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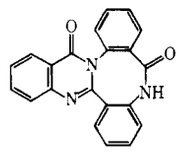

i

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Synthetic Approaches to Adriamycin. 2. Degradation of Daunorubicin to a Nonasymmetric Tetracyclic Ketone and Refunctionalization of the A Ring to Adriamycin

Thomas H. Smith,* Allan N. Fujiwara, William W. Lee, Helen Y. Wu, and David W. Henry

Bio-Organic Chemistry Department, Stanford Research Institute, Menlo Park, California 94025

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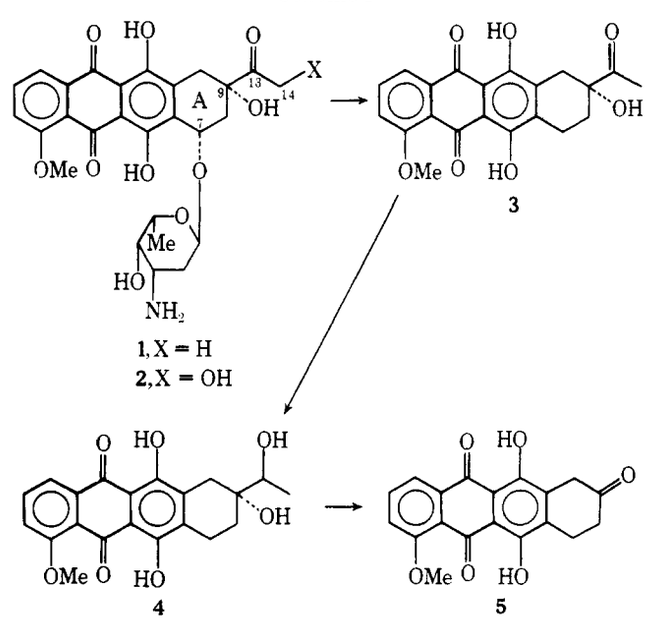
A synthesis of adriamycin (**2**) via elaboration of the functionalities at the 7 and 9 positions of the nonsymmetric tetracyclic ketone **5** is described. Daunorubicin (**1**) was degraded in high yield to **5** by a three-step procedure. Addition of HCN to **5** afforded the cyanohydrin **18**. The 9-OH was protected by conversion to the THP ether **19**, which afforded (±)-7-deoxydaunomycinone (**20**) upon reaction with excess MeMgI followed by acid workup. Model studies employing β-tetralones **6a** and **6b** as substrates showed this sequence to be superior to several other potential methods of side-chain elaboration. Stepwise stereo- and regiospecific hydroxylation of the 7 and 14 positions of 7-deoxydaunomycinone (**3**) afforded adriamycinone (**29**). By a minor modification of the 7-hydroxylation procedure, 7-epidaunomycinone (**27**) is obtained as the major product. The 14-OH was protected by conversion to the *p*-anisyldiphenylmethyl ether **30**. This was condensed with the protected 1-chlorodaunosamine derivative **36** under Koenigs–Knorr conditions to afford adriamycin (**2**) after deprotection.

The anthracycline antibiotics daunorubicin (**1**)[2] and adriamycin (**2**)[3] are clinically useful antineoplastic agents, with adriamycin having an especially broad spectrum of activity. However, chemotherapy employing these drugs is hampered by a number of undesirable side effects, the most serious being dose-related cardiotoxicity.[3b,4] As part of this laboratory's ongoing efforts to prepare anthracyclines having improved therapeutic properties, the possibility of developing a practical total synthesis of **2** was investigated. We now report the results of those studies.

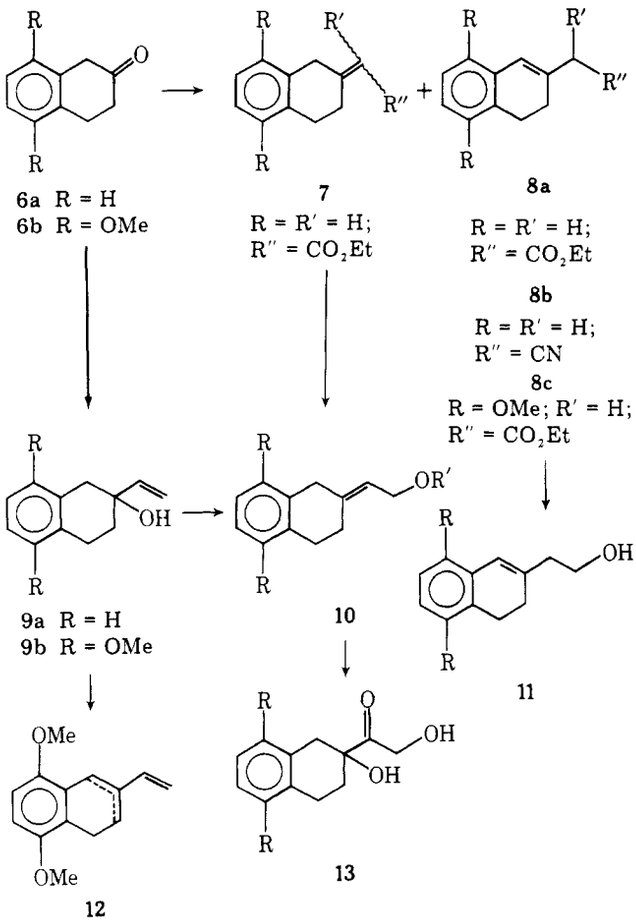
Due to the important biological activities of **1** and **2** considerable interest has been shown in their synthesis and several aspects have been explored.[1,5] Since practical syntheses of the daunosamine sugar moiety[5c,f] and a circuitous synthesis of the aglycone[5b] had been reported, the formal total synthesis of **1** was completed in 1974 with the report of stereospecific coupling of the aglycone and sugar moiety.[1c] In this paper, we describe the elaboration of the tetracyclic nonasymmetric ketone **5** to adriamycin (**2**). In our work, **5** was obtained by degradation of daunorubicin, but a total synthesis of **5** which was subsequently elaborated to (±)-daunomycinone was recently described by Kende et al.[5a] via a Diels–Alder sequence, an approach that has received much recent attention.[6]

Treatment of daunorubicin (**1**) with sodium dithionite (Scheme I) resulted in reductive cleavage of the glycoside bond to afford 7-deoxydaunomycinone (**3**) in quantitative yield. Reduction of the 13-carbonyl was achieved with $LiAl(t\text{-}BuO)_3H$ in THF to afford the 13-dihydro compound **4** as a diastereomeric mixture in 80% yield. Periodate cleavage of the glycol was unusually slow, requiring 2 equiv of $NaIO_4$ at 23 °C for 16 h to produce a 99% yield of **5** with 71% conversion of **4**.

Scheme I



Scheme II



Having the tetracyclic ketone **5** in hand, several problems remained to be solved to allow its successful elaboration to **2**. Methods for the elaboration of the dihydroxyacetone side chain from the 9-keto function and for the regio- and stereospecific hydroxylation of the 7 position needed to be developed. The dihydroxyacetone side chain had to be blocked in such a way as to direct the sugar moiety to the 7 position during coupling and to protect the side chain during the alkaline deprotection of the sugar. However, the protecting group must be removable under conditions compatible with the acid-sensitive glycoside bond.

A number of possible methods of side-chain elaboration were evaluated using β-tetralone (**6a**) and 5,8-dimethoxy-2-tetralone (**6b**)[7] as model compounds. In general, these methods could be classified either as two-carbon homologations in which the potential 13- and 14-carbon atoms are introduced in a single operation and the resultant intermediate is subsequently transformed by conventional operations to the desired target (Scheme II), or two sequential one-carbon homologations in which the side-chain carbon atoms are introduced in discrete steps.

In the first of the two-carbon homologation sequences that we explored the ketone was to be converted to an exocyclic α,β-unsaturated ester such as **7**. The ester could then be reduced, the primary hydroxyl protected, and the olefin oxidized with the OsO_4–*N*-methylmorpholine–H_2O_2 reagent[8] to afford **13**. The reaction of β-tetralone (**6a**) with the sodio anion of triethyl phosphonoacetate proceeded smoothly to afford a single homogeneous (TLC, GLC) product with spectral properties (NMR, IR, MS) in apparent agreement with those expected of **7**. Reduction of this material with $LiAlH_3OEt$[9] afforded a single product in good yield. However, in the ^1H NMR spectrum of this material the new methylene protons appeared as a triplet instead of the doublet expected for **10**.

Table I. ^1H NMR Analysis of the Products of the Wadsworth–Emmons Condensation

	Chemical shift, δ		
	Olefinic	Methylene singlet	
Compd	proton	Found	Calcd
8a	6.29	3.18	3.10
7	5.80	3.52	3.34
11	6.29		

This indicated that the reduction product was the alcohol **11** and cast doubt on the identity of the condensation product of the Wadsworth–Emmons reaction. Reexamination of the ^1H NMR spectrum (Table I) of this material indicated its correct structure to be **8a**. This was assigned on the basis of the identical chemical shifts of the olefinic protons of the ester and **11** and the correlation of the chemical shift of the methylene singlet of the product with that calculated for a methylene flanked by a phenyl group and a carbon–carbon double bond[10] (see Table I).

Isomerization of the olefinic double bond into conjugation with an aromatic moiety during the Wadsworth–Emmons reaction has previously been reported and successfully suppressed by modifying the reaction conditions.[11] In this case, upon lowering the reaction temperature from 23 to 0 °C a new product in approximately a 1:3 ratio with **8a** was detected by GLC. While separation on a preparative scale could not be achieved, the ^1H NMR spectrum of the mixture showed two new signals at δ 3:52 and 5.80 corresponding to the methylene and olefinic protons of **7**. The ratio of **7** to **8a** could be improved by the use of less polar solvents, e.g., ether or benzene, and further lowering of the reaction temperature, but the overall yield of ester fell to unacceptable levels.

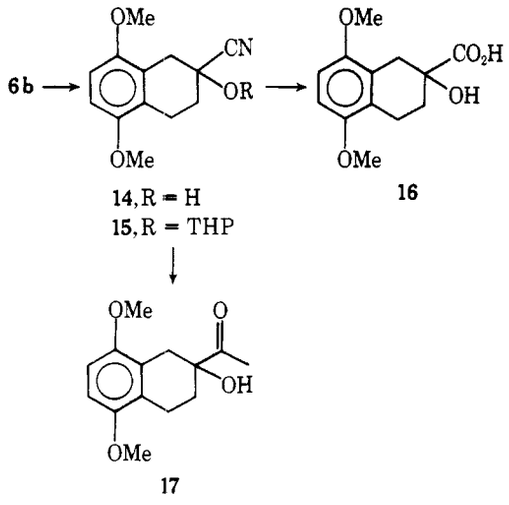
To evaluate the possibility of stabilizing the thermodynamically less favored exocyclic isomer through variation of R″, the reaction of β-tetralone with the anion of diethyl cyanomethylphosphonate in THF at 0 °C was examined and found to afford the endocyclic olefin **8b** exclusively. While the electron-releasing methoxy groups of **6b** might be expected to suppress the double-bond isomerization observed in the reactions of **6a**, the condensation of **6b** with the sodio anion of triethyl phosphonoacetate at 0 °C afforded only the endocyclic olefin **8c**.

Although the reaction of carbethoxymethylenetriphenylphosphorane with ketones is generally considered to be inferior to the Wadsworth–Emmons reaction as a method for the synthesis of α,β-unsaturated esters,[12] it was hoped that the absence of base would serve to suppress the isomerization of the olefinic bond. The phosphorane and β-tetralone were reacted under nitrogen at 110 °C without solvent to afford exclusively the endocyclic olefin **8a** in 76% yield. Reaction of β-tetralone with the lithium enolates of ethyl and *tert*-butyl trimethylsilylacetates[13] afforded only starting material.

Both the Wadsworth–Emmons and Wittig condensations appear to be excellent methods for effecting the required two-carbon homologation. However, at least in the models examined, the isomerization of the resultant olefin to the thermodynamically more stable endocyclic isomer poses serious problems in the subsequent synthetic steps leading to side-chain formation.

In another two-carbon homologation sequence that we explored, the keto function is transformed to a tertiary vinyl carbinol such as **9** via 1,2 addition. This intermediate could then be rearranged to an exocyclic olefin acetate **10** (R′ = Ac)[14] suitable for subsequent elaboration to the side chain. Reaction of vinylmagnesium chloride with **6a** and **6b** afforded the vinyl carbinols **9a** and **9b** in 34 and 45% yield, respectively, along with substantial amounts of unreacted ketone. The recovery

Scheme III

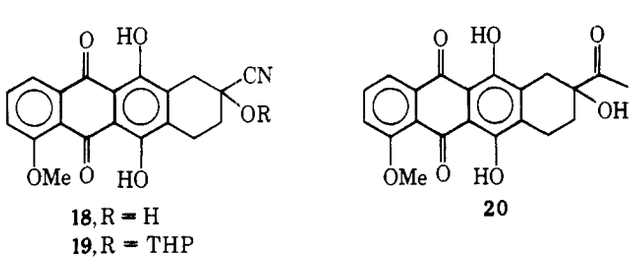


of starting material was probably due to base-catalyzed enolization of the starting ketone. Consistent with this explanation was the observation that only starting material could be recovered from the reaction of the more basic reagent, vinyllithium, with the model ketones. This problem was again encountered in the use of acyl anion equivalents such as 2-lithio-2-methyl-1,3-dithiane and α-methoxyvinyllithium[15] which also afforded only starting material upon reaction with **6a**.

Initial attempts to effect allylic rearrangement of **9b** to **10** with HOAc afforded diene **12** as the major product. This result, together with the rather poor yield of the vinyl carbinols, caused us to drop this approach.

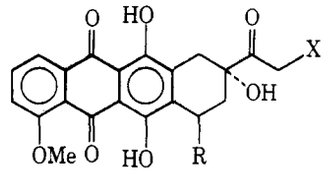
The ultimately successful route involved two sequential one-carbon homologations (Scheme III). 5,8-Dimethoxy-2-tetralone (**6b**) was readily converted to the cyanohydrin **14** which afforded the hydroxyacid **16** in high yield upon acid hydrolysis. However, reaction of **16** with methyllithium failed to yield any significant amounts of **17**. Conversion of **14** to its tetrahydropyranyl ether **15** was accomplished in 77% yield and subsequent reaction of **15** with excess methylmagnesium iodide produced **17** in 64% yield.[16] The trimethylsilyl and *tert*-butyldimethylsilyl protecting groups were less satisfactory; in the former case loss of the protecting group was observed during the Grignard reaction, while in the latter the silylation reaction was so slow as to render this approach impractical.

This sequence was also successful when applied to the tetracyclic ketone **5**. (±)-7-Deoxydaunomycinone (**20**) was obtained via the intermediates **18** and **19** in a 36% overall yield from **5**. In their synthesis of (±)-daunomycinone, Kende et al.[5a] elaborated the side chain via addition of ethynylmagnesium bromide to **5** followed by hydration of the triple bond.

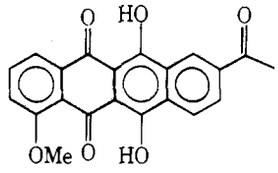


Hydroxylation of the 7 and 14 positions of **20** would afford (±)-adriamycinone which would lead to a mixture of diastereomers upon coupling with daunosamine. To avoid this complication, subsequent experiments were performed using 7-deoxydaunomycinone (**3**) obtained by reductive cleavage of **1**.

The 14-hydroxylation of **3** via ionic bromination with pyrrolidone hydrotribromide in THF to afford **21**, and subsequent reaction of **21** with 1 equiv of NaOH in aqueous acetone to produce 7-deoxyadriamycinone (**22**) proceeded readily. However, as **3** was more soluble than **22** in organic solvents, we chose to introduce the 7-hydroxyl first.



21, X = Br; R = H
22, X = OH; R = H
23, X = H; R = ~Br
24, X = H; R = ~OAc
25, X = H; R = ~$OCOCF_3$
26, X = H; R = ···OH
27, X = H; R = –OH
28, X = Br; R = ···OH
29, X = OH; R = ···OH
30, X = $OC(Ph)_2$-*p*-$OMeC_6H_4$; R = ···OH



31

A model for the hydroxylation of the 7 position of **3** (benzylic bromination, AgOAc displacement, transesterification with F_3AcOH, methanolysis) was first provided Goodman et al.[17] with a simplified daunomycinone analogue and by Wong et al.[5b] who used a closely related sequence in the first daunomycinone synthesis. Bromination of **3** with several reagents afforded, besides bromide **23**, considerable amounts of unreacted **3** and bis(anhydro)daunomycinone (**31**), presumably arising from aromatization of **23**. Efforts to achieve complete reaction resulted in increased yields of **31** at the expense of **23**. Although this problem was not fully overcome, the benzylic bromination was achieved most satisfactorily by using Br_2 (1.5 equiv) in refluxing CCl_4 with 2,2′-azobis(isobutyronitrile) (ABN) as catalyst. Wong[5b] postulated that steric hindrance about the 10 position allows benzylic bromination to proceed regiospecifically at the 7 position. 14-Bromo-7-deoxydaunomycinone (**21**), arising from ionic bromination of the 14 position, was not observed in the reactions of **3** with Br_2, NMe_4Br_3, or NBS in CCl_4. However, **21** was formed exclusively upon treatment of **3** with Br_2 or NMe_4Br_3 in $CHCl_3$, regardless of the presence of radical initiators.

The unstable bromide **23**, without isolation, could be converted to the acetate **24** with excess AgOAc in refluxing HOAc. However, subsequent transesterification to **25** (F_3AcOH, 48 h, 23 °C) was incomplete, as **24** was always detectable in the reaction mixture after methanolysis (MeOH, 23 °C, 4 h).

This problem was avoided by converting **23** directly to trifluoroacetate **25** with $NaOCOCF_3$ in Me_2SO[18] (16 h, 23 °C). Intermediates **23** and **25** were used without purification because of their instability. 7-Deoxydaunomycinone (**3**) was brominated, treated with $NaOCOCF_3$, and subjected to methanolysis as a continuous operation. Chromatography of the methanolysis product on silica gel afforded, in order of elution, bis(anhydro)daunomycinone (**31**), starting material (**3**, 17%), daunomycinone (**26**, 9%), and 7-*epi*-daunomycinone (**27**, 35%).

Characterization of **27** was based on its ^1H NMR spectra. The benzylic H-7 proton signal appeared as a multiplet at δ

5.42 ($\nu_{1/2}$ = 17 Hz) characteristic of an axial proton.[19] The spectrum of daunomycinone is similar except that the H-7 signal appears as a narrower ($\nu_{1/2}$ = 7 Hz) multiplet due to the equatorial orientation of H-7. The mass spectrum and elemental analysis of **27** showed it to be isomeric with daunomycinone.

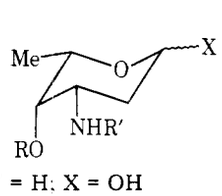
Anthracyclinones having an axial proton at C-7 have been epimerized with acid.[18] To obtain aglycone possessing the natural stereochemistry, the crude trifluoroacetate **25** was dissolved in F_3AcOH (23 °C, 1.5 h) before methanolysis. Silica gel chromatography of this crude product afforded **31**, starting material (**3**, 18%), daunomycinone (**26**, 35%), and 7-*epi*-daunomycinone (**27**, 6%). Reaction of **26** with bromine in $CHCl_3$[5h] afforded 14-bromodaunomycinone (**28**) which was treated directly with 1 equiv of NaOH in aqueous acetone to afford adriamycinone (**29**) in 87% yield.

The partial stereospecificity of the 7-hydroxylation can be explained by an S_N1 mechanism for the $NaOCOCF_3$ displacement. Approach of the trifluoroacetate anion to the planar benzylic carbonium ion arising from ionization of the bromide **23** should be more favorable from the side trans to the axial hydroxyl at C-9. Methanolysis would then result in the observed predominant formation of **27** over **26**.

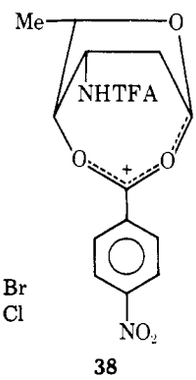
The problem of protecting the dihydroxyacetone side chain was solved via conversion of **29** to the monomethoxytrityl ether **30** in 84% yield. We elected to use **30** since it could be prepared in high yield without the formation of diastereomers, and probe experiments demonstrated that it could be removed without affecting the glycosidic bond. The highly lipophilic trityl moiety also facilitated the separation of the glycoside from the water-soluble sugar by-products of the coupling reaction by simple solvent extraction.

In alternative approaches to this problem, Arcamone et al.[5e] bridged the 9,14-diol system with an orthoester to provide side-chain protection during removal of an *N*-trifluoroacetyl group. The same investigators also employed a double ketal system in coupling work with 4-*epi*-daunosamine[5i] as well as daunosamine.[5e]

The sugar moiety was protected as previously described.[1c] Reaction of daunosamine (**32**) with *S*-ethyl trifluorothioacetate afforded *N*-trifluoroacetyldaunosamine (**33**) which upon treatment with *p*-nitrobenzoyl chloride in pyridine afforded the α anomer of **34** in 93% yield. Saturation of a suspension of **34** in CH_2Cl_2 with the appropriate hydrogen halide afforded **35** or **36** after filtration to remove the precipitated *p*-nitrobenzoic acid and evaporation. The crude 1-halo sugars so obtained were added to the reaction mixture without further purification.



32, R = R' = H; X = OH
33, R = H; R' = CF_3CO; X = OH
34, R = *p*-$NO_2C_6H_4CO$; R' = CF_3CO; X = *p*-$NO_2C_6H_4CO_2$
35, R = *p*-$NO_2C_6H_4CO$; R' = CF_3CO; X = Br
36, R = *p*-$NO_2C_6H_4CO$; R' = CF_3CO; X = Cl
37, R = R' = CF_3CO; X = Cl



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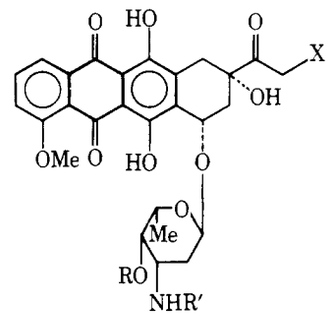
Previous work from this laboratory established that the daunosaminyl bromide derivative **35** coupled stereospecifically with daunomycinone, giving only the α anomer.[1c] Arcamone et al.[5e] found that the chloro derivative **37** provided a 7:3 ratio of α to β anomers in the same reaction.

Good precedent for steric control by a 4-*O*-*p*-nitrobenzoyl group in the coupling reactions of related sugars to give trans C-4, C-1 products is provided by the work of Dejter-Juszynski and Flowers.[20] They have also shown that a 4-*O*-acetyl group, while still exerting considerable steric control, is somewhat less effective in directing the steric course of the glycosidation.[21] Presumably, the carbonyl oxygen provides anchimeric assistance to the halide displacement, allowing the coupling to proceed via a 7-membered *p*-nitrobenzoyloxonium intermediate such as **38**. The poorer stereospecificity observed[5e,22] with the 4-*O*-trifluoroacetyl derivative **37** is consistent with this argument, as the greater electron withdrawing power of the trifluoromethyl group should inhibit participation of the carbonyl oxygen.

For the present work we have preferred to use **36**, retaining the *O*-*p*-nitrobenzoate for stereospecificity and the 1-chloro for greater stability toward elimination and adventitious hydrolysis during handling. The chloro sugar **36** is superior to **35** in the coupling with daunomycinone affording **39** in 77% yield, as opposed to the 53% yield obtained from **35**.



39, X = H; R = *p*-$NO_2C_6H_4CO$; R' = CF_3CO
40, X = $OC(Ph)_2$-*p*-$OMeC_6H_4$; R = *p*-$NO_2C_6H_4CO$; R' = CF_3CO
41, X = $OC(Ph)_2$-*p*-$OMeC_6H_4$ R = R' = H

The protected aglycone **30** was condensed with **36** under Koenigs–Knorr conditions to afford exclusively α-glycoside **40**. The unpurified product was deacylated with 0.1 N NaOH in aqueous THF at 0 °C to afford **41** which could be separated from the water-soluble sugar by-products of the coupling reaction by extraction with $CHCl_3$.

Treatment of **41** with 80% HOAc afforded adriamycin (**2**) which was isolated as the hydrochloride in 40% yield from **30**. This material is identical in all respects, including biological activity as measured by inhibition of DNA and RNA synthesis of cultured L-1210 cells, with the natural product. The synthetic material provided ED_{50} values of 1.5 and 0.44 μM for DNA and RNA synthesis, respectively, as compared with 1.5 and 0.58 μM values from the natural product.

Experimental Section

Melting points are uncorrected. Ultraviolet–visible spectra, infrared spectra, and 60-MHz ^1H NMR measurement were made by the Pharmaceutical Analysis Department under the direction of Dr. Peter Lim. Measurements of 100-MHz ^1H NMR were performed by Mr. L. Cary using a Varian XL-100 spectrometer. The NMR spectra were measured in $CDCl_3$ with tetramethylsilane as an internal standard and the IR spectra were measured from Nujol mulls unless otherwise noted. Elemental microanalyses were provided by Ms. E. M. McCarthy (SRI) or the microanalytical laboratory of Stanford University. Mass spectra were recorded by Dr. D. W. Thomas on an LKB Model 9000 mass spectrometer at 70 eV unless otherwise stated.

Thin-layer chromatograms (TLC) were obtained on 250-μm silica gel G or H plates. Preparative layer chromatograms (PLC) were obtained on 20 × 20 × 0.2 silica gel 60 F-254 plates (E. Merck). Column chromatography was performed with Bio Sil A 200–305 mesh (Bio-Rad) or E. Merck prepacked silica gel 60 columns. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ immediately prior to use. Solvent extracts of aqueous solutions were dried over anhydrous Na_2SO_4. Petroleum ether refers to the fraction boiling from 30 to 60 °C, unless

otherwise stated. Solutions were concentrated under reduced pressure using a rotary evaporator.

7-Deoxydaunomycinone (3). To daunorubicin hydrochloride (1, 5.0 g, 8.87 mmol) in THF (100 mL)/MeOH (120 mL) under N_2 was added a solution of $Na_2S_2O_4$ (3.09 g, 17.8 mmol) and $NaHCO_3$ (5.96 g, 71.0 mmol) in H_2O (120 mL) over 5 min. The mixture was stirred for 15 min at 23 °C, poured into ice–water (250 mL), and extracted with CH_2Cl_2 (8 × 75 mL). The extracts were combined, dried, and evaporated to afford 3.85 g (99%) of **43**; mp 229–231 °C; IR 2.85 (OH), 5.85 (C=O), 6.19, 6.29 μm (H-bonded quinone); NMR δ 1.95 (m, 2 H, 8-H_2), 2.42 (s, 3 H, Ac), 3.00 (m, 4 H, 7 and 10-H_2), 3.84 (br s, 1 H, 9-OH), 4.10 (s, 3 H, OMe), 7.36 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.73 (t, 1 H, J = 8 Hz, 2 H), 7.99 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.37 (s, 1 H, phenolic OH), 13.79 (s, 1 H, phenolic OH); MS m/e (%), 383 (9), 382 M (33), 364 (6), 340 (21), 339 (100), 321 (13), 43 (13).

Anal. Calcd for $C_{21}H_{18}O_7 \cdot 0.5H_2O$: C, 64.45, H, 4.91. Found: C, 64.71; H, 4.75.

7-Deoxy-13-dihydrodaunomycinone (4). 7-Deoxydaunomycinone (**3**, 300 mg, 0.79 mmol) and $LiAl(t\text{-}BuO)_3H$ (480 mg, 1.84 mmol) were stirred in THF (30 mL) under N_2 for 6 h. Additional $LiAl(t\text{-}BuO)_3H$ (120 mg) was added, and after 16 h a third portion of $LiAl(t\text{-}BuO)_3H$ (240 mg) was introduced. After the last addition, stirring was continued for 24 h. The reaction mixture was poured into 2 N HCl (50 mL) and heated on the steam bath for 1 h. The mixture was allowed to cool and extracted with CH_2Cl_2 (three 40-mL portions). The extracts were combined, dried, and evaporated. The residue was recrystallized from $CH_2Cl_2/CHCl_3$ to afford 161.6 mg of **4**. The mother liquors were evaporated and the residue was chromatographed (PLC silica gel, 93:7 $CHCl_3$/MeOH) to afford 35.4 mg of starting material **3** and an additional 79.5 mg of **4**. Combined yield was 240.1 mg (80%) of **4**: mp 230–233 °C; IR 2.85 (OH), 6.20, 6.30 μm (chelated quinone); MS m/e (%), 385 (18), 384 M (94), 340 (25), 339 (100); NMR δ 1.87 (two overlapping doublets, 3 H, 14-H_3), 2.06 (m, 2 H, 8-H_2), 2.63 (d, 1 H, J = 19 Hz, 10β-H), 2.8–3.1 (m, 3 H, 10α-H and 7-H_2), 3.79 (q, 1 H, 13-H), 4.11 (s, 3 H, OMe), 7.37 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.75 (t, 1 H, J = 8 Hz, 2-H), 8.03 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.48 (s, 1 H, phenolic OH), 13.84 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.61; H, 5.25. Found: C, 65.28; H, 5.39.

7,8-Dihydro-6,11-dihydroxy-4-methoxy-5,9(10*H*),12-naphthacenetrione (5). To 7-deoxy-13-dihydrodaunomycinone (**4**, 377.6 mg, 0.98 mmol) in THF (60 mL) was added $NaIO_4$ (462 mg, 2.16 mmol) in 50% aqueous MeOH (2 mL). The solution was stirred under N_2 for 16 h at 23 °C. The reaction mixture was concentrated to ca. 10 mL and extracted with CH_2Cl_2 (two 30-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed (40 g of Bio Sil A, 98:2 $CHCl_3$/MeOH) to afford in order of elution 237.2 mg (99% yield, 71% conversion) of **4**: IR 5.82 (C=O), 6.15, 6.35 μm (H-bonded quinone); NMR δ 2.64 (t, 2 H, 8-H_2), 3.25 (t, 2 H, 7-H_2), 3.61 (s, 2 H, 10-H_2), 4.09 (s, 3 H, OMe), 7.38 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.77 (t, 1 H, J = 8 Hz, 2-H), 8.04 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.30 (s, 1 H, phenolic OH), 13.80 (s, 1 H, phenolic OH); MS 12 eV m/e (%) 338 M (100).

Anal. Calcd for $C_{19}H_{14}O_6 \cdot 0.5H_2O$: C, 65.7; H, 4.35. Found: C, 66.1; H, 4.49. Further elution afforded 110.6 mg of starting material **4**.

Ethyl 3,4-Dihydro-2-naphthylacetate (8a). Sodium hydride (0.865 g of 57% dispersion in mineral oil, 20.6 mmol) was placed in THF (60 mL) and cooled to 0 °C. Triethyl phosphonoacetate (4.60 g, 20.6 mmol) in THF (5.0 mL) was added dropwise with stirring. After the addition was complete, stirring was continued at 0 °C for 0.5 h when a homogenous solution formed. β-Tetralone (**6a**, 3.00 g, 20.6 mmol) in THF (5 mL) was added dropwise. After the addition was complete, stirring was continued at 0 °C for 0.5 h, at 23 °C for 3 h and at reflux for 0.5 h. The reaction mixture was allowed to cool and quenched with H_2O (200 mL), and the mixture was extracted with $CHCl_3$ (four 25-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed (300 g of Bio Sil A, benzene) to yield 3.53 g (80%) of **8a**: IR (neat) 5.75 (C=O), 6.03 (C=C), 7.98, 8.45, 8.65 (COC), 9.65, 13.18 μm (Ar); NMR δ 1.23 (t, 3 H, $CO_2CH_2CH_3$), 2.31 (t, 2 H, 3-H_2), 2.81 (t, 2 H, 4-H_2), 3.18 (s, 2 H, CH_2CO_2), 4.14 (q, 2 H, $CO_2CH_2CH_3$), 6.29 (s, 1 H, 1-H), 7.03 (s, 4 H, Ar H's); MS m/e (%) 216 M (27), 143 (83), 142 (90), 141 (78), 128 (100), 115 (22).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.7; H, 7.44. Found: C, 77.3; H, 7.18.

2-Cyanomethyl-3,4-dihydronaphthalene (8b). Sodium hydride (0.433 g of 57% dispersion in mineral oil, 10.3 mmol) was placed in THF (60 mL) and cooled to 0 °C. Diethyl cyanomethylphosphonate (1.82 g, 10.3 mmol) in THF (5 mL) was added dropwise with stirring which was continued for 15 min at 0 °C when a homogeneous solution formed. β-Tetralone (**6a**, 1.50 g, 10.3 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and at 25 °C for 2.5 h. The reaction mixture was poured into ice/H_2O (200 mL) and extracted with $CHCl_3$ (three 50-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed (100 g of Bio Sil A, 1:1 petroleum ether/benzene) to afford 1.55 g (89%) of **8b**: IR (neat) 4.40 (CN), 6.72 (Ar), 13.16 μm; NMR δ 2.30 (t, 2 H, 3-H_2), 2.88 (t, 2 H, 4-H_2), 3.21 (d, 2 H, J = 1 Hz, CH_2CH), 6.52 (t, 1 H, J = 1 Hz, 1-H), 7.12 (s, 4 H, Ar H's); MS m/e (%) 170 (4), 169 M (29), 141 (10), 130 (9), 129 (100), 128 (28), 127 (11).

Anal. Calcd for $C_{12}H_{11}N \cdot 0.25H_2O$: C, 82.95; H, 6.68; N, 8.06. Found: C, 83.29; H, 6.79; N, 8.09.

Ethyl 3,4-Dihydro-5,8-dimethoxy-2-naphthylacetate (8c). In a procedure similar to that described above, 5,8-dimethoxy-2-tetralone (**6b**, 2.0 g, 9.72 mmol) was reacted with an equivalent amount of the sodio anion of triethyl phosphonacetate to afford 1.96 g (74%) of **8c**: IR (neat), 5.72 (C=O), 6.00 (C=C), 6.71, 7.95, 8.48, 8.62 (COC), 9.15, 9.25, 9.65, 12.60, 13.25, 13.95 μm (Ar); NMR δ 1.23 (t, 3 H, $CO_2CH_2CH_3$), 2.28 (m, 2 H, 3-H_2), 2.82 (m, 2 H, 4-H_2), 3.22 (s, 2 H, CH_2CO_2Et), 3.79 (s, 6 H, OMe), 4.17 (q, 2 H, $CO_2CH_2CH_3$), 6.68 (s, 3 H, 1-H and Ar H's); MS m/e (%) 277 (11), 276 M (67), 203 (63), 202 (26), 201 (15), 189 (16), 188 (53), 187 (21), 173 (25), 171 (19), 86 (65), 84 (100), 49 (17), 47 (20).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.31. Found: C, 69.19; H, 7.11.

3,4-Dihydro-2-(2′-hydroxyethyl)naphthalene (11). To $LiAlH_4$ (0.6 g, 15.8 mmol) in ether (50 mL) was added EtOH (0.92 mL, 15.8 mmol) in ether (10 mL). This reagent was added in 0.5-mL portions at 0.5-h intervals to a stirred solution of ethyl 3,4-dihydro-2-naphthylacetate (**8a**, 107.1 mg, 0.496 mmol) in ether (5 mL). After 2.5 h, the reaction was complete as judged by TLC. Excess reagent was destroyed by addition of EtOAc (5 mL) followed by H_2O (5 mL). The mixture was filtered and diluted with $CHCl_3$. The organic phase was separated and the aqueous phase extracted with $CHCl_3$ (10 mL). The organic solutions were combined, dried, and evaporated to afford 59.8 mg (69%) of **11**: IR (neat) 2.95 (OH), 9.62, 13.22 μm (Ar); NMR δ 2.1–2.9 (m, 6 H, 1-, 3-, and 4-H_2's), 3.76 (t, 2 H, 2′-H_2), 6.26 (s, 1 H, 1-H), 7.02 (s, 4 H, Ar H's).

This material was further characterized as the p-nitrobenzoate: mp 93–94 °C; IR 5.78 (C=O), 6.17 (C=C), 7.25, 7.40, 7.85 (COC), 8.90, 9.05, 13.00, 13.90, 14.00 μm (Ar); NMR δ 2.1–3.0 (m, 6 H, 1′-, 3- and 4-H_2's), 4.52 (t, 2 H, 2′-H_2), 6.26 (s, 1 H, 1-H), 7.02 (s, 4 H, Ar H's), 8.19 (s, 4 H, PNB Ar H's); MS m/e (%) 323 M (1), 157 (11), 156 (100), 141 (21), 128 (29), 115 (14).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.29; N, 4.33. Found: C, 70.44; H, 5.57; N, 4.46.

1,2,3,4-Tetrahydro-2-hydroxy-2-vinylnaphthalene (9a). To vinylmagnesium chloride (1.00 mL of 2.3 M solution in THF, 2.23 mmol) under N_2 at 0 °C was added β-tetralone (150.4 mg, 1.03 mmol) dropwise and the mixture was stirred at 0 °C for 1 h and at 23 °C for 16 h. The reaction mixture was cooled to 0 °C and saturated NH_4Cl was added dropwise until vigorous reaction subsided. Additional saturated NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (two 10-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed (PLC 9:1 $CHCl_3$/EtOAc) to afford 40.4 mg (39%) of **9a**: IR (neat) 3.10 (OH), 10.00, 10.80, 13.20, 13.50 μm (Ar); NMR δ 1.88 (t, 2 H, 3-H_2), 2.89 (m, 4 H, 1- and 4-H_2), 5.09 (dd, 1 H, J = 10 and 1.5 Hz, 2′-*cis*-H), 5.27 (dd, 1 H, J = 17 and 1.5 Hz, 2′-*trans*-H), 6.06 (dd, 1 H, J = 17 and 10 Hz, 1′-H), 7.09 (s, 4 H, Ar H's); MS m/e (%) 175 (3), 174 M (20), 159 (16), 156 (21), 145 (18), 141 (12), 129 (14), 128 (31), 119 (16), 117 (15), 115 (28), 105 (20), 104 (100), 103 (20), 91 (22), 85 (23), 83 (35), 78 (22), 55 (20).

This material was further characterized as the p-nitrobenzoate: mp 77 °C; IR 5.80 (C=O), 6.21 (Ar), 6.60 (NO_2), 13.95 μm (Ar).

Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.29; N, 4.33. Found: C, 70.2; H, 5.51; N, 4.24.

1,2,3,4-Tetrahydro-2-hydroxy-5,8-dimethoxy-2-vinylnaphthalene (9b). To vinylmagnesium chloride (10 mL of 2.3 M solution in THF, 23.0 mmol) under N_2 at 0 °C was added 5,8-dimethoxy-2-tetralone (**6b**, 2.00 g, 9.72 mmol) in THF (5 mL) over 10 min. The solution was stirred at 0 °C for 1 h and at 23 °C for 3.5 h. The reaction mixture was cooled at 0 °C and the excess Grignard reagent destroyed by dropwise addition of saturated NH_4Cl (5 mL). Saturated NaCl (40 mL) was added and the mixture was extracted with EtOAc (three 15-mL portions). The extracts were combined, dried, and evaporated, and the residue was chromatographed (E. Merck silica gel 60 prepacked column (size C), 95:5 $CHCl_3$/EtOAc) to afford 0.39 g (20%) of **6b** and 0.95 g (42%) of **9b**: IR (neat) 3.10 (OH), 10.80 ($CH=CH_2$), 12.67, 13.15, 13.60, 13.95 μm (Ar); NMR δ 1.82 (t, 2 H, 3-H_2), 2.80 (m,

4 H, 1- and 4-H_2's), 3.86 (s, 6 H, OMe), 5.08 (dd, 1 H, J = 10.5 and 1.5 Hz, *cis*-CH=C**H**$_2$), 5.30 (dd, 1 H, J = 16.5 and 1.5 Hz, *trans*-CH=C**H**$_2$), 6.08 (dd, 1 H, J = 16.5 and 10.5 Hz, C**H**=CH$_2$), 6.63 (s, 2 H, Ar H's); MS *m/e* (%) 234 M (22), 216 (8), 164 (17), 149 (11), 75 (60), 73 (100).

This material was further characterized as the *p*-nitrobenzoate: mp 149–150 °C; IR 5.81 (C=O), 6.59 (NO_2), 13.80, 14.25 μm (Ar); MS 12 eV *m/e* (%) 383 M (25), 216 (100).

Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.53; N, 3.65. Found: C, 65.60; H, 5.83; N, 3.54.

2-Cyano-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalene (14). 5,8-Dimethoxy-2-tetralone (**6b**, 1.00 g, 4.85 mmol) and KCN (5 g) were placed in $CHCl_3$ (125 mL)/EtOH (37.5 mL) and cooled to 0 °C. HOAc (7.5 mL) was added over 10 min. The mixture was diluted with EtOH (25 mL) and stirred at 23 °C for 2 h. The mixture was diluted with H_2O (150 mL) and extracted with $CHCl_3$ (three 40-mL portions). The extracts were combined, dried, and evaporated. The residue was crystallized from toluene to afford 0.90 g (80%) of **14**: mp 117–119 °C; IR 2.92 (OH), 4.42 (CN), 13.95 μm (Ar); NMR δ 2.13 (t, 2 H, 3-H_2), 2.7–3.3 (m, 5 H, OH, 1 and 2-H_2's), 3.79 (s, 6 H, OMe), 6.68 (s, 2 H, Ar H's); MS *m/e* (%) 234 (7), 233 M (75), 218 (12), 206 (89), 164 (100), 163 (22), 149 (67), 91 (18).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.01; H, 6.49; N, 6.00.

1,2,3,4-Tetrahydro-2-hydroxy-5,8-dimethoxy-2-naphthoic Acid (16). 2-Cyano-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalene (**14**, 1.00 g, 4.49 mmol) was placed in concentrated HCl (30 mL) at 0 °C. The mixture was stirred at 0 °C for 3 h and kept at 0 °C for an additional 20 h. The mixture was heated on a steam bath for 45 min and allowed to cool. The solution was extracted with CH_2Cl_2 (four 30-mL portions). The extracts were combined, dried, and evaporated. The residue was recrystallized from xylene to afford 0.77 g (71%) of **16**: mp 169–170 °C; IR 3.10 (OH), 5.82 (C=O), 12.70, 14.05 μm (Ar); NMR ($CDCl_3$/Me_2SO-d_6) δ 2.02 (t, 2 H, 3-H_2), 2.7–3.1 (m, 4 H, 1- and 3-H_2's), 3.77 and 3.81 (two singlets, 6 H, OMe), 6.68 (s, 2 H, Ar H's); MS *m/e* (%) 234 M (22), 216 (8), 164 (17), 149 (11), 75 (60), 73 (100).

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.38. Found: C, 61.78; H, 6.38.

2-Cyano-1,2,3,4-tetrahydro-5,8-dimethoxy-2-(2′-tetrahydropyranyloxy)naphthalene (15). 2-Cyano-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalene (**14**, 109.4 mg, 0.464 mmol) was placed in dihydropyran (1.5 mL) with concentrated HCl (1 drop) and refluxed for 1.5 h. The reaction mixture was allowed to cool, diluted with ether (15 mL), washed with 10% NaOH (5 mL) and saturated NaCl (5 mL), and dried. The solvent was removed and the residue was chromatographed (PLC, 9:1 $CHCl_3$/EtOAc) to afford 113.8 mg (77%) of **15**: IR (neat) 4.41 (C≡N), 6.21 (Ar), 7.95 (COC), 12.55, 13.65, 14.00 μm (Ar); NMR δ 1.4–1.7 (m, 6 H, 3′-, 4′-, 5′-H_2's), 2.25 (m, 2 H, 3-H_2), 2.95 (m, 2 H, 4-H_2), 3.23 (s, 2 H, 1-H_2), 3.54 (m, 2 H, 6′-H_2), 3.86 (s, 6 H, OMe), 5.18 (m, 1 H, 2′-H), 6.62 (s, 2 H, Ar H's).

2-Acetyl-1,2,3,4-tetrahydro-2-hydroxy-5,8-dimethoxynaphthalene (17). 2-Cyano-1,2,3,4-tetrahydro-5,8-dimethoxy-2-(2′-tetrahydropyranyloxy)naphthalene (**15**, 106.1 mg, 0.335 mmol) in THF (1.5 mL) was added to MeMgI (0.4 mL of 2.5 M solution in ether, 1.00 mmol) under N_2 and was stirred at 23 °C for 16 h. The reaction mixture was added to 60% HOAc (10 mL) and heated on a steam bath for 0.75 h. The mixture was allowed to cool and extracted with $CHCl_3$ (two 10-mL portions). The extracts were combined, dried, and evaporated, and the residue was chromatographed (PLC, 85:15 $CHCl_3$/EtOAc) to afford 53.4 mg (64%) of **17** which could be crystallized from petroleum ether (60–110 °C): mp 97 °C; IR 2.95 (OH), 5.89 (C=O), 6.26 (Ar), 8.00 (COC), 12.60, 13.00, 14.00 μm (Ar); NMR δ 1.90 (m, 2 H, 3-H_2), 2.33 (s, 3 H, Ac), 2.90 (m, 5 H, 1- and 4-H_2 and OH), 3.78 and 3.81 (two singlets, 6 H, OMe), 6.66 (s, 2 H, Ar H's); MS 12 eV *m/e* (%) 250 M (100), 220 (58), 207 (51), 206 (36).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.20; H, 7.23. Found: C, 67.27; H, 7.11.

9-Cyano-7,8,9,10-tetrahydro-6,9,11-trihydroxy-4-methoxy-5,12-napthacenedione (18). 7,8-Dihydro-6,11-dihydroxy-4-methoxy-5,9(10*H*), 12-napthacenetrione (**5**, 45.3 mg, 0.134 mmol) and KCN (300 mg) were placed in 50% $CHCl_3$/EtOH (8 mL) and cooled at 0 °C. HOAc (0.4 mL) was added and the mixture was stirred at 23 °C for 5 h. The reaction mixture was diluted with H_2O (15 mL), the organic phase separated, and the aqueous phase extracted with $CHCl_3$ (10 mL). The organic solutions were combined, dried, and evaporated. The residue was chromatographed (8 g of Bio Sil A, 98:2 $CHCl_3$/MeOH) to afford 38.0 mg (77%) of **18**: mp 232–235 °C (dec); IR 2.93 (OH), 6.20, 6.31 μm (H-bonded quinone); NMR δ 2.1–2.4 (m, 2 H, 8-H_2), 2.8–3.4 (m, 5 H, 7 and 10-H_2's and 9-OH), 4.08 (s, 3 H, OMe), 7.36 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.74 (t, 1 H, J = 8 Hz, 2-H), 7.99 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.28 (s, 1 H, phenolic OH), 13.68 (s, 1 H, phenolic OH).

9-Cyano-7,8,9,10-tetrahydro-6,11-dihydroxy-4-methoxy-9-(2′-tetrahydropyranyloxy)-5,12-naphthacenedione (19). 9-Cyano-7,8,9,10-tetrahydro-6,9,11-trihydroxy-4-methoxy-5,12-napthacenedione (**18**, 37.0 mg, 0.11 mmol) was placed in 50% dihydropyran/THF (10 mL) with concentrated HCl (1 drop) and the solution was refluxed for 5 h. Pyridine (2 mL) was added and the solvents were removed. The residue was dissolved in $CHCl_3$ (10 mL), washed with H_2O (3 mL), dried, and evaporated. The residue was crystallized from $CHCl_3$/petroleum ether to afford 36.9 mg (90%) of **19**: mp 204–206 °C; IR 6.20, 6.30 μm (H-bonded quinone); NMR δ 1.64 (m, 6 H, 3′-, 4′-, and 5′-H_2's), 2.32 (m, 2 H, 8-H_2), 3.05 (m, 2 H, benzylic CH_2), 3.34, (t, 2 H, benzylic CH_2), 3.58 (m, 2 H, 6′-H_2), 4.10 (s, 3 H, OMe), 5.18 (m, 1 H, 2′-H), 7.35 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.75 (t, 1 H, J = 8 Hz, 2-H), 8.02 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.40 (s, 1 H, phenolic OH), 13.76 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{25}H_{23}NO_7$: C, 66.80; H, 5.16; N, 3.11. Found: C, 66.70; H, 5.25; N, 3.14.

(±)-7-Deoxydaunomycinone (20). Methylmagnesium iodide (0.4 mL of 2.5 M solution in ether, 1.00 mmol) was added under N_2 to a stirred solution of 9-cyano-7,8,9,10-tetrahydro-6,11-dihydroxy-4-methoxy-9-(2′-tetrahydropyranyloxy)-5,12-naphthacenedione (**19**, 15 mg, 0.033 mmol) in THF (1.5 mL). The mixture was stirred at 23 °C for 4 h and at 55 °C for 10 h. The reaction was quenched with 60% HOAc (10 mL) and the solution was heated on a steam bath for 0.75 h. The mixture was diluted with water (10 mL) and extracted with $CHCl_3$ (two 10-mL portions). The extracts were combined, washed with saturated $NaHCO_3$ (5 mL), dried, and evaporated. The residue was chromatographed (PLC, 85:15 $CHCl_3$/EtOAc) and crystallized from $CHCl_3$/petroleum ether to afford 5.7 mg (45%) of **20**: mp 230–232 °C; IR 2.85 (OH), 5.82 (C=O), 6.20, 6.30 μm (H-bonded quinone); NMR δ 1.95 (m, 2 H, 8-H_2), 2.42 (s, 3 H, Ac), 3.00 (m, 4 H, 7- and 10-H_2's), 3.74 (br s, 1 H, 9-OH), 4.10 (S= 3 H, OMe), 7.36 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.73 (t, 1 H, J = 8 Hz, 2-H), 7.99 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.37 (s, 1 H, phenolic OH), 13.79 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{21}H_{18}O_7 \cdot 0.5H_2O$: C, 64.45; H, 4.91. Found: C, 64.14; H, 4.56.

14-Bromo-7-deoxydaunomycinone (21). 7-Deoxydaunomycinone (**3**, 96.7 mg 0.253 mmol) and pyrrolidone hydrotribromide (132 mg, 0.265 mmol) were placed in THF (11 mL) and stirred at 23 °C for 24 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (10 mL) and saturated NaCl (10 mL), dried, and evaporated. The residue was precipitated from CH_2Cl_2 with petroleum ether to afford 96.8 mg (83%) of **21**: mp 250–254 °C; IR 2.85 (OH), 5.74 (C=O), 6.19, 6.29 μm (H-bonded quinone); NMR (Me_2SO-d_6) δ 1.90 (m, 2 H, 8-H_2), 2.67 (m, 4 H, 7- and 10-H_2's), 3.85 (s, 3 H, OMe), 4.75 (s, 2 H, 14-H_2), 7.2–7.7 (m, 3 H, Ar H's), 13.07 (s, 1 H, phenolic OH), 13.57 (s, 1 H, phenolic OH); MS 12 eV *m/e* (%) 462 (14), 460 M (14), 340 (18), 339 (100).

Anal. Calcd for $C_{21}H_{17}BrO_7 \cdot H_2O$: C, 52.63; H, 4.01. Found: C, 52.80; H, 3.76.

7-Deoxyadriamycinone (22). 14-Bromo-7-deoxydaunomycinone (**21**, 99.0 mg, 0.215 mmol) and NaOH (10.3 mg, 0.258 mmol) were placed in 4:1 acetone/H_2O (50 mL) and refluxed under N_2 for 20 min. The acetone was removed and the residue diluted with H_2O (80 mL). The red precipitate was filtered and dried to afford 83.0 mg (97%) of **22**: IR 2.95 (OH), 5.79 (C=O), 6.20, and 6.30 μm (H-bonded quinone); NMR (Me_2SO-d_6) δ 1.84 (m, 2 H, 8-H_2), 2.6–2.9 (m, 4 H, 7- and 10-H_2's), 3.96 (s, 3 H, OMe), 4.5–4.9 (m, 3 H, 14-H_2 and OH), 5.60 (br s, 1 H, OH), 7.54 (br s, 1 H, 3-H), 7.76 (m, 2 H, 1- and 2-H), 13.48 (s, 1 H, phenolic OH), 14.02 (s, 1 H, phenolic OH); MS *m/e* (%) 398 M (20), 380 (4), 335 (100).

Anal. Calcd for $C_{21}H_{18}O_8 \cdot H_2O$: C, 60.58; H, 4.85. Found: C, 60.74; H, 4.51.

Daunomycinone (26). 7-Deoxydaunomycinone (**3**, 100 mg, 0.262 mmol), Br_2 (3.0 mL of 0.125 M solution in CCl_4, 0.375 mmol) and ABN (6.4 mg, 0.04 mmol) were placed in CCl_4 (20 mL) under N_2 and refluxed for 3 h. Additional Br_2 (0.19 mmol) was introduced and refluxing was continued for another hour. The solvent was removed and the residue was placed in Me_2SO (20 mL) with $NaOCOCF_3$ (200 mg) and stirred under N_2 for 16 h. The reaction mixture was poured into H_2O (50 mL) and extracted with $CHCl_3$ (three 15-mL portions). The extracts were combined, washed with H_2O (10 mL) and saturated NaCl (10 mL), dried, and evaporated. The residue was dissolved in F_3AcOH (10 mL) and stirred at 23 °C for 1.5 h. The solvent was removed and the residue dissolved in 4:1 MeOH/THF (20 mL) and stirred at 23 °C for 4 h. The solution was poured into H_2O (50 mL) and

extracted with $CHCl_3$ (three 15-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed [E. Merck silica gel 60 prepacked column (size B), 99:1 to 97:3 CH_2Cl_2/MeOH] to afford in order of elution 17.7 mg (18%) of **3** and 37.0 mg (35%) of **26**: mp 215–217 °C; IR 2.90 (OH), 5.85 (C=O), 6.20, 6.31 μm (H-bonded quinone); NMR δ 2.05–2.35 (m, 2 H, 8-H_2), 2.48 (s, 3 H, Ac), 2.93 (d, 1 H, J = 19 Hz, 10 β-H), 3.25 (d, 1 H, J = 19 Hz, 10 α-H), 3.68 (s, 1 H, 9-OH), 4.14 (s, 3 H, OMe), 4.53 (s, 1 H, 7-OH), 5.36 (m, 1 H, $\nu_{1/2}$ = 7 Hz, 7-H), 7.40 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.79 (t, 1 H, J = 8 Hz, 2-H), 8.06 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.35 (s, 1 H, phenolic OH), 14.07 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{21}H_{18}O_8 \cdot H_2O$: C, 60.58; H, 4.85. Found: C, 60.96; H, 4.45.

Continued elution afforded 6.1 mg (6%) of 7-epidaunomycinone (**27**): mp 218–220 °C; IR 2.85 (OH), 5.85 (C=O), 6.20, 6.30 μm (H-bonded quinone); NMR δ 2.2–2.5 (m, 2 H, 8-H_2), 2.43 (s, 3 H, Ac), 2.90 (d, 1 H, J = 17 Hz, 10 β-H), 3.16 (d, 1 H, J = 17 Hz, 10 α-H), 3.82 (s, 1 H, 9-OH), 4.12 (s, 3 H, OMe), 4.33 (d, 1 H, 7-OH), 5.37 (m, 1 H, $\nu_{1/2}$ = 17 Hz, 7-H), 7.40 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.79 (t, 1 H, J = 8 Hz, 2-H), 8.06 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.26 (s, 1 H, phenolic OH), 14.33 (s, 1 H, phenolic OH); MS 12 eV *m/e* (%) 399 (22), 398 M (87), 380 (56), 362 (45), 355 (17), 339 (15), 338 (64), 337 (100); $[\alpha]_D$ − 184° (*c* 0.02, $CHCl_3$).

Anal. Calcd for $C_{21}H_{18}O_8 \cdot 0.25H_2O$: C, 62.61; H, 4.64. Found: C, 62.68; H, 4.51.

7-Epidaunomycinone (27). 7-Deoxydaunomycinone (**3**, 100 mg, 0.262 mmol), Br_2 (3.0 mL of 0.125 M solution in CCl_4, 0.375 mmol), and ABN (6.4 mg, 0.040 mmol) were placed in CCl_4 (20 mL) under N_2 and refluxed for 2 h. Br_2 (1.5 mL of 0.125 M solution in CCl_4) was added and refluxing was continued for 1 h. The solvent was removed and the residue was placed in Me_2SO (20 mL) with $NaOCOCF_3$ (200 mg) and stirred under N_2 for 16 h. The reaction mixture was poured into H_2O (50 mL) and extracted with $CHCl_3$ (three 15-mL portions). The extracts were combined, washed with H_2O (10 mL) and saturated NaCl (10 mL), dried, and evaporated. The residue was dissolved in 4:1 MeOH/THF (20 mL) and stirred at 23 °C for 4 h. The solution was poured into H_2O (50 mL) and extracted with $CHCl_3$ (three 15-mL portions). The extracts were combined, dried, and evaporated. The residue was chromatographed [E. Merck silica gel 60 prepacked column (size B), 99:1 to 97:3 CH_2Cl_2/MeOH] to afford in order of elution 17.2 mg (17%) of **3**, 9.1 mg (9%) of **26**, and 36.8 mg (35%) of **27**.

Adriamycinone (29). Daunomycinone (**26**, 10 mg, 0.025 mmol) was placed in $CHCl_3$ (1 mL). Br_2 (13.5 mg) in $CHCl_3$ (0.25 mL) was added and the solution stirred at 23 °C for 16 h. The solvent was removed and the residue was dissolved in 4:1 acetone/H_2O (5 mL). NaOH (1.1 mg, 0.028 mmol) was added and the blue solution was refluxed for 5 min when the red color returned. The solution was concentrated to ca. 2 mL, diluted with water (10 mL), and extracted with 1:1 $CHCl_3$/MeOH (three 10-mL portions). The extracts were combined, dried, and evaporated. The residue was crystallized from $CHCl_3$/MeOH/petroleum ether to afford 9.0 mg (87%) of **29**: IR 2.85 (OH), 5.75 (C=O), 6.15, 6.28 μm (H-bonded quinone); NMR δ 2.0–2.5 (m, 2 H, 8-H_2), 2.8–3.2 (m, 2 H, 10-H_2), 3.34 (m, 1 H, 9-OH), 4.09 (s, 3 H, OMe), 4.70 (d, 2 H, J = 16 Hz, 14-H_2), 5.34 (m, 1 H, $\nu_{1/2}$ = 8 Hz, 7-H), 7.38 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.76 (t, 1 H, J = 8 Hz, 2-H), 8.00 (dd, 1 H, J = 8 and 1 Hz, 1-H), 13.24 (s, 1 H, phenolic OH), 13.99 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{21}H_{18}O_9 \cdot 0.5H_2O$: C, 59.57; H, 4.54. Found: C, 59.63; H, 45.4.

14-*O*-*p*-Anisyldiphenylmethyladriamycinone (30). Adriamycinone (**29**, 369 mg, 0.90 mmol) was dissolved in pyridine (36 mL) and cooled to 5 °C. *p*-Anisylchlorodiphenylmethane (2.77 g, 9.48 mmol) was added in one portion with stirring, and the solution was kept at 5 °C for 5 days. The reaction mixture was poured into ice–water (200 mL) and extracted with $CHCl_3$ (two 100-mL portions). The extracts were combined, washed with 3 N H_2SO_4 (two 100-mL portions), saturated $NaHCO_3$ (100 mL), and water (100 mL), dried, and evaporated. The residue was crystallized from $CHCl_3$/petroleum ether to afford 520 mg (84%) of **30**: mp 198–203 °C; IR 2.90 (OH), 5.78 (C=O), 6.20, 6.30 μm (H-bonded quinone); NMR δ 2.08 (m, 2 H, 8-H_2), 2.78 (m, 2 H, 10-H_2), 3.83 (s, 3 H, Tr-OMe), 4.00 (s, 3 H, 4-OMe), 4.52 (s, 2 H, 14-H_2), 5.10 (m, 1 H, $\nu_{1/2}$ = 7 Hz, 7-H), 6.8–7.8 (m, 17 H, Ar H's), 13.00 (s, 1 H, phenolic OH), 13.58 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{41}H_{34}O_{10} \cdot 1.5H_2O$: C, 69.0; H, 5.23. Found: C, 69.1; H, 5.37.

2,3,6-Trideoxy-3-trifluoracetamido-α,β-L-*lyxo*hexopyranose (33). Sodium methoxide (7.0 g, 0.13 mol) was added to a solution of daunosamine hydrochloride (**32**, 23.5 g, 0.13 mol) in MeOH (400 mL) at 0 °C, and the mixture was stirred for 0.5 h. *S*-Ethyl trifluorothioacetate (25.3 g, 0.16 mol) was added and stirring was continued at 23 °C for 16 h. The reaction mixture was filtered and evaporated. The residue was triturated with hot acetone (250 mL) and filtered. The filtrate was dried and evaporated to afford 25 g of a solid residue. This was recrystallized from ethyl acetate to afford 18.9 g (68%) of **33**: mp 146–147 °C; IR 2.95–3.0 (OH, NH), 5.85 (C=O), 6.55 (amide II), 8.6 (CF_3) μm; NMR δ 1.2 (two overlapping d, 3 H, 6-H_3), 1.5–2.4 (m, 2 H, 2-H_2), 3.3–5.0 (m, 3 H, 3-, 4-, and 5-H's), 5.3 (m, 0.5 H, 1-H), 5.6 (m, 0.5 H, 1-H), 8.2 (br, 1 H, NH).

Anal. Calcd for $C_8H_{12}F_3NO_4$: C, 39.51; H, 4.98; N, 5.76. Found: C, 39.51; H, 5.00; N, 5.99.

2,3,6-Trideoxy-1,4-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*hexopyranose (34). *p*-Nitrobenzoyl chloride (40.4 g, 217.6 mmol) was added to a solution of 2,3,6-trideoxy-3-trifluoroacetamido-α,β-L-*lyxo*hexopyranose (**33**, 18.9 g, 77.7 mmol) in pyridine (600 mL) at 0 °C and stirred at 0 °C for 16 h. Water (50 mL) was added and the mixture was stirred for 0.5 h. The reaction mixture was poured into water (1.5 L) and extracted with $CHCl_3$ (four 1-L portions). The extracts were combined and washed successively with 3 N H_2SO_4 (two 2-L portions), H_2O (2 L), saturated $NaHCO_3$ (five 2-L portions), and H_2O (2 L), dried, and evaporated. The residue was recrystallized from acetone/$CHCl_3$/hexanes to afford 39.3 g (93%) of **34**: mp 202–203 °C; IR 2.98 (NH), 5.78 (C=O), 6.51 (aryl), 6.57 (NO_2), 8.67 μm (CF_3); NMR (Me_2SO-d_6) 1.13 (d, 3 H, 6-H_3), 2.08 (dm, 1 H, 2-H_{ax}), 2.58 (m, overlapped with Me_2SO-d_6 signal, 2-H_{eq}), 4.60 (m, 2 H, 3- and 5-H's), 5.50 (br s, 1 H, 4-H), 6.62 (br s, 1 H, 1-H), 8.42 (m, 8 H, Ar H's), 9.63 (d, 1 H, NH); $[\alpha]^{21}_D$ − 125° (*c* 0.03, 95% EtOH).

Anal. Calcd for $C_{22}H_{18}F_3N_3O_{10}$: C, 48.81; H, 3.34; N, 7.76. Found: C, 48.97; H, 3.76; N, 7.70.

4′-*O*-*p*-Nitrobenzoyl-3′-*N*-trifluoroacetyldaunorubicin (39). Daunomycinone (**26**, 99.5 mg, 0.25 mmol), $Hg(CN)_2$ (520 mg), $HgBr_2$ (236 Mg), and powdered molecular sieve 3A (1.2 g) were placed in THF (25 mL) and stirred at 50–55 °C for 2 h. Three 1 M equivalent portions of freshly prepared **36** in CH_2Cl_2 (2 mL) were added at 0, 4, and 22 h while the temperature was maintained at 50–55 °C. The chloro sugar **36** was prepared by bubbling anhydrous HCl into a suspension of 2,3,6-trideoxy-1,4-di-*O*-*p*-nitrobenzoyl-3-trifluoroacetamido-α-L-*lyxo*hexopyranose (**34**, 135 mg, 0.25 mmol) in CH_2Cl_2 (4 mL) at 0 °C for 3 min. The mixture was allowed to stand at 23 °C for 10 min, filtered to remove the precipitated *p*-nitrobenzoic acid, and evaporated. The residue was dissolved in CH_2Cl_2 (2 mL) and added to the reaction mixture. Additional $Hg(CN)_2$ (520 mg), $HgBr_2$ (236 mg), and powdered molecular sieve 3A (0.60 g) were added at 4 h. The total reaction time after the first addition of **36** was 25 h. The reaction mixture was filtered, the solids were washed with THF, and the washings and filtrate were combined and evaporated. The residue was triturated with $CHCl_3$ (75 mL), and filtered. The filtrate was washed with 30% KI (two 25-mL portions) and H_2O (50 mL), dried, and evaporated. The residue was chromatographed (PLC, six plates, 2:1 benzene/ethyl acetate) to afford 150 mg (77%) of **39**: IR 2.95 (NH, OH), 5.78 (C=O), 6.15, 6.30 (H-bonded quinone), 6.45 (amide II), 6.55 (NO_2), 8.55 (CF_3) μm; NMR δ 1.24 (d, 3 H, 6-H_3), 2.0–2.32 (m, 4 H, 8- and 2′-H_2's), 2.45 (s, 3 H, Ac), 2.95 (d, 1 H, J = 19 Hz, 10 β-H), 3.30 (d, 1 H, J = 19 Hz, 10 α-H), 4.10 (s, 3 H, OMe), 4.3–4.6 (m, 2 H, 3′- and 5′-H's), 5.33 (br s, 1 H, 7-H), 5.50 (m, 1 H, 4′-H), 5.67 (br s, 1 H, 1′-H), 6.20 (d, 1 H, NH), 7.39 (dd, 1 H, J = 8 and 1 Hz, 3-H), 7.79 (t, 1 H, J = 8 Hz, 2-H), 8.06 (dd, 1 H, J = 8 and 1 Hz, 1-H), 8.33 (m, 4 H, Ar H's), 13.09 (s, 1 H, phenolic OH), 14.07 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{36}H_{31}F_3N_2O_{14}$: C, 55.96; H, 4.04, N, 3.62. Found: C, 56.09, H, 4.42; N, 3.84.

Adriamycin Hydrochloride (2). 14-*O*-*p*-Anisyldiphenylmethyladriamycinone (**30**, 58.0 mg, 0.085 mmol), $Hg(CN)_2$ (250 mg), $HgBr_2$ (130 mg), and powdered molecular sieve 3A (500 mg) were placed in THF (9 mL) and refluxed for 2 h. Then 1 M equivalent portions of freshly prepared **36** were added at 3, 6, 11, 24, 28, 31, 36, 47, and 49 h while the mixture was maintained at 60 °C. The chloro sugar **36** was prepared as described in the previous experiment. Additional portions of $Hg(CN)_2$ (250 mg), $HgBr_2$ (130 mg), and molecular sieve 3A (500 mg) were added at 23 h. The total reaction time after the first addition of **36** was 50 h. The reaction mixture was filtered and evaporated. The residue was triturated with $CHCl_3$ (10 mL), filtered, washed with 30% KI, saturated $NaHCO_5$, and water, dried, and evaporated.

The residue was dissolved in THF (8 mL) and cooled to 5 °C. NaOH (17 mL of 0.2 N aqueous solution) was added and the solution was stirred at 5 °C for 5.25 h. After neutralization to pH 8 with 0.2 N HCl, the solution was extracted with 4:1 $CHCl_3$/MeOH, and the organic extract was washed with H_2O, dried, and evaporated.

The residue was dissolved in 80% HOAc (4 mL) and the solution was stirred at 23 °C for 16 h. The solution was lypophilized with temperature maintained below 0 °C, and the residue was dissolved in 2:1 MeOH/$CHCl_3$ (5 mL) and filtered. HCl (1.5 mL of a 0.1 N so-

lution in MeOH) was added to the filtrate followed by ether (50 mL). The precipitate was collected by centrifugation and decantation and reprecipitated from MeOH with ether to afford 20 mg (40%) of **2**: IR 3.00 (OH, NH), 5.83 (C=O), 6.20, 6.35 μm (H-bonded quinone); UV-vis (MeOH) λ_{max} (ϵ) 252 (25 391), 287 (9716), 478 (12 063), 492 (12 091), 531 (6913); NMR (Me_2SO-d_6) δ 1.18 (d, 3 H, 6′-H_3), 1.80 (m, 2 H, 2′-H_2), 2.12 (m, 2 H, 8-H_2), 2.78 (d, 1 H, J = 19 Hz, 10 β-H), 3.04 (d, 1 H, J = 19 Hz, 10 α-H), 3.61 (m, 2 H, 3′- and 4′-H's), 3.92 (s, 3 H, OMe), 4.17 (m, 1 H, 5′-H), 4.61 (s, 2 H, 14-H_2), 4.87 (br s, 1 H, 7-H), 5.28 (br s, 1 H, 1′-H), 5.47 (br s, 1 H, 9-OH), 7.57 (m, 1 H, 3-H), 7.80 (m, 2 H, 1- and 2-H's), 13.11 (s, 1 H, phenolic OH), 13.93 (s, 1 H, phenolic OH).

Anal. Calcd for $C_{27}H_{29}NO_{11}$·HCl·0.75H_2O: C, 54.64; H, 5.35; N, 2.36. Found: C, 54.34; H, 5.03; N, 2.02.

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Registry No.—**1**, 20830-81-3; **1** HCl, 23541-50-6; **2**, 23214-92-8; **2** HCl, 25316-40-9; **3**, 32384-98-8; **4**, 40940-87-2; **5**, 59325-97-2; **6a**, 530-93-8; **6b**, 37464-90-7; **7**, 63625-93-4; **8a**, 63625-94-5; **8b**, 63625,95-6; **8c**, 63625-96-7; **9a**, 63625-97-8; **9a** PNB, 63625-98-9; **9b**, 63625-99-0; **9b** PNB, 63626-00-6; **11**, 63626-01-7; **11** PNB, 63626-02-8; **14**, 63626-03-9; **15**, 63626-04-0; **16**, 63626-05-1; **17**, 33628-85-2; **18**, 59325-99-4; **19**, 59326-00-0; **20**, 59367-18-9; **21**, 63626-06-2; **22**, 38554-25-5; **26**, 21794-55-8; **27**, 59325-98-3; **29**, 24385-10-2; **30**, 59326-04-4; **32** HCl, 19196-51-1; **33**, 52471-40-6; **34**, 63700-24-3; **36**, 63700-25-4; **39**, 52583-24-1; triethyl phosphonoacetate, 867-13-0; diethyl cyanomethylphosphonate, 2537-48-6; sodium triethylphosphonoacetate, 22822-85-1; vinyl chloride, 75-01-4; dihydropyran, 110-87-2; methyl iodide, 74-88-4; *p*-anisylchlorodiphenylmethane, 14470-28-1; *S*-ethyl trifluorothioacetate, 383-64-2; *p*-nitrobenzoyl chloride, 122-04-3; pyrrolidone hydrotribromide, 52215-12-0.

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Macrocyclic Spermidine Alkaloids from *Maytenus serrata* and *Tripterygium wilfordii*[1a]

S. Morris Kupchan,[1b] Harold P. J. Hintz, Roger M. Smith,* [1c] Aziz Karim, Malcolm W. Cass, William A. Court, and Mitsuyoshi Yatagai

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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Four new spermidine alkaloids, celacinnine (**1**), celallocinnine (**2**), celafurine (**3**), and celabenzine (**4**), have been isolated in studies of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek and *Tripterygium wilfordii* Hook. The 13-membered macrocyclic structures of the alkaloids were elucidated by chemical degradation and by a study of the spectral properties of the alkaloids and their derivatives.

The twigs of *Maytenus serrata* (Hochst., ex A. Rich.) R. Wilczek (Celastraceae) have yielded two novel spermidine alkaloids, celacinnine (**1**) and celallocinnine (**2**), as the principal basic components.[2] Celacinnine (**1**) has also been isolated from the roots of *Tripterygium wilfordii* Hook (Celastraceae), together with the related alkaloids celafurine (**3**) and celabenzine (**4**).[2] We report herein our detailed studies on the isolation and structural elucidation of these four alkaloids. Studies of the fruit of *M. serrata* in these laboratories have yielded the nicotinoyl sesquiterpene alkaloids maytoline, maytine, and maytolidine,[3] and the highly active tumor-inhibitory ansa-macrolide maytansine,[4] but these compounds could not be detected in the twigs and no spermidine alkaloids were detected in the fruit. A series of complex nicotinoyl sesquiterpene alkaloids has been previously reported from the roots of *T. wilfordii*.[5]