

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

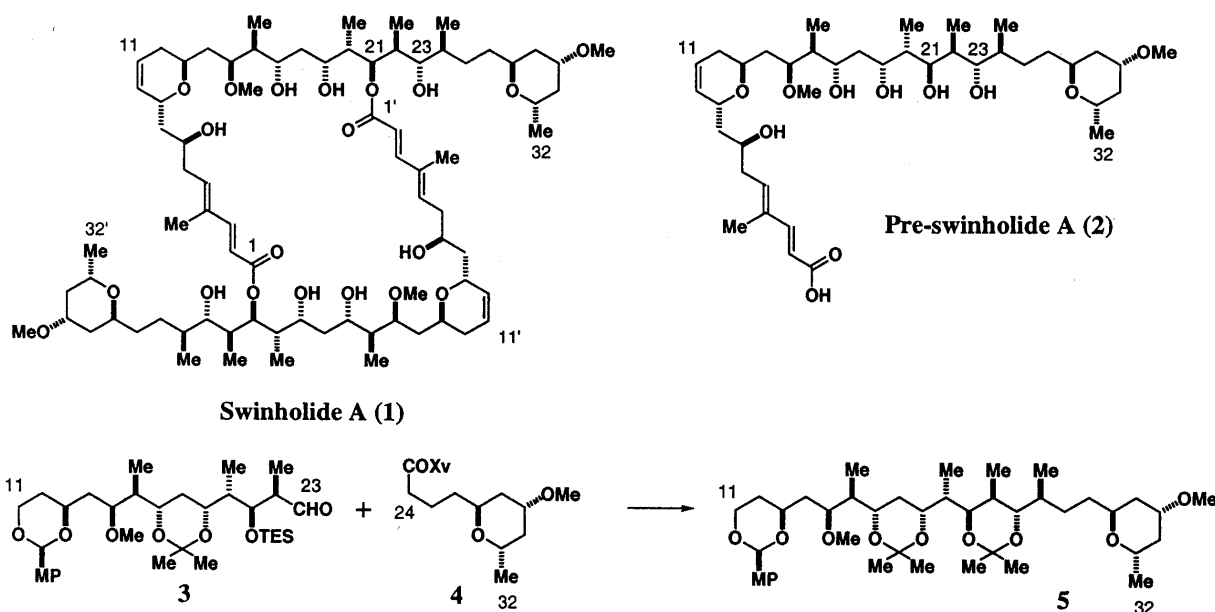
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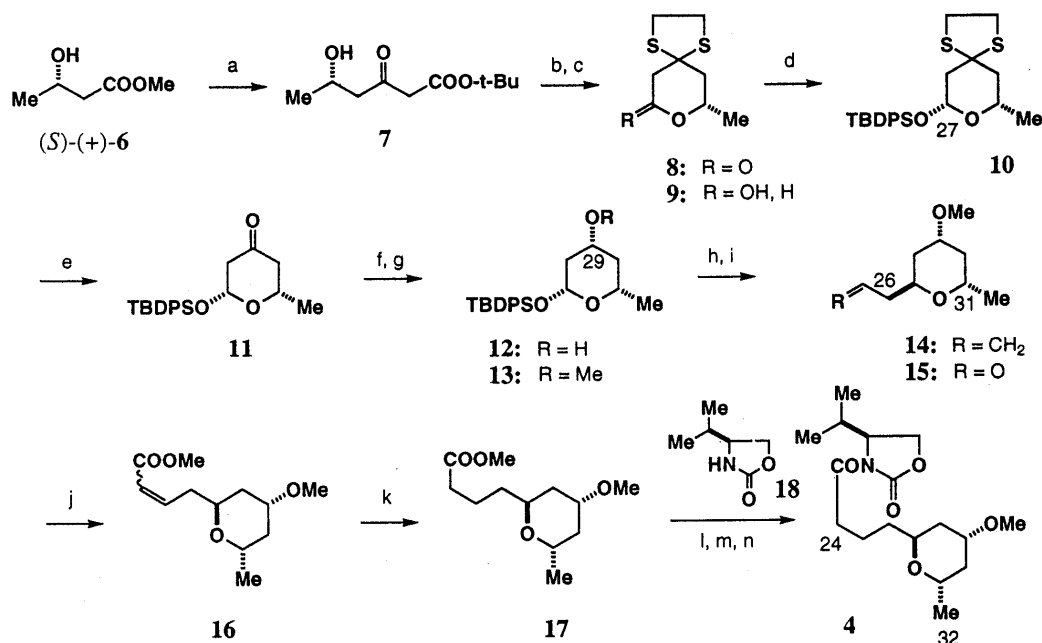
The C24-C32 segment **4** of swinholid A (**1**) was stereoselectively synthesized starting from (*S*)-methyl 3-hydroxybutyrate, and the convergent synthesis of the C11-C32 segment **5** was accomplished *via* stereoselective aldol condensation of **3** and **4**

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

Swinholid A (**1**),¹⁾ isolated from the marine sponge *Theonella swinhoei*, is a unique 44-membered dimeric macrolide and exhibits potent cytotoxic activity. Recently, pre-swinholid 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 laboratory⁵⁾ and its coupling with segment **3** leading to the C11-C32 segment **5** are described.

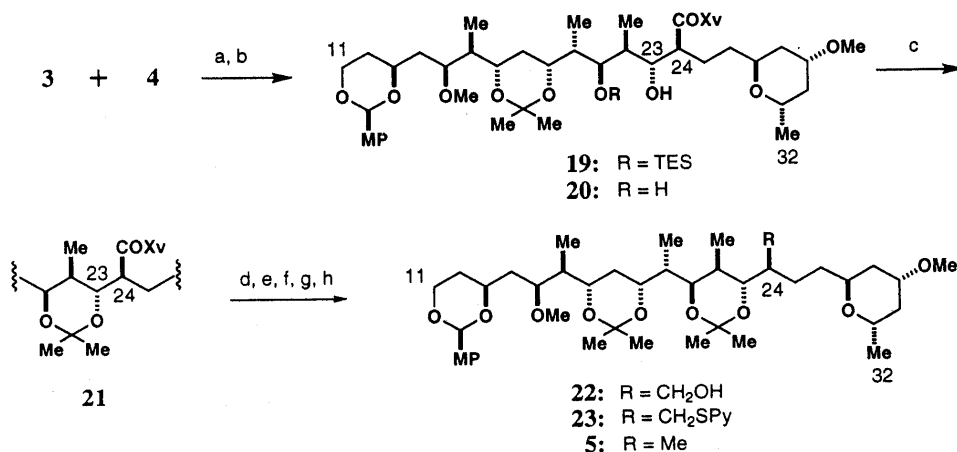


(*S*)-Methyl 3-hydroxybutyrate (**6**),⁶⁾ prepared from (*S*)-threonine, was chosen as a starting material for the synthesis of the C24-C32 segment **4**. Treatment of the ester **6** with LDA and MeCOO-*t*-Bu gave β -keto ester **7**,⁷⁾ which was treated with ethanedithiol in the presence of BF₃·Et₂O 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*-BuPh₂SiCl and imidazole in DMF produced a single isomer **10**⁵⁾ having the 27 α (*equatorial*) silyloxy group; ¹H 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 LiAlH₄ took place, as expected, from the less hindered β -side, producing the desired 29 α -alcohol **12** exclusively. The configuration of the hydroxyl group in **11** was assigned as *equatorial* by ¹H 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) HSCH₂CH₂SH, BF₃·Et₂O, CH₂Cl₂, rt (81%); (c) DIBAL, PhMe, -78°C (88%); (d) *t*-BuPh₂SiCl, imidazole, DMF, rt (99%); (e) NBS, AgNO₃, Na₂CO₃, aq MeCN, 0°C (94%); (f) LiAlH₄, Et₂O, 0°C (89%); (g) KH, MeI, THF, 0°C (93%); (h) allyltrimethylsilane, BF₃·Et₂O, CH₂Cl₂, 0°C; (i) O₃, MeOH, -78°C; Me₂S, -78°C ~ rt (64% from 13); (j) Ph₃P=CHCOOMe, PhH, reflux (98%); (k) H₂, 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 BF₃·Et₂O⁸) in CH₂Cl₂ to give a single isomer 14⁹) 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 Me₂S 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*-Bu₂BOTf, imide 4, *i*-Pr₂NEt, aldehyde 3, CH₂Cl₂, -78°C ~ rt; (b) HF-py, py, MeCN, 0°C; (c) Me₂C(OMe)₂, PPTS, CH₂Cl₂, rt (54% from 3); (d) LiOH, 30% H₂O₂, aq THF, 0°C; (e) CH₂N₂, Et₂O, rt (75% from 21); (f) LiAlH₄, THF, 0°C ~ rt (100%); (g) PySSPy, *n*-Bu₃P, 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*-Bu₂BOTf in the presence of *i*-Pr₂NEt in CH₂Cl₂ 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 Me₂C(OMe)₂ and PPTS to give acetone **21**. Hydrolysis of **21** with LiOOH,¹¹⁾ esterification with diazomethane, and LiAlH₄ 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*-Bu₃P in pyridine proceeded smoothly, giving the corresponding 2-pyridyl sulfide **23**,¹³⁾ which was reduced with Raney Ni in EtOH¹⁴⁾ 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 swinholid A (**1**) was synthesized with virtually complete stereoselection. Further investigation toward the synthesis of swinholid A from **5** is now in progress.

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- 15) Data for **5**: [α]_D +5.6° (c 0.12, CHCl₃), ¹H NMR (500 MHz; CDCl₃): δ 0.810 (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; acetone 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-CH₂), 3.80 (s; Ar-OMe), 4.20 ~ 4.31 (m; O-CH x 2), 5.47 (s; O-CH-O).

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