SYNTHESIS OF PENTACYCLIC STRUCTURE OF GRISEUSIN A

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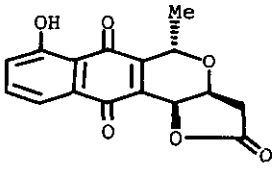
Abstract ——— A synthetic method of the framework of griseusin A was presented. The key step involved an intramolecular ketalization of the δ,δ'-dihydroxyketone derivative which was prepared from 2-allyl-3-bromo-1,4-dimethoxynaphthalene.

Pyranonaphthoquinone antibiotics such as nanaomycin D (1),[1] griseusin A (2),[2,3] and granaticin (3),[4] have recently received considerable attention by synthetic chemists because of their potent biological activities.[2,5] Up to date, however, only nanaomycins of relatively simple structures have been the target molecules, as reported in our recent papers.[6] Our continuing efforts aimed at exploring synthetic methods applicable to the complex molecules of this class of antibiotics has now yielded an efficient method for the construction of the pentacyclic framework of griseusin which includes elaboration of the unique 1,7-dioxaspiro[5,5]undecane ring system.[7]



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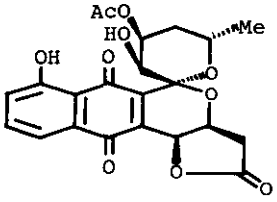

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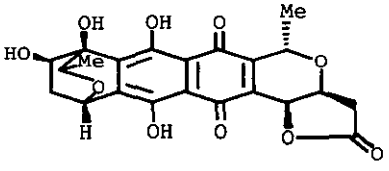

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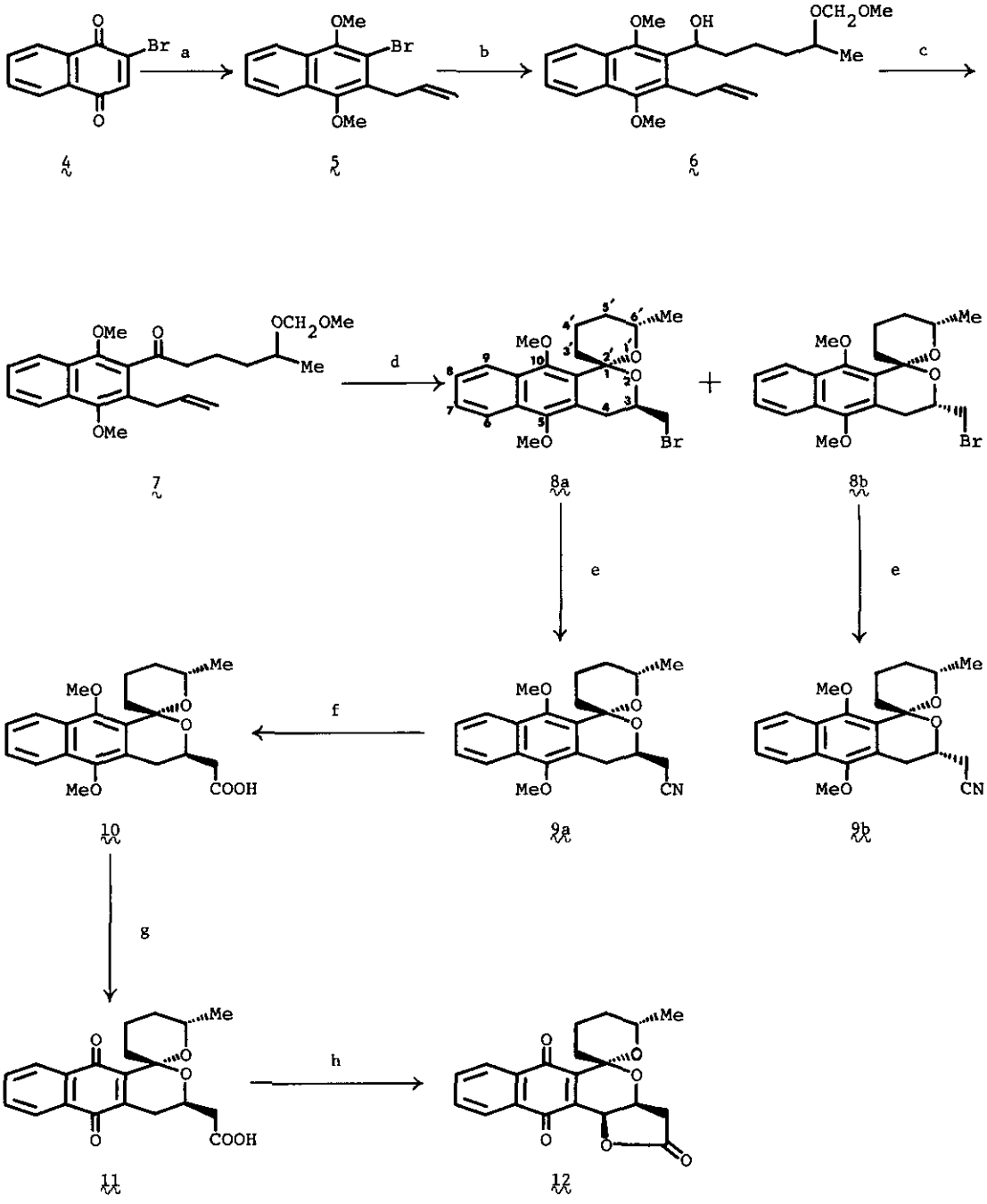
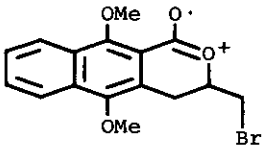
2-Allyl-3-bromo-1,4-dimethoxynaphthalene (5) prepared from 2-bromonaphthoquinone (4) by the method reported in our nanaomycin synthesis[6] was treated with BuLi in THF at -78°C and the resulting lithio compound was alkylated with the methoxymethyl ether derivative of 5-hydroxyhexanal[8] to give the carbinol (6) in 55% yield, bp 140-160°C(bath temp.) / 1.2×10^{-4} Torr. Oxidation of the alcohol 6 with PCC afforded the corresponding ketone (7) in 79% yield, bp 140-150°C(bath temp.) / 6.5×10^{-4} Torr ; ir(neat) 1695cm^{-1}(CO) ; ms m/e 386(M^+). Addition of hypobromous acid to the allyl group of 7 was carried out by treatment with aqueous N-bromoacetamide in the presence of perchloric acid. The crude bromohydrin obtained by this procedure was then treated, without purification, with 10%



Reagents : (a) CH_2=CHCOOH/$(NH_4)_2S_2O_8$/$AgNO_3$/3h/60°C, $Na_2S_2O_4$/room temp., Me_2SO_4/KOH/12h/room temp. ; (b) BuLi/$CH_3CH(OCH_2OCH_3)CH_2CH_2CH_2CHO$/1h/-78°C ; (c) PCC/5h/room temp. ; (d) aq.NBA/$HClO_4$/1h/0°C, 10% HCl/2.5h/50°C ; (e) NaCN/DMF/16.5h/80°C ; (f) KOH/H_2O_2/4h/40°C ; (g) $Ce(NH_4)_2(NO_3)_6$/0.5h/room temp. ; (h) O_2/pyr/24h/room temp.

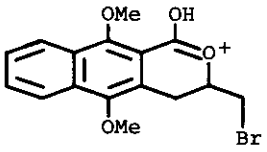
HCl at 50°C for 2.5h, which resulted in deprotection of the methoxymethyl group with concomitant intramolecular ketalization.[9]

Two isomeric spiroketals formed here in a ca. 1 : 1 ratio could be separated by silica gel column chromatography : less polar 8a, Rf=0.31;[10] bp 120-145°C(bath temp.) / $1x10^{-4}$ Torr ; more polar 8b, Rf=0.26;[10] bp 160-165°C(bath temp.) / $8x10^{-5}$ Torr, and their spiroketal structures were confirmed by spectral data;[11] specifically based on the presence of two characteristic fragment ions in their ms spectra (i and ii).[12] The mixture of 8a and 8b was then reacted with NaCN in DMF at 80°C to



m/e 350, 352

i



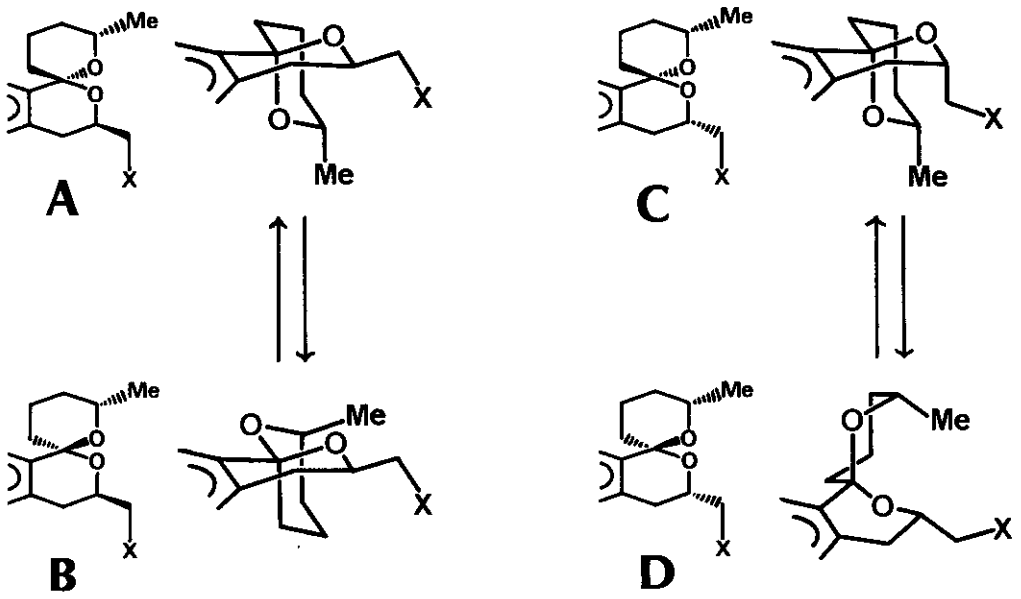
m/e 351, 353

ii

give the nitriles 9a and 9b (ratio of formation = 3 : 2 by hplc) in a total yield of 68% after silica gel chromatography : 9a, Rf=0.15;[13] mp 119-121°C, ir($CHCl_3$) 2280cm^{-1}(CN), ms m/e 367(M^+), 297(M^+-70, base peak);[11] 9b, Rf=0.13;[13] mp 170-172°C, ir($CHCl_3$) 2280cm^{-1}(CN), ms m/e 367(M^+), 297(M^+-70, base peak).[11] The isomerization of 9b to 9a under the conditions of nitrile formation was proved by a separate experiment, using pure 9b. This isomerization is most reasonably explained as involving β-elimination——addition at the cyanomethyl side chain associated with C(3). Stereochemistry of the spiroketal compounds, 8a,b and 9a,b, was demonstrated to be those depicted in the chart, based on the following considerations. Of the four possible diastereomers (partial structures A ——— D), 8a and 8b must be the more stable isomers within a pair of diastereomers differing only in configuration of the ketal carbon respectively, since the ketal functionality is formed under thermodynamic control. Comparison of energies —— nonbonded interactions and anomeric oxygen effect —— of the preferred conformations of each isomer leads to the conclusion that structures A and C are more stable than their counterparts B and D, respectively. Since A is undoubtedly more stable than C, assignment of stereochemistry A for 8a and 9a therefore C for 8b and 9b is secured.

Detailed analyses of the 200 MHz ^1H nmr spectra were also in accord with this conclusion. The two methylene hydrogens adjacent to the nitrile group of 9a appear at δ 2.80 as a doublet (J = 6 Hz), whereas for 9b, the corresponding protons are magnetically nonequivalent, giving signals at δ 2.72 and 2.92 as a doublet of doublets (J = 16, 6 Hz, and 16, 8 Hz respectively), resulting from restricted rotation of the axial side chain.

The nitrile 9a now shown to possess the same spiroketal configuration as griseusin, was subjected



X = Br, CN

to hydrolysis with aq.KOH in the presence of H_2O_2 to afford the spiroketal acid (10) in 70% yield, mp 195-199°C, ir($CHCl_3$) 1710cm^{-1}(COOH), ms m/e 386(M^+), 317(M^+-69, base peak).[11] Compound 10 was readily transformed to the quinone (11) in 47% yield by carrying out the oxidation with ceric ammonium nitrate, mp 192-195°C, ir($CHCl_3$) 1715cm^{-1}(COOH), 1665cm^{-1}(C=C-CO), ms m/e 356.1264(M^+, calcd 356.1259).[11] Finally, oxidative γ-lactone formation of the quinone 11 was accomplished by a usual procedure[3] — air oxidation in pyridine. The target compound 12, mp 107-109°C, was isolated in 25% yield by preparative tlc and its stereochemical structure was confirmed by the following spectral data : ir($CHCl_3$) 1795cm^{-1}(COO), 1670cm^{-1}(C=C-CO), ms m/e 354.1142(M^+, calcd 354.1104), nmr ($CDCl_3$)δ, 1.21(3H, d, J=7Hz, C(6')-CH_3), 1.3-1.4(5H, m, C(5')H_2-C(4')H_2-C(3')H_{eq}), 2.70(1H, td, J=13,5Hz, C(3')H_{ax}), 2.78(1H, d, J=17Hz, C(3)-CH_2COO), 3.00(1H, dd, J=17,5Hz, C(3)-CH_2COO), 4.76(1H, dd, J=5,3Hz, C(3)H), 5.35(1H, d, J=3Hz, C(4)H), 7.7-8.2(4H, m, aromatic protons).

We are now engaged in the total synthesis of griseusin A employing the efficient methodology for the construction of basic framework presented in this communication.

References and Notes

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8. This compound was prepared as follows. Reduction of 6,6-dimethoxyhexan-2-one[14] with $LiAlH_4$ in THF gave 6,6-dimethoxyhexan-2-ol in 82% yield(bp 88-89°C / 1.8 Torr ; nmr(CCl_4)δ, 3.50(1H, m, CH-OH) ; ir(neat) 3400cm^{-1}(OH)). Protection of the alcohol with methoxymethyl chloride and diisopropylethylamine afforded methoxymethyl ether of 6,6-dimethoxyhexan-2-ol in 62% yield (bp 87-89°C / 2 Torr ; nmr($CDCl_3$)δ, 3.34(3H, s, OCH_3), 4.06(2H, s, OCH_2O)). Hydrolysis of the methoxymethyl ether with 5N sulfric acid produced methoxymethyl ether of 5-hydroxyhexanal in 78% yield(bp 56°C / 1.5 Torr ; ir(neat) 1720cm^{-1}(CHO) ; nmr($CDCl_3$)δ, 9.66(1H, m, CHO)).

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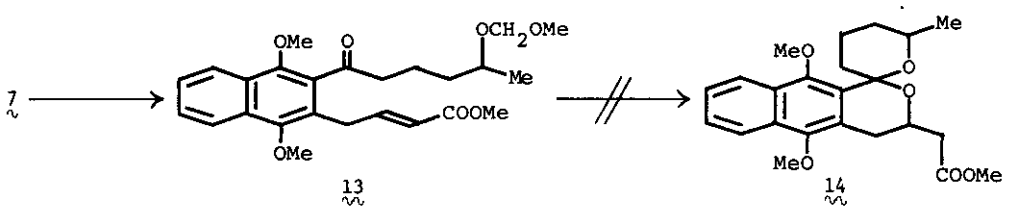
10. solvent system ; benzene:n-hexane=2:1

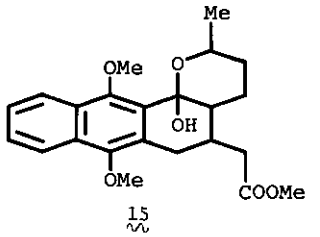
11. The 200 MHz ^1H nmr spectra($CDCl_3$,δ) of the compounds 8a,b, 9a,b, 10, and 11 are as follows. 8a ; 1.21(3H, d, J=6Hz, C(6')-CH_3), 1.3-2.2(5H, m, C(5')H_2-C(4')H_2-C(3')H_{eq}), 2.65(1H, dd, J=16,12Hz, C(4)H_{ax}'), 3.02(1H, td, J=12,4Hz, C(3')H_{ax}), 3.22(1H, dd, J=16,3Hz, C(4)H_{eq}'), 3.63(2H, d, J=6Hz, C(3)-CH_2Br), 3.87(3H, s, OCH_3), 4.02(3H, s, OCH_3), 4.30(2H, m, C(6')H and C(3)H), 7.5-8.2(4H, m, aromatic protons). 8b ; 1.27(3H, d, J=6Hz, C(6')-CH_3), 1.3-2.2(5H, m, C(5')H_2-C(4')H_2-C(3')H_{eq}), 2.50(1H, td, J=12,4Hz, C(3')H_{ax}), 3.15(2H, m, C(4)H_2), 3.65(2H, m, C(3)-CH_2Br), 3.90(3H, s, OCH_3), 4.05(3H, s, OCH_3), 4.25(1H, m, C(3)H), 4.40(1H, m, C(6')H), 7.5-8.2(4H, m, aromatic protons). 9a ; 1.24(3H, d, J=6Hz, C(6')-CH_3), 1.2-2.2(5H, m, C(5')H_2-C(4')H_2-C(3')H_{eq}), 2.70(1H, dd, J=16,12Hz, C(4)H_{ax}'), 2.80(2H, d, J=6Hz, C(3)-CH_2CN), 3.05(1H, td, J=12,4Hz, C(3')H_{ax}), 3.20(1H, dd, J=16,3Hz, C(4)H_{eq}'), 3.90(3H, s, OCH_3), 4.04(3H, s, OCH_3), 4.25(1H, m, C(6')H), 4.38(1H, m, C(3)H), 7.5-8.2(4H, m, aromatic protons). 9b ; 1.27

(3H, d, J=6Hz, C(6')-CH_3), 1.2-2.2(5H, m, C(5')H_2-C(4')H_2-C(3')H_{eq}), 2.55(1H, td, J=12,4Hz, C(3')H_{ax}), 2.72(1H, dd, J=16,6Hz, C(3)-CH_2CN), 2.92(1H, dd, J=16,8Hz, C(3)-CH_2CN), 3.02(1H, dd, J=16,7Hz, C(4)H_{ax}'), 3.20(1H, dd, J=16,5Hz, C(4)H_{eq}'), 3.90(3H, s, OCH_3), 4.05(3H, s, OCH_3), 4.40(2H, m, C(3)H and C(6')H), 7.5-8.2(2H, m, aromatic protons). 10 ; 1.20(3H, d, J=7Hz, C(6')-CH_3), 1.5-2.2(5H, m, C(5')H_2-C(4')H_2-C(3')H_{eq}), 3.00(1H, td, J=12,4Hz, C(3')H_{ax}), 2.70(1H, dd, J=16,12Hz, C(4)H_{ax}'), 2.80(2H, d, J=6Hz, CH_2COO), 3.15(1H, dd, J=16,3Hz, C(4)H_{eq}'), 3.88(3H, s, OCH_3), 4.00(1H, m, C(6')H), 4.02(3H, s, OCH_3), 4.60(1H, m, C(3)H), 7.5-8.2(4H, m, aromatic protons). 11 ; 1.17(3H, d, J=7Hz, C(6')-CH_3), 1.3-2.0(5H, m, C(5')H_2-C(4')H_2-C(3')H_{eq}), 2.38(1H, dd, J=20,11Hz, C(4)H_{ax}'), 2.65(1H, td, J=13,5Hz, C(3')H_{ax}), 2.75 (2H, d, J=6Hz, CH_2COO), 2.89(1H, dd, J=20,4Hz, C(4)H_{eq}'), 4.03(1H, m, C(6')H), 4.49(1H, m, C(3)H), 7.7-8.3(4H, m, aromatic protons).

12. An alternative route for the construction of spiroketal structure was also attempted without success. Lemieux-Johnson oxidation of the allyl derivative (7) gave the unstable keto-aldehyde, which was immediately reacted with methoxycarbonylmethylenetriphenylphosphorane to



yield the conjugated ester (13). Treatment of the ester 13 with methanolic hydrochloric acid failed to afford the expected spiroketal ester 14, presumably resulted in the formation of the alcohol 15 from its ir(neat, 3440cm^{-1}(OH)) and ms(m/e 400(M^+), 382(M^+-H_2O, base peak)) spectra.



13. solvent system ; benzene

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