reactive and photochemically generated singlet oxygen led only to decomposition. However, in a remarkably clean conversion, treatment of **8b** with manganese dioxide in sulfuric acid (0 °C, 35 min) gave a 92% yield of the nitro quinone **9** as bright orange crystals, mp 241–245 °C dec. Catalytic hydrogenation of **9** in methanol (10% palladium/charcoal, 1 atm, 4 h) gave the 3-aminohydroquinone **10** quantitatively as a black solid, which in turn could be diazotized (sodium nitrite, concentrated hydrochloric acid, 0 °C, 30 min) to the orange diazo quinone **11**. Reduction of **11** was accomplished with a large excess of 50% hypophosphorous acid in acetic acid (25 °C, 20 min), which led to some quinone reduction also; the quinone functionality was restored by washing with aqueous basic potassium ferricyanide in the workup. Thus the methoxatin triester **12** was obtained as orange crystals, mp 199–205 °C dec, 82% overall yield from **10**. The triester **12** was saponified by Weinreb's procedure[8] (0.5 M LiOH in 1:1 H_2O–THF, 25 °C, 6 h). After acidification the solution was passed through a C-18 reverse-phase silica cartridge or a column of silanized silica gel, leaving methoxatin behind as a red-orange band at the origin. After being washed with dilute (pH 2) hydrochloric acid, the methoxatin was eluted with methanol–water (7:3) and obtained as a red solid (89% yield) on evaporation.

Spectral data for **1** (^{1}H NMR and UV)[19] are in agreement with those published for native,[3b,18] and synthetic[7,8] methoxatin. In addition, TLC comparison [cellulose, 2% aqueous NH_4OAc–propanol (1:1)] of synthetic **1** with methoxatin synthesized by Weinreb and Gainor[8,18] through a different route proved their identity. Further proof was obtained by converting **1** into its acetone aldol condensation product **2** [NH_4OH (pH 9.0)–acetone (9:1), 25 °C, 30 min]. The material obtained in this way was identical spectroscopically (^{1}H NMR, UV)[8,19] and in reverse-phase HPLC behavior[2c] with the authentic sample,[18] the two also moving together as a sharp peak when mixed.

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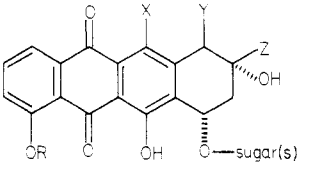
Regiospecific Synthesis of Bicyclic 6-Alkoxy-2-pyrones and Their Use in the Production of Tetracyclic Intermediates for 11-Deoxyanthracycline Synthesis

Summary: A regiospecific approach to the preparation of bicyclic 6-alkoxy-2-pyrones and their utilization in anthracycline synthesis is described.

Sir: Several anthracycline antitumor agents, e.g., adriamycin (**1**) and daunorubicin (**2**), are extensively used today in cancer chemotherapy.[1] Their use in cancer treatment is limited by their severe cumulative cardiotoxicity.[1] In the past few years, several 11-deoxyanthracyclines have been isolated, e.g., aclacinomycin A (**3**) and marcellomycin (**4**), which possess good tumor-inhibitory properties and, more importantly, exhibit much lower cardiotoxicity.[2] Very recently three groups have reported the total synthesis of aklavinone, the aglycon of aclacinomycin A (**3**).[3] We herein communicate our recent work in this area.



1, R = Me; X = OH; Y = H; Z = $COCH_2OH$
2, R = Me; X = OH; Y = H; Z = $COCH_3$
3, R = H; X = H; Y = COOMe; Z = Et
4, R = H; X = H; Y = COOMe; Z = Et

A few years ago, we reported a synthetic approach to this new class of anthracyclines in which juglone (**5**) was added to a 1,1-bisoxygenated diene, namely, a 6-methoxy-2-pyrone **6**, to produce the tricyclic analogue chrysophanol (**7**) as the only product in 62% overall yield.[4] Two further

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(17) Alewood, P. F.; Calder, I. C.; Richardson, R. L. *Synthesis* **1981**, 121.
(18) We thank Professor H. S. Forrest for an authentic sample of the adduct (**2**) of native methoxatin and Professor S. M. Weinreb for a sample of synthetic methoxatin.
(19) Spectral data are as follows. **4c**: ^{1}H NMR ($CDCl_3$) δ 8.57 (1 H, d, J = 1.5 Hz), 8.32 (1 H, d, J = 1.5 Hz), 4.73 (2 H, s), 4.03 (3 H, s), 4.01 (3 H, s). *trans*-**5**: ^{1}H NMR ($CDCl_3$) δ 9.32 (1 H, br s), 8.40 (1 H, d, J = 1.5 Hz), 8.07 (1 H, d, J = 1.5 Hz), 7.64 (1 H, d, J = 16.2 Hz), 7.18 (1 H, s), 7.15 (1 H, s), 7.04 (1 H, d, J = 16.2 Hz), 4.33 (2 H, q, J = 7.0 Hz), 4.03 (3 H, s), 4.00 (3 H, s), 1.38 (3 H, t, J = 7.0 Hz); UV (EtOH) λ_{max} 231 nm, 327. *cis*-**5**: ^{1}H NMR (Me_2SO-d_6) δ 12.21 (1 H, br s), 8.53 (1 H, br s), 8.22 (1 H, d, J = 1.5 Hz), 8.05 (1 H, d, J = 1.5 Hz), 7.41 (1 H, br s), 6.73 (1 H, d, J = 13.4 Hz), 6.48 (1 H, d, J = 13.4 Hz), 4.27 (2 H, q, J = 7.0 Hz), 4.08 (3 H, s), 3.94 (3 H, s), 1.30 (3 H, t, J = 7.0 Hz); UV (EtOH) λ_{max} 325 nm. **6**: ^{1}H NMR ($CDCl_3$) δ 12.46 (1 H, br s), 8.89 (1 H, s), 8.02 (2 H, s), 7.35 (1 H, d, J = 2.0 Hz), 4.47 (2 H, q, J = 7.0 Hz), 4.17 (3 H, s), 4.12 (3 H, s), 1.46 (3 H, t, J = 7.0 Hz), in benzene-d_6 the singlet at δ 8.02 disappears and two doublets evolve [δ 8.05 (1 H, d, J = 9.0 Hz), 7.59 (1 H, d, J = 9.0 Hz)]; UV (EtOH) λ_{max} 212 nm, 274, 306, 378. **7**: ^{1}H NMR (Me_2SO-d_6) δ 8.90 (1 H, s), 8.69 (1 H, s), 4.48 (2 H, q, J = 7.0 Hz), 4.12 (3 H, s), 3.99 (3 H, s), 1.40 (3 H, t, J = 7.0 Hz); UV (EtOH) λ_{max} 261 nm, 307, 413. **8b**: ^{1}H NMR ($CDCl_3$–CD_3OD) δ 8.92 (1 H, s), 7.67 (1 H, s), 4.52 (2 H, q, J = 7.0 Hz), 4.19 (3 H, s), 4.10 (3 H, s), 1.48 (3 H, t, J = 7.0 Hz); UV (EtOH) λ_{max} 215 nm, 261, 330, 412. **9**: ^{1}H NMR ($CDCl_3$–CD_3OD) δ 8.80 (1 H, s), 4.42 (2 H, q, J = 7.0 Hz), 4.17 (3 H, s), 4.08 (3 H, s), 1.36 (3 H, t, J = 7.0 Hz); UV (EtOH) λ_{max} 243 nm, 280, 344. **10**: ^{1}H NMR ($CDCl_3$) δ 12.56 (1 H, br s), 8.83 (1 H, s), 6.10 (2 H, br s), 4.38 (2 H, d, J = 7.0 Hz), 4.13 (3 H, s), 4.03 (3 H, s), 1.41 (3 H, t, J = 7.0 Hz); UV (EtOH) λ_{max} 249 nm, 340, 430. **11**: IR (CH_2Cl_2) 2225 cm^{-1}. **12**: ^{1}H NMR ($CDCl_3$) δ 12.90 (1 H, s), 8.83 (1 H, s), 7.42 (1 H, d, J = 2.0 Hz), 4.30 (2 H, q, J = 7.0 Hz), 4.17 (3 H, s), 4.07 (3 H, s), 1.42 (3 H, t, J = 7.0 Hz); UV (CH_3OH) λ_{max} 250 nm, 313, 377. **1**: ^{1}H NMR (CD_3OD) δ 8.73 (1 H, s), 7.27 (1 H, s); UV (H_2O, pH 5) λ_{max} 250 nm, 327. **2**: ^{1}H NMR (Me_2SO-d_6) δ 13.42 (1 H, br s), 8.42 (1 H, s), 7.16 (1 H, d, J = 2.3 Hz), 4.04 (1 H, d, J = 17.0 Hz), 3.61 (1 H, d, J = 17.1 Hz), 2.03 (3 H, s); UV (H_2O) λ_{max} 250 nm, 320, 363. Acceptable elemental analyses were obtained for compounds **4c–9**; high-resolution mass spectra of **10** and **12** were consistent with their formulations.

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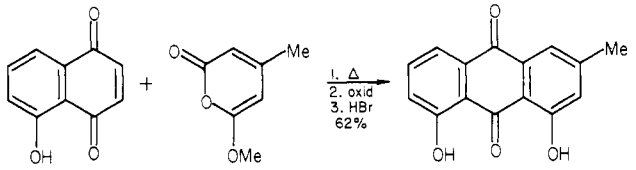
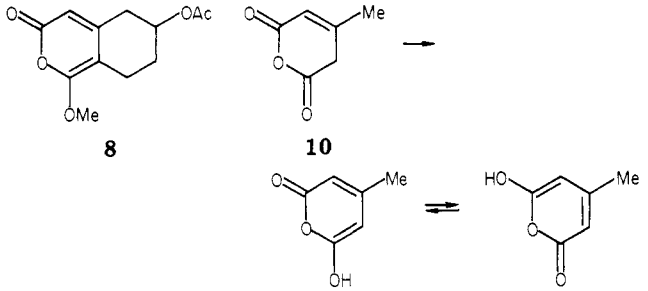


5 6 7

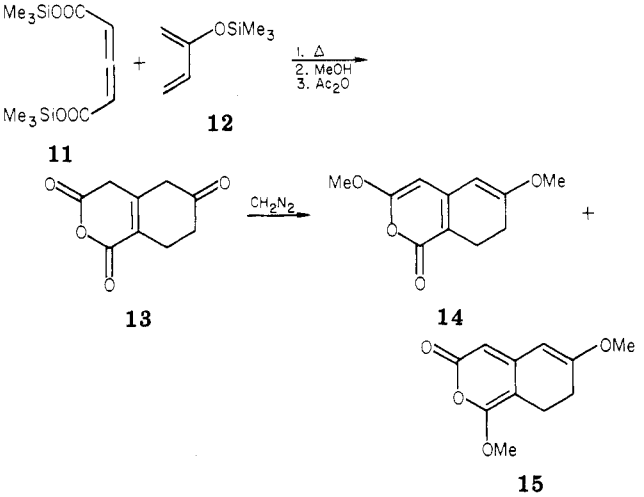
examples[5,6] of the use of this regiospecific approach for the synthesis of anthracycline intermediates and models have recently been described. In order to apply this general method to the synthesis of the 11-deoxyanthracyclines, it was necessary to prepare a bicyclic pyrone such as the acetoxypyrone 8. We report here a new general method for the regiospecific synthesis of substituted 6-alkoxy-2-pyrones, e.g., 8, and the use of these pyrones for the preparation of tetracyclic intermediates for the synthesis of the 11-deoxyanthracyclines.



8 10 9

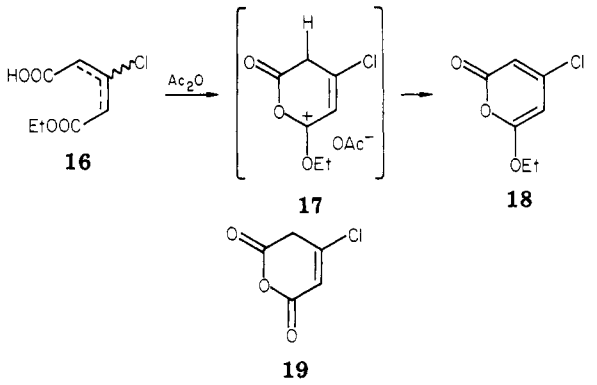
The preparation of 4-methyl-6-methoxy-2-pyrone (6) was greatly simplified by the fact that due to symmetry there was only one hydroxypyrone tautomer 9 of the anhydride 10, thus producing only one possible product upon O-methylation. However, the corresponding anhydride 13—prepared from bis(trimethylsilyl) allenedicarboxylate (11)[7] and 2-[(trimethylsilyl)oxy]butadiene (12)[8] by cycloaddition, hydrolysis, and cyclization—no longer possesses this symmetry element and thus can and does afford two regioisomers upon O-methylation with diazomethane.[9] Unfortunately the undesired isomer 14 is the major isomer of a 2:1 mixture, the formation of 15 being unfavorable perhaps due to increased steric hindrance in the O-methylation to produce this isomer.

Thus we were forced to develop a new procedure for the synthesis of substituted 6-alkoxy-2-pyrones which would be regiospecific. We reasoned that a substitued glutaconic half-ester would cyclize regiospecifically under dehydration conditions. This general principal was tested on the isomeric mixture of β-chloroglutaconic acid monoethyl ester (16), produced in fair yield by treating diethyl ace-



11 12 13 14 15

tonedicarboxylate with PCl_5.[10] When 16 was refluxed in acetic anhydride or acetyl chloride, 4-chloro-6-ethoxy-2-pyrone (18) was produced as the predominate product. Thus, the presumed intermediate 17 (or its double-bond isomer) undergoes loss of H^+ to give 18 rather than deethylation which would have furnished the anhydride 19.



16 17 18 19

Therefore the problem of the production of molecules such as 8 was reduced to the problem of preparing the specific half-acid half-ester 20. This was solved by the route described below.

Hydroxyethylation of *tert*-butyl propargyl ether 21 (available in 92% yield from propargyl alcohol and isobutylene) afforded in 50% yield the alcohol 22 which was oxidized, hydrolyzed, and esterified to give the hydroxy ester 23 (Scheme I). Upon silylation of the alcohol with *tert*-butyldimethylsilyl chloride in triethylamine/methylene chloride with catalytic 4-(dimethylamino)pyridine (DMAP), the β,γ-acetylenic ester was completely converted into the allenic ester 24. Cycloaddition of 24 with the silyloxy diene 12 followed by direct reduction with sodium borohydride in ethanol afforded a mixture of two products with the desired cyclohexanol 25 forming the major component. The cyclobutane 26[11] could be converted into the

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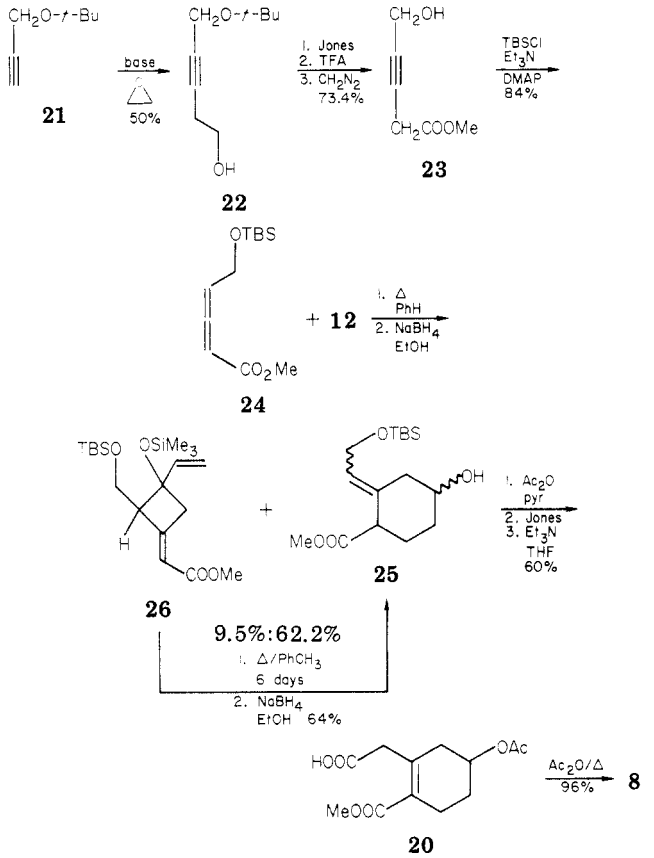
(9) All new compounds possessed spectroscopic data (NMR, IR, mass spectra) in complete accord with the structures assigned. Moreover, crystalline compounds gave correct elemental analyses.

(10) This reaction has been described, but it appears that no thorough investigation of the intermediate products was undertaken, but rather the entire mixture was hydrolyzed to the diacid and then HCl eliminated to produce allenedicarboxylic acid. We have obtained nearly 35% of the mixture of acid esters 16 by this route. For earlier work, see Burton, B. S.; von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1889**, *20*, 145. Ingold, C. K.; Nickolls, L. C. *J. Chem. Soc.* **1922**, *121*, 1642. van der Zanden, J. M. *Recl. Trav. Chim. Pays-Bas* **1935**, *54*, 291.

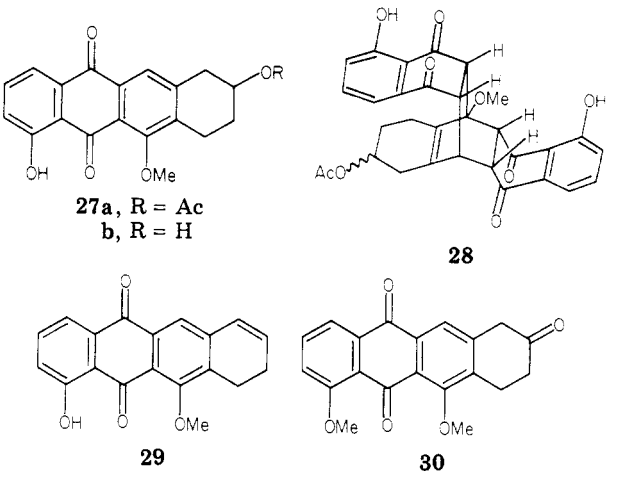
(11) The production of cyclobutane derivatives from the reaction of silyl enol ethers and very electron-deficient olefins has been reported before. See Hall, H. K., Jr.; Ykman, P. *J. Am. Chem. Soc.* **1975**, *97*, 800. In general, this reaction does not work well with simple unsaturated esters such as acrylates. It is interesting that upon heating, these isomers can be easily converted into the more stable cyclohexene cycloadducts, presumably via a zwitterionic intermediate (or perhaps an oxy-Cope rearrangement).

Scheme I



desired **25** by extended heating in toluene followed by reduction. The ester **25** was converted into the desired glutaconic half-acid half-ester **20** by initial acetylation (quantitative yield) followed by direct oxidation of the *tert*-butyldimethylsilyl ether to the acid with Jones reagent and a final treatment with base to move the double bond into the ring.[12] Cyclization of the ester acid **20** by the method described above for the preparation of **18**, namely, refluxing acetic anhydride for 3 h, gave a 96% crude yield of the pyrone **8** which could be recrystallized from ether [89%; mp 106–107 °C; mass spectrum, (*m/e*) 238; NMR ($CDCl_3$) δ 5.1 (1 H, quintet, J = 5 Hz), 5.05 (1 H, s), 3.8 (3 H, s), 2.8–2.4 (4 H, m), 2.0 (3 H, s), 2.2–1.7 (2 H, m); IR (Nujol) 1725, 1650, 1580, 1235 cm^{-1}]. Thus the specific bicyclic 6-methoxy-2-pyrone **8** is available from **21** in over 10% yield.

This facile preparation of **8** allowed us to apply our earlier method[4] to the synthesis of tetracyclic material as follows. Refluxing a solution of **8** with juglone (**5**) in xylene for 5 days followed by oxidation afforded a 63% yield of the desired acetate **27a** as yellow crystals (mp 164–165 °C).[13] In addition, we isolated 15% of a compound tentatively assigned structure **28**, the product of the cycloaddition of 2 equiv of juglone (**5**) with one of the pyrone **8**. It is very interesting that upon treatment with basic methanol, the bisadduct **28** produced up to 7% of the alcohol **27b**, corresponding to the acetate **27a**, and juglone.[14] Thus, the overall yield of the alcohol **27b** from this route is nearly 70%. The alcohol could also be produced directly without isolation of the acetate by direct treatment of the oxidation reaction mixture with base. In this manner, we obtained 48% of the pure crystalline alcohol **27b** (mp 203–204 °C) along with 7% of the olefin **29**. By very careful and repeated chromatography, it was possible to isolate all of the products formed in the Diels–Alder reaction of **5** and **8** and thus to verify spectroscopically that no regioisomeric materials were produced in this reaction, indicating that the cycloaddition is regiospecific. The overall structure of the adducts **27a** and **27b** was established by the conversion of **27a** to the ketone **30** by methylation (Ag_2O, MeI, 92%), hydrolysis (Na_2CO_3, 100%), and Jones oxidation. This same ketone was also prepared by a different route,[5] and the two samples were shown to be identical.



The further conversion of the tetracyclic material, e.g., **27**, **29**, and **30**, into the important 11-deoxyanthracyclines such as **3** is currently under investigation.

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(12) Compound **25**, the derived acetate, and the acid resulting from oxidation are all isomeric mixtures at both the carbon bearing the hydroxy (or acetoxy) function and the double bond. However, all of the isomers are converted into the same compound, namely, **20**, upon base-catalyzed isomerization of the double bond into the ring.

(13) Spectroscopic data for **27a**: mass spectrum (*m/e*) 366 (M^+), 306 (base); ^1H NMR ($CDCl_3$) δ 13.0 (1 H, s), 7.88 (1 H, s), 7.78 (1 H, dd, J = 8, 1 Hz), 7.65 (1 H, dd, J = 8 Hz), 7.29 (1 H, dd, J = 8, 1 Hz), 5.26 (1 H, quintet, J = 5 Hz), 3.94 (3 H, s), 3.3–3.0 (4 H, m), 2.06 (3 H, s), 2.2–2.0 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 188.5, 182.3, 170.5, 162.6, 159.2, 143.3, 138.9, 136.0, 132.8, 124.6 (2 peaks), 123.0, 122.6, 118.8, 116.9, 68.0, 63.1, 35.1, 26.5, 23.4, 20.8.

(14) We can only speculate about possible mechanisms for this process until the structure of **28** is firmly established. However, it is likely that after initial base-catalyzed enolization of one of the hydroquinone units of **28**, a facile retro-Diels–Alder reaction could take place, probably via ionic intermediates. This process could also be considered as two sequential retro-Michael additions. Either process would produce the hydroquinone corresponding to **27b** which would be converted into **27b** by air oxidation.

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(17) IBM Research Fellow, 1978–1979.

(18) Recipient of the Winstein Dissertation Award, 1977.

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