Synthesis of 4-Demethoxy-6,11-dideoxydaunomycinone. A Highly Deoxygenated Anthracyclinone

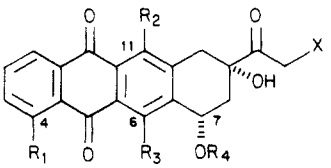
K. Ravichandran, Francis A. J. Kerdesky, and Michael P. Cava*[1]

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104, and Department of Chemistry, University of Alabama, University (Tuscaloosa), Alabama 35486

Received October 8, 1985

The first synthesis of 4-demethoxy-6,11-dideoxydaunomycinone (11) is described. The new daunomycinone analogue, which bears no alkoxyl or hydroxyl functions in the anthraquinone moiety, was prepared by an efficient reaction sequence starting from the readily available 2,3-dimethylanthraquinone. Key steps in the synthesis include the trapping of a tricyclic *o*-quinodimethane intermediate and the first use of benzeneboronic acid for the conversion of completely constructed *cis,trans*-anthracyclinone mixtures into pure cis isomers.

The efficacy of adriamycin (1) and daunomycin (2) as major chemotherapeutic agents in the treatment of human malignancies[2] has spawned unabated interest in the area of anthracycline synthesis. The intercalation complex of the anticancer anthracyclines with double stranded cell DNA is stabilized by $\pi-\pi$ interaction of the base pairs with the drug planar chromophore moiety. The phenolic groups of the latter may also take part in the intercalation process as deduced by spectroscopic evidence.[3] On the other hand, it has been suggested that the hydroquinone type B ring of 1 and 2 might participate in redox reactions leading to radical species responsible for various side effects, especially the important cumulative dose dependent cardiotoxicity.[4]



1, R_1=OMe; R_2=R_3=X=OH; R_4=daunosaminyl
2, R_1=OMe; R_2=R_3=OH; X=H; R_4=daunosaminyl
3, R_1=OMe; R_2=X=H; R_3=OH; R_4=daunosaminyl
4, R_1=X=H; R_2=R_3=OH, R_4=daunosaminyl
5, R_1=R_2=X=H; R_3=OH; R_4=daunosaminyl
6, R_1=R_4=X=H; R_2=R_3=OH
7, R_2=R_4=X=H; R_1=OMe; R_3=OH
8, R_1=R_2=R_4=X=H; R_3=OH
9, R_1=OMe; R_3=R_4=X=H; R_2=OH
10, R_1=R_3=R_4=X=H; R_2=OH
11, R_1=R_2=R_3=R_4=X=H

Support for this supposition has come from the pharmacological properties of the naturally derived second generation anthracycline 11-deoxydaunomycin (3): this drug has anticancer properties comparable to daunomycin but shows reduced dose-limiting side effects.[5] The 4-methoxy substituent of 1 and 2 is also known to be nonessential for anticancer activity; indeed, the totally synthetic 4-demethoxydaunomycin (4) has been found to be more active than daunomycin,[6] and the less oxygenated analogue 4-demethoxy-11-deoxydaunomycin (5) is more effective than 3.[7]

Since the daunomycin-derived sugar L-daunosamine can be effectively coupled to synthetic anthracyclinones,[8] the synthesis of a variety of partially deoxygenated anthracyclinones, especially those not available from natural sources, remains as the only means of systematically determining the effect of substituents on the aglycon portion as a function of the therapeutic index of the derived glycosides. Partially deoxygenated daunomycinones which have been synthesized include the 4-demethoxy (6),[9] 11-deoxy (7),[10] 4-demethoxy-11-deoxy (8),[7,11] and 6-deoxy (9),[12] derivatives.

4-Demethoxy-6,11-dideoxydaunomycinone (11) represents the simplest daunomycinone analogue in which the A ring structure and stereochemistry remain intact, but all three oxy substituents have been stripped from the anthraquinone nucleus. The literature records only one approach to this molecule, in which a potential tetracyclic diester intermediate was obtained by an ingenious intramolecular Diels–Alder reaction.[13] We now report an efficient, regiocontrolled synthesis of 11 from readily prepared aromatic precursors.

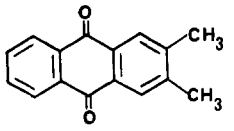
Results and Discussion

Our approach to the synthesis of 11 was based upon the *o*-quinodimethane methodology which we employed earlier in our synthesis of 4-demethoxydaunomycinone.[16] The starting material was the readily available 2,3-dimethylanthraquinone (12), which was easily prepared in quantity from phthalic anhydride and *o*-xylene by minor modifications of the classical literature procedures.[14,15] Benzylic bromination of 12 to the symmetrical dibromide 13 was

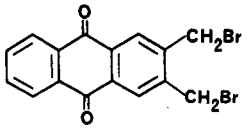
(1) Present address: Department of Chemistry, University of Alabama, P.O. Box H, University, AL 35486.
(2) For a recent comprehensive review, see: Arcamone, F. *Doxorubicin* Academic Press: New York, 1981.
(3) Manfait, M.; Alix, A. J. P.; Jeanneson, P. Jardillier, J. C.; Theophanides, T. *Nucleic Acid Res.* **1982**, *10*, 3803.
(4) (a) Pietronigro, D.; Seligman, M. L.; Demopaulos, H. B. *Physiol. Chem. Phys.* **1979**, *11*, 405. (b) Kleyer, D. L.; Koch, T. H. *J. Am. Chem. Soc.* **1983**, *105*, 5911.
(5) Arcamone, F.; Cassinelli, J.; DiMatteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigevani, A., Clardy, J.; McCabe, T. *J. Am. Chem. Soc.* **1980**, *102*, 1462.
(6) Arcamone, F.; Bernardi, L.; Giardino, P.; Patelli, B.; DiMarco, A.; Casazza, A. M.; Pratessi, G.; Reggiani, P. *Cancer Treat. Rep.* **1976**, *60*, 829.
(7) Umezawa, H.; Takahashi, Y.; Kinoshita, M.; Naganawa, H.; Tatsuta, K.; Takeuchi, T. *J. Antibiot.* **1980**, *33*, 1581.
(8) Kimura, Y.; Suzuki, M.; Matsumoto, T.; Abe, R.; Terashima, S. *Chem. Lett.* **1984**, 501.
(9) Dominguez, D.; Ardecky, R. J.; Cava, M. P. *J. Am. Chem. Soc.* **1983**, *105*, 1608 and references cited therein.
(10) Hauser, F. M.; Baghdanov, V. M. *Tetrahedron* **1984**, *80*, 4719 and references cited therein.
(11) (a) Rao, A. V. R.; Deshpande, V. H.; Ravichandran, K.; Rao, B. R. *Synth. Commun.* **1963**, *13*, 1219. (b) Deshpande, V. H.; Ravichandran, K.; Rao, B. R. *Synth. Commun.* **1984**, *14*, 477.
(12) Penco, S.; Angelucci, F.; Ballabio, M.; Barchielli, G.; Suarato, A.; Vanotti, E.; Vigevani, A.; Arcamone, F. *Tetrahedron* **1984**, *40*, 4677.
(13) Kraus, G. A.; Pezzanite, J. O. *J. Org.* Chem. **1982**, *47*, 4337. Several further reactions of this diester leading to a more advanced intermediate were mentioned briefly, although experimental details were not recorded.
(14) Elbs, K.; Emich, H. *Chem. Ber.* **1887**, *20*, 1361. The slow addition of *o*-xylene to the mixture of phthalic anhydride and $AlCl_3$ was carried out at −20 °C, rather than at 0–5 °C. The mixture was then stirred at −20 °C for a futher 2 h before warming to 0 °C. The lower temperature employed prevented the formation of tarry products.
(15) Fairborne, A. *J. Chem. Soc.* **1921**, *119*, 1573.
(16) Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikantham, M. V.; Cava, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 1994.

0022-3263/86/1951-2044$01.50/0

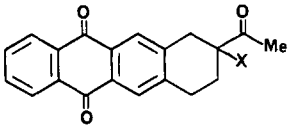
best achieved by the use of elemental bromine under photochemical conditions.



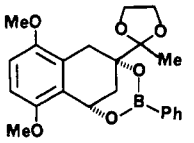
12



13



14 X = H
15 X = Br
16 X = OH



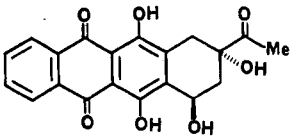
17

Conversion of 13 to the tetracyclic ketone 14 was carried out by dehalogenating it to a transient *o*-quinodimethane in the presence of a large excess of methyl vinyl ketone. Our initial preparations of 14 were obtained using zinc dust as the debrominating agent, but the yields of the desired product were highly erratic and usually very low. Replacement of the zinc by sodium iodide gave far more satisfactory results, as in the case of the 4-demethoxydaunomycinone series;[16] yields of about 60% were obtained from pure dibromide 13. It was soon found, however, that the isolation of crystalline 13 was not necessary and that ketone 14 could be prepared directly from 12 in multigram quantities in 65% overall yield.

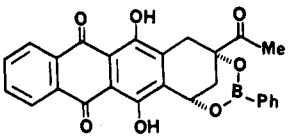
Conversion of 14 to its 9-hydroxy derivative 16 was achieved in 77% yield by a simple two-step procedure. Thus, selective bromination of 14 by cupric bromide in hot chloroform–ethyl acetate afforded the 9-bromo ketone 15. Reaction of 15 with cold dilute sodium hydroxide led to a clean conversion to the corresponding hydroxy ketone 16 in 85% yield by a carbonyl-participating hydrolysis mechanism.[18]

The introduction of a 7-cis hydroxyl group into a 7-deoxyanthracycline has been a traditionally troublesome step in anthraquinone synthesis. Mixtures of 7-cis and 7-trans isomers are always obtained. Tedious chromatographic separations are always required, as well as partial recycling of the trans isomer by acid-catalyzed processes which can also lead to unwanted naphthacenes.[19]

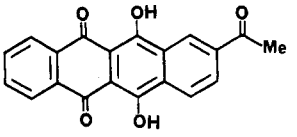
The elegant studies of Hassall and co-workers have shown that the stable benzeneboronate 17 may serve as an intermediate in the synthesis of 4-demethoxydaunomycinone (6).[20,21] This work suggested to us that mixtures of *cis*- and *trans*-7,9-dihydroxylated anthracyclinones might be funneled over completely to the desired cis isomers by way of cyclic benzeneboronates. We first investigated this possibility using a 1:1 mixture of demethoxydaunomycinone (6) and its 7-epimer 18. Treatment of this mixture with benzeneboronic acid in the presence of a catalytic amount of *p*-toluenesulfonic acid gave the benzeneboronate (19) of 6 together with unchanged 18; a complete chromatographic separation of these two compounds is easily achieved due to the relatively nonpolar nature of 19. In our hands, partial epimerization of 18 to



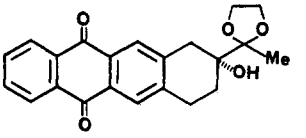
18



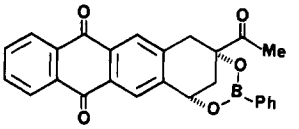
19



20



21



22

6 in trifluoroacetic acid was accompanied by the formation of a considerable amount of the completely aromatic ketone 20; however, when benzeneboronic acid was present the cyclic boronate 19 was produced almost to the exclusion of the aromatized ketone. The 1:1 mixture of 6 and 18 was therefore reacted with benzeneboronic acid in trifluoroacetic acid to give the readily purified 19 in 85% isolated yield. Transboronation of 19 using 1,3-propanediol in acetone gave pure 4-demethoxydaunomycinone in 90% yield.

It was now possible to effect a conversion of the 9-hydroxy ketone 16 into the target molecule 11. Since attempts to brominate 16 directly gave complex mixtures, it was converted to its ethylene ketal 21 prior to bromination. In other anthracyclinone syntheses, it has been observed that ketalization of the 9-acetyl chain improves the regioselectivity of the benzylic bromination at C-7, presumably by steric hindrance.[12] Indeed, reaction of 21 with NBS, followed by treatment with silver acetate and subsequent methanolysis, afforded a mixture of epimeric 7-hydroxy derivatives. This mixture was converted by benzeneboronic acid in trifluoroacetic acid into the cyclic boronate 22 in a process in which concommitant deketalization took place. Deboronation of 22 afforded pure 11, mp 200–203 °C, in 40% overall yield from ketal 21. While the overall yield of 11 from 21 is only modest, we believe that this is due to the known difficulty of brominating an anthracyclinone precursor at C-7 in the absence of an oxygen substituent at C-6.[12]

In conclusion, the highly deoxygenated anthracyclinone 11 has been synthesized for the first time by a regiospecific route from 2,3-dimethylanthraquinone in about 16% overall yield. This synthesis represents a second example of the *o*-quinodimethane route to symmetrically substituted anthracyclinones. It also represents the second example of our simple, new clean methodology for the introduction of the C-9 anthracyclinone hydroxyl. Finally, it illustrates the successful application of the Hassall boronate procedure to the conversion of stereoisomeric C-7,C-9 anthracycline-type diol mixtures to the pure cis isomers. The combination of the last two steps probably illustrates the simplest known protocol for the introduction of the critical *cis*-7,9-diol function into the basic anthracycline system; it should be useful for the upgrading of other earlier reported anthracyclinone syntheses.

Experimental Section

General Methods. Melting points (mp) were determined on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were determined on a V.G. 70-70 Micromass. ^{1}H NMR spectra

(17) King, L. C.; Ostrum, G. K. *J. Org. Chem.* **1964**, *29*, 3459.
(18) Lakshmikantham, M. V.; Ravichandran, K.; Gosciniak, D.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4703.
(19) Kende, A. S.; Rizzi, J. P. *Anthracycline Antibiotics*; Academic Press: New York, (1982); pp 141–166.
(20) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc. Perkin Trans. 1* **1982**, 2229.
(21) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2239.

were recorded on a Bruker 250 FT instrument using Me_4Si as an internal standard and are reported in δ units. Elemental analyses were performed by Galbraith Laboratories. All organic extracts were washed and dried over anhydrous Na_2SO_4 prior to filtration and evaporation.

2,3-Bis(bromomethyl)anthraquinone (13). To a refluxing solution of 2,3-dimethylanthraquinone (**12**) (4.72 g, 0.02 mol) in CCl_4 (200 mL) was added dropwise a solution of bromine (8.0 g, 0.05 mol) in CCl_4 (30 mL) while irradiating with a sun lamp. After 2 h the reaction was stopped, the mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Crystallization of the crude residue from benzene afforded **13** (5.10 g, 65%); mp 249–250 °C; ^1H NMR 4.61 (s, 4 H, 2 × CH_2Br), 7.60–8.30 (m, 6 H aromatic); IR 1670 (C=O); MS (CI), *m/e* (relative intensity) 394 (M^+, 9.90), 312 (38.39), 235 (100), 207 (20.52). Anal. Calcd (CI high resolution mass spectrum) for $C_{16}H_{10}Br_2O_2$: 393.8891. Found 393.9027. Anal. Calcd for $C_{16}H_{10}Br_2O_2$; C, 48.73; H, 2.54; Br. 40.61. Found: C, 48.75, H, 2.54; Br, 40.59.

9-Acetyl-7,8,9,10-tetrahydro-5,12-naphthacenedione (14). Compound **13** (2.0 g, 0.005 mol) dissolved in 30 mL of *N,N*-dimethylacetamide (by warming on a steam bath) was added in a dropwise manner to a preheated solution of methyl vinyl ketone (30 mL), sodium iodide (15.0 g), and *N,N*-dimethylacetamide (10.0 mL) at 70 °C under N_2 atmosphere. After stirring for 4 h at this temperature, the reaction mixture was cooled to room temperature and then poured over crushed ice. The yellow solid was filtered and washed thoroughly with water. Chromatography (SiO_2 70:30 CH_2Cl_2–hexane) followed by recrystallization from methanol gave **14** as light yellow crystals (0.92 g, 60%): mp 159–160 °C, ^1H NMR 1.60 (m, 2 H, CH_2), 2.10 (m, 1 H, CH), 2.27 (s, 3 H, $COCH_3$), 3.00 (m, 4 H, benzylic), 7.71–8.25 (m, 6 H, aromatic); IR 1710 (C=O), 1670 (C=O); MS (CI), *m/e* (relative intensity) 305 (M^+ + H, 100), 304 (54.61), 262 (21.31), 250 (14.4). Anal. Calcd (CI high resolution mass spectrum) for $C_{20}H_{16}O_3$ (M + H): 305.1100. Found 305.1180. Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.45; H, 5.26. Found: C, 78.42; H, 5.25.

9-Acetyl-9-bromo-7,8,9,10-tetrahydro-5,12-naphthacenedione (15). To a refluxing solution of compound **14** (1.0 g, 3.2 mmol) in a 1:1 mixture of $CHCl_3$–EtOAc (50 mL) was added finely powdered $CuBr_2$ (1.40 g, stoichiometric equiv). After 2 h the reaction mixture was cooled, diluted with $CHCl_3$, and washed with H_2O. The organic extract was concentrated, and the residue was crystallized from EtOH–$CHCl_3$ to give **15** as tan colored crystals (1.13 g, 90%): mp 199–201 °C; ^1H NMR 2.25 (m, 2 H, aliphatic), 2.52 (s, 3 H, $COCH_3$), 3.42 (m, 4 H, benzylic), 7.80 (m, 2 H), 8.07 (s, 1 H), 8.10 (s, 1 H), 8.32 (m, 2 H); MS (CI) Br (80), *m/e* (relative intensity) 383 (M^+, 0.92), 306 (16.43), 303 (100), 260 (29.00). Anal. Calcd (CI high resolution mass spectrum) for $C_{20}H_{15}BrO_3$: 383.0130. Found: 383.0280.

9-Acetyl-9-hydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione (16). To a solution of **15** (1.0 g, 2.6 mmol) in THF (30 mL) and H_2O (40 mL) at 0 °C under N_2 atmosphere was gradually added 25 mL (1% w/v) of aqueous NaOH. After the addition was completed, the reaction mixture was warmed to room temperature, stirred for 30 min and acidified with acetic acid. The yellow precipitate was filtered and recrystallized from EtOH–CH_2Cl_2 to give **16** as yellow crystals (0.71 g, 85%): mp 176 °C, ^1H NMR 2.20 (m, 2 H, aliphatic), 2.40 (s, 3 H, $COCH_3$), 3.20 (m, 4 H, benzylic), 3.82 (s, 1 H, 9-OH), 7.80 (m, 2 H), 8.0 (s, 1 H), 8.08 (s, 1 H), 8.32 (m, 2 H); MS (CI), *m/e* (relative intensity) 321 (M^+ + H, 48.96), 277 (100), 261 (28.64), 247 (14.45). Anal. Calcd (CI high resolution mass spectrum) for $C_{20}H_{16}O_4$: (M + H) 321.1129. Found: 321.1130.

4-Demethoxydaunomycinone (6). To a crude mixture of **6** and **18** (approximately in ratio of 1:1) (0.2 g, 5.4 mmol) was added phenylboric acid (80 mg, 0.65 mmol); after cooling to 0 °C, TFA (10 mL) was added. After being stirred at this temperature for 2 h the reaction mixture was gradually warmed to room temperature and stirred for an additional 10 h. The solvent was removed under reduced pressure. The crude residue thus obtained was extracted with methylene chloride, washed thoroughly with 10% $NaHCO_3$ solution and H_2O, and then evaported under reduced pressure. Chromatography (SiO_2, 70:30 CH_2Cl_2–hexane) followed by crystallization from ether–hexane gave **19** as orange crystals (0.120 g, 85%): mp 192–195 °C dec; ^1H NMR 2.30 (m, 2 H, aliphatic), 2.60 (s, 3 H, $COCH_3$), 3.30 (m, 2 H, benzylic), 7.40 (m, 5 H), 7.84 (m, 2 H), 8.34 (m, 2 H), 13.31 (s, 1 H), 13.59 (s, 1 H); MS (CI), *m/e* (relative intensity) 455 (M^+ + H, 100), 454 (90.3), 333 (51.4), 279 (14.3). Anal. Calcd (CI high resolution mass spectrum) for $C_{26}H_{19}BO_7$: (M + H) 455.1310. Found: 455.1325.

The *cis*-benzeneboronate **19**, obtained as above, was dissolved in acetone (10 mL), 1,3 propanediol (0.5 mL) was added under N_2 atmosphere, and the solution was stirred overnight. After removal of solvent under reduced pressure, the gummy residue was triturated with petroleum ether. This petroleum ether extract was discarded and the crude solid that remained was crystallized from $CHCl_3$–MeOH to afford 4-demethoxydaunomycinone (**6**) (150 mg) identical in all respects (mp, ^1H NMR, M^+) with an authentic sample.[9]

9-Acetyl-9-hydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione 13-Ethyleneglycol Ketal (21). A suspension of **16** (1.6 g, 0.005 mol) in benzene (100 mL), ethylene glycol (4.0 mL), and *p*-toluenesulfonic acid (approximately 25 mg) was refluxed for 4 h using a Dean–Stark apparatus. The mixture was cooled, washed with aqueous $NaHCO_3$, and H_2O. Removal of solvent under reduced pressure followed by crystallization (95% EtOH) afforded **21** (1.6 g, 90%): mp 180–182 °C; ^1H NMR 2.20 (m, 2 H, aliphatic), 3.20 (m, 4 H, benzylic), 4.10 (s, 4 H, 2 × CH_2), 7.80 (m, 2 H), 8.00 (s, 1 H), 8.10 (s, 1 H), 8.32 (m, 2 H); MS (CI), *m/e* (relative intensity) 364 (M^+, 40.92), 278 (100), 248 (15.42). Anal. Calcd (CI high resolution mass spectrum) for $C_{22}H_{20}O_5$: 364.1305. Found: 364.1262.

4-Demethoxy-6,11-dideoxydaunomycinone (11). To a refluxing solution of compound **21** (0.2 g, 0.54 mmol) in CCl_4 (15 mL) under N_2 atmosphere were added *N*-bromosuccinimide (0.14 g, 0.81 mmol) and AIBN (10 mg) while irradiating with a sun lamp. After 1 h, the solvent was evaporated and the yellow residue was dissolved in glacial acetic acid (25 mL) and silver acetate (0.2 g) was added in the dark. The mixture was stirred in the dark for 10 h under N_2 and then the solvent was evaporated. Dichloromethane (100 mL) was added to the residue, the mixture was filtered, and the filtrate was washed with 10% $NaHCO_3$ solution, dried, and evaporated to a yellow gum. This was dissolved in MeOH (25 mL) and NaH (50 mg of a 50% dispersion in mineral oil) was added and the mixture was stirred at room temperature for 3 h. After acidifying with acetic acid, the solvent was removed under reduced pressure.

The crude mixture was treated with phenylboric acid (60 mg), cooled to 0 °C, and TFA (10 mL) added. After being stirred at this temperature for 2 h, the reaction mixture was gradually warmed to room temperature and stirred for an additional 10 h. The solvent was removed under reduced pressure. The crude residue thus obtained was extracted with methylene chloride, washed thoroughly with 10% $NaHCO_3$ solution and H_2O, and then evaporated under reduced pressure. Chromatography (SiO_2, 60:40 CH_2Cl_2–hexane) afforded the *cis*-benzeneboronate **21** (100 mg) as a yellow solid [^1H NMR 2.40 (m, 2 H, aliphatic), 2.62 (s, 3 H, $COCH_3$), 3.52 (m, 2 H, benzylic), 7.38 (m, 5 H), 7.82 (m, 2 H), 8.18 (s, 1 H), 8.34 (m, 2 H), 8.40 (s, 1 H)], which on treatment with acetone and 1,3-propanediol as described for the model experiment followed by crystallization from MeOH–THF afforded **11** as pale yellow crystals (70 mg, 40%): mp 200–203 °C dec; ^1H NMR 2.2–2.4 (m, 2 H, aliphatic), 2.41 (s, 3 H, $COCH_3$), 3.10 (d, J = 18 Hz, 10-H ax), 3.37 (d, J = 18 Hz, 10-H eq), 4.08 (d, J = 10 Hz, 7-OH), 4.48 (s, 1 H, 9-OH), 5.03 (bd, J = 9 Hz, 7-H eq), 7.82 (m, 2 H)), 8.08 (s, 1 H), 8.35 (m, 2 H), 8.41 (s, 1 H); MS (CI), *m/e* (relative intensity) 336 (M^+, 1.92), 247 (100). Anal. Calcd (CI high resolution mass spectrum) for $C_{20}H_{16}O_5$: 336.1025. Found: 336.0998.

Acknowledgment. We thank Dr. M. V. Lakshmikantham for a generous gift of the mixture of 4-demethoxydaunomycinone and its 7-epimer. Technical assistance from John Dykins and Roger Powers in the determination of mass spectra is gratefully acknowledged. This work was supported by NIH-CA 30377.

Registry No. **6**, 70005-90-2; **11**, 101402-00-0; **12**, 6531-35-7; **13**, 74214-85-0; **14**, 101401-96-1; **15**, 101401-97-2; **16**, 101401-98-3; **18**, 70005-91-3; **19**, 101470-19-3; **21**, 101401-99-4; **22**, 101402-01-1; methyl vinyl ketone, 78-94-4; phenylboric acid, 98-80-6.