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Synthesis of 1-Fluoro-, 4-Fluoro-, and 1,4-Difluoro-4-demethoxydaunomycinone. Interesting D-Ring Analogues of Adriamycin

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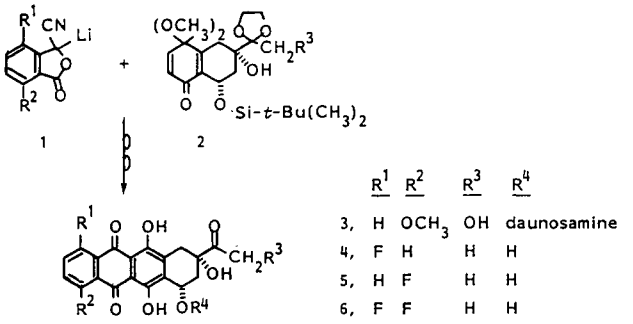
The syntheses of racemic 1-fluoro- (**4**), 4-fluoro- (**5**), and 1,4-difluoro-4-demethoxydaunomycinone (**6**) as well as the (+) antipodes of the latter two compounds are reported. The synthetic route involved the annelation of a highly functionalized quinone monoketal with the appropriate cyanophthalide anion followed by deprotection. The cyanophthalides were obtained from the corresponding hydroxyphthalides, prepared by metalation routes. Interestingly, the oxazoline directing group afforded much better yields of metalation products than the similarly substituted *N,N*-diethylamide compound in these fluorinated systems. The high reactivity of these D-ring-fluorinated anthracyclinones in nucleophilic aromatic substitution reactions was demonstrated by reaction of **5** and **6** with 2-[(2-aminoethyl)amino]ethanol to produce mitoxantrone analogues. The biological activity of the daunosamine coupling products of **4–6** in the P388 antitumor screen was comparable to 4-demethoxydaunomycinone, but the potency was dependent upon the fluorine substitution pattern.

Synthetic routes to anthracyclinones have been of major interest in organic chemistry for the last decade.[1] A major objective of this work has been the development of viable syntheses of anthracyclinone aglycons that upon coupling with daunosamine or other glycon analogues, would yield new anthracycline systems. A more specific goal of such studies is to develop an efficacious and less toxic alternative to the widely used antineoplastic drug adriamycin[2] (doxorubicin, **3**). A popular synthetic strategy to rhodomycinone analogues of anthracyclinones has been the annelation of a 1,4-dipole equivalent to quinone monoketals (Scheme I).[3-6] This convergent route allows the formation

Scheme I. Annelation Strategy to Anthracyclinones



	R1	R2	R3	R4	
3,	H	OCH_3	OH	daunosamine	
4,	F	H	H	H	
5,	H	F	H	H	
6,	F	F	H	H	

of the fully functionalized anthracyclinone in one key step and is an ideal strategy for synthesis of D-ring anthracyclinone analogues.

Analogues **4–6**, in which the hydrogens in the D-ring of anthracyclinones are replaced by fluorine, were especially interesting candidates for synthesis. Substitution of hydrogen with fluorine in a drug often leads to significant biological effects, especially if metabolism at the site of substitution is an important in vivo process.[6] Further-

(1) For leading references and a recent review of anthracyclinone chemistry, see: Kelly, T. R., Ed. *Tetrahedron* **1984**, *40*, 4539–4793; *Tetrahedron Symposia-in-Print N. 17.*

(2) Arcamone, F. *Doxorubicin*; Academic: New York, 1981.

(3) (a) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 932. (b) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263. (c) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318. (d) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625.

(4) (a) Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1981**, 108. (b) Russell, R. A.; Krauss, A. S.; Warrener, R. N. *Tetrahedron Lett.* **1984**, *25*, 1517. (c) Russell, R. A.; Irvine, R. W.; Krauss, A. S. *Tetrahedron Lett.* **1984**, *25*, 5817. (d) Russell, R. A.; Gee, P. S.; Irvine, R. W.; Warrener, R. N. *Aust. J. Chem.* **1984**, *37*, 1709. (e) Becker, A. M.; Irvine, R. W.; McCormick, A. S.; Russell, R. A.; Warrener, R. N. *Tetrahedron Lett.* **1986**, *27*, 3431. (f) Russell, R. A.; Irvine, R. W.; Warrener, R. N. *J. Org. Chem.* **1986**, *51*, 1595.

(5) Keay, B. A.; Rodrigo, T. *Can. J. Chem.* **1983**, *61*, 637.

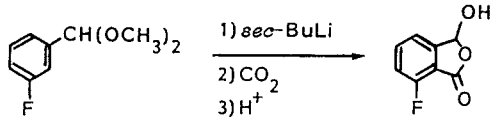
(6) (a) *Carbon-Fluorine Compounds*, A *CIBA* Foundation Symposium; Associated Scientific Publishers: Amsterdam, 1972. (b) Smith, F. A. *CHEMTECH* **1973**, 422–429.

0022-3263/87/1952-0713$01.50/0

more, it is known that aromatic fluorine substituents are often subject to facile nucleophilic aromatic substitution if other electron-withdrawing groups are present on the ring. In fact, the room-temperature displacement of aromatic fluoro substituents by amino groups has recently been reported in simple anthraquinone systems.[7]

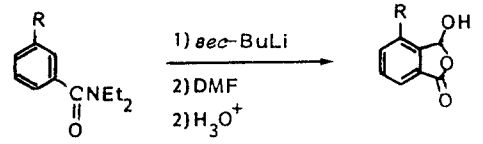
We report herein the preparation of 1-fluoro- (4), 4-fluoro- (5), and 1,4-difluoro (6) derivatives of 4-demethoxydaunomycinone, the nucleophilic aromatic substitution chemistry of the latter two molecules with 2-[(2-aminoethyl)amino]ethanol, and the biological activity of the resultant anthracyclines and (alkylamino)anthracyclinones.[8]

Preparation of 7-Fluoro-, 4-Fluoro-, and 4,7-Difluoro-3-cyano-1(3*H*)-isobenzofuranones. Previous studies[3c,d] have established the superiority of 3-cyano-1-(3*H*)-isobenzofuranones (1), hereinafter referred to as cyanophthalides, as annelating agents for functionalized quinone monoketals. A variety of methods are available for the preparation of hydroxyphthalides,[9] which in turn may be conveniently converted to the corresponding cyanophthalides.[9,10] The hydroxyphthalide **7a** was readily available from metalation/carboxylation of the dimethyl acetal of commercially available *m*-fluorobenzaldehyde.[9] At the time, the hydroxyphthalides **7c** and **7d** were unknown.[10]



7a (86%)

Metalation/functionalization of appropriate commercially available fluoro-substituted aromatic compounds would be the most direct route to the required hydroxyphthalides. Because we had prepared **7b**, the 7-methoxy

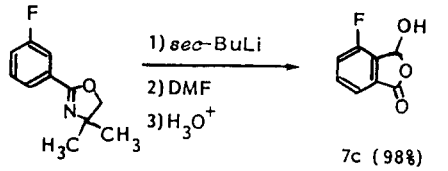


8, R = OCH_3
9, R = F

7b, R = OCH_3 (54%)
c, R = F (< 15%)

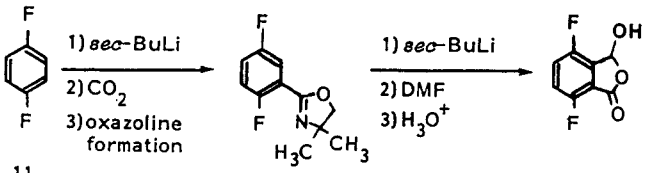
analogue of **7c**, in good yield by metalation of the *N,N*-diethylamide of *m*-methoxybenzoic acid followed by reaction of the resulting organolithium reagent with dimethylformamide,[3c] an analogous route to **7c** was studied. Unfortunately, reaction of the diethylamide of *m*-fluorobenzoic acid, as for the corresponding methoxy derivative noted above, never afforded more than 15% yield of the corresponding hydroxyphthalide.[9,10] However, when the oxazoline derivative **10**[11] of *m*-fluorobenzoic acid was employed in this reaction sequence, crude hydroxyphthalide was obtained in 98% yield.

For preparation of the 4,7-difluoro system **7d**, a route analogous to that used for preparation of **7a** mentioned above was examined first. When the metalation/carboxylation sequence was applied to 2,5-difluorobenzaldehyde dimethyl acetal, a poor yield of the desired hydroxyphthalide resulted. This parallels results obtained in the metalation of the dimethyl acetal of 2,5-dimethoxybenzaldehyde wherein a poor yield of a hydroxyphthalide was reported.[9] Thus, the oxazoline route was examined for this system in spite of the concern that displacement of the *o*-fluoro group by the alkyllithium reagent could compete with the metalation step.[12] The required 2,5-difluorobenzoic acid was prepared in good yield by metalation of 1,4-difluorobenzene followed by carboxylation of the resulting organolithium compound. Conversion of the above acid to the oxazoline **12**, followed by metalation and subsequent reaction with dimethylformamide and hydrolysis, gave **7d** in 93% yield. It is interesting that the choice of directing group (diethyl amide vs. oxazoline) is so important in the metalation reactions of these particular systems.



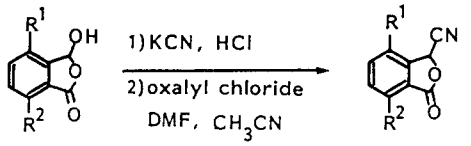
10

7c (98%)



11 12 7d (93%)

Initially, some difficulty was experienced in conversion of the fluoro-substituted hydroxyphthalides **7c,d** to the corresponding cyanophthalides **1c,d**. It appears that these



7a, R^1 = H, R^2 = F
c, R^1 = F, R^2 = H
d, R^1, R^2 = F

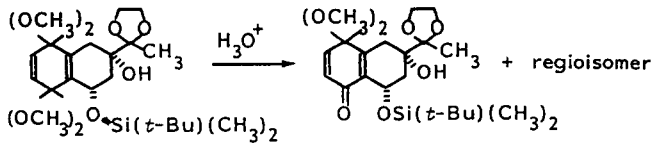
1a (57%)
c (68%)
d (71%)

cyanohydrin intermediates are more subject to hydrolysis and/or decomposition than are the compounds studied previously.[9] In reactions wherein cyanohydrin formation was allowed to occur at 0 °C for several hours, products showing an amide carbonyl in the IR spectrum could be isolated. While these crude amides were dehydrated under the Vilsmeier conditions to the corresponding cyanophthalides, the overall yields were not high since the further hydrolysis of the amide to the carboxylic acid was difficult to control during the cyanohydrin formation. This complication was avoided by allowing cyanohydrin formation to proceed at 0 °C for 5 min and extracting the crude product directly from the reaction mixture with cold ethyl acetate. This material was then immediately reacted with the Vilsmeier reagent, yielding the cyanophthalides **1c,d** in overall yields of 68 and 71%, respectively.

Synthesis of 1-Fluoro, 4-Fluoro-, and 1,4-Difluoro-4-demethoxydaunomycinone. With the required cyanophthalides **1a,c,d** readily available, the annelation reaction previously utilized[3c,d] in the synthesis of dauno-

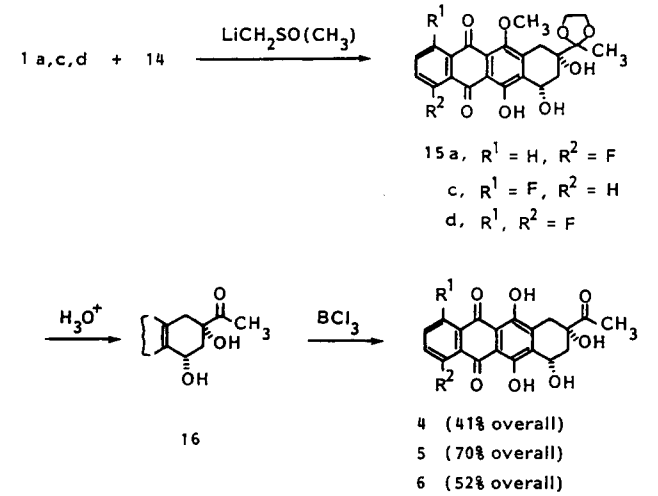
(7) Krapcho, A. P.; Getahun, Z. *Synth. Commun.* **1985**, 907.
(8) (a) This work was reported by G. W. Morrow and J. S. Swenton at the 18th Central Regional Meeting of the American Chemical Society, Bowling Green, OH, June 1–5, 1986; Paper 275. (b) The parent cyanophthalide was first employed in an annelation of cyclohexenones: Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263. Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439.
(9) For leading references see: Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805–810.
(10) Russell R. A.; Pilley, B. A. *Synth. Commun.* **1986**, *16*, 425–430.
(11) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.
(12) Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682–685 and references cited therein.

mycinone and its 4-demethoxy analogue was used to prepare the anthracyclinones **4–6**. The hydrolysis of bisketal **13** afforded a ca. 85:15 mixture of **14** and its regioisomer.[3b,c,13] For racemic material, the major regioisomer may be obtained by recrystallization of the mixture of quinone monoketals and used directly for the coupling step, affording the desired regioisomer of the tetracyclic product.



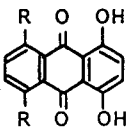
13 14

However, in the optically active series, the major regioisomer **14** could not be obtained crystalline, and the mixture of regioisomeric monoketals was used for the coupling reaction. In such cases, recrystallization of the crude coupling product afforded the regiochemically pure tetracyclic ketals **15a,c,d**. The ^{19}F NMR spectrum was especially useful in establishing regiochemical purity of these products since the ^{19}F resonances of the regioisomeric anthracyclinones are distinguishable. Thus, recrystallization of the crude product from reaction of **1a** and the hydrolysis mixture from **13** gave **15a**, which showed in the ^{19}F NMR spectrum a quartet centered at δ −113.3. The mother liquors from the crystallization showed in the ^{19}F NMR spectrum two quartets (central signal overlapping) centered at δ −113.3 and −113.5. A similar result was obtained for the products from the coupling reaction of **1c** and **14** (see the Experimental Section).



The final steps in the synthetic route involved deprotection of the tetracyclic products obtained from the coupling reactions.[3d] Deblocking of the ethylene glycol ketal proceeded in aqueous acid while demethylation of the aromatic ether was accomplished with boron trichloride as detailed in the Experimental Section. Thus, racemic anthracyclinones **4–6** were obtained in respective overall yields of 41, 70, and 52% from the quinone monoketals from **13** and the cyanophthalides **1a,c,d**.

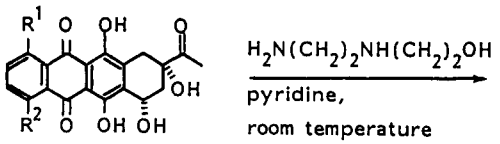
Daunomycinone–Mitoxantrone Hybrids. Replacement of fluorine(s) in the D-ring of the anthracyclinones **4–6** via nucleophilic substitution would afford a convenient route to a variety of D-ring analogues. An especially interesting nucleophile for such purposes is 2-[(2-aminoethyl)amino]ethanol since the aminoanthraquinone mitoxantrone[14,15] **17** has shown significant antitumor activity



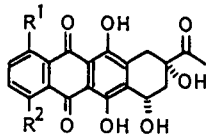
17, mitoxantrone
R = $NH(CH_2)_2NH(CH_2)_2OH$

and analogues of **17** have been prepared by just such an approach.[7] Although **17** shares with the anthracyclines a planar polycyclic aromatic structure, no report has appeared of a synthetic strategy toward hybrid analogues in which the key structural features of both have been incorporated.

The fluorinated aglycons, racemic **5** and optically pure **6**, were dissolved in pyridine and treated with 2-[(2-aminoethyl)amino]ethanol and reacted at room temperature (**5**) or 75 °C (**6**). Concentration in vacuo and chromatography on silica gel afforded **18** as a dark purple semisolid (44%) and **19** as a deep blue solid (57%). While these hygroscopic compounds were obtained as amorphous solids that did not show sharp melting points, they were homogeneous by thin-layer chromatography. Additionally, the 500-MHz NMR, UV, IR, and FAB mass spectra indicated incorporation of the side chains and retention of A-ring integrity. In the case of **19**, the high optical rotation suggests retention of chirality in the product, which would be expected in view of the mild reaction conditions. As with other anthracycline aglycons, compounds **18** and **19** were of very marginal activity in P388 screens, and no attempt to prepare the corresponding anthracycline derivatives has been undertaken.



5, R^1 = H, R^2 = F
6, R^1, R^2 = F



18, R^1 = H, R^2 = $NH(CH_2)_2NH(CH_2)_2OH$
19, R^1, R^2 = $NH(CH_2)_2NH(CH_2)_2OH$

This approach serves as an exceedingly mild and efficient method for the regiospecific introduction of an alkylamino side chain on the D-ring of fully functionalized daunomycinone derivatives. Furthermore, although no other nucleophilic agents were explored, this method suggests nucleophilic aromatic substitution on D-ring-fluorinated anthracyclinones as a viable strategy for the synthesis of other daunomycinone D-ring analogues. In view of the mild reaction conditions, nucleophilic substitution on the fluorine-substituted anthracycline derivatives themselves may be possible, thus allowing attachment of

(13) Chen, C.-P.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 4569.

(14) Johnson, R.; Zee-Cheng, R.; Lee, W.; Acton, E.; Henry, D.; Cheng, C. *Cancer Treat. Rep.* **1979**, *63*, 425.

(15) Schabel, F., Jr.; Corbett, T.; Griswold, D., Jr.; Laster, W., Jr.; Trader, M. *Cancer Treat. Rev.* **1983**, *10* (Supplement B), 13–21. Durr, F.; Wallace, R.; Citarella, R. *Ibid.* **1983**, *10* (Supplement B), 3–11. McDonald, M.; Posner, L.; Dukart, G.; Scott, S. *Drugs Exp. Clin. Res.* **1984**, *11*, 745–752. Durr, F. *Semin. Oncol.* **1984**, *11* Suppl. 1, 3. Lown, J.; Morgan, A.; Yen, S.; Wang, Y.; Wilson, W. *Biochemistry* **1985**, *24*, 4028.

Table I. Biological Data for Daunosamine Derivatives of 4–6

compound	opt dose, mg/kg	T/C	toxic dose, mg/kg
4-fluoro-4-demethoxydaunomycin	0.5	165	2
1-fluoro-4-demethoxydaunomycin	0.75	171	>6
1,4-difluoro-4-demethoxy-daunomycin	4.20	182	25
4-demethoxydaunomycin	0.5	172	1

anthracyclines to biologically interesting macromolecules such as antibodies.

Biological Results for Daunomycin Analogues. The anthracyclinones 4–6 prepared were coupled with daunosamine[16] and tested in a P388 antitumor screen. The antitumor responses to a single intraperitoneal injection of each test compound are summarized in Table I. The 1- and 4-fluoro derivatives show similar efficacy and activity to 4-demethoxydaunomycin, a derivative which is 5–8 times more potent than naturally occurring daunomycin.[17,18] However, the 1,4-difluoro derivative, while showing good activity and diminished toxicity, is substantially less potent than 4-demethoxydaunomycin. Thus, substitution of fluorine for hydrogen in the D-ring of anthracyclines appears to have minimal effect on biological activity, as measured by the P388 screen. In view of the diminished potency of the 1,4-difluoro system, it would be of academic interest to examine the biological activity of the anthracycline in which the D-ring is fully fluorinated.

Experimental[19] Section

(+)- and (±)-4-Fluoro-4-demethoxydaunomycinone (5). To a 0 °C solution of Me_2SO (35 mL) and THF (34 mL) was added CH_3Li (8.9 mL of a 1.29 M solution). After 5 min, 7-fluoro-3-cyano-1(3*H*)-isobenzofuranone (2.04 g, 11.5 mmol) in $(CH_3)_2SO$ (34 mL) was added, giving a golden brown solution. After an additional 5 min, the monoketal (3.9 g, 8.86 mmol) in THF (34 mL) was added, whereupon the solution turned deep red. The reaction mixture was allowed to stir at room temperature for 2 h, and then the reaction was quenched by the addition of 5% HCl (100 mL). The majority of the THF was removed in vacuo, $(CH_3)_2CO$ (250 mL) was added, and the solution was allowed to stir for 12 h. TLC analysis indicated that the *tert*-butyldimethylsilyl group was not completely removed, $CHCl_3$ was added to render the solution homogeneous, and the reaction mixture was stirred for an additional 48 h. Removal of the majority of the solvent in vacuo afforded a yellow solid that was filtered and dried to give the tetracyclic ketal [3.62 g (92%); mp 215–218 °C], which was used directly in the next step. Recrystallization of a portion of this material from $CH_3OH/CHCl_3$ gave the analytically pure material: mp 227–229 °C; IR (KBr) 3500–3380 (br, m), 1670 (s), 1630 (s), 1600 (s), 1430 (s), 1385 (s), 1355 (s), 1230 (br, s) cm^{-1}; ^1H NMR δ 13.83 (s, 1 H), 8.12 (br d, J = 7 Hz, 1 H), 7.8–7.2 (highly str m, 2 H), 5.37–5.30 (str m, 1 H), 4.06 (s, 4 H), 3.86 (s, 3 H), 3.67 (d, J = 4 Hz, disappears with D_2O, 1 H), 3.25 (s, disappears with D_2O, 1 H), 3.01 (AB q, $\Delta\nu$ = 42 Hz, J_{AB} = 19 Hz with lower field component further coupled, 2 H), 2.2 (AB q, $\Delta\nu$ = 40 Hz, J_{AB} = 14 Hz with lower field component split into pseudotriplet and higher field component split into doublet, J = 4 Hz, 2 H), 1.46 (s, 3 H); ^{19}F NMR δ −113.3 (ABX, dd, J_{AX} = 15 Hz, J_{BX} = 4.5 Hz, 1 F). Anal. Calcd for $C_{23}H_{21}O_8F$: C, 62.16; H, 4.73. Found: C, 61.79; H, 4.79.

The optically pure compound obtained in 54% yield showed the following: mp 217–221 °C; $[\alpha]^{20}_D$ (1:1 $CHCl_3/CH_3OH$) +127°.

A mixture of THF (500 mL) and 30% HCl (180 mL) was cooled to 0 °C, and the above ketal (3.62 g) was added. This mixture was then stirred for 24 h at room temperature, after which TLC analysis showed no change. Additional THF (1200 mL) and concentrated HCl (15 mL) were added, and the solution was warmed to 40 °C, whereupon it became homogeneous. After the mixture was stirred for 48 h at room temperature, TLC analysis indicated complete hydrolysis of the ketal. The reaction mixture was then concentrated in portions at room temperature, and the resulting slurry was extracted with $CHCl_3$ (3 × 100 mL), washed with brine, and dried. Concentration and drying in vacuo gave 4-fluoro-4-demethoxy-11-methoxy-11-deoxydaunomycinone, 3.0 g (91%). This material was used directly in the next step. A small portion recrystallized from $CHCl_3/CH_3OH$ gave the analytically pure material: mp 215–216 °C; IR (KBr) 3500–3300 (br, m), 1715 (s), 1670 (s), 1635 (s), 1600 (s), 1420 (s), 1385 (s), 1355 (s), 1250 (s), 1230 (br, s) cm^{-1}; ^1H NMR (200 MHz) δ 13.82 (s, 1 H), 8.15 (d, J = 8 Hz, 1 H), 7.8 (str m, 1 H), 7.48 (str m, 1 H), 5.38–5.32 (str m,1 H), 4.55 (s, 1 H), 3.87 (s, 3 H), 3.67 (d, J = 4 Hz, 1 H), 3.11 (AB q, $\Delta\nu$ = 44 Hz, J_{AB} = 18 Hz with lower field component further coupled, 2 H), 2.44 (s, 3 H), 2.26 (AB q, $\Delta\nu$ = 48 Hz, J_{AB} = 14 Hz with lower field component split into pseudotriplet and higher field component split into doublet, J = 4 Hz, 2 H); ^{19}F NMR δ −110.63 (ABX, dd, J_{AX} = 10.5 Hz, J_{BX} = 4.5 Hz, 1 F). Anal. Calcd for $C_{21}H_{17}O_7F$: C, 63.00; H, 4.25. Found: C, 62.34; H, 4.38.

The optically pure compound obtained in 76% yield showed the following: mp 158–159.5 °C; $[\alpha]^{20}_D$ (1:1 $CH_3OH/CHCl_3$) +153°.

To a −78 °C solution of the above material (3.0 g) in CH_2Cl_2 (630 mL) was added BCl_3 (80 mL of a 1 M solution in CH_2Cl_2). The resulting dark purple solution was stirred for 2 h at −78 °C. The reaction was quenched with CH_3OH, the solvent was removed in vacuo, and the resulting solid was dried overnight in vacuo. This material was dissolved in a boiling mixture of $CHCl_3/CH_3OH$ (ca. 1:1), and the solution was refluxed for 1 h. Cooling and concentration in vacuo produced a voluminous red/orange solid that was filtered and dried in vacuo to give in three crops 4-fluoro-4-demethoxydaunomycinone: 2.39 g (83%); mp 238–241 °C; IR (KBr) 3500–3300 (br, m), 1715 (s), 1625 (s), 1595 (s), 1450 (s), 1440–1400 (br, m), 1270–1220 (br, m) cm^{-1}; ^1H NMR (500 MHz) δ 13.69 (s, 1 H), 13.26 (s, 1 H), 8.24 (d, J = 8 Hz, 1 H), 7.82 (str m, 1 H), 7.53 (str m, 1 H), 5.34 (str m, 1 H), 4.54 (s, 1 H), 3.75 (d, J = 5 Hz, 1 H), 3.1 (AB, q, $\Delta\nu$ = 115 Hz, J_{AB} = 19 Hz with lower field component further coupled, 2 H), 2.43 (s, 3 H), 2.27 (AB q, $\Delta\nu$ = 90 Hz, J_{AB} = 14 Hz with lower field component split into pseudotriplet and higher field component split into doublet, 2 H); ^{19}F NMR δ −109.62 (ABX, dd, J_{AX} = 11.3 Hz, J_{BX} = 4.5 Hz, 1 F). Anal. Calcd for $C_{20}H_{15}O_7F$: C, 62.18; H, 3.91. Found: C, 62.04; H, 3.98.

The optically pure material obtained in 83% yield showed the following: mp 213–215 °C; $[\alpha]^{20}_D$ (1:1 $CHCl_3/CH_3OH$) +147°.

2-(3-Fluorophenyl)-4,4-dimethyl-2-oxazoline (10). The 3-fluorobenzoyl chloride was prepared in the usual fashion by reacting 3-fluorobenzoic acid (10 g, 0.017 mol) with excess $SOCl_2$ at reflux for several hours. Distillation at reduced pressure afforded the acid chloride [9.9 g (87%); bp 95–100 °C (30 mm)] as a yellow oil that was then dissolved in CH_2Cl_2 (20 mL) and added

(16) The coupling reactions with daunosamine were conducted by Drs. D. Horton and W. Priebe and will be reported separately.

(17) Neidel, S. *Nature (London)* **1977**, *268*, 195.

(18) Arcamone, F.; Bernadi, L.; Giardino, P. *Cancer Treat. Rep.* **1976**, *60*, 829.

(19) Melting points were determined in capillaries in a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 283B spectrometer as KBr disks unless otherwise noted. Routine ^1H NMR spectra were determined at 80 MHz on an IBM NR 80 spectrometer using deuteriochloroform as solvent and residual chloroform as standard. The ^{13}C NMR and ^{19}F NMR spectra were determined at 20 and 75.3 MHz on the above instrument. The ^{19}F NMR determinations used hexafluorobenzene as internal standard, and the chemical shifts are reported upfield from $CClF_3$. The 500-MHz spectra were measured by Dr. Charles Cottrell in deuteriochloroform on a Bruker Model AM-500 spectrometer. Mass spectral and exact-mass measurements were obtained by Richard Weisenberger on a Kratos MS-30 spectrometer. The FAB spectra were determined on the above instrument using xenon gas at a potential of 8000 V with air Ion-Tek gun. A 50:50 mixture of glycerol and thioglycerol was used as matrix with methanol and chloroform as solvent. The peak intensities are reported relative to glycerol. Alumina and silica gel were obtained from E. Merck Co. Tetrahydrofuran was purified by distillation from benzophenone ketyl although, for the coupling reaction, solvent from a freshly opened bottle gave comparable yields with purified material. Throughout the Experimental Section the following abbreviations are used: petroleum ether, bp 35–60 °C (PE); diethyl ether (Et_2O); tetrahydrofuran (THF); dimethyl sulfoxide ($(CH_3)_2SO$); ethyl acetate (EtOAc); dimethylformamide (DMF).

dropwise to a 0 °C solution of 2-amino-2-methyl-1-propanol (11.1 g, 0.125 mol) in CH_2Cl_2 (75 mL). After stirring for 12 h, the milky suspension was poured into an equal volume of H_2O, the layers were separated, and the organic phase was dried through $CaSO_4$. Concentration in vacuo afforded the crude hydroxy amide as an oil that was treated directly with $SOCl_2$ (15 mL). After the mixture was stirred for 12 h, the resulting viscous oil was treated with Et_2O (50 mL) and stirred vigorously until the hydrochloride salt was a crystalline precipitate. Vacuum filtration gave the white salt, which was washed several times with Et_2O and then dissolved in a 20% KOH solution (50 mL). The heterogeneous mixture was extracted with Et_2O (2 × 100 mL), and the combined organics were dried over $CaSO_4$. Concentration in vacuo, followed by distillation at reduced pressure, afforded the oxazoline **10** [7.36 g (54% from starting acid)] as a water-white oil: bp 115–120 °C (5 mm); IR (NaCl plates) 2960 (s), 1650 (s), 1590 (s), 1490 (m), 1450 (s), 1355 (s), 1310 (s), 1195 (m), 1180 (m), 1065 (m), 1050 (m), 970 (m), 720 (s) cm^{-1}; ^1H NMR δ 7.8–7.0 (highly str m, 4 H), 4.09 (s, 2 H), 1.36 (s, 6 H); mass spectrum, exact mass for $C_{11}H_{12}NOF$, calcd m/e 193.0903, obsd m/e 193.0918.

4-Fluoro-3-hydroxy-1(3*H*)-isobenzofuranone (7c). To a −78 °C solution of oxazoline **10** (7.36 g, 38.1 mmol) in THF (50 mL) was added over 15 min *s*-BuLi (31 mL of a 1.3 M solution). After 30 min, DMF (6.0 mL) was added, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was then quenched by the addition of concentrated HCl (5 mL), the solvents were removed via rotary evaporator, and the residue was taken up in 6 N HCl (400 mL) and heated for 12 h on a steam bath. After cooling to 0 °C, the aqueous mixture was extracted with EtOAc (3 × 150 mL), and the organic phase was washed with brine (100 mL) and dried through $CaSO_4$. Concentration followed by drying in vacuo afforded 6.26 g (98%) of a light tan solid, mp 106–110 °C, suitable for use in the next step. Recrystallization of a portion from $CHCl_3$ gave the analytically pure material: mp 117–119.5 °C (lit.[10] mp 113–116 °C); IR (KBr) 3500–3150 (br, m), 1785 (s), 1610 (m), 1490 (s), 1350 (m), 1285 (m), 1268 (s), 1255 (s), 1202 (m), 1095 (m), 1080 (m), 1050 (m), 975 (s), 930 (s), 750 (s) cm^{-1}; ^1H NMR δ 7.8–7.3 (str m, 3 H), 6.8 (s, 1 H); mass spectrum, exact mass for $C_8H_5O_3F$, calcd m/e 168.0223, obsd m/e 168.0208.

4-Fluoro-3-cyano-1(3*H*)-isobenzofuranone (1c). The above hydroxyphthalide (0.5 g, 3.0 mmol) and KCN (1.5 g) were dissolved in water (5 mL) and cooled to 0 °C. A little ice was added, followed by dropwise addition of concentrated HCl (10 mL), whereupon the solution turned cloudy. The mixture was stirred for 5 min and then extracted with EtOAc (2 × 75 mL). Workup and drying gave a thick yellow oil that was used directly in the next step. To the Vilsmeier salt prepared in the usual way from CH_3CN (7 mL), oxalyl chloride (0.92 g), and DMF (0.86 mL) was added the above material in CH_3CN (6 mL). After the mixture was stirred for 1 min, pyridine (1.2 mL) was added, and the mixture was stirred for an additional 15 min. The reaction mixture was then poured into 5% HCl (75 mL). Extractive workup (EtOAc) and concentration gave an orange/yellow solid that was chromatographed on silica gel (CH_2Cl_2 as eluant) to give the title compound [0.36 g (68%)] from the hydroxyphthalide as light yellow crystals, mp 93–96 °C. Recrystallization of a portion from CH_3OH gave the analytically pure material as white needles: mp 99–101 °C (lit.[10] mp 99–101 °C); IR (KBr) 2940 (w), 1790 (s), 1488 (m), 1284 (m), 1265 (m), 1080 (m), 1025 (m) cm^{-1}; ^1H NMR δ 7.9–7.3 (highly str m, 3 H), 6.15 (s, 1 H); mass spectrum, exact mass for $C_9H_4O_2F$, calcd m/e 177.0226, obsd m/e 177.0217.

(±)-1-Fluoro-4-demethoxydaunomycinone (4). To a 0 °C solution of $(CH_3)_2SO$ (13 mL) and THF (13 mL) was added CH_3Li (3.3 mL of a 1.29 M solution). After 5 min, 4-fluoro-3-cyano-1-(3*H*)-isobenzofuranone (**1c**; 0.75 g, 0.42 mmol) in $(CH_3)_2SO$ (13 mL) was added, giving a yellow-brown solution. After an additional 2 min, the monoketal (1.43 g, 3.26 mmol) in THF (11.3 mL) was added rapidly, whereupon the solution turned a deep red color. The reaction mixture was allowed to stir at room temperature for 2 h, and then the reaction was quenched by the addition of 5% HCl (40 mL). The majority of the THF was removed in vacuo, $(CH_3)_2CO$ (100 mL) was added, and the solution was allowed to stir for 12 h. The heterogeneous solution was then cooled in an ice bath and filtered. The resulting ketal was obtained as an orange-yellow solid [1.19 g (81% crude); mp 224–227 °C] that was used directly in the next step. Crystallization of a portion from $CHCl_3/CH_3OH$ gave the analytically pure material: mp 226–228 °C; IR (KBr) 3600–3200 (br, m) 1675 (s), 1630 (m), 1597 (s), 1420 (m), 1370 (br, s), 1260 (s), 1220 (s) cm^{-1}; ^1H NMR (500 MHz) δ 13.6 (s, 1 H), 8.08 (d, J = 8 Hz, 1 H), 7.68 (str m, 1 H), 7.43 (str m, 1 H), 5.22 (str m, 1 H), 4.02 (str m, 4 H), 3.84 (s, 3 H), 3.65 (d, 1 H), 3.07 (s, 1 H), 3.0 (AB q, $\Delta\nu$ = 221 Hz, J_{AB} = 19 Hz with lower field component further coupled, 2 H), 2.15 (AB q, $\Delta\nu$ = 230 Hz, J_{AB} = 14 Hz with lower field component split into pseudotriplet and higher field component split into doublet, 2 H), 1.48 (s, 3 H); ^{19}F NMR δ −113.30 (ABX, dd, J_{AX} = 105 Hz, J_{BX} = 4.5 Hz, 1 F). Anal. Calcd for $C_{23}H_{21}O_8F$: C, 62.16; H, 4.76. Found: C, 61.73; H, 4.82.

A mixture of THF (125 mL) and concentrated HCl (18 mL) was cooled to 0 °C, and the above ketal (1.10 g) was added. This mixture was then stirred for 24 h at room temperature, and the resulting homogeneous mixture was diluted with water (35 mL). The acid was neutralized by cautious addition of solid Na_2CO_3. The aqueous layer was then separated and extracted with $CHCl_3$ (2 × 30 mL), and the combined organic phase was concentrated in vacuo. This material was dissolved in $CHCl_3$, dried, and concentrated to give a dark residue that crystallized after addition of CH_3OH to give 1-fluoro-4-demethoxy-11-methoxy-11-deoxydaunomycinone as an orange powder: 0.77 g (77%); mp 157–159 °C. This material was used directly in the next step. Recrystallization of a portion from $CHCl_3/CH_3OH$ gave the analytical sample: mp 175–176 °C; IR (KBr) 3600–3200 (br, m), 1710 (br, m), 1670 (s), 1630 (m), 1597 (s), 1360 (s), 1260 (s), 1215 (s) cm^{-1}; ^1H NMR (500 MHz) δ 13.62 (s, 1 H), 8.15 (d, J = 8 Hz, 1 H), 7.75 (str m, 1 H), 7.50 (str m, 1 H), 5.34 (str m, 1 H), 4.50 (s, 1 H), 3.90 (s, 3 H), 3.66 (d, 1 H), 3.10 (AB q, $\Delta\nu$ = 105 Hz, J_{AB} = 19 Hz, with lower field component further coupled, 2 H), 2.43 (s, 3 H), 2.24 (AB q, $\Delta\nu$ = 90 Hz, J_{AB} = 14 Hz, with lower field component split into pseudotriplet and higher field component split into doublet, 2 H); ^{19}F NMR δ −112.95 (ABX, dd, J_{AX} = 10.5 Hz, J_{BX} = 4.5 Hz, 1 F). Anal. Calcd for $C_{21}H_{17}O_7F$: C, 63.00; H, 4.28. Found: C, 62.45; H, 4.29.

To a −78 °C solution of the above material (0.77 g) in CH_2Cl_2 (160 mL) was added BCl_3 (19.3 mL of a 1 M solution in CH_2Cl_2). The resulting dark purple solution was stirred for 2 h at −78 °C. The reaction was quenched by addition of CH_3OH (90 mL), the solvent was removed in vacuo, and the resulting solid was dried overnight in vacuo. Recrystallization of this material from $CHCl_3/CH_3OH$ gave (±)-1-fluoro-4-demethoxydaunomycinone: 0.48 g (66%); mp 205–208 °C. An additional recrystallization of a small portion gave the analytically pure material: mp 215–216 °C; IR (KBr) 3600–3200 (br, m), 1710 (m), 1625 (s), 1592 (s), 1452 (s), 1415 (br, s), 1382 (s), 1260 (br, s), 1240 (s), 1215 (s) cm^{-1}; ^1H NMR (500 MHz) 13.55 (s, 1 H), 13.44 (s, 1 H), 8.25 (d, J = 8 Hz, 1 H), 7.82 (str m, 1 H), 7.53 (str m, 1 H), 5.32 (str m, 1 H), 4.50 (s, 1 H), 3.77 (d, 1 H), 3.10 (AB q, $\Delta\nu$ = 122 Hz, J_{AB} = 19 Hz, with lower field component further coupled, 2 H), 2.42 (s, 3 H), 2.28 (AB q, $\Delta\nu$ = 75 Hz, J_{AB} = 14 Hz, with lower field component split into pseudotriplet and higher field component split into doublet, 2 H); ^{19}F NMR δ −109.68 (ABX, dd, J_{AX} = 11.3 Hz, J_{BX} = 4.5 Hz, 1 F). Anal. Calcd for $C_{20}H_{17}O_7F$: C, 62.18; H, 3.91. Found: C, 61.82; H, 4.25.

2,5-Difluorobenzoic Acid. To a −78 °C solution of 1,4-difluorobenzene (18.7 g, 0.164 mol) in THF (180 mL) was added *s*-BuLi (129 mL of a 1.3 M solution) dropwise via addition funnel over 15 min. The resulting yellow solution was stirred for 0.5 h, and then dry CO_2 was bubbled beneath the surface for about 10 min. After stirring for 15 min at −78 °C, the reaction mixture was allowed to warm to room temperature and then poured into cold, concentrated HCl. After separation of the layers, the aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organics were washed with brine and dried through $CaSO_4$. Concentration in vacuo gave a tacky yellow solid (21.3 g) with a broad melting range that was used directly in the next step. Careful recrystallization of a portion from $CHCl_3$ gave a white solid, mp 125–128 °C (lit.[20a,b] mp 132–134, 118–119 °C).

2-(2,5-Difluorophenyl)-4,4-dimethyl-2-oxazoline (12). The crude acid from above (21.0 g, 0.133 mol) was reacted with excess $SOCl_2$ (35 mL) at reflux for 4 h. Distillation at reduced pressure

(20) (a) Aldrich Chemical Co. Catalog, 1986, p 482. (b) German Patent 1 080 999; *Chem. Abstr.* **1961**, *55*, 16488f.

afforded the crude acid chloride [bp 90–95 °C (30 mm)] as a yellow oil [17.2 g (73%)] that was then dissolved in CH_2Cl_2 (30 mL) and added dropwise to a 0 °C solution of 2-amino-2-methyl-1-propanol (17.5 g, 0.196 mol) in CH_2Cl_2 (118 mL). The resulting milky suspension was stirred at room temperature for 6 h and then poured into an equal volume of H_2O. Standard workup afforded the crude hydroxy amide as a yellow oil that was treated directly with $SOCl_2$ (20.5 mL). After 12 h, the thick oil was treated with Et_2O (150 mL) and the oily hydrochloride salt vigorously stirred. After decantation of the Et_2O, the salt was dissolved in a 20% KOH solution (50 mL), the aqueous layer was extracted with Et_2O (3 × 25 mL), and the combined organics were washed with brine and dried over $CaSO_4$. Concentration in vacuo afforded a brown oil that was distilled at reduced pressure to give the title compound [7.95 g (23% from 1,4-difluorobenzene)] as a light yellow oil: bp 92–96 °C (0.4 mm); IR (neat) 3100 (m), 1640 (s), 1480 (s), 1430 (s), 1330 (m), 1270 (m), 1240 (m), 1190 (m), 1165 (s), 1030 (s), 960 (s), 760 (s) cm^{-1}; ^1H NMR δ 7.7–7.0 (str m, 3 H), 4.2 (s, 2 H), 1.4 (s, 6 H); mass spectrum, exact mass for $C_{11}H_{11}NOF_2$, calcd m/e 211.0809, obsd m/e 211.0805.

4,7-Difluoro-3-hydroxy-1(3*H*)-isobenzofuranone (7d). To a −78 °C solution of the oxazoline **12** (7.95 g, 37.7 mmol) in THF (50 mL) was added over 15 min *s*-BuLi (29 mL of a 1.3 M solution). After 30 min, DMF (6.0 mL) was added, and the reaction mixture was stirred at −78 °C for 2 h. The reaction was then quenched by addition of concentrated HCl (5 mL). The solvents were removed in vacuo, and the residue was taken up in 5 N HCl (500 mL) and heated on the steam bath overnight. After cooling to room temperature, the reaction mixture was extracted with EtOAc (3 × 200 mL). Standard workup gave a light brown solid [6.5 g (93%); mp 125–128 °C] suitable for use in the next step. Recrystallization of a portion from $CHCl_3$ gave the analytically pure material: mp 135–138 °C; IR (KBr) 3600–3400 (br, m), 1780 (s), 1510 (s), 1275 (br, s), 1170 (m), 1115 (m), 1030 (m), 895 (br, s), 825 (m), 775 (m) cm^{-1}; ^1H NMR (80 MHz) δ 7.5–7.1 (str m, 2 H), 6.75 (s, 1 H); mass spectrum, exact mass for $C_8H_4O_3F_2$, calcd m/e 186.0128, obsd m/e 186.0125.

4,7-Difluoro-3-cyano-1(3*H*)-isobenzofuranone (1d). The above hydroxyphthalide (2 g, 10.7 mmol) and NaCN (5.0 g) were dissolved in water (10 mL) and cooled to 0 °C. Ice (2 g) was added, followed by dropwise addition of concentrated HCl (40 mL). The mixture was stirred for 5 min and then extracted with EtOAc (3 × 50 mL). Workup and drying gave a thick yellow oil that was used directly in the next step. To the Vilsmeier salt prepared in the usual way from CH_3CN (26 mL), oxalyl chloride (2.3 mL), and DMF (3.1 mL) was added the above material in CH_3CN (21 mL). After the mixture was stirred for 1 min, pyridine (4.8 mL) was added, and the mixture was stirred for an additional 15 min. The reaction mixture was then poured into 5% HCl (125 mL). Extractive workup (EtOAc, 3 × 50 mL) and concentration gave an orange-yellow solid that was chromatographed on silica gel (CH_2Cl_2 as eluant) to give the title compound [1.49 g (71%)] from the hydroxyphthalide as light yellow crystals, mp 84–86 °C. Recrystallization of a portion from EtOAc/PE gave the analytically pure compound: mp 87–89 °C; IR (KBr) 1760 (s), 1475 (s), 1240 (s), 1230 (s), 1050 (s), 975 (br, s), 890 (s), 822 (s) cm^{-1}; ^1H NMR (80 MHz) δ 7.75–7.20 (highly str m, 2 H), 6.09 (s, 1 H); mass spectrum, exact mass for $C_9H_3O_2NF_2$, calcd m/e 195.0132, obsd m/e 195.0143.

(+)-1,4-Difluoro-4-demethoxydaunomycinone (6). To a 0 °C solution of $(CH_3)_2SO$ (8.5 mL) and THF (8.5 mL) was added methyllithium (1.75 mL of a 1.7 M ether solution) via syringe over 5 min, and after stirring for an additional 5 min, a solution of 4,7-difluoro-1(3*H*)-isobenzofuranone (0.575 g, 2.95 mmol) in $(CH_3)_2SO$ (8.5 mL) was added via syringe to give a yellow-brown solution. After 5 more min, a solution of optically pure monoketal (1.0 g, 2.27 mmol) in THF (8.5 mL) was added rapidly via syringe to give a dark green solution that slowly turned deep red after about 15 min. After stirring 12 h at room temperature, the reaction was quenched with 5% HCl (50 mL), and the mixture was stirred for 1 h, after which the THF was removed in vacuo and replaced with acetone (100 mL). The resulting mixture was warmed and stirred for about 2 h until desilylation was complete. Concentration in vacuo followed by filtration and drying afforded the desired ketal [0.791 g (75%); mp 231–233 °C] as a mixture of regioisomers. Recrystallization of a portion from $CHCl_3$/CH_3OH gave the analytical sample as light orange needles: mp 248.5–250 °C; $[\alpha]^{20}_D$ +111° (1:1 $CHCl_3$/CH_3OH); IR (KBr) 3450–3350 (br, s), 2920 (w), 1675 (s), 1635 (m), 1590 (w), 1465 (m), 1420 (s), 1380 (m), 1350 (m), 1250 (s), 1200 (s) cm^{-1}; ^1H NMR (500 MHz) δ 13.48 (s, 1 H), 7.5–7.3 (str m, 2 H), 5.29 (s, 1 H), 4.11–4.06 (str m, 4 H), 3.90 (s, 3 H), 3.71 (d, 1 H), 3.19 (s, 1 H), 3.04 (AB q, $\Delta\nu$ = 220 Hz, J_{AB} = 19 Hz with lower field component further coupled, 2 H), 2.21 (AB q, $\Delta\nu$ = 240 Hz, J_{AB} = 15 Hz, with lower field component split into pseudotriplet, higher field component split into doublet, 2 H), 1.47 (s, 3 H). Anal. Calcd for $C_{23}H_{20}O_8F_2$: C, 59.74; H, 4.36. Found: C, 59.61; H, 4.41.

The ketal from above (0.700 g, 1.52 mmol) was dissolved in THF (300 mL), 30% HCl (30 mL) was added, and the resulting homogeneous mixture was stirred for 12 h after which time ketal hydrolysis was only about 50% complete. Concentrated HCl (15 mL) was then added and the resulting mixture stirred an additional 12 h until hydrolysis was complete. The reaction mixture was then concentrated in vacuo at room temperature and poured into cold H_2O (100 mL). The product was extracted into $CHCl_3$ (3 × 50 mL), washed with water (2 × 50 mL), dried through $CaSO_4$, and then concentrated and dried in vacuo to give a dark red semisolid that was recrystallized from $CHCl_3$/CH_3OH. The desired 1,4-difluoro-4-demethoxy-11-methoxy-11-deoxyduanomycinone (0.367 g) was obtained as an orange-brown crystalline solid, mp 203–206 °C. The mother liquors were rapidly chromatographed through a short silica gel column (95:5 $CHCl_3$/CH_3OH as eluant) to yield an additional 0.218 g of a regioisomeric mixture, for a total of 0.585 g (92% from ketal) of material suitable for use in the next step. Recrystallization of a portion from $CHCl_3$/CH_3OH gave the analytically pure material: mp 215.5–217 °C; $[\alpha]^{20}_D$ +165° (1:1 $CHCl_3$/CH_3OH); IR (KBr) 3600–3200 (br, s), 2920 (br, w), 1710 (m), 1670 (s), 1630 (m), 1590 (m), 1460 (m), 1420 (s), 1380 (m), 1350 (m), 1250 (s), 1200 (s) cm^{-1}; ^1H NMR (500 MHz) δ 13.5 (s, 1 H), 7.48 (highly str m, 2 H), 5.34 (str m, 1 H), 4.54 (s, 1 H), 3.89 (s, 3 H), 3.69 (s, 1 H), 3.16 (AB q, $\Delta\nu$ = 95 Hz, J_{AB} = 18 Hz with lower field component split into doublet, 2 H), 2.43 (s, 3 H), 2.25 (AB q, $\Delta\nu$ = 103 Hz, J_{AB} = 14 Hz with lower field component split into pseudotriplet and higher field component split into doublet, 2 H). Anal. Calcd for $C_{21}H_{16}O_7F_2$: C, 60.29; H, 3.85. Found: C, 60.29; H, 3.92.

To a −78 °C solution of the material prepared above (0.218 g, 0.52 mmol) in CH_2Cl_2 (35 mL) was added BCl_3 (5.2 mL of a 1.0 M solution in CH_2Cl_2) dropwise via syringe. After the mixture was stirred for 2 h, CH_3OH (30 mL) was added, and the mixture was allowed to warm to room temperature and was then poured into cold H_2O (100 mL). The product was extracted into CH_2Cl_2, dried through $CaSO_4$, and concentrated in vacuo. The resulting dark red semisolid was dissolved in 1:1 $CHCl_3$/CH_3OH (75 mL) and refluxed for 30 min to remove any residual complexed boron compounds. Concentration afforded a voluminous red precipitate that was filtered and dried to yield desired product: 0.112 g (54%); mp 207–212 °C. Recrystallization of a portion from $CHCl_3$/CH_3OH gave pure 1,4-difluoro-4-demethoxydaunomycinone: mp 215.5–217 °C; $[\alpha]^{20}_D$ +130°. The mother liquors were concentrated to yield 75 mg of slightly less pure material that was suitable for use in the subsequent step. The analytical sample showed the following: IR (KBr) 3600–3200 (br, m), 1710 (m), 1620 (br, s), 1590 (s), 1440–1400 (br, s), 1260 (s), 1200 (m) cm^{-1}; ^1H NMR (500 MHz) δ 13.56 (s, 1 H), 13.29 (s, 1 H), 7.53 (t, J = 7 Hz, 2 H), 5.30 (t, J = 4.5 Hz, 1 H), 4.54 (s, 1 H), 3.80 (d, 1 H), 3.07 (AB q, $\Delta\nu$ = 116 Hz, J_{AB} = 9 Hz, with lower field component further coupled, 2 H), 2.43 (s, 3 H), 2.26 (AB q, $\Delta\nu$ = 88 Hz, J_{AB} = 15 Hz, with lower field component split into pseudotriplet and higher field component split into doublet, 2 H). Three separate samples were submitted for combustion analysis, and while all three analyses were within experimental error, the analysis for carbon was about 0.8% below theory. Anal. Calcd for $C_{20}H_{14}O_7F_2$: C, 59.41; H, 3.49. Found: C, 58.22; H, 3.63.

For the racemic series, the intermediates **15d** and **16d** were not characterized, and the overall yield for **6** was 52%. While this material showed spectroscopic properties identical with those of the optically pure compound, variable melting points between 110 and 125 °C were obtained.

(±)-4-[[2-[*N*-(Hydroxyethyl)amino]ethyl]amino]-4-demethoxydaunomycinone (18). To a solution of 4-fluoro-4-demethoxydaunomycinone (5; 100 mg, 0.227 mmol) in pyridine

(30 mL) was added 2-[(2-aminoethyl)amino]ethanol (118 mg, 1.13 mmol) whereupon the solution immediately turned dark purple. After 12 h at room temperature, no starting material remained by TLC analysis. The pyridine was removed in vacuo, and the dark purple residue was chromatographed on flash silica gel column (75:25 $CHCl_3/CH_3OH$ as eluant). The highly polar product was finally eluted from the silica gel by adding a small amount of concentrated NH_4OH solution to the eluant. In this way, after concentration and drying in vacuo, a deep purple semisolid (54 mg) was obtained, melting over a broad range and decomposing above 150 °C: IR (KBr) 3600–3200 (br, s), 2920 (w), 1720 (w), 1600 (s), 1520 (w), 1440 (br, m), 1230 (br, m) cm^{-1}; ^1H NMR (500 MHz) δ 9.65 (t, disappears with D_2O wash, 1 H), 7.54 (str m, 2 H), 7.02 (q, 1 H), 5.28 (d, 1 H), 3.72 (t, 2 H), 3.45 (q, collapses to triplet with D_2O wash, 2 H), 3.06 (t, 2 H), 3.02 (AB q, J_{AB} = 18 Hz with higher field component partially obscured, 2 H), 2.43 (s, 3 H), 2.25 (AB q, $\Delta\nu$ = 115 Hz, J_{AB} = 20 Hz with higher field component split into doublet, 2 H); ^{13}C NMR δ 215.8, 186.7, 185.7, 154.3 (2 C), 150.5, 136.1, 135.1, 132.5 (2 C), 119.0, 116.6, 111.7, 110.6 (2 C), 77.0, 61.1, 56.9, 49.9, 46.1, 38.8, 35.8, 31.7, 24.6; FAB, *m/e* 471 (0.21% of base peak).

(−)-1,4-Bis[[2-[*N*-(hydroxyethyl)amino]ethyl]amino]-4-demethoxydaunomycinone (19). To a solution of (+)-4-demethoxy-1,4-difluorodaunomycinone (10 mg, 0.025 mmol) in pyridine (0.25 mL) was added 2-[(2-aminoethyl)amino]ethanol (0.124 mL of a 1.0 M pyridine solution), and the resulting mixture was stirred for 2 h at 75 °C. The pyridine was then removed in vacuo, and the residue was deposited on silica gel and chromatographed ($CHCl_3/CH_3OH$ as eluant) until the product band remained behind. This was then eluted with an 80:20 mixture of $CHCl_3/CH_3OH$ containing 2.5% concentrated NH_4OH. Concentration of the main fractions and drying in vacuo afforded the title compound [8.1 mg (57%)] as a deep blue hygroscopic semisolid with a broad melting range (100–150 °C): $[\alpha]^{436}_{25}$ −188° (1:1 $CHCl_3/CH_3OH$); IR (KBr) 3600–3200 (br, s), 2920 (m), 2850 (w), 1720 (m), 1640 (m), 1600 (s), 1565 (s), 1200 (br, s) cm^{-1}; ^1H NMR (500 MHz, pyridine-d_5) δ 10.74 (s, 2 H), 7.23 (d, 2 H), 5.69 (s, 2 H), 3.99 (s, 4 H), 3.56 (s, 4 H), 3.47 (AB q, $\Delta\nu$ = 139 Hz, J_{AB} = 18 Hz, 2 H), 3.01 (d, 8 H), 2.52 (s, 3 H), 2.47 (AB q, $\Delta\nu$ = 158 Hz, J_{AB} = 14 Hz, 2 H); FAB, *m/e* 573 (0.52% of base peak); UV (1:1 $CHCl_3/CH_3OH$) 680 nm (ϵ 16486), 626 (ϵ 12657).

Testing in Mice against the P388 Lymphocytic Leukemia Model. Test compounds were dissolved in 0.9% saline. Female CDF_1 and DBA_2 (Harlan Laboratory, Indianapolis, IN) housed in gang cages were fed Purina Laboratory Chow and water ad libitum and adapted to this regime for at least 1 week before use. The P388 tumor was maintained by continuous passage in DBA_2 mice. On day 0, ascitic fluid was removed and diluted with Hank's balanced salt solution, cells were counted, and 10^6 tumor cells were implanted ip in a total volume of 0.1 mL. Twenty-four hours later, mice were randomly segregated into treatment groups, and drug was given ip to groups of seven mice for each dilution. The mice were observed for 30 days and T/C (percent) values were determined from the survival rate as compared to the controls.[21]

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Asymmetric Induction in the Addition Reactions of Chiral Sulfinylallyl Anions (Ambident Nucleophiles) with Enones (Ambident Electrophiles). Ring Closure of Enol Thioether Ketones[1]

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The regio- and stereochemical aspects of reactions of sulfinylallyl anions possessing chiral sulfur with various cyclic enones are reported. The 1,4-γ-adducts (Michael-type adducts) were obtained with excellent enantioselectivity in most cases (70–96% ee). Hydrolytic desulfurization followed by intramolecular cyclization of the adducts were demonstrated. These two methods constitute a mild and versatile method for the synthesis of chiral cyclic molecules.

The regiospecific addition reactions of cyclopentenones with carbanions of allylic sulfoxides constitute a mild and versatile method for the formation of carbon–carbon bonds. Kraus and Frazier[2] were the first to disclose the Michael additions of allylic sulfone anions to α,β-unsaturated ketones and esters. The addition reactions of allylic sulfide[3] and racemic allylic sulfoxide[4-6] anions with cyclic enones were then reported. The present paper describes the asymmetric induction exhibited in the conjugate addition reaction of the carbanion derived from allylic sulfoxides possessing chiral sulfur with various cyclic enones and the intramolecular cyclization of the adduct enol

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