Swinholide A, a complex polyketide metabolite isolated from the marine sponge *Theonella swinhoeti*, was first reported by Carmely and Kashman in 1985. Using NMR methods and chemical derivatization, its gross structure was initially misassigned as a monomeric 22-membered macrolide. Subsequently, Kitagawa and co-workers elucidated the true dimeric nature of swinholide A (1), as well as determining the full stereochernistry, by mass spectroscopy and X-ray crystallographic studies. Swinholide A exhibits potent cytotoxic activity against a variety of human tumor cell lines (e.g., IC50 0.03 μg mL⁻¹ for L1210 cells, 0.04 μg mL⁻¹ for KB cells). The symmetrical, highly oxygenated structure 1, based on a very large macrolide ring, is a striking feature, which appears to be essential for activity. The limited natural supply and potential utility in anticancer studies, combined with the structural complexity of this unique class of macrolide, have recently inspired synthetic efforts directed toward the swinholides. Here, we report the completion of the first total synthesis of swinholide A, which relies on a strategic macrolideization to generate the key 44-membered ring. We also describe the synthesis of the 22-membered macrolide 2, designated hemiswinholide A, corresponding to the erroneous monomeric structure initially proposed for swinholide A.

Our strategy for generating the symmetrical 44-membered ring system of swinholide A required the selective deprotection and controlled dimerization of 3. This fully protected version of the monomeric secoacid, preswinholide A, has already been isolated in the synthesis, we elected to install a cyclic di-tert-butylsilylene group in 3 by HF-npyridine complex gave the C21 diol, which was followed by base hydrolysis to generate the corresponding macrolides 2 (81%) and 8 (88%), respectively. Hemiswinholide A (2), [α]D = -43.1° (c 1.95, CHCl₃), showed subtle differences in its 1H and 13C NMR spectra relative to swinholide A.

The synthesis of swinholide A itself exploited the differentiation of the C21 and C23 hydroxyls uncovered above. Thus hydrolysis of the C2 ester in 3 gave the corresponding acid, which was used to selectively esterify the C21 hydroxyl in the diol 5. Activation of this acid using the Yamaguchi conditions in THF, followed by addition to DMAP and DMAP-HCl, led to a 20:1 mixture of 7 and 6 (94% from 5). Only monomeric lactones were obtained, as judged by FABMS analysis of the crude product mixtures. After separation of 6 and 7, treatment with aqueous HF (MeCN) led to clean removal of the acetal and silyl protecting groups to give the corresponding macrolides 2 (81%) and 8 (88%), respectively. Hemiswinholide A (2), [α]D = -43.1° (c 1.95, CHCl₃), showed subtle differences in its 1H and 13C NMR spectra relative to swinholide A.

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(6) This corresponds to the size of the macrocycle obtained by counting around the carbon skeleton of the dihydropropion. If the dihydropropion oxygen is counted instead, the ring size is reduced by two and four atoms for the monomer and dimer, respectively.


(9) The chemical shift of protons attached to C21 or C23 (CDCl₃) proved diagnostic for the site of acylation/ring size: swinholide A (1), 2, 6, and 9 and 11-14 had C21-H in the range 4.50-4.55 ppm, whereas 7, 8, and 10 had C23-H in the range 4.75-4.87 ppm.


(11) Changing the solvent to toluene, as in the Yamaguchi cyclization, dramatically affected the outcome, now giving a 60:40 mixture of 7 and 6 (73%). Hence, the macrolactonization selectivity appears to be sensitive to solvent polarity, which presumably alters the conformational preferences of the activated secoacid.


(13) See the supplementary material.
Scheme 1

Reagents and conditions: (a) HF-py, py, THF, 20 °C, 20 min. (b) NaOH, MeOH, H2O, 60 °C, 2 h. (c) 2,4,6-C13(CH2)4COCl, Et3N, PhMe, 20 °C, 1 h; add to DMAP, PhMe, 0 °C, 4 h. (d) Add 4 over 16 h to DCC, DMAP, DMAP-HCl, CHCl3.60 OC, 36 h. (e) Ba(OH)2·8H2O, MeOH, 20 OC, 97 h. SiCl (Et3N, DMAP, DMF) gave an 80% yield of 11. Silylene removal by HF-pyridine complex, 11 → 12, was then followed by selective methyl ester hydrolysis, using barium hydroxide (MeOH), to give the dimeric secoacid 13 (81%).

The high degree of functionality and substitution in secoacid 13, combined with the very large ring size and use of the C11-TBS ether, contributed to serious concern over the feasibility of achieving macrocyclization to give the desired 44-membered ring. Nevertheless, submitting 13 to the optimum Yamaguchi conditions established earlier for 4 gave a gratifying 84% yield of macrodiolides, as a 6:1 mixture in favor of the desired 14 (acylation at C21' hydroxyl) over the larger ring in 15 (acylation at C23' hydroxyl). Remarkably, facile cyclization occurred even at ambient temperature, without the need for high-dilution techniques, leading after 17 h to a 60% yield of macrodiolides in a similar ratio. As with 4 → 6 + 7, the selectivity in ring size was sensitive to the macrocyclization conditions: using the Keck conditions (CHCl3) gave a 1:10 mixture of 14 and 15 (65%), where selective formation of the 46-membered ring 15 corresponding to isoswinholide A13,15 now occurred.

Finally, the complete removal of all five protecting groups was accomplished by treatment of the mixture of 14 and 15 with aqueous HF. After purification by reverse-phase HPLC, this gave swinholide A (1) in 43% yield from 14,15 which was identical13 by 1H NMR (500 MHz, CDCl3), CD, UV, IR, FABMS, and TLC to an authentic sample provided by Prof. Kitagawa. The synthetic swinholide A also had 13C NMR data in agreement13 with an authentic spectrum and published values.a,9,10 In summary, the first total synthesis of the marine macrodiolide swinholide A has been completed, together with the monomeric versions 2 and 8. Significantly, the critical macrocyclization steps are high yielding and selective, where the resulting ring size (44- or 46-membered or 22- or 24-membered) is controlled without differential hydroxyl protection. The ready availability4b,d,e of the acyclic precursor 3 should allow scale-up and the generation of further novel swinholide analogues.

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Supplementary Material Available: Listing of spectroscopic and physical data for compounds 1, 2 and 6-9, together with copies of 1H and 13C NMR spectra (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) Isoswinholide A, a minor congener of swinholide A, was also isolated from the deprotection of 15 and had 1H NMR data (supplementary material) in accord with published values (ref 3a). Specific rotation for synthetic isoswinholide A: [α]25D = -44.5° (c 0.51, CHCl3) (lit. [a]25D = -42.0° (c 0.51, CHCl3)).