tumor cell lines in the ng/mL range[9] due to its ability to dimerize actin ($K_d \approx 50$ nM)[10a] and cleave actin filaments.[10] High levels of potency are critically dependent on the symmetric 44-membered diolide ring of swinholide A, as congeners such as isoswinholide A are significantly less potent.[9] A high resolution (2 Å) crystal structure of swinholide A bound to two actin molecules has been obtained,[10c] enabling the rational design of simplified actin-binding compounds.[11]

Total syntheses of swinholide A were reported by Paterson[12] and Nicolaou.[13] The total synthesis of preswinholide A was reported by Nakata,[14] and numerous syntheses of swinholide A substructures have been disclosed.[15] Broadly speaking, these syntheses all exploit classical carbonyl additions involving stoichiometric organometallic reagents. We have developed catalytic enantioselective methods that enable direct stereo- and site-selective conversion of lower alcohols to higher alcohols.[16] These methods streamline or eliminate protecting group manipulations and discrete alcohol-to-carbonyl redox reactions, providing the most concise routes ever reported to diverse polyketide natural products.[16b] Here, we apply these methods to the construction of the C(19)−C(32) fragment of swinholide A and the formal synthesis of premisakinolide A (bistheonellic acid B),[15h] the monomer of the macrodiolide misakinolide A (bistheonellide A).[7]

Our retrosynthetic analysis of premisakinolide A (bistheonellic acid B) and the C(19)−C(32) substructure of swinholide A is as follows (Scheme 1). Aldehydes **11** and **12** were envisioned to arise through cross-metathesis of vinyl pyran **5** with iodoether **8**. The synthesis of vinyl pyran **5** takes advantage of site-selective *C*-allylation of (*S*)-1,3-butane diol **1**.[17] The iodoether **8** is readily prepared from 2-methyl-1,3-propane diol **6** via bidirectional enantioselective double *anti*-crotylation.[18] The strategic advantage of these methods is borne out by the brevity our route, which delivers Miyashita's premisakinolide A (bistheonellic acid B) intermediate **12**[15h] in nine steps, a substructure previously prepared in 16−27 steps.[12b,i,15b,h]

The synthesis of vinyl pyran **5** begins with the established stereo- and site-selective allylation of commercially available (*S*)-1,3-butane diol **1**.[17] Exposure of the resulting homoallylic alcohol **2** to the second generation Grubbs catalyst in the presence of *cis*-1,4-diacetoxy-2-butene delivered the product of cross metathesis **3** as a 5:1 mixture of alkene geometrical isomers.[19] Tsuji−Trost cyclization of **3** using the chiral palladium catalyst modified by the indicated chiral ligand delivered the 2,6-*trans*-disubstituted pyran **4** in 90% yield as a 4:1 mixture of diastereomers. As previously established, the presence of alkene geometrical isomers at the stage of

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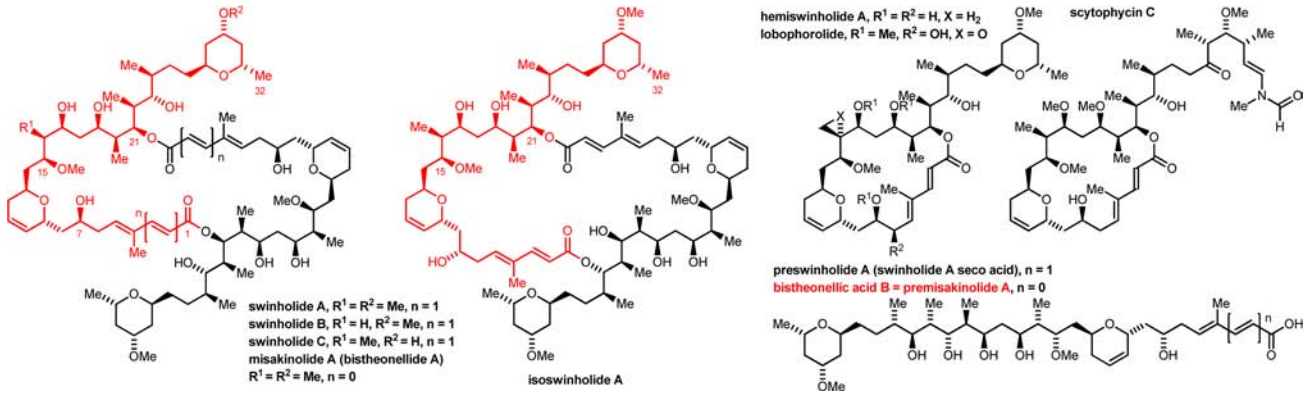
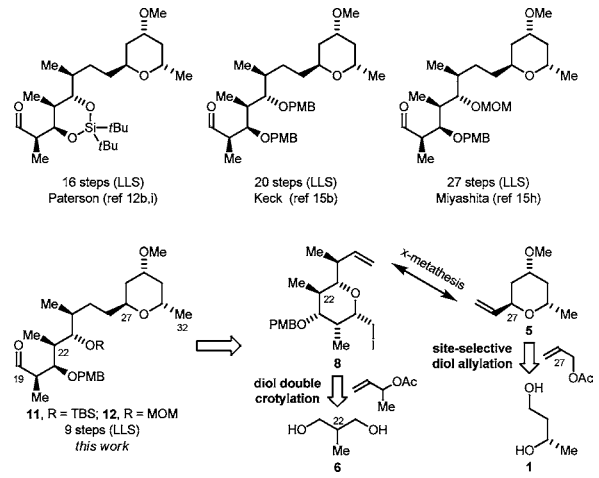


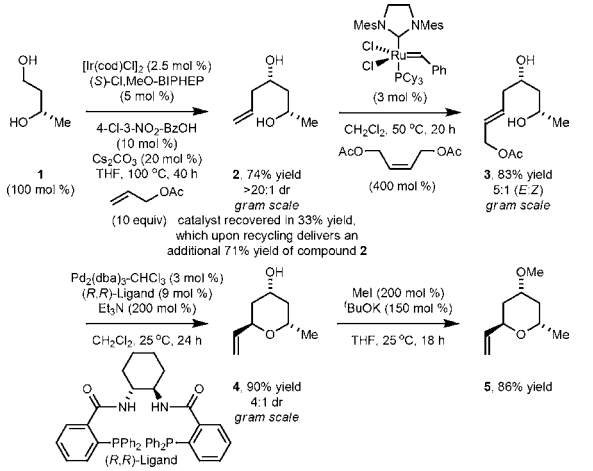
Figure 1. Swinholide A and selected naturally occurring congeners. For the structures of swinholides D−K, see ref 5.

Scheme 1. Retrosynthetic Analysis of Premisakinolide A (Bistheonellic Acid B) and C(19)−C(32) of Swinholide A and Prior Fragment Syntheses[a]



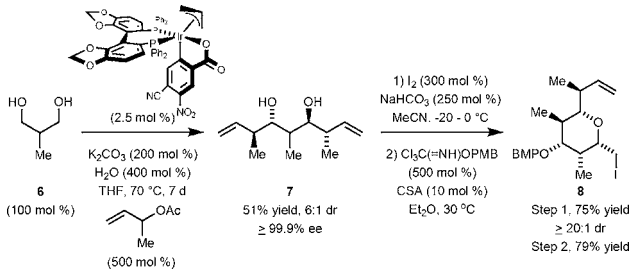
[a]For graphical summaries of prior total syntheses, see Supporting Information. Longest Linear Sequence (LLS). The carbon numbering scheme of swinholide A is used.

Scheme 2. Synthesis of Vinyl Pyran 5 via Site-Selective Allylation of Diol 1[a]



[a]Cited yields are of diastereomeric mixtures isolated by silica gel chromatography. Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. See Supporting Information for further experimental details, including recovery and recycling of the iridium catalyst.

Scheme 3. Synthesis of Iodoether 8[a]



[a]Cited yields are of diastereomeric mixtures isolated by silica gel chromatography. Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. See Supporting Information for further experimental details.

compound **3** does not influence diastereoselectivity in the cyclization to form pyran **4**. While pyran **4** was previously prepared in our laboratory,[17] the present route is an improved gram-scale synthesis with recycling of the iridium catalyst. Finally, methylation of the 4-hydroxyl moiety delivers vinyl pyran **5** (Scheme 2).

The PMB-protected iodoether **8** was prepared by a procedure previously established in our laboratory (Scheme 3).[18] Specifically, diol **6** was subjected to double *anti*-crotylation to provide **7**, which incorporates a triketide stereopolyad. A single enantiomer of **7** is formed due to Horeau's principle.[20] That is, the minor diastereomer of the monoadduct is converted predominantly to the *meso*-stereoisomer.[21] In the conversion of diol **6** to adduct **7**, it was found that use of α-methyl allyl acetate prepared from the corresponding alcohol using acetic anhydride and triethylamine (rather than pyridine) gave optimal results. Iodoetherification differentiates the diol and terminal olefin moieties and defines the chirotopic nonstereogenic center at C(22). Conversion of the remaining free hydroxyl to the PMB-ether delivers compound **8**.

With vinyl pyran **5** and iodoether **8** in hand, conversion to aldehydes **11** and **12** (Miyashita's intermediate) was attempted. The cross-metathesis of vinyl pyran **5** and iodoether **8** was especially challenging due to competing isomerization of the terminal olefin of iodoether **8** to the internal olefin. Although related cross-metatheses of vinyl pyrans are known,[22] they involve equatorially disposed vinyl moieties, unlike the vinyl moiety of pyran **5**. After considerable optimization, it was found that use of the second generation Grubbs−Hoveyda catalyst in

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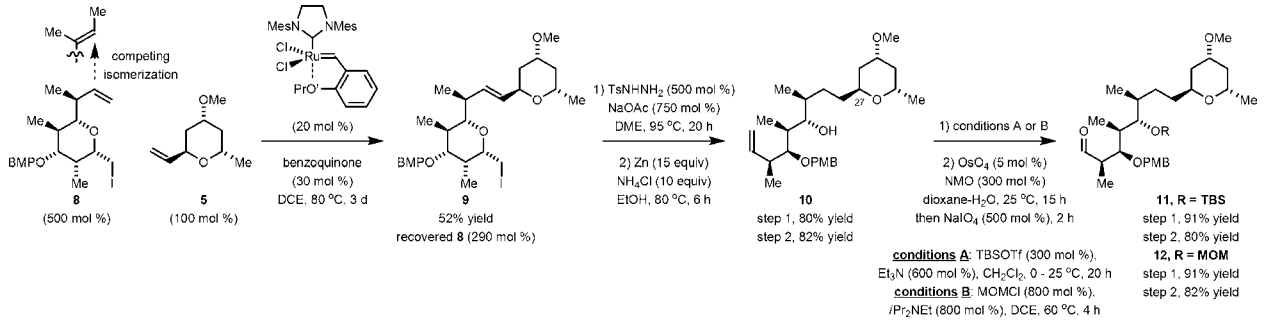
Scheme 4. Formal Synthesis of Premisakinolide A (Bistheonellic Acid B) and Synthesis of the C(19)−C(32) Substructure of Swinholide A[a]



[a]Cited yields are of diastereomeric mixtures isolated by silica gel chromatography. Diastereomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. See Supporting Information for further experimental details.

combination with 1,4-benzoquinone[23] delivered the desired product of metathesis **9** in 52% yield. Hydrogenation of the C(25)−C(26) double bond of compound **9** using palladium on carbon resulted in partial hydrogenation of the carbon−iodine bond. Use of Crabtree's catalyst[24] prevented this side reaction but led to complete epimerization of C(27). In contrast, diimide-mediated hydrogenation of the C(25)−C(26) double bond occurred smoothly.[25] Subsequent Bernet−Vasella cleavage[26] of the iodoether delivered the terminal olefin **10**, which upon TBS-protection followed by Johnson−Lemieux oxidative cleavage provides the aldehyde **11**. Similarly, Miyashita's premisakinolide A (bistheonellic acid B) intermediate **12** is prepared through MOM-protection followed by alkene oxidative cleavage in a total of 9 steps (LLS) from (*S*)-1,3-butane diol **1**.

In summary, using technology for the direct stereo- and site-selective conversion of lower alcohols to higher alcohols via C−C bond forming transfer hydrogenation, we report a formal synthesis of premisakinolide A (bistheonellic acid B). The intercepted substructure, which was previously made in 16−27 steps (LLS),[12b,i,15b,h] is now made in only 9 steps (LLS). This fragment also represents a synthesis of C(19)−C(32) of the actin-binding macrodiolide swinholide A. This study, along with prior work from our laboratory,[16b] highlights the strategic advantages of site-selectivity and redox-economy in chemical synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02056.

Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, and HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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