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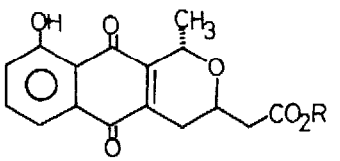
Total Synthesis of (±)-Nanaomycin A and (±)-Frenolicin[1)]

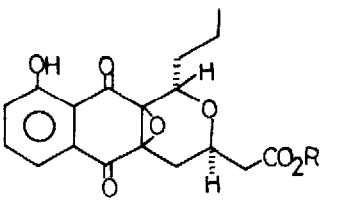
Akitami Ichihara*, Makoto Ubukata, Hideaki Oikawa,
Kazuo Murakami, and Sadao Sakamura
Department of Agricultural Chemistry, Faculty of Agriculture,
Hokkaido University, Sapporo 060, Japan

Summary. Efficient synthesis of (±)-nanaomycin A and (±)-frenolicin from a versatile intermediate is described.

Nanaomycin A (1)[2a)] and frenolicin (2)[2b)] are typical member of naphthoquinone antibiotics. The former (1) also possesses significant antineoplastic activity as one of the bioreductive alkylating agents.[3)] In this communication we report efficient synthesis of (±)-nanaomycin A and (±)-frenolicin from a versatile intermediate 3a, which also serves as a potential starting material for the synthesis of other members of the antibiotics.



1 R = H
11 R = CH_3



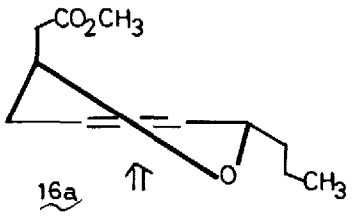
2 R = H
21 R = CH_3

The Diels-Alder reaction of juglone with acetoxybutadiene in the presence of boron trifluoride according to known procedure[4)] gave the adduct 4 in 96.8% yield. Reduction of 4 with sodium borohydride (THF, 5°C) proceeded regio- and stereoselectively to give the keto alcohol 5 in a quantitative yield.[5)] Treatment of 5 with acetone-dimethoxypropane-$BF_3O(C_2H_5)_2$ yielded the acetonide 6, mp 215~219°C (70.2%)[6)], which was converted to the diol 7, mp 162.8~164.8°C (96.7%) by lithium aluminum hydride reduction (Et_2O). The Lemieux-Johnson oxidation (OsO_4-$NaIO_4$, t-BuOH-H_2O) of the diol 7 and subsequent treatment with sodium acetate and DABCO afforded an equilibrated mixture (99%) of the aldehyde 3a and the hemiacetal 3b, from which only the latter compound 3b, mp 130~137°C, was isolated in pure state. From the mixture of 3a and 3b, nanaomycin A (1) and frenolicin (2) have been synthesized as follows.

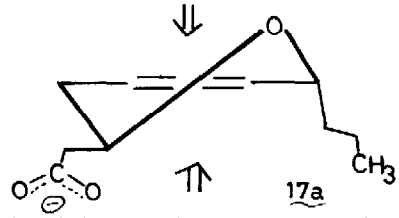
Synthesis of (±)-nanaomycin A[7)] (1): Reverse addition of the Grignard reagent (CH_3MgI, Et_2O) to the mixture of 3a and 3b gave the alkylated products 8[8)] (59.4% as a diastereomeric mixture arising from two asymmetric centers, C-1 and C-3. The Wittig-Horner reaction (methyl diethylphosphonoacetate, n-BuLi, THF) of 8

yielded cyclized methyl ester 9 (oil, 74.4%), which was oxidized to the ketone 10 (94.6%) with pyridinium chlorochromate (CH_2Cl_2, rt). DDQ oxidation (dioxane, reflux) of 10 in the presence of p-toluenesulfonic acid[9] gave nanaomycin A methyl ester 11, mp 118~120°C. Hydrolysis of 11 with 0.1N-KOH (EtOH-H_2O, 1hr, rt) yielded quantitatively nanaomycin A (1), mp 177~181°C, whose spectral data are identical with natural nanaomycin A in all respects. Since (±)-nanaomycin A was converted to (±)-kalafungin by air oxidation[7a], present synthesis also means formal total synthesis of (±)-kalafungin.

Synthesis of (±)-frenolicin (2)[10,11]: Similarly, treatment of the mixture (3a, 3b) with n-propyl magnesium bromide (Et_2O) yielded stereoselectively the hemiacetal 12[8] (65.5%), mp 155.6~156.9°C. The stereoselective alkylation would be explained by the formation of a chelated intermediate in the course of the reaction. The Wittig reaction (methyl diethylphosphonoacetate, n-BuLi, DMSO, 2hr. rt) of 12 afforded regio- and stereoselectively the methyl ester 13 (oil, 60.9%), which was oxidized with pyridinium chlorochromate (CH_2Cl_2, rt) to the keto ester 14 (98.2%), mp 139.9~140.9°C. On the other hand, the Wittg reaction of 12 with trimethylphosphonoacetate (n-BuLi, DMSO, rt, overnight) yielded the methyl ester 13 (9.4%) and the diol 15 (oil, 40.7%). The latter was converted to the keto ester 14 (52.2%) via manganese dioxide oxidation (benzene, rt) and base treatment (Triton B, rt, overnight). The stereoselective formation of the keto ester 14 from 12 and 15 would be rationalized by a stable transition state in the Michael type cyclization, in which bulky n-propyl and carbomethoxymethyl groups are oriented in trans manner. Oxidation (DDQ, TsOH, MeOH, reflux 9hr and additional 12 hr after addition of dioxane) of 14 afforded (±)-deoxyfrenolicin methyl ester 16 (80%), mp 140.5~141°C, whose ^1H NMR data are identical with those of reported sample[2b] derived from natural frenolicin (2). Saponification (KOH, MeOH-H_2O) of 16 gave deoxyfrenolicin (17), which, by refluxing in $CHCl_3$, was easily transformed to the pyranolactone 18 (oil, quantitative). Epoxidation (t-BuOOH, Triton B, dioxane-EtOH, rt) of the ester 16 gave epifrenolicin methyl ester (19), which would be derived from a stable conformation 16a. On the other hand, epoxidation of deoxyfrenolicin (17) under the same conditions described above yielded via a

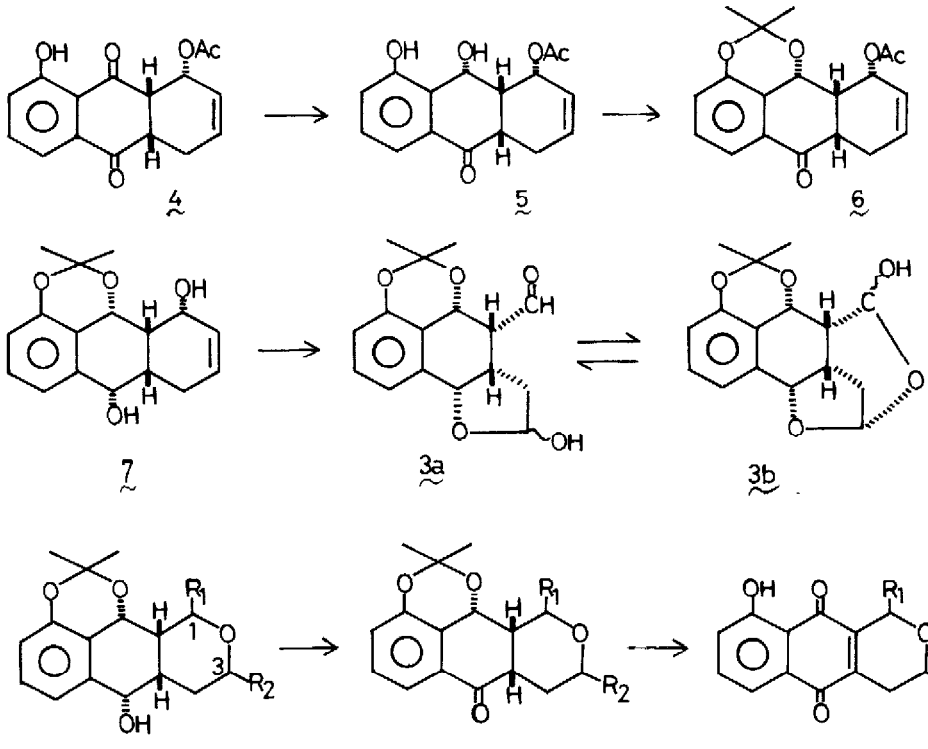


16a



17a

conformation 17a, a mixture of (±)-frenolicin (2) and (±)-epifrenolicin (20) in a ratio of 1 : 1. Since direct separation of the mixture was difficult, the mixture was methylated with diazomethane and separated to give (±)-frenolicin methyl ester 21 and (±)-epifrenolicin methyl ester 19. The spectral data of the former 21 were identical with those of 21 derived from natural sample.



4 5 6

7 3a 3b

8 $R_1 = \sim CH_3$, $R_2 = \sim OH$

9 $R_1 = \sim CH_3$, $R_2 = \sim CH_2CO_2CH_3$

12 $R_1 = \cdots CH_2CH_2CH_3$, $R_2 = -OH$

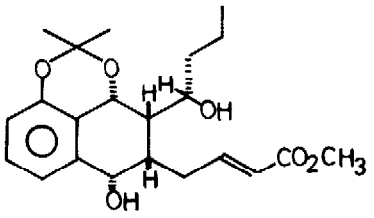
13 $R_1 = \cdots CH_2CH_2CH_3$, $R_2 = -CH_2CO_2CH_3$

10 $R_1 = \sim CH_3$ $R_2 = \sim CH_2CO_2CH_3$

14 $R_1 = \cdots CH_2CH_2CH_3$, $R_2 = -CH_2CO_2CH_3$

16 $R_1 = \cdots CH_2CH_2CH_3$, $R_2 = -CH_2CO_2CH_3$

17 $R_1 = \cdots CH_2CH_2CH_3$, $R_2 = -CH_2CO_2H$



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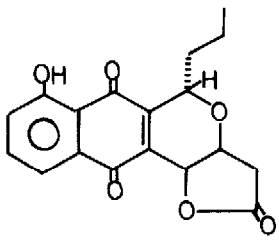

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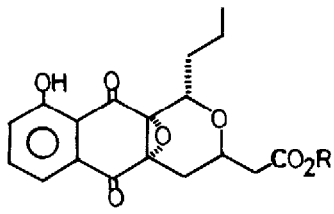


19 R = CH_3

20 R = H

Saponification (KOH, CH_3OH- H_2O, rt) of the methyl ester 21 afforded (±)-frenolicin (2), mp 175.2~181.0 °C, whose IR, ^{1}H-NMR and mass spectra are identical with those of natural frenolicin.

Acknowledgement. The authors are indebted to Professor S. Omura, Kitasato University, for a gift of nanaomycin A and also to Dr. M. P. Kunstmann, American Cyanamid Company, for a gift of frenolicin.

References and Notes

(1) Taken for the Ph. D. Thesis of M. Ubukata, Hokkaido University, 1980.

(2) (a) Tanaka, H.; Koyama, Y.; Nagai, T.; Marumo, H.; Omura, S. J. Chem. Soc. Chem. Commun., 1976, 320. (b) Ellestad, G. A.; Kunstmann, M. P.; Whaley, H. A.; Patterson, E. L.; J. Am. Chem. Soc., 1968, 90, 1325.

(3) Moore, H. W.; Science, 1977, 197, 527.

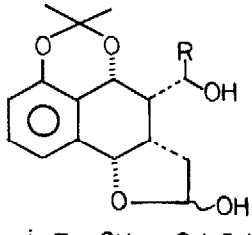
(4) Trost, B. M.; Ippen, J.; Vladuchick, W. C. J. Am. Chem. Soc., 1977, 99, 8116. Stork, G.; Hagedorn, AA. III, ibid., 1978, 100, 3609.

(5) $LiAlH_4$ reduction of 4 afforded 5 in 66% yield; cf Inhoffen, H. H.; Muxfeldt, H.; Schaefer, H.; Kramer, H. Croat. Chem. Acta., 1957, 29, 329.

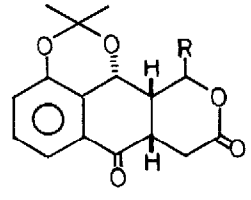
(6) Satisfactory elemental composition (combustion analyses or exact mass spectroscopy) and spectral data were obtained on all new compounds.

(7) (a) Recently synthesis of (±)-nanaomycin A and (±)-kalafungin was reported: Li, T.; Ellison, R. H. J. Am. Chem. Soc., 1978, 100, 6263. (b) The synthesis of 8-deoxynanaomycin A was also reported. Pyrek, J. St.; Achmatowicz, Jr. O.; Zamojski, A. Tetrahedron, 1977, 33, 673.

(8) Another possible hemiacetal i was excluded by the fact that oxidation of 8 and 12 yielded the keto lactone ii, IR (film) 1735, 1680 cm^{-1}.



i R = CH_3, $CH_2CH_2CH_3$



ii R = CH_3, $CH_2CH_2CH_3$

(9) Acid treatment of a diastereomeric mixture of nanaomycin A ethyl ester gave predominantly trans isomer.

(10) Natural frenolicin is depicted as an antipode of 2.

(11) The synthesis of a model compound of frenolicin was reported. Grunwell, J. R.; Rieck, J. A.; 173rd ACS National Meeting, 1977, symposium papers 171

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