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

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

Keywords: concanolide A; concananycin F; vacular 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).

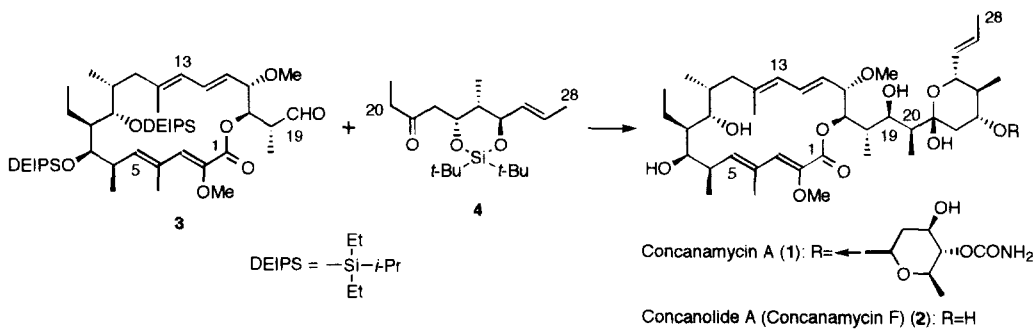

Figure 1

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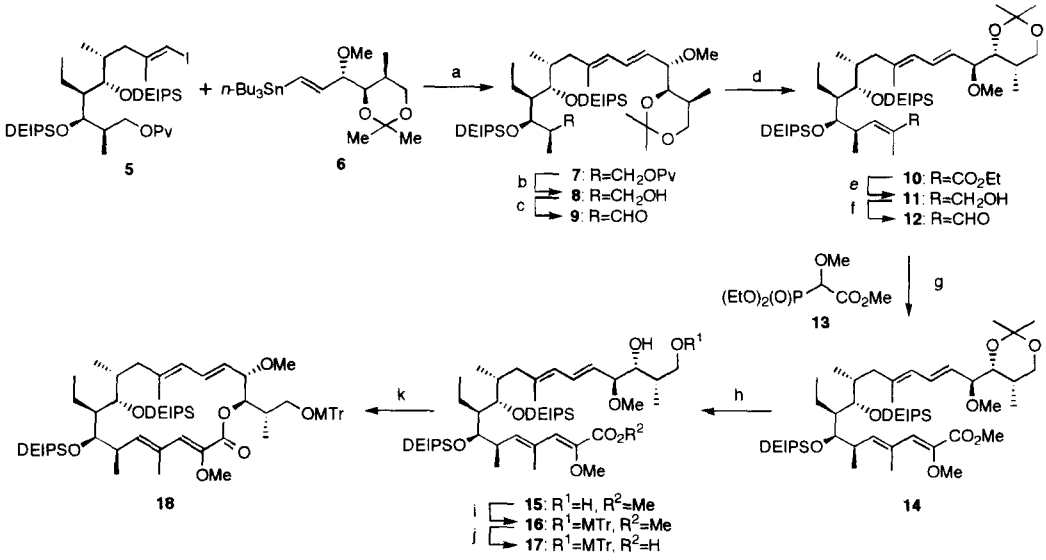
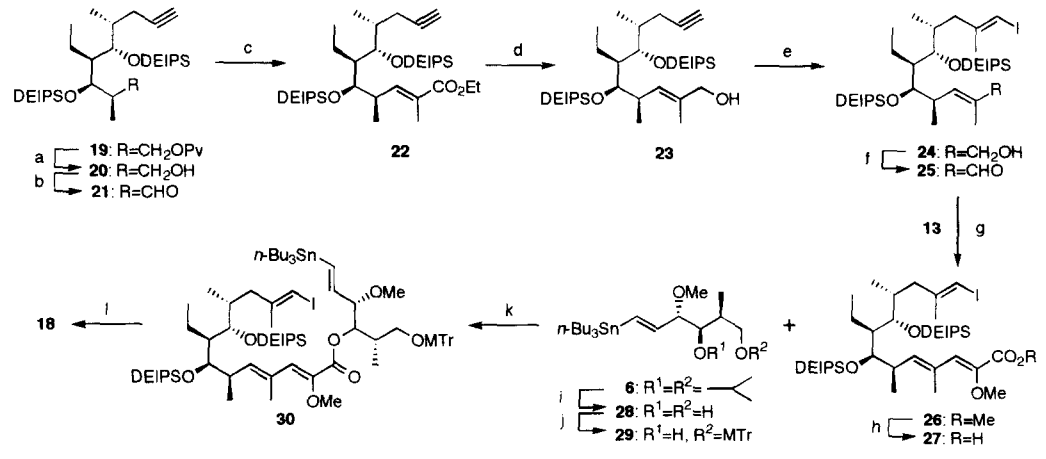
The synthesis of the C1~C19 macrocyclic lactone via macrolactonization was first addressed (Scheme 1). The cross-coupling reaction between the vinyl iodide **5** [4] (1 equiv.) and the vinyl tributyltin **20** (1 equiv.), which was recently synthesized in our laboratory [5], by Stille method [6] using a catalytic amount of $Pd_2(dba)_3$, Ph_3As, 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 MnO_2 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, Et_3N, 4-DMAP, CH_2Cl_2) 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 MnO_2 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 deisopropylidenation 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 $Pd_2(dba)_3$, Ph_3As, *i*-Pr_2NEt 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.

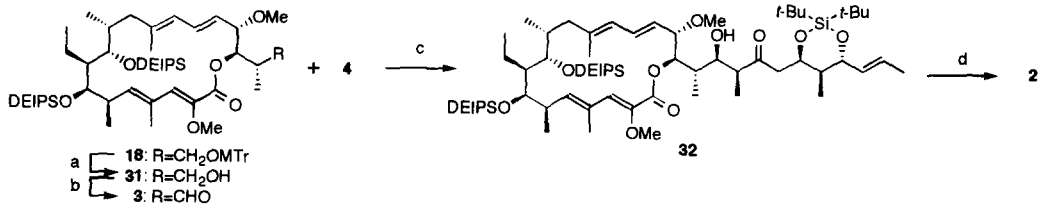
With the effective synthesis of the 18-membered lactone **18**, total synthesis of **2** was addressed (Scheme 3). Treatment of **18** with PPTS in MeOH gave the alcohol **31** which was subjected to Swern oxidation to furnish the aldehyde **3** in 89% overall yield. We next attempted the stereoselective 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 $PhBCl_2$ [5b,c,13-16] and *i*-Pr_2NEt in CH_2Cl_2 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 concanolide A (concanamycin F) based on ^{1}H-NMR, $[\alpha]_D$ (synthetic: $[\alpha]^{25}_D$ +10.3° (c=0.17, $CHCl_3$); natural: $[\alpha]^{20}_D$ +11.0° (c=0.30, $CHCl_3$)) and TLC behaviors in several solvent systems [1e,3].



Scheme 1. *Reagents and conditions*: a) $Pd_2(dba)_3$, Ph_3As, LiCl, NMP, 40 °C, 16 h, 72%; b) MeLi, Et_2O, r. t., 0.5 h, 96%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 20 min; d) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 100 °C, 16 h, 89% from **8**; e) DIBAL, PhMe, -78 °C, 0.5 h, 90%; f) MnO_2, CH_2Cl_2, r. t., 1.5 h; g) KHMDS, 18-crown-6, THF, -20 °C, 16 h, 99% from **11**; h) PPTS, MeOH, r. t., 1 h, 96%; i) MTrCl, Et_3N, 4-DMAP, CH_2Cl_2, r. t., 3 h; j)1*N* KOH, 1,4-dioxane, 80 °C, 3 h, 82% from **15**; k) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF (0.01 M for **17**) , 4-DMAP, PhMe (0.002 M for **17**), 110 °C, 14 h, 82%.



Scheme 2. *Reagents and conditions*: a) DIBAL, PhMe, -78 °C, 15 min, 90%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 20 min; c) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 100 °C, 16 h, 92% from **20**; d) DIBAL, PhMe, -78 °C, 15 min, 92%; e) Cp_2ZrCl_2, $AlMe_3$, I_2, $(CH_2Cl)_2$, r. t., 16h, 84%; f) MnO_2, CH_2Cl_2, r. t., 1.5 h, 95%; g) KHMDS, 18-crown-6, THF, 0 °C, 5 h, 96%; h) 1*N* KOH, 1,4-dioxane, 80 °C, 3 h, 95%; i) PPTS, MeOH, r. t., 2 h, 79%; j) MTrCl, Et_3N, 4-DMAP, CH_2Cl_2, r. t., 1 h, 96%; k) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 4-DMAP, PhMe, r. t., 16 h, 79%; l) $Pd_2(dba)_3$, Ph_3As, *i*-Pr_2NEt, DMF-THF, 60 °C, 18 h, 72%.



Scheme 3. *Reagents and conditions*: a) PPTS, MeOH, r. t., 5 h, 94%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 20 min, 94%; c) $PhBCl_2$, *i*-Pr_2NEt, CH_2Cl_2, -78 °C, 1.5 h, 84%; d) 1. HF-Py, THF, 0° C, 15 min, 2. TBAF, THF, r. t., 2.5 h, 55%.

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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. Saeki, T. Katsuki, M. Ymamaguchi, *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. Sugasawa, *Chem. Lett.* **1984**, 1729-1732.