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TOTAL SYNTHESES OF (+)-NOGARENE AND (+)-7,8-DIHYDRONOGARENE

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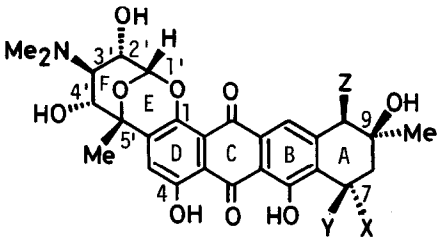
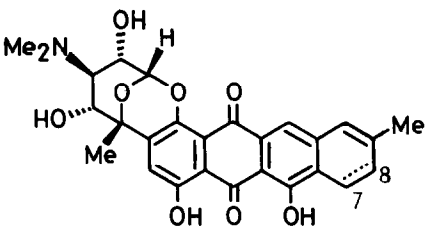
Abstract: Total syntheses of the title compounds, the simplest and the hitherto unknown novel nogalamycin congeners, were first accomplished by elaborating the CDEF-ring system (5) from the methyl ketone (6) and subjecting 5 to regioselective Diels-Alder reaction with the bistrimethylsilyl keteneacetal (22).

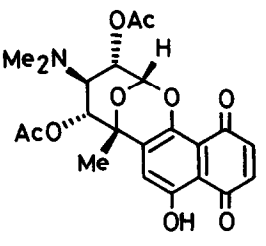
Nogalamycin (1) and its congeners are notable members of the anthracycline family because of their unique structures and prominent antitumor activities. Especially, 7-con-O-methylnogarol (2) which can be chemically derived from 1, has been reported to exhibit more promising anticancer activity than the parent compound (1).[1]



1 : X=O, Y=H, Z=CO_2Me 2 : X=Z=H, Y=OMe



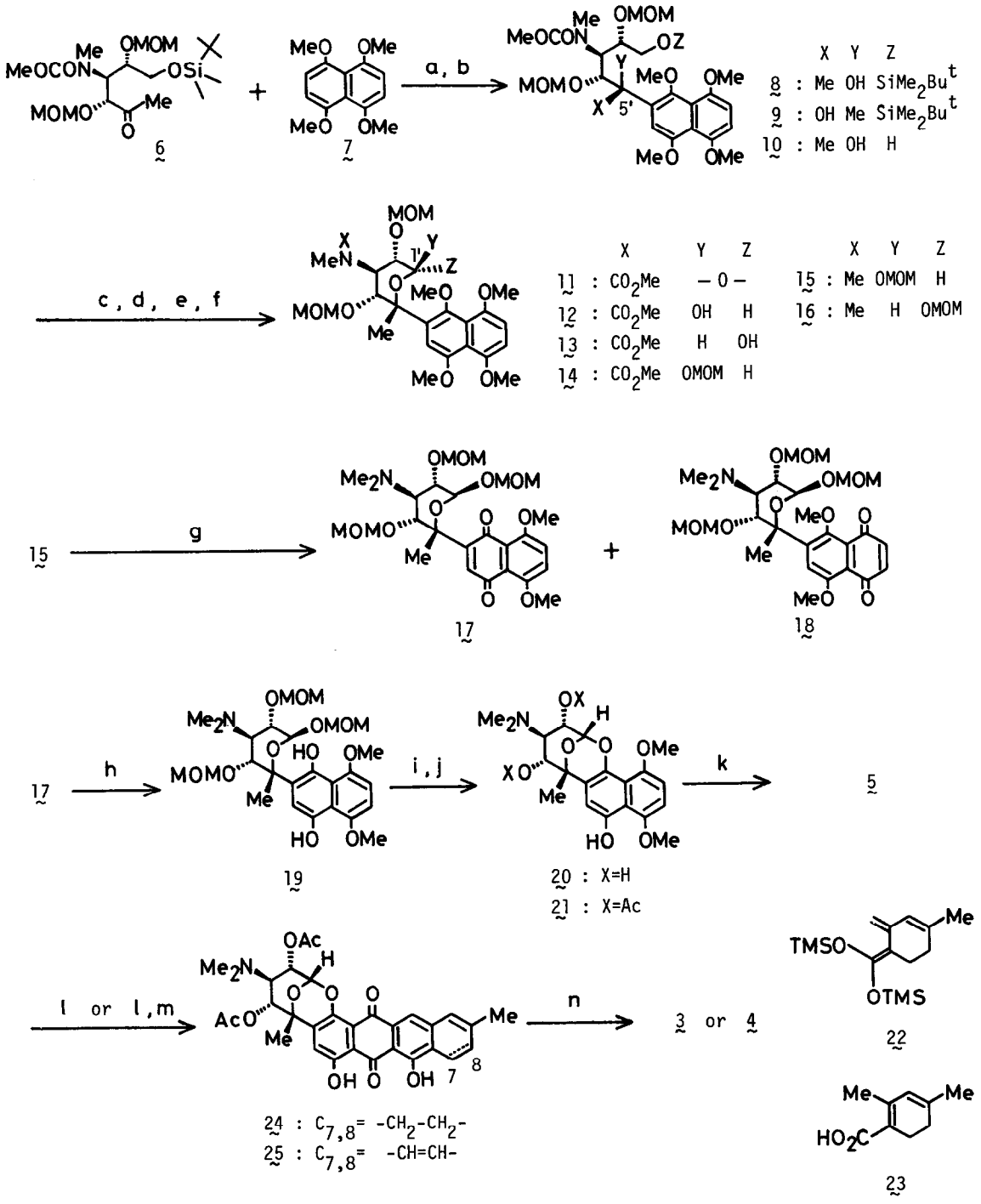
3 : $C_{7,8}$= -CH=CH-
4 : $C_{7,8}$= $-CH_2-CH_2-$



5

In the course of our synthetic studies on 1 and 2, we have already developed an efficient synthetic process for stereoselectively constructing their characteristic DEF-ring system in an optically active form from D-arabinose.[2] Based on the results accumulated in these studies, we next examined the total synthesis of (+)-nogarene (3), the simplest congener of 1, which is reported to be prepared from 1 similarly to 2.[1] We wish to report here the first total syntheses of 3 and its hitherto unknown 7,8-dihydro derivative, (+)-7,8-dihydronogarene (4). Our synthetic plan features stereoselective construction of the CDEF-ring system (5) of 1 and its congeners according to the synthetic scheme similar to that previously explored, and regioselective Diels-Alder reaction of 5 with the bistrimethylsilyl keteneacetal (22).

For the synthesis of 5, it is necessary to introduce a protected 1,4,5,8-tetrahydroxynaphthalene moiety into the methyl ketone (6)[2] to construct the bicyclic acetal system at the later stage of the synthesis. After several experiments using various tetraalkoxynaphthalene derivatives, it was finally found that 1,4,5,8-tetramethoxynaphthalene (7)[3] was only usable for this purpose. Addition of the aryllithium generated from 7 and n-butyllithium to 6 proceeded in a highly stereoselective manner to give the desired alcohol (8) and its epimer (9) in 14 : 1 ratio with a recovery of 6. The stereochemistry at $C_{5'}$-position of the separable isomers (8



(a) 7(1.4 eq), n-BuLi(1.4 eq), THF, 0°C, 3 min, 57%(8), 4%(9), 22%(6) (b) Bu_4NF, THF, r.t., 1 h, 98% (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -60-0°C, 95% (d) DIBAL, toluene, -78°C, 20 min, then K_2CO_3, MeOH, reflux, 30 min, 82% (e) MOMCl, $(i\text{-}Pr)_2NEt$, THF, reflux, 3 h, 90% (f) $LiAlH_4$,

ether, reflux, 1 h, 94% (g) CAN, EtOH-H_2O, -40-0°C, 72%(17), 21%(18) (h) $Na_2S_2O_4$, $CHCl_3$-H_2O, r.t. (i) Me_3SiBr, CH_2Cl_2, reflux, 10 min (j) Ac_2O, AcOK, EtOH, r.t., 20 min, 78% (3 steps) (k) BBr_3, CH_2Cl_2, 0°C, 30 min, then Et_3N, finally CAN, EtOH-H_2O, -78°C, 10 min, 71% (l) 22, THF, r.t., 30 min, 85% (m) DDQ, CSA, PhH, reflux, 5 h, 85% (n) 1N HCl, reflux, 12 h, 88% (for 24), or 87%(for 25)

and 9) could not be rigorously determined at this stage. However, the major alcohol (8) was assumed to have the desired stereochemistry by taking into account the previous result which had clearly disclosed that the addition of an aryllithium to 6 proceeds under the usual chelation control.[2] Accordingly, 8 was subjected to further chemical elaborations.

After desilylation of 8, oxidation of the resulting primary alcohol (10) followed by reduction of the formed lactone (11) afforded the lactols (12 and 13) as an epimeric mixture at C_{11}-position. This was equilibrated under the basic conditions, resulting in exclusive formation of the thermodynamically more stable β-isomer (12).[4] After protecting the lactol function in a form of methoxymethylether, the formed acetal (14) was subjected to reduction to readily afford the dimethylamine (15). Similarly, the α-lactol (13) could be also derived to the epimeric dimethylamine (16).

As expected from the model study,[5] oxidation of 15 with ceric ammonium nitrate (CAN) was found to occur in a notably regioselective manner, yielding the desired naphthoquinone (17) as a major product along with the minor regioisomer (18) in 3.5 : 1 ratio. These regioisomers (17 and 18) could be readily separated by a column chromatography (SiO_2). After reduction of 17 with sodium hydrosulfite, brief exposure of the formed unstable dihydroxynaphthoquinone (19) to trimethylsilyl bromide effected simultaneous cleavage of the three methoxymethylether groups and intramolecular acetal formation. Acetylation of the resulting bicyclic acetal (20) gave the diacetate (21) as a white powder, m.p. 182-183°C and $[\alpha]_D^{20}$+79.7°(c 0.31, $CHCl_3$). The chemical shifts and coupling constants of the 1'~4'-positions of 21 clearly established the structure of 21.[2] Cleavage of the two methyl ethers of 21 with boron tribromide followed by quenching with triethylamine gave the demethylated product as a triethylamine complex. This was further subjected to oxidation with CAN to give 5 as a reddish orange powder, m.p. 153-155 °C and $[\alpha]_D^{20}$+420°(c 0.050, $CHCl_3$).

With 5 in hand, regioselective Diels-Alder reaction was examined using 5 as a dienophile to construct the whole carbon framework of 3. The bistrimethylsilyl keteneacetal (22), which can be produced by treating the dianion of the carboxylic acid (23)[6] [LDA(2 eq), THF, -60°C] with trimethylsilyl chloride (THF, r.t.), was selected as a favorable diene.[7,8] Diels-Alder reaction of 5 with 22 followed by concomitant air oxidation of the addition product during mild acidic work-up was found to give 2',4'-di-O-acetyl-7,8-dihydronogarene (24) as a sole product, m.p. 171-172°C and $[\alpha]_D^{20}$+468°(c 0.070, $CHCl_3$). The regioselectivity observed for this reaction can be well explained by the hypothesis proposed by Boeckman.[9] Acidic hydrolysis of 24 effected clean deacetylation to produce 4 as an orange powder, m.p. 251-257°C (decomp.) and $[\alpha]_D^{20}$+571°(c 0.070, $CHCl_3$). On the other hand, dehydrogenation of 24 afforded (+)-2',4'-di-O-acetylnogarene (25), m.p. 177-179°C and $[\alpha]_D^{20}$+445°(c 0.062, $CHCl_3$). This was shown to be identical with the sample independently prepared from authentic 3 by our hands (Ac_2O, EtOH, r.t., 1 h, 79%) in all respects (m.p., m.m.p., $[\alpha]_D^{20}$, ^{1}H-NMR, IR, MS). Similar deacetylation of 25 gave 3 as an orange powder, m.p. 277-281°C (decomp.) and $[\alpha]_D^{20}$+946°(c 0.070, $CHCl_3$). The

synthetic sample was found to be identical with authentic 3 in all respects (m.p., m.m.p., $[\alpha]_D^{20}$, ^{1}H-NMR, IR, MS).

Utilizing 24, total synthesis of 2, the most eminent nogalamycin congener showing prominent anticancer activity, is being examined in our laboratory.[10]

Acknowledgement: We are grateful to Dr. P.F. Wiley, The Upjohn Company, for providing us with an authentic sample and spectral data of 3.

References and Notes

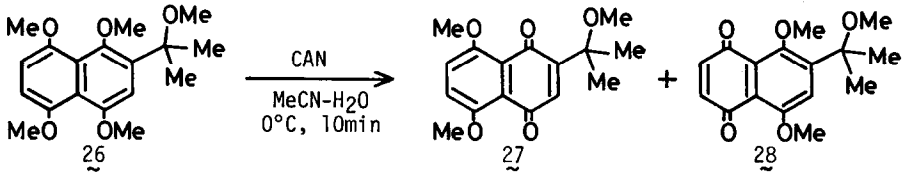
(1) P.F. Wiley, Lloydia, 42, 569 (1979); Idem., "Anthracycline Antibiotics," ed. by H.S. El Khadem, Academic Press, New York (1982), pp.97-117.

(2) M. Kawasaki, F. Matsuda, and S. Terashima, Tetrahedron Lett., 26, 2693 (1985).

(3) 1,4,5,8-Tetramethoxynaphthalene (7), m.p. 167-169°C, was prepared from naphthazarin (5,8-dihydroxy-1,4-naphthoquinone) by sequential reduction (H_2, 10%Pd-C, DMF, r.t., 5 min) and methylation [NaH, Me_2SO_4, DMF, r.t., 20 min, 72% (2 steps)].

(4) The stereochemistry at $C_{1'}$-position of 12 and 13 was determined by ^{1}H-NMR spectra at the stage of the dimethylamines (15 and 16).

(5) Regioselectivity of the CAN oxidation of 15 was studied using the tetramethoxynaphthalene derivative (26). Interestingly, oxidation of 26 with CAN gave a mixture of naphthoquinones (27 and 28) in 6 : 1 ratio and 89% combined yield. This remarkable regioselectivity may be rationalized by considering the electron density of naphthalene ring affected by the electrondonating (1-methoxy-1-methyl)ethyl group. Structural assignment of 17 and 18 was determined by comparing ^{1}H-NMR spectra of these compounds with those of 27 and 28.



26 27 28

(6) The carboxylic acid (23) was prepared by treating the corresponding ethyl ester with aluminum tribromide and tetrahydrothiophene. See, M. Node, K. Nishide, M. Sai, K. Fuji, and E. Fujita, J. Org. Chem., 46, 1991 (1981).

(7) The ethyltrimethylsilyl keteneacetal produced from the ethyl ester of 23 was first anticipated to be one of the most suitable dienes, based on the results reported for 11-deoxyanthracyclinone synthesis.[8] However, preliminary experiments revealed that the conditions required to effect cleavage of the resulting phenolic ethylether[8] was too drastic to employ this compound for the synthesis of 3.

(8) J.P. Gesson, J.C. Jaquesy, and B. Renoux, Tetrahedron, 40, 4743 (1984).

(9) R.K. Boeckman, Jr., T.M. Dolak, and K.O. Culos, J. Am. Chem. Soc., 100, 7098 (1978).

(10) Some synthetic intermediates (5, 17, 18, 21, 24, and 25) and the objective compounds (3 and 4) were subjected to P388 murine leukemia in vitro cytotoxicity assay. Following IC_{50} values were recorded : 3, 0.11 μg/ml ; 4, 0.13 μg/ml ; 5, 0.10 μg/ml ; 17, 16 μg/ml ; 18, 0.14 μg/ml ; 21, >5 μg/ml ; 24, 0.58 μg/ml ; 25, 0.17 μg/ml. It is of interest that the bicyclic and the monocyclic acetals (5 and 18) show comparable cytotoxicity to 3 and 4. We are indebted to Dr. K. Sakai and Miss K. Yamada, Sagami Chemical Research Center, for performing in vitro cytotoxicity assay.

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