dried over Na_2SO_4, and evaporated to dryness in vacuo to give a crystalline product as a salt of benzoic acid. Column chromatography of the salt on silica gel with $CHCl_3$–MeOH (10:1) gave a free base as an oil: yield 1.2 g (71%); bp 132 °C (1 mmHg); mass spectrum, *m/e* 164.0994 (calcd for $C_9H_{12}N_2O$, 164.0949).

Nonyl 3-Benzoyl-2,3-dimethyldithiocarbazate (20). Compound **20** was prepared from 1-benzoyl-1,2-dimethylhydrazine (1.32 g, 8 mmol) by the same procedure as that for 1. The product was obtained as a colorless viscous oil: yield 0.47 g (16%): NMR($CDCl_3$) δ 3.26 (s, 3 H, N^2-CH_3), 3.39 (s, 3 H, N^3-CH_3); mass spectrum *m/e* 366.1768 (calcd for $C_{19}H_{30}N_2OS_2$, 366.1799).

***S*-Methyl-*S'*-nonyl *N*-Benzoyl-*N*-methylcarbonohydrazonodithioate (21).** Compound **21** was prepared by methylation of **19** with methyl iodide by the same procedure as that for 17. The product was obtained as a colorless viscous oil: NMR ($CDCl_3$) δ 2.44 (s, 3 H, S-CH_3), 3.20 (s, 3 H, N-CH_3); mass spectrum, *m/e* 367.1871 (MH^+) (calcd for $C_{19}H_{31}N_2OS_2$, 367.1877).

Uncoupling Activity. Rat liver mitochondria were isolated as described previously.[10] The change in the respiratory rate of state 4 mitochondria on addition of test compound was monitored with a Clark oxygen electrode (Yellow Spring Instruments) with 10 mM succinate (plus 1 μg/mg of the protein rotenone) as substrate in an incubation medium consisting of 200 mM sucrose, 2 mM $MgCl_2$, 1 mM EDTA, and 10 mM potassium phosphate buffer, pH 7.2, at 25 °C. The amount of mitochondria was, in most cases, 0.7 mg/mL, and the volume of the reaction mixture was 4.35 mL. The uncoupling activity of the test compound was determined as the concentration required for maximal release of the respiration of mitochondria.

Acknowledgment. The authors thank Mrs. M. Ohe for elemental analyses and Mr. K. Kida and Mrs. Y. Yoshioka for recording NMR and mass spectra, respectively. This work was supported in part by a grant from the Ministry of Education, Science and Culture of Japan.

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Structure-Activity Relationships of Nogalamycin Analogues[1]

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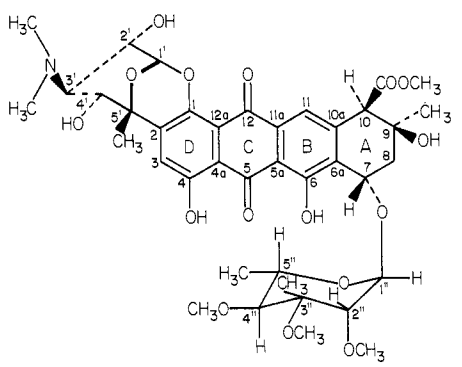
Nogalamycin (1) has been modified by changes at C-10 and C-7 and in the dimethylamino group to prepare an extensive series of analogues. The chemistry involved in the modifications and structure–activity relationships among these nogalamycin analogues are discussed, as well as comparisons with previously reported compounds 1, 7-con-*O*-methylnogarol (**2**), and disnogamycin (11).

Nogalamycin (**1**) is an antibiotic of the anthracycline



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family, and it, as is typical of members of this family, has long been known as an antitumor agent.[2] Because of the outstanding antitumor activity of Adriamycin and daunomycin, two members of the anthracycline family, it seemed worthwhile to prepare by chemical modification an extensive series of analogues of 1. Very early in this work it was found that replacement of the neutral sugar of 1 by various alkoxy groups gave compounds with considerable antitumor activity.[3] One of the members of this group, 7-con-*O*-methylnogarol (**2**), has been found to be sufficiently active that phase I clinical trials will be initiated in the near future. Introduction of groups other than alkoxy at C-7 in 1 and in disnogamycin (11) appeared warranted and are reported in this article, as are modifications involving the carbomethoxy group at C-10, the dimethylamino group, and acylation and alkylation of hydroxyl groups. The structure–activity relationships of these compounds based on in vitro cytotoxicity and in vivo activity against a murine leukemia are discussed.

Chemistry. The preparation of a series of analogues in which the carbomethoxy group at C-10 has been retained (the nogalarol series) and in which it has been removed (the nogarol series) and in which nogalose has been replaced by alkoxy groups has been reported.[1,4] Four more compounds of this type are reported here. Three of these (**3–5**) were prepared by the trifluoroacetic acid procedure previously reported[4] in which only the con[5] isomer is formed. In this reaction, disnogamycin (11) is treated with trifluoroacetic acid, followed by treatment with nucleophiles, which for these compounds were alkoxide anions. As has been the case previously, molecular ions in the mass

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(2) Bhuyan, B. K.; Reusser, F. *Cancer Res.* **1970**, *30*, 984.
(3) Neil, G. L.; Kuentzel, S. L.; McGovren, J. P. *Cancer Treat. Rep.* **1979**, *63*, 1971.
(4) Wiley, P. F.; Elrod, D. W.; Houser, D. J.; Johnson, J. L.; Pschigoda, L. M.; Krueger, W. C.; Moscowitz, A. *J. Org. Chem.* **1979**, *44*, 4030.
(5) Structure 1 is assigned to nogalamycin based on X-ray crystallography of **2** and on an extensive series of circular dichroism studies.[4] The X-ray studies have provided only relative stereochemistry, and it is felt that aside from the nogalose moiety, absolute stereochemistry is not sufficiently established to use *R* and *S* designations for compounds isomeric at C-7. Consequently, nomenclature is not based on absolute stereochemistry at C-7 and C-9 but on relative stereochemistry. Those compounds in which hydroxyls at C-9 and C-7 are cis are called con. If these groups are trans, the prefix dis is used. The cis–trans nomenclature was not used because a third group, the amino sugar, can also be cis or trans to a substituent at C-7. **Note Added in Proof:** Dr. S. K. Arora of the University of Arizona has recently established the complete stereochemistry of 1 by X-ray crystallography studies. C-7, C-9, and C-10 are *S*, *S*, and *R*, respectively, with the amino sugar having the α-L configuration. Because of these findings, the nomenclature has been changed so that con compounds are 7*R* and dis compounds are 7*S*.

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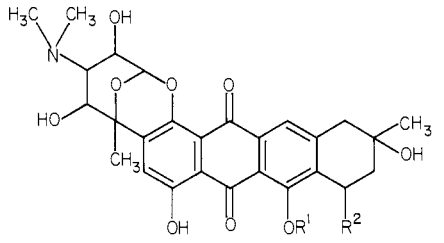
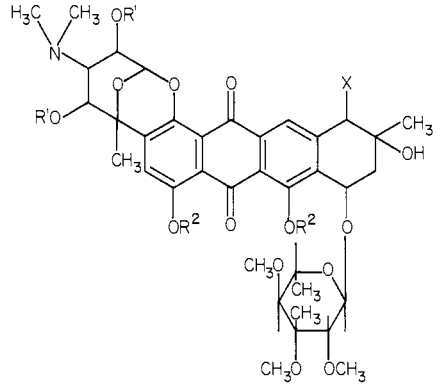


2, R^1 = H; R^2 = CH_3O
3, R^1 = H; R^2 = CH_2=$CHCH_2O$
4, R^1 = H; R^2 = $CH{\equiv}CCH_2O$
5, R^1 = H; R^2 = $BrCH_2CH_2O$
6, R^1 = CH_3; R^2 = CH_3O
7, R^1 = H; R^2 = NH_2
8, R^1 = H; R^2 = $CH_3OCH_2CH_2NH$
9, R^1 = H; R^2 = N_3
10, R^1 = H; R^2 = CH_3S



11, R^1 = R^2 = X = H
12, R^1 = CH_3CO; R^2 = CH_3CO or H; X = H
13, R^1 = CH_3CO; R^2 = H; X = $COOCH_3$
14, R^1 = CH_3CO; R^2 = X = H

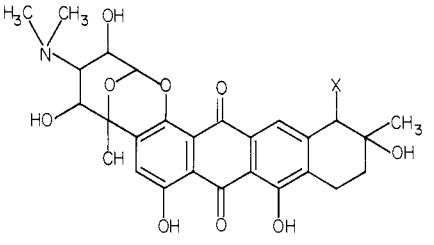
spectra were difficult to obtain because of ready loss of groups in ring A. Analyses were usually poor for carbon, which is at least partially due to retention of solvent. A compound (6) having methoxyl groups at C-6 and C-7 was prepared by treatment of 7-con-*O*-methylnogarol (2) with diazomethane. The assignment of methylation to oxygen at C-6 rather than to the more readily accessible oxygen at C-4 was based on the ^{13}C NMR spectrum in which the downfield shift of the resonances arising from C-5a and C-6a was much greater than were those for C-3 and C-4a.

A fairly large series of 7-amino analogues was prepared, but these compounds proved extremely difficult to purify, and most are not reported here due to failure to obtain compounds approaching purity. These compounds (7 and 8) were prepared in the same manner as the 7-alkoxy compounds, except that appropriate amines were used as nucleophiles. An amine variant (9) having an azido group at C-7 was prepared similarly. Here again these compounds gave rather poor carbon analyses, but mass spectra did show a molecular ion. The introduction of nitrogen at C-7 could be readily detected, as the chemical shift for C-7 moved substantially upfield in the ^{13}C NMR spectra.

Only one compound (10) was prepared having sulfur substituted at C-7. Introduction of CH_3S at C-7 was by the procedure already discussed.

Acetylation of nogalamycin and its analogues has, in general, given mixtures which were difficult to purify, partly because of the presence of compounds having varying numbers of acetyl groups and partly because the acetates were somewhat unstable. However, a poor yield of a triacetylated disnogamycin (12) has been obtained by acetyl chloride treatment of disnogamycin (11) in refluxing THF. Mass spectra and NMR spectra established the presence of three acetyl groups, but their positions were not rigorously established. The chemical shift for C-5 in the ^{13}C NMR spectrum showed that it was still hydrogen bonded[6] so not more than one phenolic hydroxyl can be acetylated, and it was assumed that C-2′, C-4′, and phenolic hydroxyls would be acetylated in preference to the C-9 hydroxyl. Consequently, acetylation must be at C-2′, C-4′, and either C-4 or C-6. The C-2′ and C-4′ hydroxyls of 1 and 11 have been acetylated selectively in good yield by treatment of these compounds in methanol with acetic anhydride to give 13 and 14. Presumably, such acetylation is possible because of the neighboring basic group. The presence of two acetyl groups and their position (downfield shift of protons at C-2′ and C-4′) were established by ^{13}C and ^1H NMR spectra.

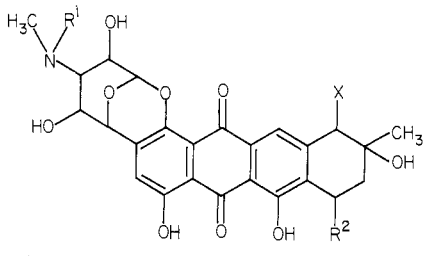
Compounds lacking substitution at C-7 have been reported previously.[2-4,6] Preparation was by catalytic hydrogenolysis of the C-7 carbon–oxygen bond to give 15,



15, X = $COOCH_3$
16, X = COOH
17, X = H

followed by further modification. Two more such compounds have been prepared in which the group at C-10 has been altered. Treatment of 7-deoxynogalarol (15) with half normal base by the previously reported procedure,[4] followed by acidification, gave 7-deoxynogalarolic acid (16), which was readily decarboxylated to 7-deoxynogarol (17).

Solutions of nogalamycin and its analogues have long been known to degrade if not protected from light. It has now been found that the change occurring involves loss of the methyl group from the nitrogen or its conversion to a formyl group. Solutions of 1, 2, 11, and 17 in $CHCl_3$ or $CHCl_3$–CH_3OH were placed in a window so that outside light impinged on them directly. In a few hours in bright sunlight, conversion to the degradation products 18, 19,



18, R^1 = H; R^2 = nogalosyl; X = $COOCH_3$
19, R^1 = HCO; R^2 = nogalosyl; X = $COOCH_3$
20, R^1 = CH_3CO; R^2 = nogalosyl; X = $COOCH_3$
21, R^1 = H; R^2 = nogalosyl; X = H
22, R^1 = HCO; R^2 = nogalosyl; X = H
23, R^1 = H; R^2 = CH_3O; X = H
24, R^1 = HCO; R^2 = CH_3O; X = H
25, R^1 = HCO; R^2 = X = H

and 21–25 occurred. In cloudy weather the reactions required up to 2 weeks, but under a commercial irradiation apparatus it occurred in about 2 h. Purification of the

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Table I. In Vitro and In Vivo Activities

no.	L1210 in vitro act.[a]		P-388 in vitro act.[b]		wt change, g/mouse
	ID_{50}	ID_{90}	opt dose, (mg/kg)/day	% ILS	
1	0.078	0.18	1	49	−0.5
2	0.061	0.13	12.5	197	−0.4
3	0.18	0.53	5	25	+0.3
4	0.15	0.32	10	41	−0.7
5	0.024	0.071	16	60	−1.3
6	4.5	9.7	20	25	+0.6
7	0.97	2.0	40	47	+0.2
8	1.04	2.91	40	40	+0.2
9	0.83	1.76	5	33	−0.3
10	0.13	0.34	8	37	−3.1
11	0.18	0.27	5	93	−0.2
12	0.017	0.041	20	37	−0.1
13	0.069	0.185	6.25	3	−0.3
14	0.076	0.21	50	41	−0.6
15	0.58	1.51	50	27	−0.7
16	5.6	14.5	400	−4	+0.2
17	0.94	1.76	100	21	−1.2
18	0.36	0.90	25	59	−0.5
19	>1	>1	25	12	−0.1
21	0.88	>1	33	24	−0.6
22	>1	>1	50	0	+0.1
23	0.38	0.11	1.25	73	−1.3
24	4.3	>5			

[a] Activities against L1210 cells are expressed as the micromolar concentration necessary to inhibit cell growth by 50 and 90%. [b] P-388 leukemia cells (10^6) were injected intraperitoneally on day 0, and drug was injected daily on days 1–9 except for 12–14, 18, 19, and 21–23, which were injected on days 1, 5, and 9.

N-demethyl products was quite difficult. Consequently, *N*-demethylnogalamycin (**18**) was purified as its *N*-acetyl derivative (**20**), and 7-con-*O*-methyl-*N*-demethylnogarol (**23**) was purified as its hydrochloride. The loss of an N-CH_3 group was shown by isolation of methylamine from **18**, **22**, and **25** and by the absence of the resonance due to a dimethylamino group in the NMR spectra. The presence of the N-CHO group was shown by lack of basicity, mass spectra, and a chemical shift in the ^{13}C NMR spectra at about δ 165. N-Demethylation by irradiation has been observed previously, but the departing methyl was isolated as formaldehyde.[7] In the present case, it seems probable that formylation occurs during workup, since TLC shows little of the *N*-formyl compounds at the end of the conversion.

Biological Activity. Cytotoxicity against L1210 cells in vitro was determined using a previously reported technique,[8] and values are expressed as micromolar concentrations necessary to inhibit the growth of cells by 50% and 90%, with smaller numbers indicating greater activity. The in vivo assays were done in mice infected with P-388 leukemia cells by a standard protocol recommended by the National Cancer Institute.[3] Both types of activity are reported in Table I with activities of nogalamycin (**1**), disnogamycin (**11**), and 7-con-*O*-methylnogarol (**2**) reported for comparison.

The compounds reported here, except for **6** and the acetylated compounds, represent modifications at C-10, C-7, and the dimethylamino group. Modification at C-10 involves only three variants, which are $COOCH_3$, COOH, and no substituent. Elimination of the carbomethoxy group at C-10 may or may not improve activity. In going from **1** to **11** and from **13** to **14**, in vitro activity decreases, but in vivo activity increases. Removal of $COOCH_3$ from **18** to give **21** reduced activity. The effect of the carboxyl group is not clear, as the in vitro activity of **16** is substantially reduced from the activities of **15** and **17**, but the in vivo activities of the 7-deoxy compounds are, at best, marginal. Replacement of nogalose at C-7 with alkoxy groups in the nogarol series (no substituent at C-10) results in good in vitro activity, as shown by comparing the activities of **3**–**5** to those of **2** and **11**. In vivo activity is retained but is not high. A modification of **2** involving methylation of a phenolic hydroxyl to give **6** essentially destroys activity both in vitro and in vivo. A similar effect was found with 6-O-methylation of carminomycin.[9] Those compounds having nitrogen at C-7 have rather poor in vitro activity, but the amino compounds do retain in vivo activity comparable to **1**. However, their potency is quite low. The 7-methylthio compound (**10**) has good in vitro activity but modest in vivo activity. All of the acetyl derivatives (**12**–**14**) are quite active in vitro, perhaps caused by complete or partial conversion to the parent compound during assay, but only **14** has any degree of in vivo activity. In those compounds having a methyl on nitrogen replaced by formyl, both in vitro and in vivo activity is totally destroyed. In vitro activity of compounds in which one methyl group has been removed from nitrogen (**18**, **21**, and **23**) is rather low, being substantially less than that of their dimethylamino analogues in every case. However, **18** is more active than **1** in vivo, although less potent. *N*-Demethyldisnogamycin (**21**) is far less active and less potent than is **11** and is less active than **18**, the nogalamycin analogue. While **23** is less active than **2**, it is more active than any of the other compounds in Table I except **2** and **11**. Furthermore, its potency equals that of **1**.

The data in Table I indicate a lack of correlation between the L1210 in vitro assays and the P-388 in vivo tests. It is rather striking that such substantial and diverse modifications as reported here retain in vivo activity in such a large percentage of cases. In vivo activities are reported for 21 nogalamycin analogues, and of these, 15

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(8) Li, L. H.; Kuentzel, S. L.; Murch, L. L.; Pschigoda, L. M.; Krueger, W. C. *Cancer Res.* **1979**, *39*, 4816.
(9) Arcamone, F. "Doxorubicin Anticancer Antibiotics"; Academic Press: New York, 1981; p 295.

show in vivo activity as defined by the National Cancer Institute. Five compounds are more active than nogalamycin itself.

Experimental Section

7-Con-*O*-allylnogarol (3). A solution of 0.5 g of 11 in 10 mL of CF_3COOH was stirred at room temperature for 1.5 h, followed by concentration in vacuo. The residue was dissolved in 25 mL of anhydrous THF, and 10 mL of allyl alcohol, which had been treated with an excess of sodium, was added. The reaction mixture was stirred for 1 h and then evaporated to dryness in vacuo. The residue was dissolved in 25 mL of H_2O (pH 7.1) and extracted with 30-mL portions of $CHCl_3$. The extracts were combined and evaporated in vacuo to give a residue, which was chromatographed on 13 g of silica gel developing with $CHCl_3$–CH_3OH (95:5) and collecting 10-mL fractions. Fractions 6 and 7 were combined and evaporated in vacuo, yielding 56 mg of homogeneous **3** as judged by TLC in $CHCl_3$–CH_3OH–H_2O (78:20:2; R_f 0.74). Fractions 8–45 were combined and evaporated in vacuo to a residue, which was chromatographed on 10 g of silica gel developing with CH_3CN–$CHCl_3$–CH_3OH (75:25:10) and collecting 10-mL fractions. Fractions 22–38 were combined and evaporated in vacuo to yield 101 mg (26%) of **3**: homogeneous by TLC as above; $[\alpha]_D$ +723° (*c* 1.66, $CHCl_3$); UV (EtOH) λ_{max} 236 nm (ϵ 48 550), 259 (23 100) 289 sh (9300), 477 (14 650); IR (Nujol) 3460, 3200, 2700 sh, 1665, 1620, 1590, 1575, 1290, 1220, 1105, 1055, 1010, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 and 1.73 (2 s, 6 H, 2 CH_3C), 1.91–2.50 (2 m, 2 H), 2.58 [s, 6 H, $(CH_3)_2N$], 2.70–3.84 (m, 5 H, CHO and CHN), 4.03–4.45 (m, 4 H, CHO), 5.0–5.50 (m, 3 H, CHO), 5.73–6.07 (m, 2 H, CHO and olefinic), 6.54 (s, 1 H, H-3), 7.27 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 191.0 (C-5), 179.5 (C-12), 161.3 (C-6), 155.7 (C-4), 148.4 (C-1), 146.5 (C-10a), 137.9 (C-2), 134.3 (olefinic), 132.9 (C-11a), 129.6 (C-6a), 125.6 (C-3), 120.6 (C-11), 117.7 (olefinic), 116.1 (C-12a), 114.4 (C-4a), 112.6 (C-5a), 97.7 (C-1′), 75.1 (C-5′), 72.8 (C-2′), 71.7 (C-7), 70.6 (C-4′), 69.5 (allyl CH_2), 68.0 (C-9), 66.1 (C-3′), 44.2 (C-10), 41.6 [$(CH_3)_2N$], 37.1 (C-8), 30.2 (C-9 CH_3), 23.9 (C-5′ CH_3); mass spectrum, *m/e* 567 (M, calcd 567). Anal. Calcd for $C_{30}H_{33}NO_{10}$: C, 63.55; H, 5.83; N, 2.47. Found: 60.80; H, 5.75; N, 2.16.

7-Con-*O*-propargylnogarol (4). A solution of 0.5 g of 11 in 10 mL of CF_3COOH was stirred at room temperature for 1.5 h. The excess acid was removed by evaporation under reduced pressure, and the residue was dissolved in 15 mL of anhydrous THF. The solution was stirred while adding, dropwise, a mixture prepared by adding an equivalent of Na to a solution of 3.0 mL of propargyl alcohol in 10 mL of anhydrous THF. Addition was stopped when the reaction mixture turned purple. After the mixture was stirred for 1 h, the solvent was removed by reduced pressure evaporation. The resulting residue was dissolved in 50 mL of H_2O and adjusted to pH 8.0 with 1 N HCl. The aqueous solution was extracted with two 25-mL portions of $CHCl_3$. The extracts were combined and evaporated in vacuo to give a residue, which was chromatographed on a 30-g silica gel column developing with CH_3CN–$CHCl_3$–CH_3OH (75:15:10) and collecting 10-mL fractions. Fractions 61–100 were combined on the basis of a color peak and evaporated in vacuo. The residue was chromatographed on a 20 cm × 20 cm × 2 mm preparatory TLC plate developing with $CHCl_3$–CH_3OH–H_2O (78:20:2). The strongest band was removed and eluted with $CHCl_3$–CH_3OH (9:1). Evaporation of the eluate in vacuo gave 69 mg (18%) of **4**: TLC R_f 0.50 (SiO_2; CH_3COCH_3–CH_3OH–H_2O, 80:18:2); $[\alpha]_D$ + 663° (*c* 0.16, $CHCl_3$); UV (EtOH) λ_{max} 234 nm (ϵ 46 150), 259 (21 900), 290 sh (8950), 478 (13 900); IR (Nujol) 3452, 3294, 2118, 1663, 1619, 1589, 1572, 1287, 1220, 1147, 1105, 1056, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 and 1.76 (2 s, 6 H, 2 CH_3C), 1.95–2.30 (m, 1 H), 2.59 [s, 6 H, $(CH_3)_2N$], 2.93–4.42 (m, 6 H, CHO and CHN), 4.50 (d, 2 H, CH_2O), 5.14 (m, 1 H, H-7), 5.96 (d, 1 H, H-1′, *J* = 3.0 Hz), 6.57 (s, 1 H, H-3), 7.26 (s, 1 H, H-1); ^{13}C NMR ($CDCl_3$) δ 190.8 (C-5), 179.3 (C-12), 161.2 (C-6), 155.7 (C-4), 148.4 (C-1), 146.4 (C-10a), 137.8 (C-2), 132.9 (C-11a), 129.2 (C-6a), 125.5 (C-3), 120.5 (C-11), 116.2 (C-12a), 114.5 (C-4a), 112.6 (C-5a), 97.7 (C-1′), 75.5, 75.2 (2 C, C-5′), 75.1 and 72.7 (2 C, C-2′), 70.5 (C-7), 70.0 (C-4′), 67.8 (C-9), 66.0 (C-3′), 58.3, 44.0 (C-10), 41.6 [$(CH_3)_2N$], 37.9 (C-8), 30.2 (C-9 CH_3), 23.9 (C-5′ CH_3); mass spectrum, *m/e* 491 (M – $CH{\equiv}CH_2OH$ – H_2O). Anal. Calcd for $C_{30}H_{31}NO_{10}$: C, 63.71; H, 5.53; N, 2.48. Found: C, 59.70; H, 5.68; N, 2.25.

7-Con-*O*-(2-bromoethyl)nogarol (5). A solution of 0.5 g of 11 in 10 mL of CF_3COOH was stirred for 1.25 h, and then excess acid was removed by reduced pressure evaporation. The residue was dissolved in 30 mL of anhydrous THF, and 20 mL of 2-bromoethanol, which had been treated with a slight excess of Na, was added. The reaction mixture was stirred for 60 h, followed by evaporation in vacuo to a solid residue. The residue was dissolved in 40 mL of H_2O, which was then adjusted to pH 7.3 with 1 N NaOH. The product was extracted with three 25-mL portions of $CHCl_3$, which were combined and evaporated to dryness in vacuo. The residue was chromatographed on 20 g of silica gel developing with $CHCl_3$–CH_3OH (95:5) and collecting 10-mL fractions. Fractions 6–20 were combined and evaporated in vacuo. The residue was chromatographed on a 20 cm × 20 cm × 2 mm silica gel plate using CH_3COCH_3–CH_3OH–H_2O (80:18:2). The strongest band was eluted with $CHCl_3$–CH_3OH (95:5), and the product was isolated by reduced pressure evaporation. The residue was chromatographed on 10 g of silica gel eluting with CH_3CN–$CHCl_3$–CH_3OH (75:15:10) and collecting 5-mL fractions. Fractions 20–40 were combined and evaporated in vacuo to give 112 mg (26%) of **5**: TLC R_f 0.41 (SiO_2; CH_3COCH_3–CH_3OH–H_2O, 80:20:2); $[\alpha]_D$ +703° (*c* 0.158, $CHCl_3$); UV (EtOH) λ_{max} 236 nm (ϵ 46 850), 258 (22 500), 289 sh (8900), 477 (14 400); IR (Nujol) 3460, 1665, 1620, 1570, 1290, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 and 1.74 (2 s, 6 H, 2 CH_3C), 1.82–2.50 (2 m, 2 H), 2.60 [s, 6 H, $(CH_3)_2N$], 2.71–4.52 (m, CHO, CHN, and CH_2Br), 5.02 (m, 1 H, H-7), 5.97 (d, 1 H, H-1′, *J* = 3.0 Hz), 6.56 (s, 1 H, H-3), 7.27 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 191.0 (C-5), 179.7 (C-12), 161.1 (C-6), 155.7 (C-4), 148.3 (C-1), 146.5 (C-10a), 137.8 (C-2), 133.1 (C-11a), 129.0 (C-6a), 125.3 (C-3), 120.6 (C-11), 116.1 (C-12a), 114.4 (C-4a), 112.7 (C-5a), 97.6 (C-1′), 75.2 (2 C), 72.6 (C-2′), 70.5 and 70.4 (2 C), 68.0 (C-9), 66.2 (C-3′), 44.0 (C-10), 41.6 [$(CH_3)_2N$], 37.4 (C-8), 30.3 (C-9 CH_3), 30.2 (CH_2Br), 23.9 (C-5′ CH_3); mass spectrum, *m/e* 553 (M – HBr). Anal. Calcd for $C_{29}H_{32}BrNO_{10}$: C, 54.90; H, 5.08; N, 2.21; Br, 12.59. Found: C, 54.34; H, 5.26; N, 2.20; Br, 12.5.

6,7-Condi-*O*-methylnogarol (6). A solution of diazomethane prepared from 4.3 g of *N*-methyl-*N*-nitroso-*N*′-nitroguanidine in 30 mL of ether was added to a solution of 1.1 g of **2** in 100 mL of CH_2Cl_2–CH_3OH (95:5). The mixture was stirred for 18 h at room temperature. The solvent was removed by reduced pressure evaporation, and the residue was chromatographed on 50 g of silica gel eluting with $CHCl_3$–CH_3OH (93:7) and collecting 10-mL fractions. Fractions 23–32 were combined on the basis of TLC (CH_3COCH_3–CH_3OH–H_2O, 80:18:2; R_f 0.42) and evaporated in vacuo, yielding 634 mg (56%) of **6**: $[\alpha]_D$ +293° (*c* 0.3, $CHCl_3$); UV (EtOH) λ_{max} 231 nm (ϵ 27 000), 262 (23 450), 285 sh (10 100), 350 (3050), 462 (8150); IR (Nujol) 3440, 1660, 1635, 1585, 1425, 1415, 1350, 1245, 1225, 1120, 1105, 1060, 1005, 755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 and 1.74 (2 s, 6 H, 2 CH_3C), 2.53 [s, 6 H, $(CH_3)_2N$], 2.60–3.10 (m, 2 H), 3.54 and 3.80 (2 s, 6 H, 2 CH_3O), 3.80–4.96 (m, 4 H, CHO and CHN), 5.95 (d, 1 H, H-1′), 6.79 (s, 1 H, H-3), 7.26 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 186.8 (C-5), 180.0 (C-12), 160.5 (C-6), 155.8 (C-4), 147.3 (C-1), 144.6 (C-10a), 136.6 (C-2), 136.2 (C-11a), 135.0 (C-6a), 125.7 (C-3), 124.3 (C-11), 121.7 (C-12a), 115.8 (C-4a), 115.4 (C-5a), 97.6 (C-1′), 75.0 (C-5′), 72.8 (C-2′), 72.8 (C-7), 70.8 (C-4′), 68.1 (C-9), 66.1 (C-3′), 62.7 and 56.6 (2 CH_3O), 43.8 (C-10), 41.6 [$(CH_3)_2N$], 34.8 (C-8), 30.0 (C-9 CH_3), 23.9 (C-5′ CH_3); mass spectrum, *m/e* 555 (M, calcd for 555). Anal. Calcd for $C_{29}H_{33}NO_{10}$: C, 62.69; H, 5.99; N, 2.53. Found: C, 60.57; H, 5.94; N, 2.16.

7-Conamino-7-deoxynogarol (7). A solution of 1 g of 11 in 5 mL of CF_3COOH was stirred 0.5 h at room temperature and evaporated to dryness in vacuo. The residue was dissolved in 20 mL of freshly distilled THF, and the solution was cooled in an ice bath while NH_3 was bubbled in until a purple color was obtained. The mixture was evaporated in vacuo, redissolved in 40 mL of THF, and HCl was bubbled through until the product had precipitated. The precipitate was removed by filtration, air-dried for a brief period, and then dissolved in CH_3OH and precipitated with CH_3COCH_3. This was repeated twice. The resulting material was dissolved in 40 mL of H_2O, and the solution was adjusted to pH 8.0 with 1 N NaOH. The organic material was extracted with four 40-mL portions of CH_2Cl_2, which were combined and evaporated to dryness in vacuo, yielding 216 mg (30%) of **7**: TLC R_f 0.06 (SiO_2; $CHCl_3$–CH_3OH–H_2O, 78:20:2);

UV (EtOH) λ_{max} 235 nm (ϵ 25 340), 252 (15 490), 260 (15 030), 290 (7360), 478 (8896); IR (Nujol) 3440, 1660, 1620, 1590, 1285, 1215, 1140, 1100, 1050, 1000, 935, 910, 830, 775 cm^{-1}; ^1H NMR ($CDCl_3$–CD_3OD) δ 1.42 and 1.72 (2 s, 6 H, 2 CH_3), 2.52 [s, 6 H, (CH_3N)], 3.10–4.05 (m, CHO and CHN), 5.88 (br s, 1 H, H-1′), 6.58 (s, 1 H, H-3), 7.22 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 190.8 (C-5), 179.7 (C-12), 160.3 (C-6), 155.6 (C-4), 148.1 (C-1), 146.0 (C-10a), 137.6 (C-2), 132.3 (C-11a), 132.2 (C-6a), 125.6 (C-3), 120.8 C-11), 116.1 (C-12a), 114.5 (C-4a), 112.5 (C-5a), 97.5 (C-1′), 75.2 (C-5′), 72.8 (C-2′), 70.6 (C-4′), 68.4 (C-9), 66.0 (C-3′), 44.3 (C-7), 44.1 (C-10), 41.4 [(CH_3)$_2$N], 39.8 (C-8), 30.3 (C-9 CH_3), 23.8 (C-5′ CH_3); mass spectrum, m/e (4 Me_3Si) 814 (M, calcd 814). Anal. Calcd for $C_{27}H_{30}NO_9$: C, 61.59; H, 5.74; N, 5.32. Found: C, 60.57; H, 5.63; N, 4.23.

7-Con[(2-methoxyethyl)amino]-7-deoxynogarol (8). A solution of 0.5 g of 11 in 5 mL of CF_3COOH was allowed to stand at room temperature for 2 h. The excess acid was removed by evaporation in vacuo, and the residue was dissolved in anhydrous THF. The solution was cooled in an ice bath while adding 2-methoxyethylamine dropwise until the solution became purple. It was then neutralized with 1 N HCl to a pH of 7.2 and extracted exhaustively with CH_2Cl_2. The combined extracts were evaporated in vacuo, yielding 450 mg. The residue was extracted with Skellysolve B, and the insoluble material was dissolved in 25 mL of dry THF. Dry HCl was bubbled into the solution for a short time, and the resulting precipitate was collected by filtration. A solution of the solid in H_2O was adjusted to pH 8.0 with 0.1 N NaOH and kept at that pH while extracting exhaustively with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo, yielding 107 mg (27%) of 8: homogeneous by TLC (SiO_2; $CHCl_3$–CH_3OH–H_2O 78:20:2; R_f 0.50); UV (EtOH) λ_{max} 234 nm (ϵ 26 952), 252 (18 890), 260 sh (16 790), 289 sh (8468), 478 (10 220); IR (Nujol) 3410, 1660, 1610, 1580, 1290, 1210, 1095, 1045, 975, 905, 875, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 and 1.75 (2 s, 6 H, 2 CH_3), 2.58 [s, 6 H, (CH_3)$_2$N], 2.71–3.20 (m, CH_2, CHN), 3.35 (s, 3 H, CH_3O), 3.48–3.78 (m, CHO), 4.35 (m, 1 H, C-7), 6.00 (d, 1 H, H-1′), 6.57 (s, 1 H, H-3), 7.29 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) 191.0 (C-5), 179.4 (C-12), 160.1 (C-6), 155.7 (C-4), 148.4 (C-1), 147.3 (C-10a), 137.8 (C-2), 132.2 (C-11a), 131.4 (C-6a), 125.6 (C-3), 120.9 (C-11), 116.0 (C-12a), 114.4 (C-4a), 112.4 (C-5a), 97.7 (C-1′), 75.1 (C-5′), 72.7 (C-2′), 71.6 (C-2″), 70.6 (C-4′), 68.1 (C-9), 66.0 (C-3′), 58.8 (CH_3O), 50.6 (C-7), 47.1 (C-1″), 44.6 (C-10), 41.6 [(CH_3)$_2$N], 34.3 (C-8), 30.5 (C-9 CH_3), 23.8 (C-5′ CH_3); mass spectrum, m/e 584 (M, calcd 584), 511 (M – $CH_3OCH_2CH_2N$). Anal. Calcd for $C_{30}H_{36}N_2O_{10}$: C, 61.63; H, 6.21; N, 4.79. Found: C, 59.18; H, 6.22; N, 4.50.

7-Conazido-7-deoxynogarol (9). A solution of 1 g of 11 in 10 mL of CF_3COOH was stirred for 2.5 h at room temperature, and the volatile material was removed by reduced pressure evaporation. The residue was dissolved in 30 mL of acetone to which was added 2 g of NaN_3, and the mixture was stirred for 18 h. The reaction mixture was poured into 100 mL of H_2O. The pH was adjusted to 7.3 with $NaHCO_3$ solution. Extraction with three 50-mL portions of CH_2Cl_2, followed by combination and evaporation in vacuo, gave 978 mg. This was chromatographed on 100 g of silica gel using CH_3COCH_3–CH_2Cl_2–CH_3OH (75:15:10) and collecting 5-mL fractions. Those fractions containing only 9 as determined by TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2; R_f 0.50) were combined and evaporated in vacuo, yielding 242 mg (31%) of 9: UV (EtOH) λ_{max} 236 nm (ϵ 33 762), 258 (17 685), 287 (7717), 476 (11 093); IR (Nujol) 3425, 2100, 1660, 1615, 1570, 1285, 1215, 1115, 1050, 1000, 945, 915, 880, 835, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45, 1.73 (2 s, 6 H, 2 CH_3), 2.60 [s, 6 H, (CH_3)$_2$N], 3.0–4.15 (m, CHO and CHN), 5.10 (d, 1 H, H-7), 5.85 (d, 1 H, H-1′), 6.75 (s, 1 H, H-3), 7.25 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 189.6 (C-5), 176.0 (C-12), 160.8 (C-6), 155.7 (C-4), 147.1 (C-1), 146.0 (C-10a), 137.0 (C-2), 133.1 (C-11a), 128.8 (C-6a), 125.8 (C-3), 120.4 (C-11), 115.1 (C-12a), 114.5 (C-4a), 112.0 (C-5a), 97.4 (C-1′), 75.3 (C-5′), 72.6 (C-2′), 70.2 (C-4′), 68.6 (C-9), 66.3 (C-3′), 55.6 (C-7), 43.9 (C-10), 42.1 (C-8), 41.6 [(CH_3)$_2$N], 29.8 (C-9 CH_3), 24.0 (C-5′ CH_3); mass spectrum, m/e 552 (M, calcd 552). Anal. Calcd for $C_{27}H_{32}N_4O_9$: C, 58.70; H, 5.11; N, 10.14. Found: C, 57.34; H, 5.64; N, 8.81.

7-Con(methylthio)-7-deoxynogarol (10). After a solution of 0.5 g of 11 in 10 mL of CF_3COOH had stood at room temperature for 1.25 h, the acid was removed by reduced pressure evaporation. The residue was dissolved in 15 mL of anhydrous THF. The solution was stirred while CH_3SNa was added until a purple tinge appeared. After THF was removed by reduced pressure evaporation, the residue was dissolved in 100 mL of H_2O. The solution was adjusted to pH 7.4 with 1 N HCl. The aqueous solution was extracted with two 50-mL portions of $CHCl_3$, which were combined and evaporated to dryness in vacuo. The residue was chromatographed on 30 g of silica gel developing with $CHCl_3$–CH_3OH (95:5) and collecting 10-mL fractions. On the basis of TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2; R_f 0.56), fractions 34–69 were combined. Evaporation in vacuo gave 204 mg (53%) of 10: $[\alpha]_D$ +719° (c 0.115, $CHCl_3$); UV (EtOH) λ_{max} 237 nm (ϵ 46 100), 262 (23 250), 290 sh (10 800), 479 (16 050); IR (Nujol) 3440, 1660, 1620, 1575, 1285, 1245, 1220, 1105, 1055, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48, 1.73 (2 s, 6 H, 2 CH_3C), 2.16–2.32 (m, 1 H), 2.37 (s, 3 H, CH_3S), 2.54 [s, 6 H (CH_3)$_2$N], 2.70–3.14, 3.35–3.82, 4.0–4.52 (3 m, 6–7 H, CHO and CHN), 5.92 (d, 1 H, H-1′), 6.50 (s, 1 H, H-3), 7.23 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$–CD_3OD) δ 191.1 (C-5), 179.7 (C-12), 160.3 (C-6), 155.7 (C-4), 148.2 (C-1), 146.1 (C-10a), 137.7 (C-2), 132.1 (C-11a), 130.3 (C-6a), 125.5 (C-3), 120.6 (C-11), 116.2 (C-12a), 114.5 (C-4a), 112.5 (C-5a), 97.6 (C-1′), 75.1 (C-5′), 72.7 (C-2′), 70.5 (C-4′), 68.7 (C-9), 66.1 (C-3′), 43.9 (C-10), 41.6 [(CH_3)$_2$N], 38.5 (C-8), 36.9 (C-7), 31.2 (C-9 CH_3), 23.9 (C-5′ CH_3), 16.5 (CH_3S); mass spectrum, m/e 557 (M, calcd 557). Anal. Calcd for $C_{28}H_{31}NO_9S$: C, 60.30; H, 5.60; N, 2.52; S, 5.75. Found: C, 58.05; H, 5.60; N, 2.98; S, 5.44.

2′,4′,4(6)-Tri-*O*-acetyldisnogamycin (12). One gram of 11 was dissolved in 75 mL of anhydrous THF, and 0.5 mL of CH_3COCl was added. The solution was heated under reflux, and a few drops of CH_3COCl was added from time to time until TLC ($CHCl_3$–CH_3OH, 9:1) indicated nearly complete conversion of 11 to the least polar product. The reaction mixture was evaporated in vacuo to a small volume. The residue was dissolved in benzene, and the solution was washed with three equal volumes of H_2O. The organic layer was filtered and evaporated to dryness in vacuo to give 415 mg of product, of which 300 mg was chromatographed on 15 g of silica gel packed in Skellysolve B–acetone (9:1), and 90 5-mL fractions were eluted with the same system. At this point the eluent was changed to 1:1, and elution was continued until the color peak was eluted. Fractions 118–121 were combined on the basis of TLC ($CHCl_3$–CH_3OH, 9:1; R_f 0.75) and evaporated in vacuo, yielding 146 mg of 12: mp 168–180 °C; $[\alpha]_D$ +338° (c 0.1915, $CHCl_3$); UV (EtOH) λ_{max} 234 nm (ϵ 52 400), 258 (24 250), 286 sh (9800), 468 (14 250); IR (Nujol) 3560, 3420, 1745, 1730, 1660, 1615, 1565, 1290, 1215, 1100, 1030, 940, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 3 H, C-3″ CH_3), 1.42 (d, 3 H, C-5″ CH_3, J = 6.5 Hz), 1.58 (s, 3 H, C-9 CH_3), 1.73 (s, 3 H, C-5′ CH_3), 1.96, 2.15, and 2.17 (3 s, 9 H, 3 CH_3CO), 2.28 [s, 6 H, (CH_3)$_2$N], 2.45 (m, 2 H, H-10), 3.23 (s, 3 H, CH_3O), 3.28 (m, CHO), 3.55 (s, 6 H, 2 CH_3O), 5.0–5.5 (m, CHO), 5.93 (d, 1 H, H-1′, J = 4.0 Hz), 7.08 (s, 1 H, H-3), 7.51 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 192.3 (C-5), 179.8 (C-12), 170.2, 170.1, and 169.4 (3 CH_3CO), 161.5 (C-6), 156.2 (C-4), 146.2 (C-1), 146.1 (C-10a), 135.7 (C-2), 134.1 (C-11a), 129.7 (C-6a), 123.7 (C-3), 120.5 (C-11), 117.4 (C-12a), 115.5 (C-4a), 113.7 (C-5a), 100.3 (C-1″), 92.7 (C-1′), 84.5 (C-4″), 81.3 (C-2″), 79.5 (C-3″), 78.0 (C-5′), 74.0 (C-2′), 72.4 (C-7), 71.7 (C-9), 70.1 (C-4′), 67.4 (C-5″), 62.5 (C-3′), 61.4, 58.5, and 48.6 (3 CH_3O), 42.0 (C-10), 41.5 (C-8), 41.2 [(C-H_3)$_2$N], 24.7, 23.5, 22.3, 21.1, and 21.0 (C-9 CH_3, C-5″ CH_3, 3 CH_3CO), 18.2 (C-5″ CH_3), 15.0 (C-3″ CH_3); mass spectrum (FD), m/e 855 (M, calcd 855). Anal. Calcd for $C_{43}H_{53}NO_{17}$: C, 60.35; H, 6.19; N, 1.63. Found: C, 59.65; H, 6.54; N, 1.62.

2′,4′-Di-*O*-acetylnogalamycin (13). One gram of 1 was suspended in 15 mL of CH_3OH, and 3 mL of $(CH_3CO)_2O$ was added. Solution occurred rapidly. The solution was allowed to stand at room temperature for 4 h and then evaporated to dryness in vacuo. The residue was chromatographed on 100 g of silica gel eluting with $CHCl_3$–CH_3COCH (85:15) and collecting 265 5-mL fractions. Fractions 125–183 were combined on the basis of TLC using the above solvent system (R_f 0.28) and evaporated to dryness in vacuo, yielding 753 mg (67%) of 13: $[\alpha]_D$ +416° (c 0.217, $CHCl_3$); UV (EtOH) λ_{max} 235 nm (ϵ 70 300), 257 (29 600), 288 sh (12 930), 473 (22 800); IR (Nujol) 3450, 1740, 1665, 1615, 1565, 1285, 1210, 1135, 1090, 1015, 940, 920, 815, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17, 1.46, and 1.62 (3 s, 9 H, 3 CH_3C), 1.27 (d, 3 H, CH_3CH), 2.23 and 2.26 (2 s, 6 H, 2 CH_3CO), 2.28 [s, 6 H, (CH_3)$_2$N], 2.67 (dd, 1 H, H-3′), 3.20, 3.52, 3.54, and 3.78 (4 s, 12 H, 4 CH_3O), 3.11

(d, 1 H, H-4″), 3.26 (d, 1 H, H-2″), 3.70 (m, 1 H, H-5″), 3.98 (s, 1 H, H-10), 5.06–5.26 (m, 3 H, H-2′, H-4′, and H-7), 5.41 (br s, 1 H, H-1″), 5.87 (d, 1 H, H-1′), 7.04 (s, 1 H, H-3), 7.59 (s, 1 H, H-11), 12.28 and 12.67 (2 s, 2 H, 2 phenolic OH); ^{13}C NMR ($CDCl_3$) δ 192.4 (C-5), 179.7 (C-2), 172.1 ($COOCH_3$), 170.1, 169.4 (2 CH_3CO), 161.8 (C-6), 156.4 (C-4), 146.4 (C-1), 143.2 (C-10a), 136.0 (C-2), 134.1 (C-11a), 130.6 (C-6a), 123.9 (C-3), 120.0 (C-11), 117.2 (C-12a), 115.5 (C-4a), 114.5 (C-5a), 100.7 (C-1″), 92.8 (C-1′), 84.5 (C-4″), 81.2 (C-2″), 77.9 (C-3″), 74.0 (C-5′), 72.5 (C-2′), 72.3 (C-7), 70.2 (C-4′), 69.8 (C-9), 67.4 (C-5″), 62.4 (C-3′), 61.4, 58.5, 52.7, and 48.6 (4 CH_3O), 56.7 (C-10), 41.2 [$(CH_3)_2N$], 40.7 (C-8), 29.0 (C-9 CH_3), 23.5 (C-5′ CH_3), 21.2 and 21.1 (2 CH_3CO), 18.3 (C-5″ CH_3), 14.9 (C-3″ CH_3); mass spectrum, *m/e* 871 (M, calcd 871), 650 (M – nogalose – H). Anal. Calcd for $C_{43}H_{53}NO_{18}$: C, 59.23; H, 6.01; N, 1.61. Found: C, 57.33; H, 5.89; N, 1.61.

2′,4′-Di-*O*-acetyldisnogamycin (14). Three milliliters of $(CH_3CO)_2O$ was added to a solution of 1 g of **11** in 15 mL of CH_3OH, and the mixture was stirred for 5 h. Filtration gave 332 mg, and evaporation of the filtrate in vacuo gave 815 mg. The residue was triturated with CH_3OH, and the mixture was filtered; yielding 243 mg. This material was chromatographed on 24 g of silica gel eluting with $CHCl_3$–CH_3COCH_3 (85:15) and collecting 5-mL fractions. Fractions 51–130 were combined on the basis of TLC (SiO_2; $CHCl_3$–CH_3OH, 9:1; R_f 0.63) and evaporated in vacuo: yield 206 mg. This material was combined with the 332 mg first obtained, and the mixture was chromatographed on 54 g of silica gel eluting with $CHCl_3$–CH_3COCH_3 (85:15) and collecting 10-mL fractions. Fractions 64–125 were combined on the basis of TLC as above and evaporated to dryness in vacuo, yielding 366 mg (33%) of **14**: homogeneous by TLC in the above system; mp 248–251 °C; $[\alpha]_D$ +382° (*c* 0.9695, $CHCl_3$); UV (EtOH) λ_{max} 235 nm (ε 50 505), 254 (21 810), 290 sh (9300), 470 (15 250); IR (Nujol) 3475, 1760, 1675, 1610, 1575, 1305, 1230, 1125, 1045, 960, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19, 1.25, 1.44, and 1.60 (3 s and 1 d, 12 H, 4 CH_3C), 2.12 and 2.13 (2 s, 6 H, 2 CH_3CO), 2.26 [s, 6 H, $(CH_3)N$], 3.20 and 3.52 (2 s, 9 H, 3 CH_3O), 4.82–5.37 (m, 4 H, CHO), 5.84 (br s, 1 H, H-1′), 7.03 (s, 1 H, H-3), 7.48 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 192.1 (C-5), 179.7 (C-12), 170.1 and 169.4 (2 CH_3CO), 161.7 (C-6), 156.2 (C-4), 147.2 (C-10a), 146.2 (C-1), 135.7 (C-2), 133.7 (C-11a), 130.2 (C-6a), 123.7 (C-3), 120.7 (C-11), 117.4 (C-12a), 115.4 (C-4a), 113.6 (C-5a), 100.1 (C-1″), 92.7 (C-1′), 84.6 (C-4″), 81.2 (C-2″), 77.9 (C-3″), 74.0 (C-5′), 72.4 (C-2′, C-7), 7.01 (C-4′), 69.1 (C-9), 67.3 (C-5″), 62.4 (C-3′), 61.4, 58.5, and 48.6 (3 CH_3O), 45.1 (C-10), 44.0 (C-8), 41.2 [$(CH_3)_2N$], 29.3 (C-9 CH_3), 23.5 (C-5′ CH_3), 21.2 and 21.1 (2 CH_3CO), 18.3 (C-5″ CH_3), 15.0 (C-3″ CH_3); mass spectrum, *m/e* 813 (M, calcd 813), 753 (M – CH_3COOH). Anal. Calcd for $C_{41}H_{51}NO_{16}$: C, 60.58; H, 6.32; N, 1.72. Found: C, 58.46; H, 6.16; N, 1.59.

7-Deoxynogalarolic Acid (16). A solution of 9.4 g of **15** in 217 mL of 0.53 N KOH was stirred at room temperature for 17 h. The precipitate that was obtained by acidification to pH 5.0 with H_2SO_4 was collected by centrifugation and washed thoroughly with four 50-mL portions of water by centrifugation and decantation. The residue was dried under reduced pressure, yielding 7.15 g.

Two grams was chromatographed on 120 g of silica gel eluting with $CHCl_3$–CH_3OH (7:3) and collecting 10-mL fractions. Those fractions containing only **16** as indicated by TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2; R_f 0.48) were combined, and the solution was evaporated to dryness in vacuo, yielding 1.21 g of **16**: UV (EtOH) λ_{max} 236 nm (ε 25 750), 264 (18 400), 295 sh (6350), 483 (11 450), 500 sh (10 800); IR (Nujol) 3325, 1650, 1610, 1590, 1275, 1220, 1195, 1095, 1035, 1000, 950, 925, 910, 825, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 and 1.85 (2 s, 6 H, 2 CH_3C), 2.18–2.75 (m, 4 H, 2 CH_2), 3.03 [s, 6 H, $(CH_3)_2N$], 3.32–3.38 (m, 2 H, CHO and CHN), 3.75–4.02 (m, 2 H, CHO), 5.91 (d, 1 H, H-1′), 6.96 (s, 1 H, H-3), 7.41 (s, 1 H, H-11); ^{13}C NMR (D_2O–NaOD) δ 189.7 (C-5), 189.3 (COO), 182.3 (C-12), 169.6 (C-6), 164.4 (C-4), 142.1 (C-1), 140.8 (C-10a), 138.2 (C-2), 135.0 (C-11a), 132.1 (C-6a), 131.7 (C-3), 122.3 (C-11), 120.3 (C-12a), 119.6 (C-4a), 114.3 (C-5a), 97.1 (C-1′), 76.9 (C-5′), 74.2 (C-2′), 70.9 (C-4′), 70.4 (C-9), 66.3 (C-3′), 59.7 (C-10), 42.1 [$(CH_3)_2N$], 33.9 (C-8), 29.0 (C-9 CH_3), 24.4 (C-5′ CH_3), 23.9 (C-7). Anal. Calcd for $C_{28}H_{29}NO_{11}$: C, 60.65; H, 5.05; N, 2.53. Found: C, 55.92; H, 5.34; N, 2.26; $CHCl_3$–CH_3OH, 5.56; ash, 2.83.

7-Deoxynogarol (17). A solution of 8.5 g of **16** in 850 mL of DMF was heated to 65 °C. The solution was filtered, and the filtrate was evaporated to dryness in a current of air, yielding 7.2 g. One gram was chromatographed on 95 g of silica gel eluting with 92.5:7.5 benzene–acetone for 72 fractions (10 mL) and then with 87.5:12.5 benzene–acetone. Fractions 110–200 were combined on the basis of TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2; R_f 0.52) and evaporated in vacuo, yielding 594 mg. Three hundred fifty milligrams was dissolved in 4.5 mL of hot $CHCl_3$, and the solution was refrigerated for several days to give 101 mg of **17**: mp 265–267 °C dec; $[\alpha]_D$ +1150° (*c* 0.32, $CHCl_3$); UV (EtOH) λ_{max} 236 nm (ε 39 750), 261 (24 800), 291 sh (8400), 475 (14 050); IR (Nujol) 3440, 1660, 1620, 1575, 1415, 1390, 1290, 1220, 1110, 1050, 1005, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$–CD_3OD) δ 1.40 and 1.72 (2 s, 6 H, 2 CH_3C), 1.90 and 2.25 (2 m, 2 H, CH_2), 2.52 [s, 6 H, $(CH_3)_2N$], 2.85 (m, 2 H, CH_2), 3.45 (m, 1 H, H-3′), 3.75 (d 1 H, H-4′), 4.10 (d, 1 H, H-2′), 5.80 (d, 1 H, H-1′), 6.57 (s, 1 H, H-3), 7.15 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 190.7 (C-5), 179.5 (C-12), 159.8 (C-6), 155.4 (C-4), 147.5 (C-1), 145.2 (C-10a), 136.9 (C-2), 132.2 (C-11a), 130.5 (C-6a), 125.0 (C-3), 120.3 (C-11), 116.1 (C-12a), 114.4 (C-4a), 112.5 (C-5a), 97.1 (C-1′), 74.4 (C-5′), 72.5 (C-2′), 70.3 (C-4′), 67.7 (C-9), 66.0 (C-3′), 43.1 (C-10), 41.4 [$(CH_3)_2N$], 33.7 (C-8), 30.2 (C-9 CH_3), 23.7 (C-5′ CH_3), 19.9 (C-7); mass spectrum, *m/e* 511.1838 (calcd for $C_{27}H_{29}NO_4$, 511.1842).

A sample was recrystallized from DMF for analysis. Anal. Calcd for $C_{27}H_{29}NO_9$: C, 63.40; H, 5.72; N, 2.74. Found: C, 61.26; H, 5.53; N, 2.59.

***N*-Acetyl-*N*-demethylnogalamycin (20).** A solution of 1 g of **1** in 500 mL of $CHCl_3$ was exposed to outside light for 3 days. It was then extracted with three 50-mL portions of 0.1 N HCl, which were combined and adjusted to pH 7.8 with 1 N NaOH. Extraction with three 50-mL portions of $CHCl_3$, combination, and evaporation in vacuo gave 618 mg. TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2) showed the presence of a principal component (**18**), R_f 0.24, and two less polar components: UV (EtOH) λ_{max} 208 nm (ε 18 500), 236 (46 700), 259 (22 480), 292 (8540), 478 (14 030); IR (Nujol) very similar to **1**. Anal. Calcd for $C_{38}H_{47}NO_{16}$: C, 58.02; H, 6.12; N, 1.81. Found: C, 56.03; H, 5.94; N, 1.42.

Material similar to the above product (880 mg) was dissolved in CH_3OH (10 mL) and $(CH_3CO)_2O$ (2 mL) was added. After the solution had stood at room temperature for 4 h, it was evaporated to dryness in vacuo. The residue was chromatographed on 90 g of silica gel using $CHCl_3$–CH_3OH (95:5) and collecting 201 5-mL fractions. Fractions 100–201 were combined on the basis of TLC and evaporated in vacuo, yielding 470 mg of **20**: homogeneous by TLC (SiO_2; $CHCl_3$–CH_3OH, 9:1; R_f 0.38); UV (EtOH) λ_{max} 236 nm (ε 39 300), 258 (19 250), 290 sh (9460), 474 (12 800); IR (Nujol) 3375, 1725, 1650, 1615, 1565, 1280, 1220, 1130, 1100, 1045, 1000, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12–1.78 (m, 12 H, 4 CH_3C), 2.16 (s, 3 H, CH_3CO), 3.10 (s, 3 H, CH_3N), 3.22, 3.56, 3.62, and 3.70 (4 s, 12 H, 4 CH_3O), 3.85–5.30 (m, CHO and CHN), 5.45 (d, 1 H, H-1″), 5.82 (d, 1 H, H-1′), 7.13 (s, 1 H, H-3), 7.42 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 191.1 (C-5), 179.8 (C-12), 171.7 (CH_3CO), 171.6 ($COOCH_3$), 161.6 (C-6), 155.8 (C-4), 146.9 (C-1), 143.8 (C-10a), 136.5 (C-2), 133.5 (C-11a), 130.4 (C-6a), 125.2 (C-3), 120.2 (C-11), 116.1 (C-12a), 114.2 (C-4a), 113.9 (C-5a), 100.7 (C-1″), 95.9 (C-1′), 84.3 (C-4″), 81.0 (C-2″), 77.8 (C-3″), 75.7 (C-5′), 74.0 (C-2′), 71.5 (C-7), 69.4 (C-9, C-4′), 67.4 (C-5″), 58.2 (C-3′), 61.1, 587, 52.2, and 48.5 (4 CH_3O), 56.8 (C-10), 40.0 (C-8), 32.2 (CH_3N), 29.1 (C-9 CH_3), 23.6 (C-5′ CH_3), 22.4 (CH_3CO), 18.0 (C-5″ CH_3), 14.6 (C-3″ CH_3); mass spectrum (FD), *m/e* 815 (M, calcd 815). Anal. Calcd for $C_{40}H_{49}NO_{17}$: C, 58.89; H, 6.06; N, 1.72. Found: C, 56.97; H, 5.89; N, 1.62.

Methylamine from 18. A solution of 800 mg of **18** containing some **1** in 20 mL of 1 N HCl was boiled for 1 h. The nogalose was removed by $CHCl_3$ extraction, and 2.4 g of NaOH was added to the aqueous solution. The basic solution was steam distilled until no more volatile base was being formed. The distillate was collected in a 0.1 N HCl solution and freeze-dried. ^{1}H NMR of the residue gave chemical shifts at δ 2.65 (CH_3NH_2·HCl) and 2.77 [$(CH_3)_2NH$·HCl] in a ratio of 84:16.

***N*-Formyl-*N*-demethylnogalamycin (19).** A solution of 1 g of **1** in 500 mL of $CHCl_3$–CH_3OH (9:1) was exposed to outside light for 4 days. It was then evaporated to dryness in vacuo. The residue was chromatographed on 25 g of silica gel developing with CH_2Cl_2–CH_3OH (9:1) and collecting 5-mL fractions. On the basis of TLC (SiO_2; $CHCl_3$–CH_3OH–H_2O, 78:20:2; R_f 0.77), fractions 15–45 were combined, and the pool was evaporated in vacuo,

yielding 340 mg. Rechromatography in a similar fashion gave 118 mg (11.7%) of **19**: mp 226–233 °C; $[\alpha]_D$ +399° (*c* 0.229, $CHCl_3$); UV (EtOH) λ_{max} 236 nm (ϵ 49 670), 258 (22 285), 290 (8545), 476 (13 690); IR (Nujol) 3375, 1720, 1650, 1610, 1560, 1280, 1215, 1135, 1080, 1040, 1000, 910, 755, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10–1.80 (3 s and 1 d, 12 H, 4 CH_3C), 2.85 (s, 3 H, CH_3N), 3.15, 3.42, 3.58, and 3.90 (4 s, 12 H, 4 CH_3O), 5.48 (d, 1 H, H-1″), 5.84 (d, 1 H, H-1′), 7.10 (s, 1 H, H-3), 7.35 (s, 1 H, H-11); ^{13}C NMR ($CDCl_3$) δ 191.3 (C-5), 180.6 (C-12), 171.8 (*C*OOCH$_3$), 165.4 (*H*CO), 161.9 (C-6), 155.8 (C-4), 147.2 (C-1), 143.8 (C-10a), 137.0 (C-2), 133.5 (C-11a), 130.3 (C-6a), 126.3 (C-3), 119.9 (C-11), 116.5 (C-12a), 114.5 (C-4a), 114.1 (C-5a), 100.9 (C-1″), 96.4 (C-1′), 84.6 (C-4″), 81.4 (C-2″), 78.0 (C-3″), 75.6 (C-5′), 72.0 (C-3′), 71.2 (C-7), 69.3 (C-9), 68.6 (C-4′), 67.6 (C-5″), 62.9 (C-3′), 57.3 (C-10), 61.4, 58.9, 52.4, and 48.7 (4 CH_3O), 39.9 (C-8), 29.1 (C-9 CH_3), 25.0 (CH_3N), 24.5 (C-5′ CH_3), 18.2 (C-5″ CH_3), 14.9 (C-3″ CH_3); mass spectrum, *m/e* 801 (M, calcd 801, 0.037), 581 (M – nogalose, 14.07), 563 (M – nogalose – H_2O, 99.99). Anal. Calcd for $C_{39}H_{47}NO_{17}$: C, 55.42; H, 5.91; N, 1.75. Found: C, 54.54; H, 5.71; N, 1.49.

***N*-Demethyldisnogamycin (21).** A solution of 1 g of **11** in 500 mL of $CHCl_3$–CH_3OH (9:1) was exposed to outside light for 3 days. The solution was evaporated to dryness in vacuo, and the residue was chromatographed on 50 g of silica gel developing with 9:1 $CHCl_3$–CH_3OH for 118 fractions (5 mL) and then changing to 82.5:17.5 $CHCl_3$–CH_3OH and collecting a total of 265 fractions. On the basis of TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2; R_f 0.32) fractions 175–257 were combined and evaporated in vacuo, yielding 267 mg (27%). TLC in the above system indicated **21** as the major component and two less polar minor components: $[\alpha]_D$ +328° (*c* 0.186, $CHCl_3$); UV (EtOH) λ_{max} 236 nm (ϵ 41 585), 262 (25 275), 290 sh (9135), 472 (14 620); IR (Nujol) 3300, 1660, 1620, 1570, 1290, 1225, 1110, 1055, 1005, 915, 755 cm^{-1}; ^1H NMR (Me_2SO–d_6) δ 1.08, 1.23, 1.29, and 1.59 (3 s and 1 d, 12 H, 4 CH_3C), 2.08 (m, 2 H, CH_2), 3.07, 3.39, and 3.41 (3 s, 9 H, 3 CH_3O), 5.24 (d, 1 H, H-1″), 5.55 (d, 1 H, H-1′), 7.10 (s, 1 H, H-3), 7.37 (s, 1 H, H-11); ^{13}C NMR (Me_2SO-d_6) δ 191.5 (C-5), 179.2 (C-12), 160.8 (C-6), 154.6 (C-4), 147.4 (C-1), 147.6 (C-10a), 137.0 (C-2), 133.3 (C-11a), 129.5 (C-6a), 124.0 (C-3), 119.6 (C-11), 116.4 (C-12a), 114.6 (C-4a), 113.2 (C-5a), 99.9 (C-1″), 95.7 (C-1′), 84.2 (C-4″), 80.3 (C-2″), 77.5 C-3″), 75.2 (C-5′), 74.5, 72.8, 72.6, and 71.8 (C-2′, C-4′, C-7, C-9), 67.1 (C-5″), 66.5 (C-3′), 60.8, 59.0, and 48.7 (3 CH_3O), 44.7 (C-10), 43.4 (C-8), 33.8 (CH_3N), 28.6 (C-9 CH), 23.5 (C-5′ CH_3), 18.0 (C-5″ CH_3), 14.6 (C-3″ CH_3), 14.6 (C-3″ CH_3); mass spectrum (FD), *m/e* 715 (M, calcd 715). Anal. Calcd for $C_{36}H_{45}NO_{14}$: C, 60.41; H, 6.33; N, 1.96. Found C, 56.76; H, 5.94; N, 1.72.

***N*-Formyl-*N*-demethyldisnogamycin (22).** The photolytic reaction was run as was that in the previous experiment with a very similar workup. Fractions 40–60 were pooled on the basis of TLC in the same system (R_f 0.77) and evaporated in vacuo to give 241 mg (24%) of **22**: homogeneous by TLC in four systems; mp 280–284 °C dec; $[\alpha]_D$ +454° (*c* 0.156, $CHCl_3$); UV (EtOH) λ_{max} 235.5 nm (ϵ 48 755), 259 (23 927), 289 (9445), 479 (14 750); IR (Nujol) 3370, 1665, 1620, 1570, 1290, 1225, 1100, 1050, 1005, 915, 845, 760, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30, 1.35, and 1.65 (2 s and 1 d, 12 H, CH_3C), 2.92 (s, 3 H, CH_3N), 3.18, 3.32, and 3.63 (3 s, 9 H, 3 CH_3O), 5.07 (br s, 1 H, H-7), 5.18 (d, 1 H, H-1″), 5.68 (d, 1 H, H-1′), 6.65 (s, 1 H, H-3), 7.03 (s, 1 H, H-11), 8.17 (s, 1 H, HCO); ^{13}C NMR ($CDCl_3$) δ 190.6 (C-5), 180.1 (C-12), 165.8 (CHO), 161.1 (C-6), 155.5 (C-4), 148.5 (C-1), 146.9 (C-10a), 136.5 (C-2), 132.3 (C-11a), 130.9 (C-6a), 126.1 (C-3), 120.6 (C-11), 116.2 (C-12a), 114.2 (C-4a), 112.8 (C-5a), 99.8 (C-11″), 96.4 (C-1′), 84.6 (C-4″), 81.4 (C-2″), 78.0 (C-3″), 75.3 (C-5′), 71.1 (C-2′), 70.9 (C-7), 69.1 (C-9), 68.5 (C-4′), 67.6 (C-5′), 62.9 (C-3′), 61.4, 59.0, and 48.8 (3 CH_3O), 43.9 and 43.8 (C-10, C-8), 30.0 (C-9 CH_3), 24.9 (CH_3N), 24.5 (C-5′ CH_3), 18.2 (C-5″ CH_3), 15.2 (C-3″ CH_3); mass spectrum (FD), *m/e* 743 (M, calcd for 743, 0.275), 505 (M – nogalose – H_2O, 99.99). Anal. Calcd for $C_{37}H_{45}NO_{15}$: C, 59.75; H, 6.11; N, 1.88. Found: C, 56.21; H, 5.77; N, 1.63.

Methylamine from 22. The same procedure was used as in obtaining volatile base from **18** except that the acid-hydrolysis step was eliminated and 1.4 g of **22** was dissolved in 40 mL of 2 N NaOH. In this case, ^1H NMR indicated the formation of only CH_3NH_2 (chemical shift δ 2.66).

7-Con-*O*-methyl-*N*-demethylnogarol (23). A solution of 1.98 g of **2** in 1 L of $CHCl_3$–CH_3OH (9:1) was exposed to outside light until TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2) indicated almost all of the starting material had disappeared. The solution was evaporated to dryness in vacuo, and the residue was dissolved in 200 mL of $CHCl_3$. This solution was extracted with three 100-mL portions of 0.1 N HCl. The extracted $CHCl_3$ solution was dried ($MgSO_4$) and evaporated to dryness in vacuo to give 169 mg of **24**. The combined acidic extracts were adjusted to pH 7.7 with 1 N NaOH and extracted with three 100-mL portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo, yielding 1.00 g.

The residue was chromatographed on 50 g of silica gel eluting with 9:1 $CHCl_3$–CH_3OH for 60 fractions and then with 82.5:17.5 $CHCl_3$–CH_3OH. A total of 236 10-mL fractions were collected. Fractions were combined on the basis of TLC in the above solvent system. Fractions 30–60 were combined (R_f 0.64) and evaporated in vacuo to give 188 mg of **24**. Fractions 134–236 were combined (R_f 0.31) and evaporated in vacuo, yielding 476 mg of **23** (25%). Two hundred milligrams of **23** was stirred in 100 mL of H_2O, and 0.1 N HCl was added dropwise until the pH was stable at 4.7. The acidic solution was extracted with six 50-mL portions of $CHCl_3$ and freeze-dried, yielding 56 mg, homogeneous by TLC in the above system. One hundred milligrams of such material was dissolved in 1 mL of C_2H_5OH, and $(C_2H_5)_2O$ was added. Refrigeration and filtration gave 95 mg of product: UV (EtOH) λ_{max} 234 nm (ϵ 47 800), 257 (22 120), 288 sh (10 340), 472 (16 020); IR (Nujol) 3420, 1665, 1620, 1575, 1330, 1290, 1230, 1110, 1075, 1015, 925, 785, 760 cm^{-1}; ^1H NMR (DMF-d_7) δ 1.30 and 1.72 (2 s, 6 H, CH_3C), 2.89 (s, 3 H, $CH_3NH_2^+$), 3.48 (s, 3 H, CH_3O), 5.70 (br s, 1 H, H-1′), 6.92 (s, 1 H, H-3), 7.13 (s, 1 H, H-11); ^{13}C NMR (DMF-d_7) δ 191.4 (C-5), 180.2 (C-12), 161.7 (C-6), 156.1 (C-4), 147.6 (C-1), 147.0 (C-10a), 136.3 (C-2), 133.4 (C-11a), 130.1 (C-6a), 125.8 (C-3), 120.8 (C-11), 117.1 (C-12a), 115.3 (C-4a), 113.1 (C-5a), 96.0 (C-1′), 76.2 (C-5′), 72.6 (C-2′), 72.1 (C-7), 70.2 (C-4), 68.7 (C-9), 61.9 (C-3′), 57.7 (CH_3O), 44.6 (C-10), 32.7 (C-8), 29.8 (CH_3N), 29.5 (C-9 CH_3), 23.4 (C-5′ CH_3); mass spectrum (on free base), *m/e* 527 (M, calcd 527). Anal. Calcd for $C_{27}H_{29}NO_{10}$·HCl: C, 57.49; H, 5.36; N, 2.49; Cl, 6.29. Found: C, 55.35; H, 5.44; N, 2.01; Cl, 6.20.

7-Con-*O*-methyl-*N*-formyl-*N*-demethylnogarol (24). The acid-insoluble material and the less polar material from chromatography from the previous experiment were combined (357 mg) and chromatographed on 36 g of silica gel eluting with $CHCl_3$–CH_3OH (9:1) and collecting 145 5-mL fractions. On the basis of TLC as in the previous experiment, fractions 20–50 were combined and evaporated in vacuo, yielding 325 mg (16%) of **24**: homogeneous by TLC in the solvent system of the previous experiment; UV (EtOH) λ_{max} 236 nm (ϵ 46 150), 259 (21 600), 289 (9050), 475 (13 850); IR (Nujol) 3440, 1665 (strong), 1620, 1575, 1300, 1215, 1115, 995, 790 cm^{-1}; ^1H NMR (DMF-d_7) δ 1.28 and 1.72 (2 s, 6 H, 2 CH_3C), 1.90–2.61 (m, CH_2), 2.85 (s, 3 H, CH_3N), 3.47 (s, 3 H, CH_3O), 3.12, 3.88, 4.00, and 4.67 (CHO and CHN), 5.80 (br s, 1 H, H-1′), 6.98 (s, 1 H, H-3), 7.22 (s, 1 H, H-11); ^{13}C NMR (DMF-d_7) δ 190.9 (C-5), 179.1 (C-12), 163.5 (HCO), 160.6 (C-6), 154.9 (C-4), 146.6 (C-10a), 146.3 (C-1), 136.3 (C-2), 132.8 (C-11a), 129.0 (C-6a), 124.5 (C-3), 119.3 (C-11), 115.7 (C-12a), 114.3 (C-4a), 112.3 (C-5a), 96.0 (C-1′), 75.4 (C-5′), 71.1 (C-2′), 70.6 (C-7), 68.0 (C-4′), 67.0 (C-9), 61.4 (C-3′), 56.5 (CH_3O), 43.8 (C-10), 36.4 (C-8), 29.0 (C-9 CH_3), 23.4 (C-5′ CH_3), 22.9 (CH_3N); mass spectrum, *m/e* 555 (M, calcd 555), 505 (M – CH_3OH – H_2O). Anal. Calcd for $C_{28}H_{29}NO_{11}$: C, 60.54; H, 5.27; N, 2.53. Found: C, 57.83; H, 5.37; N, 2.20.

***N*-Formyl-*N*-demethyl-7-deoxynogarol (25).** A solution of 1 g of **17** in 500 mL of $CHCl_3$–CH_3OH (9:1) was exposed to outside light until TLC ($CHCl_3$–CH_3OH–H_2O, 78:20:2) indicated the almost total disappearance of **17**. The solution was evaporated to dryness in vacuo, and 480 mg of the residue was chromatographed on 48 g of silica gel. The column was eluted with $CHCl_3$–CH_3OH (9:1), collecting 117 5-mL fractions. Fractions 35–80 were combined on the basis of TLC in the above system (R_f 0.75) and evaporated to dryness in vacuo, yielding 140 mg (29%) of **25**. A sample of 220 mg of similar material was recrystallized from $CHCl_3$–CH_3OH (9:1) to give 142 mg: homogeneous by TLC in the above system and in $CHCl_3$–CH_3OH (9:1); mp 288–292 °C dec; $[\alpha]_D$ +874° [*c* 0.1585, $CHCl_3$–CH_3OH (1:1)]; UV (EtOH) λ_{max} 236 nm (ϵ 41 585), 262 (25 275), 290 sh (9135), 472 (14 620); IR (Nujol) 3410, 1655 (strong), 1610, 1570, 1320, 1290, 1225, 1185, 1110, 1085, 1050, 1010, 965, 940, 925, 890, 850, 780

cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.25 and 1.66 (2 s, 6 H, 2 CH_3C), 2.67 (m, CH_2), 2.75 (s, 3 H, CH_3N), 3.62–4.17 (m, CHO and CHN), 4.45 (s, 1 H, exchangeable), 5.38 (d, 1 H, exchangeable), 5.76 (d, 1 H, H-1′), 5.9 (d, 1 H, exchangeable), 7.15 (s, 1 H, H-3), 7.72 (s, 1 H, H-11), 7.72 (s, 1 H, CHO); ^{13}C NMR (Me_2SO-d_6) δ 191.1 (C-5), 179.2 (C-12), 163.8 (HCO), 159.0 (C-6), 154.6 (C-4), 146.5 (C-10a), 146.3 (C-1), 136.0 (C-2), 131.3 (C-11a), 131.0 (C-6a), 124.1 (C-3), 119.8 (C-11), 116.3 (C-12a), 114.8 (C-4a), 111.7 (C-5a), 95.8 (C-1′), 75.5 (C-5′), 70.4 (C-2′), 67.7 (C-4′), 66.1 (C-9), 61.4 (C-3′), 43.5 (C-10), 33.7 (C-8), 29.4 (C-9 CH_3), 24.4 (CH_3N), 23.7 (C-5′ CH_3), 20.4 (C-7); mass spectrum, *m/e* 525 (M, calcd 525), 507 (M – H_2O). Anal. Calcd for $C_{27}H_{27}NO_{10}$: C, 61.71; H, 4.79; N, 2.06. Found: C, 57.99; H, 5.01; N, 2.46; $CHCl_3$, 4.85.

Methylamine from 25. This was done as previously using 600 mg of **25** and 20 mL of 2 N NaOH. ^{1}H NMR on the volatile base hydrochloride gave a chemical shift of δ 2.65, identifying the product as CH_3NH_2·HCl.

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Agents for the Treatment of Brain Injury. 1. (Aryloxy)alkanoic Acids

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Blunt and ischemic injuries of the brain have been shown to result in swelling that is predominantly limited to a single cell type, the astrocyte, within the complex cellular mosiac of cerebral gray matter. Evaluation of various diuretic (aryloxy)acetic acids in vitro using incubating cat brain slices and primary astrocyte cultures identified compounds with marked ability to inhibit brain tissue swelling. Some of the compounds significantly reduced the mortality and morbidity following acceleration/deceleration brain injury in anesthesized cats. A variety of (indanyloxy)alkanoic acids were synthesized which were analogous to the dually active (indanyloxy)acetic acids. Some of the 4-(indanyloxy)butanoic acids were found to be devoid of diuretic activity but to possess equal or greater activity than the dually active compounds in the in vitro and in vivo brain assays. Selected examples from both the (indanyloxy)acetic and 4-(indanyloxy)butanoic acid series showed marked chiral effects, with one enantiomer generally exhibiting a much greater activity than the other. A clinical study of severely head-injured patients treated with ethacrynic acid demonstrated a significantly improved outcome when compared to controls. These data suggest a clinical advantage for the nondiuretic (aryloxy)alkanoic acids which possess in vitro and in vivo activities in the cat brain assays that are comparable or superior to dually active compounds.

Accidental death in the United States is the leading cause of mortality for individuals under the age of 45 and the fourth leading cause of death in all age groups following heart disease, cancer, and stroke.[1,2] Fatal vehicular-related brain injury is the single most common source of accidental mortality;[1,2] approximately 52 000 Americans die in automobile accidents yearly.[3] Moreover, morbidity following brain injury is the chief cause of persisting disability of the survivors of accidental injury in developed countries.[1,2] It was estimated in 1974 that survivors of brain injury accounted for the loss of 9.6 million days of normal activities and required 6.6 million days of hospitalization; moreover, the lifetime cost of medical care for a patient with serious brain injury may be very high.[1]

Diverse types of brain insult, including ischemic stroke, cardiac arrect, Reye's Syndrome, and hydrocephalus, exhibit pathological and even life-threatening increases in tissue-water content of the skull-encased brain which are similar to those resulting from accidental head injury. Of these cerebral edema-producing insults, ischemic cerebrovascular stroke is the third leading cause of death in the United States, being responsible for 200 000 deaths and double that number of hospitalized patients annually.[4,5] Those people who have survived one or more strokes number approximately 1.8 million.[4,5]

There is an incomplete understanding of the molecular mechanisms associated with both the cause and resolution of edema of cerebral white matter related to altered cerebrocapillary permeability. Specifically effective therapeutic agents do not exist. Therefore, a large number of nonspecific compounds have been evaluated. The principal aim in their use is the control of brain bulk and/or intracranial pressure. These agents include various osmotic diuretics,[6-12] steroids,[13-15] barbiturates,[16-20] carbonic an-

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