Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8225-8228, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01750-6

Synthetic Study of Marine Macrolide Swinholide A. Stereocontrolled Synthesis of the C11 - C23 Segment

Tadashi Nakata,* Toshiya Komatsu, Kazuo Nagasawa, Haruo Yamada,† and Takashi Takahashi†

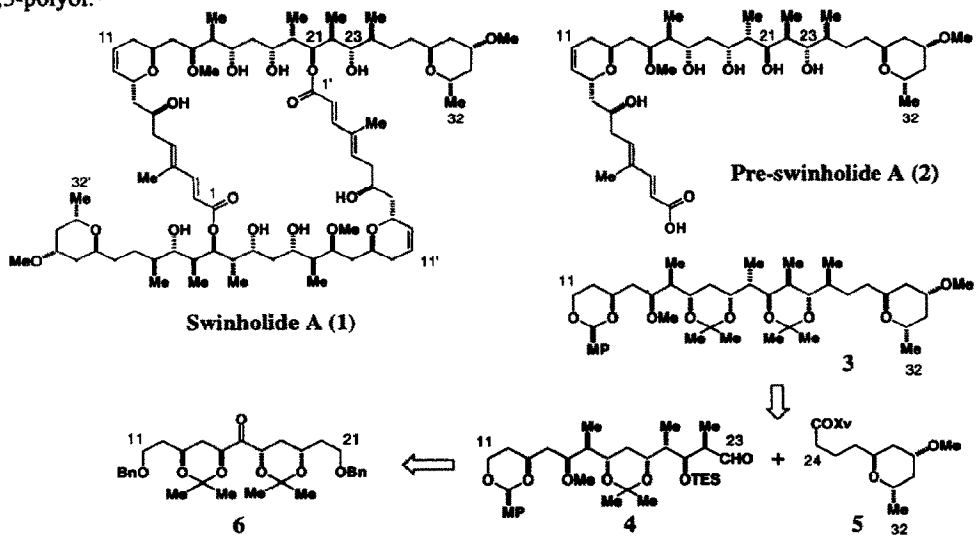
The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama 351-01, Japan

† Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Abstract: The C11-C23 segment **4** of swinholide A (**1**) was synthesized stereoselectively starting from (*S*)-malic acid *via* double nitroaldol reaction under high pressure and differentiation of the left and right parts of the symmetric compound **10** as the key steps.

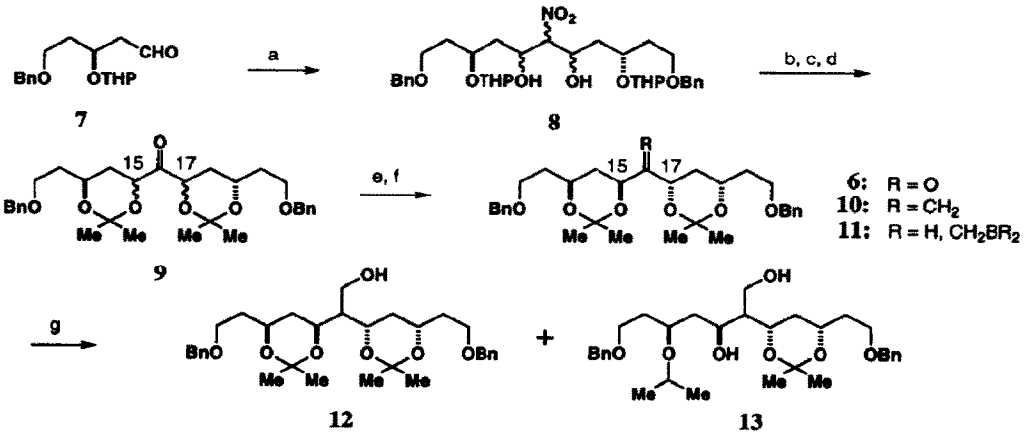
Swinholide A (**1**),[1] isolated from the marine sponge *Theonella swinhoei*, exhibits potent cytotoxic activity and the unique structure was finally established by Kitagawa *et al.*[2] as a 44-membered dimeric macrolide. Recently, pre-swinholide A (**2**), a monomeric seco acid of **1**, was also isolated from *Theonella swinhoei*[3] and the first total synthesis of **2** has been reported by Paterson *et al.*[4] We have also engaged in the synthesis of these compounds[5] and now report the stereocontrolled synthesis of the C11-C23 segment **4**.

Retrosynthetic analysis of **1** (and **2**) reveals that the polyol part **3** corresponding to the C11-C32 segment could be synthesized stereoselectively *via* aldol reaction of segments **4** and **5**.[6] Segment **4** would be synthesized from the C_2 symmetric ketone **6** prepared based on our method for the convergent synthesis of 1,3-polyol.[7]



The optically active aldehyde **7**[7] prepared from (*S*)-malic acid was used as a starting material for the synthesis of **4**. Addition of nitromethane to 2 equiv of aldehyde **7** in Et_3N under high pressure (5.5 kbar, 5

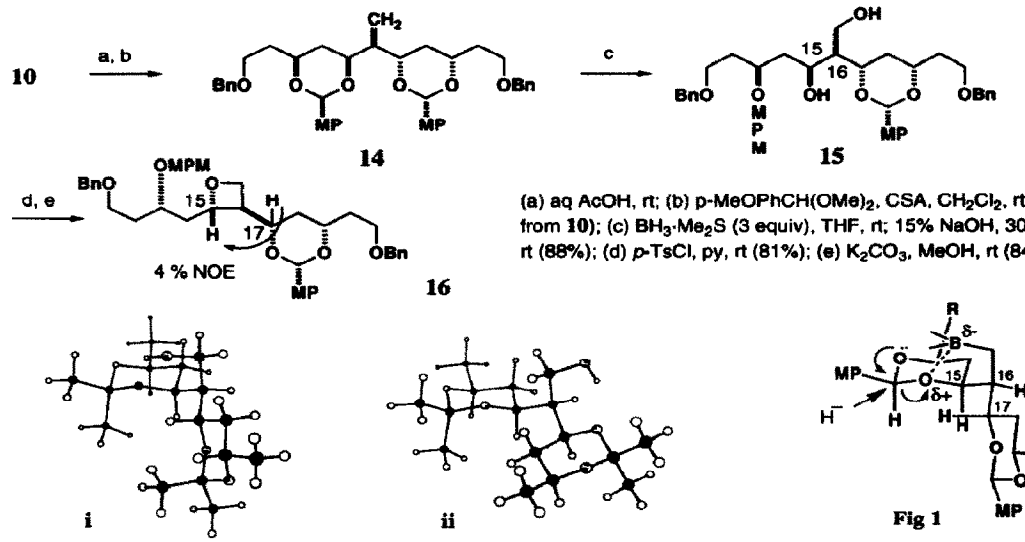
h) caused double nitroaldol reaction effectively producing a mixture of diols **8** in 90% yield.[8] Deprotection of the THP group in **8**, and protection of the resulting tetrol as isopropylidene acetal followed by $KMnO_4$ oxidation of the nitro group gave a mixture of three ketones **9** due to the isomers at the C15 and C17 positions. On treatment of the mixture **9** with K_2CO_3 in MeOH, epimerization took place producing the C_2 symmmetric ketone **6** (^{1}H NMR: δ 4.69 (dd, J=3.0, 12.0 Hz; C15-and C17-H)), exclusively.[7]



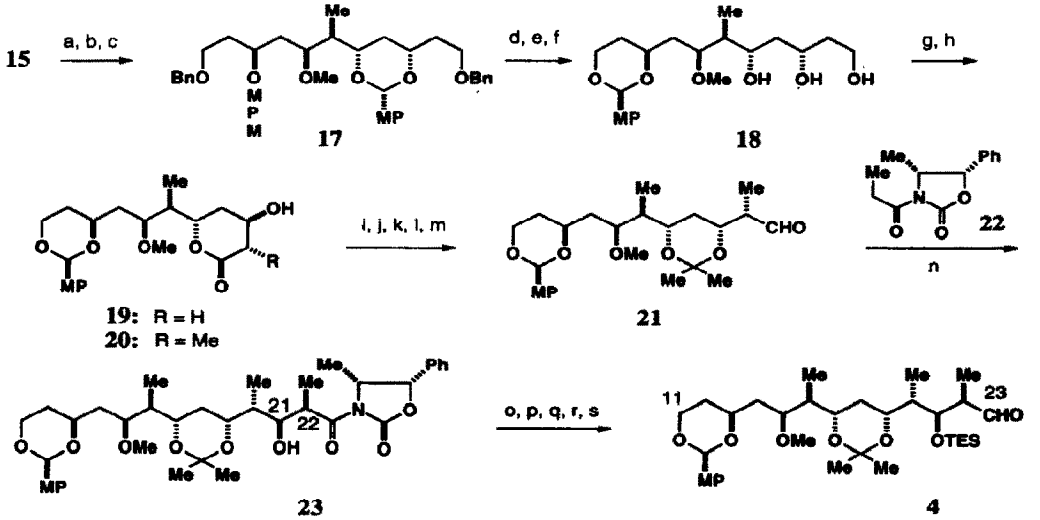
(a) $MeNO_2$ (1 equiv), aldehyde **7** (2 equiv), Et_3N, at 5.5 kbar, rt (90%); (b) aq AcOH, rt; (c) $Me_2C(OMe)_2$, CSA, acetone, rt; (d) *t*-BuONa, $KMnO_4$, $MgSO_4$, H_2O, PhH, rt; (e) K_2CO_3, MeOH, rt (54% from **8**); (f) $Ph_3P^+MeI^-$, *n*-BuLi, THF, rt (98%); (g) BH_3-Me_2S, THF, rt; 30%H_2O_2, 15% NaOH, rt.

Next, we examined the introduction of methyl group to the C16 position. After introduction of exomethylene group by Wittig reaction, the resulting **10** was subjected to hydroboration with BH_3·Me_2S (1 equiv) giving the alcohol **12** (42%; 84% based on the consumed **10**) and the partially reduced product **13** (8%). On treatment of **10** with an excess of BH_3·Me_2S (5 equiv), this single isopropyl ether **13** was obtained as the major product in 48 % yield along with **12** (24%).[9] Formation of **13** shows that hydroboraion of the exomethylene group and differential reductive cleavage of the isopropylidene acetal took place simultaneously in the present reaction, which was expected to enable the complete differentiation of the right and left parts of the C_2 symmetric **10**. Thus, after replacement of the isopropylidene acetals by *p*-methoxybenzylidene acetals, the same reaction was carried out for **14**. Treatment of **14** with an excess of BH_3·Me_2S gave, as expected, the fully differentiated diol **15** as a single diastereomer in 88% yield. The stereochemistry of **15** was confirmed based on the NOE measurement of oxetane **16** prepared from **15**; NOE was observed between C15-H and C17-H.

Conformational analyses of the probable intermediate **11** in the present reaction were undertaken. MM2 calculations[10] of **11** (CH_2BR_2 and CH_2CH_2OBn were replaced by CH_2OH and Me, respectively) revealed that the most stable conformation was i; the energy difference between i and an alternative conformation ii leading to the other diastereomer was *ca.* 1.5 kcal/mol. Therefore, the present reaction would proceed *via* the transition state shown in Fig 1, in which boron atom can coordinate with only one oxygen atom (C15-O) of two acetals producing exclusively the MPM ether **15** by the successive reductive cleavage of the acetal ring.



Diol **15** was then converted into **17** in three steps; 1) tosylation of the primary alcohol, 2) $LiAlH_4$ reduction, 3) O-methylation with MeI-KH. Deprotection of the benzyl groups in **17** with Raney Ni, acid hydrolysis of the benzylidene group, and treatment with DDQ produced triol **18**. After oxidation of **18** with Ag_2CO_3-Celite, the resulting β-hydroxy-δ-lactone **19** was methylated with LDA and MeI giving **20**



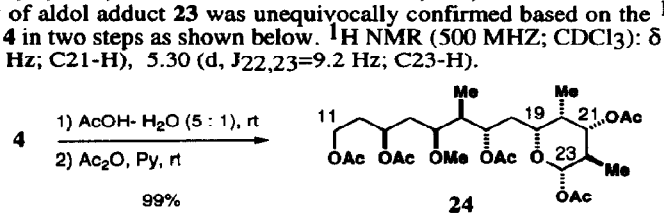
(a) *p*-TsCl, py, rt; (b) $LiAlH_4$, Et_2O, 0°C; (c) KH, MeI, THF, 0°C (76% from **15**); (d) H_2, Raney Ni, EtOH, rt; (e) aq AcOH, rt; (f) DDQ, CH_2Cl_2, rt (61% from **17**); (g) Ag_2CO_3-Celite, PhH, reflux (51%); (h) LDA, MeI, HMPA, THF, -78 ~ -40°C (71%; 83% based on the consumed **19**); (i) $LiBH_4$, THF, rt; (j) *t*-$BuPh_2SiCl$, imidazole, DMF, rt; (k) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, rt; (l) *n*-Bu_4NF, THF, rt; (m) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, -78 ~ 0°C (61% from **20**); (n) imide **22**, *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, -78°C ~ rt (88%; 95% based on the consumed **21**); (o) 30% H_2O_2, LiOH, aq THF, 0°C; (p) CH_2N_2, Et_2O, rt; (q) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0°C; (r) DIBAH, CH_2Cl_2, -78°C; (s) PDC, MS3A, CH_2Cl_2, rt (56% from **23**).

stereoselectively.[11] δ-Lactone **20** was converted into aldehyde **21** in five steps; 1) $LiBH_4$ reduction, 2) silylation of the primary alcohol, 3) acetonization of diol, 4) deprotection of silyl ether, 5) Swern oxidation. The aldehyde **21** was subjected to aldol reaction with optically active imide **22** producing 21,22-*syn*-aldol adduct **23** stereoselectively.[12,13] Finally, the aldol **23** was successfully converted into the desired aldehyde **4**,[14] corresponding to the C11-C23 segment, in five steps; 1) hydrolysis of imide with LiOOH, 2) esterification, 3) silylation of C21-hydroxyl group, 4) DIBAH reduction, 5) PDC oxidation.

Acknowledgments: This work was supported in part by Grants-in-Aid for Scientific Research on Priority Area (Asymmetric Synthesis of Chiral Molecules) from the Ministry of Education, Science, and Culture, Japan and by Special Coordination Funds of the Science and Technology Agency of the Japanese Government. We thank Messrs. H. Omori and A. Matsumoto for their technical assistance in high pressure reaction, Dr. K. Iida for large scale preparation of **6**, and Ms. K. Harata for mass spectral measurements. We also thank Prof. T. Oishi (Meiji College of Pharmacy) for useful discussions and encouragement during this work.

References and Notes

1. Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511.
2. (a) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 2963. (b) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710. (c) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Yamashita, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2409. (d) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I.; *J. Org. Chem.* **1991**, *56*, 3629.
3. (a) Tsukamoto, S.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc. Perkin Trans. 1* **1991**, 3185. (b) Todd, J. S.; Alvi, K. A.; Crews, P. *Tetrahedron Lett.* **1992**, *33*, 441.
4. (a) Paterson, I.; Smith, J. D.; Ward, R. A.; Cumming, J. G. *J. Am. Chem. Soc.* **1994**, *116*, 2615. (b) Paterson, I.; Cumming, J. G.; Smith, J. D. *Tetrahedron Lett.* **1994**, *35*, 3405. After the submission of this manuscript, synthetic studies of swinholide A from Nicolaou group were reported. (c) Patron, A. P.; Richter, P. K.; Tomaszewski, M. J.; Miller. R. A.; Nicolaou, K. C. *J. Chem. Soc. Chem. Commun.* **1994**, 1147. (d) Richter, P. K. Tomaszewski, M. J.; Mller, R. A.; Patron, A. P.; Nicolaou, K. C. *J. Chem. Soc. Chem. Commun.* **1994**, 1151.
5. Nakata, T.; Komatsu, T.; Nagasawa, K.; Oishi, T. Presented at the 34th Symposium on the Chemistry of Natural Products, Tokyo, Oct. 1992; Symposium papers, p. 174.
6. We have recently completed the stereoselective synthesis of the C24-C32 segment **5** and convergent synthesis of the C11-C32 segment **3** from **4** and **5**, which will be reported elsewhere.
7. Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525.
8. This reaction at atmospheric pressure (rt, 18 hr) gave **8** in only 15 % yield. High pressure reaction was carried out by using the apparatus made by Instrumentation and Characterization Center of this institute (RIKEN). The RIKEN apparatus is capable of holding a 150 ml volume at 15 kbar or 50 ml volume at 20 kbar.
9. *Cf.*, Horita, K.; Inoue, T.; Tanaka, K.; Yonemitsu, O. *Tetrahedron Lett.* **1992**, *33*, 5537.
10. Molecular modeling studies were carried out with the MacroModel program using MM2* force field (MacroModel V4.0). In the case of **11** (CH_2BR_2 and CH_2CH_2OBn were replaced by Et and Me, respectively), the most stable conformation was also the similar one as **i**.
11. Fukui, M.; Okamoto, S.; Sano, T.; Nakata, T.; Oishi, T. *Chem. Pharm. Bull.* **1990**, *38*, 2890.
12. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
13. The stereochemistry of aldol adduct **23** was unequivocally confirmed based on the ^1H NMR analysis of **24** prepared from **4** in two steps as shown below. ^1H NMR (500 MHZ; $CDCl_3$): δ 4.71 (dd, $J_{20,21}$= 4.9 Hz, $J_{21,22}$=11.3 Hz; C21-H), 5.30 (d, $J_{22,23}$=9.2 Hz; C23-H).



14. Data for **4**: IR (neat): 1730, 1615, 1520 cm^{-1}, $[\alpha]_D$ -0.8° (c 1.75, $CHCl_3$), ^1H NMR (500 MHz; $CDCl_3$): δ 0.83, 0.90, 1.11 (each d, J=7.1 Hz; Me x 3), 3.35 (s; OMe), 3.80 (s; Ar-OMe), 4.27 (dd, J=4.1, 11.3 Hz; O-CH), 4.32 (dd, J=2.8, 7.1 Hz; O-CH), 5.48 (s; O-CH-O), 9.72 (s; CHO).

(*Received in Japan* 7 *June* 1994; *accepted* 17 *August* 1994)