reactive and photochemically generated singlet oxygen led only to decomposition. However, in a remarkably clean
cconversion, 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% palladi-
um/charcoal, 1 atm, 4 h) gave the 3-aminohydroquinone 10
quantitatively as a black solid, which in turn could be
diazotized (sodium nitrate, concentrated hydrochloric acid,
0 °C, 30 min) to the orange diazo quinone 11. Reduction
of 11 was accomplished with a large excess of 50% hy-
droxylamine hydrochloride 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 procedure8 (0.5 M LiOH in 1:1 H2O-THF,
25 °C, 6 h). After acidification the solution was passed
through a C-18 reverse-phase silica gel 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 (6H NMR and UV)19 are in agree-
ment with those published for native,20,21 and synthetic2,4
methoxatin. In addition, TLC comparison [cellulose, 2
× 2 cm; 25 °C, 6 h). After acidification the solution was passed
through a C-18 reverse-phase silica gel 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 (6H NMR and UV)19 are in agree-
ment with those published for native,20,21 and synthetic2,4
methoxatin. In addition, TLC comparison [cellulose, 2
× 2 cm; 25 °C, 6 h). After acidification the solution was passed
through a C-18 reverse-phase silica gel 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 (6H NMR and UV)19 are in agree-
ment with those published for native,20,21 and synthetic2,4
methoxatin. In addition, TLC comparison [cellulose, 2
× 2 cm; 25 °C, 6 h). After acidification the solution was passed
through a C-18 reverse-phase silica gel 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 (6H NMR and UV)19 are in agree-
ment with those published for native,20,21 and synthetic2,4
methoxatin. In addition, TLC comparison [cellulose, 2
× 2 cm; 25 °C, 6 h). After acidification the solution was passed
through a C-18 reverse-phase silica gel 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 (6H NMR and UV)19 are in agree-
ment with those published for native,20,21 and synthetic2,4
methoxatin. In addition, TLC comparison [cellulose, 2
× 2 cm; 25 °C, 6 h). After acidification the solution was passed
through a C-18 reverse-phase silica gel 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 (6H NMR and UV)19 are in agree-
ment with those published for native,20,21 and synthetic2,4
methoxatin. In addition, TLC comparison [cellulose, 2
× 2 cm; 25 °C, 6 h). After acidification the solution was passed
through a C-18 reverse-phase silica gel 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 (6H NMR and UV)19 are in agree-
ment with those published for native,20,21 and synthetic2,4
methoxatin. In addition, TLC comparison [cellulose, 2
× 2 cm; 25 °C, 6 h). After acidification the solution was passed
through a C-18 reverse-phase silica gel 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.
examples\(^{6,8}\) 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-pyriones, e.g., 8, and the use of these pyrones for the preparation of tetracyclic intermediates for the synthesis of the 11-deoxyanthracyclines.

The preparation of 4-methyl-6-methoxy-2-pyrone (6) was greatly simplified by the fact that due to symmetry there was only one hydroxydp pryone 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-[(trimethylsilyloxy)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-pyriones which would be regiospecific. We reasoned that a substituted glutaric acid half-ester would cyclize regiospecifically under dehydration conditions. This general principal was tested on the isomeric mixture of \(\beta\)-chloroglutaric acid monoethyl ester (16), produced in fair yield by treating diethyl acetylenedicarboxylate 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 dehydroxylation which would have furnished the anhydride 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-butyl(chloromethyl)chloride in triethylamine/methylene chloride with catalytic 4-(dimethylaminopyridine (DMAP), the \(\beta\),\(\gamma\)-acytlenic ester was completely converted into the allenic ester 24. Cycloaddition of 24 with the silylox 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
desired 25 by extended heating in toluene followed by reduction. The ester 25 was converted into the desired glutarconic 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 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 (CDCl₃) δ 5.1 (1 H, quintet, J = 8, 1 Hz), 7.65 (1 H, s), 2.72–2.17 (2 H, m); IR (Nujol) 1725, 1650, 1580, 1205 cm⁻¹. Thus the specific bicyclic 6-methoxy-3-pyrene 8 is available from 21 in over 10% yield.

This facile preparation of 8 allowed us to apply our earlier method4 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 (Ag₂O, MeI, 92%), hydrolysis (Na₂CO₃, 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 1-deoxyxanthacyclines such as 3 is currently under investigation.

Acknowledgment. The financial support of the National Institutes of Health (Grant No. CA-21968), The Camille and Henry Dreyfus Foundation (Teacher-Scholar award to M.E.J., 1978–1983), and the Alfred P. Sloan Foundation (award to M.E.J., 1979–1981) is gratefully acknowledged.

Michael E. Jung,* Manabu Node†
Rudolf W. Pfluger,* Mark A. Lyster17,18
John A. Lowe, III18

Department of Chemistry
University of California
Los Angeles, California 90024

Received August 25, 1981

(12) Compound 25, the derived acetate, and the acid resulting from oxidation are all isomeric mixtures at both 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 (CDCl₃) δ 13.0 (1 H, s), 7.85 (1 H, s), 7.81 (1 H, dd, J = 8, 1 Hz), 7.48 (1 H, d, J = 5 Hz), 7.39 (4 H, d), 6.06 (3 H, s), 4.5–2.0 (2 H, m); ¹³C NMR (CDCl₃) δ 198.5, 182.3, 170.5, 162.6, 159.2, 143.3, 138.9, 136.0, 132.5, 124.6 (2 peaks), 120.0, 118.8, 116.5, 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 a cycloaddition. 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.


