mixture was subjected to a reductive aqueous workup with Na_2SO_3 as in the above experiments to obtain the crude product (mixture of cis and trans β-lactams) as a pale yellow oil. Purification by chromatography on silica gel (ethyl acetate/hexanes) followed by crystallization from methylene chloride/hexanes yielded pure cis product *cis*-**5h** as white crystals (52%). However, the trans product was contaminated with some cis product. The combined yield of the products was 89.9%. *cis*-**5h**: mp 95–97 °C; ^{1}H NMR (300 MHz, chloroform-*d*) δ 3.35–3.6 (m, 2 H), 4.45–4.58 (m, 1 H), 5.15 (s, 2 H), 5.1–5.25 (m, 1 H), 5.27 (s, 2 H), 5.73–5.87 (br d, 1 H), 7.3–7.45 (2 s, 10 H); IR 1818, 1790, 1725 cm^{-1}. Anal. Calcd for $C_{20}H_{19}BrN_2O_6$: C, 51.85; H, 4.13; N, 6.05. Found: C, 51.66; H, 4.17; N, 6.16.

Acylation of Hydroxamic Acid 4d with Acetyl Chloride To Form 4i. Hydroxamic acid **4d** (0.70 g, 2.8 mmol, 100 mol %) was dissolved in dry THF (28 mL, 0.1 M), and the solution was cooled to 0 °C. Pyridine (0.24 mL, 2.94 mmol, 105 mol %) was added followed by acetyl chloride (0.21 mL, 2.94 mmol, 105 mol %) 5 min later. A white precipitate formed immediately. After being stirred for 10 min, the reaction mixture was transferred to a separatory funnel with 150 mL of ether, washed successively with 30 mL each of water, 0.5 M HCl, and brine, and dried over $MgSO_4$. Filtration, followed by removal of the solvent under aspirator pressure, yielded product **4i** as a white solid of almost pure product. An analytically pure sample was obtained by crystallization from MeOH/ether/hexanes (white needle-shaped crystals, 86% yield): mp 119–122 °C ^{1}H NMR (300 MHz, chloroform-*d*/TMS) δ 2.182 (s, 3 H) (s, 3 H), 4.88–5.03 (br, 1 H), 5.10 (s, 2 H), 5.28–5.5 [dd, 2 H, *J* = 17.1 (trans), 10.2 (cis) Hz], 5.75–5.85 (br d, 1 H), 5.83 (br d, 1 H), 5.83–6.0 (m, 1 H), 7.33 (s, 5 H); IR ($CDCl_3$) 3275, 3200, 1720–1685 cm^{-1} (br, overlapping carbonyls). Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.53; H, 5.59; N, 9.63.

Oxidative Cyclization of *O*-Acetyl *N*-Carbobenzyloxy-L-vinylglycinehydroxamate (4i). The hydroxamate derivative (**4i**; 0.2 g, 0.68 mmol, 100 mol %) was dissolved in 30 mL of MeCN at room temperature. Potassium carbonate (0.999 g, 0.72 mmol, 105 mol %) followed by water (6.8 mL) was added, and the mixture was vigorously stirred for 1 min. A solution of bromine (38.6 μL, 0.75 mmol) in MeCN (4 mL) was added to the reaction mixture over a period of 3 min (vigorous stirring was maintained throughout the reaction). After 1 min more of stirring, the reaction mixture was transferred to a separatory funnel with 100 mL of ether. The ethereal layer was washed successively with 25 mL each of water, 10% aqueous sodium thiosulfate, and brine, dried over $MgSO_4$, and filtered. Removal of solvents yielded a white solid residue (0.20 g), which was a mixture of cis and trans products (64:36 as determined from the crude NMR spectrum). The cis product (94 mg) was obtained in almost pure form by a single crystallization from acetone/$CHCl_3$/hexanes: mp 161.5–163.5 °C dec; ^{1}H NMR (300 MHz, acetone-d_6/TMS) δ 2.2 (s, 3 H), 3.5–3.8 (ddd, 2 H, *J* = 10.5, 7.5, 6.3 Hz), 4.48–4.6 (br q, *J* = 6.3, 7.5, *5.4* Hz), 5.140 (s, 2 H), 5.25–5.33 (dd, 1 H, *J* = *5.4*, 9.45 Hz), 7.23–7.35 (m, 5 H).

Acknowledgment. We gratefully acknowledge support from the National Instututes of Health (NIH) and Eli Lilly and Co. Kathleen Peterson recorded the 300-MHz NMR spectra on an instrument provided by grants from NIH and the University of Notre Dame. Structure drawings were produced with ChemDraw by S. Rubenstein.

Stereospecific Total Synthesis of 9-Aminoanthracyclines: (+)-9-Amino-9-deoxydaunomycin and Related Compounds

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9-Amino-9-deoxydaunomycin and related compounds, in which the hydroxyl group at the 9-position of daunomycin is replaced by an amino group, have been synthesized. Asymmetry was introduced into the synthetic sequence for the AB synthon by resolution of the intermediate amino ester or acetamido acid to afford (*R*)-(−)-2-acetyl-2-acetamido-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene, which was converted to the tetracyclic amido ketones by Friedel–Crafts acylation with phthalic anhydride or its 3-methoxy derivative. The resulting regioisomers 4- and 1-methoxy compounds were separated, after methylation and selective demethylation, by crystallization and preparative TLC. The required introduction of the C7-hydroxyl function proceeded stereospecifically via a three-step reaction sequence involving formation of an oxazine compound. The silver trifluoromethane assisted glycosidation of the resulting aglycons with 2-deoxy-3,4-di-*O*-acetyl-D-*erythro*-pentopyranosyl bromide or *N*,*O*-bis(trifluoroacetyl)daunosaminyl chloride, followed by alkaline hydrolysis afforded the target glycosides. The work reported herein comprises an efficient, practical synthesis of 9-amino-9-deoxydaunomycin and its analogues with the same stereochemistry as in the naturally occurring anthracyclines.

The clinically important antitumor antibiotics daunomycin (**1**) and adriamycin (**2**) are believed to exert their primary effect by blocking DNA function by means of drug–DNA binding intercalations.[1] Recent X-ray crystallographic study of daunomycin intercalated into a self-complementary DNA fragment has pointed out that the C9-OH in ring A interacts through hydrogen bonding with the DNA base pairs and provides an anchoring function. It was suggested that modifications of the anchor function may change the manner in which the anthracycline interacts with the DNA and thereby change its activity against different types of tumors.[2] Here, we report a practical total synthesis of the new anthracyclines 9-amino-9-deoxydaunomycin (**3**) and related compounds in which the hydroxyl group at the 9-position of daunomycin (**1**) is replaced by an amino group.

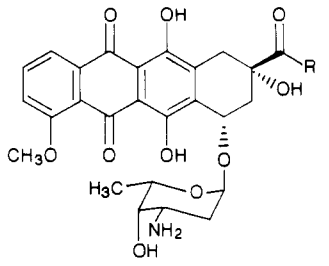
Our synthetic plan leading to the aglycons is shown in Scheme I and is analogous to Wong's scheme for the synthesis of daunomycinone.[3]

(1) Neidle, S. *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Halsted: New York, 1978; Vol. 2.

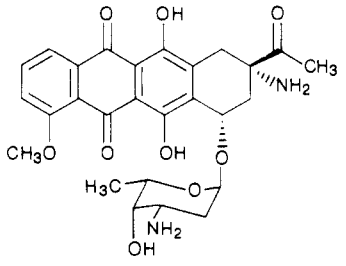
(2) Quiglry, G. J.; Wang, A.; Ughetto, G.; van der Marel, G.; van Boom, J.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 7204.

(3) Wong, C. M.; Schwenk, R.; Popien, D.; Ho, T.-L. *Can. J. Chem.* **1973**, *51*, 466.

0022-3263/87/1952-4477$01.50/0



1, R = CH_3
2, R = CH_2OH



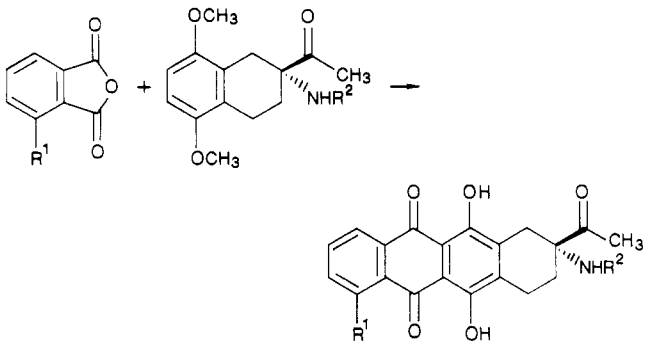
3

The required AB synthon was prepared from readily available tetralone **4**[4] by the sequence outlined in Scheme II. Asymmetry was introduced into the scheme by resolution of the amino ester **6**, prepared by the literature methods[5] in 86% overall yield from **4**. Treatment of the racemic (±)-**6** with D-(−)-mandelic acid in methanol afforded crystals that yielded the levorotatory ester (−)-**6a** in 33% yield. Similarly, L-(+)-mandelic acid gave a salt of **6b**, which provided the dextrorotatory product. The enantiomeric purities of the resolved amino esters were determined as ~100% ee by HPLC using an optically active stationary phase. The absolute configuration of the optical isomers was solved by X-ray crystallography,[6] using the D-(−)-mandelic salt. Data showed that (−)-**6a** had the C2-*R* configuration, corresponding to the C9-*S* of the naturally occurring anthracyclines related to daunomycin. Sodium methylsulfinyl methide treatment of (*R*)-**6a** followed by reduction yielded amino ketone (*R*)-**7a**,[7] which was immediately subjected to N-acetylation to afford the optically pure amido ketone (*R*)-**8a** in 81% overall yield from (*R*)-**6a**.

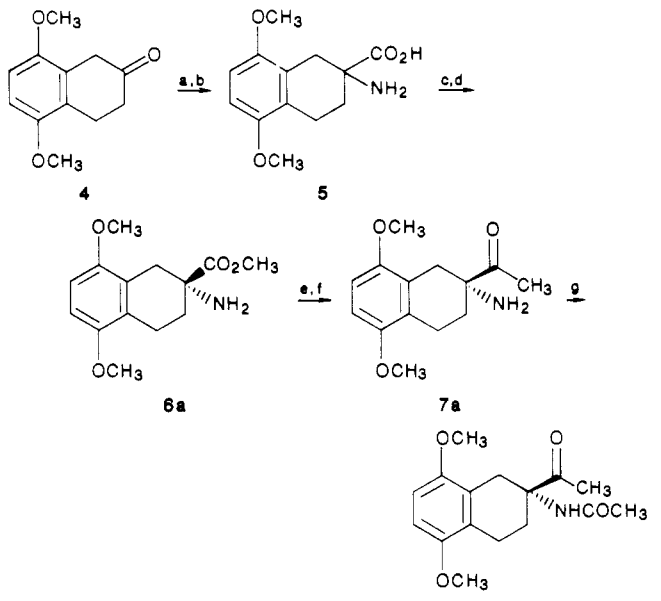
The amido ketone (*R*)-**8a** was also prepared in 17% overall yield from **5** by the sequence of reactions shown in Scheme III.

We selected the simple case leading to 9-amino-4-demethoxy-9-deoxydaunomycinone (**14**) as the initial target for the construction of tetracyclic ring system, as shown in Scheme IV. Conversion of **8a** to tetracyclic amido ketone **11a** was achieved in one step by heating with phthalic anhydride in the presence of $AlCl_3$–NaCl at 170 °C. The reaction proceeded without racemization to afford optically pure **11a** in 94% yield. This is in contrast to the experience reported for the synthesis of 4-demethoxydaunomycinone which always accompanied a partial racemization to give the product being 70–75% ee.[8,9] The required introduction of the C7-hydroxyl function was achieved most satisfactorily via a three-step reaction sequence involving formation of an oxazine compound. In order to provide for subsequent regiospecific bromination, the C13-carbonyl group in **11a** was protected as a ketal to give

Scheme I

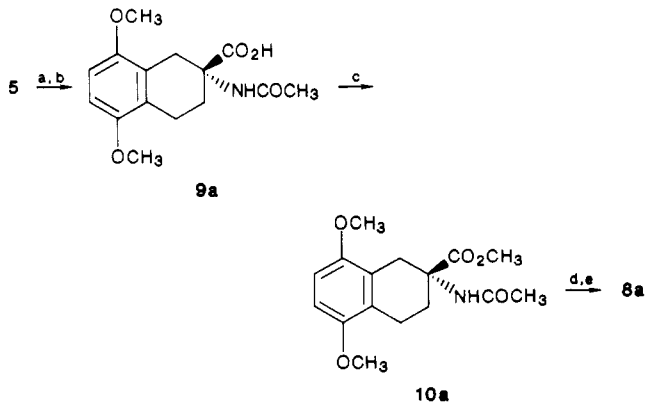


Scheme II[a]



[a] (a) KCN/$(NH_4)_2CO_3$/50% EtOH/reflux; (b) $Ba(OH)_2/H_2O$/reflux/36 h; (c) HCl/MeOH/reflux; (d) D-(−)-mandelic acid/MeOH, then aqueous $NaHCO_3$; (e) NaH/DMSO/THF/5–10 °C; (f) Zn/NaOH/H_2O/toluene/65 °C; (g) $(CH_3CO)_2O$/pyridine/toluene.

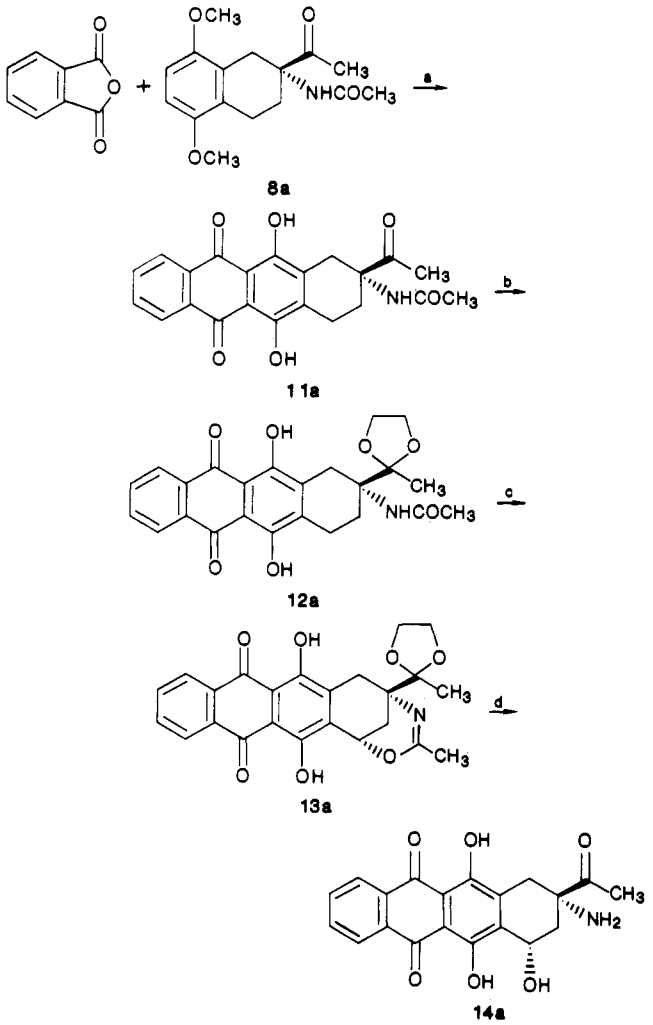
Scheme III[a]



[a] (a) $(CH_3CO)_2O$/pyridine/room temperature; (b) *l*-α-phenylethylamine, then 3% HCl; (c) H_2SO_4/MeOH/reflux; (d) NaH/DMSO/THF/room temperature; (e) Al–Hg/H_2O/THF/room temperature.

(4) Alexander, J.; Mitscher, L. A. *Tetrahedron Lett.* **1978**, 3403.
(5) Rastogi, S. N.; Bindra, J. S.; Anand, N. *Indian J. Chem.* **1971**, *9*, 1175.
(6) We are indebted to Dr. M. Minobe, Takatsuki Laboratories, Sumitomo Chemical Company, for carrying out X-ray analysis.
(7) In a preliminary experiment with racemic **6** the amino ketone (*RS*)-**7** could be isolated as the hydrochloride (mp 204–205 °C).
(8) Tanno, N.; Terashima, S. *Chem. Pharm. Bull.* **1983**, *31*, 821. Terashima, S.; Tamoto, K.; Sugimori, M. *Tetrahedron Lett.* **1982**, 4107.
(9) The results obtained by Tanno and Terashima are different from those reported earlier by Arcamone and co-workers.[11]

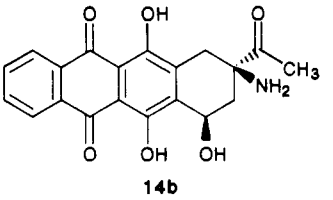
Scheme IV[a]



[a] (a) $AlCl_3$/NaCl/170 °C/4 min; (b) ethylene glycol/TsOH/$PhCH_3$/reflux; (c) DDH/PhH/$h\nu$/reflux; (d) aqueous sulfuric acid/reflux.

12a in 88% yield. Treatment of **12a** with 1,3-dibromo-5,5-dimethylhydantoin led to the formation of oxazine (7*S*,9*S*)-**13a** in 89% yield. Deketalization and hydrolysis of the oxazine ring were simultaneously effected by heating **13a** with aqueous sulfuric acid to give the desired cis (7-OH, 9-NH_2) derivative (7*S*,9*S*)-**14a** (82% yield), which was separated from a small amount of its C7 epimer by preparative TLC.[10] This result contrasts sharply with the reported 7-hydroxylation via bromination solvolysis procedure for daunomycinone series, which generated predominantly the undesired epi configuration at C7.[11,12]

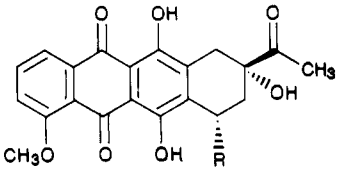
In scale-up work, it was possible to carry out the transformation of **4** to **14a** in about 10% overall yield without chromatographic purification. To obtain aglycone possessing the unnatural configuration at C7 and C9, the seven-step synthesis described for the preparation of **14a** was repeated with (*S*)-**9b** to yield (7*R*,9*R*)-**14b**.



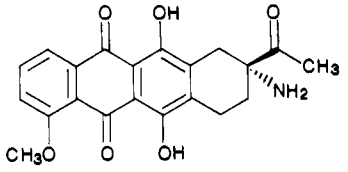
14b

A reaction sequence parallel with the one described for 4-demethoxy compound **14** was employed to prepare 9-amino-9-deoxydaunomycinone **23** (Scheme V). Condensation of **8a** with 3-methoxyphthalic anhydride under the same conditions afforded a crude mixture of **15** and **16**. Because of the difficulty in separating the compounds, they were carried through together for two more steps, where separation was easily performed. Methylation of the crude mixture of **15** and **16** gave a mixture of trimethyl ethers **17** and **18** in 36% overall combined yield from **8a**. Selective demethylation of the phenolic groups to **19** and **20** was achieved by treatment with BCl_3 in CH_2Cl_2 at −5 to 0 °C.[13] The 4-methoxy compound **19** (47% yield) was separated as crystals directly from a solution of the reaction mixture in CH_2Cl_2 by aqueous $NaHCO_3$ workup, while 1-methoxy compound **20** (18% yield) was obtained by preparative TLC of the filtrate. Ketalizations of the individual isomers **19** and **20** followed by bromination afforded oxazines **21** and **22**, which were hydrolyzed completely to yield the desired compound **23** (36% overall yield from **19**) and its regioisomer **24** (45% overall yield from **20**).

The regiochemistry at the C1 and C4 positions of the oxazines **21** and **22** was assigned on the basis of their differentiated chemical shifts of phenolic protons (6-OH and 11-OH) in the ^1H NMR spectra, which were similar to those reported for daunomycinone **26** and its 1-MeO isomer.[14] This assignment was confirmed by successful



25, R = H
26, R = OH



27

transformation of **19** and **23** to 7-deoxydaunomycinone (**25**) and daunomycinone (**26**). Namely, hydrolysis of **19** with concentrated hydrochloric acid in acetic acid gave **27** in 67% yield. Nitrous acid treatment of **27** and **23** in a mixture of 50% acetic acid/dioxane followed by aqueous $NaHCO_3$ workup and chromatographic purification afforded **25** (12% yield) and **26** (7% yield). These substances were found to be identical with authentic samples synthesized from natural daunomycin[15] by comparison of ^1H

(10) The C7 epimer was probably formed by epimerization of initially formed (7*S*,9*S*)-**14a** under the acidic reaction conditions. The stereochemistry at C7-H in (7*S*,9*S*)-**14a** and its C7 epimer was assigned on the basis of a comparison of the corresponding ^1H NMR values with those of daunomycinone (**26**) and 7-epidaunomycinone ($\nu_{1/2}$ = 7 Hz in (7*S*,9*S*)-**14a** and 15 Hz in the C7 epimer, respectively).[12]

(11) Arcamone, F.; Bernardi, L.; Patelli, B.; Giardino, P.; Dimarco, A.; Casazza, A. M.; Soranzo, C.; Pratesi, G. *Experientia* **1978**, *34*, 1255.

(12) Kende, A. S.; Tsay, Y.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967. Smith, T. H.; Fujiwara, A. N.; Henry, D. W.; Lee, W. W. *Ibid.* **1976**, *98*, 1969.

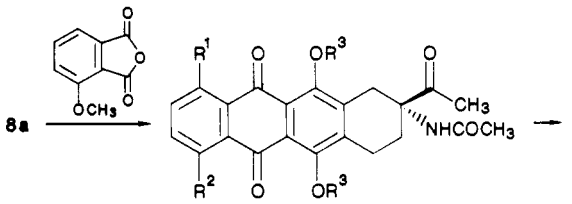
(13) Broadhurst, M. J.; Hassall, C. H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2227.

(14) Krohn, K.; Tolkiehn, K. *Chem. Ber.* **1979**, *112*, 3453.

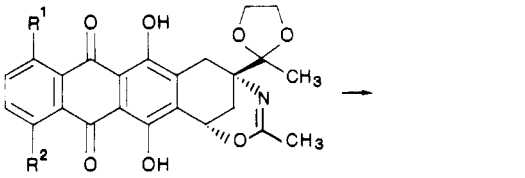
(15) An authentic sample of 7-deoxydaunomycinone **25** was prepared by catalytic hydrogenation of daunomycin (**1**),[16] while that of daunomycinone (**26**) was obtained by hydrolysis of **1**.[17]

(16) Arcamone, F.; Franceschi, G.; Orezzi, P.; Penco, S. *Tetrahedron Lett.* **1968**, 3349.

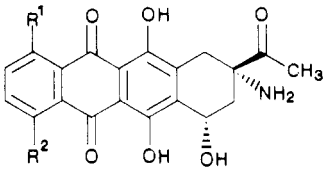
Scheme V



15, R^2 = OH, R^1 = R^3 = H
16, R^1 = OH, R^2 = R^3 = H
17, R^2 = OCH_3, R^1 = H, R^3 = CH_3
18, R^1 = OCH_3, R^2 = H, R^3 = CH_3
19, R^2 = OCH_3, R^1 = R^3 = H
20, R^1 = OCH_3, R^2 = R^3 = H

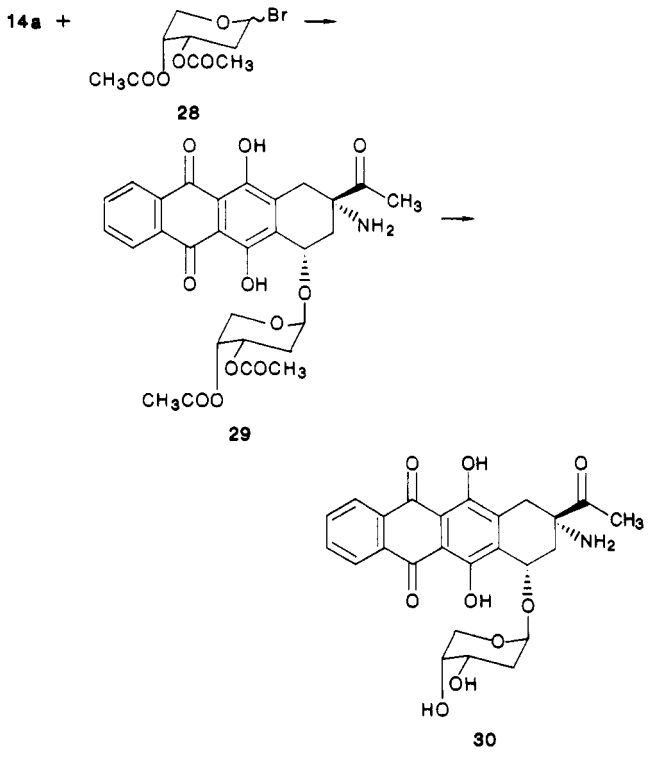


21, R^1 = H, R^2 = OCH_3
22, R^1 = OCH_3, R^2 = H



23, R^1 = H, R^2 = OCH_3
24, R^1 = OCH_3, R^2 = H

Scheme VI



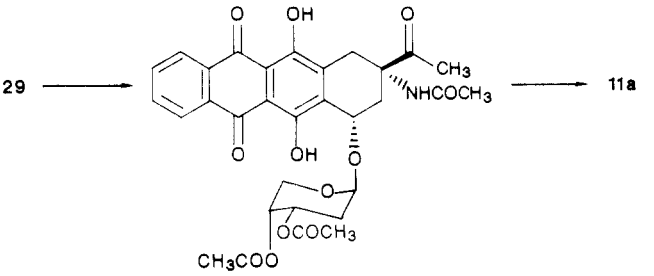
28
29
30

NMR and TLC data.[18]

Efforts were then directed at the synthesis of new anthracycline glycosides. The Arcamone silver trifluoromethane assisted glycosidation procedure was found to be effective for the coupling of **14a** with 2-deoxy-3,4-di-*O*-acetyl-D-*erythro*-pentopyranosyl bromide (**28**)[19,20] selected as a model compound for our initial glycosidation explorations. A slight modification of the Arcamone conditions ($AgOSO_2CF_3$ in ether/tetramethylurea/CH_2Cl_2/0–5 °C, followed by aqueous $NaHCO_3$ workup) afforded almost exclusively glycoside **29** in 86% yield after purification of preparative TLC. Alkaline hydrolysis of **29** gave the deacetylated glycoside **30** in 90% yield (Scheme VI).

The proof for the position of the sugar moiety in the new glycosides was provided by acetylation of **29** to **31** followed

Scheme VII



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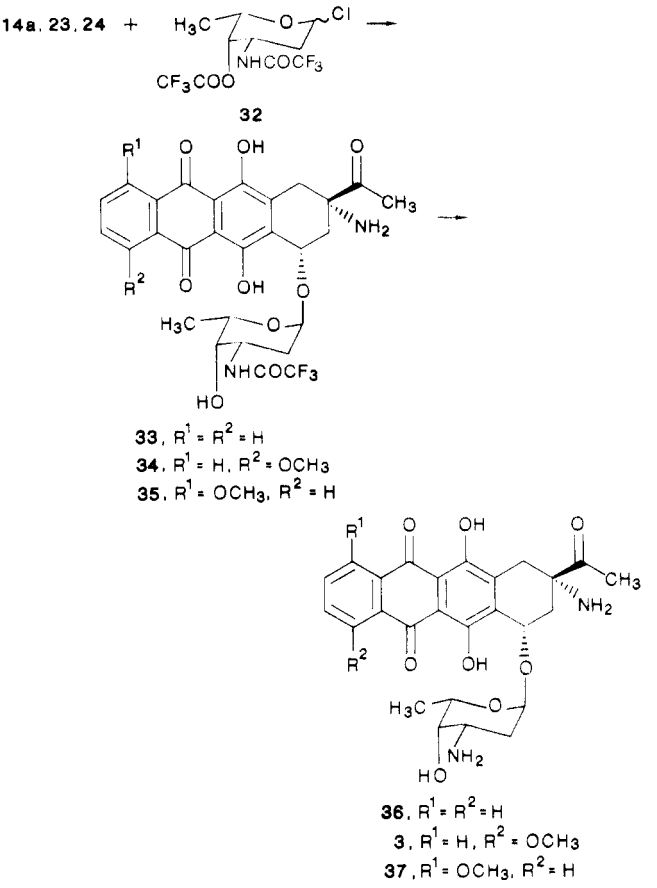
Scheme VIII



32
33, R^1 = R^2 = H
34, R^1 = H, R^2 = OCH_3
35, R^1 = OCH_3, R^2 = H
36, R^1 = R^2 = H
3, R^1 = H, R^2 = OCH_3
37, R^1 = OCH_3, R^2 = H

(17) Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassirelli, G.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334.

(18) The deaminated product **25** showed $[\alpha]_D$ −39.3° ($CHCl_3$), while the specific rotation of natural 7-deoxydaunomycinone is known to be −91° in chloroform.[16] We were unable to obtain a large quantity of the deaminated product **26** to measure its specific rotation.

(19) The bromo sugar **28** used for coupling was prepared in quantitative yield from acetyl 3,4-di-*O*-acetyl-2-deoxy-β-D-ribopyranoside[20] by an adaptation of the method of Israel. Gillard, J. W.; Israel, M. *Tetrahedron Lett.* **1981**, 513.

(20) Davoll, J.; Lythgoe, B. *J. Chem. Soc.* **1949**, 2526.

by catalytic hydrogenolysis[16] to afford **11a** in 66% overall yield from **29** (Scheme VII).

Couplings of aglycons **14a**, **23**, and **24** with *N,O*-bis(trifluoroacetyl)daunosaminyl chloride (**32**)[21] were carried out in a similar manner as above[22] to yield, after chromatographic purification, *N*-(trifluoroacetyl)glycosides **33** (92% yield), **34** (57% yield), and **35** (60% yield).[23] Subsequent alkaline hydrolysis of **33**, **34**, and **35** afforded the desired glycosides **36** (98% yield), **3** (92% yield), and **37** (76% yield) (Scheme VIII).

In all glycosides the glycosidic linkage was shown to have the same stereochemistry as in natural daunomycin on the basis of C1′-H ^{1}H NMR signal. Thus, for example, the anomeric proton for **36** appeared at δ 5.42 as a characteristic broad ($\nu_{1/2}$ = 7 Hz) singlet, establishing its conformation as α-L.

Target compounds, compared with adriamycin, were screened for antitumor properties by using lymphocytic leukemia P388 in mice.[24] Aglycon **14a** exhibited moderate antileukemia activity, in contrast to biological inactivity of daunomycinone **26**,[25] thus indicating the contribution of the C9-amino function for the exhibition of antitumor activity. Aglycon **14b** with the unnatural configuration at C7 and C9 was devoid of biological activity.

All glycosides showed moderate to significant antitumor activity. It was interesting to find, however, that 4-demethoxy-3′-deamino compounds **29** and **30** exhibited in vivo activity comparable to that of adriamycin and significantly higher than those of the daunosaminyl analogues **36**, **3**, and **37**. Compound **30** is undergoing extensive antitumor and toxicological screening.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra (Nujol mulls, unless otherwise stated) were measured on Hitachi 260-10 infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on Varian EM-390 (90 MHz) and JEOL JNM-GX270 (270 MHz) FT instruments in $CDCl_3$ solution (unless otherwise stated) containing tetramethylsilane as internal standard and are reported in δ units. Mass spectra (MS) were obtained on Hitachi DF/GC/MS M-80 and DPS M-003 (3 kV) spectrometers. Optical rotations were made on JASCO DIP-181 polarimeter. The ee measurements for amino compounds **6** and **14** were performed by converting the free bases to the corresponding amide derivatives by reaction with 3,5-dinitrobenzoyl chloride in the presence of pyridine and analyzing the presence of enantiomers by HPLC using OA-1000 (Sumitomo Chemical Company) as an optically active stationary phase. For amide compounds **8** and **11**, the optical purities were determined by direct HPLC analysis of them on OA-1000 and OA-4000. Analytical TLC was performed on silica gel plates (0.25 mm, E. Merck), preparative TLC on 2-mm silica gel plates (E. Merck), and column chromatography with E. Merck silica gel 60 (230–400 mesh). All organic extracts were dried over anhydrous sodium sulfate, and solvents were evaporated under water-aspirator pressure.

2-Amino-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (5). The procedure of Rastogi[5] was employed. A mixture of 82.4 g of tetralone 4,[4] 34 g of potassium cyanide, and 345.6 g of ammonium carbonate in 2.4 L of 50% ethanol was stirred at reflux for 1 h. After removal of the ethanol, the reaction mixture was cooled, and the precipitate was collected by filtration to give 109.3 g (98.7%) of spirohydantoin, mp 275–278 °C. A mixture of 102.5 g of the spirohydantoin and 630 g of barium hydroxide (octahydrate) in 3 L of water was stirred at reflux under nitrogen for 36 h. After being cooled, the reaction mixture was diluted with 1 L of water and acidified with 6 N sulfuric acid. The filtered solution was adjusted to pH 6.0 and cooled. The precipitate was collected by filtration to give 85.7 g (92%) of **5**, mp 264–266 °C. Recrystallization from water afforded an analytical sample as colorless plates: mp 274–277 °C. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.20; H, 6.91; N, 5.63.

Methyl 2-Amino-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (6). Hydrogen chloride (69.1 g) was passed into a stirred suspension of 29 g of **5** in 575 mL of methanol in an ice bath. The mixture was allowed to stand at 25 °C for 24 h and concentrated to give a residue, which was dissolved in 930 mL of water. The solution was made basic with 30% aqueous sodium hydroxide and extracted with two 300-mL portions of toluene. The combined organic extracts were washed with water, dried, and evaporated to give 29.05 g (94.9%) of **6**, mp 57–60 °C. Recrystallization from hexane afforded an analytical sample: mp 61–62 °C; IR 3400, 3320, 1705, 1600 cm^{-1}; ^{1}H NMR 1.62 (s, 2 H), 1.73–2.27 (m, 2 H), 2.60–3.23 (m, 4 H), 3.73 (s, 3 H), 3.77 (s, 6 H), 6.55 (s, 2 H). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.30; H, 7.22; N, 5.20. Found: C, 63.28; H, 7.42; N, 5.33.

(*R*)-(−)-Methyl 2-Amino-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (6a). To a solution of 29.05 g of racemic **6** in a mixture of 51 mL of isopropyl alcohol and 469 mL of toluene was added 16.46 g of D-(−)-mandelic acid at 22 °C. After the mixture was stirred for 3 h at the same temperature, the resulting precipitate was filtered and recrystallized from toluene–isopropyl alcohol to yield 15.1 g (33.0%) of the salt: mp 138–139 °C; $[\alpha]^{25}_D$ −54° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.31; H, 6.64; N, 3.41.

The above mandelate salt was basified with 5% aqueous sodium bicarbonate and extracted with toluene. The combined extracts were dried and evaporated to give 9.53 g (99.3%) of the free amino ester **6a**: light yellow syrup; $[\alpha]^{26}_D$ −7.57° (*c* 1.03, $CHCl_3$); optical purity by HPLC ~100% ee; IR (neat) 3390, 3300, 1720, 1600 cm^{-1}. Its ^{1}H NMR spectrum was identical with that of racemic **6**.

(*S*)-(+)-Methyl 2-Amino-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (6b). The procedure described for the preparation of **6a** was repeated with L-(+)-mandelic acid to yield dextrorotatory **6b**. The IR and ^{1}H NMR properties were identical with **6a**.

2-Acetamido-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (9). A mixture of 46.5 g of **5**, 90 g of acetic anhydride, and 900 mL of dry pyridine was stirred at room temperature for 15 h. The pyridine was evaporated and 700 mL of 3% hydrochloric acid was added to the residue. After the mixture was stirred for 3 h, the precipitate was collected by filtration to afford 51.5 g (94.9%) of **9**. Recrystallization from methanol–chloroform gave colorless needles: mp 282–284 °C; IR 3340, 1710, 1615, 1550 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.09; H, 6.81; N, 4.87.

Resolution of 9. Racemic **9** (30.1 g) and *l*-α-phenylethylamine (12.5 g) were dissolved in 2.5 L of boiling methanol and allowed to cool to room temperature without agitation. The precipitate was collected by filtration and recrystallized from methanol to yield 11.8 g of the salt: mp 295–298 °C; $[\alpha]^{20}_D$ −61.0° (*c* 0.32, DMF). Anal. Calcd for $C_{23}H_{31}N_2O_5$: C, 66.68; H, 7.52; N, 6.74. Found: C, 66.55; H, 7.31; N, 6.83. The above salt (11.7 g) was stirred in 800 mL of 3% hydrochloric acid for 1 h and the precipitate was collected by filtration to afford 7.7 g (25.6% from **9**) of *R*-(−)-acid **9a**: mp 300–302 °C; $[\alpha]^{20}_D$ −69.6° (*c* 1.0, DMF); IR 3340, 1700, 1620, 1550 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.18; H, 6.61; N, 4.82.

The mother liquors that were combined from the reaction mixture and the recrystallization were concentrated, and the residue was stirred in 1 L of 3% hydrochloric acid for 2 h. The precipitate (19.0 g) obtained by filtration and *d*-α-phenylethylamine (9.0 g) were dissolved in 900 mL of boiling methanol, and the solution was allowed to cool to room temperature. Recrystallization of the precipitate from methanol gave 7.8 g of the salt: mp 295–298 °C; $[\alpha]^{20}_D$ +60.1° (*c* 0.30, DMF). The salt (7.5 g) was converted to the free *S*-(+)-acid **9b** (5.3 g, 17.6% from **9**): mp

(21) Societa Farmaceutic Italia S.p.A. British Patent 1 457 560, 1977; *Chem. Abstr.* **1977**, *87*, 23686.
(22) In this case, molecular sieves (4A, Merck) were used instead of tetramethylurea.
(23) O-Deacylation occurred during the workup procedure.
(24) Details of the biological evaluation of these compounds will be reported elsewhere.
(25) Henry, D. W. *Cancer Treat. Rep.* **1979**, *63*, 845.

300–302 °C; $[\alpha]^{20}_D$ +68.8° (*c* 0.98, DMF).

(*R*)-(−)-Methyl 2-Acetamido-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthoate (10a). A mixture of 10.8 g of **9a**, 2 mL of concentrated sulfuric acid and 430 mL of methanol was heated under reflux for 1.5 h. After evaporation of the methanol, the residue was stirred for 1 h in 1 L of saturated aqueous sodium bicarbonate. The precipitate was collected by filtration, washed with water and dried to give 10.9 g (96%) of **10a**, mp 169–170 °C. Recrystallization from toluene afforded colorless needles: mp 175–176 °C; $[\alpha]^{26}_D$ −117.7° (*c* 1.0, $CHCl_3$); IR 3290, 1750, 1660, 1540 cm^{-1}; ^1H NMR 1.91 (s, 3 H), 1.80–2.40 (m, 2 H), 2.40–3.30 (m, 4 H), 3.76 (s, 6 H), 3.78 (s, 3 H), 5.54 (br s, 1 H), 6.65 (s, 2 H). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.50; H, 6.90; N, 4.46.

(*R*)-(−)-2-Acetyl-2-acetamido-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (8a). A. From 6a. A 60% mineral oil dispersion of sodium hydride (4.75 g) was suspended in 25 mL of dimethyl sulfoxide and 35 mL of tetrahydrofuran and the mixture stirred under a nitrogen atmosphere at 65 °C for 1.5 h. To the cooled solution was added dropwise a solution of 9.53 g of **6a** in 33 mL of tetrahydrofuran at 5–10 °C. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with 200 mL of water, and the pH was adjusted to 2.5 with hydrochloric acid. The mixture was then washed with toluene to remove mineral oil, made basic with 30% aqueous sodium hydroxide, and extracted with ethyl acetate at 30–35 °C. The combined extracts were washed with saturated brine, dried, and evaporated to give 10.9 g of the β-keto sulfoxide, mp 74–77 °C.

Aqueous sodium hydroxide (30%, 67 mL) was added to a slurry of 13.2 g of zinc dust and 135 mL of water at 65 °C, and the mixture was stirred at the same temperature for 1 h. To the resulting solution was added a warmed solution of 10.9 g of the β-keto sulfoxide in 237 mL of toluene. After being stirred at 65 °C for 2 h, the reaction mixture was filtered, and the filtrate was adjusted to pH 9.0 with hydrochloric acid. The toluene layer was separated, the aqueous layer was extracted with 75 mL of toluene, and the organic layers were combined and dried. To the resulting solution of **7a** in toluene was added 6.38 g of dry pyridine followed by 3.74 g of acetic anhydride. After being stirred at 20 °C for 1 h, the reaction mixture was heated to 70 °C for 30 min and then cooled to 5 °C. The precipitate was collected by filtration to afford 8.42 g (80.5%) of **8a**: mp 228–229 °C; $[\alpha]^{26}_D$ −130° (*c* 1.0, $CHCl_3$); optical purity by HPLC ~100% ee; IR 3350, 1700, 1660, 1600 cm^{-1}; ^1H NMR 1.77–2.47 (m, 2 H), 1.92 (s, 3 H), 2.23 (s, 3 H), 2.47–3.13 (m, 4 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 5.92 (br s, 1 H), 6.65 (s, 2 H). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.73; H, 7.43; N, 4.73.

B. From 10a. A 60% mineral oil dispersion of sodium hydride (4.0 g) was washed under a nitrogen atmosphere three times with petroleum ether by decantation and suspended in 50 mL of dry dimethyl sulfoxide. The mixture was stirred at 68–75 °C for 40 min and cooled in an ice bath. A solution of 10.2 g of **10a** in 120 mL of tetrahydrofuran was then added dropwise during 15 min below 10 °C. After being stirred at room temperature for 1.5 h, the mixture was poured into 500 mL of water, and the pH was adjusted to 3.1 with hydrochloric acid. It was then extracted with chloroform, and the combined extracts were washed with water, dried, and concentrated. The residue was triturated with benzene and filtered to give 9.26 g (81.0%) of β-keto sulfoxide, mp 191–192 °C.

Aluminum amalgam (7.0 g) was added to a solution of 9.1 g of the β-keto sulfoxide in 600 mL of tetrahydrofuran–water (9:1, v/v) during 30 min at room temperature. After being stirred for 30 min, the reaction mixture was filtered, and the solvent was evaporated. The residue was triturated with isopropyl ether to afford 6.87 g (91.7%) of **8a**: mp 228–229 °C; $[\alpha]^{25}_D$ −131° (*c* 1.0, $CHCl_3$). This compound was identified by comparison (IR, ^1H NMR) with the sample prepared by A.

(*RS*)-2-Acetyl-2-amino-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (7). Condensation of (*RS*)-**6** with sodium (methylsulfinyl)methide and reduction with zinc dust were conducted in the same manner as described for the preparation of **8a**. Thus, the ester **6** (2.49 g) was converted to 2.67 g of the β-keto sulfoxide, mp 121–123 °C, which was then reduced and worked up to give a solution of **7** in 80 mL of toluene. The solvent was evaporated, and the residue was dissolved in 30 mL of dry ether. Hydrogen chloride gas was passed into the cooled solution. The precipitate was collected by filtration to yield 2.01 g (90.0% from **6**) of the hydrochloride of **7**: mp 204–205 °C; IR 1705, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) 2.13 (t, 2 H, *J* = 6 Hz), 2.33 (s, 3 H), 2.43–2.80 (m, 2 H), 3.05 (q, *J* = 18 Hz, 2 H), 3.76 (s, 6 H), 6.73 (s, 2 H), 8.77 (br s, 2 H). Anal. Calcd for $C_{14}H_{20}ClNO_3$: C, 58.84; H, 7.05; Cl, 12.46; N, 4.90. Found: C, 58.72; H, 7.26; Cl, 12.28; N, 4.88.

In another run, a toluene solution of racemic **7** was acetylated in the same manner as **7a** to give (*RS*)-**8**, mp 224–226 °C. This compound gave a ^1H NMR spectrum identical with that reported for the (−)-enantiomer.

(*R*)-(−)-9-Acetyl-9-acetamido-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (11a). The compound **8a** (11.7 g) was thoroughly mixed with 142.2 g of phthalic anhydride, 42.9 g of sodium chloride, and 160 g of anhydrous aluminum chloride. The mixture was transferred into a reaction flask previously heated at 130–135 °C, and the resulting melt was stirred under a nitrogen atmosphere at the same temperature for 45 min. The hot reaction mixture was added by portions into a warmed solution of 216 g of oxalic acid in 1.6 L of water. After the mixture was stirred at 50–60 °C for 1 h, the precipitate was collected by filtration, washed with water, and suspended in 410 mL of toluene. Water was removed by azeotropic distillation, and the suspension was cooled to room temperature. The precipitate was collected by filtration to give 14.2 g (90%) of **11a** as orange crystals: mp >300 °C; $[\alpha]^{27}_D$ −110° (*c* 0.01, $CHCl_3$); optical purity by HPLC ~100% ee; IR 3360, 1705, 1660, 1620, 1525 cm^{-1}. Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56. Found: C, 67.24; H, 4.93; N, 3.59.

In another run, the same reaction was carried out at 170 °C for 4 min to give a 94% yield of optically pure **11a**.

(*R*)-(−)-9-Acetamido-9-[1,1-(ethylenedioxy)ethyl]-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (12a). A mixture of 3.93 g of **11a**, 13.7 mL of ethylene glycol, and 571 mg of *p*-toluenesulfonic acid in 390 mL of toluene was stirred and heated at reflux for 4 h, and water was collected through a Dean–Stark condenser. The resulting solution was washed successively with water, 0.5% aqueous sodium bicarbonate, and water and concentrated to a small volume under atmospheric pressure. After the mixture was allowed to cool, the precipitate was collected by filtration, washed with toluene, and dried to give 3.85 g (88%) of **12a**: mp 279–280 °C; $[\alpha]^{27}_D$ −291.7° (*c* 0.01, $CHCl_3$); IR 3390, 1660, 1640, 1580 cm^{-1}; ^1H NMR 1.48 (s, 3 H), 1.90 (s, 3 H), 1.50–2.10 (m, 1 H), 2.60–3.70 (m, 5 H), 4.08 (s, 4 H), 5.80 (br s, 1 H), 7.70–7.90 (m, 2 H), 8.20–8.40 (m, 2 H), 13.40 (br s, 1 H), 13.47 (br s, 1 H). Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N, 3.20. Found: C, 65.99; H, 5.34; N, 3.17.

(4*S*,14*S*)-(+)-4-[1,1-(Ethylenedioxy)ethyl]-4,5-dihydro-6,13-dihydroxy-4,14-methano-2-methyl-14*H*-anthra[3,2-*f*]-[1,3]oxazocine-7,12-dione (13a). (*R*)-(−)-Deoxy aglycon **12a** (875 mg, 2 mmol) was dissolved in 175 mL of benzene by heating under reflux. 1,3-Dibromo-5,5-dimethylhydantoin (572 mg, 2 mmol) was added under a nitrogen atmosphere, and the mixture was stirred and refluxed under illumination with a LPL brom cine light (100 V, 500 W) for 15 min. To the solution were added 60 mL of saturated aqueous sodium bicarbonate and 60 mL of 10% aqueous sodium thiosulfate. After the mixture was stirred at 50–60 °C for 1 h, the benzene layer was separated, washed with hot water and extracted with five 100-mL portions of 3 N hydrochloric acid. The combined extracts were washed with 50 mL of ethyl acetate and reextracted with three 100-mL portions of chloroform. The combined organic layers were washed successively with water and saturated aqueous sodium bicarbonate, dried, and evaporated. Trituration of the residue with isopropyl ether afforded 771 mg (88.5%) of **13a**: mp 195–197 °C; $[\alpha]^{27}_D$ +407.2° (*c* 0.29, $CHCl_3$); IR 1660, 1620, 1580 cm^{-1}; ^1H NMR 1.48 (s, 3 H), 1.88 (s, 3 H), 1.90 (dd, *J* = 3 and 14 Hz, 1 H), 2.27 (dd, *J* = 4 and 14 Hz, 1 H), 2.97 (d, *J* = 19 Hz, 1 H), 3.21 (d, *J* = 19 Hz, 1 H), 4.08 (s, 4 H), 5.80 (br s, 1 H, $\nu_{1/2}$ = 6 Hz), 7.70–7.93 (m, 2 H), 8.20–8.47 (m, 2 H), 13.27 (s, 1 H), 13.57 (s, 1 H); MS, *m/e* 435 (M^+).

When the same reaction was repeated by using 712 mg (4 mmol) of *N*-bromosuccinimide, there was obtained a 80% yield of **13a**.

(+)-9-Amino-4-demethoxy-9-deoxydaunomycinone (14a). A mixture of 435 mg of **13a** and 44 mL of 3 N sulfuric acid was stirred and heated at 80 °C for 30 h. After cooling to 50 °C, the reaction mixture was washed with three 20-mL portions of ethyl

acetate. The combined washings were extracted with three 10-mL portions of water. All aqueous layers were combined, and the pH was adjusted to 4.5 with 3 N sodium hydroxide. The product was extracted with four 40-mL portions of chloroform. After the pH of the aqueous layer was adjusted to 8–9 with saturated aqueous sodium bicarbonate, the extraction procedure was repeated with four 40-mL portions of chloroform. All organic extracts were combined, washed successively with saturated aqueous sodium bicarbonate, water, and brine, dried, and evaporated. The crude product was chromatographed on silica gel preparative TLC with 1:19 methanol–methylene chloride. Two bands were collected. The band with R_f 0.50 provided 300 mg (81.8%) of **14a**: mp 158–159 °C; $[\alpha]^{27}_D$ +207° (*c* 0.1, $CHCl_3$); IR (KBr) 3340, 1700, 1620, 1585 cm^{-1}; ^1H NMR 2.13–2.30 (m, 2 H), 2.39 (s, 3 H), 2.97 (d, J = 18 Hz, 1 H), 3.05 (d, J = 18 Hz, 1 H), 5.19 (br s, 1 H, $\nu_{1/2}$ = 7 Hz), 7.80–7.90 (m, 2 H), 8.30–8.40 (m, 2 H). Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.43; H, 4.79; N, 3.79. The band with R_f 0.30 afforded 28 mg (7.6%) of the 7-epi isomer: mp 185–188 °C; IR (KBr) 3520, 1715, 1630, 1595 cm^{-1}; ^1H NMR 2.13–2.33 (m, 2 H), 2.36 (s, 3 H), 2.67 (d, J = 18 Hz, 1 H), 3.28 (d, J = 18 Hz, 1 H), 5.30 (dd, 1 H, $\nu_{1/2}$ = 15 Hz), 7.73–7.93 (m, 2 H), 8.23–8.47 (m, 2 H).

In another experiment, purification of **14a** was effected without chromatographic separation. The crude product (350 mg) obtained after evaporation of the chloroform extracts was dissolved in 35 mL of hot benzene. The solution was seeded with crystals of pure **14a**, followed by addition of 55 mL of hexane. After the mixture was stirred at room temperature for 1 h, the resulting precipitate was collected by filtration, washed with 2:3 benzene–hexane, and dried to give 227 mg (75.4%) of **14a**, mp 157–159 °C.

(–)-9-Amino-4-demethoxy-9-deoxydaunomycinone [(–)-14b]. The seven-step synthesis described for the preparation of **14a** was repeated with (*S*)-(+)-**9b** to yield (–)-**14b**. The IR and ^1H NMR properties were identical with **14a**.

(*R*)-4-Hydroxy- and (*R*)-1-Hydroxy-9-acetyl-9-acetamido-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (15 and 16). In a similar manner to that described for **11a**, 6.75 g of **8a** was mixed with 9.97 g of 3-methoxyphthalic anhydride,[26] 96.6 g of anhydrous aluminum chloride and 19.3 g of sodium chloride, and heated with stirring at 180 °C for 7 min. After cooling, the reaction mixture was quenched with 1 L of saturated aqueous oxalic acid. The resulting precipitate was collected by filtration, washed with water, and dried to yield 7.7 g (81%) of a mixture of **15** and **16**: mp 287–290 °C; IR 3340, 1695, 1660, 1595, 1520 cm^{-1}.

(*R*)-4,6,11-Trimethoxy- and (*R*)-1,6,11-Trimethoxy-9-acetyl-9-acetamido-7,8,9,10-tetrahydro-5,12-naphthacenedione (17 and 18). The mixture of **15** and **16** (10 g) was dissolved in 2 L of acetone, and 20.4 g of anhydrous potassium carbonate and 14.0 g of dimethyl sulfate were added. The mixture was stirred and heated at reflux for 22 h. The insoluble material was filtered off and discarded. The filtrate was concentrated to dryness, dissolved in ethyl acetate, washed successively with 1 N hydrochloric acid and water, and dried. After evaporation of the solvent, the residue was chromatographed over 400 g of silica gel with ethyl acetate as eluant to afford 4.94 g (44.8%) of a mixture of **17** and **18**: mp 151–154 °C; IR 3600, 3350, 1710, 1680, 1590, 1530 cm^{-1}.

(*R*)-4-Methoxy- and (*R*)-1-Methoxy-9-acetyl-9-acetamido-6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (19 and 20). The mixture of **17** and **18** (1.0 g) was dissolved in 50 mL of methylene chloride, and the solution was cooled to 0 °C. Boron trichloride (5.6 g) in 56 mL of methylene chloride was added, and the mixture was stirred for 16 min at –5 to 0 °C. The reaction was then quenched with 44 mL of ice–water, and the pH was adjusted to 7.8 with saturated aqueous sodium bicarbonate. After the mixture was stirred for 30 min, the resulting precipitate was collected by filtration, washed successively with water, methylene chloride and ether, and dried to give 440 mg (47%) of **19**: mp 290–293 °C; $[\alpha]^{20}_D$ –52.6° (*c* 0.023, DMF); IR 3480, 3340, 1725, 1660, 1615, 1585, 1535 cm^{-1}; MS, *m/e* 423 (M^+). The filtrate and washings were combined, and the organic solvent was evaporated. The aqueous phase that remained was mixed with 50 mL of ethanol and stirred at 50 °C. The resulting precipitate was collected by filtration and washed with water and ether. The crude product was chromatographed on silica gel plates with 1:19 methanol–methylene chloride as the solvent to afford 168 mg (18%) of **20**: mp 280–284 °C; IR 3350, 1705, 1675, 1610, 1570, 1530 cm^{-1}; MS, *m/e* 423 (M^+).

(4*S*,14*S*)-(+)-4-[1,1-(Ethylenedioxy)ethyl]-4,5-dihydro-6,13-dihydroxy-4,14-methano-11-methoxy-2-methyl-14*H*-anthra[3,2-*f*][1,3]oxazocine-7,12-dione (21). The ketalization procedure described for the preparation of **12a** was repeated with **19** (42.3 mg) to yield 40 mg (85.7%) of the C13 ketal, mp 282–286 °C. This compound, without further purification, was dissolved in a mixture of 5 mL of chloroform and 10 mL of carbon tetrachloride by heating under reflux. *N*-Bromosuccinimide (20 mg) and cyclohexene oxide (42 mg) were added under a nitrogen atmosphere, and the mixture was stirred and refluxed under illumination with a LPL brom cine light (100 V, 500 W) for 2.5 h. The cooled solution was washed successively with saturated aqueous sodium bicarbonate, 5% aqueous sodium thiosulfate, and water. The organic layer was dried and concentrated, and the residue was chromatographed over silica gel with 1:19 methanol–methylene chloride to afford 28 mg (60%) of **21**: mp 175–178 °C; $[\alpha]^{20}_D$ +450.3° (*c* 0.1, $CHCl_3$); IR 1660, 1620, 1580 cm^{-1}; ^1H NMR 1.47 (s, 3 H), 1.80–2.40 (m, 2 H), 1.87 (s, 3 H), 2.98 (d, J = 18 Hz, 1 H), 3.20 (d, J = 18 Hz, 1 H), 4.07 (s, 4 H), 4.10 (s, 3 H), 5.80 (br s, 1 H, $\nu_{1/2}$ = 7 Hz), 7.36 (dd, J = 2 and 8 Hz, 1 H), 7.73 (t, J = 8 Hz, 1 H), 8.01 (dd, J = 2 and 8 Hz, 1 H), 13.22 (s, 1 H), 13.91 (s, 1 H); MS, *m/e* 465 (M^+ + 1).

(4*S*,14*S*)-(+)-4-[1,1-(Ethylenedioxy)ethyl]-4,5-dihydro-6,13-dihydroxy-4,14-methano-8-methoxy-2-methyl-14*H*-anthra[3,2-*f*][1,3]oxazocine-7,12-dione (22). By the same procedure as described above, **22** was prepared from **20** in 61.4% yield: mp 226–228 °C; ^1H NMR 1.50 (s, 3 H), 1.80–2.37 (m, 2 H), 1.87 (s, 3 H), 2.97 (d, J = 18 Hz, 1 H), 3.22 (d, J = 18 Hz, 1 H), 4.08 (s, 7 H), 5.78 (br s, 1 H, $\nu_{1/2}$ = 7.5 Hz), 7.35 (dd, J = 2 and 8 Hz, 1 H), 7.75 (t, J = 8 Hz, 1 H), 8.03 (dd, J = 2 and 8 Hz, 1 H), 13.59 (s, 1 H), 13.70 (s, 1 H); MS, *m/e* 465 (M^+ + 1).

(+)-9-Amino-9-deoxydaunomycinone (23). A mixture of 197 mg of **21** and 9.9 mL of concentrated hydrochloric acid in 80 mL of 1:1 dioxane–water was heated under reflux for 13 h. After evaporation of the solvent, the residue was dissolved in 70 mL of methanol, and 30 mg of activated charcoal powder was added. After being stirred, the mixture was filtered, and the filtrate was concentrated. The residue was crystallized from isopropyl alcohol to yield 143 mg of the hydrochloride of **23**, mp 212–219 °C. The hydrochloride was dissolved in 100 mL of 3% hydrochloric acid, washed with ethyl acetate, and made basic with saturated aqueous sodium bicarbonate. The liberated free base was extracted with chloroform, and the organic extracts were washed with saturated brine, dried, and evaporated. The residue was triturated with ether to afford 101 mg (60.0%) of **23**: mp 162–163 °C; $[\alpha]^{20}_D$ +113° (*c* 0.1, $CHCl_3$); IR 3360, 1710, 1620, 1585 cm^{-1}; ^1H NMR 2.19 (m, 2 H), 2.38 (s, 3 H), 3.00 (s, 2 H), 4.08 (s, 3 H), 5.19 (br s, 1 H, $\nu_{1/2}$ = 9 Hz), 7.37 (dd, J = 2 and 8 Hz, 1 H), 7.76 (t, J = 8 Hz, 1 H), 8.02 (dd, J = 2 and 8 Hz, 1 H); MS, *m/e* 398 (M^+ + 1).

(+)-9-Amino-4-demethoxy-9-deoxy-1-methoxydaunomycinone (24). By the same procedure as described above, **24** was prepared from **22** in 72.5%: mp 178–180 °C; $[\alpha]^{20}_D$ +123° (*c* 0.1, $CHCl_3$); IR 3550, 3340, 1705, 1620, 1585 cm^{-1}; ^1H NMR 2.19 (m, 2 H), 2.33 (s, 3 H), 3.03 (s, 2 H), 4.10 (s, 3 H), 5.20 (br s, 1 H, $\nu_{1/2}$ = 9 Hz), 7.37 (dd, J = 2 and 8 Hz, 1 H), 7.77 (t, J = 8 Hz, 1 H), 8.03 (dd, J = 2 and 8 Hz, 1 H); MS, *m/e* 398 (M^+ + 1).

(–)-9-Amino-7,9-dideoxydaunomycinone (27). A mixture of 250 mg of **19**, 30 mL of concentrated hydrochloric acid, and 59 mL of acetic acid was heated at reflux under a nitrogen atmosphere for 6.5 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in ice-cold water, made basic with saturated aqueous sodium bicarbonate, and extracted with chloroform. The combined organic layers were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel plates with 1:30 methanol–methylene chloride as the solvent to afford 150 mg (66.7%) of **27**: mp 173–176 °C; $[\alpha]^{20}_D$ –4.97° (*c* 0.1, $CHCl_3$); IR 3370, 3300, 1700, 1615, 1580, 1575 cm^{-1}; ^1H NMR 1.73–2.20 (m, 2 H), 2.36 (s, 3 H), 2.50–3.20 (m, 4 H), 4.08 (s, 3 H), 7.35 (dd, J = 2 and 8 Hz, 1 H), 7.75 (d, J = 8 Hz,

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1 H), 8.01 (dd, J = 2 and 8 Hz, 1 H); MS, m/e 381 (M^+).

Deamination of 27 to 7-Deoxydaunomycinone (25). To a solution of 66 mg of **27** in 6.6 mL of 50% acetic acid and 16.5 mL of dioxane was added a solution of 117 mg of sodium nitrite in 2 mL of water at 0–5 °C. After being stirred at 0–5 °C for 5 h, the mixture was let stand overnight in a refrigerator. After basification with aqueous sodium bicarbonate, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel plates using 1:99 methanol–methylene chloride as the solvent to afford 8 mg (12%) of **25**: mp 224–230 °C; $[\alpha]^{20}_D$ −39.3° (c 0.046, $CHCl_3$). The ^1H NMR, IR, and mass spectra of this compound were indistinguishable from an authentic sample.[15]

Deamination of 23 to Daunomycinone (26). The deamination procedure described above was repeated with **23** (15 mg). The crude product was chromatographed on silica gel plates with 3:97 methanol–methylene chloride as the solvent to yield 1 mg (7%) of **26**, mp 210–212 °C, whose ^1H NMR spectrum was indistinguishable from that of an authentic sample.[15]

(+)-9-Amino-4-demethoxy-9-deoxy-7-*O*-(2-deoxy-3,4-di-*O*-acetyl-β-D-*erythro*-pentopyranosyl)daunomycinone (29). A mixture of 848 mg of acetyl 3,4-di-*O*-acetyl-2-deoxy-β-D-ribopyranoside[20] and 999 mg of trimethylsilyl bromide in 8 mL of chloroform was stirred for 2 h at room temperature and concentrated to dryness, yielding 917 mg of bromo sugar **28**. To a solution of 400 mg of **14a** in 120 mL of methylene chloride was added a solution of 917 mg of **28** in 32 mL of methylene chloride and 417 mg of tetramethylurea. The mixture was cooled to −5 °C, and a solution of 924 mg of silver trifluoromethanesulfonate in 32 mL of ether was added with stirring over a period of 7 min. After being stirred further at 0–5 °C for 30 min, the mixture was poured into a cooled aqueous sodium bicarbonate solution. The insoluble material was filtered off, and the organic layer was separated, washed with saturated brine, dried, and evaporated. The residue was dissolved in benzene and washed successively with water and saturated brine to remove the tetramethylurea. The benzene solution was dried, evaporated, and purified by preparative TLC with 1:19 methanol–methylene chloride to give 531 mg (86%) of **29**: mp 141–143 °C; $[\alpha]^{20}_D$ +119.8° (c 0.1, $CHCl_3$); IR 1740, 1705, 1620, 1590 cm^{-1}; ^1H NMR 1.98 (s, 3 H), 2.13 (s, 3 H), 2.33 (s, 3 H), 1.95–2.57 (m, 4 H), 3.10 (s, 2 H), 3.87 (dd, J = 3 and 13 Hz, 1 H), 4.29 (dd, J = 3 and 13 Hz, 1 H), 5.06–5.33 (m, 3 H), 5.67 (br s, 1 H, $\nu_{1/2}$ = 7.5 Hz), 7.80–8.00 (m, 2 H), 8.33–8.57 (m, 2 H); MS, m/e 568 (M^+).

A portion of the free base was dissolved in methylene chloride and converted with 5% anhydrous hydrogen chloride in ether to the hydrochloride, which was precipitated by adding ether: mp 159–161 °C. Anal. Calcd for $C_{29}H_{30}ClNO_{11}\cdot 1.5H_2O$: C, 55.20; H, 5.27; Cl, 5.62; N, 2.22. Found: C, 55.42; H, 4.93; Cl, 6.01; N, 2.14.

(+)-9-Amino-4-demethoxy-9-deoxy-7-*O*-(2-deoxy-β-D-*erythro*-pentopyranosyl)daunomycinone (30). To a stirred solution of **29** (1.46 g) in 210 mL of 2:5 methanol–dichloroethane was added 1.49 g of anhydrous potassium carbonate at −5 °C. After being stirred further at the same temperature for 18 h, the reaction mixture was added dropwise to a buffer (1 N sodium hydroxide–85% phosphoric acid) at pH 2.5. The pH was maintained with 85% phosphoric acid below 4.5 during the period of addition and at 2.5 at the end of the addition. The aqueous solution was washed with chloroform, brought to pH 6.5 with 5% aqueous sodium bicarbonate, and extracted with chloroform. The chloroform extracts were combined, washed, dried, and evaporated. Trituration of the residue with 100 mL of chloroform afforded 1.12 g (90%) of **30**: mp 172–174 °C; $[\alpha]^{20}_D$ +119° (c 0.02, $CHCl_3$); IR 1710, 1620, 1590 cm^{-1}; ^1H NMR (DMSO-d_6, D_2O) 1.55 (m, 1 H), 1.90 (m, 1 H), 2.03 (dd, J = 5 and 16 Hz, 1 H), 2.16 (dd, J = 3 and 16 Hz, 1 H), 2.28 (s, 3 H), 2.91 (s, 2 H), 3.50–3.65 (m, 2 H), 3.72 (m, 1 H), 3.95 (dd, J = 3 and 12 Hz, 1 H), 4.87 (m, 1 H), 5.27 (br s, 1 H, $\nu_{1/2}$ = 6.5 Hz), 8.10–8.30 (m, 2 H), 7.80–8.00 (m, 2 H); MS, m/e 484 (M^+ + 1).

The free base was converted in the usual manner to the hydrochloride: mp 145–151 °C.

(+)-9-Acetamido-4-demethoxy-9-deoxy-7-*O*-(2-deoxy-3,4-di-*O*-acetyl-β-D-*erythro*-pentopyranosyl)daunomycinone (31). To a solution of 100 mg of **29** in 20 mL of methylene chloride were added 20 mL of acetic anhydride, 17 mL of pyridine, and 2 mg of (dimethylamino)pyridine. After being stirred at room temperature for 22 h, the reaction mixture was cooled, washed successively with aqueous sodium bicarbonate, water, 3% hydrochloric acid, water, aqueous sodium bicarbonate, and saturated brine, dried, and concentrated. The residue was triturated with ether to yield 85 mg (79.4%) of **31**: mp 165–167 °C; $[\alpha]^{20}_D$ +162° (c 0.1, $CHCl_3$); IR 3350, 1740, 1720, 1675, 1630, 1590 cm^{-1}; ^1H NMR 2.00 (s, 3 H), 2.07 (s, 3 H), 2.16 (s, 3 H), 2.30 (s, 3 H), 1.80–2.60 (m, 4 H), 3.27 (d, J = 20 Hz, 1 H), 3.62 (d, J = 20 Hz, 1 H), 3.83–4.23 (m, 2 H), 5.07–5.36 (m, 3 H), 5.63 (br s, 1 H, $\nu_{1/2}$ = 7.5 Hz), 7.68 (s, 1 H), 7.73–7.97 (m, 2 H), 8.20–8.48 (m, 2 H); MS, m/e 610 (M^+ + 1).

Hydrogenolysis of 31 to 7-Deoxyaglycon 11a. A solution of 15 mg of **31** in 6 mL of 1:2 ethyl acetate–methanol was hydrogenated over 100 mg of 5% palladium on barium sulfate at atmospheric pressure for 30 min. The mixture was diluted with methanol and filtered to remove the catalyst. The filtrate was concentrated, and the residue was redissolved in methylene chloride, washed with 1 N hydrochloric acid and water, and dried. After evaporation of the solvent, the residue was triturated with ether to afford 8 mg (82.7%) of **11a**, mp >300 °C, which was identical in all physical and spectral properties with the previously prepared sample from **8a**.

(+)-9-Amino-4-demethoxy-9-deoxy-3′-*N*-(trifluoroacetyl)daunomycin (33). To a stirred mixture of 50 mg of **14a** and 100 mg of powdered 4A molecular sieves in 15 mL of methylene chloride were added 146 mg of **32**[21] in 8 mL of methylene chloride and a solution of 116 mg of silver trifluoromethanesulfonate in 8 mL of ether. After being stirred for 2 h, the mixture was poured into a cooled aqueous sodium bicarbonate solution. The insoluble material was filtered off, and the organic layer was separated, washed with water, dried, and evaporated. Purification of the residue by preparative TLC with 1:19 methanol–methylene chloride afforded 74 mg (92%) of **33**: mp 143–145 °C; $[\alpha]^{25}_D$ +184° (c 0.12, $CHCl_3$); IR 1710, 1620, 1585 cm^{-1}; ^1H NMR 1.30 (d, J = 6.6 Hz, 3 H), 1.60–2.40 (m, 4 H), 2.39 (s, 3 H), 3.07 (s, 2 H), 3.67 (br s, 1 H), 4.05–4.60 (m, 2 H), 5.06 (m, 1 H), 5.48 (br s, 1 H, $\nu_{1/2}$ = 6.0 Hz), 7.70–7.90 (m, 2 H), 8.20–8.40 (m, 2 H). Anal. Calcd for $C_{28}H_{27}F_3N_2O_9\cdot H_2O$: C, 55.07; H, 4.78; N, 4.58. Found: C, 55.26; H, 4.54; N, 4.48.

A portion of the free base was converted in the usual manner to the hydrochloride: mp 173–174 °C.

(+)-9-Amino-9-deoxy-3′-*N*-(trifluoroacetyl)daunomycin (34). By the same procedure as described above, **34** was prepared in 57% yield: mp 155–157 °C; $[\alpha]^{20}_D$ +243.8° (c 0.1, $CHCl_3$); ^1H NMR 1.32 (d, J = 7 Hz, 3 H), 1.72–2.30 (m, 4 H), 2.42 (s, 3 H), 2.95 (d, J = 8 Hz, 2 H), 3.70 (br s, 1 H), 4.02 (s, 3 H), 4.10–4.59 (m, 2 H), 5.00 (br s, 1 H), 5.43 (br s, 1 H, $\nu_{1/2}$ = 6.5 Hz), 7.10 (d, J = 7.5 Hz, 1 H), 7.38 (d, J = 8 Hz, 1 H), 7.78 (t, J = 8 Hz, 1 H), 8.01 (d, J = 8 Hz, 1 H); MS, m/e 623 (M^+ + 1).

(+)-9-Amino-4-demethoxy-9-deoxy-1-methoxy-3′-*N*-(trifluoroacetyl)daunomycin (35). By the same procedure as described for the preparation of **33**, **35** was prepared in 60% yield: mp 147–150 °C; $[\alpha]^{20}_D$ +162.4° (c 0.1, $CHCl_3$); ^1H NMR 1.30 (d, J = 7 Hz, 3 H), 1.70–2.29 (m, 2 H), 2.40 (s, 3 H), 2.96 (d, J = 8 Hz, 2 H), 3.65 (br s, 1 H), 4.06 (s, 3 H), 4.10–4.60 (m, 2 H), 4.92 (br s, 1 H), 5.43 (br s, 1 H, $\nu_{1/2}$ = 6.0 Hz), 7.00 (d, J = 7.5 Hz, 1 H), 7.30 (d, J = 8 Hz, 1 H), 7.69 (t, J = 8 Hz, 1 H), 7.85 (d, J = 8 Hz, 1 H); MS, m/e 623 (M^+ + 1).

(+)-9-Amino-4-demethoxy-9-deoxydaunomycin (36). To a solution of 35 mg of **33** in 3 mL of methanol was added 2.2 mL of 10% aqueous potassium carbonate at 0 °C. After being stirred further at 0 °C for 2 days, the mixture was poured into 10 mL of 2% hydrochloric acid cooled to 0 °C, and the pH was adjusted to 9 with saturated aqueous sodium bicarbonate. The aqueous solution was saturated with sodium chloride and extracted with chloroform. The combined extracts were dried and evaporated. Trituration of the residue with ether gave 29 mg (98%) of **36**: mp 179–180 °C; IR 1710, 1620, 1590 cm^{-1}; ^1H NMR 1.33 (d, J = 6.6 Hz, 3 H), 1.50–2.30 (m, 4 H), 2.39 (s, 3 H), 3.02 (s, 2 H), 3.49 (br s, 1 H), 4.20 (m, 2 H), 5.00 (m, 1 H), 5.42 (br s, 1 H, $\nu_{1/2}$ = 7 Hz), 7.60–7.90 (m, 2 H), 8.10–8.40 (m, 2 H).

A small quantity was converted into the hydrochloride for analysis: mp 181–185 °C; $[\alpha]^{23}_D$ +56.5° (c 0.12, H_2O); IR 1720, 1620, 1580 cm^{-1}. Anal. Calcd for $C_{26}H_{30}Cl_2N_2O_8\cdot 2.25H_2O$: C,

51.19; H, 5.70; Cl, 11.62; N, 4.59. Found: C, 51.37; H, 5.49; Cl, 11.31; N, 4.54.

(+)-9-Amino-9-deoxydaunomycin (3). By the same procedure as described above, the hydrochloride of **3** was prepared in 92% yield: mp 197–200 °C; $[\alpha]^{20}_D$ +148.1° (*c* 0.1, methanol); IR 1725, 1620, 1580 cm^{-1}; MS, *m/e* 527 (M^+ + 1).

(+)-9-Amino-4-demethoxy-9-deoxy-1-methoxydaunomycin (37). By the same procedure as described for the preparation of **36**, the hydrochloride **37** was prepared in 76% yield: mp 198–202 °C; $[\alpha]^{20}_D$ +78.9° (*c* 0.1, methanol); IR 1730, 1620, 1585 cm^{-1}; MS, *m/e* 527 (M^+ + 1).

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Synthesis of Halodimethoxy-1,2-benzoquinones

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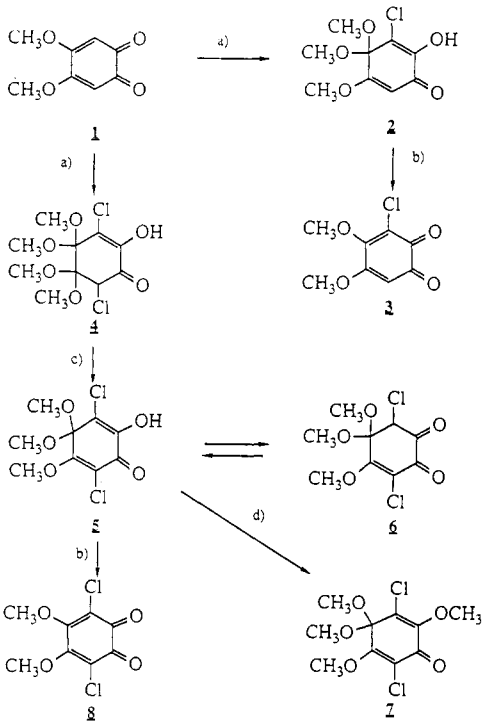
Syntheses of a large number of halodimethoxy-1,2-benzoquinones are described. A key reaction in these syntheses is the chlorination of methoxy-1,2-benzoquinones upon treatment with *tert*-butyl hypochlorite.

We have recently observed a number of interesting transformations associated with 1,2-benzoquinones. These include the conversion of 4,5-dimethoxy-1,2-benzoquinone to 2-alkynyl-5-methoxy-1,4-benzoquinones,[1] the generation of vinylketenes from the thermolysis of 3-azido-1,2-quinones,[2] and the rearrangement of 4-alkynyl-3-azido-1,2-benzoquinones to highly substituted cyanophenols.[3] Many of these transformations depend upon the availability of halodimethoxy-1,2-benzoquinones, compounds that until now have not been readily available.[4] Reported here are viable synthetic routes to such quinones. Specifically, syntheses of examples of nearly all possible regioisomeric mono- and dihalodimethoxy-1,2-benzoquinones are described in this paper (Schemes I–V).

A key reaction in many of these syntheses is the chlorination of methoxy-1,2-benzoquinones upon treatment with *tert*-butyl hypochlorite.[5] For example, treatment of 4,5-dimethoxy-1,2-benzoquinone (**1**)[6] with 1 equiv of *tert*-butyl hypochlorite in methanol gave a 46% yield of the quinone ketal **2** (Scheme I). This was converted to 3-chloro-4,5-dimethoxy-1,2-benzoquinone (**3**) in 91% yield upon treatment with a mixture of trifluoroacetic anhydride and trifluoroacetic acid followed by aqueous workup. When 2 equiv of the hypochlorite were employed, the quinone **1** gave **4** in 53% yield. This resulted in an equilibrium mixture of **5** and **6** when treated with $KHSO_4$ at 110 °C. Subsequent hydrolysis of this mixture gave 3,6-dichloro-4,5-dimethoxy-1,2-benzoquinone (**8**) in 91% yield (Scheme I). The structures of **5** and **6** are based upon their spectral properties as well as upon the observation that **5** gave the quinol **7** upon treatment with diazomethane.

The *tert*-butyl hypochlorite chlorination was also employed in the synthesis of 3-bromo-6-chloro-4,5-dimethoxy-1,2-benzoquinone (**13**) (Scheme II). Here, 2-hydroxy-4,5-dimethoxybenzaldehyde (**9**) was converted to

Scheme I[a]



[a] Key: (a) $(CH_3)_3COCl/CH_3OH$; (b) $(CF_3CO)_2O/CF_3CO_2H$; (c) $KHSO_4$; (d) CH_2N_2.

the catechol **11** in 72% overall yield via the bromo aldehyde **10**. Chloranil oxidation of **11** resulted in 3-bromo-4,5-dimethoxy-1,2-benzoquinone (**12**) (99%). Treatment of **11** with *tert*-butyl hypochlorite in dichloromethane gave **13** in 48% yield. It is noteworthy that the catechol **11** undergoes direct oxidative chlorination under these conditions. In an analogous fashion, 5-chloro- and 5,6-dichloro-3,4-dimethoxy-1,2-benzoquinone (**16** and **17**) were obtained from 5-chloro-1,2-dihydroxy-3,4-dimethoxybenzene (**15**), which, in turn, was prepared by SO_2Cl_2 chlorination of 1,2-dihydroxy-3,4-dimethoxybenzene (**14**) (Scheme III).

Scheme IV outlines the synthesis of 3,5-dibromo-4,6-dimethoxy-1,2-benzoquinone (**21**) starting from 2,4-dimethoxy-6-hydroxybenzaldehyde (**18**). This aldehyde was converted to the catechol **20** via **19**; *o*-chloranil oxidation

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