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Synthetic Studies on Concanamycin A: Synthesis of the C5~C13 and C20~C28 Segments

Takaaki Jyojima, Masataka Katohno, Naoki Miyamoto, 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

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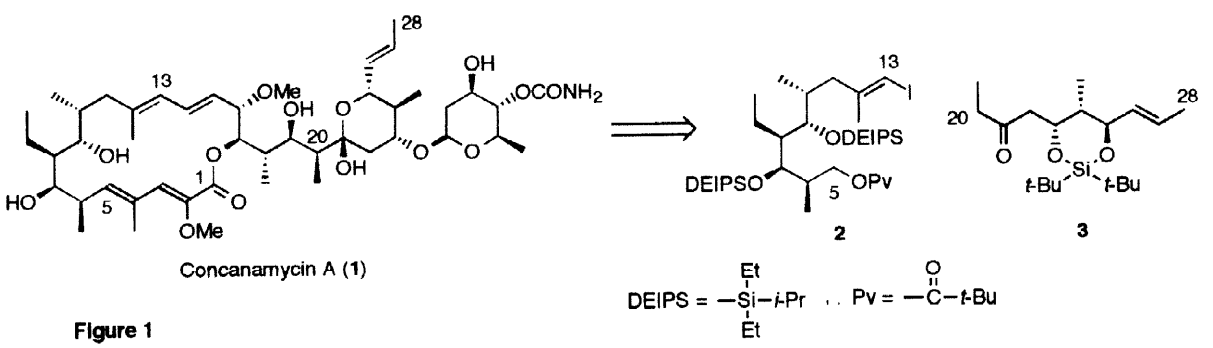
Abstract: The enantioselective synthesis of the C5~C13 (**2**) and C20~C28 (**3**) segments, which are promising synthetic intermediates toward the total synthesis of the 18-membered macrolide antibiotic, concanamycin A (**1**), were described.

Keywords: concanamycin A; macrolides; vacuolar H^+-ATPase inhibitor; segment synthesis.

Concanamycin A (**1**) [1], first isolated in 1981 by Kinashi *et al.* [1a,c], is a potent and specific inhibitor of vacuolar H^+-ATPase attracting particular interest [2]. The structure and absolute configuration of **1** has been established by chemical degradation [1a], NMR analysis [1a] and X-ray crystallographic analysis [1d] of its diacetate derivative. Concanamycin A (**1**) belongs to a family of structurally related polyketide macrolide antibiotics. Although the other macrolide antibiotics such as the bafilomycins [3,4], the hygrolidins [5,6] and recently discovered formamicin [7] are closely related to the concanamycins, the concanamycins possess most complex structures among them. The most unique and striking structural feature of this macrolide are an unusual 18-membered tetraenic lactone ring with an methyl enol ether and a β-hydroxy hemiacetal side chain incorporating 4'-carbamoyl-2'-deoxy-β-D-rhamnose moiety.



Concanamycin A (**1**)

Figure 1

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

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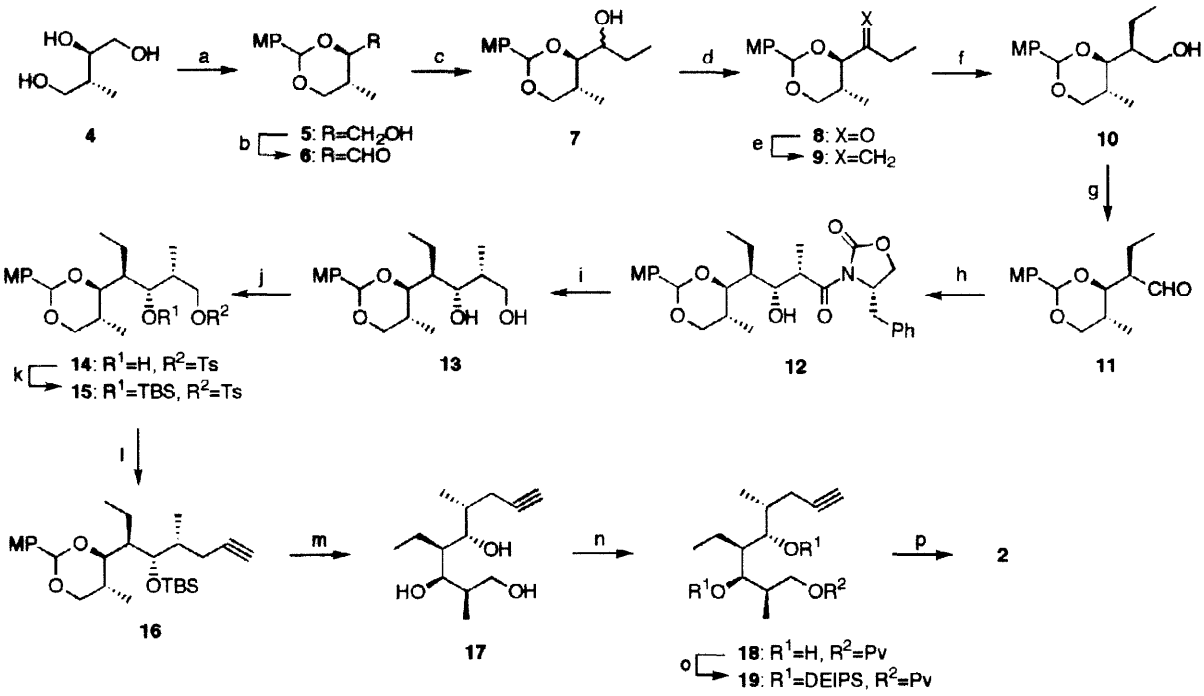
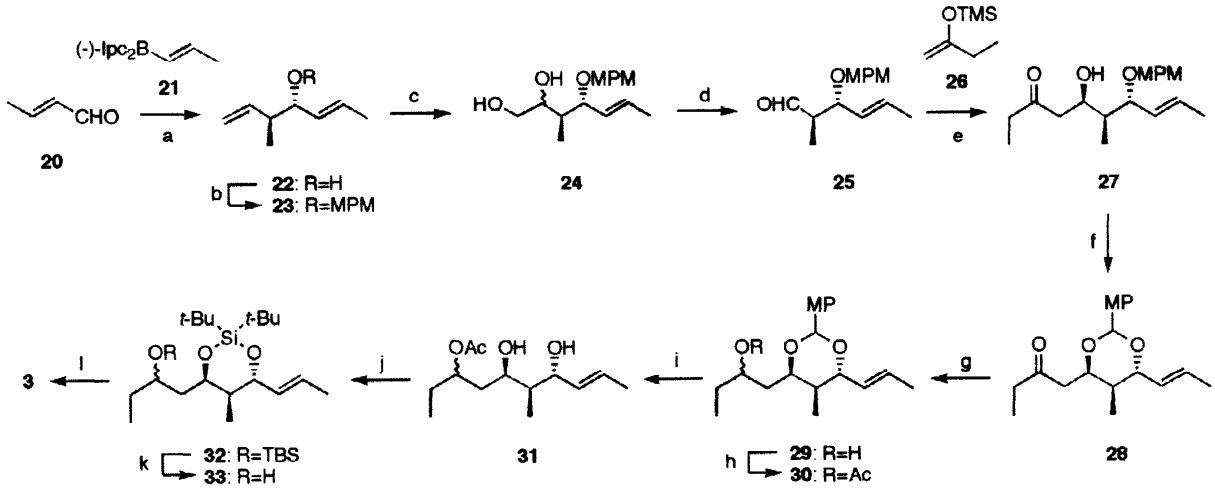
Previously, we reported the synthesis of the C20-C28 fragment of **1** starting from carbohydrate building blocks [8]. Very recently, elegant synthetic studies of the C19~C28 [9] and C1~C13 [10] segments of **1** have been announced by Paterson and co-workers. Herein we now disclose the effective synthesis of the C5~C13 segment (**2**) and the improved and asymmetric synthesis of the C20~C28 segment (**3**), both of which are promising synthetic intermediates [11] toward the total synthesis of the biologically important natural products, concanamycin A (**1**) and other concanamycins (Figure 1).

The synthesis of the suitably protected vinyl iodide **2** corresponding to the C5~C13 segment of **1** is summarized in Scheme 1. The 1,3-diol of the starting material **4** (erythro/threo=85:15), which was readily obtained from D-malic acid by Seebach's alkylation [12], was first regioselectively protected by *p*-methoxybenzylidene group to give the pure primary alcohol **5** in 64% yield. Swern oxidation of **5** followed by Grignard reaction using EtMgBr in Et_2O at 25 °C for 3 h afforded **7** in 87% overall yield. The secondary alcohol **7** was subjected to Swern oxidation and then Wittig reaction employing $Ph_3P{=}CH_2$ in benzene to furnish **9** in 88% overall yield. Hydroboration of **9** utilizing dicyclohexylborane in THF at room temperature for 3 h was found to proceed with complete stereoselectivity to give only the desired alcohol **10** in 89% yield after the subsequent oxidative workup [4a,c]. Swern oxidation of the resultant alcohol **10** yielded the aldehyde **11** which was subjected to Evans' aldol reaction [13] using *N*-propionyl-(4*S*)-benzyl-2-oxazolidinone, *n*-Bu_2BOTf and Et_3N in CH_2Cl_2 to give the desired aldol **12** in 81% overall yield. Removal of the chiral auxiliary in **12** using $LiBH_4$ and EtOH in Et_2O at -10 °C for 1 h gave the diol **13** in quantitative yield. Regioselective tosylation of the primary alcohol in **13** (TsCl, Py, 97%) and the silylation with *t*-butyldimethylsilyl (TBS) group (TBSOTf, 2,6-lutidine, CH_2Cl_2, 99%) of the resultant alcohol **14** yielded the tosylate **15** which was subjected to the reaction with lithium acetylide (5 equiv.) in dimethyl sulfoxide (DMSO) to give the acetylene **16** in 69% yield. After concurrent deprotection of the *p*-methoxybenzylidene and silyl groups in **16** under acidic conditions (HF(aq.), THF-MeCN, 70%), the resultant triol **17** was selectively pivaloylated (PvCl, Py, 4-dimethylaminopyridine (4-DMAP), CH_2Cl_2) at the primary alcohol and then silylated with diethylisopropylsilyl (DEIPS) group [14] using DEIPSOTf and 2,6-lutidine in CH_2Cl_2 to furnish the acetylene **19** in 82% overall yield. Finally, treatment of **19** with Cp_2ZrCl_2, Me_3Al and I_2 in 1,2-dichloroethane [15] afforded the *tri*-substituted *trans* vinyl iodide **2** in 88% yield.

The improved and asymmetric synthesis of the ethyl ketone **3** corresponding to the C20~C28 segment of concanamycin A (**1**) from *trans*-crotonaldehyde (**20**) is depicted in Scheme 2. The reaction of *trans*-crotonaldehyde and the Brown's chiral (*E*)-crotyldiisopinocamphenylborane **21** [16], which was prepared from *trans*-butene, *n*-BuLi and (-)-Ipc_2BOMe, in the presence of $BF_3{\bullet}Et_2O$ in THF-Et_2O at -78 °C for 2 h gave the allyl alcohol **22** (>99% e.e.) [17] in 58% yield with 1:14 syn/anti selectivity. *p*-Methoxybenzylation of the resultant alcohol **22** with *p*-methoxylbenzyl trichloroacetimidate [18] gave **23** in 75% yield. Regioselective dihydroxylation of the terminal olefin in **23** was best effected by Sharpless method [19] using the bulky reagent, AD-mixα, in *t*-BuOH-H_2O to give the diol **24** in 50% yield. Oxidative cleavage of the diol in **24** using $NaIO_4$ gave the aldehyde **25** in 95% yield. Mukaiyama aldol reaction [20] of **25** and the silyl enol ether **26** using $BF_3{\bullet}Et_2O$ in CH_2Cl_2 at -78 °C for 1 h proceeded smoothly to furnish the Cram-product, ethyl ketone **27**, in 62% yield as a sole aldol product. Treatment of **27** with DDQ in CH_2Cl_2 gave the fully protected ethyl ketone **28** in 62% yield [21]. However, the ethyl ketone **28** was unfortunately found to be not suitable for aldol reactions using several boron reagents [11]. Therefore, **28** was converted into the suitably protected ethyl ketone **3** [11] by standard procedures. Reduction of **28** using $NaBH_4$, followed by acetylation gave the acetate



Scheme 1. *Reagents and conditions*: a) $(MeO)_2CHC_6H_4OMe$, CSA, CH_2Cl_2, r. t., 16 h, 64%; b) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 20 min; c) EtMgBr, Et_2O, r. t., 3 h, 87% from **4**; d) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 20 min; e) $Ph_3P{=}CH_2$, PhH, r. t., 0.5 h, 88% from **6**; f) $BH_3{\cdot}Me_2S$, C_6H_{10}, THF, r. t., 3 h then NaOH-H_2O, H_2O_2, 50 °C, 1 h, 89%; g) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 20 min; h) *N*-propionyl-(4*S*)-benzyl-2-oxazolidinone, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h, 81% from **9**; i) $LiBH_4$, EtOH, Et_2O, -10 °C, 1 h, 100%; j) TsCl, Py, r. t., 2 h, 97%; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, r. t., 2 h, 99%; l) HC≡CLi, DMSO, r. t., 3 h, 69%; m) HF(aq.), THF, MeCN, 40 °C, 48 h, 70%; n) PvCl, 4-DMAP, Py, CH_2Cl_2, r. t., 16 h, 83%; o) DEIPSOTf, 2,6-lutidine, CH_2Cl_2, r. t., 16 h, 99%; p) Cp_2ZrCl_2, Me_3Al, I_2, $(ClCH_2)_2$, r. t., 16 h, 88%.



Scheme 2. *Reagents and conditions*: a) $BF_3{\cdot}Et_2O$, THF/Et_2O, -78 °C, 2h, 58%; b) $MeOC_6H_4CH_2OC(=NH)CCl_3$, CSA, CH_2Cl_2, r. t., 14 h, 75%; c) AD-mixα, t-BuOH/H_2O, r. t., 19 h, 50%; d) $NaIO_4$, MeOH/H_2O, r. t., 0.5 h, 95%; e) $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78 °C, 1 h, 60%; f) DDQ, CH_2Cl_2, 0 °C, 0.5h, 62%; g) $NaBH_4$, MeOH/CH_2Cl_2, 0 °C, 2 h, 67%; h) Ac_2O, 4-DMAP, Py, r. t., 17 h, 95%; i) AcOH:THF:H_2O= 1:1:1, 40 °C, 0.5 h, 90%; j) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, DMF, 0 °C, 0.5 h, 80%; K) NaOMe, MeOH, 0 °C, 4 h, 91%; l) Dess-Martin periodinane, Py, CH_2Cl_2, r. t., 2 h, 82%.

30 in 64% overall yield. Deprotection of *p*-methoxybenzylidene group under acidic conditions gave the diol **31** which was silylated with a di-*t*-butylsilyl group to give **32** in 68% overall yield. Finally, deacetylation of **32** followed by Dess-Martin oxidation [22] gave the suitably protected ethyl ketone **3** in 75% overall yield.

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