

PII: S0040-4039(96)01504-3

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 7 β -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 reaction³ of the aldehyde 3 and the imide 4⁴ 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 H₂O₂,^{6,7} esterification of the resulting carboxylic acid with TMSCHN₂,⁸ deprotection of the TBS ether with TBAF, and protection of the diol with Me₂C(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 Me₂C(OMe)₂ and CSA in the presence of MeOH in CH₂Cl₂ quantitatively.⁹ Reduction of the ester 6 with LiAlH₄ provided alcohol (90%) which was treated with (PyS)₂ and *n*-Bu₃P in pyridine to give pyridylsulfide 8 in 95% yield.^{4,10} Treatment of 8 with Raney nickel⁴ 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 oxidation¹¹ 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, H₂O₂, THF-H₂O, 0 °C; (c) TMSCHN₂, PhH-MeOH, rt (65% 2steps); (d) TBAF, THF, rt; (e) Me₂C(OMe)₂, CSA, CH₂Cl₂, rt (67% of 6 and 29% of 7); (f) Me₂C(OMe)₂, CSA, MeOH, CH₂Cl₂, rt (100%); (g) LiAlH₄, Et₂O, 0 °C ~ rt (90%); (h) (PyS)₂, *n*-Bu₃P, pyridine, rt (95%); (i) Raney-Ni, H₂, EtOH, rt (93%); (j) DMSO, (COCI)₂, Et₃N, CH₂Cl₂, -78 °C ~ rt; (k) (CF₃CH₂O)₂P(O)CH₂CO₂Me, (TMS)₂NK, 18-crown-6, THF, -78 °C (79% 2steps); (i) DDQ, CH₂Cl₂-H₂O, rt (88%); (m) LiOH, THF-H₂O, 0 °C; (n) PhCH₃, 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 studies¹³ 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 Ac₂O 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 OsO₄-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 aldehyde¹⁵ in the presence of BF₃-Et₂O stereoselectively provided the 7 β -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-H₂O.¹⁷



Reagents and conditions: (a) DIBAH, PhCH₃, -78 °C (100%); (b) CSA, MeOH, rt; (c) Ac₂O, pyridine, DMAP, rt; (d) allyITMS, TMSOTf, CH₃CN, 0 °C (95% 3 steps); (e) OsO₄, NMO, acetone-H₂O, rt; (f) Pb(OAc)₄, PhCH₃, rt (85% 2 steps); (g) CH₂=C(Me)CH=CHOTMS, BF₃Et₂O, CH₂Cl₂-Et₂O (10:1), -78 °C; (h) (MeO)₂P(O)CH₂CO₂Me, *n*-BuLi, 0 °C ~ rt; (i) Ac₂O, 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.

Acknowledgements: This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Area (Asymmetric Synthesis of Chiral Molecules) from the Ministry of Education, Science, and Culture, Japan.

We thank Prof. I. Kitagawa (Kinki Univ.) and Prof. M. Kobayashi (Osaka Univ.) for kindly providing us with an authentic sample of swinholide A and ¹H NMR spectra of 16 and 17.

References and Notes

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(Received in Japan 5 July 1996; revised 26 July 1996; accepted 29 July 1996)