



Pergamon

Tetrahedron Letters 39 (1998) 6007–6010

TETRAHEDRON
LETTERS

Synthetic Studies on Concanamycin A: Total Synthesis of Concanolide A (Concanamycin F)

Takaaki Jyojima, Naoki Miyamoto, Masataka Katohno,
Masaya Nakata, Shuichi Matsumura and Kazunobu Toshima*¹

Department of Applied Chemistry, Faculty of Science and Technology, Keio University,
3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Received 14 May 1998; revised 11 June 1998; accepted 12 June 1998

Abstract: Enantioselective first total synthesis of concanolide A (concanamycin F), which is one of a new class of macrolide antibiotics, concanamycins, has been achieved by a highly effective and convergent route.

© 1998 Elsevier Science Ltd. All rights reserved.

Keywords: concanolide A; concanamycin F; vacuolar H⁺-ATPase inhibitor; lactonization, Stille reaction; aldol reaction.

The concanamycins A-F [1], a new class of 18-membered macrolide antibiotics, are potent and specific inhibitors of vacuolar H⁺-ATPase attracting particular interest [2]. Concanamycin A (**1**), first isolated in 1981 by Kinashi *et al.* [1a,c], is a major component of concanamycins. On the other hand, concanolide A (**2**) is the common aglycon of both concanamycins A and C; it also identical with natural concanamycin F [1e,3]. In a previous paper [4], we described the effective synthesis of the enantiomerically pure C5–C13 and C20–C28 segments as promising synthetic intermediates toward the total synthesis of concanamycins. Herein we now disclose the enantioselective first total synthesis of concanolide A (concanamycin F) (**2**) which has comparable biological properties to those of **1** [1e,2]. This total synthesis involves a highly stereoselective aldol reaction between the 18-membered lactonic aldehyde **3** and the ethyl ketone **4** [4]. (Figure 1).

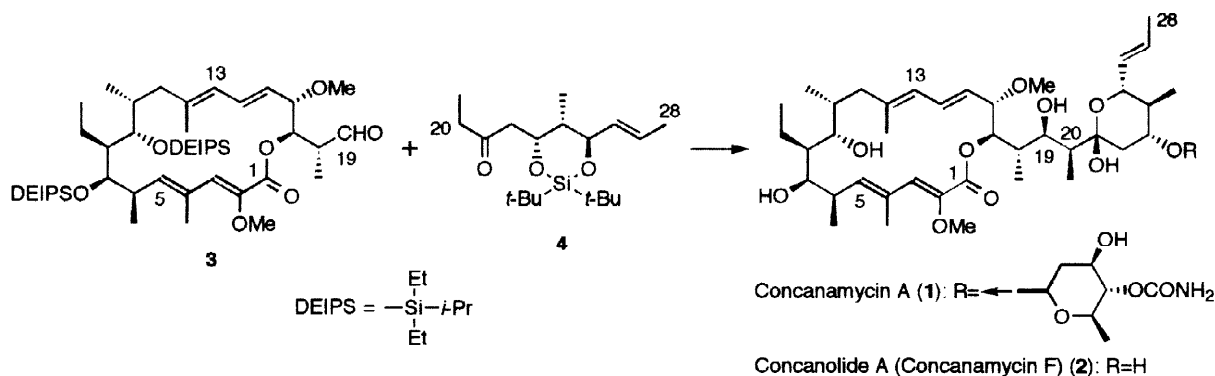
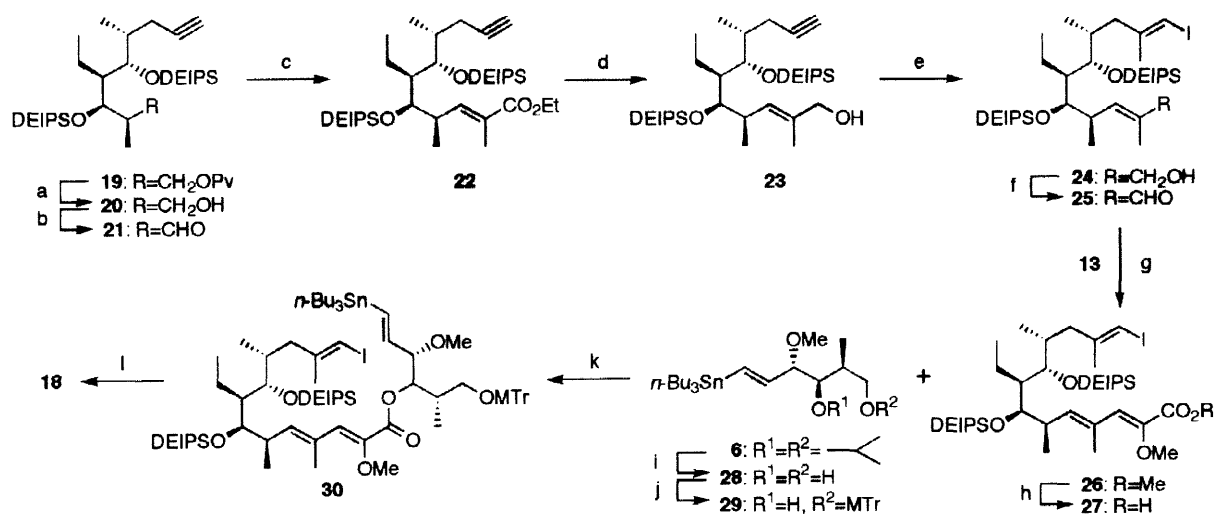
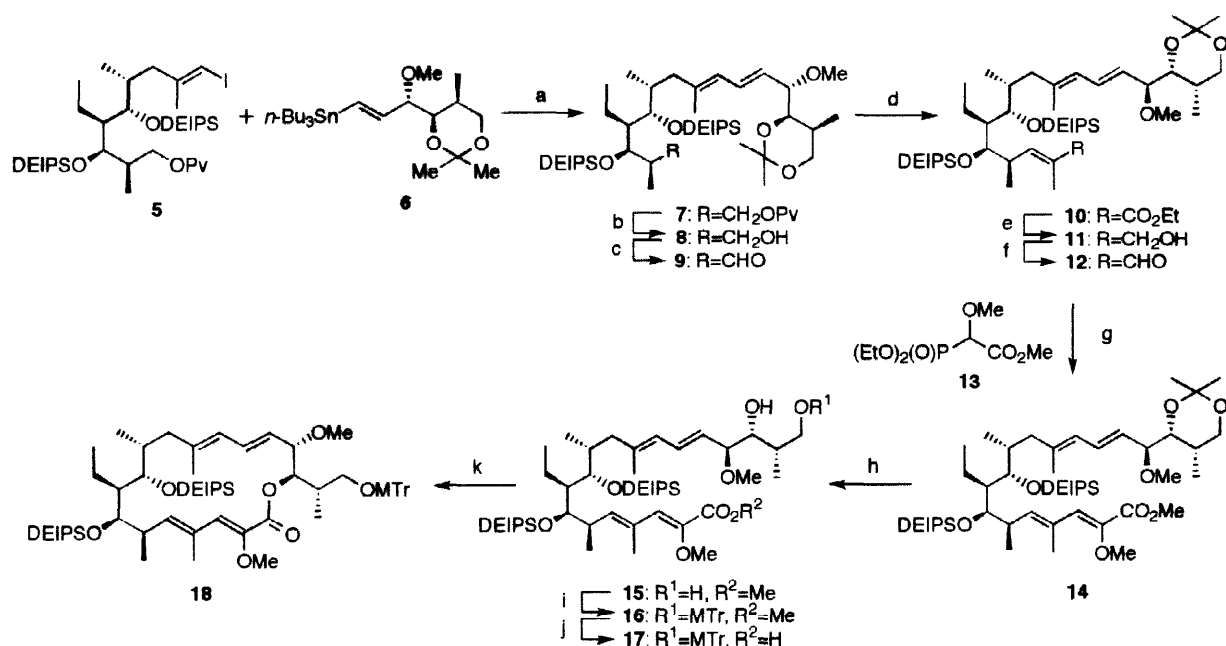


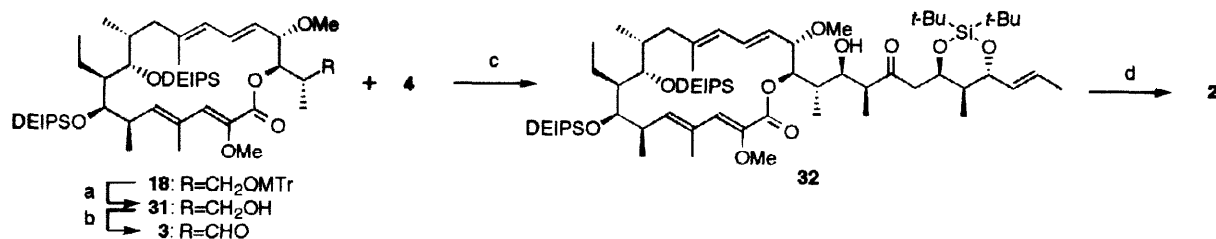
Figure 1

1. E-mail: toshima@applc.keio.ac.jp

The synthesis of the C1–C19 macrocyclic lactone via macrolactonization was first addressed (Scheme 1). The cross-coupling reaction between the vinyl iodide **5** [4] (1 equiv.) and the vinyl tributyltin **20** (1 equiv.), which was recently synthesized in our laboratory [5], by Stille method [6] using a catalytic amount of Pd₂(dba)₃, Ph₃As, LiCl in *N*-methylpyrrolidinone (NMP) [7] at 40 °C for 16 h proceeded effectively to afford the desired *E,E*-diene **7** in 72% yield as the only isolated product. Deprotection of the pivaloyl group in **7** using methyl lithium, followed by Swern oxidation of the resultant alcohol **8** gave the aldehyde **9**. The Wittig reaction of **9** with ethyl 2-(triphenylphosphoranylidene)propionate in toluene at 100 °C for 16 h proceeded smoothly to yield only the *trans* isomer **10** in 85% overall yield from **8**. Reduction of the ethyl ester in **10** using diisobutylaluminum hydride (DIBAL) in toluene at -78 °C afforded the allyl alcohol **11** in 90% yield. Oxidation of **11** employing MnO₂ provided the α,β -unsaturated aldehyde **12** which was subjected to Horner-Wadsworth-Emmons reaction with the phosphonic ester **13** [8] using potassium bis(trimethylsilyl)amide (KHMDs) in the presence of 18-crown-6 [9] in THF at -20 °C to give the desired *cis*-isomer **14** (*E/Z*=1:>99) in 99% overall yield. The isopropylidene group in **14** was removed under mild acidic conditions (pyridinium *p*-toluenesulfonate (PPTS), MeOH), and then the resultant diol **15** was selectively protected (MTrCl, Et₃N, 4-DMAP, CH₂Cl₂) with a monomethoxytrityl (MTr) group to afford the secondary alcohol **16**. Hydrolysis of the methyl ester of **16** under basic conditions (1*N* KOH, 1,4-dioxane) yielded the carboxylic acid **17** in 79% overall yield from **14**. The macrolactonization of the seco-acid **17** to construct the 18-membered lactone ring was best effected by Yamaguchi method [10] under high dilution conditions to give the macrocyclic lactone **18** in 82% yield. Another effective synthesis of the macrocyclic lactone **18** was achieved by the new route involving intramolecular Stille coupling [11] (Scheme 2). The fully protected acetylene **19** [4] was first converted into the allyl alcohol **23** in high overall yield (4 steps, 76% overall yield) by a series of reactions presented in the synthesis of **11** from **7**. At this stage, the acetylene **23** was effectively transformed to the vinyl iodide **24** in 84% yield via the zirconium-catalyzed carboalumination [12]. Oxidation of **24** using MnO₂ provided the α,β -unsaturated aldehyde **25** which was subjected to the previously mentioned Horner-Wadsworth-Emmons reaction with **13** [8] to give the desired *cis*-isomer **26** (*E/Z*=5:95) in 91% overall yield. Hydrolysis of **26** under basic conditions (1*N* KOH, 1,4-dioxane) yielded the carboxylic acid **27** in 95% yield. The esterification of the carboxylic acid **27** and the secondary alcohol **29**, which was prepared from **6** in two steps involving deisopropylidene and selective protection with MTr group, proceeded smoothly by Yamaguchi method [10] to give the ester **30** in 79% yield. The macrocyclization of **30** was effectively realized by intramolecular Stille coupling [6] using a catalytic amount of Pd₂(dba)₃, Ph₃As, *i*-Pr₂NEt in DMF-THF(1:1) [7] at 60 °C for 18 h to furnish the 18-membered lactone **18** in 72% yield as the only isolated product.

With the effective synthesis of the 18-membered lactone **18**, total synthesis of **2** was addressed (Scheme 3). Treatment of **18** with PPTS in MeOH gave the alcohol **31** which was subjected to Swern oxidation to furnish the aldehyde **3** in 89% overall yield. We next attempted the stereoselective connection of **3** and **4** [4] by an aldol reaction. The aldol condensation between **3** (1 equiv.) and **4** (2 equiv.) was best achieved using PhBCl₂ [5b,c,13-16] and *i*-Pr₂NEt in CH₂Cl₂ at -78 °C for 1.5 h to produce the desired aldol **32** in 84% yield with >95:5 diastereoselectivity as a major product. Finally, the desilylation of **32** in 2 steps using HF-Py and tetrabutylammonium fluoride (TBAF) gave **2** in 55% yield. Thus, the obtained **2** was identical to an authentic sample of natural concanolid A (concanamycin F) based on ¹H-NMR, [α]_D (synthetic: [α]_D²⁵ +10.3° (*c*=0.17, CHCl₃); natural: [α]_D²⁰ +11.0° (*c*=0.30, CHCl₃)) and TLC behaviors in several solvent systems [1e,3].





Scheme 3. Reagents and conditions: a) PPTS, MeOH, r. t., 5 h, 94%; b) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 20 min, 94%; c) PhBCl₂, *i*-Pr₂NEt, CH₂Cl₂, -78 °C, 1.5 h, 84%; d) 1. HF-Py, THF, 0° C, 15 min, 2. TBAF, THF, r. t., 2.5 h, 55%.

Acknowledgment. We are grateful to Prof. Dr. Keiji Hasumi and Prof. Dr. Akira Endo (Tokyo Noko University) for kindly providing us with the authentic samples of concanamycin A and concanamycin F (concanolide A). Financial support by The Naito Foundation is gratefully acknowledged.

References

- [1] a) H. Kinashi, K. Someno, K. Sakaguchi, T. Higashijima, T. Miyazawa, *Tetrahedron Lett.* **1981**, 22, 3857-3860 and 3861-3864; b) H. Kinashi, K. Sakaguchi, T. Higashijima, T. Miyazawa, *J. Antibiot.* **1982**, 35, 1618-1620; c) H. Kinashi, K. Someno, K. Sakaguchi, *J. Antibiot.* **1984**, 37, 1333-1343; d) J. W. Westley, C.-M. Liu, L. H. Sello, R. H. Evans, N. Troupe, J. F. Blount, A. M. Chiu, L. J. Todaro, P. A. Miller, *J. Antibiot.* **1984**, 37, 1738-1740; e) J.-T. Woo, C. Shinohara, K. Sakai, K. Hasumi, A. Endo, *J. Antibiot.* **1992**, 45, 1108-1116; f) T. Ishii, T. Hida, S. Iinuma, M. Muroi, Y. Nozaki, *J. Antibiot.* **1995**, 48, 12-20.
- [2] a) E. J. Bowman, A. Siebers, K. Altendorf, *Proc. Natl. Acad. Sci. U.S.A.* **1988**, 85, 7972-7976; b) S. Dröse, K. U. Bindseil, E. J. Bowman, A. Siebers, A. Zeeck, K. Altendorf, *Biochemistry* **1993**, 32, 3902-3906.
- [3] K. U. Bindseil, A. Zeeck, *J. Org. Chem.* **1993**, 58, 5487-5492.
- [4] T. Jyojima, M. Katohno, N. Miyamoto, M. Nakata, S. Matsumura, K. Toshima, *Tetrahedron Lett.* proceeding paper.
- [5] a) K. Toshima, T. Jyojima, H. Yamaguchi, H. Murase, T. Yoshida, S. Matsumura, M. Nakata, *Tetrahedron Lett.* **1996**, 37, 1069-1072; b) K. Toshima, H. Yamaguchi, T. Jyojima, Y. Noguchi, M. Nakata, S. Matsumura, *Tetrahedron Lett.* **1996**, 37, 1073-1076; c) K. Toshima, T. Jyojima, H. Yamaguchi, Y. Noguchi, T. Yoshida, H. Murase, M. Nakata, S. Matsumura, *J. Org. Chem.* **1997**, 62, 3271-3284.
- [6] J. K. Stille, B. L. Groh, *J. Am. Chem. Soc.* **1987**, 109, 813-817.
- [7] a) V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, 113, 9585-9595; b) V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.* **1994**, 59, 5905-5911.
- [8] W. Grell, H. Machleidt, *Liebigs Ann. Chem.* **1966**, 699, 53-67.
- [9] a) W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, 41, 4405-4408; b) I. Paterson, M. D. McLeod, *Tetrahedron Lett.* **1997**, 38, 4183-4186.
- [10] J. Inanaga, K. Hirata, H. Sacki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, 52, 1989-1993.
- [11] Macrolide construction by Stille coupling: a) J. K. Stille, M. Tanaka, *J. Am. Chem. Soc.* **1987**, 109, 3785-3786; b) E. J. Baldwin, R. M. Adlington, S. H. Ramcharitar, *Synlett* **1992**, 875-877; c) K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, P. Bertinato, *J. Am. Chem. Soc.* **1993**, 115, 4419-4420; d) G. Pattenden, S. M. Thom, *Synlett* **1993**, 215-216; e) C. Boden, G. Pattenden, *Synlett* **1994**, 181-182; f) K. C. Nicolaou, A. D. Piscopio, P. Bertinato, T. K. Chakraborty, N. Minowa, K. Koide, *Chem. Eur. J.* **1995**, 1, 318-333; g) A. B. Smith, III, S. M. Condon, J. A. McCauley, J. L. Leazer, Jr., J. W. Leahy, R. E. Maleczka, Jr., *J. Am. Chem. Soc.* **1995**, 117, 5407-5408; h) R. J. Boyce, G. Pattenden, *Tetrahedron Lett.* **1996**, 37, 3501-3504; i) A. B. Smith, III, S. M. Condon, J. A. McCauley, J. L. Leazer, Jr., J. W. Leahy, R. E. Maleczka, Jr., *J. Am. Chem. Soc.* **1997**, 119, 962-973; j) I. Paterson, J. Man, *Tetrahedron Lett.* **1997**, 38, 695-698.
- [12] a) C. L. Rand, D. E. Van Horn, M. W. Moore, E. Negishi, *J. Org. Chem.* **1981**, 46, 4093-4096; b) T. Yoshida, E. Negishi, *J. Am. Chem. Soc.* **1981**, 103, 4985-4987.
- [13] D. A. Evans, M. A. Calter, *Tetrahedron Lett.* **1993**, 34, 6871-6874.
- [14] K. Makino, N. Nakajima, S. Hashimoto, O. Yonemitsu, *Tetrahedron Lett.* **1996**, 37, 9077-9080.
- [15] D. A. Evans, D. M. Fitch, *J. Am. Chem. Soc.* **1997**, 62, 454-455.
- [16] H. Hamana, K. Sasakura, T. Sugawara, *Chem. Lett.* **1984**, 1729-1732.