# Total Synthesis of (-)-Preswinholide A

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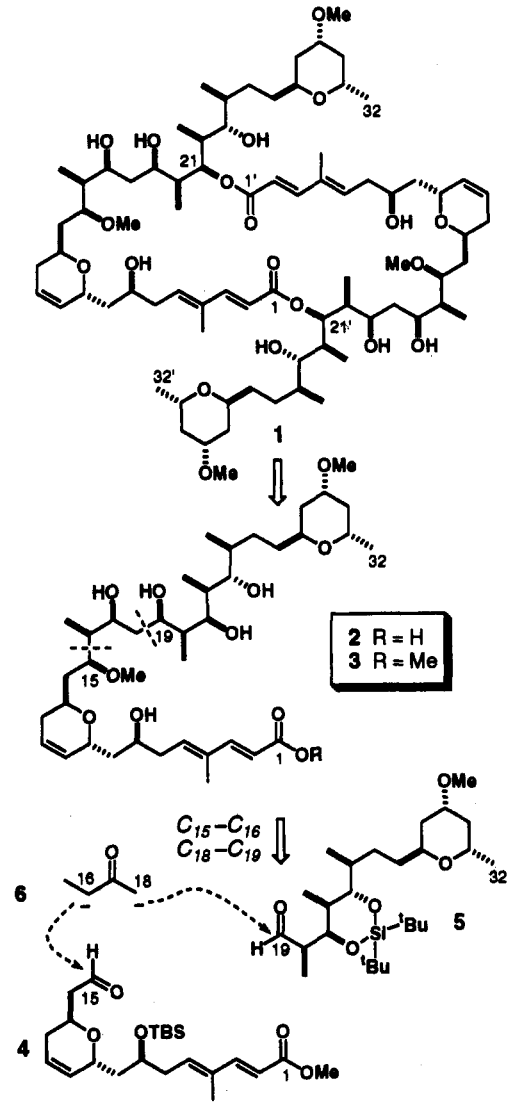
The members of the swinholide family of marine-derived macrodiolides exhibit potent cytotoxic activity against a variety of human carcinoma cell lines.[1-3] Swinholide A (**1**), isolated[1] from the marine sponge *Theonella swinhoei*, is a symmetrical dimer[2] formed through the union of two monomeric units **2** to generate a 44-membered macrocyclic ring (Scheme 1). This secoacid **2**, termed preswinholide A, has recently been isolated[3a,4] from *Theonella swinhoei*, and its methyl ester **3** has been obtained by methanolysis of swinholide A.[2c] The structural complexity of this unique class of polyketide, combined with the associated biological activity and scarcity of natural supply, makes the swinholides and other related macrolides[5d] important targets for chemical synthesis. Herein, we report the first total synthesis of preswinholide A (**2**), the biosynthetic precursor of **1**.[6]

As outlined in Scheme 1, the complete carbon skeleton of preswinholide A (**2**) was anticipated to arise from the union of $C_1$–$C_{15}$ aldehyde **4**[5b] with $C_{19}$–$C_{32}$ aldehyde **5**[5c] using butanone synthon **6** as a linking unit. Such an approach should provide optimum flexibility in the order of events required for stereocontrol in this demanding coupling process. We initially decided to attach the $C_{16}$–$C_{18}$ linker unit to **5** and investigate the stereoselectivity of the $C_{15}$–$C_{16}$ aldol bond construction between the derived ethyl ketone and aldehyde **4**.

The stereocontrolled conversion of **5** into ethyl ketone **8** was readily accomplished in three steps (Scheme 2). Reaction of aldehyde **5** with allylsilane **7**[7] promoted by $TiCl_4$ (1 equiv, $CH_2Cl_2$, -90 °C) gave the 19*R* allylic alcohol in 94% yield with 95% ds (*via* Felkin–Anh control).[5d] Ozonolysis of the olefin and formation of the *p*-methoxybenzyl (PMB) ether then gave **8** (57% overall yield from **5**). Regio- and stereoselective coupling of the enantiomerically pure subunits **4**[5b] and **8** was best achieved using a boron-mediated anti aldol reaction.[8] Addition of *(E)*-enol dicyclohexylborinate **9**, selectively generated from **8** using $(c\text{-}C_6H_{11})_2BCl/Et_3N$ in $Et_2O$,[9] to **4** gave an 83% yield of diastereomeric aldol products (52:35:13). Separation by preparative HPLC gave the two anti aldol isomers **10** and **11**.[10,11] The major isomer **10** (40% yield) had the correct relative stereochemistry[11] of the $C_{16}$ methyl but required inversion of the $C_{15}$ hydroxyl group. Using catecholborane in THF,[12] reduction of the $C_{17}$ ketone in **10** gave the corresponding syn 1,3-diol in 93% yield and ≥95% ds. Treatment with DDQ under anhydrous conditions induced

**Scheme 1**

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(6) Presented at the 13th International Symposium on Organic Synthesis of the Royal Society of Chemistry (Perkin Division), Oxford, UK (July 22, 1993).

(7) Allylsilane **7** was prepared from $EtCO_2Et$ by (i) $Me_3SiCH_2MgCl$, $CeCl_3$, THF; (ii) $SiO_2$, $CH_2Cl_2$. Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.

(8) A syn aldol coupling of the *(Z)*-enol di-*n*-butylborinate derived from **8** (*n*-$Bu_2BOTf$, *i*-$Pr_2NEt$) with aldehyde **4** was first explored. This led to the undesired syn isomer (*i.e.*, having the bis-epi 15*R*,16*S* stereochemistry for the swinholides) with 77% ds. Attempted use of (+)-$Ipc_2BOTf$ in this reaction, to confer *reagent control*, was unsuccessful and only gave traces of aldol products. Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

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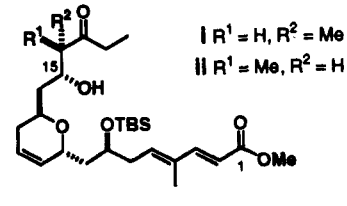
(10) The anti relative stereochemistry assignment at $C_{15}$ and $C_{16}$ was based primarily on the well-precedented use of $(c\text{-}C_6H_{11})_2BCl$ to generate anti aldol products (*cf.* ref 9) and on the fact that the two isomers formed using this reagent were clearly different from those isolated from the syn-selective aldolization using *n*-$Bu_2BOTf$ (*cf.* ref 8). Unambiguous determination of the $C_{15}$–$C_{16}$ relative stereochemistry by $^1H$ NMR was not possible since one syn and and both anti aldol products show similar *J* values (*ca.* 7 Hz).

(11) The 15*R* stereochemistry in **10** was inferred on the basis of similarities in the $^1H$ NMR spectra to model compounds **i** and **ii**, where the configuration had been determined by $^1H$ NMR analysis of the derived (*R*)- and (*S*)-MPTA esters. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

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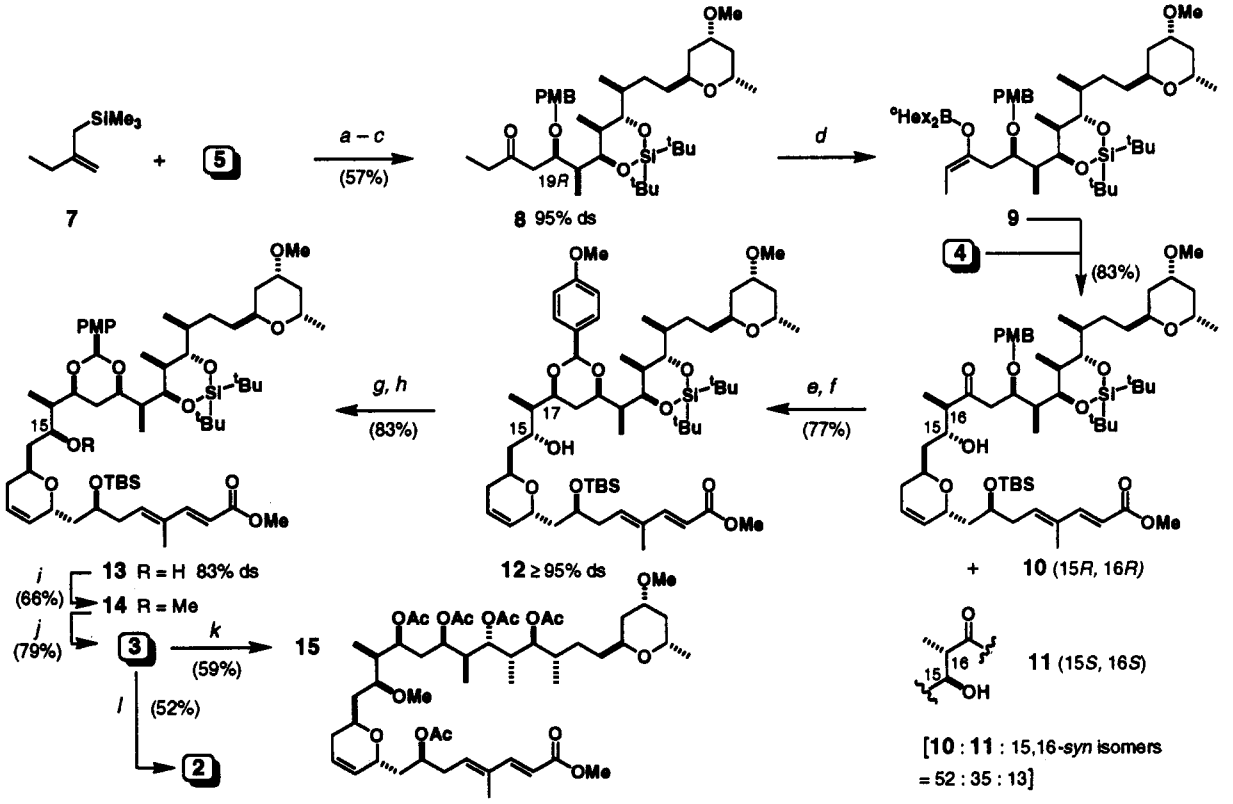
0002-7863/94/1516-2615$04.50/0 

**Scheme 2**[a]




[a] Reagents and conditions: (a) $TiCl_4$, $CH_2Cl_2$, –90 °C, 0.5 h; (b) $O_3$, $CH_2Cl_2$/MeOH, –78 °C, 15 min; $Me_2S$, –78 → 20 °C, 3 h; (c) PMBOC($CCl_3$)=NH, TfOH (0.5 mol %), $Et_2O$, 20 °C, 1 h; (d) $(c\text{-}C_6H_{11})_2BCl$, $Et_3N$, $Et_2O$, –40 → 0 °C, 2 h; **4**, –78 → 20 °C, 20 h; $H_2O_2$, MeOH, 0 °C, 0.5 h; (e) catecholborane, THF, –78 → 20 °C, 23 h; (f) DDQ, 4-Å molecular sieve powder, $CH_2Cl_2$, 20 °C, 0.5 h; (g) Dess–Martin periodinane, $CH_2Cl_2$, 20 °C, 0.5 h; (h) $LiAlH(O\text{-}t\text{-}Bu)_3$, $Et_2O$, THF, 0 °C, 0.5 h, then –20 °C, 18 h; (i) MeOTf, 2,6-di-*tert*-butylpyridine, 50 °C, 4.25 h; (j) 40% aqueous HF, MeCN, 0 → 20 °C, 2 h; (k) $Ac_2O$, pyridine, DMAP, 20 °C, 18 h; (l) NaOH, MeOH, $H_2O$, 20 °C, 5 h.

the cyclization of the strategically positioned $C_{19}$ PMB ether[13] onto the $C_{17}$ hydroxyl to give an 83% yield of the *p*-methoxybenzylidene acetal **12**. Subsequent oxidation using the Dess–Martin periodinane,[14] followed by reduction using $LiAlH(O\text{-}t\text{-}Bu)_3$, gave the 15*S* alcohol **13** in 83% overall yield and up to 83% ds.[15] Aldol adduct **11** can also be used productively in the synthesis of preswinholide A,[16] by conversion into the ketone precursor of **13** by a four-step sequence involving epimerization at $C_{16}$. With all the stereocenters required for preswinholide A intact, the $C_{15}$ hydroxyl group was methylated (MeOTf/2,6-di-*tert*-butylpyridine[17]) to give the fully protected secoacid **14**, $[\alpha]^{20}_D = -84.3°$ (*c* 1.6, $CHCl_3$), in 66% isolated yield (plus 12% recovered starting material).

Removal of all the hydroxyl-protecting groups was accomplished in a single step in 79% yield using aqueous HF in MeCN. The resulting, known[2b] pentaol **3**, $[\alpha]^{20}_D = -42°$ (*c* 0.61, $CHCl_3$) (*cf.* lit.[2] $[\alpha]^{20}_D = -31°$ (*c* 2.8, $CHCl_3$)), exhibited $^1H$ NMR data ($CDCl_3$ and $C_6D_6$) in accord[18] with the published values and copies of the $^1H$ NMR spectrum ($CDCl_3$) provided by Professor Kitagawa. In addition, **3** was converted into its pentaacetate **15**, $[\alpha]^{20}_D = -26°$ (*c* 0.45, $CHCl_3$) (*cf.* lit.[3b] $[\alpha]^{20}_D = -22°$ (*c* 0.62, $CHCl_3$)), which has also been prepared from natural material.[3b] All NMR data ($^1H$, $^{13}C$, COSY and HETCOR) were in total agreement[18] with the literature values. Finally, **3** was hydrolyzed (NaOH, aqueous MeOH) to give preswinholide A (**2**), $[\alpha]^{20}_D = -24.0°$ (*c* 0.25, MeOH) (*cf.* lit.[3a] $[\alpha]^{20}_D = -29.0°$ (*c* 1.0, MeOH)), in 52% yield following reverse-phase HPLC.

In summary, the first total synthesis of (–)-preswinholide A, the biosynthetic precursor to swinholide A, has been completed using a boron-mediated anti aldol reaction for the coupling of the complex fragments **4** and **8**. This work shows that we have all of the 15 stereogenic centers and suitable protecting groups in place for eventual elaboration of secoacid derivative **14** into swinholide A.

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**Supplementary Material Available:** Listing of spectroscopic and physical data for compounds **2**, **3**, **10**, and **15**, and copies of $^1H$ and $^{13}C$ NMR spectra (16 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.

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(14) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(15) The minor component from this reaction is alcohol **12** and is therefore recyclable.
(16) The methyl ester of 16-*epi*-preswinholide A was also prepared from **11**. It showed substantially different $^1H$ NMR spectral data from that of **3**.
(17) (a) Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046. (b) Evans, D. A.; Sheppard. G. S. *J. Org. Chem.* **1990**, *55*, 5192.
(18) While the $^1H$ NMR spectrum of synthetic **2** in $CDCl_3$ was identical to that obtained for a sample of **3** derived from natural material, the spectra acquired in $C_6D_6$ exhibited a significant concentration dependence. This effect was more pronounced in the $^{13}C$ NMR spectra obtained for synthetic **3** in both $CDCl_3$ and $C_6D_6$. In the latter solvent, all of the $^{13}C$ chemical shifts of our most concentrated sample agreed within ±0.5 ppm. These observations led us to prepare the less polar pentaacetate **15**, which exhibited $^1H$, $^{13}C$, COSY and HETCOR NMR ($CDCl_3$), IR ($CCl_4$), and FAB (glycerol matrix) mass spectral data in full agreement with the literature values (*cf.* ref 3b).