Total Synthesis of Swinholide A

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Swinholide A (1, Figure 1) is a marine natural product isolated^{1a,2} from the sponge Theonella swinhoei and fully characterized by NMR and X-ray crystallographic techniques.² Faulkner and co-workers^{1b} have recently demonstrated, contrary to previous beliefs, that the producer organisms of this natural product are heterotrophic unicellular bacteria rather than cyanobacteria. This complex natural product displays impressive biological properties including antifungal activity and potent cytotoxicity² against a number of tumor cells. Its cytotoxicity has been attributed to its ability to dimerize actin and disrupt the actin cytoskeleton.³ The molecular structure of swinholide A (1) is distinguished by a C2 symmetric 44-membered macrolide ring, two conjugated diene systems, two trisubstituted pyran systems, and two disubstituted dihydropyran systems. In addition, a total of 30 stereogenic centers are present in the carbon backbone of 1. The important biological properties of swinholide A (1) and its natural scarcity, coupled with its challenging molecular architecture, made it a prime target for synthesis.^{4–6} Paterson and his group at Cambridge have already reported the first total synthesis⁷ of 1. In this communication we wish to report an alternative strategy for the total synthesis of 1 that includes a number of conceptually new elements and is flexible enough to allow entry into a variety of designed members of the swinholide class.

Figure 1 outlines the retrosynthetic analysis which led to the evolution of the synthetic strategy that culminated in the present total synthesis of swinholide A (1). The symmetry of the molecule allowed the double disconnections indicated and the adoption of a highly convergent plan using simple building blocks. Thus, sequential disconnection of the two ester linkages

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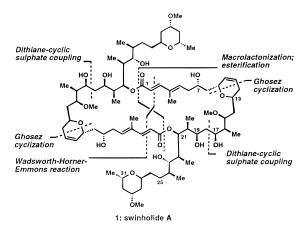


Figure 1. Structure of swinholide A (1) and retosynthetic analysis.

in 1 defined a macrolactonization and an esterification as the final key reactions in the synthesis. Two Wadsworth–Horner–Emmons reactions (see Figure 1) pointed to a common precursor, a C3–C31 fragment, for both halves of the target molecule (compound 10, Scheme 1). Disconnection of the C17–C18 and C17′–C18′ bonds using a retro dithiane⁸ –cyclic sulfate⁹ coupling reaction allowed the utilization of the two segments C3–C17 and C18–C31 [see compounds 3 and 4 (Scheme 1)]. Finally, disassembly of the dihydropyran systems as shown identified a Ghosez cyclization¹⁰ as a potential means to construct these systems. The execution of this strategy proceeded as follows.

Diol 26b was converted to cyclic sulfate 3 in 95% yield upon treatment⁹ with SOCl₂ in the presence of Et₃N followed by oxidation with RuCl3 catalyst and NaIO4. Coupling of this sulfate with the lithio derivative of dithiane 4,6a generated by the action of t-BuLi in the presence of HMPA, followed by aqueous acid treatment led to dithiane 5 in 72% overall yield. The success of this coupling method with such complex substrates is unprecedented to our knowledge and bodes well for the potential of this method in complex molecule synthesis. Removal of the dithiane moiety from 5 with NBS and AgClO₄¹¹ revealed ketone 6, which upon reduction with NaBH4 in the presence of n-Bu₃B¹² followed by basic hydrogen peroxide workup gave the requisite β -alcohol in 92% yield. Protection of the generated syn-1,3-diol as a p-methoxybenzylidene system was then carried out with p-methoxybenzaldehyde dimethyl acetal and a catalytic amount of CSA, furnishing intermediate 7 in 90% yield. Sequential removal of the benzoate (Dibal-H. 95%) and TBS (HF·pyr, 90%) groups afforded diol 9 via compound 8. Aldehyde 10 was then generated in 99% yield from allylic alcohol 9 by selective oxidation with MnO₂. Extension of this aldehyde via a Wadsworth-Horner-Emmons olefination reaction using the lithio derivative obtained from trimethyl phosphonoacetate and n-BuLi furnished selectively the (E,E)-ester 11 in 97% yield. Finally, hydrolysis of the methyl ester in 11 was achieved by exposure to NaOH in aqueous MeOH-THF to give hydroxy acid 12 (92%) from which the trimethylsilyl ether 13 was generated by treatment with TMSOTf in the presence of Hünig's base (89%).

Esterification of carboxylic acid 11 with alcohol 13 in the presence of DIC 13 and 4-DMAP at 35 °C gave the expected coupling product albeit in low yield (4–13%). A higher yield

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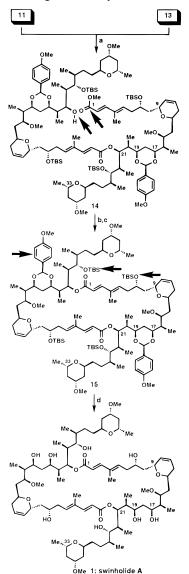
Scheme 1. Construction of Key Intermediates 11 and 13^a

^a Reagents and conditions: (a) 1.5 equiv of SOCl₂ (6 M solution in CH₂Cl₂), 4.0 equiv of Et₃N, CH₂Cl₂, 0 °C, 10 min, then 0.03 equiv of RuCl₃, 4.0 equiv of NaIO₄, CCl₄:CH₃CN:H₂O (2:2:3, v:v), 0 °C, 1.5 h, 95%; (b) 1.2 equiv of t-BuLi (1 M hexanes), 4.0 equiv of HMPA, THF (0.25 M), −78 °C, 10 min, then 1:1 equiv of **3** (0.125 M in THF), -78 °C, 10 min; (c) 2.0 equiv of 10% aqueous H₂SO₄, THF, 25 °C, 1 h, 72% (2 steps); (d) 2.0 equiv of NBS, 2.2 equiv of AgClO₄, 10% aqueous acetone, 0 °C, 1 min, 90%; (e) 1.1 equiv of n-Bu₃B (1 M, in THF), air, THF, 25 °C, 2 h, then 2.2 equiv of NaBH₄, -78 °C, 8 h, then 30% H₂O₂, 10% aqueous NaOH, 0 °C, 3 h, 92%; (f) 2.0 equiv of p-MeO-C₆H₄CH(OMe)₂, 0.1 equiv of CSA, CH₂Cl₂, 0 °C, 3 h, 90%; (g) 4.0 equiv of DibalH, CH₂Cl₂, -78 °C, 2.5 h, 95%; (h) HF•pyr, pyr, CH₂Cl₂, 0 °C, 2 h, 90%; (i) 10.0 equiv of MnO₂, CH₂Cl₂, 25 °C, 4 h, 99%; (j) 20.0 equiv of (MeO)₂P(O)CH₂CO₂Me, 15.0 equiv of *n*-BuLi (1.6 M in hexanes), THF, $0 \rightarrow 25$ °C, 18 h, 97%; (k) 4.0 equiv of NaOH, MeOH:THF:H₂O, 25 °C, 6 h, 92%, plus 6% recovered 11; (1) 12.5 equiv of TMSOTf, 25 equiv of *i*-Pr₂NEt, CH₂Cl₂, $0 \rightarrow 25$ °C, 18 h, 89%.

(46%) of the coupling product was obtained when the Yamaguchi procedure 14 (2,4,6-trichlorobenzoyl chloride, Et₃N, 4-DMAP) was employed affording hydroxy ester **14** (Scheme 2) which had suffered concomitant TMS removal. Selective saponification 7b of the ester **14** [Ba(OH)₂, H₂O, MeOH, 96 h, 83% yield], followed by macrolactonization of the resultant hydroxy acid using Yamaguchi's protocol (0.0005 M in toluene, $25 \rightarrow 110$ °C), gave the protected swinholide A **15** (38% yield, based on 75% conversion). Finally, concurrent removal of all the protecting groups from **15** with aqueous HF in acetonitrile liberated swinholide A (**1**) in 60% yield. Comparison [TLC, HPLC, 1 H NMR, 13 C NMR, IR, and [α]_D] with an authentic sample 15 confirmed the identity of the synthetic compound.

The reported total synthesis of swinholide A (1) is characterized by a highly convergent strategy, features a number of relatively new reactions, and besides rendering the natural

Scheme 2. Final Stages of the Synthesis^a



^a Reagents and conditions: (a) 1.0 equiv of 13, 3.7 equiv of 2,4,6-Cl₃(C₆H₂)COCl, 4.5 equiv of Et₃N, PhMe, 25 °C, 1.5 h, then add 2 equiv of 11, 1.6 equiv of 4-DMAP, PhMe, 105 °C, 12 h, 46%; (b) large excess Ba(OH)₂·8H₂O, MeOH, 25 °C, 96 h, 83%; (c) 15.0 equiv of 2,4,6-Cl₃(C₆H₂)COCl, 18.0 equiv of Et₃N, PhMe, 25 °C, 2.5 h, then add 1.65 equiv of 4-DMAP, PhMe, 110 °C, 24 h, 38% based on 75% consumed acid; (d) aqueous HF, MeCN, 0 °C, 2 h, 60%.

substance available for further biological studies, provides access to a variety of designed mimics.¹⁶

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Supporting Information Available: Listing of selected data for compounds 3, 6, 9–11, 13–15, and 1 (17 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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⁽¹⁶⁾ All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.