CHEMISTRY LETTERS, pp. 609-612, 1982. 

# NEW SYNTHETIC APPROACH TO PYRANONAPHTHOQUINONE ANTIBIOTICS, (±)-NANAOMYCIN A AND (±)-DEOXYFRENOLICIN[1)]

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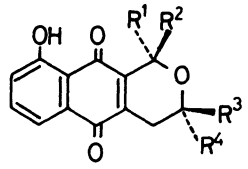
The new total synthesis of pyranonaphthoquinone antibiotics, (±)-nanaomycin A (1) and (±)-deoxyfrenolicin (2), is discussed. The key step in the reaction sequence is Lewis acid mediated Michael addition of acylnaphthoquinone (5) with methyl 2-(dimethylphenylsilyl)-3-butenoate (7).

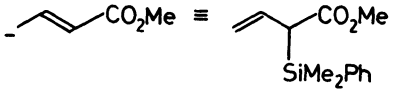
Nanaomycin A (1)[2a-c)] and deoxyfrenolicin (2)[2h,i)] are members of pyranonaphthoquinone antibiotics[2)] and have been shown to be extremely active against mycoplasma. Synthetic efforts[3)] in this area have been appeared, while the stepwise construction of the required framework causes lack of efficiency. 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 1).

Our retrosynthetic scheme (Scheme I) is based on the intermediate 4. 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 5a with allylsilane 7 ($CH_2Cl_2$/room temperature) gave no



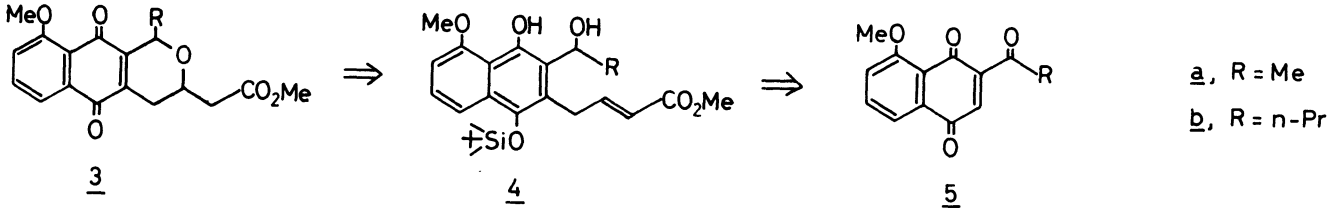
1 $R^1$=Me, $R^2$=H
$R^3$=$CH_2CO_2H$, $R^4$=H

2 $R^1$=H, $R^2$= n-Pr
$R^3$=H, $R^4$=$CH_2CO_2H$



6 7

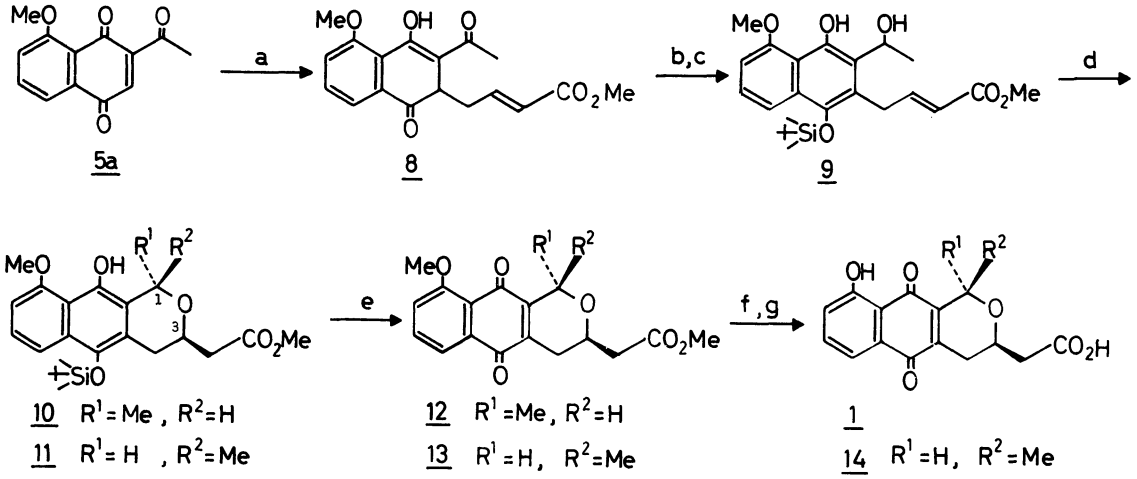
Scheme I



3 4 5

a, R = Me
b, R = n-Pr

Scheme II[a]

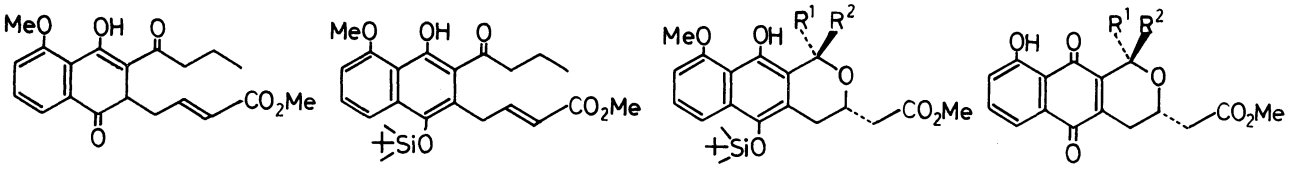


5a 8 9

10 $R^1$=Me, $R^2$=H
11 $R^1$=H, $R^2$=Me
12 $R^1$=Me, $R^2$=H
13 $R^1$=H, $R^2$=Me
1
14 $R^1$=H, $R^2$=Me

[a] Reagent a, 7/$SnCl_4$/$CH_2Cl_2$/-78 to -30°C; b, t-Bu$Me_2$SiCl/imidazole/DMF; c, $NaBH_4$/MeOH; d, NaOMe MeOH; e, CAN/aq. $CH_3CN$; f, $AlCl_3$/$CH_2Cl_2$/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 ($SnCl_4$, 1.0 equiv. to the quinone) mediated addition of 7 to the quinone 5a[9,10] ($CH_2Cl_2$/-78 to -30°C/1 h). 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 8 with t-Bu$Me_2$SiCl (TBDMS-Cl; imidazole in DMF/room temperature/3 h) afforded the corresponding *mono*silyl ether (73%). Reduction of the silyl ether with $NaBH_4$ (MeOH/room temperature/14 h) followed by base catalyzed intramolecular Michael addition (NaOMe/MeOH/room temperature/1 h) afforded the mixture of two stereoisomers;[13] the stereochemistry for the C-1 and C-3 substituent, trans:cis = ca. 1:1 (89% yield from 8). Chromatographic separation of the two diastereoisomers (silica gel, hexane/$CH_2Cl_2$ eluted) afforded pure 10[11,14] and 11[11,14] (1:1 ratio). Oxidation of 10 and 11 with ceric (IV) ammonium nitrate (CAN; $CH_3CN$/5 min) gave 12[11] (mp >152°C decomp., 91% yield) and 13[11] (mp >138°C decomp., 73% yield), respectively. Each of them was separately demethylated with $AlCl_3$ ($CH_2Cl_2$/room temperature/1h) to give nanaomycin A methyl ester[11] (94%) and its epimer[11] (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.



15 16

17 $R^1$=n-Pr, $R^2$=H
18 $R^1$=H, $R^2$=n-Pr
19 $R^1$=n-Pr, $R^2$=H
20 $R^1$=H, $R^2$=n-Pr

Synthesis of (±)-deoxyfrenolicin (2), the second example, supports the generality of the present route. Lewis acid mediated addition of allylsilane 7 to 5b ($SnCl_4$/-78 to 0°C/1 h) quantitatively afforded 15[11,14] (isolated yield 82% after recrystallization), which was immediately silylated to the corresponding TBDMS ether 16[11] (82%). Reductive cyclization of 16 (excess amount of $NaBH_4$/dioxane/room temperature/14 h) afforded isomeric mixture, 17[11] and 18[11] (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 $AlCl_3$ ($CH_2Cl_2$/room temperature/40 min) afforded 19[11] and 20[11,14] (total yield 66% from 17 and 18) with maintenance of isomeric ratio. Acid catalyzed epimerization (conc $H_2SO_4$/0°C/0.5 h) gave mainly desirable form 20 (19:20 = 1:5.3), which was purified and was successively hydrolyzed to give (±)-deoxyfrenolicin (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 (±)-nanaomycin A and (±)-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.

Acknowledgement The financial support of the Kurata Foundation is greatefully appreciated. We also express our appreciation to Shin-etsu Chemical Co., Ltd. for a gift of organochlorosilanes.

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(4) Allyldimethylphenylsilane was treated with *sec*-BuLi and N,N,N',N'-tetramethylethylenediamine at -78°C to -30°C followed by addition of $Et_3Al$ in hexane at

-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 7 (isolated yield 85%). Studies demonstrating the general utility of 7, as well as analogues thereof, will be forthcoming in the near future.

(5) Concerning control of the regiochemistry in the reaction of allylic carbanion via allylic aluminate, see: Y.Yamamoto, H.Yatagai, and K.Maruyama, J. Org. Chem., 45, 195 (1980).

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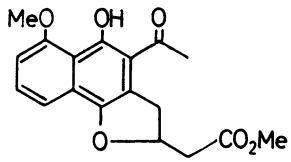
(8) (a) F.Farina and J.Valdename, Synthesis, 315 (1971). (b) G.A.Kraus and B.Roth, J. Org. Chem., 43, 4923 (1978).

(9) We have developed an efficient synthesis of 5a and 5b, see ref. 1.

(10) For the simple allylation of 2-alkanoyl-1,4-quinones with allyltrimethylstannane, see: Y.Naruta, H.Uno, and K.Maruyama, Tetrahedron Lett., 22, 5221 (1981).

(11) This substance gave satisfactory elemental analysis and/or MS spectra and IR and $^1$H-NMR spectra consisted with the assigned structure.

(12) Either under chromatographic purification (silica gel) or even on standing at room temperature, 8 spontaneously turned into I.



I

(13) The signals of the phenolic proton in the $^1$H-NMR spectrum of 12 and 13, 17 and 18, are very useful to determine the regioselectivity.

(14) $^1$H-NMR data of typical compounds (in $CDCl_3$): 8: 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).
15: 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 17 and 18 were separated by column chromatography (silica gel, $CH_2Cl_2$/hexane eluted).

( Received February 25, 1982)