SYNTHETIC STUDY OF MARINE MACROLIDE SWINHOLIDE A. STEREOCONTROLLED SYNTHESIS OF THE C11 - C32 SEGMENT

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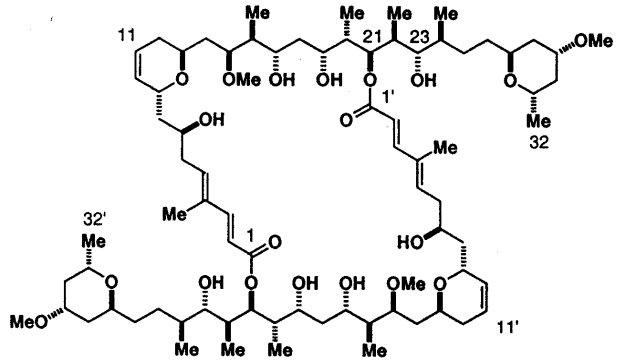
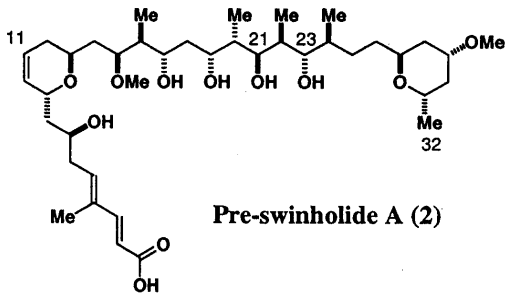
The C24-C32 segment **4** of swinholide A (**1**) was stereoselectively synthesized starting from (*S*)-methyl 3-hydroxybutyrate, and the convergent synthesis of the C11-C32 segment **5** was accomplished *via* stereoselective aldol condensation of **3** and **4**

KEYWORDS swinholide A; stereocontrolled synthesis; C11-C32 segment; 1,3-polyol; aldol condensation

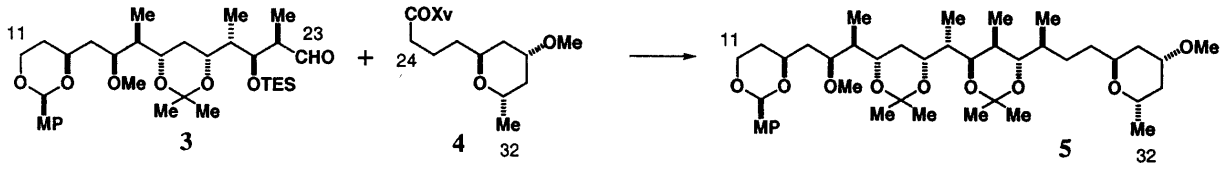
Swinholide A (**1**),[1] isolated from the marine sponge *Theonella swinhoei*, is a unique 44-membered dimeric macrolide and exhibits potent cytotoxic activity. Recently, pre-swinholide A (**2**), a monomeric seco acid of **1**, was also isolated from *Theonella swinhoei*,[2] and the first total synthesis of **2** has been reported by Paterson *et al.*[3] We have also engaged in the synthesis of these compounds and already synthesized the C11-C23 segment **3** stereoselectively.[4] In this paper, the stereoselective synthesis of the C24-C32 segment **4** based on the synthetic method for 1,3-*anti*-polyol developed in this laboratory[5] and its coupling with segment **3** leading to the C11-C32 segment **5** are described.



Swinholide A (1)

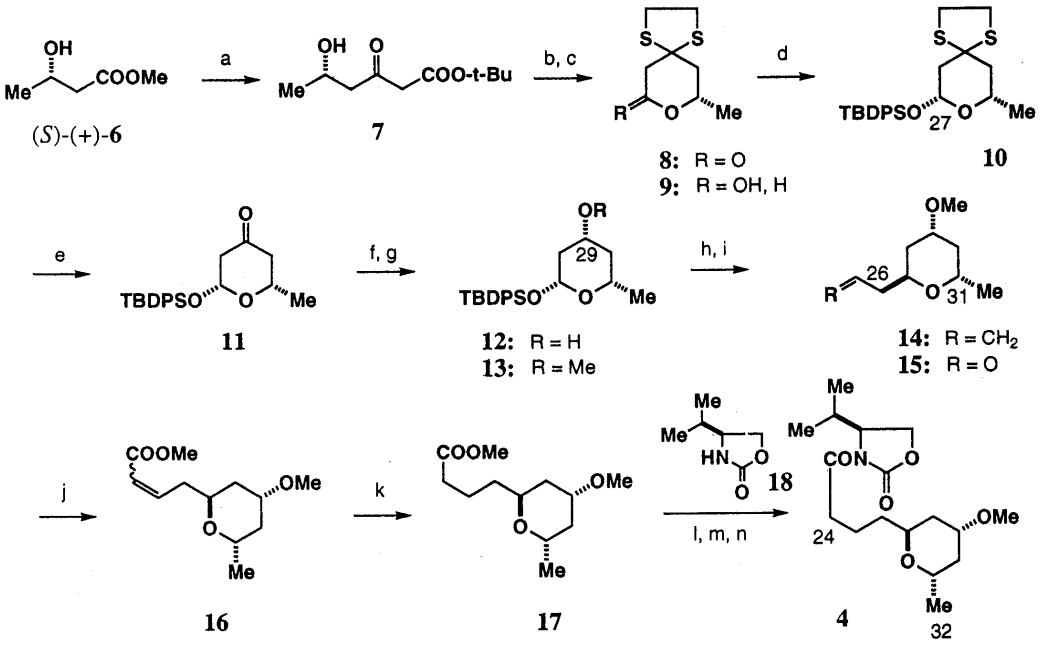


Pre-swinholide A (2)



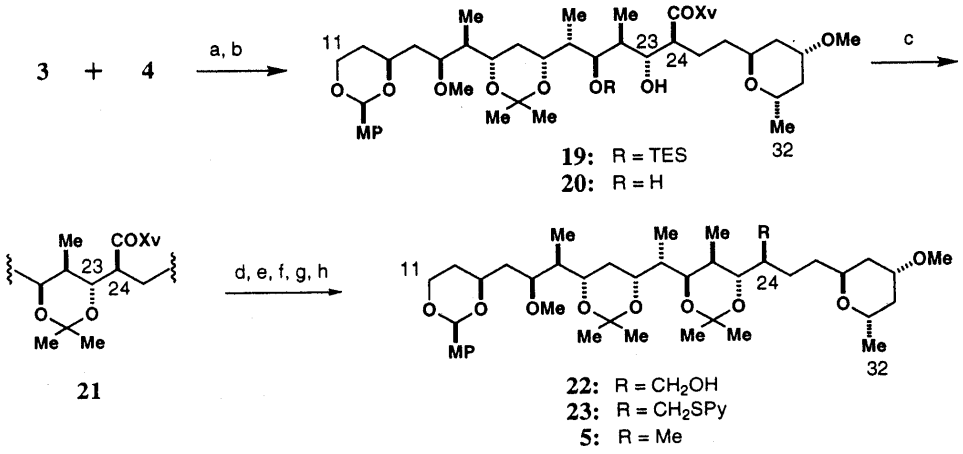
3 **4** **5**

(*S*)-Methyl 3-hydroxybutyrate (**6**),[6] prepared from (*S*)-threonine, was chosen as a starting material for the synthesis of the C24-C32 segment **4**. Treatment of the ester **6** with LDA and MeCOO-*t*-Bu gave β-keto ester **7**,[7] which was treated with ethanedithiol in the presence of BF_3·Et_2O to give thioacetal-δ-lactone **8**. Reduction of **8** with DIBAH gave lactol **9** as a 4 : 1 mixture of α- and β-hydroxy anomers, which on treatment with *t*-BuPh_2SiCl and imidazole in DMF produced a single isomer **10**[5] having the 27α(*equatorial*) silyloxy group; ^{1}H NMR: δ 4.77 (dd, J=2.0, 9.0 Hz; C27-H). This fixing of the anomeric silyloxy group to *equatorial* is quite important to induce the complete stereoselection in the following reduction.[5] After deprotection of thioacetal group in **10** with NBS, reduction of the resulting ketone **11** with $LiAlH_4$ took place, as expected, from the less hindered β-side, producing the desired 29α-alcohol **12** exclusively. The configuration of the hydroxyl group in **11** was assigned as *equatorial* by ^{1}H NMR analysis; δ 3.63 (dddd, J=4.8, 4.8, 11.1, 11.1 Hz; C29-H). After methylation of the hydroxyl group in **12** with



(a) LDA, MeCOO-*t*-Bu, THF, -78 ~ -15°C (94%); (b) $HSCH_2CH_2SH$, BF_3·Et_2O, CH_2Cl_2, rt (81%); (c) DIBAH, PhMe, -78°C (88%); (d) *t*-$BuPh_2SiCl$, imidazole, DMF, rt (99%); (e) NBS, $AgNO_3$, Na_2CO_3, aq MeCN, 0°C (94%); (f) $LiAlH_4$, Et_2O, 0°C (89%); (g) KH, MeI, THF, 0°C (93%); (h) allyltrimethylsilane, BF_3·Et_2O, CH_2Cl_2, 0°C; (i) O_3, MeOH, -78°C; Me_2S, -78°C ~ rt (64% from **13**); (j) Ph_3P=CHCOOMe, PhH, reflux (98%); (k) H_2, 10% Pd-C, AcOEt, rt; (l) LiOH, aq THF, rt; (m) $(COCl)_2$, PhH, DMF, rt; (n) *n*-BuLi, **18**, THF, -78 ~ 0°C (93% from **16**).

MeI-KH, the resulting methyl ether **13** was treated with allyltrimethylsilane in the presence of BF_3·Et_2O[8] in CH_2Cl_2 to give a single isomer **14**[9] having β-*axial* allyl group. The configuration of the allyl group was confirmed on the bases of observation of NOE between C26-H and C31-H. Ozonolysis of **14** in MeOH followed by Me_2S treatment gave aldehyde **15**, which was subjected to Wittig reaction giving a mixture of (*E*)- and (*Z*)-unsaturated esters **16** in a ratio of 8.4 : 1 (by ^1H NMR analysis). Catalytic hydrogenation of **16** in AcOEt in the presence of 10% Pd-C produced saturated ester **17**, which was effectively converted into the desired imide **4** in three steps: 1) hydrolysis of ester with LiOH, 2) acid chloride formation with oxalyl chloride, 3) imide formation by treatment with Li salt of **18**.



a) *n*-Bu_2BOTf, imide **4**, *i*-Pr_2NEt, aldehyde **3**, CH_2Cl_2, -78°C ~ rt; (b) HF-py, py, MeCN, 0°C; (c) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt (54% from **3**); (d) LiOH, 30% H_2O_2, aq THF, 0°C; (e) CH_2N_2, Et_2O, rt (75% from **21**); (f) $LiAlH_4$, THF, 0°C ~ rt (100%); (g) PySSPy, *n*-Bu_3P, py, rt (100%); (h) Raney Ni, EtOH, rt (99%).

With the requisite segments **3** and **4** in hand, we then undertook their coupling under Evans' aldol reaction conditions.[10] Boron enolate formation of the imide **4** by treatment with *n*-Bu_2BOTf in the presence of *i*-Pr_2NEt in CH_2Cl_2 followed by an addition of the aldehyde **3** gave 23,24-*anti*-hydroxy imide **19** exclusively. Removal of TES protective group in **19** with HF-pyridine gave diol **20** which was treated with $Me_2C(OMe)_2$ and PPTS to give acetonide **21**. Hydrolysis of **21** with LiOOH,[11] esterification with diazomethane, and $LiAlH_4$ reduction produced alcohol **22**. Finally, conversion of the C24-hydroxymethyl group in **22** into methyl group was examined. After several attempts,[12] 2-pyridylsulfide formation and the successive reduction was found to afford the desired **5** effectively; i.e., reaction of **22** with di-2-pyridyl disulfide in the presence of *n*-Bu_3P in pyridine proceeded smoothly, giving the corresponding 2-pyridyl sulfide **23**,[13] which was reduced with Raney Ni in EtOH[14] to give the desired C24-methyl compound **5**,[15] corresponding to the C11-C32 segment of **1**.

In summary, the C11-C32 segment **5** of swinholide A (**1**) was synthesized with virtually complete stereoselection. Further investigation toward the synthesis of swinholide A from **5** is now in progress.

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12) Several other methods gave unsatisfactory results; *e.g.*, a) mesylation with MsCl-DMAP followed by $LiAlH_4$ reduction, b) xantate formation with NaH-CS_2-MeI followed by reduction with *n*-Bu_3SnH-AIBN, c) tosylation with *p*-TsCl-KH in DMF-THF, and d) iodination with I_2-PPh_3-imidazole in benzene.

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15) Data for **5**: $[\alpha]_D$ +5.6° (c 0.12, $CHCl_3$), ^1H NMR (500 MHz; $CDCl_3$): δ0.810 (d, J=7.0 Hz; Me), 0.813 (d, J=6.7 Hz; Me), 0.85 (d, J=6.4 Hz; Me), 0.95 (d, J=6.7 Hz; Me), 1.21 (d, J=6.1 Hz; C31-Me), 1.30, 1.32, 1.36, 1.41 (each s; acetonide Me x 4), 3.09 (t, J=6.1 Hz; O-CH), 3.34 (s; OMe), 3.35 (s; OMe), 3.53 (dddd, J=4.6, 4.6, 10.2, 10.2 Hz; O-CH), 3.69 ~ 4.00 (m; O-CH, O-CH_2), 3.80 (s; Ar-OMe), 4.20 ~ 4.31 (m; O-CH x 2), 5.47 (s; O-CH-O).

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