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 cytotoxicity[2] 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 *C*2 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 synthesis[7] 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

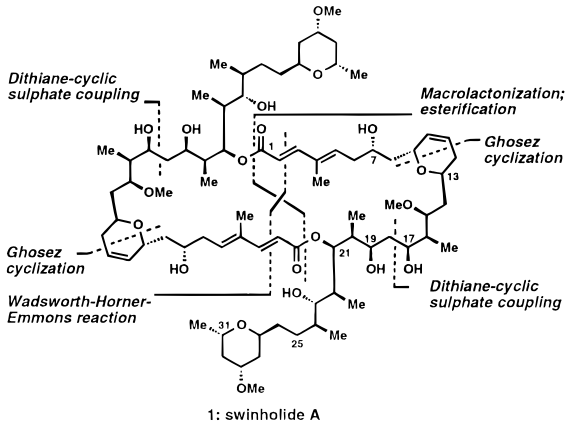

Figure 1. Structure of swinholide A (**1**) and retosynthetic analysis.

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 dithiane[8] −cyclic sulfate[9] 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 cyclization[10] as a potential means to construct these systems. The execution of this strategy proceeded as follows.

Diol **2**[6b] was converted to cyclic sulfate **3** in 95% yield upon treatment[9] with $SOCl_2$ in the presence of Et_3N followed by oxidation with $RuCl_3$ catalyst and $NaIO_4$. 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 $AgClO_4$[11] revealed ketone **6**, which upon reduction with $NaBH_4$ in the presence of *n*-Bu_3B[12] 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 MnO_2. 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

(1) (a) Carmely, S.; Kashman, Y. *Tetrahedron Lett*. **1985**, *26*, 511. (b) Bewley, C. A.; Holland, N. D.; Faulkner, D. J. *Experientia*, in press, 1996.

(2) (a) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsura, M.; Kitagawa, I. *Tetrahedron Lett*. **1989**, *30*, 2963. (b) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629. (c) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M. *J. Am. Chem. Soc.* **1990**, *112*, 3710. (d) Kobayashi, M.; Tanaka, J.; Katori, T.; Yamashita, M.; Matsuura, M.; Kitagawa, I. *Chem. Pharm. Bull*. **1990**, *38*, 2409. (e) Kobayashi, M.; Tanaka, J.; Katori, T.; Kitagawa, I. *Chem. Pharm. Bull*. **1990**, *38*, 2960.

(3) Bubb, M. R.; Spector, I.; Bershadsky, A. D.; Korn, E. D. *J. Biol. Chem*. **1995**, *270*, 3463.

(4) (a) Paterson, I.; Cumming, J. *Tetrahedron Lett*. **1992**, *33*, 2847. (b) Paterson, I.; Smith, J. D. *J. Org. Chem*. **1992**, *57*, 3261. (c) Paterson, I.; Yeung, K. *Tetrahedron Lett*. **1993**, *34*, 5347. (d) Paterson, I.; Smith, J. D. *Tetrahedron Lett.* **1993**, *34*, 5354. (e) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 3405. (f) Paterson, I.; Smith, J. D.; Ward, R. A.; Cumming, J. G. *J. Am. Chem. Soc.* **1994**, *116*, 2615. (g) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (h) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (i) Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K. *Tetrahedron* **1995**, *51*, 9437.

(5) (a) Nakata, T.; Komatsu, T.; Nagasawa, K. *Chem. Rev. Bull.* **1994**, *42*, 2403. (b) Nakata, T.; Komatsu, T.; Nagasawa, K.; Yamada, H.; Takahashi, T. *Tetrahedron Lett*. **1994**, *35*, 8225. (c) Mulzer, J.; Meyer, F. Buschmann, J.; Luger, P. *Tetrahedron Lett.* **1995**, *36*, 3503.

(6) (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.

(7) (a) Paterson, I.; Yeung, K.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc*. **1994**, *116*, 9391. (b) Paterson, I.; Yeung, K.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9467.

(8) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl*. **1965**, *4*, 1075. (b) Bulman Page, P. C.; Van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643.

(9) Sharpless, K. B.; Gao, Y. *J. Am. Chem. Soc.* **1988**, *110*, 7538.

(10) Carretero, J.; Ghosez, L. *Tetrahedron Lett*. **1988**, *29*, 2059.

(11) Modified procedure from the following: (a) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553. (b) Cain, E. N.; Welling, L. L. *Tetrahedron Lett*. **1975**, *16*, 1356.

(12) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233.

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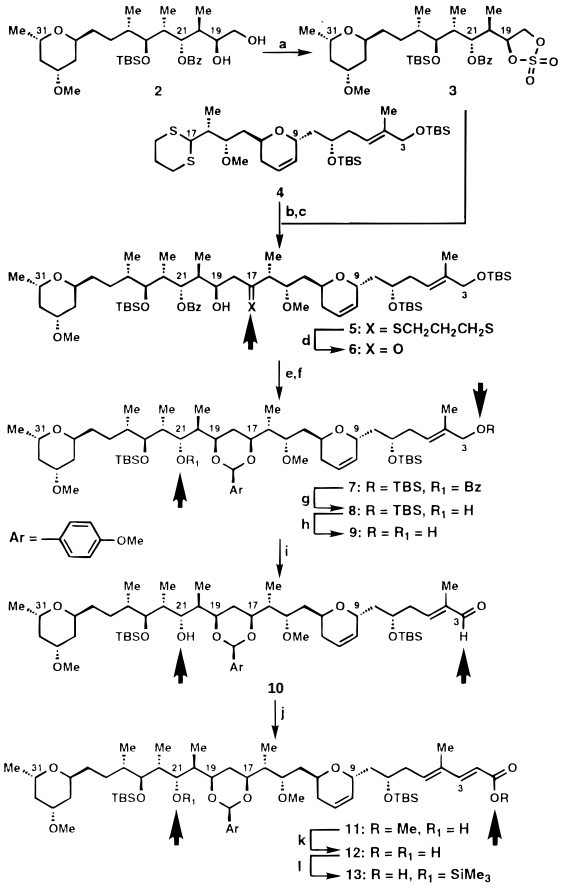
Scheme 1. Construction of Key Intermediates **11** and **13**[a]

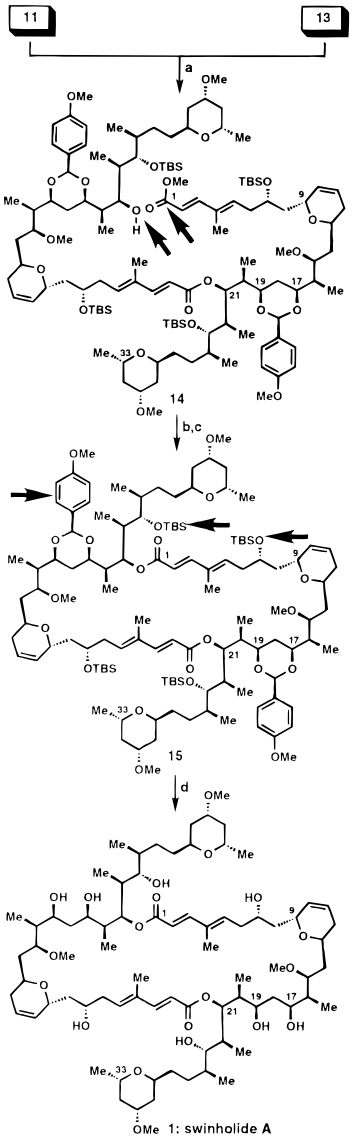


[a] Reagents and conditions: (a) 1.5 equiv of $SOCl_2$ (6 M solution in CH_2Cl_2), 4.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 10 min, then 0.03 equiv of $RuCl_3$, 4.0 equiv of $NaIO_4$, CCl_4:CH_3CN:H_2O (2:2:3, v:v), 0 °C, 1.5 h, 95%; (b) 1.2 equiv of *t*-BuLi (1 M hexanes), 4.0 equiv of HMPA, THF (0.25 M), −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 H_2SO_4, THF, 25 °C, 1 h, 72% (2 steps); (d) 2.0 equiv of NBS, 2.2 equiv of $AgClO_4$, 10% aqueous acetone, 0 °C, 1 min, 90%; (e) 1.1 equiv of *n*-Bu_3B (1 M, in THF), air, THF, 25 °C, 2 h, then 2.2 equiv of $NaBH_4$, −78 °C, 8 h, then 30% H_2O_2, 10% aqueous NaOH, 0 °C, 3 h, 92%; (f) 2.0 equiv of *p*-MeO-$C_6H_4CH(OMe)_2$, 0.1 equiv of CSA, CH_2Cl_2, 0 °C, 3 h, 90%; (g) 4.0 equiv of DibalH, CH_2Cl_2, −78 °C, 2.5 h, 95%; (h) HF·pyr, pyr, CH_2Cl_2, 0 °C, 2 h, 90%; (i) 10.0 equiv of MnO_2, CH_2Cl_2, 25 °C, 4 h, 99%; (j) 20.0 equiv of $(MeO)_2P(O)CH_2CO_2Me$, 15.0 equiv of *n*-BuLi (1.6 M in hexanes), THF, 0 → 25 °C, 18 h, 97%; (k) 4.0 equiv of NaOH, MeOH:THF:H_2O, 25 °C, 6 h, 92%, plus 6% recovered **11**; (l) 12.5 equiv of TMSOTf, 25 equiv of *i*-Pr_2NEt, CH_2Cl_2, 0 → 25 °C, 18 h, 89%.

(46%) of the coupling product was obtained when the Yamaguchi procedure[14] (2,4,6-trichlorobenzoyl chloride, Et_3N, 4-DMAP) was employed affording hydroxy ester **14** (Scheme 2) which had suffered concomitant TMS removal. Selective saponification[7b] of the ester **14** [$Ba(OH)_2$, H_2O, MeOH, 96 h, 83% yield], followed by macrolactonization of the resultant hydroxy acid using Yamaguchi's protocol (0.0005 M in toluene, 25 → 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, ^1H NMR, ^{13}C NMR, IR, and $[\alpha]_D$] 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 substance available for further biological studies, provides access to a variety of designed mimics.[16]

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-$Cl_3(C_6H_2)COCl$, 4.5 equiv of Et_3N, 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 $Ba(OH)_2$·$8H_2O$, MeOH, 25 °C, 96 h, 83%; (c) 15.0 equiv of 2,4,6-$Cl_3(C_6H_2)COCl$, 18.0 equiv of Et_3N, 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%.

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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.

JA954211T

(13) Kappe, T.; Frühwirth, F. *J. Prakt. Chem.* **1990**, *332*, 475.
(14) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(15) We thank Dr. John Faulkner for a sample of authentic swinholide A (**1**).
(16) All new compounds exhibited satisfactory spectral and exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.