followed by conversion to the Grignard reagent and reaction with propargyl bromide (procedure **B**) gave **9a**.

1,2-Heptadiene-*6,6-d*$_2$ (9b) was prepared analogously to **9a** starting with bromoethane-*1,1-d*$_2$.

3,4-Heptadiene (11).[32] Reaction of ethylmagnesium bromide with 3-bromo-1-pentyne (procedure B) gave **11**.

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Structure of Nogalamycin

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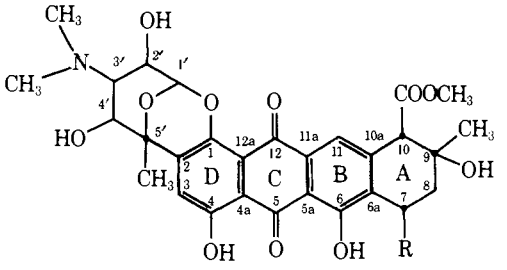
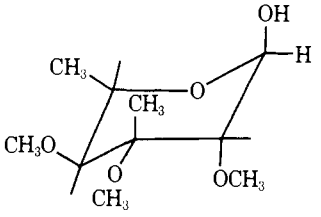
Abstract: A combination of chemical degradation and spectral data has established the structure of nogalamycin to be that shown in **1**.

Nogalamycin (**1**) is an antitumor antibiotic produced by the organism *Streptomyces nogalater* var. *nogalater* sp.n.[2] Its isolation, some of its reactions, and a partial provisional structure have been reported,[1] and the structure of nogalose (**2**), the neutral sugar moiety of nogalamycin, has been published.[3] The present communication proposes a complete structure for nogalamycin (**1**), except for absolute stereochemistry, and discusses the evidence supporting the proposed structure as well as some of the chemistry of nogalamycin. It also presents a complete assignment of the carbon atoms in the ^{13}C NMR spectrum of **1**.

Nogalamycin is an orange-red solid having a molecular formulaof $C_{39}H_{45}NO_{16}$ rather than the previously reported[1] $C_{39}H_{49}NO_{17}$. Analytical values derived from **1, 3a, 3b, 3c,** and **4** are in better agreement with the formula proposed earlier, but mass spectral data derived from **1** and its degradation products establish the revised molecular formula. The analytical values obtained probably resulted from retention of solvent. Nogalamycin dissolves readily in both acids and bases, being orange-red in the former and purple in the latter. A pK_a' value of 7.45 in 60% EtOH is due to the basic nitrogen present as a dimethylamino group, as will be shown subsequently. The groups accounting for base solubility are only weakly acidic and are phenolic hydroxyls, as will also be shown later. The ultraviolet spectrum[1] of **1** is quite similar to those of the anthracycline antibiotics daunomycin[4] and aklavin[5] and suggests that nogalamycin is a member of that class. Its visible spectrum has a maximum at 480 nm, which moves to 553 nm in base. The infrared spectrum indicates the presence of hydroxyl groups (3390, 3270 cm^{-1}), a ketonic or ester carbonyl (1740 cm^{-1}), and an α-hydroxyanthraquinone in that a strong band at 1620 cm^{-1} is typical of a carbonyl hydrogen bonded to a peri hydroxyl group with a weaker band at 1670 cm^{-1} arising from a nonbonded carbonyl in an anthraquinone.[6] Sodium hydrosulfite reduction of **1** converts it to a light yellow unstable solid, confirming the presence of a quinonoid system. Pyrolysis of **1** with zinc dust gave a product in very low yield whose visible spectrum was identical with that of tetracene,[7] indicating a linear tetracyclic system in nogalamycin. These data are all consistent with the view that **1** is a member of the anthracycline family and contains a hydroxylated anthraquinone system having one or more α-hydroxyl groups. The visible spectrum is characteristic of anthraquinones having two α-hydroxyl groups in that a single maximum is present,[8-11] and the max-



1, R = 2 (–H)
3a, R = OH
3b, R = OCH_3
3c, R = H



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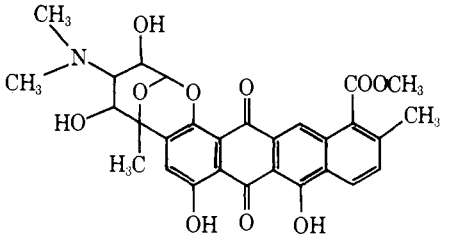

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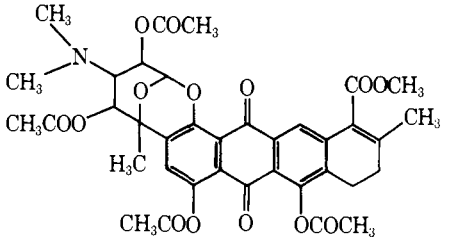

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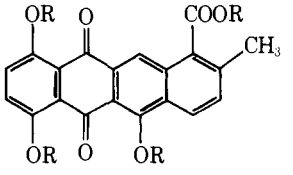
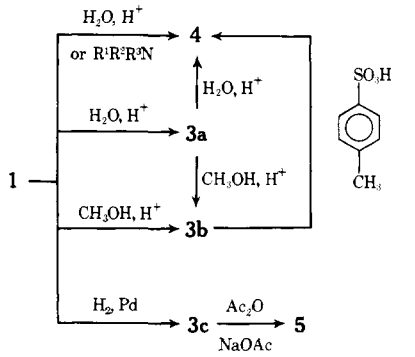


6, R = H
7, R = CH_3

imum at 480 nm shifting to 553 nm in base suggests a 1,4-dihydroxyanthraquinone structure.[8] However, one of the anthraquinone carbonyl groups does not seem to be hydrogen bonded, since it gives rise to a band at 1670 cm^{-1} in the infrared spectrum. Furthermore, the ^{13}C NMR spectrum has chemical shifts at δ 191.6 and 179.4 arising from the carbonyl groups of the anthraquinone system. The considerable divergence in chemical shifts shows that one (the downfield carbonyl) is hydrogen bonded, and the other is not.[12] Supporting this is the fact that degradation products of **1** in which both phenolic groups are alkylated or acylated (**5** and **7**), have almost identical chemical shifts for these two carbonyls. This is also the case for daunomycinone tetraacetate.[12] In view of these considerations, it is clear that **1** is a 1,8-dihydroxyanthraquinone whose visible spectrum deviates from the typical 1,8-dihydroxyanthraquinone pattern becuse of other oxygenation present. Furthermore, the anthraquinone nucleus has attached linearly a fourth ring (ring A) which is not aromatic.

Mild acid hydrolysis of nogalamycin formed three isolable products, although TLC clearly showed the presence of others.[1] One of the isolated materials was **2**. The other two were designated nogalarol (**3a**) and nogalarene (**4**). Analytical data from **3a** and a molecular weight determined by mass spectrometry showed that its molecular formula was $C_{29}H_{31}NO_{12}$. Its various properties[1] such as ultraviolet and visible spectra, infrared spectrum, pK_a', and NMR spectra were very similar to those of nogalamycin, taking into account the loss of **2**. This product must then be derived from **1** by a simple hydrolysis with addition of 1 mol of water to give **2** and **3a**. The third product (**4**) isolated has a molecular formula of $C_{29}H_{27}NO_{10}$, again established by analysis and mass spectral molecular weight determination, suggesting that it arises from **1** by loss of **2** and a molecule of water by elimination, or from **3a** by elimination of two molecules of water. The infrared spectrum of **4** indicates retention of the 1,8-dihydroxyanthraquinone system and another carbonyl group, but the electronic spectra are consistent with more unsaturation than is present in **3a**. Methanolysis of **1** in methanolic hydrogen chloride gave only one isolable colored compound, 7-*O*-methylnogalarol (**3b**).[1] Its molecular formula of $C_{30}H_{33}NO_{12}$ suggested that it was a methyl ether of **3a**, as did its close resemblance in electronic, vibrational, and NMR spectra. Catalytic reduction of **1** under low pressure formed 7-deoxynogalarol (**3c**) and **2**. The molecular formula of **3c** as determined by analysis and molecular weight derived from the mass spectrum is $C_{29}H_{31}NO_{11}$. Again its electronic and vibrational spectra are very similar to those of **1**, **3a**, and **3b**, suggesting that the tetracyclic hydroxyanthraquinone system remains intact. In spite of numerous attempts to prepare acetates of nogalamycin and its degradation products, only one pure well-characterized acetate was isolated. Reaction of 7-deoxynogalarol with acetic anhydride at elevated temperature in the presence of sodium acetate gave a crystalline compound (**5**) which had the molecular formula $C_{37}H_{37}NO_{14}$. The molecular formula, in agreement with the NMR spectra, demonstrated that a tetraacetate of **3c** minus a molecule of water was formed. Compound **4** could also be obtained from nogalamycin by base elimination with organic bases and from the action of acid on **3a** and **3b**. Nogalarol formed **3b** under the same conditions as did **1**. These conversions are indicated in Scheme I.

Scheme I



In spite of very extensive attempts to remove a possible aminosugar from the tetracyclic nucleus of **1**, **3a**, **3b**, **3c**, and **4** with isolation of the sugar and the second step aglycone, such a result was never achieved. However, treatment of **1**, **3a**, **3b**, or **4** with strong base at elevated temperatures resulted in isolation of the complete aglycone in its bisanhydro form (**6**). In addition, dimethylamine, acetic acid, and formic acid were isolated. The product **6** was a strongly colored compound which

Table I. ^{13}C NMR Chemical Shifts[a]

Position	1 $CDCl_3$	3a DMF-d_7	3b DMF-d_7	3c DMF-d_7	4 DMF-d_7	5 DMF-d_7	6 D_2O-NaOD	7 $CDCl_3$
5	191.6	192.3	191.9	191.2	191.9	183.6	188.4	183.31
12	179.4	179.8	179.5	179.3	179.6	182.8	181.2	183.19
Ester C=O	171.9	171.9	171.8	171.7	168.9		177.3	168.9
6	162.2	161.6	161.8	159.4	162.5	147.5	169.5	156.7
4	155.8	155.7	155.5	155.2	155.8	149.6	159.4	153.4
1	148.2	148.0	147.9	147.7	147.8	146.8	156.2	152.8
10a	143.9	144.0	144.2	143.4	140.2	142.7	142.9	137.4
2	138.1	138.4	138.2	137.6	137.8	138.6	137.1	120.5
11a	133.5	134.1	134.3	132.2	126.0	124.0	132.0	126.5
6a	130.9	131.3	130.8	131.2	132.9	131.8		133.1
3	126.0	125.2	125.2	125.2	124.7	127.3	127.6	120.1
11	119.0	119.8	119.4	120.1	118.0	119.6	112.8	118.6
4a	116.1	117.2	116.9	116.3	116.8	120.6		
12a	114.1	115.4	115.0	114.6	115.8		114.1	123.6
5a	114.0	114.6	114.5	112.5	109.3		119.8	121.1
7	69.7	63.0	72.5	21.4	131.6		137.1	131.3
8	40.9		36.2		131.2			125.6
9	69.8	69.7	69.2	68.7	134.4	134.4	134.3	132.3
10	57.1	56.9	58.9	57.2	133.5	130.2	131.2	129.2
1′	97.5	97.8	97.8	97.6	97.5	94.1		
2′	72.9	73.5	73.5	73.1	73.5	72.6		
3′	65.8	66.8	66.6	66.4	66.7	62.7		
4′	71.1	70.8	70.8	70.8	70.7	70.9		
5′	75.2	76.0	76.0	76.6	76.2	74.6		
Ester CH_3O	52.4	52.1	52.1	51.9	53.1	52.3		52.6
$(CH_3)_2N$	41.4	41.4	41.4	41.3	41.8	40.9		
C-9 CH_3	29.7	29.9	30.1	28.5	20.5	21.8	22.6	20.3
C-5′ CH_3	24.4	24.2	24.2	23.8	24.2	23.3		

[a] In parts per million downfield from Me_4Si.

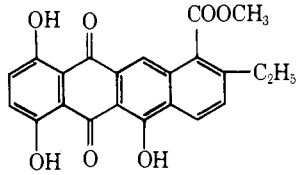
was totally insoluble in most organic solvents, but did dissolve to a limited extent in DMF and was quite soluble in strong base. The only purification achieved was by solution in base and precipitation. A good analysis was never obtained as the material always retained ash. A high resolution mass spectrum established that the molecular formula was $C_{20}H_{12}O_7$. A much more tractable compound (**7**) was prepared by exhaustive methylation of **6** using the Purdie method. The product **7** had a molecular formula of $C_{24}H_{20}O_7$ also shown by high resolution mass spectrometry. Its infrared spectrum showed carbonyl bands at 1725 and 1660 cm^{-1}, indicating the absence of hydrogen-bonded anthraquinone carbonyl. The presence of four methoxyl groups (singlets at δ 3.95, 3.96, 4.07, and 4.15 in the ^1H NMR spectrum) showed that three phenolic hydroxyl groups in **6** had been methylated and probably a carboxyl group in view of the 1725 cm^{-1} band in the infrared spectrum.

A study of the NMR spectra of **1, 3a, 3b, 3c,** and **4** established the presence of a number of groups in these compounds. As nogalamycin contains nogalose, and the structure of **2** is known, the NMR spectra of the degradation products were more valuable than was that of **1.** In the ^1H NMR spectra of these compounds the presence of a chemical shift as a singlet representing 6 H at δ 2.39–2.64 was consistent with the presence of a dimethylamino group. Base hydrolysis of nogalamycin gave a volatile base, which was identified as dimethylamine as its *p*-hydroxyazobenzene-*p*′-sulfonate. In addition to the two CH_3C groups in **2,** two other such groups were present, as shown by singlets at δ 1.51 and 1.72 in **3a** with equivalent chemical shifts in the spectra of the other compounds. A methoxyl group was present (δ 3.66 and 3.68 in **3a** and **3b,** respectively) which combined with its absence in **6** and a carbonyl giving rise to an infrared band at ca. 1730^{-1} suggested a carbomethoxy group. A chemical shift of δ 171.7–171.9 in the ^{13}C NMR spectra of **1, 3a, 3b,** and **3c** further supports the presence of such a group.[13] Two protons appearing in the spectrum of **1** as singlets at δ 6.97 and 7.08 must arise from aromatic protons which are para to each other or in different rings. This establishes that the anthraquinone system has six substituents. As has already been shown, two of these are a fourth ring and two are phenolic hydroxyl groups. The NMR spectra of **5** show the presence of four acetyl groups, and its infrared spectrum indicates no hydroxyl groups are present. Two acetyl groups are attached to oxygen atoms on carbon also bearing protons, as shown by the downfield shift of protons at the positions designated 2′ and 4′ (3.66 and 4.00 to 5.23 and 5.42) on going from **3c** to **5.** The other two acetyl groups would then be on the former phenolic hydroxyl group. Since the ^{13}C NMR spectrum of **5** shows a substantial upfield shift for one anthraquinone carbonyl and a slight downfield shift for the other, there can be only one hydrogen-bonded carbonyl in **1** and its degradation products, and both phenolic groups must be α to the same carbonyl as already argued. The ^1H NMR spectrum of **3a** shows a doublet at δ 5.87 coupled with a proton with a chemical shift of δ 4.16. The latter is coupled with a proton at δ 2.86, which in turn is coupled with a proton appearing at δ 3.66. These signals are ones to be expected arising from an aminosugar. The ^{13}C NMR spectra of **3a, 3b, 3c,** and **4** have one resonance in the neighborhood of δ 97.5, which is that expected for an anomeric carbon of a sugar. In addition, a group of four signals at δ 66–76 arise from carbon atoms substituted with oxygen or nitrogen as in an aminosugar.

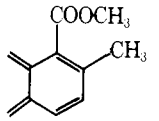
The ^{13}C NMR spectra of **1, 3a, 3b, 3c,** and **4** are completely assigned (Table I). This was done on the basis of comparisons of the different spectra with each other, off-resonance decoupling, long-range coupling constants, theoretical considerations, and comparison with models. It is felt that assignments in rings A, B, C, and D are reasonably certain, although C-7 in nogalamycin is somewhat doubtful. The aminosugar and C-9 CH_3 assignments also are clear cut, but there is some

doubt about some assignments in nogalose. These assignments are consistent with the recently reported results for daunomycinone tetraacetate.[12c]

The molecular formula of **4**, as previously mentioned, is consistent with the loss of two molecules of water from **3a**, which could arise from aromatization of ring A if two hydroxyl groups were present in that ring. The ready conversion of **1** to **4** with base indicates again such hydroxyl groups in **3a**, but also suggests that they are substituted β and δ to a carbonyl group. In the ^{1}H NMR spectrum of **4** the resonance of one CH_3C group has shifted downfield to δ 2.56. Such a shift must result from aromatization of the ring substituted by the methyl group. As NMR spectra indicate retention of that portion of the molecule attributed to the aminosugar, aromatization must have occurred in ring A. Consistent with this is the appearance of two doublets in the ^{1}H NMR spectrum in the aromatic region representing two new aromatic protons with coupling constants indicating they are ortho to each other (δ 7.12 and 8.21, J = 8.5 Hz). Compound **4** is oxidized by permanganate to form benzene-1,2,3,4-tetracarboxylic acid, isolated as its tetramethy ester (**8**), which must arise from ring A as the other rings are oxygenated in such a fashion that these conditions would destroy them. It has already been shown that oxidation of **9** with alkaline permanganate gave **8**.[14] By analogy it ap-

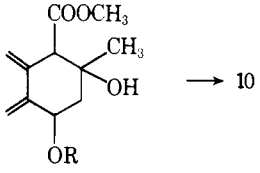


9



10

pears probable that ring A of **4** would be as shown in **10**. ^{1}H NMR data as well as the data cited above establish that the system shown in **11** is present in **3a** and **3b** and is converted to **10**. A doublet of doublets centered at δ 5.21 in **3a** and at 4.71 in **3b** (DMF-d_7) is part of an ABX system in which the other



11, R = H or CH_3

protons also give rise to doublets of doublets centered at δ 1.93 and 2.49 in **3a** (DMF-d_6), J_{AB} = 13.5, J_{AX} = 6.25, and J_{BX} = 6.75 Hz (all in **3a**). Such a pattern is consistent with the expression **11**. A singlet at δ 3.86 in **3a** and 3.94 in **3b** is due to a proton α to a carbonyl group and with no adjacent proton. These data clearly establish the ring A structure in **1** and its degradation products. Such a pattern is very common in the anthraquinone antibiotics, as is the formation of bisanhydroaglycones similar to **4**. The loss of **2** by reduction to form **3c** establishes the attachment of nogalose to the oxygen atom at the C-7 position of **1** and **3a**. This would also be consistent with the conversion of **1** to **4** by base treatment.

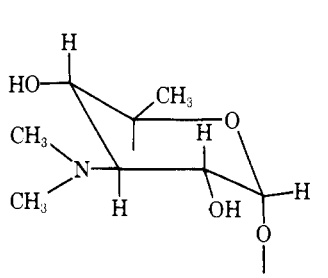
As it seemed that nogalamycin was an anthracycline antibiotic having one nitrogen atom, it was probable that it contained an aminosugar. Vigorous attempts to isolate such a sugar by acid hydrolysis failed. However, as has already been mentioned, there is considerable NMR spectral evidence for the presence of an aminosugar in **1, 3a, 3c,** and **4**. A series of four carbon atoms (1′, 2′, 3′, and 4′ in Table II) has protons attached which give rise to signals in the ^{1}H NMR spectrum, whose chemical shifts and coupling constants show the following. The H-1′ and H-2′ protons are coupled and are either

Table II. ^{1}H NMR Spectra

Position	3a Acetone-d_6	3b Acetone-d_6	3c $CDCl_3$	4 DMF-d_7
	A. Chemical Shifts[a]			
1′	5.87	5.89	5.89	5.72
2′	4.16	4.16	4.0	4.00
3′	2.86	2.82	2.94	2.5–2.75
4′	3.66	3.57	3.47	3.61
	B. Coupling Constants[b]			
$J_{1',2'}$	3.3	3.2		3.4
$J_{2',3'}$	10.5	10.5		10.11
$J_{3',4'}$	10.5	10.5		10.7

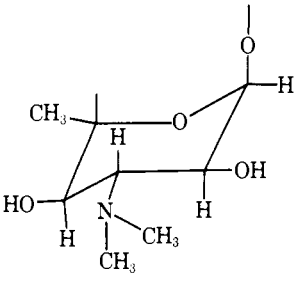
[a] In parts per million downfield from Me_4Si. [b] In hertz.

ee or ea and H-2′ is coupled with H-3′ in a diaxial arrangement, as are the latter proton and H-4′. The multiplicity of the signals and the coupling constants establish the proton assignments. In **5**, in which the hydroxyl groups are completely acetylated, there is a pronounced downfield shift (ca. 1.5) of the protons at C-2′ and C-4′, indicating hydroxyl substitution at these positions in nogalamycin. The chemical shift of H-1′ is that of an anomeric proton and that of H-3′ is consistent with substitution of $(CH_3)_2N$ at the same carbon atom. A methyl group has a chemical shift of 1.68 in **1** and appears as a singlet. The ^{13}C NMR spectra of this series of compounds is indicative of a five-carbon chain (C-1′ to C-5′) in a sugar moiety. There is no hydrogen substituted on C-5′, since there is no indication of a proton in the ^{1}H NMR spectra on the carbon beyond the C-4′ nor on the one to which a methyl roup is attached, as mentioned above. These NMR data establish the relative configurations of the first four carbon atoms of the aminosugar moiety, but they do not give any information as to the configuration of C-5′. The lack of a proton at C-5′ suggests that this carbon is attached to the anthraquinone ring. There are 12 oxygen atoms in nogalarol (**3a**), with four of these related to ring A, two as phenolic hydroxyls, and two as anthraquinone carbonyls. This leaves only four oxygen atoms to be associated with the aminosugar, and as C-1′ is a normal anomeric carbon atom and two hydroxyls are present, no oxygen remains to link C-5′ with the anthraquinone nucleus. Consequently, this must be a carbon–carbon bond. In such case and as NMR data show that C-1′ has an axial oxygen, geometrical considerations necessitate that C-5′ has an axial bond to the aromatic ring at a position ortho to the linkage with C-1′. These data limit the sugar stereochemistry to that of α-D-3,6-dideoxyglucose (**12**) or its α-L-isomer (**13**), but does not distinguish between them. This portion of the molecule would provide two substituents on the anthraquinone nucleus and thus account for all of its substituents.



α-D

12



α-L

13

The previously mentioned vigorous base treatment of compounds containing the aminosugar results in its elimination with formation of **6**, which can then be converted to **7**. In view

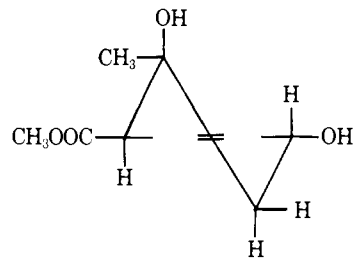
of the foregoing discussion concerning the tetracyclic nucleus of **1, 3a, 3b, 3c,** and **4,** the structures of **6** and **7** would be as indicated except for the positions of the hydroxyl and methoxyl groups, which have not yet been established. It is known that ring A is converted by base to the ring shown in **10.** Since there is no methoxyl in **6** (^{1}H NMR spectrum), the carbomethoxy group must have been converted to a carboxyl group, whose carbon in the ^{13}C NMR spectrum of **6** resonates at δ 177.3. Three phenolic groups are present, as four methoxyl groups are shown by NMR spectra to be present in **7.** That **6** and **7** are as shown is suggested by the electronic spectra of **6** in sulfuric acid. Maxima appear at 275 (ϵ 16 745), 575 (ϵ 7920), and 625 nm (ϵ 10 190) which are very similar to those of n_1-pyrromycinone and its corresponding acid,[15] which was reported to have structure **6.** The electronic spectra of **7** are strikingly similar to those of the triacetates of bisanhydro-ϵ-pyrromycinone[7] and n_1-pyrromycinones,[15] again indicating the structure **7.** The hydrogen-bonded carbonyl group formerly present has disappeared in **7,** and the chemical shifts of the anthraquinone carbonyl carbon atoms in the ^{13}C NMR spectrum are virtually identical, confirming again that **1** and its closest degradation products are 1,8-dihydroxyanthraquinones. The ^{1}H NMR spectrum of **7** shows five aromatic protons. Four of these were present in **4,** which also has ring A aromatized, but one is new The new aromatic proton must necessarily be in ring D, but cannot be para to the one already present. This follows from the fact that no new proton can appear in ring A because its structure is known to be one having a substituent at one possible aromatic position and because the phenolic hydroxyls are still present as methoxyls and preclude para hydrogens in rings B and D. The new proton and the other two in rings B and D appear as singlets in the 100-MHz NMR spectrum. The new proton could form one of an ortho pair which are very symmetrical, or it could be meta to a previously present aromatic proton. A 220-MHz spectrum of **7** showed that, in addition to the two ortho protons present in ring A, there was a second ortho pair present having J = 9.2 Hz, thus establishing that C-2 and C-3 are unsubstituted in **6** and **7.** The ^{13}C NMR spectrum of **7** showed virtually identical chemical shifts for the pairs C-1 and C-4 and C-2 and C-3, giving additional support for structure **7** and by inference **6.**

The aminosugar cannot be attached to ring B in **1** and its degradation products, as the required two positions are not available, so it must be attached to ring D. Oxygen atoms are present in **6** and **7** in ring D para to each other, and the aminosugar must have been attached through one of these, as only one is a hydroxyl group in **1,** and also to the adjacent carbon by a carbon–carbon bond which is broken by the base treatment and replaced by an aromatic proton in **6** and **7,** thus accounting for the new aromatic proton which appears. A very similar *m*-dioxane ring arrangement also unstable to alkali is present in the mold metabolite averufin.[16] It may be speculated that an initial proton removal occurs at C-1′ or from a hydroxyl group followed by several steps, with the last being a carbon–carbon bond cleavage as a result of a retroaldol reaction from an intermediate having a carbonyl at C-1 and a hydroxy group at C-5′.

On the basis of evidence presented thus far, the aminosugar attachment can be through either C-1 and C-2 or C-3 and C-4; but, in the latter case, a phenolic hydroxyl would be present at C-11 rather than C-6. The determination of the position of this hydroxyl group was done largely on the basis of mass spectra, with supplementary evidence from ^{1}H NMR spectra. Reed and Reid[17] have found that the mass spectra of ϵ-rhodomycinone, ϵ-isorhodomycinone, and δ-rhodomycinone, which have hydroxyl groups at C-7, C-9, and C-11 and a carbomethoxy group at C-10, have base peaks resulting from loss of two molecules of water and lactone formation at C-11 with loss of methanol (M − 68). Brockmann and co-workers[18] suggest that this fragment can be used as diagnostic for C-11 hydroxylation in the anthracyclines having carbomethoxy at C-10. Furthermore, it has been shown[18,19] that ϵ-pyrromycinone, aklavinone, and ϵ_1-pyrromycinone, which lack the C-11 hydroxyl but have hydroxyl at C-7 and C-9 and carbomethoxy at C-10, give relatively weak ions arising from loss of two water molecules and one methanol. Since nogalarol (**3a**) gives no ion which could result from aromatization of ring A with lactone formation, and nogalarene (**4**) gives no fragment formed by loss of methanol, it is evident that C-11 must have no hydroxyl substituent and that a hydroxyl is present at C-6. The fact that one aromatic proton in **5** is at δ 7.90 also substantiates such an interpretation. In nogalamycin, **3a, 3b,** and **3c,** the aromatic protons are all at about δ 7.20 in all solvents. Since a double bond has been introduced at C-9 and C-10 in **5,** it is probable that the neighboring C-11 proton has been affected so as to give a downfield shift in the ^{1}H NMR spectrum. The same phenomenon occurs when ring A is aromatized in **4, 6,** and **7.** Since a hydroxyl group is a substituent at C-6, then the aminosugar must be at C-1 and C-2.

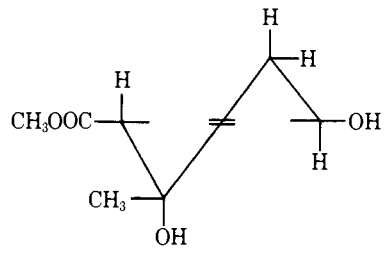
The stereochemistry at C-7, C-9, and C-10 of **1** and its degradation products has not been established. In the cases of 13-anthracyclinones, whose stereochemistry at these positions has been established, ten are 7*S* and three are 7*R*, while all are 9*R* and 10*R*. In one case it has been proposed that the stereochemistry is either 7*S*,9*R*,10*S* or 7*R*,9*S*,10*R*. Thus, the most probable configuration for **1, 3a,** and **3b** is 7*S*,9*R*,10*R*. However, there is some chemical evidence to suggest that this is not the case. Nogalamycin (**1**) is readily converted to **4** by treatment with organic bases under relatively mild conditions (reflux in CH_3OH). Such a ready elimination would be consistent with a trans diaxial C-9 OH–C-10 H arrangement and also for an axial substituent at C-7. Bowie and Johnson[20] have suggested that easy hydrolysis of the carbomethoxy group in θ-rhodomycinone indicates an equatorial conformation. An axial carbomethoxy group having two ortho substituents would be expected to be quite resistant to hydrolysis. The ester group of **1** is hydrolyzed by 0.5 N NaOH after boiling for 0.5 h. This would indicate an equatorial carbomethoxy group and an axial H at C-10, consistent with ready elimination and aromatization. In such a case, the configuration would, assuming diaxial C-9 OH–C-10 H, necessarily be 9*S*,10*R* or 9*R*,10*S* and not the normal 9*R*,10*R* and, if ease of elimination is indicative of a nearly axial hydroxyl at C-7, the total configuration would be 7*R*,9*S*,10*R* or 7*S*,9*R*,10*S*. However, evidence from ^{1}H NMR data suggests a different configuration at C-7. Coupling constants for the protons at C-7 and C-8 have been reported for a number of anthracyclinones.[21-23] In cases in which C-7 is *S* and the hydrogen at that position is equatorial, it was reported that $J_{7,8a} + J_{7,8b}$ = 6.0–7.0 Hz, while the reverse configuration gave $J_{7,8a} + J_{7,8b}$ = 16 and 16.5 Hz. The ^{1}H NMR spectrum of nogalamycin (**1**) was such that no determination of the coupling constants of protons at C-7 and C-8 could be made. Compound **3a,** which would correspond to an anthracyclinone, gave a spectrum having $J_{7,8a} + J_{7,8b}$ = 13 Hz, suggesting an axial hydrogen atom at C-7 and an equatorial hydroxyl group. The 7-O-methyl compound **3b** gives a value of 8.9 Hz and, therefore, would probably have a quasiaxial OCH_3 at C-7. Failure to obtain an acetonide[23,24] of **3a,** as was reported for other anthracyclinones, implies but does not establish a trans C-7 and C-9 hydroxyl arrangement, and thus an axial hydroxyl at C-9. The ^{1}H NMR and acetonide data would be at variance with the indications of the elimination reaction and would be more consistent with a 7*R*,9*R*,10*S* or 7*S*,9*S*,10*R* configuration, whose conformation is such that the carbomethoxy group is equatorial at least for **3a** and presumably for nogalamycin. These configurations and conformations for ring A of **3a** are shown in **14** and **15.**

Although the stereochemistry of C-2 through C-5 of noga-



7*R*,9*R*,10*S*

14



7*S*,9*S*,10*R*

15

lose has been established by x-ray crystallography to be that shown in **2**,[3] this was not the case for C-1. Since the proton on C-2 of **2** is equatorial, the assignment of the configuration at C-1 by ^{1}H NMR data is precluded. However, analogy with other anthracyclines, in which sugars in positions analogous to that of nogalose are α at C-1, suggests an α linkage. The ^{13}C NMR spectra of **1** and **2** also point to an α attachment of nogalose. The chemical shift of C-1 of nogalose, while attached as in the intact antibiotic, is at δ 100.9 (Table III), which would be more consistent with values reported[13] for C-1 of methyl α-glycosides than for the β isomers. On the basis of the ^{13}C NMR spectrum of crude **2** before extensive purification it appears that **2** is a mixture of approximately equal amounts of α and β forms. After purification there is a mixture of a major form and a minor form in a ratio of 5:1. The chemical shifts of the carbon atoms, except for C-1, of the major form are almost identical with those found for the carbon atoms of nogalose in nogalamycin (Table III). The chemical shift of the C-1 of the major form is upfield from that of the C-1 of the minor form, indicating that the major form has an axial hydroxyl at C-1. In α-L-rhamnose, which has the stereochemistry of **2**, at least at C-2 to C-5, C-5 has a chemical shift of δ 69.1, while in β-L-rhamnose it is at δ 72.8.[13] The chemical shift assigned to C-5 in the major form of **2** is δ 66.9, while in the minor form it is at δ 70.6, again suggesting that the major form of **2** is α. As the major form has the stereochemistry and conformation that it has in **1**, C-1 of nogalose also has the α configuration in **1**.

The accumulation of evidence discussed above points with considerable certainty to a structure for nogalamycin as depicted in expression **1**, although the complete absolute stereochemistry has not been established.

Experimental Section

Nogalamycin (1). The isolation and many of the properties of this compound have been described previously,[1] mass spectrum *m/e* 787.

Nogalarol (3a) and Nogalarene (4) from Nogalamycin (1) and Acid. A solution of 25 g of **1** in 500 ml of 0.4 N HCl was boiled under reflux for 0.5 h. The cooled reaction mixture was extracted with four 250-ml portions of $CHCl_3$. The aqueous solution was adjusted to pH 7.0 with solid $NaHCO_3$, and the mixture was refrigerated overnight. The precipitate which formed was collected, and the filtrate was allowed to stand at room temperature for 1 day and filtered again. The two fractions were combined and air dried, weight 17.2 g. Of this yield, 9 g was subjected to counter-current distribution in a 200-tube, 50-ml per phase machine using benzene–$CHCl_3$–CH_3OH–H_2O (25:25:30:20) as the solvent system. A total of 500 transfers were run, collecting the upper phases as they came out of the machine. Fractions 14–64 were combined (pool 1), fractions 65–120 were combined (pool 2), and fractions 121–233 were combined (pool 3). Evaporation of pool 1 to dryness under reduced pressure gave 4.3 g of a mixture of nogalarol and nogalarene, R_f's 0.16 and 0.37 in TLC in $CHCl_3$–MeOH–H_2O (78:20:2). Evaporation of pool 2 to dryness under reduced pressure gave 0.89 g of material which was mostly nogalarene. Pool 3 was concentrated under reduced pressure to a volume of about 3 l. The solid precipitate was removed and air dried to give 3.24 g of nogalarol. Further evaporation of the filtrate gave another 0.96 g of nogalarene.

Table III. ^{13}C NMR Spectra of Nogalose[a]

Position	In nogalamycin	In nogalose	
		Major form	Minor form
C-1	100.9	91.7	93.2
C-2	81.5	81.4	76.3
C-3	78.2	78.2	84.4
C-4	84.6	84.6	82.7
C-5	67.7	66.9	70.6
CH_3 C-3	15.1	15.4	14.6
CH_3 C-5	18.3	18.2	18.5
CH_3O	61.4	61.2	62.0
	59.2	58.9	58.9
	48.9	48.8	49.5

[a] Chemical shifts in parts per million downfield from Me_4Si.

A small sample of **3a** was recrystallized twice from CH_3OH: mp ca. 220 °C dec; pK_a' (60% EtOH) 7.15; equiv wt 558; IR (Nujol) 3340, 1725, 1655, 1615, 1565, 1285, 1250, 1215, 1100, 1050, and 1000 cm^{-1}; mass spectrum *m/e* 585 (no ion at 517).

Anal. Calcd for $C_{29}H_{31}NO_{12}$: C, 59.49; H, 5.34; N, 2.39; O, 32.79. Found: C, 57.66; H, 5.42; N, 2.34; O, 32.00.

4 was dissolved in hot CH_3OH and precipitated with Skellysolve B, then recrystallized from benzene: mp >230 °C dec; pK_a' (60% EtOH) 7.25; equiv wt 538.5; IR (Nujol) 3430, 3000, 1725, 1660, 1615, 1055, and 1005 cm^{-1}; mass spectrum *m/e* 549 (no ion at 517).

Anal. Calcd for $C_{29}H_{27}NO_{10}$: C, 63.39; H, 4.95; N, 2.55. Found: C, 62.66; H, 5.36; N, 2.69.

Nogalarene (4). a. From Nogalamycin (1) and Base. A mixture of 1.31 g of **1**, 0.2 ml of $(C_2H_5)_3N$, and 15 ml of anhydrous CH_3OH was boiled under reflux overnight. The reaction mixture was cooled in an ice bath and the precipitate was collected by centrifugation, yield 0.86 g. The product was dissolved in DMF and precipitated with Skellysolve B. The precipitate was recrystallized from benzene to give 0.24 g, mp >240 °C dec. This material was homogeneous by TLC ($CHCl_3$–MeOH–H_2O; 78:20:2) and had the same R_f as an authentic sample of **4**, and its ^{1}H and ^{13}C NMR spectra were the same as those of **4**.

4 was also prepared similarly using benzylamine in 1-propanol and refluxing for 4.5 h.

b. From 7-*O*-Methylnogalarol (3b) and Acid. A solution of 0.61 g of **3b** in 250 ml of toluene was boiled under reflux using a Dean–Starke water trap until the water was removed. A solution of 248 mg of anhydrous *p*-TosOH in 5 ml of toluene was added, and the mixture was boiled under reflux for 3 h. The cooled mixture was filtered and the product was dissolved in 200 ml of water, which was then passed over 20 ml of IR-45 (OH^-). The combined effluent and washings were freeze dried. The residue was dissolved in CH_3OH and insoluble material was removed by filtration. The filtrate was evaporated to dryness under reduced pressure, and the residue was purified by solution in $CHCl_3$ and precipitation with Skellysolve B, yield 250 mg. The product was identified as nogalarene by TLC in the above solvent system, UV, and ^{1}H NMR.

7-*O*-Methylnogalarol (3b). a. From Nogalamycin (1). A solution of 12.5 g of **1** in 625 ml of anhydrous CH_3OH 2 N in HCl was boiled under reflux for 2 h. The solution was concentrated under reduced pressure to about 400 ml. After addition of 1 l. of H_2O, the mixture was extracted with four 125-ml portions of $CHCl_3$, which were worked up to give methyl nogaloside. The aqueous solution was adjusted to

pH 7.2 with 50% NaOH and extracted with four 125-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with 100 ml of H_2O. Evaporation of the $CHCl_3$ solution under reduced pressure gave 4.7 g of a dark red residue. The product was subjected to countercurrent distribution in a 200-tube 50-ml per phase machine using benzene-$CHCl_3$-CH_3OH-H_2O (25:25:37.5:12.5) and running 200 transfers. The material from tubes 35–70 was combined, diluted with water, and the lower phase was removed. The upper phase was extracted with two 100-ml portions of $CHCl_3$, and these were added to the lower phase. Evaporation under reduced pressure gave 1.9 g. This was dissolved in 2.5 ml of $CHCl_3$ and 50 ml of CH_3OH was added. Refrigeration gave 0.69 g: mp 198–201 °C; R_f 0.58 (TLC, $CHCl_3$-MeOH-H_2O; 78:20:2); $[\alpha]_D$ +584° (*c* 0.059, $CHCl_3$); pK_a' (60% EtOH) 6.8; equiv wt 612; IR (Nujol) 3440, 1735, 1725, 1660, 1620, 1565, 1300, 1280, 1250, 1220, 1145, 1115, 1090, 1050, 1015, 1000, and 775 cm^{-1}; mass spectrum *m/e* 599.

Anal. Calcd for $C_{30}H_{33}NO_{12}$: C, 60.09; H, 5.55; N, 2.34. Found: C, 58.54; H, 5.48; N, 2.09.

b. From Nogalarol (3a). 3a (590 mg) was dissolved in 30 ml of absolute CH_3OH 2 N in HCl and the solution was allowed to stand at room temperature for 4 days, after which it was diluted with an equal volume of H_2O and evaporated under reduced pressure until the CH_3OH was removed. The residue was adjusted to pH 7.2 with 40% NaOH. The aqueous mixture was extracted with two 25-ml portions of $CHCl_3$ which were combined and evaporated under reduced pressure to give 550 mg of residue. Comparison by TLC using the above solvent system showed that this was a mixture of **3a** and **3b.**

7-Deoxynogalarol (3c). A mixture of 2 g of **1**, 2 g of Pd-C (10%), and 100 ml of EtOH was shaken under H_2 at an initial pressure of 45 psi for 4 days. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was partitioned between 60 ml of 0.1 N HCl and 60 ml of $CHCl_3$. The aqueous layer was washed with two 60-ml portions of $CHCl_3$, which were added to the original $CHCl_3$ layer. Evaporation under reduced pressure gave 360 mg of nogalose, which was purified as described previously and identified by its physical properties. The acidic solution was adjusted to pH 6.8 with 1 N NaOH and extracted with four 30-ml portions of $CHCl_3$. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give 405 mg of residue. Recrystallization from CH_3OH gave 156 mg: mp 227–231 °C dec; R_f 0.57 (TLC, $CHCl_3$-MeOH-H_2O; 78:20:2); IR (Nujol) 3350, 1720, 1655, 1625, 1560, 1375, 1300, 1285, 1260, 1250, 1165, 1110, 1055, 935, 885, 845, and 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.0 (br s, 2 H, phenolic OH); mass spectrum *m/e* 569.

Anal. Calcd for $C_{29}H_{31}NO_{11}$: C, 61.10; H, 5.48; N, 2.46. Found: C, 59.08; H, 5.65; N, 2.40.

4,6,2′,4′-Tetra-*O*-acetyl-7-deoxy-9,10-anhydronogalarol (5). A mixture of 1.01 g of **3c**, 206 mg of anhydrous $NaOCOCH_3$, and 24 ml of $(CH_3CO)_2O$ was boiled under reflux for 2 h. The mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 40 ml of $CHCl_3$, and the solution was washed with four 5-ml portions of water, dried ($MgSO_4$), and concentrated to dryness under reduced pressure. The residue was again dissolved in $CHCl_3$, and the solution was decolorized with charcoal and again evaporated to dryness under reduced pressure. The residue was recrystallized from $CHCl_3$-Skellysolve B to give three fractions, weight 0.85 g. The middle fraction (372 mg) was recrystallized in the same way, yield 300 mg: mp 153–155 °C; R_f 0.65 (TLC, cyclohexane-EtOAc-95% EtOH; 5:3:2); IR (Nujol) 1775, 1750, 1725, 1675, 1595, 1560, 1260, 1220, 1190, 1115, 1045, 950, and 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18, 2.22, 2.43, 2.46 (singlets, 4 CH_3COO); mass spectrum *m/e* 719.

Anal. ($C_{37}H_{37}NO_{14}$) C, H, N.

Bisanhydronogalamycinonecarboxylic Acid (6). 1 (50 g) was dissolved in 1 l. of 1 N HCl, and the solution was boiled under reflux for 40 min. The cooled reaction mixture was extracted with four 250-ml portions of $CHCl_3$. The aqueous solution was made about 2 N in NaOH by addition of 120 g of solid NaOH. The solution was steam-distilled until no more volatile base was being removed. The residue was adjusted to pH 3 with 18 N H_2SO_4, and the precipitate was collected by centrifugation. It was washed four times with 0.01 N HCl also by centrifugation. The insoluble material was dried under reduced pressure at 60 °C, yield 42.7 g. This material was dissolved in 4.27 l. of 0.1 N NaOH and the solution was filtered. The filtrate was adjusted to about pH 2.5 with concentrated HCl and the precipitate was collected by centrifugation. It was washed four times by suspension in 0.01 N HCl and centrifugation. The final precipitate was dried as above, yielding 21.2 g (92%) of very dark red amorphous material decomposing slowly above 300 °C (lit.[15] 328–330 °C): IR (Nujol, these were all broad bands and not well-resolved) 3310, 1690, 1590, 1235, and 1210 cm^{-1}; UV (0.1 N NaOH) λ_{max} 262 (ϵ 25 600), 540 nm (ϵ 8660); mass spectrum *m/e* 364.0603 (calcd for $C_{20}H_{12}O_7$, 364.0583).

Anal. Calcd for $C_{20}H_{12}O_7$: C, 65.93; H, 3.32; O, 30.58. Found: C, 63.31; H, 3.57; O, 32.81; ash, 2.49.

Although this was the procedure normally used to prepare **6**, it could also be prepared from **1, 3a, 3b,** and **4** using the above procedure without prior acid hydrolysis.

1,4,6-Tri-*O*-methylbisanhydronogalamycinone (7). A mixture of 15 g of **6**, 67.5 g of freshly prepared Ag_2O, and 180 ml of DMF was stirred for 4 h. Methyl iodide (67.5 ml) was added, and the mixture was stirred in a closed system overnight followed by shaking for 3 days. After the mixture had stood overnight, it was centrifuged, and the supernatant was decanted. The residue was washed with 150 ml of DMF and 150 ml of $CHCl_3$ by centrifugation. All three supernatants were combined, and a solution of 15 g of KCN in 150 ml of H_2O was added. The resulting solution was extracted with five 300-ml portions of $CHCl_3$. The extracts were combined, washed with four 300-ml portions of water, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a DMF concentrate. The DMF was removed by distillation at ca. 1 mm. The resulting residue was dissolved in $CHCl_3$ and the solution was again evaporated under reduced pressure, weight 18.7 g. This material was chromatographed on 935 g of silica using $CHCl_3$-MeOH (98:2) and collecting 20-ml fractions. On the basis of a color peak and TLC analysis (R_f 0.56–0.63 in $CHCl_3$-MeOH; 95:5) indicating **7**, fractions 350–375 were combined and evaporated under reduced pressure, weight 3.4 g. This material was rechromatographed on 340 g of silica using cyclohexane-EtOAc-95% EtOH (59:36:5) and collecting 10-ml fractions. Fractions 261–351 were pooled on the basis of TLC analyses (R_f 0.43 in cyclohexane-EtOAc-95% EtOH; 5:3:2) and evaporated under reduced pressure, residual weight 587 mg. This material was rechromatographed on 59 g of silica in the same way. Two fractions were obtained, with the faster moving (151 mg) being only **7** (TLC) and the slower moving (222 mg) being mostly **7.** The pure material melted at 254–265 °C: IR (Nujol) 1730, 1675, 1575, 1275, 1235, 1195, 1060, 1010, 825, and 725 cm^{-1}; mass spectrum *m/e* 420.1218 (calcd for $C_{24}H_{20}O_7$, 420.1209).

Anal. Calcd for $C_{24}H_{20}O_7$: C, 68.57; H, 4.80. Found: C, 67.83; H, 4.75.

Zinc Dust Distillation of Nogalamycin (1). 1 (100 mg) was mixed thoroughly with 5 g of zinc dust by grinding in a mortar. The mixture was placed between two asbestos plugs near one end of a 9-mm Pyrex glass tube 30-cm long. The tube was flushed out with N_2 then heated with a bunsen burner for 10 min, while continuing to sweep out with N_2. The section of the tube which contained distillate was cut out and the distillate was washed out with EtOH. The ethanolic solution was filtered and evaporated to dryness under reduced pressure. The ultraviolet and visible spectra of the residue were identical with those reported for tetracene (naphthacene).

Tetramethyl Benzene-1,2,3,4-tetracarboxylate (8). This compound was obtained by alkaline permanganate oxidation of **1, 3b,** and **4** by the method of Brockmann and Brockmann Jr.[25] **4** (1 g) gave 30 mg of **8:** mp 129–131 °C (lit.[25] 131.5 °C); IR (Nujol) 1725 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 12 H, CH_3O), 8.03 (s, 2 H, aromatic).

Anal. ($C_{14}H_{14}O_8$) C, H.

Dimethylamine from Nogalamycin (1). A solution of 1.6 g (2 mmol) of **1** in 50 ml of 0.5 N NaOH was steam-distilled, collecting the distillate in 25.0 ml of 0.1 N HCl. Distillation was continued until foaming became uncontrollable. Titration of the distillate required 12.15 ml of 0.1 N NaOH, indicating 1.28 mmol of volatile base. The titrated solution was made strongly basic with 1.0 N NaOH and steam-distilled into a solution of 0.31 g of *p*-hydroxyazobenzene-*p*′-sulfonic acid in 20 ml of water. The distillate was evaporated to dryness under reduced pressure and the residue was recrystallized twice from water, mp 215–216 °C dec, mixture melting point with dimethylammonium *p*-hydroxyazobenzene-*p*′-sulfonate, mp 220–221 °C, was 219–220 °C dec. The IR spectra of the two materials were identical.

Acetic and Formic Acids from Base Treatment of Nogalamycin (1). The mixture obtained by acid hydrolysis of **1** (25.4 g) followed by neutralization and refrigeration was dissolved in 2 l. of 2 N NaOH.

The solution was steam-distilled until no more volatile base was distilling. The residue was adjusted to pH 3 with 18 N H_2SO_4, and the precipitate was removed and washed by centrifugation. The total supernatants were combined and filtered through celite, and the filtrate was steam-distilled until no more acid was distilling. Titration of the distillate to pH 8.5 with 1 N NaOH required 36.4 ml. The titrated solution was evaporated to dryness under reduced pressure. The residue was dissolved in water, adjusted to pH 2, and again steam-distilled until the volatile acid had distilled over. The distillate was adjusted to pH 8.1 with 1 N NaOH and again evaporated to dryness under reduced pressure, yield 2.47 g, ^{1}H NMR (D_2O) δ 2.0 (s) and 8.57 (s) in addition to a DOH signal.

The sodium salts (2.26 g) were converted to the *p*-bromophenacyl ester by the procedure of Shriner and Fuson,[26] yield 3.82 g; ^{1}H NMR ($CDCl_3$) δ 2.08 (s) and 8.07 (s). Vapor-phase chromatography showed the presence of materials having the elution times of *p*-bromophenacyl formate, *p*-bromophenacyl acetate, and ω-hydroxyacetophenone.

Rate of Base Hydrolysis of Nogalamycin (1). A solution of 1 g of **1** in 40 ml of 0.5 N NaOH was boiled under reflux for 0.5 h. The cooled reaction mixture was extracted with three 20-ml portions of $CHCl_3$. The aqueous layer was acidified to pH 3 with 1 N HCl. The precipitate was collected and washed by centrifugation. The product was dried at 60 °C under reduced pressure, weight 233 mg. Its ^{1}H NMR (D_2O–NaOD) showed no signal for CH_3O.

Supplementary Material Available: UV, visible, and ^{1}H NMR spectral data (Tables I.S and II.S) (2 pages). Ordering information is given on any current masthead page.

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A Stereoselective Total Synthesis of the Antifungal Mold Metabolite 7α-Methoxy-3a,10b-dimethyl-1,2,3,3aα,5aα,7,10bβ,10cα-octahydro-4*H*,9*H*-furo[2′,3′,4′:4,5]naptho[2,1-*c*]pyran-4,10-dione

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Abstract: A stereoselective total synthesis of the antifungal mold metabolite **1a** [(±)-LL-Z1271α] from the Wieland-Miescher diketone is reported. The synthetic approach utilizes a highly stereoselective reductive-elimination-alkylation reaction for establishing the axial stereochemistry of the carbomethoxy functional group at position 4 in esters **5b** and **5c**. The synthetic approach also includes a novel bromolactonization reaction in the construction of γ-lactone **8**. Finally **1a** and anomer **1b** were produced in a favorable anomeric ratio of 70:30, respectively, by employing the Meyer–Schuster rearrangement of the Arens-van Dorp synthesis on enone acetal **13**.

The mold metabolite 7α-methoxy-3a,10b-dimethyl-1,2,3,3aα,5aα,7,10bβ,10cα-octahydro-4*H*,9*H*-furo[2′,3′,-4′:4,5]naptho[2,1-*c*]pyran-4,10-dione [(±)-LL-Z1271α] (**1a**) (Scheme II) was isolated from the fermentation products of an *Acrostalagmus* species and was found to exhibit in vitro and in vivo antifungal activity against several pathogenic fungi.[1] The structure and stereochemistry of the novel terpenoid antifungal agent **1a** were determined by degradation and spectroscopy in conjunction with biogenetic considerations.[1] A previously reported synthesis of (−)-LL-Z1271α (**1a**) from a degradation product of marrubin also establishes the structure and absolute stereochemistry of antibiotic **1a**.[2] We wish to report herein a highly stereoselective total synthesis of (±)-LL-Z1271α (**1a**) from the readily available Wieland-Miescher diketone.[3,4]

Preparation of the Starting Material, Ester 5b

β-Keto ester **2** (Scheme I) was prepared from the Wieland-Miescher diketone in approximately 50% overall yield in three synthetic stages as reported by Spencer and coworkers.[5] Alkylation of β-keto ester **2** using sodium hydride in 1,2-dimethoxyethane (DME) followed by methyl iodide