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NEW SYNTHETIC APPROACH TO PYRANONAPHTHOQUINONE ANTIBIOTICS, (\pm)-NANAOMYCIN A AND (\pm)-DEOXYFRENOLICIN<sup>1)</sup>
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The new total synthesis of pyranonaphthoquinone antibiotics, (\pm) -nanaomycin A $(\underline{1})$ and (\pm) -deoxyfrenolicin $(\underline{2})$, is discussed. The key step in the reaction sequence is Lewis acid mediated Michael addition of acylnaphthoquinone $(\underline{5})$ with methyl 2-(dimethylphenylsilyl)-3butenoate $(\underline{7})$.

Nanaomycin A $(\underline{1})^{2a-c}$ and deoxyfrenolicin $(\underline{2})^{2h,i}$ are members of pyranonaphthoquinone antibiotics²) and have been shown to be extremely active against mycoplasma. Synthetic efforts³) in this area have been appeared, while the stepwise construction of the required framework causes lack of efficiency. We note in advance that we have developed a new route to the above pyranonaphthoquinones together with a new synthon of 3-alkoxycarbonylallyl anion. This route is short, highly applicable, and efficient (i.e. proceed in 35% yield overall to <u>1</u>).

Our retrosynthetic scheme (Scheme I) is based on the intermediate <u>4</u>. We envisioned construction of the required pyranonaphthoquinone skeleton via Michael addition between benzylic alcohol and α,β -unsaturated carboxylic acid ester. Central to this strategy is the requirement that addition of 3-alkoxycarbonylallyl group takes place at the vicinal position of 3-acyl-1,4-naphthoquinone. To satisfy this requirement we

developed methyl 2-(dimethylphenylsilyl)-3-butenoate (7), which was regioselectively obtained from allylsilane via allylic aluminum "ate" complex,^{4,5)} as a new synthetic equivalent of 3-methoxycarbonylallyl anion (6).^{6,7)} While 2-acetyl-1,4-naphthoquinone is expected to be a good Michael acceptor,⁸⁾ reaction of <u>5a</u> with allylsilane 7 (CH₂Cl₂/room temperature) gave no



2 R¹=H, R²= n-Pr R³=H, R⁴=CH₂CO₂H





^a <u>Reagent</u> a, <u>7</u>/SnCl₄/CH₂Cl₂/-78 to -30°C; b, t-BuMe₂SiCl/imidazole/DMF; c, NaBH₄/MeOH; d, NaOMe MeOH; e, CAN/aq. CH₃CN; f, AlCl₃/CH₂Cl₂/room temperature; g, 0.1N KOH/room temperature.

adduct, presumably because of the lack of nucleophilicity of 7 as a Michael donor. So, we conquered the difficulty using Lewis acid (SnCl₄, 1.0 equiv. to the quinone) medi-ated addition of $\frac{7}{10}$ to the quinone $\frac{5a}{2}^{9,10}$ (CH₂Cl₂/-78 to -30°C/lh). After the reaction mixture was quenched with water and ether, the conjugate adduct 8^{11,14)} (mp >85°C decomp.) was obtained in a quantitative yield (isolated yield 74% after recrystallization). To avoid intramolecular cyclization to undesirable dihydrofuran derivative, ¹²⁾ immediate treatment of <u>8</u> with t-BuMe₂SiCl (TBDMS-Cl; imidazole in DMF/room temperature/3 h) afforded the corresponding monosily1 ether (73%). Reduction of the silyl ether with NaBH4 (MeOH/room temperature/14 h) followed by base catalyzed intramolecular Michael addition (NaOMe/MeOH/room temperature/1h) afforded the mixture of two stereoisomers;¹³⁾ the stereochemistry for the C-l and C-3 substituent, trans:cis = ca. 1:1 (89% yield from 8). Chromatographic separation of the two diastereoisomers (silica gel, hexane/CH₂Cl₂ eluted) afforded pure $10^{11,14}$ and $11^{11,14}$ (1:1 ratio). Oxidation of <u>10</u> and <u>11</u> with ceric (IV) ammonium nitrate (CAN; $CH_3CN/5$ min) gave <u>12</u>¹¹⁾ (mp >152°C decomp., 91% yield) and 13¹¹⁾ (mp >138°C decomp., 73% yield), respectively. Each of them was separately demethylated with AlCl₂ (CH₂Cl₂/room temperature/lh) to give nanaomycin A methyl ester¹¹⁾ (94%) and its epimer¹¹⁾ (98%), respectively. Acid catalyzed isomerization (conc $H_2SO_4/0$ °C/0.5h) of the latter isomer afforded the trans form (trans:cis = 2:1). Hydrolysis (0.1N KOH/ room temperature) of the trans isomer 12 afforded (+)-nanaomycin A (1) (94%), of which spectroscopic (NMR, IR, MS) and TLC data were identical with the natural ones.



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Synthesis of (\pm) -deoxyfrenolicin $(\underline{2})$, the second example, supports the generality of the present route. Lewis acid mediated addition of allylsilane $\underline{7}$ to $\underline{5b}$ (SnCl₄/-78 to 0°C/l h) quantitatively afforded $\underline{15}^{11,14}$ (isolated yield 82% after recrystallization), which was immediately silylated to the corresponding TBDMS ether $\underline{16}^{11}$ (82%). Reductive cyclization of $\underline{16}$ (excess amount of NaBH₄/dioxane/room temperature/14 h) afforded isomeric mixture, $\underline{17}^{11}$ and $\underline{18}^{11}$ ($\underline{17:18} = 5:2$, 85% yield).^{13,15}) Under the basic conditions, the cis configuration, which is undesired form, seems to be more stable than the trans one. Oxidation of the isomeric mixture with CAN and demethylation with AlCl₃ (CH₂Cl₂/room temperature/40 min) afforded $\underline{19}^{11}$ and $\underline{20}^{11,14}$ (total yield 66% from $\underline{17}$ and $\underline{18}$) with maintenance of isomeric ratio. Acid catalyzed epimerization (conc H₂SO₄/0°C/0.5 h) gave mainly desirable form $\underline{20}$ ($\underline{19:20} = 1:5.3$), which was purified and was successively hydrolyzed to give (\pm)-deoxyfrenolicin ($\underline{2}$) (mp >210°C decomp., 85% yield). Spectroscopic (NMR, IR, MS) and TLC data were identical with the natural ones.

In summary, we have completed the total synthesis of (\pm) -nanaomycin A and (\pm) deoxyfrenolicin via seven sequential steps from the corresponding alkanoylnaphthoquinones in respective overall yields of 35 and 36%.

Kalafungin^{2j,k)} (or nanaomycin D^{2e}) and frenolicin B^{2i} are easily obtained by air oxidation of 1 and 2, respectively.

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-78°C.⁵⁾ After an introduction of CO_2 to the reaction mixture at -78°C, treatment of the obtained carboxylic acid with CH_2N_2 exclusively afforded <u>7</u> (isolated yield 85%). Studies demonstrating the general utility of <u>7</u>, as well as analogues thereof, will be forthcoming in the near future.

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- (11) This substance gave satisfactory elemental analysis and/or MS spectra and IR and ¹H-NMR spectra consisted with the assigned structure.
 MeO OH O
- (12) Either under chromatographic purification (silica gel) or even on standing at room temperature, $\underline{8}$ spontaneously turned into \underline{I} .
- (13) The signals of the phenolic proton in the 1 H-NMR spectrum of <u>12</u> and <u>13</u>, <u>17</u> and <u>18</u>, are very useful to determine the regioselectivity.
- (14) ¹H-NMR data of typical compounds (in CDCl₃): <u>8</u>: δ 2.25(s,3H), 2.48(t,2H,J=8Hz),
 3.65(s and t,total 4H,J=8Hz), 3.96(s,3H), 5.59(s,1H,J=16Hz), 6.64(dt,1H,J=16,8Hz),
 7.22(dd,1H,J=8,2Hz), 7.45(m,2H), 17.19(s,1H).

10: δ 0.14(s,3H), 0.17(s,3H), 1.08(s,9H), 1.59(s,3H,J=7Hz), 2.55(dd,1H,J=16,11Hz), 2.67(m,2H), 3.02(dd,1H,J=16,3.5Hz),3.72(s,3H), 4.00(s,3H),4.36(m,1H), 5.27(q,1H, J=7Hz), 6.70(d,1H,J=8Hz), 7.20(t,1H,J=8Hz), 7.58(d,1H,J=8Hz), 9.20(s,1H). 11: δ 0.13(s,3H), 0.19(s,3H), 1.08(s,9H), 1.61(d,3H,J=7Hz), 2.53(dd,1H,J=16,10 Hz), 2.64(dd,1H,J=15,7Hz), 2.74(dd,1H,J=15,7Hz), 3.06(dd,1H,J=16,15Hz), 3.69(s, 3H), 3.75-3.95(m,1H), 3.99(s,3H), 5.23(q,1H,J=7Hz), 6.70(s,1H,J=8Hz), 7.19(t,1H, J=8Hz), 7.58(s,1H,J=8Hz), 9.32(s,1H).

<u>15</u>: δ 1.00(t,3H,J=7Hz), 1.75(m,2H,J=7Hz), 2.50(m,4H), 3.69(s and t,total 4H,J=7 Hz), 4.00(s,3H), 5.66(d,1H,J=16Hz), 6.73(dt,1H,J=16,8Hz), 7.31(dd,1H,J=8,2Hz), 7.40-7.70(m,2H), 17.36(s,1H).

20: δ 1.00(t,3H,J=7Hz), 1.3-2.0(m,4H), 2.33(ddd,1H,J=18.5,10,2Hz), 2.66(d,2H), 2.81(dd,1H,J=18.5,3.5Hz), 4.27(m,1H), 4.78(m,1H), 7.1-7.3(m,1H), 7.45-7.65(m,2H), 11.97(s,1H).

(15) Analytical samples of $\underline{17}$ and $\underline{18}$ were separated by column chromatography (silica gel, CH₂Cl₂/hexane eluted).

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