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Total Synthesis of Preswinholide A. 1. Stereoselective Synthesis of the C11-C23 Segment

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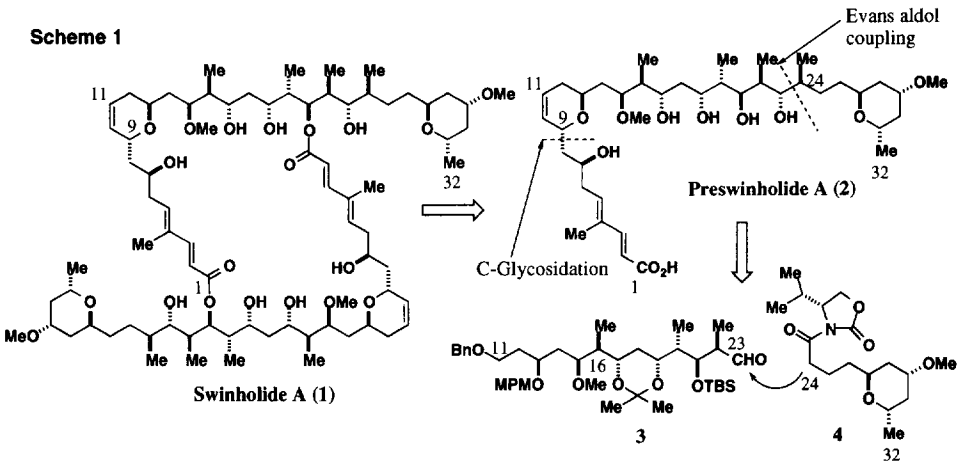
Abstract: The C11-C23 segment of preswinholide A was stereoselectively synthesized based on the iterative construction of 1,3-polyol chains using a series of sequential reactions which involves the Sharpless asymmetric epoxidation of allyl alcohol and Pd-catalyzed hydrogenolysis of alkenyl oxirane with HCOOH as the key reactions. Copyright © 1996 Elsevier Science Ltd

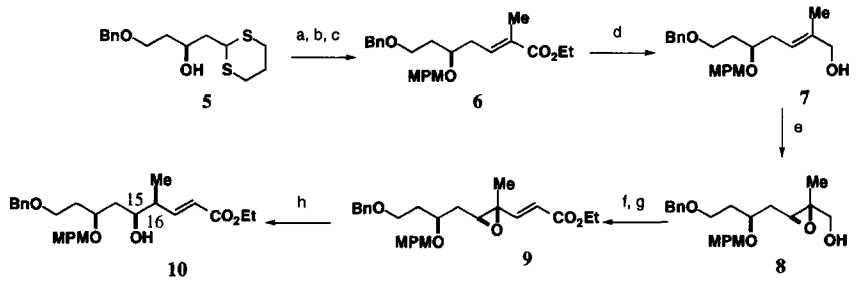
Swinholide A (**1**), isolated from the marine sponge *Theonella swinhoei*,[1] is a C_2-symmetrical 44-membered dimeric lactone which consists of two monomeric secoacid units **2**. The secoacid **2** named preswinholide A, which is regarded as the biosynthetic precursor of **1**, was also isolated from the same sponge.[2] These complex natural products show potent cytotoxicity against a variety of human tumour cell lines. The synthetically challenging structures and potent biological activities of **1** and **2** have attracted considerable attention from synthetic organic chemists.[3-6] The Paterson group has recently accomplished the first total synthesis of **2**[3e] and **1**,[7] and quite recently the Nicolaou group has reported the total synthesis of **1**.[8] We have also studied the total synthesis of the swinholides and have already reported the stereoselective synthesis of the C11-C32 segment of preswinholide A (**2**).[6] In this paper, we report an alternative method for the highly stereoselective and efficient synthesis of the C11-C23 segment **3**, and in the following paper the total synthesis of preswinholide A (**2**) will be described.

Scheme 1



Our retrosynthetic analysis divided preswinholide A (**2**) into three segments, the C1-C8, C9-C23, and C24-C32 segments, as shown in Scheme 1. The C11-C32 segment would be stereoselectively synthesized from the C11-C23 aldehyde **3** and the C24-C32 unit **4** using the Evans aldol coupling reaction.[9] Our strategy for the synthesis of **3** features the stereoselective and iterative construction of 1,3-polyol chains using a series of sequential reactions which involves the Sharpless asymmetric epoxidation[10] (AE) of allylic alcohol and Pd-catalyzed hydrogenolysis of alkenyl oxirane with HCOOH as the key reactions.[11]

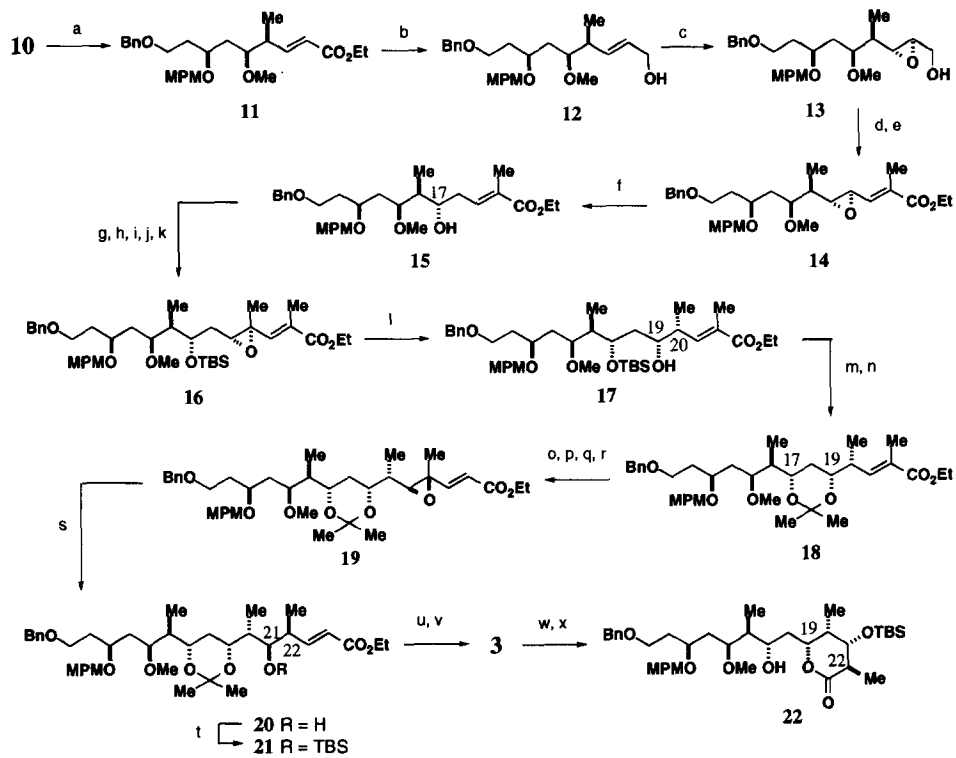
The optically active α,β-unsaturated ester **6** was prepared from thioacetal **5**[12] by protection of the hydroxyl group as the MPM ether and deprotection of the thioacetal with MeI, and the Wittig reaction in 99% yield. After DIBAH reduction of **6**, the Sharpless AE of the resulting alcohol **7** with *t*-BuOOH in the presence of (+)-DET and $Ti(O\textit{i}\text{-}Pr)_4$ stereoselectively produced the β-epoxy alcohol **8**.[13] The Swern oxidation[14] of **8** followed by the Horner-Emmons reaction with $(EtO)_2P(O)CH_2CO_2Et$ gave the alkenyloxirane **9** in 84% yield from **7**. Reaction of **9** with HCOOH-Et_3N using $Pd_2(dba)_3CHCl_3$ and *n*-Bu_3P as catalysts regio- and stereoselectively gave 15,16-*syn*-alcohol **10** in 96% yield, which has a component similar to that of the starting ester **6**. Thus, repeating a series of these sequential reactions (DIBAH reduction, Sharpless AE, Swern oxidation, Wittig reaction, and Pd-catalyzed hydrogenolysis) would convert the ester **10** into the aldehyde **3**, corresponding to the C11-C23 segment, as described hereafter.



5 **6** **7** **10** **9** **8**

Reagents and conditions: (a) MPMCl, NaH, DMF-THF, rt (97%); (b) MeI, $NaHCO_3$, acetone-H_2O, 0 °C ~ rt; (c) Ph_3P=C(Me)CO_2Et, $PhCH_3$, 110 °C (99% 2steps); (d) DIBAH, $PhCH_3$, -78 °C (88%); (e) *t*-BuOOH, L-(+)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, 4A-MS, CH_2Cl_2, -23 °C; (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C ~ rt; (g) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C ~ rt (84% 3 steps); (h) $Pd_2(dba)_3CHCl_3$, *n*-Bu_3P, HCO_2H, Et_3N, dioxane, rt (96%).

Methylation of the hydroxyl group in **10** with MeI-Ag_2O[15] followed by DIBAH reduction of the ester **11** afforded the allylic alcohol **12** in 83% yield. The alcohol **12** was effectively converted into the alkenyloxirane **14** in 75% yield via the α-epoxy alcohol **13** by the Sharpless AE,[13] Swern oxidation, and Wittig reaction. The oxirane **14** was then subjected to Pd-catalyzed hydrogenolysis with HCOOH to give the 17α-hydroxy ester **15** stereoselectively in 99% yield. After protecting the hydroxyl group as the TBS ether, **15** was converted into the 19,20-*syn*-alcohol **17** in 33% overall yield via the α-epoxy ester **16**[13] following a series of sequential reactions as mentioned above. After deprotection of the TBS ether and protection as the acetonide,[16] the ester **17** was also converted into 21,22-*syn*-alcohol **20** in 54% overall yield via the β-epoxy ester **19**[13] in 5 steps. Pd-catalyzed hydrogenolysis of **16** and **19** with HCOOH regio- and stereoselectively took place to give 19,20-*syn*-**17** and 21,22-*syn*-**20**, respectively. Protection of the alcohol **20** with TBSOTf gave the fully protected ester **21** in 82% yield. Finally, oxidative cleavage of the dobule bond in **21** was completed by successive treatment with OsO_4 and $Pb(OAc)_4$ to give the desired aldehyde **3**, corresponding to the C11-C23 segment, in 60% yield. The stereochemistry at C19 to C22 of **3** was confirmed by the NMR analysis of the δ-lactone **22**,[18] which was prepared from **3** by the selective deprotection of the acetonide with aq AcOH followed by oxidation under Fetizon's conditions.



Reagents and conditions: (a) MeI, Ag_2O, CH_3CN, 85 °C (100%); (b) DIBAH, $PhCH_3$, -78 °C (83%); (c) *t*-BuOOH, D-(-)-DET, $Ti(O\text{-}iPr)_4$, 4A-MS, CH_2Cl_2, -23 °C (87%); (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C ~ rt; (e) $Ph_3P{=}C(Me)CO_2Et$, $PhCH_3$, 120 °C (86% 2 steps); (f) $Pd_2(dba)_3CHCl_3$, *n*-Bu_3P, HCO_2H, Et_3N, dioxane, rt (99%) (g) TBSCl, imidazole, DMF, rt (95%); (h) DIBAH, $PhCH_3$, -78 °C (80%); (i) *t*-BuOOH, D-(-)-DET, $Ti(O\text{-}iPr)_4$, 4A-MS, CH_2Cl_2, -23 °C (78%); (j) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C ~ rt; (k) $Ph_3P^+CH(Me)CO_2EtBr^-$, *n*-BuLi, THF, 0 °C (74% 2 steps); (l) $Pd_2(dba)_3CHCl_3$, *n*-Bu_3P, HCO_2H, Et_3N, dioxane, rt (72%); (m) AcOH-H_2O, rt (75%); (n) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (88%); (o) DIBAH, $PhCH_3$, -78 °C (93%); (p) *t*-BuOOH, L-(+)-DET, $Ti(O\text{-}iPr)_4$, 4A-MS, CH_2Cl_2, -23 °C (76%); (q) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C ~ rt ; (r) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C ~ rt (99% 2 steps); (s) $Pd_2(dba)_3CHCl_3$, *n*-Bu_3P, HCO_2H, Et_3N, dioxane, rt (78%); (t) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (82%); (u) OsO_4, NMO, acetone-H_2O-*t*-BuOH, rt (71%); (v) $Pb(OAc)_4$, $PhCH_3$, rt (85%); (w) AcOH-H_2O, rt; (x) Ag_2CO_3-celite, $PhCH_3$, 130 °C (62% 2 steps).

In conclusion, we have accomplished the stereoselective synthesis of the aldehyde **3**, corresponding to the C11-C23 segment, based on the stereoselective and iterative construction of 1,3-polyol chains using a series of sequential rections, in which Pd-catalyzed stereoselective hydrogenolysis of optically active alkenyoxiranes was used as the key reaction. The characteristic Pd-catalyzed hydrogenolysis proceeds under mild conditions and is particularly chemoselective for the alkenyloxirane group. Thus, the iterative construction of 1,3-polyol chains would be a general and highly efficient method for the synthesis of a variety of natural products having polypropionate chains.

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