# Total Synthesis of Swinholide A and Hemiswinholide A

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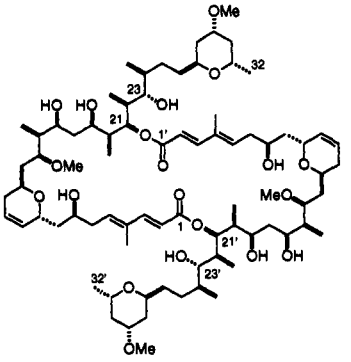
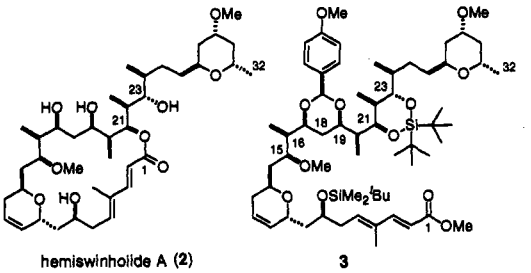
Swinholide A, a complex polyketide metabolite isolated from the marine sponge *Theonella swinhoei*, was first reported by Carmely and Kashman in 1985.[1] Using NMR methods and chemical derivatization, its gross structure was initially misassigned as a monomeric 22-membered macrolide. Subsequently, Kitagawa and co-workers elucidated the true dimeric nature of swinholide A (**1**), as well as determining the full stereochemistry, by mass spectroscopy and X-ray crystallographic studies.[2a–d] Swinholide A exhibits potent cytotoxic activity against a variety of human tumor cell lines (*e.g.*, $IC_{50}$ 0.03 $\mu g\ mL^{-1}$ for L1210 cells, 0.04 $\mu g\ mL^{-1}$ for KB cells).[2d] The symmetrical, highly oxygenated structure **1**, based on a very large macrodiolide 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 marine macrolide,[3] have recently inspired synthetic efforts[4,5] directed toward the swinholides. Here, we report the completion of the first total synthesis of swinholide A, which relies on an expedient macrocyclization to generate the key 44-membered[6] ring. We also describe the synthesis of the 22-membered[6] macrolide **2**, designated hemiswinholide A, corresponding to the erroneous monomeric structure initially proposed for swinholide A.[1]

Our strategy for generating the symmetrical 44-membered[6] 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 prepared[4a,b] by an aldol-mediated fragment coupling to construct the $C_{15}$–$C_{16}$ bond or, more efficiently, the $C_{18}$–$C_{19}$ bond. Earlier in the synthesis,[4c] we elected to install a cyclic di-*tert*-butylsilylene group and forego the opportunity for selective protection of the $C_{21}$ and $C_{23}$ hydroxyls, intending to differentiate them later, on dimerization and macrolactonization. While such a bold strategy was risky, it was fully vindicated in practice.

The synthesis of hemiswinholide A (**2**) from the monomeric secoacid **4** is described first (Scheme 1). Removal of the silylene group in **3** by HF·pyridine complex gave the $C_{21,23}$ diol **5** (94%), which was followed by base hydrolysis to generate **4**. Various macrolactonization protocols[7] were explored in an attempt to obtain controlled generation of the 22-membered macrolide. The Yamaguchi conditions[8] (2,4,6-$Cl_3(C_6H_2)COCl$, $Et_3N$, PhMe; followed by slow addition to DMAP in PhMe at 60 °C) gave a 4.5:1 mixture of 22- and 24-membered macrolides,[9] **6** and **7**, in 92% yield from **5**. Remarkably, this selectivity was completely reversed using the conditions of Keck[10] in chloroform[11] (DCC, DMAP, DMAP·HCl, 70 °C), leading 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.[12] Hemiswinholide A (**2**), $[\alpha]_D^{20} = -43.1°$ (*c* 1.95, $CHCl_3$), showed subtle differences in its $^1H$ and $^{13}C$ NMR spectra relative to swinholide A.[13]




The synthesis of swinholide A itself exploited the differentiation of the $C_{21}$ and $C_{23}$ hydroxyls uncovered above. Thus hydrolysis of the $C_1$ ester in **3** gave the corresponding acid, which was used to selectively esterify the $C_{21}$ hydroxyl in the diol **5**. Activation of this acid using the Yamaguchi conditions in THF, followed by addition to DMAP and **5** (1.3 equiv) in toluene, gave a 2:1 mixture of the desired $C_{21}$ ester **9** to the isomeric $C_{23}$ ester **10** in 85% yield. After chromatographic separation, the latter could be efficiently recycled by methanolysis ($K_2CO_3$, MeOH) to give back **3** and **5**. At this stage, it was found necessary[14] to protect the sterically hindered $C_{23}$ hydroxyl in **9** as its TBS ether. Prolonged reaction (80 °C, 36 h) with a large excess of $^tBuMe_2$-

(1) Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511.

(2) (a) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 2963. (b) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710. (c) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Yamashita, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2409. (d) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629.

(3) For other members of the swinholide family, see: (a) Kobayashi, M.; Tanaka, J.; Katori, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2960. (b) Tsukomoto, S.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3185.

(4) (a) Paterson, I.; Smith, J. D.; Ward, R. A.; Cumming, J. G. *J. Am. Chem. Soc.* **1994**, *116*, 2615. (b) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A.; Yeung, K.-S. *Tetrahedron Lett.* **1994**, *35*, 3405. (c) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 441. (d) Paterson, I.; Smith, J. D. *Tetrahedron Lett.* **1993**, *34*, 5351. (e) Paterson, I.; Cumming, J. G. *Tetrahedron Lett.* **1992**, *33*, 2847. (f) Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261.

(5) (a) Patron, A. P.; Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1147. (b) Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Patron, A. P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1151.

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

(7) For a review, see: Bartra, M.; Urpi, F.; Vilarrasa, J. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer-Verlag: Berlin, 1993; Vol. 2.

(8) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(9) The chemical shift of protons attached to $C_{21}$ or $C_{23}$ ($CDCl_3$) proved diagnostic for the site of acylation/ring size: swinholide A (**1**), **2**, **6**, **9**, and **11**–**14** had $C_{21}$–H in the range $\delta$ 5.08–5.50 ppm, whereas **7**, **8**, and **10** had $C_{23}$–H in the range $\delta$ 4.75–4.97 ppm.

(10) Keck, G. E.; Boden, E. P. *J. Org. Chem.* **1985**, *50*, 2394.

(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.

(12) These monomeric macrolides have also been prepared recently by Kitagawa and co-workers by starting from swinholide A. Kobayashi, M.; Kawazoe, K.; Okamoto, T.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 19.

(13) See the supplementary material.

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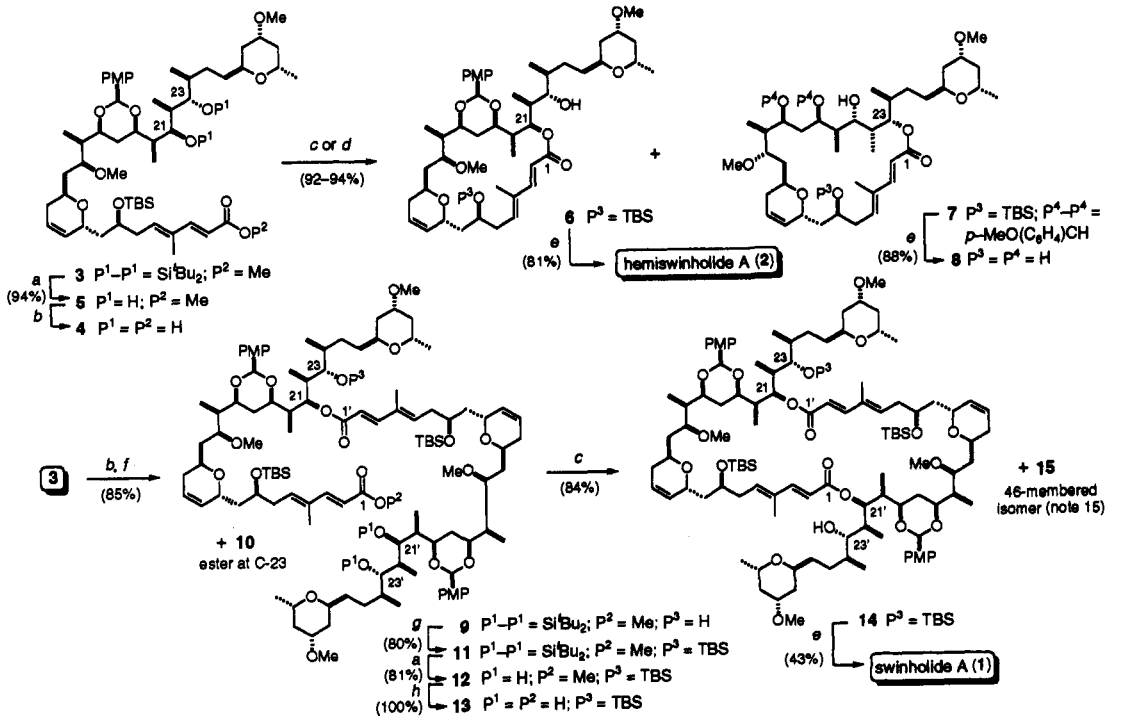
**Scheme 1**[a]




[a] Reagents and conditions: (a) HF·py, py, THF, 20 °C, 20 min. (b) NaOH, MeOH, $H_2O$, 60 °C, 2 h. (c) 2,4,6-$Cl_3(C_6H_2)$COCl, $Et_3N$, PhMe, 20 °C, 2 h; add to DMAP, PhMe, 60 °C, 2.5–4 h. (d) Add **4** over 16 h to DCC, DMAP, DMAP·HCl, $CHCl_3$, 60 °C. (e) HF, MeCN, 0 → 20 °C, 30–105 min. (f) 2,4,6-$Cl_3(C_6H_2)$COCl, $Et_3N$, THF, 20 °C, 1 h; add to **5**, DMAP, PhMe, 0 °C, 4 h. (g) $^t$BuMe$_2$SiCl, $Et_3N$, DMAP, DMF, 80 °C, 36 h. (h) $Ba(OH)_2 \cdot 8H_2O$, MeOH, 20 °C, 97 h.

SiCl ($Et_3N$, DMAP, DMF) gave an 80% yield of **11**. Silylene removal by HF·pyridine complex, **11** → **12**, was then followed by selective[14] 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 $C_{21'}$,$_{23'}$-diol, contributed to serious concern over the feasibility of achieving macrolactonization 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 $C_{21'}$ hydroxyl) over the larger ring in **15** (acylation at $C_{23'}$ hydroxyl).[9] Remarkably, facile cyclization occured 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 macrolactonization conditions: using the Keck conditions ($CHCl_3$) gave a 1:10 mixture of **14** and **15** (65%), where selective formation of the 46-membered ring **15** corresponding to isoswinholide A[3a,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 identical[13] by $^1$H NMR (500 MHz, $CDCl_3$), CD, UV, IR, FABMS, and TLC to an authentic sample provided by Prof. Kitagawa. The synthetic swinholide A also had $^{13}$C NMR data in agreement[13] with an authentic spectrum and published values.[2a,c]

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 macrolactonization steps are high yielding and selective, where the resulting ring size (44- *vs* 46-membered or 22- *vs* 24-membered) is controlled without differential hydroxyl protection. The ready availability[4b,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 $^1$H and $^{13}$C 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.

(14) The methyl ester in compound **12**, lacking the $C_{23}$ TBS ether, could not be cleanly hydrolyzed due to competing cleavage of the $C_{21}$ ester linkage and/or transesterification to the $C_{23}$ position.

(15) Isoswinholide A, a minor congener of swinholide A, was also isolated from the deprotection of **15** and had $^1$H NMR data (supplementary material) in accord with published values (ref 3a). Specific rotation for synthetic isoswinholide A: $[\alpha]^{20}_D = -44.5°$ (*c* 0.30, $CHCl_3$) (*cf.* lit.[3a] $[\alpha]^{20}_D = -42.0°$ (*c* 0.51, $CHCl_3$)).