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Total Synthesis of Preswinholide A. 2. Completion of the Synthesis

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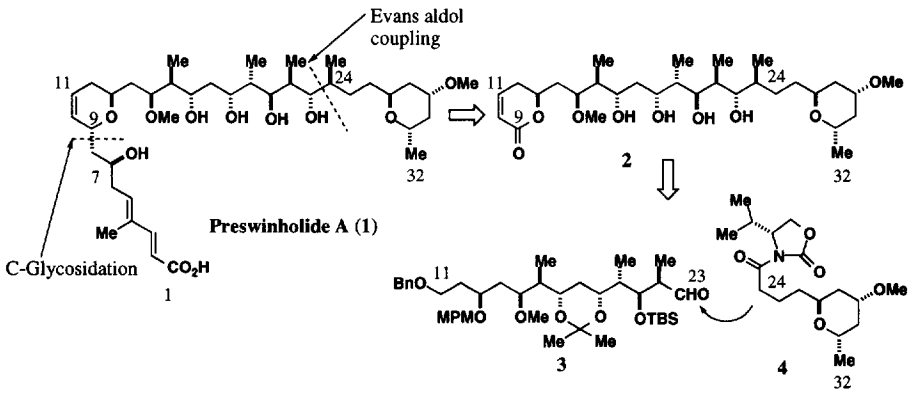
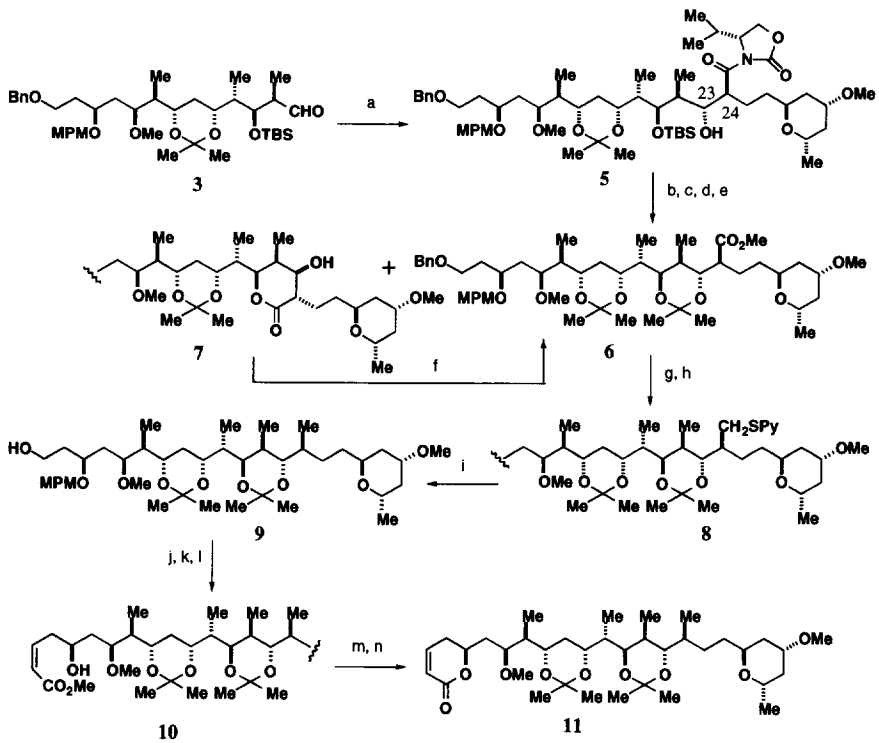
Abstract: Total synthesis of preswinholide A was stereoselectively accomplished through the aldol coupling reaction of the C11-C23 and C24-C32 segments and stereoselective introduction of the 9α side chain and 7β-hydroxyl group. Copyright © 1996 Elsevier Science Ltd

In the preceding paper,[1] the stereoselective synthesis of the aldehyde **3**, corresponding to the C11-C23 segment, has been described. We now report the stereoselective total synthesis of preswinholide A (**1**)[2] through the aldol reaction of **3** and the imide **4** and introduction of the C1-C8 side chain onto lactone **2**.



The Evans aldol coupling reaction[3] of the aldehyde **3** and the imide **4**[4] was carried out in the presence of $(TMS)_2NLi$ at -50 °C to give 23,24-*syn*-alcohol **5** stereoselectively in 70% yield along with the recovered starting aldehyde **3** (10%).[5] Removal of the chiral auxiliary of **5** with LiOH and H_2O_2,[6,7] esterification of the resulting carboxylic acid with $TMSCHN_2$,[8] deprotection of the TBS ether with TBAF, and protection of the diol with $Me_2C(OMe)_2$ gave the ester **6** (43%) and the lactone **7** (19%). Conversion of the lactone **7** into **6** was easily accomplished by treatment with $Me_2C(OMe)_2$ and CSA in the presence of MeOH in CH_2Cl_2 quantitatively.[9] Reduction of the ester **6** with $LiAlH_4$ provided alcohol (90%) which was treated with $(PyS)_2$ and n-Bu_3P in pyridine to give pyridylsulfide **8** in 95% yield.[4,10] Treatment of **8** with Raney nickel[4] effected simultaneous hydrogenolysis of the pyridylthio and terminal benzyl groups to give the alcohol **9** in 93% yield.

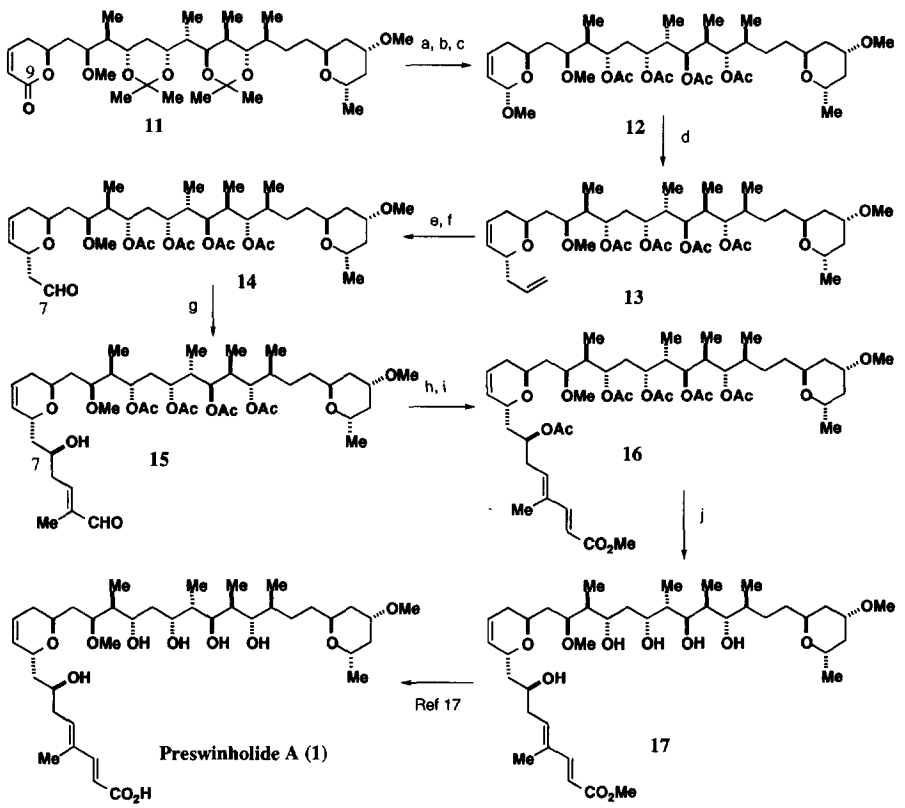
The alcohol **9** was converted into the (*Z*)-α,β-unsaturated ester **10** in 69% overall yield by the Swern oxidation[11] of the primary alcohol, Wittig reaction of the aldehyde according to Still's procedure,[12] and cleavage of the MPM protecting group with DDQ. After hydrolysis of **10** with LiOH, the resulting carboxylic acid was heated at 140 °C in toluene to give the lactone **11** in 95% yield.



Reagents and conditions: (a) **4**, $(TMS)_2NLi$, THF, -50 °C (70% for **5** and 10% of recovered **3**); (b) LiOH, H_2O_2, THF-H_2O, 0 °C; (c) $TMSCHN_2$, PhH-MeOH, rt (65% 2steps); (d) TBAF, THF, rt; (e) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (67% of **6** and 29% of **7**); (f) $Me_2C(OMe)_2$, CSA, MeOH, CH_2Cl_2, rt (100%); (g) $LiAlH_4$, Et_2O, 0 °C ~ rt (90%); (h) $(PyS)_2$, *n*-Bu_3P, pyridine, rt (95%); (i) Raney-Ni, H_2, EtOH, rt (93%); (j) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C ~ rt; (k) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, $(TMS)_2NK$, 18-crown-6, THF, -78 °C (79% 2steps); (l) DDQ, CH_2Cl_2-H_2O, rt (88%); (m) LiOH, THF-H_2O, 0 °C; (n) $PhCH_3$, 140 °C (95% 2steps).

Stereoselective introduction of the 9α-side chain and the 7β-hydroxyl group was performed by the following procedure developed in our previous studies[13] and by Paterson and his coworkers,[14] respectively. After reduction of the unsaturated lactone **11** with DIBAH, CSA treatment in MeOH underwent simultaneous acetalization and deprotection of acetonide to produce the tetraol, which was treated with Ac_2O in pyridine to give the tetraacetate **12**. Reaction of **12** with allyltrimethylsilane and TMSOTf at 0 °C in MeCN stereoselectively gave **13** in 95% overall yield from **11**.[13] Oxidative cleavage of the terminal olefin in **13** was carried out by successive treatment with OsO_4-NMO and $Pb(OAc)_4$ to afford the aldehyde **14** in 85% yield. According to Paterson's procedure,[14] the Mukaiyama aldol reaction of **14** and the silyldienol ether of tiglic aldehyde[15] in the presence of BF_3-Et_2O stereoselectively provided the 7β-alcohol **15**. The Horner-Emmons olefination of the aldehyde **15** and subsequent acetylation gave the pentaacetate of preswinholide A methyl ester **16** in 68% yield from **14**. Hydrolysis of the pentaacetate **16** was accomplished with NaOMe in MeOH to give

preswinholide A methyl ester **17** quantitatively. In this reaction, temperature of 55 °C was required to cleave all five acetates and it was interestingly found that only the acetate at the C7 position was hydrolyzed with NaOMe or K_2CO_3 in MeOH at room temperature. The ^1H NMR spectra and $[\alpha]_D$ of the synthetic **16** and **17** were identical with those of the authentic samples, **16** and **17**.[16] Conversion of **17** into preswinholide A (**2**) was already performed with NaOH in MeOH-H_2O.[17]



Reagents and conditions: (a) DIBAH, $PhCH_3$, -78 °C (100%); (b) CSA, MeOH, rt; (c) Ac_2O, pyridine, DMAP, rt; (d) allylTMS, TMSOTf, CH_3CN, 0 °C (95% 3 steps); (e) OsO_4, NMO, acetone-H_2O, rt; (f) $Pb(OAc)_4$, $PhCH_3$, rt (85% 2steps); (g) CH_2=C(Me)CH=CHOTMS, BF_3Et_2O, CH_2Cl_2-Et_2O (10:1), -78 °C; (h) $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, 0 °C ~ rt; (i) Ac_2O, pyridine, rt (68% 3 steps); (j) NaOMe, MeOH, rt ~ 55 °C (78%).

In conclusion, we have accomplished the stereoselective total synthesis of preswinholide A (**1**). The total synthesis features the steroselective and iterative construction of the 1,3-polyol chains corresponding to the C11-C23 segment, the stereoselective construction of the C11-C32 segment by the Evans aldol coupling reaction, and stereoselective introduction of the side chain by C-glycosidation at C9 and the aldol reaction of the vinylogous silyldienol ether at C7. The synthetic route we have developed is flexible enough to enable synthesis of the other members of the swinholides.

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