nitrogen for 10 min and then 20 mL of dimethyl sulfide was added. The reaction mixture was stirred at 25 °C for 3 h. After the solvent was removed under reduced pressure, the oily residue was extracted with ether, washed with water, and dried over magnesium sulfate. Removal of the solvent under reduced pressure left a yellow oil which contained a 1.5:1.0 mixture of 1-(*p*-cyano)-2,3-diphenyl-1,3-propanedione (**37**) [NMR (benzene-d_6, 100 MHz) δ 6.01 (s, 1 H), 6.6–7.7 (m, 14 H)] and 2-(*p*-cyano)-1,3-diphenyl-1,3-propanedione (**38**) [NMR (benzene-d_6, 100 MHz) δ 6.05 (s, 1 H), 6.6–7.7 (m, 14 H)]. The identity of the two products was determined by comparison with independently synthesized samples.

Independent Synthesis of 1-(*p*-Cyano)-2,3-diphenyl-1,3-propanedione (37). A mixture containing 5.98 of deoxybenzoin, 5.4 g of trimethylsilyl chloride, and 7.07 g of triethylamine in 30 mL of dimethylformamide was heated at reflux for 12 h. The usual workup followed by distillation at 115 °C (0.05 mm) gave 5.0 g of the silyl enol ether of deoxybenzoin: NMR ($CDCl_3$, 60 MHz) δ 0.04 (s, 9H), 6.08 (s, 1 H), 7.2–7.8 (m, 10 H). To a solution containing 540 mg of the silyl enol ether in 10 mL of tetrahydrofuran at −60 °C was added 45 mg of methyllithium in 8 mL of tetrahydrofuran at −60 °C. After stirring for 30 min at −60 °C, the solution was warmed to −20 °C and stirred at this temperature for an additional 45 min. A 330-mg sample of *p*-cyanobenzoyl chloride in 10 mL of tetrahydrofuran was added and the mixture was warmed to 25 °C, washed with a saturated ammonium chloride solution, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting solid was recrystallized from methanol to give 380 mg of 1-(*p*-cyano)-2,3-diphenyl-1,3-propanedione (**37**): mp 141–142 °C; IR (KBr) 2230, 1700, and 1670 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 6.51 (s, 1 H), 7.1–8.0 (m, 14 H); *m/e* 325 (M^+).

Anal. Calcd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31. Found: C, 81.09; H, 4.73; N, 4.26.

Independent Synthesis of 2-(*p*-Cyano)-1,3-diphenyl-1,3-propanedione (38). A mixture containing 2.2 g of 4-cyanodeoxybenzoin,[22] 4.4 g of trimethylsilyl chloride, and 4.4 g of triethylamine in 30 mL of dimethylformamide was heated at reflux for 12 h. The usual workup followed by bulb-to-bulb distillation at 120 °C (0.5 mm) gave 1.5 g of the trimethylsilyl enol ether of 4-cyanodeoxybenzoin as a colorless oil: NMR ($CDCl_3$, 100 MHz) δ 0.04 (s, 9 H), 6.0 (s, 1 H), 7.1–7.7 (m, 9 H). To a solution containing 1.45 g of the silyl enol ether in 20 mL of tetrahydrofuran at −60 °C was added 0.1 g of methyllithium in 10 mL of tetrahydrofuran. After stirring for 30 min at −60 °C, the solution was warmed to −20 °C and stirred at this temperature for 45 min. A 700-mg sample of benzoyl chloride in 10 mL of tetrahydrofuran was then added and the mixture was stirred for 45 min at −15 °C. After warming to room temperature, the mixture was washed with a saturated ammonium chloride solution followed by drying over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left an oily residue which was chromatographed on a silica gel column using a 10% ether–hexane mixture. The crystalline solid obtained was identified as 2-(*p*-cyano)-1,3-diphenyl-1,3-propanedione (**38**) on the basis of its spectral properties: mp 139–140 °C; NMR ($CDCl_3$, 100 MHz) δ 6.51 (s, 1 H), 7.1–8.0 (m, 14 H); IR (KBr) 2230 and 1680 cm^{-1}; *m/e* 325 (M^+).

Anal. Calcd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.31. Found: C, 81.08; H, 4.57; N, 4.28.

Sensitized Irradiation of 2,2-Dimethyl-3,5-diphenyl-5-(*p*-cyanophenyl)-2,5-dihydrofuran (34). A solution containing 32.1 mg of dihydrofuran **34** and 3.3 mg of thioxanthone in 8 mL of benzene was degassed to 5×10^{-3} mm in three freeze–thaw cycles and was then sealed and irradiated with a series of 3500-Å lamps in a Rayonet photochemical reactor for 3 h. At the end of this time the photolysate was heated at 100 °C for 75 min. The solvent was removed under reduced pressure to afford a quantitative yield of an oil which was shown to contain a 1.4:1 mixture of enones **35** and **36**. The structures of these compounds were further verified by ozonization to a mixture of diketones **37** and **38**.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation. T.B. wishes to acknowledge SUNY at Buffalo for a Graduate Fellowship (1975–1976), a Woodburn Fellowship (1976–1977), and a Samuel B. Silbert Fellowship (1977–1978). We are also grateful to Mr. G. Mullick for some experimental assistance.

Registry No. 1, 36859-02-6; **2**, 71597-51-8; **3**, 71597-52-9; **4**, 71597-53-0; **5**, 71597-54-1; **6**, 71597-55-2; **7** isomer 1, 31502-11-1; **7** isomer 2, 31615-95-9; *cis*-**8**, 71597-56-3; *trans*-**8**, 71597-57-4; **9**, 71597-58-5; **10**, 4888-39-5; **11**, 71597-59-6; **12**, 71597-60-9; **13**, 71597-61-0; **14**, 71597-62-1; **15**, 13148-19-1; **16**, 71597-63-2; **17**, 71629-34-0; **20a**, 71597-64-3; **20b**, 71597-65-4; **24**, 71597-66-5; **25**, 71597-67-6; **26**, 71597-68-7; **27**, 71597-69-8; **28**, 71597-70-1; **29**, 71597-71-2; **30**, 71597-72-3; **31**, 71597-73-4; **32**, 71597-74-5; **33**, 71597-75-6; **34**, 71597-76-7; **37**, 71597-77-8; **38**, 71597-78-9; **39** (Ar = *p*-$CH_3C_6H_4$), 68727-78-6; **39** (Ar = *p*-anisyl), 56258-94-7; **39** (Ar = *p*-BrC_6H_4), 56258-97-0; 2-methyl-3,5,5-triphenyl-3-pentene-2,5-diol, 71597-79-0; 4-(1,2-diphenylethenyl)morpholine, 18239-50-4; benzoyl chloride, 98-88-4; 5,5-dimethyl-3-phenyl-2(5*H*)-furanone, 68727-84-4; 4,5,5-triphenyl-2(5*H*)-furanone, 4080-72-2; 2-acetoxy-2,2-diphenylacetophenone, 4917-96-8; 2-hydroxy-2,2-diphenylacetophenone, 4237-46-1; 5-methyl-3,5-diphenyl-2(5*H*)-furanone, 68727-81-1; *p*-toluoyl chloride, 874-60-2; 4-methyldeoxybenzoin, 2001-28-7; trimethylsilyl chloride, 75-77-4; 4-methyldeoxybenzoin trimethylsilyl enol ether, 71597-80-3; *p*-anisoyl chloride, 100-07-2; 4-methoxydeoxybenzoin, 1023-17-2; 4-methoxydeoxybenzoin trimethylsilyl enol ether, 71597-81-4; 2,2-dimethyl-3,5-diphenyl-5-(*p*-bromophenyl)-2,5-dihydrofuran, 71597-82-5; deoxybenzoin, 451-40-1; deoxybenzoin silyl enol ether, 71597-83-6; tetrahydrofuran, 109-99-9; *p*-cyanobenzoyl chloride, 6068-72-0; 4-cyanodeoxybenzoin, 60694-99-7; 4-cyanodeoxybenzoin trimethylsilyl enol ether, 71597-84-7.

Nogalamycin. Stereochemistry and Chemical Modification

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The conversion of nogalamycin (**1a**) to a number of analogues in which the nogalose moiety is replaced by alkoxy groups and hydrogen is described. In one series of analogues the carbomethoxy group at C-10 of **1a** is removed, but in the other series this group has been retained. Preparation of these compounds by acidic alcoholysis results in formation of pairs of isomers differing only in configuration at C-7. The absolute configuration of the chiral centers at C-7, C-9, and C-10 of **1a** are assigned on the basis of CD studies.

Nogalamycin[1-3] (**1a**) is an anthracycline antibiotic which has activity against gram-positive microorganisms and is an antitumor agent.[4] As a result of previous studies[4] of compounds prepared by chemical modification of **1a**, it

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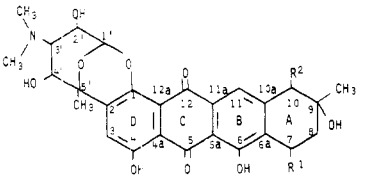

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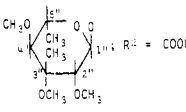
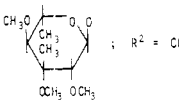
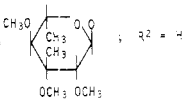
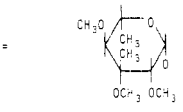
1a (dis), R¹ =  ; R² = $COOCH_3$

1b (dis), R¹ =  ; R² = COOH

1c (dis), R¹ =  ; R² = H

1d (con), R¹ =  ; R² = H

1e, R¹ = H; R² = $COOCH_3$

1f (dis), R¹ = OH; R² = $COOCH_3$

1g (dis), R¹ = CH_3O; R² = $COOCH_3$

1h (con), R¹ = CH_3O; R² = $COOCH_3$

1i (dis), R¹ = C_2H_5O; R² = $COOCH_3$

1j (con), R¹ = C_2H_5O; R² = $COOCH_3$

1k (dis), R¹ = n-C_3H_7O; R² = $COOCH_3$

1l (con), R¹ = n-C_3H_7O; R² = $COOCH_3$

1m (dis), R¹ = CH_3O; R² = H

1n (con), R¹ = CH_3O; R² = H

1o (dis), R¹ = C_2H_5O; R² = H

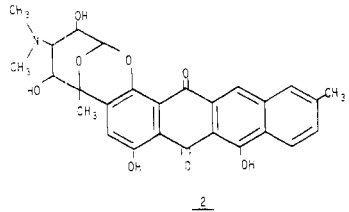
1p (con), R¹ = C_2H_5O; R² = H

1q (dis), R¹ = n-C_3H_7O; R² = H

1r (con), R¹ = n-C_3H_7O; R² = H

1s (con), R¹ = iso-C_3H_7O; R² = H

1t, R¹ = R² = H



2

seemed probable that further modification would give compounds having interesting biological activities. The present paper discusses the preparation of a number of analogues of **1a**, some of which are more active antitumor agents than is the parent compound.[5] Since it has been found that isomers of analogues differing only in chirality at C-7 can be isolated, a further study of absolute configuration at the chiral centers in ring A is also reported. A somewhat different system for naming isomeric pairs has been used previously.[1,6]

A series of analogues of **1a** was reported previously[3] in which most of the compounds prepared arose from replacement of the nogalose moiety of **1a** by other groups. These compounds were named as nogalarols. Acidic hydrolysis of **1a** formed disnogalarol (**1f**) in which there was a hydroxyl group at C-7, and acidic methanolysis gave 7-dis-*O*-methylnogalarol (**1g**). At that time only one of the two possible isomers differing in configuration at C-7 was isolated. Further experiments utilizing methanol, ethanol, and 1-propanol as alcohols in the acidic alcoholysis of **1a** have been carried out with the result that two isomers differing at C-7 have been isolated from reaction with each alcohol. The products obtained were **1g**, **1h**, **1i**, **1j**, **1k**, and **1l**. These compounds were characterized, and their structures were established by the usual analytical and spectral data. Analytical values were not entirely satisfactory as the carbon percentage found was from 1.59 to 0.47% lower than the theoretical value. However, mass spectral data and ^{13}C NMR data combined with elemental analysis required the reported molecular formulas. It is probable that the poor analytical data obtained for carbon resulted from some retention of solvent. The compounds were assigned to the appropriate series (dis or con), differing only in configuration at C-7, by relating the compounds of the nogalarol series to those of the nogarol series by CD curves which are discussed subsequently in relation to the absolute stereochemistry of **1a** and its analogues. It was found that the compound previously designated 7-*O*-methylnogalarol (**1g**) has the nogalamycin configuration at C-7, and it is now called 7-dis-*O*-methylnogalarol. Compounds of the dis series are readily distinguished from those of the con series by TLC and ^{13}C NMR curves. In the solvent system $CHCl_3$–CH_3OH–H_2O (78:20:2) the dis series compounds always have lower TLC R_f values than do the con compounds. In ^{13}C NMR spectra of dis compounds the chemical shift of C-7 is about δ 2 and that of C-6a is about δ 1.4 downfield from the corresponding carbons of the con compounds, while the chemical shift of C-11 moves upfield about δ 2.7 on going from dis to con. The CD curves for the two isomers also distinguish between the two series.

Nogalamycin (**1a**) has been converted to a different series of compounds by removal of the carbomethoxy group at C-10. Alkaline hydrolysis of **1a** is very facile occurring with 0.53 N KOH at room temperature in a few hours. The product obtained is nogalamycinic acid (**1b**) which probably exists as the zwitterion. Compound **1b** was quite difficult to purify, and it has not been obtained pure. However, its conversion to 7-dis-*O*-methylnogalarol (**1g**) by reaction with acidic methanol and the reaction products obtained from **1b** (**1m**–**1t**) establish its structure to be as indicated. The ready decarboxylation of **1b** prevented determination of molecular composition by high-resolution mass spectroscopy.

Solution of **1b** in DMF led to decarboxylation and the formation of disnogamycin (**1c**) which differed from **1a** in replacement of the carbomethoxy group at C-10 by H. Carbon dioxide evolved in the conversion was trapped and identified, establishing the occurrence of decarboxylation. Although highly pure samples of **1c** were obtained, a satisfactory carbon analysis was never achieved as is characteristic of **1a** and most of its analogues. The mass spectrum of **1c** indicated a molecular weight 58 less than that of **1a** in agreement with loss of $COOCH_3$. The infrared spectrum showed that the ester carbonyl was no longer present. The ^{13}C NMR spectrum of **1c** compared with that of **1a** was completely parallel except for the disappearance of chemical shifts at δ 178.9 and 52.4 assigned, respectively, to the ester carbonyl and ester methoxyl. These spectral data conclusively establish the structure of **1c**.

Acidic alcoholysis of **1c** with the alcohols methanol, ethanol, and 1-propanol, as was done with **1a**, also gave in each case mixtures which, in addition to other products, contained two isomers having alkoxy groups at C-7 and differing in configuration at that carbon atom. The compounds prepared, which were named as 7-dis- and 7-con-*O*-alkylnogarols, were **1m**, **1n**, **1o**, **1p**, **1q**, and **1r**.

All of the alkoxy compounds readily eliminated the elements of water and an alcohol to give nogarene (**2**), and removal of **2** from **1m** and **1n** was quite difficult. In the case of the 7-*O*-methylnogarols the ratio of con/dis in the methanolysis was about 60:40. Removal of the dis isomer (**1m**) and reexposure of it to the acidic methanolysis con-

(1) A preliminary account of a portion of this work has been published; see P. F. Wiley, J. L. Johnson, and D. J. Houser, *J. Antibiot.*, **30**, 628 (1977).

(2) B. K. Bhuyan and A. Dietz, *Antimicrob. Agents Chemother.*, 836 (1965).

(3) P. F. Wiley, R. B. Kelly, E. L. Caron, V. H. Wiley, J. L. Johnson, F. A. MacKellar, and S. A. Mizsak, *J. Am. Chem. Soc.*, **99**, 542 (1977).

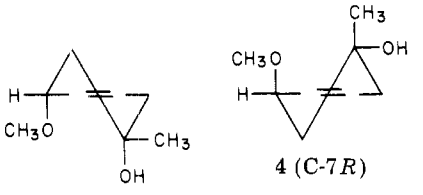
(4) B. K. Bhuyan and F. Reusser, *Cancer Res.*, **30**, 984 (1970).

(5) L. H. Li, S. L. Kuentzel, L. L. Murch, L. M. Pschigoda, and W. C. Krueger, *Cancer Res.*, in press.

(6) P. W. Rueckert, P. F. Wiley, J. P. McGovren, and V. P. Marshall, *J. Antibiot.*, **32**, 141 (1979).

ditions again resulted in a substantial amount of **1n**. As was the case with the nogalarols, good analyses for carbon were difficult to obtain, probably because of solvent retention. Melt solvate determinations usually indicated the presence of a few percent of solvent.

The ^{1}H NMR spectra of **1m** and **1n** suggest that the methoxyl groups in both compounds are pseudoaxial although their configurations are opposite. The ^{1}H NMR spectrum of **1n** has a rather broad singlet at δ 4.81 assigned to the proton at C-7. The signal assigned to this proton in the spectrum of **1m** is a triplet at δ 4.76 with a coupling constant of about 3.5 Hz. In neither case is the coupling constant large enough to allow diaxial protons at C-7 and C-8. Consequently, conformation in ring A of these two compounds must be as indicated in **3** and **4** although the



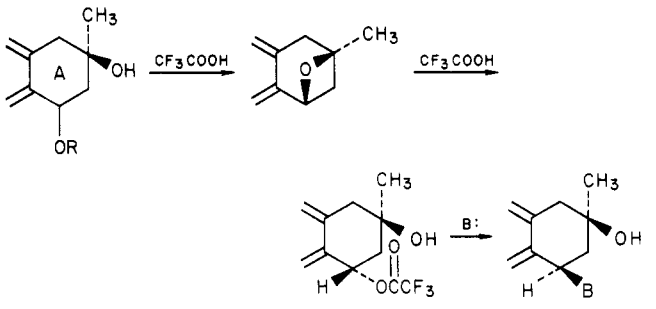
3 (C-7*S*) 4 (C-7*R*)

difference in the coupling constants suggest some difference in conformation. The conformation indicated in **3** is the one normally present in ring A of anthracyclinones.[7]

As in the case of the 7-*O*-alkylnogalarols, the dis series of 7-*O*-alkylnogarols is more polar than the con series on TLC plates using the solvent system $CHCl_3$–CH_3OH–H_2O (78:20:2). Also, as with the nogalarol series there are characteristic differences between the nogarol con and dis compounds in the chemical shifts of certain carbon atoms in the ^{13}C NMR spectra. For example, C-6a shows a downfield shift of about δ 1.5 on going from the con to the dis series, and C-10 exhibits an upfield shift of about δ 1. In the 7-*O*-ethyl pair and the 7-*O*-*n*-propyl pair, C-7 has a downfield shift of δ 1.4 and 1.8, respectively. In the 7-*O*-methyl pair the chemical shifts for C-7 are almost identical and downfield from the values for the other 7-*O*-alkyl compounds. The reason for this difference is not clear. As will be discussed subsequently, CD curves are also quite characteristic for the two series.

As a result of attempts to prepare connogamycin (an isomer of **1d**), it was found that disnogamycin (**1c**) reacts with CF_3COOH under mild conditions to replace the nogalose moiety. The resulting intermediate then reacts with nucleophiles to give essentially exclusively compounds of the con series. Utilization of the anion of nogalose results in formation of a glycoside isomeric with **1c** and methoxide reacts to give **1n**. The nature of the intermediate is not clear as it has not been characterized due to purification difficulties. In these conversions the use of compounds having the dis configuration at C-7 results in a product that is con, while starting with compounds having C-7 with the con configuration results in overall retention as indicated by conversion of **1n** to **1p**, both being con. One can envision an intermediate in which the oxygen atom at C-9 has attacked the carbonium ion formed at C-7 with formation of an oxetane ring which reacts with CF_3COO^- to give an acylate in which the C-7 substituent is on the side of ring A opposite to the hydroxyl at C-9 as is the case in the dis series (see Scheme I). An S_N2 nucleophilic substitution could then give the stereochemistry actually found. Such an oxetane intermediate would seem unlikely, but an approach to such a ring occurring by ionic binding might give

Scheme I

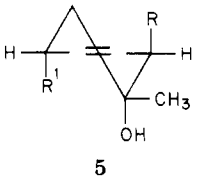


sufficient directive effect. On the basis of ^{13}C NMR, it seems probable that use of nogalose in this reaction gives the β configuration at C-1″ as indicated in **1d**. However, this is not certain.

7-Deoxynogarol (**1t**) was prepared by catalytic reduction of **1a** to 7-deoxynogalarol (**1e**)[3] followed by basic hydrolysis without purification of the resulting acid and decarboxylation by solution in DMF. Its structure was established by its method of preparation and its spectra.

All of the analogues of the nogarol series retaining oxygen at C-7 readily eliminate the elements of one molecule of water and another small molecule, either water or an alcohol, resulting in aromatization of ring A and formation of nogarene (**2**). Treatment of disnogamycin with boiling hydrochloric acid is the best preparative procedure, but **2** is quite difficult to purify, and no really pure material has been obtained. Furthermore, solubility problems precluded the obtaining of a good ^{1}H NMR spectrum. However, a ^{13}C NMR spectrum and a high-resolution mass spectrum leave no doubt that the structure is as indicated in **2**.

Although a previous publication[3] has proposed two possible configurations for the chiral carbon atoms of ring A, these proposals were based on inadequate data and were little more than guesses. In view of the commonly occurring 7*S*,9*R*,10*R* configuration (**5**) present in anthracyclines,



5

R = $COOCH_3$ or OH; R^1 = OH, *O*-alkyl, or *O*-sugar

it seemed probable that such a configuration was also present in **1a**. The preparation of compounds which seemed to differ in configuration at C-7 was a strong inducement to obtain more definitive information about the stereochemistry of ring A. This was done by the use of circular dichroism studies such as those previously used in the anthracycline field[7] and subsequently by crystallographic studies.[8]

Brockmann et al.[7] have shown that the difference CD spectrum for the region insensitive to anthraquinone hydroxyl substitution, i.e., 400–260 nm, obtained by subtracting the spectrum of a 7-deoxyanthracyclinone from that of its parent anthracyclinone allows the assignment of the absolute configuration at C-7. The difference CD spectra were related to that of daunomycinone, having the 7-*S* configuration, and that of 7-deoxydaunomycinone. The configuration at C-7 in daunomycin has been established chemically.[9] Inherent in this determination by CD

(7) H. Brockmann, H. Brockmann, Jr., and J. Niemeyer, *Tetrahedron Lett.*, 4719 (1968).

(8) E. Eckle, J. J. Stezowski, and P. F. Wiley, submitted for publication in *J. Am. Chem. Soc.*

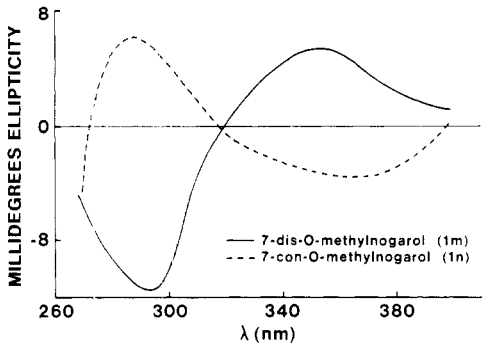


Figure 1. Difference CD curves. Parent anthraquinone minus 7-deoxy analogue (2.2×10^{-5} M, 5-cm cell, pH 7.2, 0.01 M phosphate buffer).

is the assumption that rings A of the parent and 7-deoxy compounds have the same conformations. Thus, the difference CD curve reflects the effect of the asymmetric center at C-7 on the anthraquinone chromophore, and mirror image CD difference curves are expected for the 7-*S* and 7-*R* configurations. The CD difference curves are "S" shaped with positive and negative bands near 350 and 300 nm, respectively, for the 7-*S* configuration.[7]

In the present analysis of the absolute configurations of **1a** and its analogues, the 7-*O*-methylnogarol isomers (**1m** and **1n**) were considered first. As stated earlier, these isomers differ in conformation as well as absolute configuration, and, unfortunately, the conformation of 7-deoxynogarol (**1t**) could not be determined from its ^{1}H NMR spectrum. However, if the conformation is either **3** or **4**, then one of the CD difference curves should yield the correct absolute configuration at C-7. In fact the CD difference curves have nearly mirror image shapes (Figure 1), and so the absolute configuration of the isomer **1m**, having in its CD difference curve the positive and negative bands near 350 and 260 nm, respectively, was assigned the 7-*S* configuration. If it is assumed that conformation is not crucial in determining absolute configuration at C-7 by this method, then the difference CD curves of the other **1a** analogue isomers should also have nearly mirror image shapes and hence assignable absolute configurations at C-7. In the cases of all of the compounds studied (**1a–d**, **1f–l**, **1m–s**) the C-7 isomers show nearly mirror image difference CD curves, and hence the conformation of ring A is not crucial in determining the configuration at C-7.

The CD spectra in the visible region of the spectrum of the compounds discussed above also support the absolute configurational assignments at C-7 by the CD-difference method. Thus, all 7-*S* molecules show two positive bands in the visible region between 500 and 300 nm, while the 7-*R* isomers show only one band in this region (Figure 2). Daunomycin and adriamycin have the 7-*S* configuration and show two positive bands in this region of the spectrum (Figure 3). The CD results agree without exception with the classification of isomers by TLC and ^{13}C NMR for all compounds studied. Since **1a** has a visible CD curve (Figure 2) which is similar to those of compounds in the *S* series, it too must be 7-*S*.

The absolute configuration at C-10 can also be determined by CD methods. In this determination we consider only the 7-*S* **1a** analogue isomers given under 1 and the CD between 400 and 260 nm in order to simplify the argument and compare the results to literature conclusions. If the configuration is 10-*R* and 7-*S*, then the substituents at C-7 and C-10 are trans to each other with respect to the

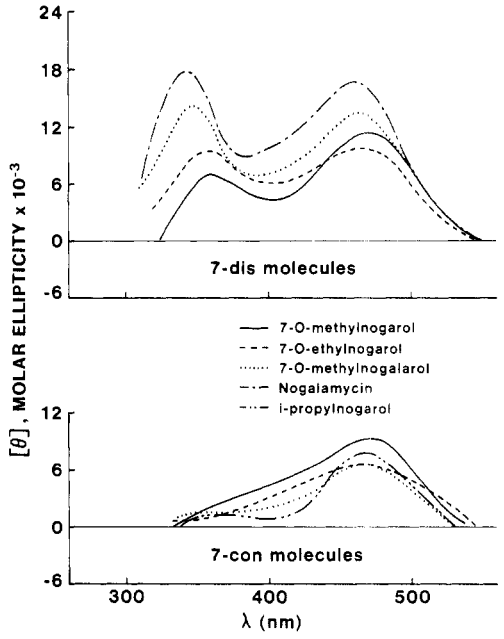


Figure 2. Comparison of the visible CD curves of some 7-*S* and 7-*R* compounds.

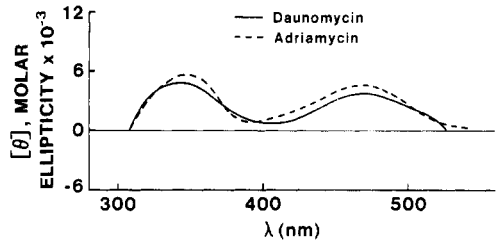


Figure 3. Visible CD curves of daunomycin and adriamycin.

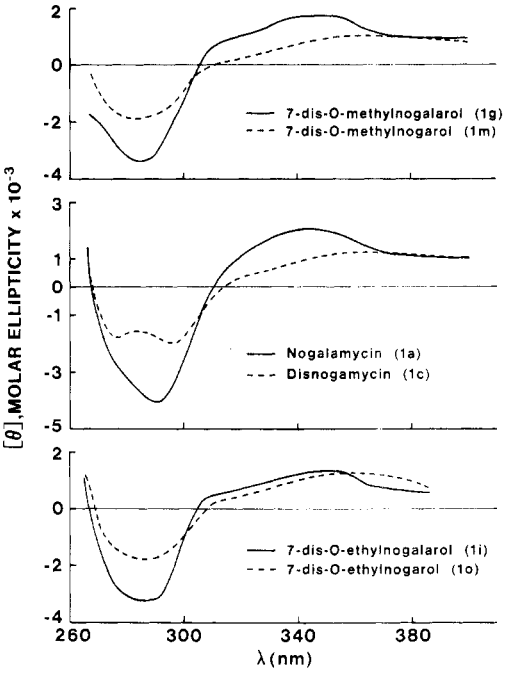


Figure 4. CD curves showing the effect of a 10-*R* carbomethoxy group on the anthraquinone chromophore.

plane of ring A (**5**), and from symmetry considerations, the compound having a substituent at C-10 such that C-10 is *R* should have a CD spectrum of greater magnitude than the compound unsubstituted at C-10.[10] What this means

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(10) H. Brockmann, Jr., and M. Legrand, *Tetrahedron*, **19**, 395 (1963).

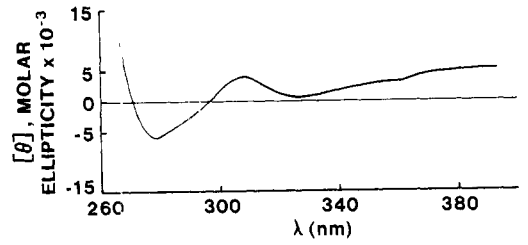
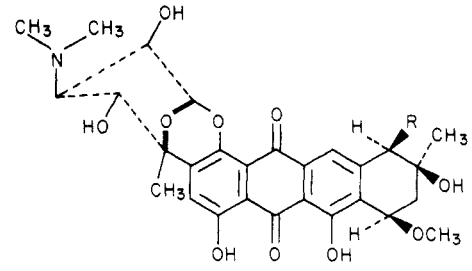


Figure 5. CD curve of 7-deoxynogarol (1t).

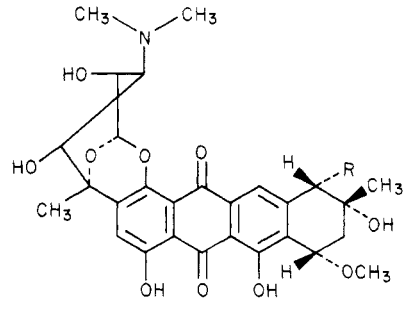
is that the compounds **1a–l** with the 7-*S*,10-*R* configuration should have greater CD curves than the 7-*S* compounds unsubstituted at C-10 (**1m–s**). The observed CD spectra (given in Figure 4 for some of the compounds) support the 10-*R* configuration for all pairs of analogues studied, and so all are taken to have the 10-*R* configuration, including **1a** since the chirality of C-10 should remain unchanged throughout the series. Again, it is assumed that the conformation of ring A is not a significant factor in determining the sign of the CD. However, since hydrolysis of the carbomethoxy group in **1a** is quite easy, suggesting an equatorial carbomethoxy substituent,[11] the conformation is probably opposite to that in **5**.

The absolute configuration at the C-9 chiral center is more difficult to determine by CD methods since its effect on the anthraquinone chromophore is small and since good models are not available. Thus, although 7-deoxynogarol (**1t**) and 7-deoxynogalarol (**1e**) show CD curves in the region 400–260 nm like those of similar anthracycline analogues having the 9-*R* configuration,[7,10] nothing firm can be said about the absolute configuration at C-9 for **1e** and **1t** since (1) the effect on the CD of the fused amino sugar on the D ring of **1e** and **1t** is unknown and (2) when C-7 and C-10 are unsubstituted and hence not chiral centers, conformation changes in ring A can make contributions to the CD comparable in magnitude to that associated with the presence of the chiral center at C-9. Nevertheless, what can be said is that the effect of the fused sugar on the CD of the chromophore is small since the CD intensity of **1t** (Figure 5) is small and almost identical with that of 7-deoxydaunomycinone.[12] Thus, for reasons which are not obvious, the stereochemistry of the fused sugar vis-à-vis that of the anthraquinone chromophore does not lead to a serious chiral perturbation of the anthraquinone chromophore, and these CD results favor the con configuration at C-9.

Quite recently Stezowski[8] has obtained X-ray crystallographic data from **1n** which establishes its entire relative stereochemistry and by extension that of disnogamycin and all its other analogues. These results indicate that in **1n** the methoxy group at C-7 and the hydroxyl group at C-9 are on the same side of the molecule and that the amino sugar is at right angles to the linear tetracyclic system and is on the side opposite to the oxygen substituents at C-7 and C-9. This could be readily reconciled with the CD data with the exception of the chirality at C-9 which would be opposite to that proposed on the basis of CD. However, **7a** would not be excluded by crystallographic data and would be more likely by analogy to other anthracyclines[7,10,13] and on biogenetic grounds. It would be at variance with CD conclusions for C-7 and C-10. In summary, the structures **6a** and **6b** are strongly favored by CD results, but the possibility of the mirror image structures, **7a** and **7b**, is not absolutely excluded.



6a, R = H
b, R = $COOCH_3$



7a, R = H
b, R = $COOCH_3$

These compounds have been tested against P388 leukemia in mice, and all were active although some only marginally. By far the most active was 7-con-*O*-methylnogarol which gave an increased life span of 197% with several cures. This activity was comparable with that of adriamycin in the same system. Complete biological data will be reported elsewhere.

Experimental Section

All CD spectra were obtained on a Cary 60 spectropolarimeter equipped with a Model 6003 CD attachment in sodium phosphate buffer (pH = 7.2) 0.01 M in phosphate and at a compound concentration of 2.4×10^{-5} M. The Cary 60 had been calibrated with 10-camphorsulfonic acid.[14] The compound was dissolved in 2 mL of CH_3OH (sonicating when necessary) and phosphate buffer added to a total volume of 100 mL. Ultraviolet spectra were obtained on a Cary 15 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Infracord 735 spectrophotometer. Proton NMR spectra were measured on Varian A60-A, T-60, XL-100, FT-80, and HR-220 instruments while the carbon NMR spectra were done on a Varian CFT-20. Mass spectra were obtained by using a Varian MAT CH5 double-focusing mass spectrometer.

Nogalamycinic Acid (1b). Forty grams of **1a** was dissolved in 356 mL of 1 N KOH solution, and 310 mL of H_2O was added. The solution was stirred at room temperature for 16 h followed by acidification (pH 3.2) with 30% H_2SO_4. Subsequently it was found that adjustment to pH 5.0 gave better results. The precipitate was collected by centrifugation and washed twice with water by the same method to yield 28.5 g. Thirteen grams of this product was chromatographed on 500 g of silica gel by starting with $CHCl_3$–CH_3OH (95:5) and gradually increasing the CH_3OH content to $CHCl_3$–CH_3OH (1:1) and collecting 10-mL fractions. Elution was monitored by TLC using $CHCl_3$–CH_3OH–H_2O (78:20:2) in which **1b** has R_f 0.25 and combining those fractions containing only **1b**. The pooled fractions were evaporated under reduced pressure: yield 2.3 g; mp 219–229 °C dec; $[\alpha]_D$ +456° (*c* 0.37, CH_3OH); UV (C_2H_5OH) 236 nm (ϵ 39 950), 269 (21 350), 291 sh (8700), 482 (13 550); IR (Nujol) 3450, 1670, 1630, 1595, 1580, 1290, 1230, 1215, 1135, 1095, 1060, 1015, 980, 920, 855, 830, 780, 763, 725 cm^{-1}, ^1H NMR ($CDCl_3$–CD_3OD) δ 1.38 (m, 9 H, 3 CH_3C), 1.80 (s, 3 H, CH_3C), 3.15 [s, 6 H, $(CH_3)_2N^+$], 3.38, 3.40, 3.68 (3 s, 9 H, 3 CH_3O), 3.2–4.0 (m, CHO, CHN), 5.24 (d, 1 H, H-1″), 5.88

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(13) D. Tresselt, K. Eckardt, and J. Tax, *Tetrahedron*, 31, 613 (1975).
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(d, 1 H, H-1′), 6.92 (s, 1 H, H-3), 7.47 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 191.4 (C-5), 181.6 (C-12), 178.9 (COO^-), 161.3 (C-6), 157.4 (C-4), 149.7 (C-1), 148.2 (C-10a), 133.9, 133.6, 133.1 (C-2, C-11a, C-6a), 128.5 (C-3), 120.3 (C-11), 117.3 (C-12a), 115.9 (C-4a), 114.5 (C-5a), 100.2 (C-1″), 97.2 (C-1′), 85.9 (C-4″), 82.0 (C-2″), 79.6 (C-3″), 77.2 (C-5′), 74.0 (C-2′), 71.5 (C-7), 70.6 (C-4′), 69.2 (C-5″), 68.5 (C-9), 62.5, 60.4, 49.9 (3 CH_3O), 58.1 (C-10), 42.5 [$(CH_3)_2N^+$], 31.1 (C-9 CH_3), 25.6 (C-5′ CH_3), 19.3 (C-5″ CH_3), 16.4 (C-3″ CH_3); mass spectrum, m/e 720 ($M^+ - CO_2$).

Anal. Calcd for $C_{38}H_{47}NO_{16}$: C, 59.04; H, 6.13; N, 1.81. Found: C, 57.48; H, 6.27; N, 1.78.

Carbon Dioxide from Nogalamycinic Acid (1b). Two grams of **1b** was put in a round-bottom flask which was swept out with N_2. Twenty milliliters of DMF was added, and N_2 was bubbled through the system until TLC indicated conversion to **1c** (ca. 3 h). During this procedure the N_2 was conducted through 100 mL of saturated $Ba(OH)_2$ solution. The resulting precipitate was removed from the $Ba(OH)_2$ solution, washed, and dried at 85 °C under reduced pressure; yield 323 mg. It was identified as Ba_2CO_3 by an IR spectrum. This was 0.63 mol of $BaCO_3$/mol of **1b**.

Conversion of Nogalamycinic Acid (1b) to 7-Dis-*O*-methylnogalarol (1g). A solution of 300 mg of **1b** in 50 mL of CH_3OH 0.5 N in HCl was boiled for 1.5 h. The solution was evaporated in vacuo to about 15 mL, and an equal volume of water was added. The mixture was adjusted to pH 7.5 with base and extracted with three 20-mL portions of $CHCl_3$ which were combined and evaporated to dryness in vacuo; yield 236 mg. The residue was chromatographed on 20 g of silica gel with 400 mL of $CHCl_3$–CH_3OH (98:2) and 1 L of 95:5, collecting 10-mL fractions. Fractions 70–80 were combined and evaporated in vacuo to give 50 mg of a product identified as **1g** by TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2) and ^{1}H NMR.

Disnogamycin (1c). Ten grams of **1b** was dissolved in 25 mL of DMF and allowed to stand overnight. The solution was centrifuged, the supernatant decanted, and the DMF was removed by evaporation in a current of air. The residue was chromatographed on 150 g of silica gel using $CHCl_3$–CH_3OH (95:5) and collecting 10-mL fractions. On the basis of TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2; R_f 0.50 for **1c**) fractions 205–224 were combined and evaporated in vacuo to give 1.6 g of product. Another 0.82 g of somewhat less pure material was obtained from fractions 195–204 and 225–285. Recrystallization from CH_3COCH_3–CH_3OH (85:15) gave **1c**: mp 210–215 °C dec; $[\alpha]_D$ +273° (c 0.923, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 51 700), 259 (25 850), 290 (10 050), 478 (16 100); IR (Nujol) 3500, 1670, 1630, 1575, 1295, 1230, 1110, 1055, 1005, 920, 890, 838, 778, 765, and 724 cm^{-1}; ^{1}H NMR (DMF-d_7) δ 1.14, 1.23, 1.37, 1.67 (m and s, 12 H, 4 CH_3C), 2.07–2.38, 2.83–3.0 (m, 4 H, 2 CH_2), 2.42 [s, 6 H, $(CH_3)_2N$], 3.13, 3.42, 3.52 (3 s, 9 H, 3 CH_3O), 3.34–4.2 (m, CHO, CHN), 4.95 (m, 1 H, H-7), 5.32 (d, 1 H, H-1″), 5.68 (d, 1 H, H-1′), 7.16 (s, 1 H, H-3), 7.32 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.8 (C-5), 179.7 (C-12), 161.4 (C-6), 156.0 (C-4), 147.8 (C-1), 147.4 (C-10a), 137.2 (C-2), 132.6 (C-11a), 131.3 (C-6a), 125.8 (C-3), 120.7 (C-11), 116.0 (C-12a), 114.1 (C-4a), 113.1 (C-5a), 99.8 (C-1″), 96.8 (C-1′), 84.6 (C-4″), 81.1 (C-2″), 78.2 (C-3″), 75.1 (C-5′), 72.7 (C-2′), 70.8 (C-7), 69.8 (C-9), 69.6 (C-4′), 67.4 (C-5″), 66.4 (C-3′), 61.4, 59.0, 48.7 (3 CH_3O), 44.4 (C-10), 44.2 (C-8), 41.5 [$(CH_3)_2N$], 30.4 (C-9 CH_3), 24.2 (C-5′ CH_3), 18.3 (C-5″ CH_3), 15.2 (C-3″ CH_3); mass spectrum, m/e 729.

Anal. Calcd for $C_{37}H_{47}NO_{14}$: C, 60.96; H, 6.55; N, 1.92. Found: C, 58.55; H, 6.42; N, 1.94.

Con-1″β-nogamycin (1d). A solution of 1 g (1.37 mmol) of **1c** was dissolved in 20 mL of CF_3COOH, and the solution was cooled in an ice bath. A 53% suspension of 821 mg of NaH in mineral oil (18.1 mmol) was washed with two 10-mL portions of anhydrous tetrahydrofuran and added to 2 g (9.1 mmol) of nogalose in 30 mL of anhydrous tetrahydrofuran. The mixture was stirred at room temperature for 1 h, and to it was added the cold CF_3COOH solution. The reaction mixture was adjusted to pH 7.1 with 1 N HCl and diluted with 100 mL of H_2O. The aqueous solution was extracted with four 100-mL portions of CH_2Cl_2. The combined extracts were evaporated to a red syrup under reduced pressure. The residue was dissolved in a little CH_2Cl_2 and precipitated with a large volume of Skellysolve B. The mixture was filtered (yield 1.52 g), and the filtrate was evaporated to a syrup under reduced pressure. The residue was chromatographed on a short column of 20 g of silica gel using CH_2Cl_2–CH_3OH (9:1), collecting the colored fractions, and evaporating the solvent. The residue was dissolved in CH_2Cl_2 and precipitated with Skellysolve B.

The combined products were chromatographed by using high-performance LC with 60 g of silica gel and the solvent system CH_2Cl_2–CH_3OH (96:4) until the light orange fractions were removed. The solvent ratio was changed to 97:3, and 105 10-mL fractions were collected. Those fractions (51–105) were combined which, as judged by TLC with $CHCl_3$–CH_3OH–H_2O (78:20:2; R_f 0.53), contained only **1d**. The combined fractions were evaporated to dryness under reduced pressure; yield 325 mg. This material was rechromatographed on 2-mm preparative thin-layer plates using the above TLC system. The appropriate band was removed and extracted with $CHCl_3$–CH_3OH (9:1). There was obtained 185 mg of **1d**: mp 217–219 °C dec; $[\alpha]_D$ +596° (c 0.147, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 51 600), 258 (24 200), 292 sh (9750), 478 (15 300); IR (Nujol) 3440, 1660, 1610, 1580, 1410, 1280, 1210, 1090, 1050, 990, 930, 910, 880, 850, 820, 770, 720, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23, 1.46, 1.74 (s, m, s, 12 H, 4 CH_3C), 2.61 [s, 6 H, $(CH_3)_2N$], 3.26, 3.42, 3.55 (3 s, 9 H, CH_3O), 2.0–2.2, 3.1–4.2 (m, CHO, CHN), 5.03 (m, 1 H, H-7), 5.23 (d, 1 H, H-1″), 5.90 (d, 1 H, H-1′), 6.60 (s, 1 H, H-3), 7.25 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.9 (C-5), 179.4 (C-12), 161.2 (C-6), 155.6 (C-4), 148.3 (C-1), 147.0 (C-10a), 137.9 (C-2), 132.7 (C-11a), 129.6 (C-6a), 125.6 (C-3), 120.8 (C-11), 116.1 (C-12a), 114.4 (C-4a), 112.5 (C-5a), 102.2 (C-1″), 97.6 (C-1′), 84.3 (C-4″), 81.5 (C-2″), 79.0 (C-3″), 75.1 (C-5′), 72.7 (C-2′), 71.0 (C-4′), 70.8 (C-7), 70.4 (C-5″), 67.6 (C-9), 66.1 (C-3′), 61.4, 61.2, 48.2 (3 CH_3O), 43.9 (C-10), 41.6 [$(CH_3)_2N$], 40.2 (C-8), 30.5 (C-9 CH_3), 24.0 (C-5′ CH_3), 18.5 (C-5″ CH_3), 15.3 (C-3″ CH_3); mass spectrum, m/e 729.3011 (calcd for $C_{37}H_{47}NO_{14}$, m/e 729.2997).

Anal. Calcd for $C_{37}H_{47}NO_{14}$: C, 60.90; H, 6.49; N, 1.92. Found: C, 59.09; H, 6.39; N, 1.83.

7-Con-*O*-methylnogalarol (1h). A solution of 10 g of **1a** in 500 mL of anhydrous CH_3OH 0.5 N in HCl was boiled for 5 h. The volume was reduced to 150 mL by evaporation under reduced pressure. The residue was diluted with 250 mL of H_2O and extracted with two 100-mL portions of $CHCl_3$. The remaining aqueous solution was adjusted to pH 7 with 50% NaOH solution and extracted with several portions of $CHCl_3$. Evaporation of the combined $CHCl_3$ extracts under reduced pressure gave 8.03 g of dark red residue.

Five grams of the crude material was chromatographed on a 250-g silica gel column by high-performance LC using $CHCl_3$–CH_3OH (95:5). A total of 305 5-mL fractions were collected. Fractions 171–200 were combined on the basis of TLC (78:20:2 $CHCl_3$–CH_3OH–H_2O; R_f 0.64) and evaporated to dryness under reduced pressure; yield 0.31 g. A further 0.59 g of the same material, but slightly less pure as judged by TLC, was obtained from fractions 151–170: mp 200 °C dec; $[\alpha]_D$ +627° (c 0.516, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 43 400), 252 (25 750), 257 sh (24 350), 290 sh (11 400), 480 (15 600); IR (Nujol) 3440, 3180, 1740, 1665, 1615, 1575, 1300, 1285, 1260, 1230, 1125, 1105, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.59, 1.71 (2 s, 6 H, 2 CH_3C), 2.03 (m, 1 H, H-8a), 2.25 (m, 1 H, H-8b), 2.56 [s, 6 H, $(CH_3)_2N$], 3.53 (s, 3 H, CH_3O), 3.70 (s, 3 H, CH_3O), 3.6–4.0 (m, 5 H, CHO, CHN), 4.87 (m, 1 H, H-7), 5.87 (d, 1 H, H-1′), 6.51 (s, 1 H, H-3), 7.24 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.8 (C-5), 179.0 (C-12), 171.1 ($COOCH_3$), 160.8 (C-6), 155.8 (C-4), 148.6 (C-1), 143.6 (C-10a), 138.2 (C-2), 132.8 (C-11a), 129.8 (C-6a), 125.8 (C-3), 121.2 (C-11), 115.8 (C-12a), 114.2 (C-4a), 112.9 (C-5a), 97.8 (C-1′), 75.2 (C-5′), 72.9 (C-2′), 70.5 (C-4′), 70.1 (C-9), 69.5 (C-7), 65.9 (C-3′), 58.0 (C-7 CH_3O), 57.5 (C-10), 52.0 ($COOCH_3$), 41.5 [$(CH_3)_2N$], 37.6 (C-8), 28.9 (C-9 CH_3), 23.9 (C-5′ CH_3); mass spectrum, m/e 599.

Anal. Calcd for $C_{30}H_{33}NO_{12}$: C, 60.16; H, 5.51; N, 2.34. Found: C, 58.57; H, 5.53; N, 2.32.

7-Dis-*O*-ethylnogalarol (1i). A solution of 10 g of **1a** in 500 mL of absolute C_2H_5OH 0.14 N in HCl was boiled for 5.5 h followed by overnight stirring at room temperature. The solution was concentrated to about 250 mL by evaporation under reduced pressure. It was diluted with 250 mL of H_2O and extracted with two 150-mL portions of $CHCl_3$. The aqueous residue was adjusted to pH 7 with 50% NaOH solution, and the neutral solution was extracted with one 200-mL portion and two 100-mL portions of $CHCl_3$. Evaporation of the combined extracts under reduced pressure gave a residue which was chromatographed on 450 g of

silica gel using $CHCl_3$–CH_3OH (95:5) and collecting 420 10-mL fractions. The fractions were pooled on the basis of TLC analysis using $CHCl_3$–CH_3OH–H_2O (78:20:2) into pool 1 (65–110) with R_f 0.74 and pool 2 (160–220) with R_f 0.64 although the second pool contained a little of the more mobile material. Evaporation of pool 2 under reduced pressure gave 1.74 g of **1i**: mp 186–190 °C dec; $[\alpha]_D$ +620° (*c* 0.131, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 47 550), 253 (25 250), 257 sh (25 100), 290 (10 500), 478 (16 250); IR (Nujol) 3440, 1735, 1665, 1620, 1575, 1285, 1250, 1220, 1145, 1100, 1055, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3 H, CH_3CH_2), 1.62, 1.74 (2 s, 6 H, 2 CH_3C), 2.62 [s, 6 H, $(CH_3)_2N$], 3.73 (s, 3 H, CH_3O), 2.18–2.46 (m, 2 H, CH_2), 2.95–4.1 (m, CH_2, CHO, CHN), 4.82 (m, 1 H, H-7), 5.87 (d, 1 H, H-1′), 6.68 (s, 1 H, H-3), 7.21 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.6 (C-5), 179.5 (C-12), 172.3 ($COOCH_3$), 161.6 (C-6), 155.8 (C-4), 148.0 (C-1), 142.9 (C-10a), 137.3 (C-2), 133.1 (C-11a), 131.6 (C-6a), 125.6 (C-3), 118.5 (C-11), 116.1 (C-12a), 114.3 (C-4a), 113.8 (C-5a), 97.5 (C-1′), 75.3 (C-5′), 72.9 (C-2′), 70.5 (C-4′), 70.5 (C-7), 69.5 (C-9), 66.0 (CH_3CH_2O), 65.6 (C-3′), 56.7 (C-10), 52.3 ($COOCH_3$), 41.5 [$(CH_3)_2N$], 38.7 (C-8), 30.0 (C-9 CH_3), 23.9 (C-5′ CH_3), 15.7 (CH_3CH_2); mass spectrum, *m/e* 613.

Anal. Calcd for $C_{31}H_{35}NO_{12}$: C, 60.69; H, 5.71; N, 2.28. Found: C, 59.85; H, 5.87; N, 2.00.

7-Con-*O*-ethylnogalarol (1j). Evaporation of pool 1, from chromatography in the previous experiment, under reduced pressure gave 1.56 g of residue. Three hundred milligrams was chromatographed by high-performance LC on 20 g of silica gel by using $CHCl_3$–CH_3OH (98:2) and collecting 65 5-mL fractions. Fractions 31–50 were pooled on the basis of TLC analysis ($CHCl_3$–CH_3OH–H_2O, 78:20:2). The pool was evaporated under reduced pressure to give 13 mg of product. An elemental analysis and IR spectrum were obtained on this sample, but other data were obtained on the 1.56-g sample: mp 255–260 °C dec; $[\alpha]_D$ +698° (*c* 0.0975, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 45 800), 258 (22 050), 288 sh (10 750), 480 (14 900); IR (Nujol) 3460, 3180, 1740, 1665, 1620, 1575, 1300, 1275, 1255, 1220, 1105, 1055, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3 H, CH_3CH_2), 1.55, 1.76 (2 s, 6 H, 2 CH_3C), 2.61 [s, 6 H, $(CH_3)_2N$], 2.1–2.5 (m, 2 H, CH_2), 3.73 (s, 3 H, CH_3O), 3.0–4.5 (m, 7 H, CHO, CHN), 4.91 (s, 1 H, OH), 5.06 (m, 1 H, H-7), 5.92 (d, 1 H, H-1′), 6.52 (s, 1 H, H-3), 7.23 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.8 (C-5), 178.9 (C-12), 171.0 ($COOCH_3$), 160.7 (C-6), 155.7 (C-4), 148.5 (C-1), 143.5 (C-10a), 138.1 (C-2), 132.7 (C-11a), 130.2 (C-6a), 125.7 (C-3), 121.3 (C-11), 115.8 (C-12a), 114.2 (C-4a), 112.8 (C-5a), 97.9 (C-1′), 75.2 (C-5′), 72.8 (C-2′), 70.5 (C-4′), 69.5 (C-9), 68.4 (C-7), 66.0 (CH_3CH_2O), 66.0 (C-3′), 57.5 (C-10), 52.0 ($COOCH_3$), 41.5 [$(CH_3)_2N$], 38.0 (C-8), 29.8 (C-9 CH_3), 23.9 (C-5′) CH_3C), 15.4 (CH_3CH_2); mass spectrum, *m/e* 613.

Anal. Calcd for $C_{31}H_{35}NO_{12}$: C, 60.69; H, 5.71; N, 2.28. Found: C, 59.42; H, 5.76; N, 2.17.

7-Dis-*O*-*n*-propylnogalarol (1k). A solution of 10 g of **1a** in 500 mL of 1-propanol 0.14 N in HCl was boiled for 2.5 h followed by evaporation under reduced pressure to a volume of ca. 200 mL. The solution was diluted with 500 mL of H_2O and extracted with two 150-mL portions of $CHCl_3$. The extracts were combined and evaporated under reduced pressure to a thick residue which was diluted with a large volume of Skellysolve B. The precipitate was removed by filtration and dissolved in 50 mL of water. The solution was adjusted to pH 7 with 50% NaOH solution and extracted with three 25-mL portions of $CHCl_3$. Evaporation of the combined extracts under reduced pressure gave 1.5 g of residue which was a mixture of two isomers as judged by TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2). The aqueous residue remaining after the $CHCl_3$ extraction was again neutralized as above and extracted with three 150-mL portions of $CHCl_3$ which were combined and evaporated to dryness under reduced pressure. The residue was dissolved in 150 mL of CH_3COCH_3, and 350 mL of Skellysolve B was added. The yield of solid after filtration was 5.6 g. This material was very similar, as judged by TLC, to the 1.5-g sample previously obtained.

The first residue isolated (1.5 g) was chromatographed by high-performance LC on a 60-g silica gel column using $CHCl_3$–CH_3OH (95:5) for elution. Ten-milliliter fractions were collected until two colored materials had been eluted. Fractions 71–90 (the second material eluted) were combined and evaporated under reduced pressure: yield 0.37 g. A 106-mg sample was chromatographed on 20 g of silica gel by using $CH_3COCH_2CH_3$–CH_3COCH_3–H_2O (73:23:4) as the eluent and collecting 10-mL fractions. Fractions 6–13 were combined on the basis of TLC (above system; R_f 0.66) and evaporated under reduced pressure to yield 56 mg of **1k**: mp 161–167 °C dec; $[\alpha]_D$ +528° (*c* 0.381, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 48 550), 259 (22 500), 288 sh (8850), 479 (14 600); IR (Nujol) 3440, 3170, 1735, 1660, 1625, 1575, 1300, 1285, 1220, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, 3 H, $CH_3CH_2CH_2$), 1.59, 1.73 (2 s, 6 H, 2 CH_3C), 2.1–2.55 (m, 4 H, CH_2), 2.62 [s, 6 H, $(CH_3)_2N$], 3.74 (s, 3 H, CH_3O), 3.1–4.5 (m, CHO, CHN), 4.85 (m, 1 H, H-7), 5.92 (d, 1 H, H-1′), 6.68 (s, 1 H, H-3), 7.22 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.6 (C-5), 179.5 (C-12), 172.2 ($COOCH_3$), 161.9 (C-6), 155.7 (C-4), 147.9 (C-1), 142.9 (C-10a), 137.3 (C-2), 133.0 (C-11a), 131.6 (C-6a), 125.6 (C-3), 118.6 (C-11), 116.1 (C-12a), 114.3 (C-4a), 113.7 (C-5a), 97.5 (C-1′), 75.2 (C-5′), 72.9 (C-2′), 72.2 ($CH_3CH_2CH_2$), 70.4 (C-4′), 70.4 (C-7), 69.8 (C-9), 65.9 (C-3′), 56.8 (C-10), 52.3 ($COOCH_3$), 41.5 [$(CH_3)_2N$], 38.2 (C-8), 30.1 (C-9 CH_3), 24.0 (C-5′ CH_3), 23.1 ($CH_3CH_2CH_2$), 11.0 ($CH_3CH_2CH_2$); mass spectrum (FD), *m/e* 627.

Anal. Calcd for $C_{32}H_{37}NO_{12}$: C, 61.30; H, 5.95; N, 2.23. Found: C, 59.86; H, 6.29; N, 1.99.

7-Con-*O*-*n*-propylnogalarol (1l). Fractions 18–40 from the first chromatography in the preceding experiment were combined and evaporated under reduced pressure. The residue was dissolved in 5 mL of CH_3COCH_3, and 75 mL of Skellysolve B was added. The resulting precipitate was removed by filtration: yield 0.48 g; homogeneous by TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2), R_f 0.73: mp 190–211 °C dec; $[\alpha]_D$ +586° (*c* 0.191, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 48 450), 258 (22 800), 287 (10 250), 481 (15 150); IR (Nujol) 3460, 3180, 1745, 1665, 1620, 1575, 1300, 1280, 1255, 1225, 1105, 1055, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, $CH_3CH_2CH_2$), 1.64, 1.70 (2 s, 6 H, 2 CH_3C), 1.95–2.5 (m, 4 H, CH_2), 2.62 [s, 6 H, $(CH_3)_2N$], 3.75 (s, 3 H, CH_3O), 2.9–4.5 (m, CHO, CHN), 4.86 (s, 1 H, OH), 5.02 (m, 1 H, H-7), 5.89 (d, 1 H, H-1′), 6.48 (s, 1 H, H-3), 7.18 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.7 (C-5), 178.9 (C-12), 171.0 ($COOCH_3$), 160.7 (C-6), 155.5 (C-4), 148.5 (C-1), 143.6 (C-10a), 138.2 (C-2), 132.6 (C-11a), 130.2 (C-6a), 125.7 (C-3), 121.2 (C-11), 115.7 (C-12a), 114.1 (C-4a), 112.8 (C-5a), 97.7 (C-1′), 75.1 (C-5′), 72.7 (C-2′), 72.3 ($CH_3CH_2CH_2O$), 70.4 (C-4′), 69.5 (C-9), 68.6 (C-7), 65.8 (C-3′), 57.5 (C-10), 51.9 ($COOCH_3$), 41.5 [$(CH_3)_2N$], 37.9 (C-8), 29.7 (C-9 CH_3), 23.9 (C-5′ CH_3), 23.1 ($CH_3CH_2CH_2$), 10.5 ($CH_3CH_2CH_2$); mass spectrum (FD), *m/e* 627.

Anal. Calcd for $C_{32}H_{37}NO_{12}$: C, 61.30; H, 5.95; N, 2.23. Found: C, 60.83; H, 6.16; N, 2.04.

7-Dis-*O*-methylnogarol (1m). A solution of 30 g of **1c** in 1.2 L of CH_3OH 0.4 N in HCl was boiled for 4 h. The reaction mixture was concentrated to 600 mL by distillation under reduced pressure, and the residue was diluted with 600 mL of H_2O. The pH was adjusted to 7.3 with 50% NaOH solution followed by extraction with five 300-mL portions of $CHCl_3$ while maintaining a constant pH in the aqueous phase by addition of more base. The combined extracts were concentrated under reduced pressure to give a dark red residue. The residue was chromatographed by high-performance LC on a 500-g silica gel column using $CHCl_3$–CH_3OH (95:5) and collecting 400-mL fractions and was analyzed by TLC using $CHCl_3$–CH_3OH–H_2O (78:20:2). Fractions 4 and 5 were combined and evaporated to give **1n** (12.3 g, R_f 0.69 in the above solvent). Fractions 7–14 were combined and evaporated under reduced pressure to give 6.7 g of crude **1m**.

Sixteen grams of material (**1m**) prepared in this fashion was chromatographed on 175 g of silica gel using $CHCl_3$–CH_3OH (95:5). After 2.8 L of effluent had been collected, **1m** began to appear in the eluate as the second color maximum, and a 2-L fraction was collected. Evaporation under reduced pressure gave 3 g. This material was chromatographed on 50 g of silica gel using the above solvent system and collecting 10-mL fractions. Fractions 75–100 were combined on the basis of TLC (78:20:2 $CHCl_3$–CH_3OH–H_2O; R_f 0.52). Evaporation under reduced pressure gave 1.05 g: mp 184–191 °C dec; $[\alpha]_D$ +480° (*c* 0.1305, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 49 750), 259.5 (24 050), 288 (9250), 476 (15 400); IR (Nujol) 3400, 3200, 1660, 1620, 1575, 1285, 1220, 1120, 1095, 1055, 1005 cm^{-1}; ^1H NMR ($CDCl_3$–CD_3OD) δ 1.43, 1.72 (2 s, 6 H, 2 CH_3C), 2.06 (dd, 1 H, *J* = 6, 14 Hz, H-8a), 2.23 (dd, 1 H, *J* = 3.5, 14 Hz, H-8b), 2.47 [s, 6 H, $(CH_3)_2N$], 2.80 (d, 1 H, *J* = 16 Hz, H-10a), 3.02 (d, 1 H, *J* = 16 Hz, H-10b), 3.35 (dd, 1 H, *J* = 12 Hz, H-3′), 3.49 (s, 3 H, CH_3O), 3.59 (d, 1 H, *J* = 12 Hz, H-4′), 4.07 (dd, 1 H, *J* = 3, 12 Hz, H-2′), 4.76 (t, 1 H, *J* = 3.5 Hz, H-7), 5.74 (d, 1

H, J = 3.0 Hz, H-1′), 7.19 (s, 1 H, H-3), 7.21 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.8 (C-5), 180.1 (C-12), 161.2 (C-6), 155.8 (C-4), 147.5 (C-1), 147.0 (C-10a), 136.9 (C-2), 133.0 (C-11a), 130.8 (C-6a), 125.4 (C-3), 119.8 (C-11), 116.7 (C-12a), 114.6 (C-4a), 113.2 (C-5a), 97.3 (C-1′), 75.0 (C-5′), 72.8 (C-2′), 71.3 (C-7), 70.4 (C-4′), 69.8 (C-9), 66.2 (C-3′), 57.5 (CH_3O), 44.7 (C-10), 41.5 [$(CH_3)_2N$], 36.2 (C-8), 30.4 (C-9 CH_3), 23.9 (C-5′ CH_3); mass spectrum, m/e 541.

Anal. Calcd for $C_{28}H_{31}NO_{10}$: C, 62.16; H, 5.78; N, 2.59. Found: C, 60.52; H, 5.89; N, 2.51.

7-Con-*O*-methylnogarol (1n). (a) By Methanolysis. Twenty-five grams of crude **1n** prepared as indicated in the previous experiment was chromatographed on 1 kg of silica gel by using CH_3CN–$CHCl_3$–CH_3OH (75:15:10) until 18 L of effluent had been collected, and then $CHCl_3$–CH_3OH (9:1) was used as eluent until a total of 30 L had been collected. The first 8 L of eluate was discarded, and the next 10 L was retained as well as 6 L more as a separate fraction. Evaporation of the first fraction under reduced pressure left 5.2 g of residue. Similar evaporation of the second fraction gave 6.0 g of product. The second residue was dissolved in 560 mL of CH_2Cl_2–CH_3OH (15:3) to which was added 300 mL of toluene. The solution was distilled until 270 mL of distillate had been collected. The resulting precipitate was collected by filtration; yield 5.15 g.

Ten grams of the combined products was dissolved in a mixture of 250 mL of 0.1 M glucuronic acid solution, 150 mL of H_2O, and 400 mL of CH_3OH. The solution was stirred for 0.5 h and filtered. The filtrate was adjusted to pH 7.3 with 50% NaOH solution and stirred for 40 min. The resulting precipitate was removed by filtration and washed with 50% CH_3OH: yield 8.2 g, mp 238–240 °C dec; $[\alpha]_D$ +895° (c 0.26, $CHCl_3$); UV (C_2H_5OH) 235 nm (ε 46 250), 252 (28 100), 257 sh (25 750), 290 sh (10 600), 478 (16 400); IR (Nujol) 3470, 1675, 1625, 1580, 1470, 1430, 1405, 1385, 1300, 1230, 1135, 1115, 1085, 1065, 1015, 950, 925, 890, 870, 850, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$–CD_3OD) δ 1.45, 1.73 (2 s, 6 H, 2 CH_3C), 1.85 (dd, 1 H, J = 3.5, 14 Hz, H-8a), 2.48 (dd, 1 H, H-8b), 2.53 [s, 6 H, $(CH_3)_2N$], 2.6–2.95 (m, H-10, H-3′), 3.57 (s, 3 H, CH_3O), 3.63 (d, 1 H, H-4′), 4.15 (dd, 1 H, J = 4, 11 Hz, H-2′), 4.84 (s, 1 H, H-7), 5.89 (d, 1 H, J = 4 Hz, H-1′), 6.68 (s, 1 H H-3), 7.22 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 190.9 (C-5), 179.7 (C-12), 161.1 (C-6), 155.6 (C-4), 148.2 (C-1), 146.2 (C-10a), 137.7 (C-2), 133.0 (C-11a), 129.3 (C-6a), 125.6 (C-3), 120.5 (C-11), 116.2 (C-12a), 114.5 (C-4a), 112.6 (C-5a), 97.6 (C-1′), 75.2 (C-5′), 72.8 (C-2′), 71.4 (C-7), 70.5 (C-4′), 68.3 (C-9), 66.1 (C-3′), 57.9 (CH_3O), 44.1 (C-10), 41.6 [$(CH_3)_2N$], 36.1 (C-8), 30.0 (C-9 CH_3), 23.9 (C-5′ CH_3); mass spectrum, m/e 541.

Anal. Calcd for $C_{28}H_{31}NO_{10}$: C, 62.10; H, 5.78; N, 2.59. Found: C, 61.93; H, 5.96; N, 2.58.

(b) By the CF_3COOH Procedure. A solution of 1 g of **1c** in 20 mL of CF_3COOH was cooled in an ice bath and stirred for 5 h. Stirring was continued while a solution of CH_3ONa in CH_3OH was added dropwise until the reaction mixture turned purple. A 100-mL portion of H_2O was added, the pH was adjusted to 7.0 with additional CH_3ONa, and the mixture was extracted with three 100-mL portions of CH_2Cl_2. The combined extracts were evaporated to dryness under reduced pressure to yield 1.004 g of residue. A mixture of 0.5 g of the residue, 15 mL of 0.1 M glucuronic acid solution, 10 mL of H_2O, and 10 mL of CH_3OH was stirred for 15 min and filtered. The filtrate was neutralized (pH 7.0) with 1 N NaOH solution and stirred while being maintained at pH 7. After about 30 min, the precipitate was collected by filtration; yield 211 mg. TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2) indicated the material was homogeneous and identical with **1n** prepared by methanolysis: $[\alpha]_D$ +897° (c 0.1525, $CHCl_3$); ^{13}C NMR identical with that of **1n**; mass spectrum, m/e 541.

Anal. Found: C, 61.65; H, 5.82; N, 2.56.

7-Dis-*O*-ethylnogarol (1o). A solution of 2 g of **1c** in 150 mL of absolute C_2H_5OH 0.093 N in HCl was boiled for 8 h. It was then stirred overnight at room temperature. About half of the C_2H_5OH was removed by evaporation under reduced pressure, and the remainder was diluted with 100 mL of H_2O. Extraction of the aqueous solution with three 100-mL portions of $CHCl_3$ and combination and evaporation of the extracts under reduced pressure gave 1.98 g of residue. This material was chromatographed by high-performance LC on 60 g of silica gel, eluting with $CHCl_3$–CH_3OH (95:5); 150 10-mL fractions were collected. On the basis of TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2), fractions 17–36 were combined as pool 1, and fractions 110–145 were combined as pool 2 which was evaporated under reduced pressure to yield 0.32 g of **1o**: mp 172–175 °C dec; $[\alpha]_D$ +487° (c 0.218, $CHCl_3$); R_f 0.55 in the above system; UV (C_2H_5OH) 236 nm (ε 43 700), 260 (22 300), 288 sh (8550), 476 (13 950); IR (Nujol) 3400, 3250, 3080, 1655, 1620, 1605, 1575, 1280, 1220, 1120, 1055, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, 3 H, CH_3CH_2), 1.38, 1.72 (2 s, 6 H, 2 CH_3C), 2.04–2.24 (m, 2 H, H-8), 2.50 [s, 6 H, $(CH_3)_2N$], 2.68–4.25 (m, 9 H, CHO, CHN), 4.81 (m, 1 H, H-7), 5.74 (d, 1 H, H-1′), 7.19 (s, 2 H, H-3, H-11); ^{13}C NMR ($CDCl_3$) δ 190.7 (C-5), 180.1 (C-12), 161.2 (C-6), 155.6 (C-4), 147.6 (C-1), 147.4 (C-10a), 136.8 (C-2), 132.9 (C-11a), 131.3 (C-6a), 125.3 (C-3), 119.9 (C-11), 116.5 (C-12a), 114.6 (C-4a), 113.1 (C-5a), 97.1 (C-1′), 75.1 (C-5′), 72.7 (C-2′), 70.1 (C-4′), 69.7 (C-9), 69.4 (C-7), 66.1 (C-3′), 65.1 (CH_3CH_2O), 44.6 (C-10), 41.5 [$(CH_3)_2N$], 42.0 (C-8), 30.5 (C-9 CH_3), 24.0 (C-5′ CH_3), 15.7 (CH_3CH_2); mass spectrum, m/e 555.

Anal. Calcd for $C_{29}H_{33}NO_{10}$: C, 62.70; H, 5.95; N, 2.52. Found: C, 60.35; H, 5.93; N, 2.75.

7-Con-*O*-ethylnogarol (1p). Evaporation of pool 1 from the preceding experiment under reduced pressure gave 0.30 g of **1p** homogeneous by TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2; R_f 0.70): mp 190–200 °C dec; $[\alpha]_D$ +822° (c 0.114, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 38 050), 252 (33 950), 258 sh (26 250), 270 (20 800), 293 (11 555), 480 (16 700); IR (Nujol) 3440, 1660, 1615, 1570, 1285, 1220, 1120, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$–CD_3OD) δ 1.25 (t, 3 H, CH_3CH_2), 1.50, 1.77 (2 s, 6 H, 2 CH_3C), 2.01 (m, 1 H, H-8a), 2.38 (m, 1 H, H-8b), 2.62 [s, 6 H, $(CH_3)_2N$], 2.82 (m, 2 H, H-10), 3.0–4.40 (m, CHO, CHN), 5.0 (m, 1 H, H-7), 5.98 (d, 1 H, H-1′), 6.64 (s, 1 H, H-3), 7.28 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.9 (C-5), 179.5 (C-12), 161.2 (C-6), 155.7 (C-4), 148.3 (C-1), 146.3 (C-10a), 137.7 (C-2), 132.7 (C-11a), 129.7 (C-6a), 125.5 (C-3), 120.5 (C-11), 116.1 (C-12a), 114.4 (C-4a), 112.5 (C-5a), 97.6 (C-1′), 75.1 (C-5′), 72.7 (C-2′), 70.6 (C-4′), 69.7 (C-9), 68.0 (C-7), 66.1 (C-3′), 66.1 (CH_3CH_2O), 44.1 (C-10), 41.6 [$(CH_3)_2N$], 36.9 (C-8), 30.2 (C-9 CH_3), 23.9 (C-5′ CH_3), 15.4 (CH_3CH_2); mass spectrum, m/e 555.

Anal. Calcd for $C_{29}H_{33}NO_{10}$: C, 62.70; H, 5.95; N, 2.52. Found: C, 61.66; H, 6.40; N, 3.01.

7-Dis-*O*-*n*-propylnogarol (1q). A solution of 5 g of **1c** in 250 mL of n-C_3H_7OH 0.14 N in HCl was boiled for 2 h. The solution was evaporated under reduced pressure to about half of its original volume and diluted with 250 mL of H_2O. This solution was extracted with two 75-mL portions of $CHCl_3$ followed by adjustment to pH 7.0 with 50% NaOH solution. The neutralized solution was extracted with three 75-mL portions of $CHCl_3$. The combined extracts were evaporated under reduced pressure to give 3.5 g of residue.

The residue was chromatographed on 200 g of silica gel, eluting with $CHCl_3$–CH_3OH (95:5), and 350 10-mL fractions were collected. The fractions were pooled on the basis of TLC analysis ($CHCl_3$–CH_3OH–H_2O, 78:20:2) as follows. Fractions 125–175 were combined as **1r** (R_f 0.69 in the above solvent). Evaporation under reduced pressure gave 0.81 g of residue. Fractions 310–350 were combined and evaporated under reduced pressure to give 0.34 g of **1q**. A portion of this was recrystallized from acetone to give material homogeneous by TLC in the above system (R_f 0.57): mp 199–212 °C dec; $[\alpha]_D$ +469° (c 0.16, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 44 950), 260 (23 050), 290 (8700), 477 (14 500); IR (Nujol) 3440, 1660, 1620, 1575, 1290, 1220, 1115, 1095, 1055, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3 H, $CH_3CH_2CH_2$), 1.45, 1.78 (2 s, 6 H, 2 CH_3C), 2.1–2.35 (m, 2 H, H-8), 2.58 [s, 6 H, $(CH_3)_2N$], 2.7–4.2 (m, 9 H, CHO, CHN), 4.83 (m, 1 H, H-7), 5.82 (d, 1 H, H-1′), 7.22 (s, 1 H, H-3), 7.26 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.5 (C-5), 180.0 (C-12), 161.3 (C-6), 155.7 (C-4), 147.4 (C-1), 147.1 (C-10a), 136.8 (C-2), 132.8 (C-11a), 131.3 (C-6a), 125.3 (C-3), 119.8 (C-11), 116.6 (C-12a), 114.5 (C-4a), 113.1 (C-5a), 97.2 (C-1′), 75.0 (C-5′), 72.7 (C-2′), 71.8 ($CH_3CH_2CH_2O$), 70.1 (C-4′), 69.8 (C-9), 69.8 (C-7), 66.1 (C-3′), 44.6 (C-10), 41.8 (C-8), 41.8 [$(CH_3)_2N$], 30.5 (C-9 CH_3), 24.0 (C-5′ CH_3), 23.5 ($CH_2CH_2CH_2$), 10.9 ($CH_3CH_2CH_2$); mass spectrum, m/e 569.

Anal. Calcd for $C_{30}H_{35}NO_{10}$: C, 63.25; H, 6.15; N, 2.46. Found: C, 58.75; H, 5.83; N, 2.14.

7-Con-*O*-*n*-propylnogarol (1r). Three hundred milligrams of material from the previous experiment considered to be **1r** was chromatographed on 40 g of silica gel. Those fractions containing only **1r** as judged by TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2) were combined and evaporated under reduced pressure to give material

which was used for characterization: mp 193–204 °C dec; $[\alpha]_D$ +789° (c 0.199, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 53 600), 252 (33 750), 258 sh (31 300), 291 sh (13 100), 479 (19 900); IR (Nujol) 3460, 1660, 1615, 1590, 1575, 1290, 1220, 1105, 1055, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, $CH_3CH_2CH_2$), 1.48, 1.76 (2 s, 6 H, 2 CH_3C), 1.90–2.50 (m, 2 H, H-8), 2.60 [s, 6 H, $(CH_3)_2N$], 2.77–4.0 (m, 7-8 H, CHO, CHN), 4.98 (m, 1 H, H-7), 6.00 (d, 1 H, H-1′), 6.65 (s, 1 H, H-3), 7.29 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.9 (C-5), 179.5 (C-12), 161.3 (C-6), 155.7 (C-4), 148.3 (C-1), 146.2 (C-10a), 137.6 (C-2), 132.6 (C-11a), 129.7 (C-6a), 125.4 (C-3), 120.5 (C-11), 116.1 (C-12a), 114.4 (C-4a), 112.5 (C-5a), 97.7 (C-1′), 75.1 (C-5′), 72.7 (C-2′), 72.5 ($CH_3CH_2CH_2O$), 70.6 (C-4′), 69.9 (C-9), 68.0 (C-7), 66.0 (C-3′), 44.2 (C-10), 41.6 [$(CH_3)_2N$], 36.7 (C-8), 30.2 (C-9 CH_3), 23.8 (C-5′ CH_3), 23.2 ($CH_3CH_2CH_2$), 10.6 ($CH_3CH_2C-H_2$); mass spectrum, m/e 569.

Anal. Calcd for $C_{30}H_{35}NO_{10}$: C, 63.25; H, 6.15; N, 2.46. Found: C, 61.18; H, 6.52; N, 2.42.

7-Con-*O*-isopropylnogarol (1s). A solution of 250 mg of **1c** in 5 mL of CF_3COOH was stirred for 1.25 h at room temperature. A solution of $(CH_3)_2CHONa$ in $(CH_3)_2CHOH$ containing an excess of the isopropoxide was added, and the solution was stirred overnight. The volatile solvents were removed by evaporation under reduced pressure, and the residue was dissolved in 50 mL of H_2O. Extraction with three 20-mL portions of $CHCl_3$ and evaporation of the combined extracts under reduced pressure gave a red solid. The residue was chromatographed on 10 g of silica gel using CH_3CN–$CHCl_3$–CH_3OH (75:15:10) and collecting 5-mL fractions. Combination of fractions 18–40 on the basis of TLC (78:20:2 $CHCl_3$–CH_3OH–H_2O; R_f 0.62) and evaporation under reduced pressure gave 103 mg of product which still contained a small amount of a less polar component: mp 205.6–207 °C dec; $[\alpha]_D$ +779° (c 0.217, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 48 800), 259 (23 650), 289 (9150), 477 (15 250); IR (Nujol) 3420, 1660, 1615, 1565, 1455, 1370, 1280, 1210, 1140, 1110, 1095, 1050, 995, 775, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 [d, 6 H, $(CH_3)_2C$], 1.46, 1.74 (2 s, 6 H, 2 CH_3C), 2.0 (m, 1 H, H-8a), 2.33 (m, 1 H, H-8b), 2.58 [s, 6 H, $(CH_3)_2N$], 2.78–3.11 (m, 1 H, H-3′), 3.65 (d, 1 H, H-4′), 4.20 (m, 2 H, CHO), 4.95 (m, 1 H, H-7), 5.98 (d, 1 H, H-1′), 6.57 (s, 1 H, H-3), 7.27 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.9 (C-5), 179.5 (C-12), 161.2 (C-6), 155.6 (C-4), 148.3 (C-1), 146.5 (C-10a), 137.7 (C-2), 132.7 (C-11a), 130.1 (C-6a), 125.6 (C-3), 120.6 (C-11), 116.2 (C-12a), 114.4 (C-4a), 112.6 (C-5a), 97.6 (C-1′), 75.1 (C-5′), 72.7 (C-2′), 72.0 [$(CH_3)_2CHO$], 70.5 (C-4′), 68.1 (C-9), 67.4 (C-7), 66.0 (C-3′), 44.2 (C-10), 41.5 [$(CH_3)_2N$], 37.7 (C-8), 30.2 (C-9 CH_3), 23.9 (C-5′ CH_3), 23.2, 21.0 [$(CH_3)_2CH$]; mass spectrum, m/e 569.

Anal. Calcd for $C_{30}H_{35}NO_{10}$: C, 63.25; H, 6.15; N, 2.46. Found: C, 60.95; H, 5.98; N, 2.35.

7-Deoxynogarol (1t). A solution of **1e**, prepared with no purification from 13 g of **1a**,[3] in 217 mL of 0.53 N KOH was stirred overnight and adjusted to pH 5.0 with concentrated HCl. The precipitate was collected by centrifugation and dried under reduced pressure at 40 °C; yield 8.5 g. The principal component had R_f 0.68 on TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2). This material was dissolved in 950 mL of DMF by heating to 65 °C, and the DMF was removed by evaporation in a current of air; yield 7.2 g. One gram of this product was chromatographed on 95 g of silica gel using C_6H_6–CH_3COCH_3, starting with a 92.5:7.5 solvent ratio and at fraction 72 changing it to 87.5:12.5. A total of 234 5-mL fractions were collected of which fractions 110–200 were combined on the basis of TLC (above solvent, R_f 0.52). Evaporation under reduced pressure gave 594 mg of residue. Four hundred milligrams of this residue was dissolved in 5 mL of warm $CHCl_3$, and the solution was refrigerated. The precipitate which formed was collected: yield 130 mg, mp 265–267 °C dec; $[\alpha]_D$ +1150° (c 0.32, $CHCl_3$); UV (C_2H_5OH) 236 nm (ε 38 000), 261 (24 050), 290 sh (10 000), 474 (14 500); IR (Nujol) 3410, 1660, 1615, 1570, 1455, 1415, 1380, 1320, 1290, 1225, 1145, 1110, 1050, 1005, 965, 935, 915, 880, 855, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41, 1.73 (2 s, 6 H, 2 CH_3C), 1.93 (m, 1 H, H-8a), 2.55 [s, 6 H, $(CH_3)_2N$], 2.61–2.95 (m, 5 H, CH_2, CHN), 3.59 (m, 1 H, H-4′), 4.10 (dd, 1 H, H-2′), 5.80 (d, 1 H, H-1′), 6.55 (s, 1 H, H-3), 7.14 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.6 (C-5), 179.3 (C-12), 159.6 (C-6), 155.3 (C-4), 147.3 (C-1), 144.1 (C-10a), 136.7 (C-2), 132.0 (C-11a), 130.3 (C-6a), 124.9 (C-3), 120.1 (C-11), 115.9 (C-12a), 114.2 (C-4a), 111.3 (C-5a), 97.0 (C-1′), 74.7 (C-5′), 72.4 (C-2′), 70.2 (C-4′), 67.6 (C-9), 65.8 (C-3′), 42.9 (C-10), 41.3 [$(CH_3)_2N$], 33.6 (C-8), 30.0 (C-9 CH_3), 23.5 (C-5′ CH_3), 19.7 (C-7); mass spectrum, m/e 511.183 85 (calcd for $C_{27}H_{29}NO_9$, m/e 511.1842).

Anal. Calcd for $C_{27}H_{29}NO_9$: C, 63.40; H, 5.72; N, 2.76. Found: (corrected for 6.95% $CHCl_3$) C, 62.50; H, 5.68; N, 2.45.

Nogarene (2). A mixture of 2 g of **1c** and 60 mL of 0.5 N HCl was boiled for 18 h. The cooled mixture was adjusted to pH 7.7 with 2 N NaOH solution. After 48 h the precipitate was removed by filtration and sucked as dry as possible on the filter. The damp filter cake was stirred in 100 mL of H_2O for 3 h and again collected by filtration, sucking as dry as possible. Frequently this step gave a fine suspension which required centrifugation rather than filtration for collection. The filter cake was dried under reduced pressure at 55 °C: yield 1.23 g, mp 264–273 °C dec; UV (C_2H_5OH) 239 nm (ε 47 630), 260 (22 160), 294 (12 950), 476 (19 480), 498 (18 625); IR (Nujol) 3420, 3350, 1665, 1615, 1510, 1460, 1385, 1340, 1280, 1230, 1145, 1120, 1060, 1010, 980, 940, 920, 885, 865, 845, 820, 790, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (s, 3 H, C-5′ CH_3), 2.52 (s, 3 H, C-9 CH_3), 2.61 [s, 6 H, $(CH_3)_2N$], 2.90 (dd, 1 H, J = 10.5 Hz, H-3′), 3.65 (d, 1 H, J = 10.5 Hz, H-4′), 4.18 (dd, 1 H, J = 3.3, 10.5 Hz, H-2′), 5.92 (d, 1 H, J = 3.3 Hz, H-1′), 6.79 (s, 1 H, H-3), 7.19 (d, 1 H, J = 8.4 Hz, H-7), 7.28 (s, 1 H, H-10), 7.38 (s, 1 H, H-11), 8.06 (d, 1 H, J = 8.4 Hz, H-8); ^{13}C NMR ($CDCl_3$–CD_3OD) 189.4 (C-5), 180.2 (C-12), 162.0 (C-6), 155.5 (C-4), 147.4 (C-1), 142.7 (C-10a), 136.2 (C-2), 135.7 (C-9), 130.9 (C-10), 129.7 (C-7), 128.5 (C-11a), 124.8 (C-3), 124.3 (C-6a), 124.3 (C-8), 121.1 (C-11), 117.3 (C-12a), 115.4 (C-4a), 107.2 (C-5a), 97.2 (C-1′), 75.1 (C-5′), 72.7 (C-2′), 70.7 (C-4′), 66.4 (C-3′), 41.7 [$(CH_3)_2N$], 23.8 (C-5′ CH_3), 21.8 (C-9 CH_3); mass spectrum, m/e 491.1593 (calcd for $C_{27}H_{25}NO_8$, m/e 491.1580).

Anal. Calcd for $C_{27}H_{25}NO_8$: C, 65.98; H, 5.13; N, 2.85. Found: C, 64.48; H, 5.03; N, 2.58; ash, 0.81.

Conversion of 7-Con-*O*-methylnogarol (1n) to 7-Con-*O*-ethylnogarol (1p). A solution of 200 mg of **1n** in 2 mL of CF_3COOH was allowed to stand at room temperature for 0.5 h. While the reaction mixture was stirred, a solution of C_2H_5ONa in C_2H_5OH was added slowly until the mixture turned purple. The reaction mixture was poured into 50 mL of H_2O, and the solution was adjusted to pH 7.2 with 1 N HCl solution. The aqueous mixture was extracted with three 50-mL portions of CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a residue which was washed with Skellysolve B; yield 202 mg. This material was purified by preparative TLC using a 2-mm silica gel plate and the solvent system $CHCl_3$–CH_3OH–H_2O (78:20:2). The faster moving band was removed and extracted with $CHCl_3$–CH_3OH (9:1) as one fraction and the slower moving band as a second fraction. The first fraction gave 94 mg of product having the same R_f as **1p** in the above solvent system. Rechromatography of the material from the slower band gave another 30 mg of the same material and 3 mg of **1o**. The combined faster moving fractions were further identified as **1p** by mass (m/e 555) and ^1H NMR spectra.

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Registry No. **1a**, 1404-15-5; **1b**, 64267-45-4; **1c**, 64267-46-5; **1d**, 71628-92-7; **1g**, 62421-98-1; **1h**, 71628-93-8; **1i**, 71582-48-4; **1j**, 71628-94-9; **1k**, 71582-49-5; **1l**, 71628-95-0; **1m**, 64267-47-6; **1n**, 71628-96-1; **1o**, 71582-50-8; **1p**, 71628-97-2; **1q**, 71582-51-9; **1r**, 71628-98-3; **1s**, 71582-52-0; **1t**, 71582-53-1; **2**, 71582-54-2; $BaCO_3$, 513-77-9; CH_3OH, 67-56-1; C_2H_5OH, 64-17-5; *n*-propanol, 71-23-8; $(CH_3)_2CHOH$, 67-63-0.