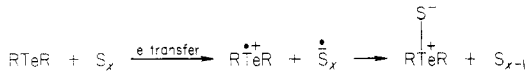
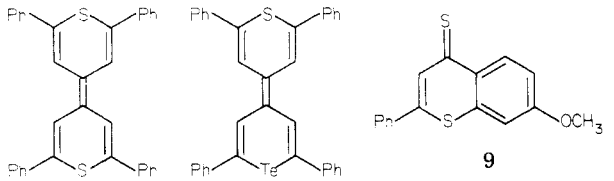
Scheme II

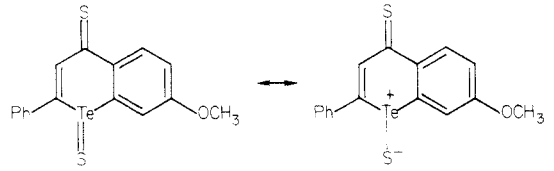


When **2** was treated with 5 equiv of sulfur in refluxing xylene for 2 h, **2** was completely consumed. Several products were detected by preparative thin-layer chromatography on silica gel eluted with methylene chloride, but only thione **9** was isolated in sufficient yield (70%) for characterization. Not only had tellurium–sulfur exchange occurred, but the bipyranylidene structure had reverted to the thione **9**.[9] The susceptibility of bipyranylidenes to add sulfur and revert to thiones has been observed.[14] The addition of triphenylphosphine to remove sulfur in the refluxing xylene/copper powder preparation of **2** improved the isolated yield of **2** to 32%.

A second product was isolated in low yield (24%) when **6** was treated with 2 mol equiv of the Lawesson reagent in benzene at room temperature for 17 h. This product was a sharp-melting (153.5–155 °C), purple-black solid that was insoluble in most solvents but moved with the solvent front on silica gel eluted with methylene chloride. The mass spectral and elemental analyses were consistent with a molecular formula of $C_{16}H_{12}OS_2Te$. The absorption spectrum with maxima (log ϵ) at 582 (3.84) and 680 nm (2.85) suggested a conjugated chromophore. The ^1H NMR spectrum displayed a one-proton singlet at δ 8.90.[9] The spectral and analytical data are consistent with structure **10**.[9]



7 8 9



10a 10b

The tellurosulfide **10** represents the first stable member of its class. In this particular example, tellurium has been "oxidized" directly by sulfur, presumably from the Lawesson reagent. The resonance forms for such a structure are many; however, resonance form **10b** helps to rationalize the deshielding of the olefinic proton in **10** relative to the same proton in **4**.

When a toluene solution of **10** was warmed at reflux for 3 h, at least seven new products were formed. The major component, isolated in 20% yield, was identified as thione **9** by ^1H NMR and field-desorption mass spectroscopy.

It is conceivable that elemental sulfur might act as an oxidant under suitable conditions. As shown in Scheme II, electron transfer from tellurium to elemental sulfur at elevated temperature might give a radical cation/radical anion pair which could then collapse to produce the tellurosulfide. As the oxidation potentials in Table I indicate, both **1** and **2** are easily oxidized with $E^{\circ\prime}_{oxid}$ for **1** being +0.34 V (average of forward and reverse) and $E^{\circ\prime}_{oxid}$ for **2** being ~+0.39 V. Both **1** and **2** should be fair reducing agents. The Lawesson reagent could serve as a source of sulfur to produce tellurosulfide **10**.

Table I. Oxidation Potentials of 1 and 2

		oxidation potential,[a] V			
		I		II	
compd	electrode	forward	reverse	forward	reverse
1	platinum	+0.37	+0.30	+0.52	+0.45
	glassy carbon	+0.39	+0.28	+0.54	+0.43
2	platinum	+0.44[b]	+0.34[c]		
	glassy carbon	+0.43[b]	+0.33[c]		

[a] Relative to standard calomel electrode (saturated aqueous NaCl) with CH_2Cl_2 as solvent with 0.1 M tetra-*n*-butylammonium tetrafluoroborate as supporting electrolyte. [b] Two-electron oxidation. [c] Adsorbed.

The tellurium–sulfur exhange observed upon heating **10** suggests that tellurosulfide species may be involved as intermediates. We are presently seeking other stable tellurosulfides. The donor properties of both **1** and **2** and other tellurobipyranylidenes as well as their conductive salts will be reported in a separate paper.

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A Convergent Total Synthesis of Methoxatin

Summary: We report a convergent total synthesis of the coenzyme methoxatin (**1**) by linking pyrrole subunit (**3**) with uvitonic acid derivative **4d** and oxidative photocyclization to deoxymethoxatin triester **6**, followed by seven refunctionalization steps to **1**.

Sir: A number of bacteria, known as methylotrophs, can utilize methanol as their sole carbon source. The organisms, of which *Pseudomonas* are typical, are of current interest as nutritive single-cell protein. The oxidation of methanol to formaldehyde and to formic acid is accomplished in these organisms by a methanol dehydrogenase which utilizes a newly discovered coenzyme, methoxatin (**1**),[1] quite different in structure from the familiar redox coenzymes such as flavin, nicotinamide, etc. The structure of methoxatin was deduced from spectroscopic data[2,3] and an X-ray crystallographic study[4] of its aldol adduct with acetone (**2**), but continued studies of its mode of action have been severely hampered by lack of adequate quantities of the natural coenzyme (**1**).

In keeping with our recent analysis[5] we conceived a convergent synthesis of methoxatin from appropriate pyridine and pyrrole starting materials, to be linked and

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(4) Salisbury, S. A.; Forrest, H. S.; Cruse, W. B. T.; Kennard, O. *Nature (London)* **1979**, *280*, 843.
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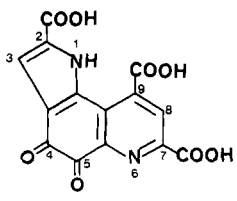
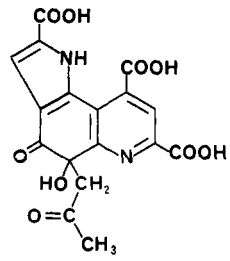


1



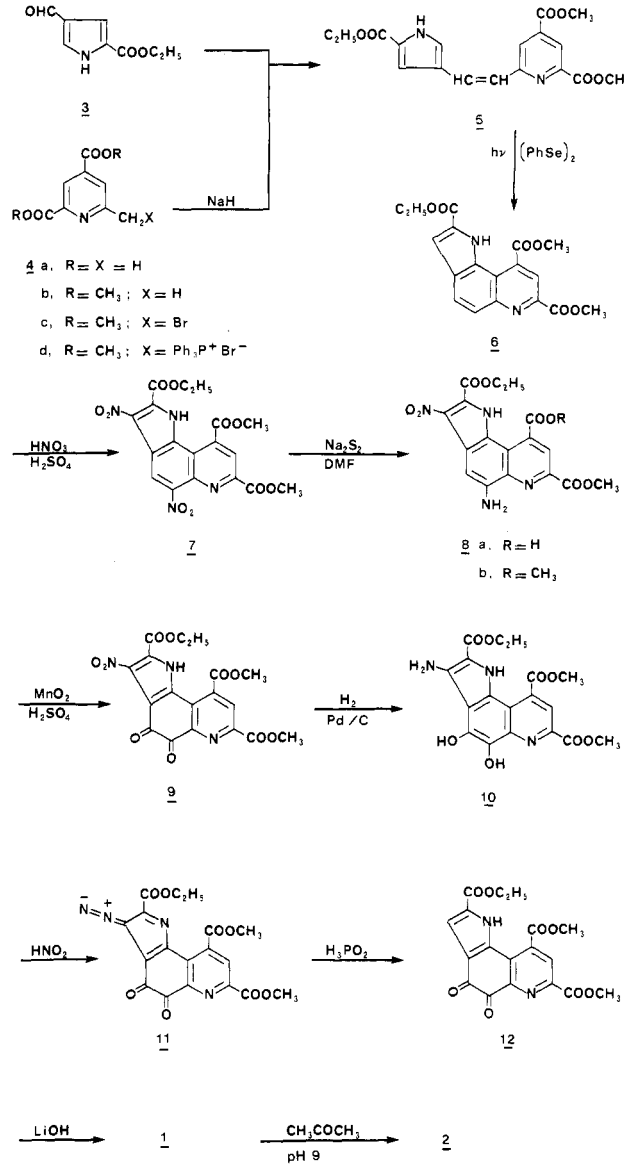
2

cyclized to 1.[6] Fortunately, these were readily available in the pyrrole aldehyde **3** and uvitonic acid ester **4b**. Uvitonic acid (**4a**) is made in one step from pyruvic acid and ammonia, and Fischer esterified to **4b**.[9] The aldehyde **3** is created from ethyl pyrrole-2-carboxylate by a Friedel–Crafts reaction of unusually high regioselectivity, using dichloromethyl methyl ether (82% yield).[10] Bromination of dimethyl uvitonate (**4b**) to **4c** with *N*-bromosuccinimide (CCl_4, reflux, light) was plagued by concomitant dibromination, best minimized by using only 0.5 equiv of NBS and recovering unreacted **4b**. With this correction the yield of **4c** is 76%. Reaction with triphenylphosphine in refluxing benzene (3 h) afforded the phosphonium bromide **4d** quantitatively.

The union of the two synthons, **3** and **4d**, was accomplished with sodium hydride in dimethylformamide (65 °C, 3.75 h); dilution with an equal volume of water gave the pure olefin **5** as a yellow solid in 84% yield, the NMR spectrum implying >95% trans configuration. Short (2 h) irradiation (Pyrex filter) in benzene–ether led only to 100% conversion to the cis isomer of **5**, even with added sulfur or selenium as oxidants. However, the desired photocyclization was successful on prolonged irradiation of **5** in the presence of diphenyl diselenide, giving deoxymethoxatin **6** in 44% yield.[11] This appears to be the first example of a stilbene-type photocyclization in which one aromatic unit is a pyrrole.[12] The alternative formulation of the photocyclization product, i.e., closed to the other pyrrole position, was excluded by NMR evidence.[13]

The oxidation of the central ring proved more difficult than anticipated since, unlike phenanthrene, the central ring bond (C-4–C-5) showed no olefinic character toward oxidants, and the open position (C-3) on the pyrrole ring was more reactive to aromatic substitution reactions.[14]

Chart I. Total Synthesis of Methoxatin



Accordingly, the deoxymethoxatin triester **6** was nitrated to a dinitro derivative (fuming niric–sulfuric acid mixture at 0 °C for 10 min) in 94% yield. The product was assigned the 3,5-dinitro structure **7** on theoretical grounds, but spectral evidence does not distinguish it from the 3,4 isomer. Zinin reduction[15] with $Na_2S_2 \cdot 5H_2O$/DMF (25 °C, 30 min) was near quantitative and totally regiospecific, reducing only the less conjugated 5-nitro group to form the amino nitro acid diester **8a**. The hydrogen bonding of the C-9 ester to the pyrrole NH[13] presumably renders it unusually sensitive to hydrolysis here, but the ester is restored by diazomethane before workup, giving triester **8b** as beautiful bordeaux-red crystals in 82% overall yield from **7**. A number of efforts to continue the synthesis in a parallel sequence of acids from **8a** were unsuccessful.

The oxidation of the amine **8b** to the quinone could be achieved only in poor yield with such oxidants as singlet oxygen (from ozone-bicyclic phosphite)[16] or 3,5-dinitrobenzoyl *tert*-butyl nitroxide,[17] while Fremy's salt was un-

(6) While our synthesis was underway two linear syntheses of methoxatin were published, i.e., plans starting with the central ring and building the two heterocyclic terminal rings onto it successively.[7,8]

(7) Corey, E. J.; Tramontano, A. *J. Am. Chem. Soc.* **1981**, *103*, 5599.

(8) Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 4317.

(9) (a) Böttinger, C. *Justus Liebigs Ann. Chem.* **1877**, *188*, 329. (b) Efimovski, O.; Rumpf, P. *Bull Soc. Chim. Fr.* **1954**, 648.

(10) Fournari, P.; Farnier, M.; Fournier, C. *Bull Soc. Chim. Fr.* **1972**, 283.

(11) Conditions: 1.5 g of **8** and 3.0 g of $(PhSe)_2$ in 5 L of dry benzene–ether (4:1) were irradiated with a 550-W medium-pressure Hg lamp (Hanovia) through a Pyrex cooling jacket for a period of 4 weeks. A continuous stream of N_2 was sparged through the solution. After evaporation of solvents, $(PhSe)_2$ was removed by extraction with hexane. The residue was purified by flash chromatography on silica, CH_2Cl_2–CH_3OH (0–2%), followed by LC/silica, CH_2Cl_2–dioxane (3%). The product was crystallized from CH_3OH, mp 174–176 °C.

(12) For a review on photocyclization reactions, see Blackburn, E. V.; Timmons, C. J. *Q. Rev.* **1969**, *23*, 482.

(13) The product shows an absorption at δ 12.46 in the NMR for the pyrrole NH. This extremely downfield position is caused by hydrogen-bond formation to the ester carbonyl at C-9. For comparison: the NH in methoxatin trimethyl ester had a δ value of 13.0 ppm,[3e] whereas for *trans*-**5** this value is 9.33 ppm.

(14) Quantitative nitration or halogenation to the monosubstituted derivatives at C-3 was easily achieved (HNO_3/Ac_2O/0 °C/1.5 h; *t*-BuOCl/CH_2Cl_2/25 °C), but our intention to block C-3 with halogen was thwarted since all these monosubstituted derivatives simply gave the 3,5-dinitro compound **7** on further nitration. Reduction of the 3-nitro to the 3-amino derivative followed by further nitration led to the 3-diazoindolenine derivative.

(15) Porter, H. K. *Org. React.* **1973**, *20*, 455. The variation here, in dimethylformamide, is much milder and briefer than the traditional reaction.

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.

Acknowledgment. In addition to gifts of samples[18] we are grateful to Waters Associates for large-scale HPLC, to Professor R. H. Abeles for interest and valuable discussions, and to the National Cancer Institute (National Institutes of Health) for partial financial support (CA-23496).

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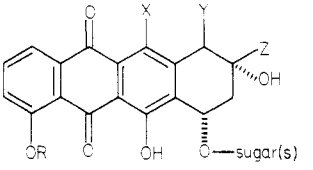
Regiospecific Synthesis of Bicyclic 6-Alkoxy-2-pyrones and Their Use in the Production of Tetracyclic Intermediates for 11-Deoxyanthracycline Synthesis

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

(16) Brennan, M. E. *J. Chem. Soc., Chem. Commun.* **1970**, 956.
(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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