6 N HCl and the extracted with dichloromethane. the dichloromethane solution was dried and concentrated to give 160 mg of a solid acid, 140 mg of which was treated immediately with ethereal diazomethane. The methyl ester was purified by chromatography using ethyl acetate-hexane (1:4) as eluent to give 130 mg of **4** as a colorless liquid. Capillary GLC of the aterial revealed that **4a** and **4b** (t_r 12.6 and 13.9 min) were present in a ratio of 1:17; M_r calcd for $C_{11}H_{16}O_4$ 212.10485, found 212.1053; ^{1}H NMR (**4b**) δ 1.11 (3 H, d, J = 7.5 Hz, 9-CH_3), 1.31 (3 H, s, 8-CH_3), 1.93 (3 H, br s, 6-CH_3), 2.75 (1 H, q, J = 7.5 Hz, 5-CH), 3.71 (3 H, s, 11-CH_3), and 4.11 (3H, s, 7-CH_3); ^{13}C NMR (**4b**) δ 8.0 (C-6), 10.4 (C-9), 17.2 (C-8), 48.4 (C-5), 52.4 (C-11), 53.2 (C-4), 59.2 (C-7), 111.4 (C-2), 174.2 (C-10), 182.4 (C-3), and 206.4 (C-1).

The mixture of esters **4a,b** (50 mg, 0.24 mmol) was treated with lithium diisopropylamide (0.3 mmol) at -78 °C for 1 h. The reaction mixture was quenched with dilute hydrochloric acid and extracted with ether. The ether solution was dried and concentrated to give a colorless liquid which was revealed by capillary GLC to be a 2:1 mixture of **4a** and **4b**. Both ^{1}H and ^{13}C NMR spectra confirmed the presence of esters **4a** and **4b**; attempts to separate them on a preparative basis were unsuccessful.

5-(Methoxycarbonyl)-3-methoxy-2,4,5-trimethylcyclopent-2-enone (5). A solution of **7** (280 mg, 1.8 mmol) in THF (~2 mL) was added dropwise to a solution of lithium diisopropylamide (2 mmol) in 10 mL of THF at -78 °C. After 30 min, the mixture was warmed to 0 °C and kept at that temperature for 30 min. Carbon dioxide was passed through the mixture at 0 °C for 30 min. Workup as in the previous carboxylation afforded the crude acid (190 mg) which was found to undergo decarboxylation on standing. The acid was, therefore, immediately treated with diazomethane. Purification by chromatography gave 150 mg (39%) of **5** as an oil which solidified at -20 °C. Capillary GLC indicated the material was a mixture of **5a** and **5b** (t_r 15.0 and 14.2 min, respectively) in a ratio of 16:1; M_r calcd for $C_{11}H_{16}O_4$ 212.10485, found 212.1058; ^{1}H NMR (**5a**) δ 1.12 (3 H, d, J = 7 Hz, 8-CH_3), 1.30 (3 H, s, 9-CH_3), 1.86 (3 H, d, J = 1.2 Hz, 6-CH_3), 3.24 (1 H, d × d, J = 7.0 and 1.2 Hz, 4-CH), 3.72 (3 H, s, 11-CH_3), and 4.14 (3H, s, 7-CH_3); ^{13}C NMR (**5a**) δ 7.7 (C-6), 13.3 (C-8), 16.0 (C-9), 41.7 (C-4), 52.5 (C-11), 57.2 (C-5), 58.4 (C-7), 110.2 (C-2), 173.0 (C-10), 185.8 (C-3), and 202.7 (C-1).

The **5a,b** mixture was treated with lithium bis(trimethylsilyl)amide (0.3 mmol) at -78 °C for 1 h, quenched with dilute HCl, and extracted with ether. The residue from the ether solution was a colorless oil which capillary GLC showed to be a 1:1.5 mixture of **5a** and **5b**. Attempts to separate the esters preparatively were unsuccessful.

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Registry No. **1**, 88389-71-3; **3**, 88367-23-1; **4a**, 91366-57-3; **4b**, 91366-59-5; **5**, 91366-60-8; **5b**, 91366-58-4; **6**, 3883-56-5; **7**, 91384-67-7; **8**, 91366-61-9; **9**, 91384-68-8; **10**, 91366-62-0; **11**, 91384-69-9; **15**, 91366-63-1; 2-methyl-1,3-cyclopentanedione, 765-69-5.

Synthetic Anthracyclinones. 25.[1] An Improved Route to 8-Demethoxyaranciamycinone and Synthesis of the α-L-Daunosamine Glycosides

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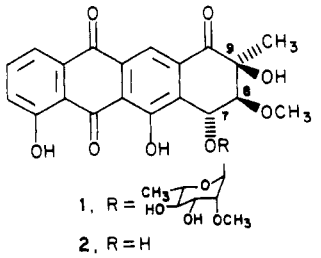
An improved regioselective synthesis for the anthracyclinone precursor **12** is reported using a combination of Diels-Alder and Marschalk reactions. The solvolysis of the benzylic bromides **19/20** with water mainly yields the 7,9-*trans*-diol 8-demethoxyaranciamycinone (**22**) whereas the treatment with sodium hydroxide affords the 7,9-*cis*-diol **21**. The α-L-daunosamine glycosides **27-30** are prepared and their absolute configurations are determined by ^{1}H NMR spectroscopy.

The anthracycline antibiotic aranciamycin (**1**) was isolated from *Streptomyces echinatus* 14 years ago.[2] However, the absolute configuration of **1** has only been determined recently by Sheldrick and Zeeck using X-ray analysis[3] and CD measurements.[4] In contrast to most other anthracyclinones,[5,6] aranciamycinone has an oxo group at C-10, an inverse configuration at C-9, a 7,9-trans configuration of the hydroxy groups, and an additional methoxy group at C-8.



Some time ago we published a synthesis of 8-demethoxyarancia mycinone (**22**)[7] starting from chrysophanol methyl ether (**12**). The preparation of **12** involved a methylation step, where expensive silver oxide had to be used, and, in addition, the yield of **12** was decreased by an elimination reaction. The new procedure is operationally simpler and better adopted for scaled up preparations of **12**, which is also a common precursor of other naturally

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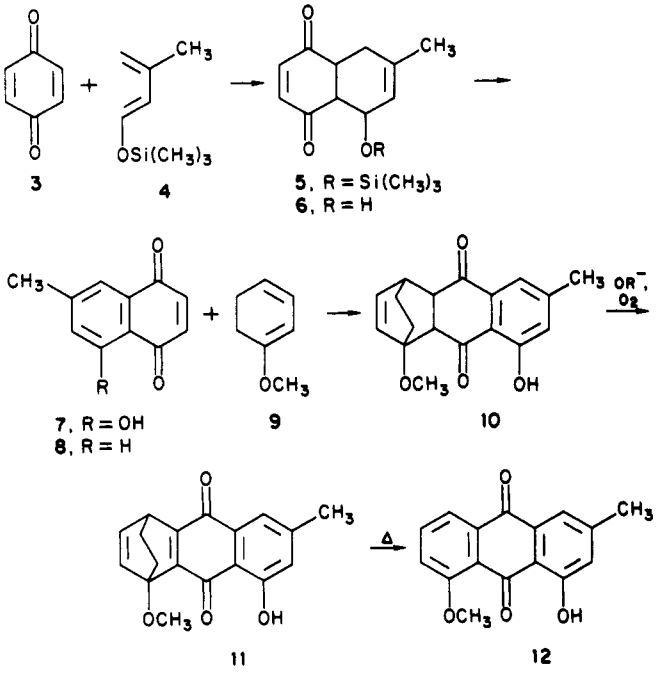
Scheme I



Scheme II

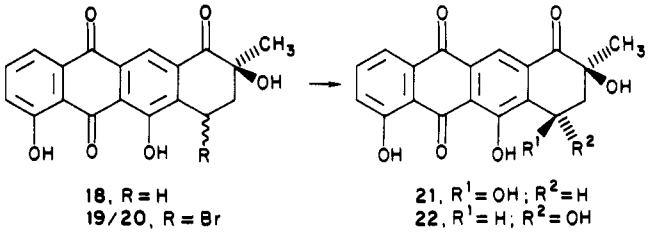


Table I. Dependence of the Cis/Trans Ratio (21/22) on the Solvolysis Conditions

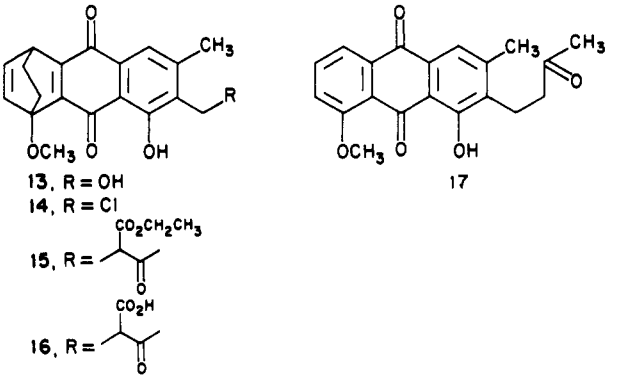
reagent	21, %	22, %	21/22
H_2O	17	42	1:2.5
0.01 N NaOH	39	21	1.4:1
0.1 N NaOH	59	8	7.4:1
0.25 N NaOH	66	2	33:1

occurring anthracylines such as aklavinone,[8a] β_1-atromycinone, and decarbomethoxyalklavinone.[8b]

For the new reaction sequence an efficient synthesis for 7-methyljuglone (7) had to be developed. Derivative 7 is a naturally occurring naphthoquinone (ramentacetone)[9] and earlier syntheses gave only unsatisfactory yields.[10,11] Reaction of benzoquinone (3) with 3-methyl-1-(trimethylsiloxy)-1,3-butadiene (4)[8b] led to 5 which was converted to 7 by acid treatment and PCC oxidation in 58% overall yield (Scheme I). Since 5 and 6 are rather labile intermediates it was necessary to work at temperatures below 0 °C. Elimination of the allylic hydroxy group in compound 6 during oxidation to yield 8 could mostly be avoided by addition of 1 equiv of acetic acid during the oxidation. Reaction of 7-methyljuglone (7) with the readily available 1-methoxy-1,3-cyclohexadiene (9)[12] provided the primary adduct 10 almost quantitatively. The structure of 10 was confirmed by oxidation to the naphthoquinone derivative 11 and retro diene cleavage (160 °C) to 12, which proved to be identical with a sample prepared earlier.[8b]

The new procedure for the preparation of 12 compares favorably with the earlier synthesis, since the methylation step is avoided. It was, however, possible to further improve the synthesis of 8-demethoxyaranciamycinone (22) by a combination of the Diels–Alder reaction with a Marschalk alkylation. The primary adduct 10 is the diketo form of a naphthohydroquinone, and the possibility of alkylation ortho to the phenolic group was therefore investigated. In the original Marschalk reaction,[13] the leuko forms of *anthra*quinones have been treated with aldehydes, and only in one case was a naphthazarine derivative hydroxymethylated in this manner.[14] In fact, treatment of 10 with formaldehyde in alkaline methanol gave an 83% yield of the hydroxymethylated compound 13 after oxidative workup. In analogy to earlier observations[14] less polar dimeric products were also formed, which could, however, easily be removed by crystallization or chromatography.

The chlorination of 13 was achieved by treatment with thionyl chloride to yield 14. Acetoacetate could be alkylated with 14 to give the keto ester 15. By pyrolysis of the corresponding acid 16, the anthraquinone intermediate 17 was obtained by simultaneous decarboxylation and retrodiene reaction in 61% overall yield from 10. Similarly anthracyclinones with an ethyl side chain are available starting from 14 and 3-oxovalerate.[15] In addition to improved overall yields, the new procedure is operationally simpler due to the better solubility of the bridged intermediates 10 to 16 compared with the corresponding anthraquinones.[7,8]



The four-step transformation of 17 to the ketol 18 has been described earlier.[7] Hydroxylation of 18 to the 7,9-*cis*-diol 21 is possible with high stereoselectivity by simple base treatment of 18 in the presence of air (Scheme II). This has recently been confirmed by Gesson, Jacquesy, and Renoux in the steffimycinon series.[16] The 7,9-*trans*-diol 22 corresponding to the natural configuration of aranciamycinone has only been isolated in moderate yield by treatment of the bromides 19/20 with silver salts.[7] We have now found that the ratio of the *cis*- and *trans*-diols 21 and 22 depends on the concentration of the sodium hydroxide used in the solvolysis of the bromides 19/20. Table I shows the stereochemical outcome of the solvolysis of 19/20.

By simple choice of solvolysis conditions it is now possible to preferentially obtain the *cis*- or *trans*-diol 21 or 22. The remarkable dependence of the stereochemical

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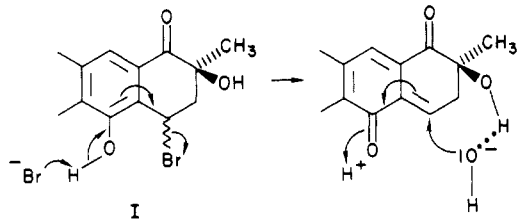
result on the pH value is probably due to a change in the reaction mechanism. The reaction with water may be simple S_N2 mechanism reflecting the original stereochemistry (with inversion) of the bromides (**19**/**20**) which has been determined by NMR to be approximately 1:3.[7] Increasing the base strength gives rise to a competitive elimination addition process (see I and II). The first step

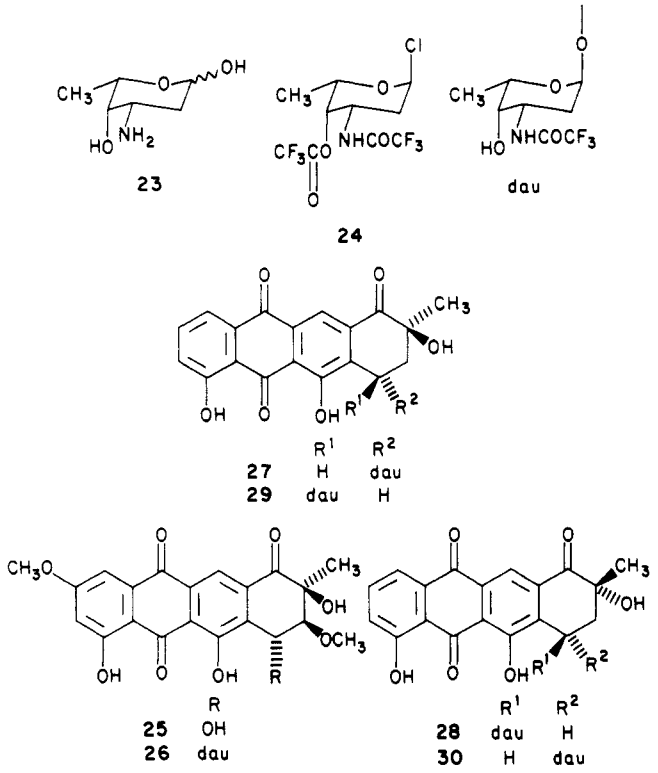


I II

is the base-induced deprotonation of the phenol, followed by elimination to an intermediate planar quinone methide. The high cis selectivity may be explained by anchimeric assistance of the neighboring axial OH group.

The improved synthesis described here provided sufficient material of both racemic isomers **21** and **22** for the preparation of the biologically active glycosides.

For the determination of the absolute configuration of the glycosides, natural steffimycinone **25**[17-19] was also transformed to the L-daunosamine glycoside **26**. The



23 **24** dau

	R^1	R^2
27	H	dau
29	dau	H

	R
25	OH
26	dau

	R^1	R^2
28	dau	H
30	H	dau

absolute configuration of steffimycinone **25** has recently been shown to correspond to that of arancianmycinone (**2**) by comparison of the CD spectra.[4]

Aranciamycine (**1**) and also the aglycon **2** are strongly active against Gram-positive bacteria.[2,20] However, the antitumor activity of the nitrogen-free glycosides is only moderate.[2] Since the cytostatically active anthracyclines such as the daunorubicins all have a nitrogen-containing sugar with definite configuration of the amino group,[21,22] we have prepared the α-L-daunosamine glycosides of **25** and of the racemic *trans*- and *cis*-diols **21** and **22**.

A synthesis of L-daunosamine (**23**)[23] and the conversion to the protected halogenose **24** has been described.[24] The coupling of the sugar to anthracyclinones to obtain the desired α-glycosides was achieved by a variety of methods.[21] Recently, silver trifluoromethanesulfonate was used as an effective catalyst in the Königs–Knorr reaction.[25,26]

First, steffimycinone (**25**) (obtained by cleavage of steffimycin B with acid) was treated with 1-chloro-3-*N*,4-*O*-bis(trifluoracetyl)daunosamine (**24**) in the presence of silver triflate. A 67% yield of the α-glycoside **26** was obtained and only a small amount of a less polar substance (probably a β-glycoside) could be detected by TLC. The amount of β-glycosides using the triflate method depends on the nature of the aglycon. Simple hydroxymethylated anthraquinones afforded 6% to 16% of the β-L-daunosamine glycosides.[27,28] α- and β-glycosides can easily be distinguished by ^1H NMR spectroscopy: In β-glycosides the anomeric proton 1′-H gives rise to a doublet of doublets with $J \simeq 12$ Hz for the trans diaxial coupling of 1′-H and 2′-H.[28] In the α-L-daunosamine glycosides the signal for 1′-H appears generally as a small doublet with $J \simeq 3$ Hz.

Next, the racemic 8-demethoxyaranciamycinone (**22**) was transformed to the diastereomeric glycosides **27** (35%) and **28** (30%) by the same procedure. The absolute configurations of **27** and **28** could be determined by comparison of the ^1H NMR spectrum with that of the semisynthetic compound **26**. (Steffimycin itself was not suitable for a direct comparison due to great differences in the sugar moiety.) In spite of the additional methoxy group at C-8, the shapes of the spectra of **26** and that of less polar isomer **27** were nearly identical with respect to the characteristic signals for 1′-, 2′-, and 7-H. In contrast, chemical shifts for these protons were quite different in the polar isomer **28**. The most characteristic feature was inversion of chemical shifts of the signals for 1′- and 7-H as shown in Figure 1. The reaction of the *cis*-diol **21** with **24** in the presence of silver triflate proceeds smoothly to yield two main products corresponding to the diastereomeric α-glycosides **29** (31%) and **30** (24%). Again, only a small amount of β-glycosides could be detected by TLC. The much slower reaction of **21** in comparison to **22** was probably due to the chelation of the axial benzylic hydroxy group with the neighboring hydroxy group at C-9. The absolute configuration of the glycosides **29** and **30** could be correlated to daunorubicin also possessing cis-oriented substituents. Only the spectrum of the less polar isomer **30** displayed similarities to the spectrum of daunorubicin.[29] Again, an inversion of the chemical shifts for the signals of 1′-H and 7-H was observed for the glycoside **29** as shown in Figure 1. In fact, this is not a singular phenomenon and

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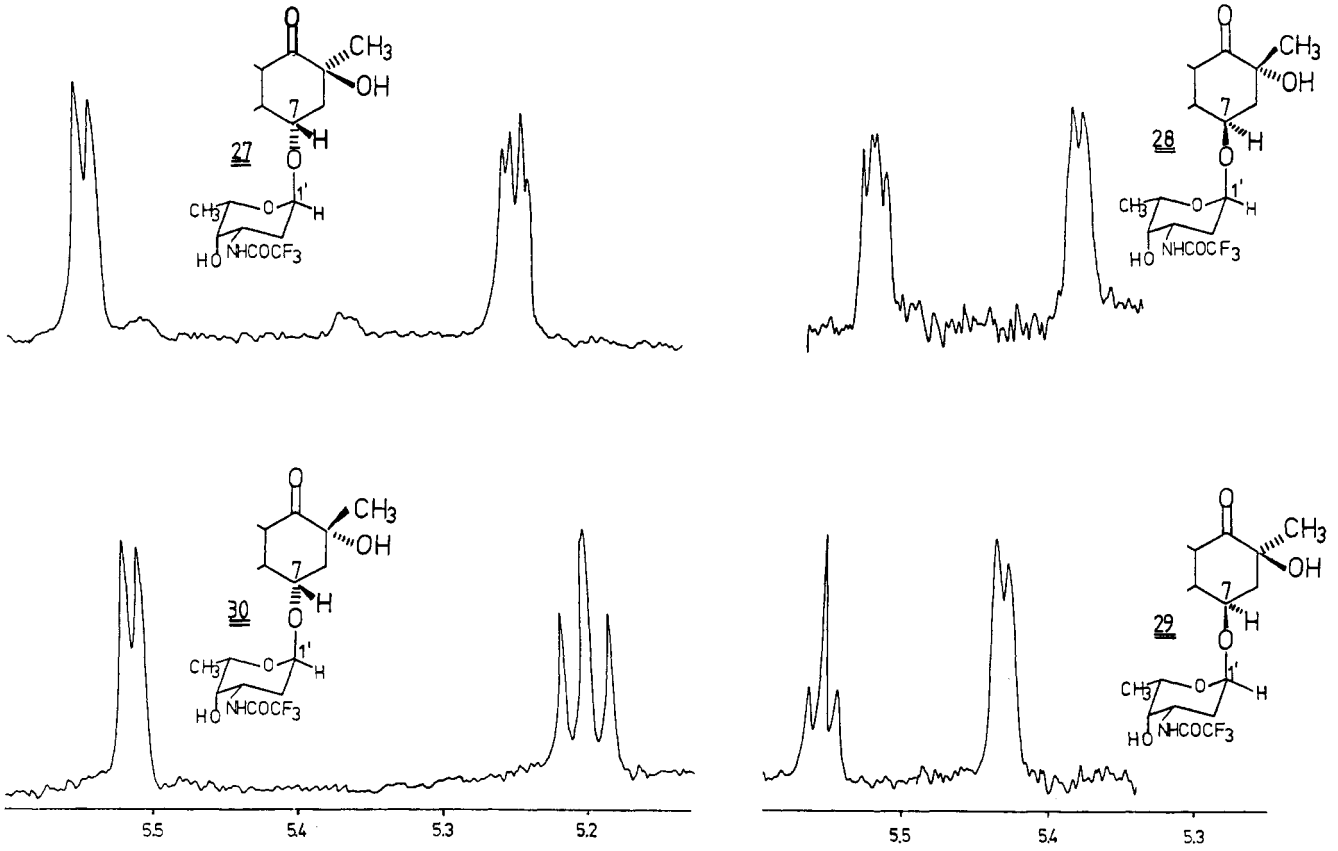

Figure 1.

has been stated for demethoxydaunorubicin,[30,31] isodaunorubicin,[31] and eight similar cis-oriented synthetic anthracyclines.[31] The striking changes in relative shielding for 1′-H and 7-H for diastereomeric glycosides such as **29** and **30** is possibly due to different orientations of the oxygen of the sugar ring to the neighboring phenolic group at C-6.[32] This is further confirmed by the finding that 6-deoxyanthracyclines apparently do not exhibit this phenomenon.[33]

Minor deviations in conformation of the 10-oxoanthracyclines in comparison to the rhodomycinone anthracyclines do not disturb the general picture, and one important generalization can be made: Chemical shifts of the ^{1}H NMR spectra of α-L-daunosamine glycosides (specially for 1′, 2′-, and 7-H) are determined by the absolute configuration of the benzylic position at C-7. The configuration of the other positions of the hydroaromatic ring at C-8 and C-9 of the aglycon are of minor importance. For instance, the ^{1}H NMR spectra of **27** and **30** or **28** and **29** show great similarity in spite of the opposite configuration at C-9 (see Figure 1). It is furthermore of importance to note that in all glycosides **26–30** the sugar moiety remains in the pseudoaxial position, which has also been shown to be the predominant conformation of the aglycons **2**, **21**, **22**, and **25**.[4,7]

The antitumor activity of the free amines of the glycosides **26–30** is presently being tested. The determination of the absolute configuration of the glycosides was also necessary in order to assign the absolute configuration of demethoxyaranciamycinone and other anthracyclinones obtained by enantioselective synthesis.[34]

Experimental Section

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer Model 1420 spectrophotometer and are reported in wavenumbers (KBr, cm^{-1}). Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker HFX 90 (90 MHz) and WM 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane as standard (in $CDCl_3$). Ultraviolet/visible (UV/vis) spectra were recorded on a Beckman UV Model 5230 spectrophotometer [in methanol; λ_{max} (log ε); nm]. Analytical TLC was performed on silica gel plates (0.25 mm, E. Merck), preparative TLC on 1-mm silica gel (Schleicher & Schüll), and column chromatography with E. Merck silica gel 60 (230–400 mesh).

5-Hydroxy-7-methyl-1,4-naphthoquinone (7) and 7-Methyl-1,4-naphthoquinone (8). To a solution of 20.00 g (0.128 mol) of diene **4**[8b] in 500 mL of dichloromethane was added 16.60 g (0.154 mol) of benzoquinone (**3**). The solution was stirred for 12 h at 20 °C, evaporated at 0 °C, and redissolved in 200 mL of methanol. After addition of 2 mL of 1 N HCl, the solution was stirred for 1 h at 0 °C, again evaporated at 5 °C, and the residue dissolved in 500 mL of dry dichloromethane. To the mixture was added 12 mL of acetic acid and under vigorous stirring portionwise 54.50 g (0.255 mol) of pyridinium chlorochromate (PCC). After 6 h, 9.8 g (0.2 mol) of sodium hydrogen carbonate was added and stirring was continued for 1 h. The solution was sucked off, filtered through a short column of silica gel (100 g), eluted with dichloromethane, and evaporated. The residue crystallized from dichloromethane/ether to afford 12.03 g (50%) of **7** (mp 116 °C): IR 1670, 1640, 1592 cm^{-1}; UV/vis 213 (4.26), 249 (4.16), 345 (3.26), 425 nm (3.44); ^{1}H NMR (90 MHz) δ 2.38 (s, 3), 6.92 (s, 2), 7.11 (s, 1), 7.47 (s, 1), 11.87 (s, 1). Anal. Calcd for $C_{12}H_8O_3$: C, 70.20; H, 4.28. Found: C, 70.19; H, 4.29.

7-Methyl-1,4-naphthoquinone (8). The mother liquor from the crystallization of **7** was separated by column chromatography (silica gel, CH_2Cl_2) to afford an additional 1.93 g of **7** from the

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less polar fraction (total yield of **7**, 58%) and 3.52 g (16%) of the elimination product **8**: mp 89 °C; IR 1664, 1602 cm^{-1}; UV/vis 208 (3.93) 249 (4.34), 256 (4.34), 340 nm (3.50); ^1H NMR (90 MHz) δ 2.48 (s, 3), 6.91 (s, 2), 7.51 (d, J = 8 Hz, 1), 7.83 (s, 1), 7.93 (d, J = 8 Hz, 1).

1,4,4a,9a-Tetrahydro-8-hydroxy-1-methoxy-6-methyl-1,4-ethano-9,10-anthraquinone (10). A solution of 10.40 g (55.2 mmol) of 7-methyljuglone (**7**) and 9.40 g (86.2 mmol) of 1-methoxy-1,3-cyclohexadiene (**9**)[12] (70% purity) was stirred under nitrogen for 24 h. The solution was evaporated and the residue crystallized from ether/petroleum ether to afford 14.42 g (87%) of the adduct **10**: mp 155 °C dec; IR 1672, 1630, 1592 cm^{-1}; ^1H NMR (400 MHz) δ 1.52 (m, 2), 1.95 (m, 2), 2.35 (s, 3), 3.15 (m, 1), 3.18 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1), 3.44 (d, J = 9.0 Hz, 1), 3.49 (s, 3), 6.01 (d, J = 8.8 Hz, 1), 6.06 (dd, J_1 = 8.8, J_2 = 6.0 Hz, 1), 7.00 (d, J = 1.3 Hz, 1), 7.29 (d, J = 1.3 Hz, 1), 12.09 (s, 1). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.43; H, 6.26.

1,4-Dihydro-8-hydroxy-1-methoxy-6-methyl-1,4-ethano-9,10-anthraquinone (11). A solution of 298 mg (1 mmol) of **10** in 20 mL of 0.5 N methanolic potassium hydroxide was stirred for 0.5 h in the presence of air. The mixture was acidified with 1% aqueous HCl and extracted with CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and evaporated, and the residue was crystallized from ether to afford 276 mg (93%) of **11**: mp 128 °C; IR 1661, 1631, 1600 cm^{-1}; UV/Vis 216 (4.44), 250 (3.95), 278 (3.93), 425 nm (3.62); ^1H NMR (90 MHz) δ 1.28 (m, 4), 2.37 (s, 3), 4.42 (m, 1), 6.36 (t, J = 7 Hz, 1), 6.58 (d, J = 8 Hz, 1), 6.93 (m, 1), 7.34 (m, 1), 11.87 (s, 1). Anal. Combustion analysis for all oxidized bridged substances (**11** to **16**) gave data approaching those calculated for the corresponding aromatic compounds (see ref 8 and 9) due to partial retrodiene elimination of ethylene during combustion.

Pyrolysis of 11: 100 mg (0.3 mmol) of **11** was heated for 0.5 h at 160 °C. Crystallization of the residue from CH_2Cl_2/Et_2O afforded 71 mg (88%) of anthraquinone **12** (mp 196–197 °C) identical with an authentic sample.

1,4-Dihydro-8-hydroxy-7-(hydroxymethyl)-1-methoxy-6-methyl-1,4-ethano-9,10-anthraquinone (13). A solution of 16 g of KOH, 40 mL of aqueous formaldehyde (40%), and 8.00 g (26.8 mmol) of **10** in 800 mL of methanol was stirred under N_2 for 45 min at 15 °C (TLC control). The mixture was then slowly poured with vigorous stirring into 1 L of ice water containing 10 mL of 50% hydrogen peroxide. After 10 min the solution was acidified with 6 N HCl and extracted twice with 300-mL portions of CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on 100 g of silica gel. Elution with CH_2Cl_2 gave 1.04 g (13%) of oxidized starting material **11** followed by 0.75 g (9%) of dimers (see below). Elution with CH_2Cl_2/5% Et_2O afforded 6.38 g (73%) of **13** (mp 210 °C). **11** could be recycled after reduction with dithionite according to the usual hydroxymethylation procedure[7] (overall yield of **13** 83%): IR 3510, 1682, 1645, 1570 cm^{-1}; UV/vis 216 (4.21), 249 (4.14), 369 (3.60), 438 nm (3.13); ^1H NMR (90 MHz) δ 1.60 (7, 2), 1.71 (m, 2), 1.89 (m, 1), 2.49 (s, 3), 3.60 (s, 3), 3.84 (m, 1), 4.76 (m, 2), 6.07–6.22 (m, 2), 7.36 (s, 1), 12.00 (s,1).

7-(Chloromethyl)-1,4-dihydro-8-hydroxy-1-methoxy-6-methyl-1,4-ethano-9,10-anthraquinone (14). A suspension of 7.35 g (22.3 mmol) of **13** in 200 mL of CH_2Cl_2 was treated with 9 mL of thionyl chloride and 0.1 mL of DMF and stirred 2 h at 20 °C. The solution was evaporated and the residue washed with petroleum ether to yield 7.59 g (98%) of chloride **14**: mp 173 °C dec; IR 1691, 1648, 1609 cm^{-1}; UV/vis 212 (4.16), 248 (4.22), 293 (3.52), 369 nm (3.69); ^1H NMR (90 MHz) δ 1.64 (m, 4), 2.51 (s, 3), 3.59 (s, 3), 3.79 (m, 1), 4.71 (s, 2), 6.07 (m, 2), 7.36 (s, 1), 12.00 (s, 1).

Ethyl 2-[(1,4,9,10-Tetrahydro-8-hydroxy-1-methoxy-6-methyl-9,10-dioxo-1,4-ethano-7-anthryl)methyl]-3-oxobutyrate (15). A solution of 6.19 g (17.8 mmol) of **14** in 300 mL of dry DMF was added under N_2 within 30 min to a cooled (0–5 °C) solution of 7.04 g (54.4 mmol) of ethyl acetoacetate in 400 mL of 0.2 N ethanolic sodium ethoxide. After 1 h the mixture was poured into 1 L of cold 1 N HCl and extracted 3 times each with 300 mL of ether. The combined organic phases were dried over magnesium sulfate and evaporated. The residue was washed with cold petroleum ether to remove excess ethyl acetoacetate and crystallized from ether/petroleum ether to afford 7.24 g (92%) of β-keto ester **15**: mp 111 °C dec; IR 1690, 1642, 1605, 1580 cm^{-1}; UV/vis 211 (4.27), 249 (3.35), 296 (3.64), 369 nm (3.83); ^1H NMR (90 MHz) δ 1.22 (t, J = 7 Hz, 3), 1.61 (m, 4), 2.26 (s, 3), 3.44 (m, 2), 3.59 (s, 3), 3.78 (m, 1), 4.18 (t, 1), 6.04 (m, 2), 7.33 (s, 1), 11.92 (s, 1).

1-Hydroxy-8-methoxy-3-methyl-2-(3-oxobutyl)-9,10-anthraquinone (17). A solution of 9.96 g (22.6 mmol) of ester **15** in 200 mL of ethanol was treated with 750 mL of 1 N aqueous NaOH for 6 h (TLC control). The solution was acidified with concentrated HCl and extracted 3 times each with 200 mL of ethyl acetate. The solution was dried over sodium sulfate and evaporated, and the residue was heated 30 min at 160 °C. The residue was crystallized from ether/petroleum ether to yield 4.17 g of **17**, identical with an authentic sample.[7] The mother liquor was evaporated and again heated for 30 min at 160 °C to afford another 2.43 g of **17** (total yield 82%; mp 192 °C).

Solvolysis of the Bromides 19/20. In each experiment 20 mg of ketol **18**[7] was dissolved in dry CCl_4 and brominated with Br_2 in the presence of light as described earlier.[7] The solvent was evaporated and the residue redissolved in 20 mL of dry THF. The cold (0 °C) solutions were treated with 10 mL of water, 0.01 N NaOH, 0.1 N NaOH, and 0.25 N NaOH, respectively, and stirred 5 min. The mixtures were acidified with cold diluted HCl and extracted with 30 mL of CH_2Cl_2. The CH_2Cl_2 solutions were dried over Na_2SO_4 and evaporated, and the residue was separated by TLC (CH_2Cl_2/1% CH_3OH). For yields of **21** and **22**, see Table I.

General Procedure for the Glycosidation of the Aglycons *rac*-21, *rac*-22, and 25. A solution of 0.1 mmol of aglycon in 10 mL of dry CH_2Cl_2 was first treated with 0.3–0.4 mmol of halogenose **24**[25,35] and then dropwise with a solution of 0.3 mmol of silver triflate in 5 mL dry ether. The mixture was stirred for 1–5 h in the dark (TLC control) and shaken with a diluted solution of sodium hydrogen carbonate. The organic phase was dried over Na_2SO_4, evaporated to dryness, and boiled under reflux for 0.5 h with methanol. The solution was again evaporated and the residue separated by preparative TLC (CH_2Cl_2/2% CH_3OH).

7-*O*-(2,3,6-Trideoxy-3-(trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl)steffimycinon (26): 4.1 mg of **25**[36] afforded 4.3 mg of **26**: mp 120–130 °C dec; reaction time 1 h; IR 1710, 1675, 1621, 1590 cm^{-1}; ^1H NMR (270 MHz) δ 1.23 (d, J = 6.6 Hz, H-6′), 1.59 (s, CH_3), 1.91 (td, J = 13.2, J = 12.4, J = 3.7 Hz, H-2$_a$′), 2.07 (dd, J = 13.2, J = 5.0 Hz, H-2$_e$′), 3.55 (s, OCH_3), 3.64 (m, H-4′), 3.71 (m, H-8), 5.24 (m, 7-H), 5.64 (d, J = 3.7 Hz, H-1′), 6.73 (d, J = 2.4 Hz, H-3), 6.77 (d, J = 8.5 Hz, NH), 7.44 (d, J = 2.4 Hz, 1-H), 8.35 (s, H-11), 12.11 (s, OH-4), 12.91 (s, OH-6). Anal. Calcd for $C_{29}H_{28}O_{12}NF_3$: C, 54.46; H, 4.41. Found: C, 54.12; H, 4.47.

8-Demethoxy-7-*O*-(2,3,6-trideoxy-3-(trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl)aranciamycinone (27): 24.0 mg of the *rac*-**22** afforded 13.6 mg (35%) of the less polar glycoside **27**: mp 178 °C; IR 3440, 2930, 1712, 1672, 1625, 1595 cm^{-1}; ^1H NMR (400 MHz) δ 1.35 (d, J = 7.0 Hz, H-6′), 1.61 (s, CH_3), 1.86 (dt, J = 12.8, J = 4.0 Hz, H-2$_a$′), 2.03 (dd, J = 12.8, J = 5.0 Hz, H-2$_e$′), 2.48 (dd, J = 14.4, J = 4.8 Hz, H-8), 2.57 (dd, J = 14.4, J = 2.0 Hz, H-8), 3.68 (m, H-4′), 4.34 (m, H-5′), 5.26 (dd, H-7), 5.54 (d, J = 3.5 Hz, H-1′), 6.73 (d, J = 8.5 Hz, NH), 7.31 (dd, J = 8.3, J = 1.0 Hz, H-3), 7.78 (t, H-2), 7.92 (dd, J = 7.6, J = 1.0 Hz, H-1), 8.46 (s, H-11), 11.92 (s, OH-4), 12.80 (s, OH-6). EI mass spectra (70 eV and 25 eV) did not show a molecular ion but gave the pattern characteristic for the aglycons.[7] FD mass spectra showed a peak at 581 (M^+ + 1). Anal. Calcd for $C_{27}H_{24}O_{10}NF_3$: C, 55.96; H, 4.17. Found: C, 55.78; H, 4.18.

7,9-Diepi-8-demethoxy-7-*O*-(2,3,6-trideoxy-3-(trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl)aranciamycinon (28). From the polar fraction of the chromatography (see above) 5.8 mg of the polar glycoside **28** (mp 226 °C; 30%) was obtained: IR and UV/vis see **29**; ^1H NMR (400 MHz) δ 1.33 (d, J = 6.7 Hz, H-6′), 1.63 (s, CH_3), 1.92 (m, H-2′), 2.24 (dd, J = 15.3, J = 3.9 Hz, H-8), 2.76 (dd, J = 15.3, J = 2.0 Hz, H-8), 3.56 (s, OH-9), 3.66 (m,H-4′), 4.38 (m, H-3′), 4.56 (q, J = 6.4 Hz, H-5′), 5.38 (d, J = 2.9 Hz, H-1′), 5.52 (dd, H-7), 6.72 (d, J = 8.5 Hz, NH), 7.38 (dd, J = 8.3, J = 1.0 Hz, H-3), 7.78 (t, H-2), 7.93 (dd, J = 7.6, J = 1.0

(35) We thank Mrs. H. Müller for the preparation of **24**.
(36) We thank Dr. P. F Wiley for a generous gift of steffimycin B.

Hz, H-1), 8.52 (s, H-11), 11.92 (s, OH-4), 11.84 (s,OH-6). Anal. Calcd for $C_{27}H_{24}O_{10}NF_3$: C, 55.96; H, 4.17. Found: C, 55.69; H, 4.23.

7-Epi-8-demethoxy-7-*O*-(2,3,4-trideoxy-3-(trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl)aranciamycinon (29): 20.0 mg of the *cis*-diol **21** afforded after TLC 3.4 mg (24%) of the polar glycoside **29**: mp 134 °C dec.; IR 3420, 2980, 1710, 1673, 1621, 1593 cm^{-1}; UV/vis 210 (4.38), 239 (4.45), 261 (4.30), 438 nm (4.04); ^1H NMR (400 MHz) δ 1.25 (d, J = 6.7 Hz, H-6'), 1.47 (s, CH_3), 1.94 (m, H-2') 2.30 (dd, J = 15.2, J = 3.9 Hz, H-8), 2.68 (dd, J = 15.2, J = 3.9 Hz, H-8), 3.64 (m, H-4'), 4.13 (s, OH-9), 4.31 (m, H-3'), 4.38 (q, J = 6.7 Hz, H-5'), 5.43 (d, J = 3.5 Hz, H-1'), 5.55 (t, H-7), 6.65 (d, J = 8.4 Hz, NH), 7.37 (dd, J = 8.4, J = 1.0 Hz, H-3), 7.78 (t, H-2), 7.92 (dd, J = 7.6, J = 1.0 Hz, H-1), 8.51 (s, H-11), 11.91 (s, OH-4), 12.83 (s, OH-6).

9-Epi-8-demethoxy-7-*O*-(2,3,6-trideoxy-3-(trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl)aranciamycinon (30). From the less polar zone of the chromatography (see above) 5.0 mg (31%) of glycoside **30** was isolated: mp 147 °C; IR 3460, 3920, 1707, 1672, 1621, 1595 cm^{-1}; UV/vis see **29**; ^1H NMR (400 MHz) δ 1.33 (d, J = 6.5 Hz, H-6'), 1.42 (s, CH_3), 1.87 (dt, J = 12.6, J = 3.6 Hz, H-2_a'), 2.00 (d, J = 8.2 Hz, OH), 2.08 (dd, J = 5.2, J = 3.6 Hz, H-2_e'), 2.47 (dd, J = 14.7, J = 7.0 Hz, H-8), 2.64 (dd, J = 14.7, J = 6.0 Hz, H-8), 3.66 (m, H-4'), 4.25 (q, H-5'), 4.29 (m, H-3'), 5.20 (t, H-7), 5.51 (d, J = 3.6 Hz, H-1'), 6.69 (d, J = 8.4 Hz, NH), 7.37 (dd, J = 8.4, J = 1.1 Hz, H-3), 7.76 (t, H-2), 7.90 (dd, J = 7.6, J = 1.1 Hz, H-1), 8.45 (s, H-11), 11.90 (s, OH-4), 12.81 (s, OH-6).

Registry No. **3**, 106-51-4; **4**, 58274-64-9; **5**, 76695-89-1; **7**, 14787-38-3; **8**, 605-93-6; **9**, 2161-90-2; **10**, 91295-25-9; **11**, 91295-26-0; **12**, 3300-25-2; **13**, 91295-27-1; **14**, 91295-28-2; **15**, 91310-97-3; **16**, 91295-29-3; **17**, 84340-89-6; **18**, 84341-05-9; **19**, 91295-30-6; **20**, 91310-98-4; **21**, 91295-31-7; **22**, 91295-32-8; **24**, 57785-90-7; **25**, 91382-92-2; **26**, 91310-99-5; **27**, 91295-33-9; **28**, 91295-34-0; **29**, 91382-93-3; **30**, 91382-94-4; ethyl acetoacetate, 141-97-9.

The Bromination of 5,8-Diacetoxy-1,4-dihydro-1,4-ethanonaphthalene

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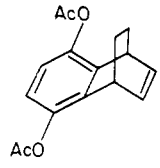
The bromination of 5,8-diacetoxy-1,4-dihydro-1,4-ethanonaphthalene has been found to give only one product, the dibromide produced via a Wagner–Meerwein rearrangement with accompanying aryl migration. The structure of the product was determined by ^1H–^{13}C correlation NMR and ^{13}C–^{13}C double quantum coherence NMR. The bromine configurations and the molecular conformation were determined by chemical shift considerations coupled with a complete analysis of the proton–proton spin coupling constants. Structures reported in related studies are brought into question by this result which has a bearing also on recent investigations of homoconjugation in 1,4-dihydro-1,4-ethanonaphthalene systems.

The addition of bromine to benzobicyclooctadienes such as 5,8-diacetoxy-1,4-dihydro-1,4-ethanonaphthalene (**1**) may lead to a multiplicity of products. Attack on the



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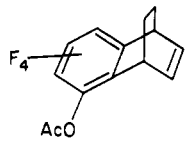

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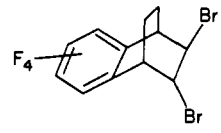

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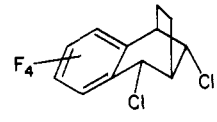
double bond may be syn or anti to the aromatic ring. The intermediate(s), whether bromonium ion or carbocation, may react directly with bromide ion to give nonrearranged product or may undergo Wagner–Meerwein rearrangement involving either the aryl group or the ethano bridge before reacting to give rearranged dibromides. The Barkhash group in Russia have examined the addition of bromine to tetrafluorobenzobicyclooctadiene (**2**).[1] The product was reported as the unrearranged dibromide (**3**). The addition of chlorine gave a mixture of the 1,2-addition product and the rearranged compound (**4**). As a matter for future reference, it may be mentioned that the treatment of the tetrafluorobenzobarrelene (**5**) with *tert*-butyl hypochlorite in acetic acid gave a mixture of rearranged chloroacetates **6** and **7**.[2] The principal method of structure determination in these studies was proton magnetic resonance aided by spin decoupling. If one bears in mind the uncertainties



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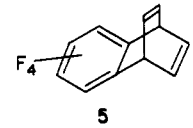

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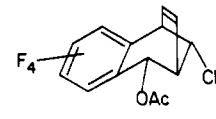

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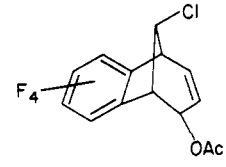

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imposed by the small range of vicinal axial–equatorial and equatorial–equatorial spin–spin coupling constants along with the even greater uncertainties introduced by the effects of electronegative groups such as bromine, chlorine, and acetoxy[3] on these coupling constants, then one feels justified in expressing reservations about structural assignments in such closely related compounds as those encountered in these studies.

Recently, Paquette and co-workers[4] have studied the addition of a series of weak electrophiles to 2-methyl-1,4-dihydro-1,4-ethanonaphthalene and its 5,8-dimethoxy and 5,6,7,8-tetrafluoro analogues. Predominent syn stereoselectivity was observed for photooxygenation, cyclopropanation, oxymercuration, hydroboration, and epoxidation. On the basis of these results a case was made

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