8.10. Found: C, 68.65; H, 8.39.

4β-(2,5β,6,6-Tetramethyl-2-cyclohexenyl)-3(*E*)-buten-2-one (2a,*cis*-α-Irone). The ketone **18a** (35 mg, 0.09 mmol) in dry THF (3 mL) was added to MeONa (30 mg, 0.57 mmol) dissolved in *t*-BuOH (6 mL) at 5 °C under N_2. The mixture was stirred at room temperature for 7 h. The usual workup and chromatography (SiO_2, benzene–AcOEt (10:1)) provided **2a** (16 mg, 86%) as a colorless oil. The synthetic **2a** was homogeneous on VPC (SE-30, 4φ-3m, 170 °C), and its IR and NMR spectra were superimposable with those of the authentic sample (Shinetsu). Similarly, **1** and **2b** were prepared from **17** and **18b** in 84 and 85% yield, respectively. The published spectral data of **1**, **2a**, and **2b** were in agreement with those of the synthetic samples.[19]

Registry No. (±)-**1**, 72074-84-1; (±)-**2a**, 72074-85-2; (±)-**2b**, 72074-86-3; (±)-**5a**, 72049-66-2; (±)-**5b**, 72049-67-3; **6a**, 72049-68-4; **6c**, 56881-52-8; **6d**, 56691-80-6; (±)-**7**, 72049-69-5; (±)-**8a**, 72049-70-8; (±)-**8b**, 72049-71-9; (±)-**8c**, 64418-55-9; (±)-**9a**, 72049-72-0; (±)-**9b**, 72049-73-1; (±)-**10a**, 72049-74-2; (±)-**10b**, 72065-27-1; **11a**, 72049-75-3; **11b**, 72049-76-4; (±)-**17**, isomer 1, 72049-77-5; (±)-**17**, isomer 2, 72049-78-6; (±)-**18a**, isomer 1, 72049-79-7; (±)-**18a**, isomer 2, 72074-87-4; (±)-**18b**, isomer 1, 72074-88-5; (±)-**18b**, isomer 2, 72074-89-6; nerol, 106-25-2; methyl iodide, 74-88-4; propylene oxide, 75-56-9; 4-(2,5,6,6-tetramethyl-2-cyclohexenyl)-4-(phenylsulfonyl)-2-butanol, 72049-80-0.

Methylation and Hydroxylation Studies on Aloe-emodin

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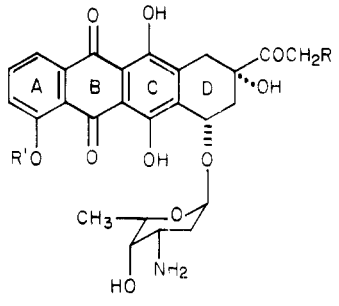
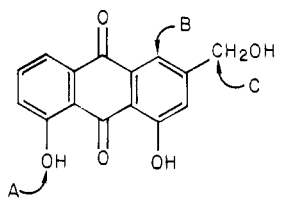
The chemistry of aloe-emodin (**3**) has been explored with a view toward its use as a synthon for the regiospecific synthesis of adriamycin and analogues of it. Routes for satisfactory large-scale monomethyl ether formation at C_8 (**4**) and regiospecific introduction of a phenolic oxygen function at C_4 (**21**) are described. Interesting side reactions were encountered, including an apparent peri O to O acyl wandering reaction during methylation and a reductive debromination reaction during displacement of an aryl bromide by methanolic methoxide.

The anthracycline antibiotics adriamycin (doxorubicin) (**1**) and daunomycin (**2**) are clinically effective antitumor



1, R = OH, R^1 = CH_3
2, R = H, R^1 = CH_3



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agents of considerable contemporary interest.[1] Despite their gratifying spectrum, potency, and clinical acceptance, they are not perfect drugs because of their costliness and toxicity and the resistance which is developed by some cell lines. As a consequence, there have been numerous attempts to solve one or more of these problems by the chemical synthesis of suitable aglycones.[1,2]

Many of the syntheses published to date suffer at a fairly advanced stage from a lack of regiospecificity in joining the AB and CD or ABC and D rings because of the inherent symmetry of ring C. The regiospecificity problem can be overcome, and the production of novel analogues can be achieved, in principle, through the use of starting materials which incorporate at the outset as many asymmetric features of the final target antibiotics as possible. These considerations have led to a considerable recent resurgence of interest in the chemistry of anthraquinones.[3-14]

One of our approaches to anthracyclines has been to explore the chemistry of aloe-emodin (**3**), readily available from oxidation of aloin, a *C*-glycoside present in substantial quantity in aloes, the dried juice of the leaves of various succulent tropical plants of the family Lilaceae. This material is available inexpensively in quantity because of its venerable medicinal use as a carthartic. Three essential problems must be addressed successfully if aloe-emodin is to be used for adriamycin synthesis: (A) one must be able to methylate selectively the phenolic OH group in the future A ring, (B) one must introduce a phenolic OH group into the future C ring, and (C) one must add additional carbons to the benzyl alcohol moiety such that the future D ring can be assembled and still retain suitable functionality for completion of the synthetic sequence. Some of our experiences in finding solutions to problems A and B are reported here.

Results

A. Monomethylation of Aloe-emodin. The two phenolic hydroxyls of aloe-emodin are of similar reactivity so that direct methylation with either Me_2SO_4–K_2CO_3 or, less effectively, with diazomethane, when stopped at the monomethylation stage, produces a nearly equimolar

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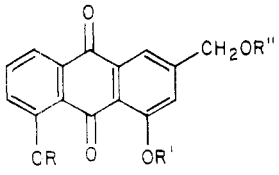
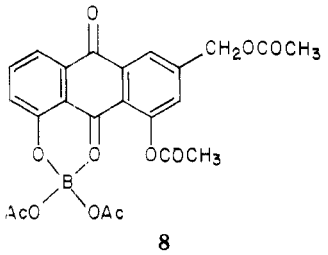
mixture of 4 and 5. Convenient separation was achieved



4, R = CH_3, R′ = R″ = H
5, R′ = CH_3, R = R″ = H
6, R = CH_3, R′ = R″ = $COCH_3$
7, R′ = CH_3, R = R″ = $COCH_3$
10, R = R″ = $COCH_3$, R′ = H
11, R′ = R″ = $COCH_3$, R = H

by diacetylation to 6 and 7 followed by fractional crystallization to give the pure individual isomers. Mild base or acid hydrolysis furnished pure samples of the desired ether 4 and its isomer, 5. The structure of 4 was proven by permanganate oxidation to 3-methoxyphthalic acid.

An attempt to improve the regiospecificity of this process by the use of boroacetic anhydride produced isomeric boroacetates 8 and 9 as expected.[15] Quenching the re-



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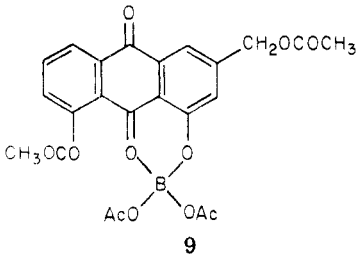

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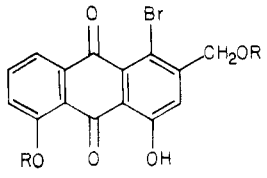
action with water produced a separable mixture of diacetates 10 and 11 in nearly equal proportions. Treatment of either diacetate 10 or 11 with Me_2SO_4–K_2CO_3, however, led to the identical mixture of isomeric ester ethers 6 and 7 with undesired isomer 7 being slightly favored. While not apparently previously encountered among anthraquinones, a similar "acetyl wandering" phenomenon has occasional precedent among naphthoquinones.[15-19]

Thus, despite its lesser elegance, the direct methylation procedure with recycling of the wrong isomer proved the most practical method for large-scale work.

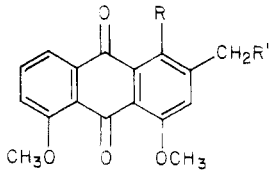
B. Introduction of a Phenolic Hydroxyl Group at Position 4 of Aloe-emodin. Direct hydroxylation of aromatic rings is difficult to accomplish in deactivated systems such as 3.[20] Such techniques as Fremy's salt oxidation,[21] use of thallic trifluoroacetate–lead tetraacetate,[22] the Bonn–Schmidt reaction,[23] and manganese dioxide–sulfuric acid[24] oxidations failed in our hands due to extensive decomposition or unacceptable yields.

Nucleophilic aromatic displacement reactions not only seemed feasible but had ample and venerable precedent in the anthraquinone literature.[25-28] To apply this concept, we found it necessary to develop a method of brominating aloe-emodin regiospecifically at C_4. It was hoped that the increased activation of a phenolic OH group as compared to an OAc group would be sufficient to lead to regiospecific bromination. The convenient availability of diacetate 10 from the boroacetate reaction allowed a test of this hypothesis.

Reaction of diacetate 10 with bromine in acetic acid containing acetamide did produce exclusively the desired monobromide 12 in 97% yield. The position of the bro-



12, R = Ac
13, R = H

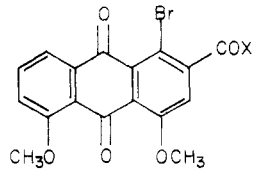


14, R = Br, R′ = OH
15, R = H, R′ = OH

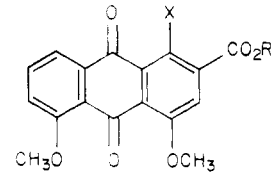
mine atom was clear from the ^1H NMR spectrum in which the C_2 proton resonated as a singlet at δ 7.17 and H_{5-7} showed a typical ABM pattern. Hydrolysis of the ester groups proceeded in 99% yield to give 13, and methylation in the standard way gave an 81% yield of ether 14.

Interestingly, attempts to replace the bromo function of 18 by an oxygenated moiety by refluxing 14 in a sodium methoxide/methanol solution for 9 h produced the debromo compound 15. Heating 13 with $NaOCH_3$ in a sealed tube at 140–150 °C for several hours produced aloe-emodin (3). While uncommon, such dehalogenations under basic conditions are precedented.[29,30] The mechanism of this curious reaction is obscure and deserves study.

Following up the hypothesis that the desired reaction could be brought about by further activation of the bromide toward displacement, we oxidized alcohol 14 to acid 16 with Jones reagent. Stirring 16 with $NaOCH_3$ in hexamethylphosphorous triamide led to bromide loss as before to give 17.



16, X = OH
18, X = OCH_3



17, R = X = H
19, R = CH_3, X = OCH_3
20, R = H, X = OH
21, R = CH_3, X = OCH_3

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Esterification to 18 followed by the same treatment gave variable results, the best being a 50% conversion to the desired product **19**. More commonly, considerable reduction to **17** was encountered. On the other hand, heating acid **16** with calcium hydroxide and copper powder in a sealed tube at 200 °C gave the desired hydroxylated quinone **20** in satisfactory yield (65%). Etherification led to **22**.

We are presently engaged in application of these findings to anthracycline synthesis. Progress toward a solution to problem C and an alternate solution to problem B are described in a companion paper.

Experimental Section

8-Hydroxy-3-(hydroxymethyl)-1-methoxy-9,10-anthraquinone (5) and 1-Hydroxy-3-(hydroxymethyl)-8-methoxy-9,10-anthraquinone (4) by Direct Methylation of Aloe-emodin. To a suspension of 0.54 g of aloe-emodin[32] in 40 mL of acetone and 20 mL of dimethylformamide were added 0.25 g of dimethyl sulfate and 0.27 g of potassium carbonate, and the mixture was refluxed for 16 h. Another 0.25 g of dimethyl sulfate and 0.27 g of potassium carbonate were then added. The reaction was hastened by adding 2 drops of dry methanol and refluxing continued (3 h) until the disappearance of the starting material. The reaction mixture was cooled, diluted with 50 mL of water, and extracted with chloroform. The chloroform extract was washed with water (three times) and brine and evaporated to yield a dark reddish residue. This was redissolved in chloroform and boiled with charcoal and filtered. Evaporation of the filtrate furnished 0.45 g of yellow crystals of a mixture of monomethyl ethers of aloe-emodin mixed with a small amount of dimethyl ether. Chromatography of the mixture of methyl ethers on silica gel failed to separate the isomers.

Consequently, the mixture of monomethyl ethers (0.8 g) was dissolved in pyridine (10 mL), acetic anhydride (20 mL) was added, and the mixture was left standing overnight at room temperature. The pyridine and acetic acid were distilled off under vacuum, and the residue was triturated with water. The suspension of yellow solid was filtered and air-dried (0.8 g). Crystallization from benzene afforded one of the diacetylmonomethylaloe-emodin isomers in practically pure form (0.123 g). Recrystallization from benzene furnished a pure sample which was proven to be 3-(acetoxymethyl)-8-acetoxy-1-methoxyanthraquinone (**7**): mp 224–225 °C; NMR ($CDCl_3$) δ 2.20 (3 H, s, CH_2OCOCH_3), 2.50 (3 H, s, C_8 $OCOCH_3$), 4.03 (3 H, s, C_1 OCH_3), 5.23 (2 H, s, Ar CH_2), 7.3 (1 H, d, J = 2 Hz, Ar H_1), 7.40 (1 H, dd, J = 8, 2 Hz, Ar H_5), 7.75 (1 H, t, J = 8 Hz, Ar H_6), 7.89 (1 H, d, J = 2 Hz, Ar H_2), 8.22 (1 H, dd, J = 8, 2 Hz, Ar H_7); IR (KBr) 3450, 1755, 1735, 1670, 1605 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.57; H, 3.85. Found: C, 65.54; H, 4.05.

The mother liquor, on standing, deposited some crystals which were filtered off and washed with benzene (65 mg). Recrystallization from benzene afforded a pure sample of 1-acetoxy-3-(acetoxymethyl)-8-methoxyanthraquinone (**6**), mp 186–188 °C. The mother liquor was a mixture in which the lower melting isomer predominated. The following physical data were recorded for 1-acetoxy-3-(acetoxymethyl)-8-methoxyanthraquinone: NMR ($CDCl_3$) δ 2.13 (3 H, s, CH_2OCOCH_3), 2.46 (3 H, s, Ar $OCOCH_3$), 3.98 (3 H, s, C_8 OCH_3), 5.21 (2 H, s, Ar CH_2), 7.3 (1 H, dd, J = 2, 8 Hz, Ar H_5), 7.35 (1 H, d, J = 2 Hz, Ar H_4), 7.66 (1 H, t, J = 8 Hz, Ar H_6), 7.88 (1 H, dd, J = 8, 2 Hz, Ar H_7), 8.11 (1 H, d, J = 2 Hz, Ar H_2); IR (KBr) 3480, 1765, 1735, 1665, 1610, 1590 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.57; H, 3.85. Found: C, 65.62; H, 4.10.

1-Acetoxy-3-(acetoxymethyl)-8-methoxy-9,10-anthraquinone (120 mg) was refluxed in methanol (30 mL) with concentrated hydrochloric acid (10 mL) and water (10 mL) for 3 h. The solvents and acid were evaporated off under vacuum, and the residue was crystallized from chloroform to obtain **4** as reddish yellow crystals (65 mg): mp 215–216 °C; IR (KBr) 3520–3460, 1670, 1635, 1585 cm^{-1}; NMR ($CDCl_3$, Me_2SO) δ 3.08 (1 H, s, CH_2OH, exchanges with D_2O), 4.03 (3 H, s, C_8 OCH_3), 4.71 (2 H, s, Ar CH_2), 7.2–7.9 (5 H, complex multiplet, Ar H), 12.83 (1 H, s, Ar OH).

Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.44; H, 4.16.

8-Acetoxy-3-(acetoxymethyl)-1-methoxy-9,10-anthraquinone (100 mg) was refluxed with 30 mL of methanol, 10 mL of concentrated HCl, and 10 mL of water for 3 h. The solvents were evaporated in vacuo. The residue was taken up in methanol and evaporated again to ensure the complete removal of HCl and was crystallized from chloroform to furnish yellow crystals (60 mg) of **5**: mp 227–228 °C; IR (KBr) 3540–3440, 1675, 1640, 1605 cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6) δ 3.08 (1 H, s, CH_2OH, exchanges with D_2O), 4.02 (3 H, d, C_1 OCH_3), 4.76 (2 H, br s, Ar CH_2), 7.1–7.8 (5 H, complex multiplet, Ar H), 12.80 (1 H, s, Ar OH).

Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.54; H, 4.20.

Oxidation of 1-Hydroxy-3-(hydroxymethyl)-8-methoxy-9,10-anthraquinone (4). A sample (0.03 g) of **4** was dissolved in 1 N KOH solution, and 5% $KMnO_4$ solution was added dropwise while the reaction mixture was heated on a steam bath with gentle swirling from time to time. Periodic addition of the $KMnO_4$ solution was continued till a drop of the reaction mixture showed the presence of excess permanganate on a filter paper. The reaction mixture was heated overnight. Excess permanganate was later destroyed with methanol, and the MnO_4 precipitates were dissolved by adding a small amount of sodium sulfite to the solution made acidic (pH 1) by concentrated sulfuric acid. To the resulting solution was added a saturated solution of sodium chloride and this was extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated to yield 3-methoxyphthalic acid, mp 164–166 °C (lit.[33] mp 159–160 °C). An authentic sample for comparison was prepared by methylation of juglone followed by permanganate oxidation, mp 163–165 °C. The mixture melting point was undepressed, and the spectra of the two samples and their methyl esters were identical.

8-Acetoxy-3-(acetoxymethyl)-1-hydroxy-9,10-anthraquinone (10) from Boroacetic Anhydride Reaction of Aloe-emodin. Boric acid (5 g) was dissolved in acetic anhydride (100 mL) by heating the mixture on a steam bath for about 0.5 h. Aloe-emodin (5 g) was added to it, and the mixture was heated on the steam bath for 6 h and left standing overnight at room temperature. It was poured into water (ca. 300 mL) and warmed to hydrolyze the acetic anhydride. The mixture was then cooled in ice, and the yellow solid that separated was filtered (6.3 g). Crystallization from chloroform–benzene–petroleum ether furnished 2.5 g of yellow crystals which was practically pure 8-acetoxy-3-(acetoxymethyl)-1-hydroxyanthraquinone (**10**): mp 194–196 °C; NMR ($CDCl_3$) δ 2.16 (3 H, s, CH_2OCOCH_3), 2.48 (3 H, s, C_8 $OCOCH_3$), 5.18 (2 H, br s, Ar CH_2), 7.25 (1 H, dd, J = 2, 0.5 Hz, Ar H_2), 7.41 (1 H, dd, J = 8, 2 Hz, Ar H_5), 7.74 (1 H, dd, J = 2, 0.5 Hz, Ar H_4), 7.81 (1 H, t, J = 8 Hz, Ar H_6), 8.28 (1 H, dd, J = 8, 2 Hz, Ar H_7); IR (KBr) 3450, 1772, 1740, 1680, 1635, 1600 cm^{-1}.

Anal. Calcd for $C_{19}H_{14}O_7$: C, 64.40; H, 3.98. Found: C, 64.61; H, 3.89.

1-Acetoxy-3-(acetoxymethyl)-8-hydroxy-9,10-anthraquinone (11). The mother liquor from the crystallization of **10**, on concentration and addition of petroleum ether, deposited 2.6 g of a yellowish black crystalline solid. NMR showed that it is substantially the other isomer, viz., 1-acetoxy-3-(acetoxymethyl)-8-hydroxyanthraquinone (**11**). Repeated crystallization from chloroform–petroleum ether furnished the pure isomer: mp 190–191 °C; NMR ($CDCl_3$) δ 2.16 (3 H, s, CH_2OCOCH_3), 2.43 (3 H, s, Ar $OCOCH_3$), 5.23 (2 H, br s, Ar CH_2), 7.25 (1 H, dd, J = 2, 8 Hz, Ar H_7), 7.36 (1 H, dd, J = 2, 0.5 Hz, Ar H_4), 7.61 (1 H, t, J = 8 Hz, Ar H_6), 7.78 (1 H, dd, J = 2, 8 Hz, Ar H_5), 8.16 (1 H, dd, J = 2, 0.5 Hz, Ar H_2), 12.5 (1 H, s, C_8 OH); IR (KBr) 3460, 1775, 1740, 1672, 1630, 1607 cm^{-1}.

Anal. Calcd for $C_{19}H_{14}O_7$: C, 64.40; H, 3.98. Found: C, 64.68; H, 3.87.

Methylation of 1-Acetoxy-3-(acetoxymethyl)-8-hydroxy-9,10-anthraquinone (11). Diacetate **11** (2 g) was refluxed in

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acetone (100 mL) with dimethyl sulfate (2.5 g) and potassium carbonate (5 g) for 16 h. The acetone was distilled off under vacuum, and the residue was suspended in water. The brown precipitate was collected by filtration and washed with water. The precipitate weighed 2.2 g. On crystallization from benzene it afforded one crop of crystals weighing 0.8 g which was found to be identical with 8-acetoxy-3-(acetoxymethyl)-1-methoxy-9,10-anthraquinone (**7**) by TLC and NMR; mp 224–225 °C. The mother liquors were concentrated and allowed to crystallize to furnish 0.42 g of an isomer which was characterized as 1-acetoxy-3-(acetoxymethyl)-8-methoxy-9,10-anthraquinone (**6**) by comparison with an authentic sample by TLC, NMR, and melting point.

Methylation of 8-Acetoxy-3-(acetoxymethyl)-1-hydroxy-9,10-anthraquinone (10). Diacetate **10** (0.26 g) was refluxed in acetone (30 mL) with potassium carbonate (0.28 g) and dimethyl sulfate (0.14 g) for 12 h. The acetone was distilled off, and the residue was suspended in water. The precipitate was filtered off and dried to give 0.27 g of a brown powder. This material, without any further purification, was hydrolyzed with aqueous methanolic hydrochloric acid, and the product was chromatographed on silica gel. From the different chromatographic fractions containing varying proportions of the mixture of monomethyl ethers of aloe-emodin, both the monomethyl ethers were crystallized. 1-Hydroxy-3-(hydroxymethyl)-8-methoxy-9,10-anthraquinone (**4**) melted at 215–216 °C, and its isomer (**5**) melted at 227–228 °C. Both had NMR spectra identical with those of the compounds which were prepared by the method described previously. The quantities isolated in this experiment (25 mg of **4** and 20 mg of **5**) probably do not represent their true proportion in the reaction mixture. Determination of the precise ratio is very difficult because of extensive chromatography overlap in every system tried.

Similar mixtures of **4** and **5** were obtained upon methylation of **10** or **11** with methyl iodide in *dry* DMF with silver oxide.

8-Acetoxy-3-(acetoxymethyl)-4-bromo-1-hydroxy-9,10-anthraquinone (12). 8-Acetoxy-3-(acetoxymethyl)-1-hydroxy-9,10-anthraquinone (**10**; 1.0 g) was dissolved in 40 mL of chloroform and 15 mL of glacial acetic acid. Acetamide (1.9 g) was added to the solution. Bromine (1.9 mL) in 10 mL of glacial acetic acid was added, and the suspension was refluxed for 9 h while being stirred with a mechanical stirrer. At the end of the reaction, the chloroform solution was washed with water, dried over Na_2SO_4, and evaporated to yield 1.19 g (97%) of **12**. Crystallization from glacial acetic acid yielded bright yellow needle-shaped crystals: mp 207–209 °C; NMR ($CDCl_3$) δ 2.2 (3 H, s, $OCOCH_3$), 2.45 (3 H, s, $OCOCH_3$), 5.2 (2 H, s, Ar CH_2O), 7.17 (1 H, s, Ar H_2), 7.33 (1 H, dd, J = 2, 8 Hz, Ar H_5), 7.74 (1 H, t, J = 8 Hz, Ar H_6), 8.18 (1 H, dd, J = 2, 8 Hz, Ar H_7), 13.25 (1 H, s, Ar OH); mass spectrum m/e 434, 432 (M^+), 391, 389 ($M^+ - COCH_3$), 353 ($M^+ - Br$), 349, 347 ($M^+ - 2\ COCH_3$), 333, 331, etc.; IR (KBr) 1770, 1750, 1675, 1640, 1230, 1180 cm^{-1}, etc.; UV λ_{max} (EtOH) 435 nm (log ϵ 3.66), 4.12 (3.81), 395 (sh, 3.79), 285 (4.00), 265 (sh, 4.36), 257 (4.42), 247 (4.42), 230 (4.35).

Anal. Calcd for $C_{19}H_{13}BrO_7$: C, 52.67; H, 3.02. Found: C, 52.30; H, 2.98.

4-Bromo-1,8-dihydroxy-3-(hydroxymethyl)-9,10-anthraquinone (13). A suspension of 3.6 g of the acetate **12** in MeOH (250 mL) and hydrochloric acid (12.5 mL) was refluxed overnight. At the end of the reaction, a part of the methanol was evaporated, and the resulting product was collected by filtration and dried to yield 2.60 g of **13**. The filtrate was evaporated, and the resulting residue was dissolved in $CHCl_3$ with a small amount of methanol. This solution was washed with water, dried over Na_2SO_4, and evaporated. The combined yield was 98.6%. Crystallization from acetic acid gave shining bright crystals of quinone **13**: mp 228–229 °C; NMR (Me_2SO) δ 4.5 (2 H, s, Ar CH_2O), 7.16–7.8 (4 H, m, Ar H), 12.45 (2 H, s, Ar OH); IR (KBr) 3300–3600, 2870–3000, 1665, 1615, 1590, 1255, 1205, 1130 cm^{-1}, etc.; mass spectrum m/e 350, 348 (M^+), 332, 330 ($M^+ - H_2O$), 322, 320 ($M^+ - CO$), 267 ($M^+ - Br$); UV λ_{max} (EtOH) 452 nm (sh, log ϵ 3.86), 433 (3.96), 412 (sh, 3.89), 292 (3.87), 258 (4.28), 228 (4.42).

Anal. Calcd for $C_{15}H_9BrO_5$: C, 51.60; H, 2.59. Found: C, 51.57; H, 2.48.

4-Bromo-1,8-dimethoxy-3-(hydroxymethyl)-9,10-anthraquinone (14). Compound **13** (2.0 g) was suspended in 130 mL of acetone and 30 mL of dioxane, and potassium carbonate (10.0 g) and dimethyl sulfate (3 mL) were added. The suspension was stirred mechanically while refluxing overnight. The resulting suspension was filtered and the residue was washed twice with hot ethyl acetate. The acetone solution was concentrated and added to the ethyl acetate washings. The combined solution was washed with 5% NaOH solution and water. After being dried over Na_2SO_4, the solvent was removed to yield 1.73 g of ether **14** (81%). Crystallization from $CHCl_3$–MeOH yielded needle-shaped crystals: mp 229–232 °C; NMR (Me_2SO) δ 3.85 (3 H, s, Ar OCH_3), 3.90 (3 H, s, Ar OCH_3), 4.5 (2 H, s, Ar CH_2O), 7.6–8.15 (4 H, m, Ar H); IR (KBr) 3500, 2950, 1670, 1575, 1315, 1275, 1230 cm^{-1}; mass spectrum m/e 378, 376 (M^+), 363, 361 ($M^+ - CH_3$), 360, 358 ($M^+ - H_2O$), 348, 346 ($M^+ - 2\ CH_3$), 347, 345 ($M^+ - OCH_3$), 316, 314 ($M^+ - 2\ OCH_3$), etc.; UV λ_{max} (EtOH) 375 nm (log ϵ 3.80), 280 (sh, 4.08), 261 (4.50).

Anal. Calcd for $C_{17}H_{13}BrO_5$: C, 54.13; H, 3.47. Found: C, 54.18; H, 3.39.

1,8-Dimethoxy-3-(hydroxymethyl)-9,10-anthraquinone (15) from 14. Sodium (0.7 g) was dissolved in 40 mL of dry methanol, and 0.13 g of bromo compound **14** was added. After being stirred at room temperature for 1 h, followed by refluxing for 9 h, the suspension was allowed to stand overnight at room temperature. It was diluted with water and extracted once with benzene and several times with chloroform. The combined organic layer was evaporated to yield 0.08 g of product. Separation of the products by preparative TLC using $CHCl_3$/EtOAc (9:1) led to isolation of small quantities of starting material (**14**) and debromo compound **15**, with compound **15** predominating. Compound **15** was chromatographically and spectroscopically identical with a sample prepared by direct methylation of aloe-emodin (see below).

1,8-Dimethoxy-3-(hydroxymethyl)-9,10-anthraquinone (15) from Aloe-emodin. Aloe-emodin (10 g) was suspended in 650 mL of acetone and 150 mL of dioxane. Potassium carbonate (50 g) was added to the suspension, and the resulting mixture was stirred with a mechanical stirrer. Dimethyl sulfate (15 mL) was added, and the reaction mixture was allowed to reflux overnight. At the end of the reaction, a residue was removed by filtration. Hot acetone treatment of the residue followed by evaporation of the filtrates gave crude product. The latter was stirred in water to decompose the dimethyl sulfate and filtered, and the product was dried to yield 8.5 g of crude **15** which, on crystallization from MeOH/$CHCl_3$, yielded 55% of bright yellow needles: mp 227–229 °C; NMR ($CDCl_3$, CD_3OD) δ 4.0 (6 H, s, OCH_3), 4.7 (2 H, s, Ar CH_2), 7.3–7.8 (5 H, m, Ar H); IR ($CHCl_3$) 3020–2980, 1670, 1605, 1590, 1255 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.39; H, 4.76.

Debromination of 16. Bromo compound **16** (0.2 g) and 0.136 g of sodium methoxide were suspended in 7 mL of methanol in a thick-walled tube. The tube was sealed and heated to 140–150 °C for 6 h. The suspension was acidified and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated to yield aloe-emodin (**3**) as the only detectable product.

4-Bromo-3-carboxy-1,8-dimethoxy-9,10-anthraquinone (16). To 0.7 g of alcohol **14**, dissolved in 145 mL of acetone and a few drops of methanol, was added at regular intervals 100 mL of Jones reagent (8 N). Stirring was continued at room temperature for 6 h. The reaction mixture was allowed to stand overnight at room temperature. Filtration was followed by washing of the residue with ethyl acetate. The combined ethyl acetate solution was washed with water, dried over Na_2SO_4, and evaporated. The product thus obtained was dissolved in saturated $NaHCO_3$ solution, filtered, and acidified with concentrated HCl. The acidified solution was extracted with ethyl acetate, followed by drying over Na_2SO_4 and evaporation to yield 0.64 g (85%) of acid: mp 257–260 °C (from EtOAc); NMR (Me_2SO-d_6) δ 3.95 (6 H, s, Ar OCH_3), 7.4–8.0 (4 H, m, Ar H); mass spectrum m/e 392, 390 (M^+), 377, 375 ($M^+ - CH_3$), 362, 360 ($M^+ - 2\ CH_3$), 361, 359 ($M^+ - OCH_3$), 330, 328 ($M^+ - 2\ OCH_3$), 311 ($M^+ - Br$); IR (KBr) 3200–2600, 1700, 1660, 1570, 1450 (sh), 1420, 1260, 1210 cm^{-1}; UV λ_{max} (EtOH) 370, nm (log ϵ 3.70), 266 (4.28), 223 (4.43).

Methyl 4-Bromo-1,8-dimethoxy-9,10-anthraquinone-3-carboxylate (18). Acid **16** (2.0 g) was suspended in 155 mL of acetone and 30 mL of dioxane. Potassium carbonate (5 g) and dimethyl sulfate (1.5 mL) were added. The suspension was stirred

mechanically while refluxing overnight. It was filtered, and the residue was washed twice with hot ethyl acetate. The solvent was removed to yield 1.86 g of ester (90%): mp 192–194 °C (from chloroform–hexane); NMR ($CDCl_3$) δ 3.90 (3 H, s, Ar OCH_3), 3.95 (3 H, s, Ar OCH_3), 4.05 (3 H, s, Ar CO_2CH_3), 7.0–7.7 (3 H, m, Ar H_5, H_6, H_7), 8.15 (1 H, s, Ar H_2); mass spectrum *m/e* 406, 404 (M^+), 391, 389 ($M^+ - CH_3$), 376, 374 ($M^+ - 2\ CH_3$), 345 ($M^+ - CO_2CH_3$), 325 (M^+ - Br), etc.; IR (KBr) 3600–3200, 3100–2820, 1735, 1665, 1625 (sh), 1575, 1535 (sh), 1355, 1270, 1205 cm^{-1}; UV λ_{max} (EtOH) 380 nm (log ε 3.80), 353 (3.77), 275 (sh, 4.09), 260 (4.35), 228 (4.45).

Anal. Calcd for $C_{18}H_{13}O_6Br$: C, 53.35; H, 3.23. Found: C, 53.00; H, 3.00.

3-Carboxy-1,8-dimethoxy-9,10-anthraquinone (17). Acid **16** (0.15 g) was dissolved in 5 mL of dry HMPA. To this solution was added 0.05 g of sodium ethoxide. The suspension was allowed to stir at 100 °C for 4 h under an N_2 atmosphere and then poured into water, acidified, and extracted with ethyl acetate. The organic layer was washed, dried over Na_2SO_4, and evaporated to yield **17**: mp 278–279 °C (from ethyl acetate); NMR (Me_2SO-d_6) δ 3.95 (6 H, s, OCH_3), 7.6–8.25 (5 H, m, Ar H); mass spectrum *m/e* 312 (M^+), 297 ($M^+ - CH_3$), 282 ($M^+ - 2\ CH_3$), 268 ($M^+ - CO_2$); IR (KBr) 3400–2800, 1730, 1670, 1610, 1590, 1480, 1460 (sh), 1445, 1260, 1285, 1235 cm^{-1}, etc.; UV λ_{max} (EtOH) 389 nm (log ε 3.54), 259 (3.95), 227 (4.17).

1,8-Dimethoxy-4-hydroxy-9,10-anthraquinone-3-carboxylic Acid (20). To 0.5 g of acid **18** was added 2.5 g of $Ca(OH)_2$ suspended in 5 mL of water. Copper powder (0.2 g) was added, and this mixture was heated in a glass-lined stainless-steel bomb at 200 °C for 10 h. After cooling, the suspension was acidified with cold concentrated HCl to give a bright yellow product. After filtration, the product was dissolved in excess chloroform and small amounts of ethyl acetate and methanol. After filtration, the filtrate was washed with water, dried over Na_2SO_4 and evaporated to yield 0.272 g of phenol **20** (65%): mp >300 °C; mass spectrum *m/e* 328 (M^+), 313 ($M^+ - CH_3$), 298 ($M^+ - 2\ CH_3$), 284 ($M^+ - CO_2$), etc.; IR (KBr) 3650–3300, 2930, 1730, 1680, 1625, 1445, 1250; UV λ_{max} (EtOH) 461 nm (sh, log ε 2.88), 434 (3.10), 410 (sh, 3.05), 286 (2.53), 267 (3.76), 258 (3.27), 228 (3.55); NMR (Me_2SO-d_6) δ 3.90 (6 H, s, OCH_3), 7.70–8.20 (4 H, m, Ar H).

Methyl 1,4,8-Trimethoxy-9,10-anthraquinone-3-carboxylate (21). The phenol **20** (0.21 g) was suspended in 30 mL of acetone and 6 mL of dioxane. Potassium carbonate (1 g) and dimethyl sulfate (0.3 mL) were added, and the suspension was stirred while refluxing overnight. It was filtered, and the residue was washed twice with hot ethyl acetate. The combined filtrate was washed with 5% NaOH solution, and after being dried over Na_2SO_4, the solvent was removed to yield 0.19 g of ester **21** (85%): mp 156–157 °C (from chloroform–hexane); NMR ($CDCl_3$) δ 3.90, 3.96, 4.0 (12 H, 3 s, 3 × OCH_3, $COOCH_3$), 7.19 (1 H, dd, *J* = 2, 8 Hz, Ar H_7), 7.56 (1 H, t, *J* = 8 Hz, Ar H_6), 7.76 (1 H, dd, *J* = 2, 8 Hz, Ar H_5), 8.26 (1 H, s, Ar H_2); IR ($CHCl_3$) 2950, 1735, 1675, 1590, 1470, 1340, 1270 cm^{-1}, etc.; mass spectrum *m/e* 357 ($M^+ + 1$), 356 (M^+), 341 ($M^+ - CH_3$), 326 ($M^+ - 2\ CH_3$), 325 ($M^+ - OCH_3$), 311 ($M^+ - 3\ CH_3$), 296 ($M^+ - 4\ CH_3$), etc.; UV λ_{max} (EtOH) 370 nm (log ε 3.62), 260 (4.15), 227 (4.25).

Anal. Calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.52. Found: C, 64.08; H, 4.51.

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Novel Ring Hydroxylation of Aloe-emodin and Further Elaboration to Anthracycline Synthons

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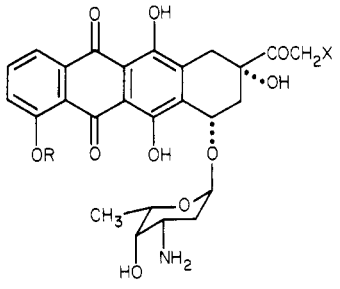
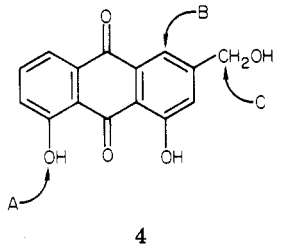
Aloe-emodin (4) has been converted in six steps to 1,4,5-trihydroxy-2-(2,3-dicarboxypropyl)-9,10-anthraquinone (17), a synthon suitable for further regiospecific elaboration into daunomycin–adriamycin analogues. A method for Friedel–Crafts acylation of anthraquinones by reduction to the anthracenone, cyclization, and reoxidation has been developed as a key feature of the synthesis.

Because of their outstanding clinical properties,[1] costliness, and side effects, interest continues unabated in the synthesis of the antitumor antibiotics adriamycin (doxorubicin) (**1**), daunomycin (**2**), and carminomycin (**3**) and novel analogues.

Part of our efforts in this area[3,4] have involved attempts to solve the regiospecificity problem through the use of aloe-emodin (**4**), a readily available natural anthraquinone. We have described previously methods for specific introduction of oxygen at C_4 (**4**, problem B).[4] In this paper we describe an alternate solution to problem B and an elaboration of functionality at the hydroxymethylene function known to be suitable for completion of the synthesis to bioactive anthracyclines (problem C).



1, R = CH_3, X = OH
2, R = CH_3, X = H
3, R = H, X = H



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Results

In our earlier work, we utilized a nucleophilic aromatic displacement reaction to introduce an oxygen function at

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