were determined by gas chromatographic analysis as described above.

Quantum Yields. Benzene solutions of **3** (10 mM) and **4a** (50 mM) in four Pyrex test tubes were degassed with four freeze–pump–thaw cycles and sealed. Quantum yields were measured relative to 0.012 M potassium ferrioxalate actinometer with parallel irradiation of the samples under the same conditions. Yields for **5a** formation were determined by gas chromatographic analysis.

Sensitizing Experiments. Benzene solutions of **3** (50 mM) and **4a** (250 mM) containing varying amounts of triphenylene (50, 100, and 250 mM) in Pyrex test tubes were degassed with a series of five freeze–pump–thaw cycles and sealed. The sample tubes were irradiated by 500-W high-pressure mercury lamp in parallel on a merry-go-round apparatus. Yield for **5a** formation by addition of triphenylene was increased to 2.1 times in comparison with that in the absence of triphenylene.

Acknowledgment. We are grateful to Professor Hitoshi Nozaki for advice. This work was supported in part by the Grant-in-Aid for Scientific Research (to Y.K.; No. 56370032, 57118006, and 58110005) from the Ministry of Education, Science and Culture, Japan.

Registry No. **1a**, 89464-69-7; **1b**, 95765-51-8; **1c**, 90088-68-9; **1d**, 95765-52-9; **2a**, 95765-53-0; **2b**, 95765-54-1; **3**, 3889-18-7; **4a**, 563-79-1; **4b**, 513-35-9; **4c**, 115-11-7; **4d**, 590-18-1; **4e**, 109-92-2; **5a**, 95765-62-1; **5b**, 95765-63-2; **5c**, 95765-64-3; **5d**, 95765-65-4; **5e**, 95765-66-5; **7**, 95765-67-6; **9**, 764-13-6; *cis*-**10**, 95784-27-3; *trans*-**10**, 95797-80-1; (*E*)-**11**, 95765-68-7; (*Z*)-**11**, 95765-69-8; **12**, 95765-57-4; **13**, 95765-70-1; **14**, 95765-56-3; **15**, 95765-71-2; **16a**, 35373-06-9; **16b**, 35409-94-0; **16c**, 95765-55-2; **17**, 35373-10-5; **18**, 95765-72-3; **19**, 95765-73-4; *cis*-**21**, 95765-74-5; *trans*-**21**, 95765-75-6; (*E*)-**22**, 95765-76-7; (*Z*)-**22**, 95765-77-8; **23**, 2043-24-5; **24**, 95765-78-9; **25**, 95765-79-0; **26**, 14160-11-3; **27**, 92172-52-6; **28**, 103-30-0; **29a**, 95840-09-8; **29b**, 95840-10-1; **30**, 95765-80-3; **31**, 95765-81-4; ferrocene, 102-54-5; ethyl 2,3-dicyano-2,3,3-trimethylpropionate, 95765-58-5; ethyl 2-cyano-3,3-dimethylacrylate, 759-58-0; potassium cyanide, 151-50-8; methyl iodide, 74-88-4; 2,3,3-trimethylsuccinic acid, 2103-16-4; methylamine, 74-89-5; 1,3,3,4-tetramethylsuccinimide, 95765-59-6; (*S*)-(+)-1-bromo-2-methylbutane, 534-00-9; (*S*)-(+)-1-bromo-3-methylpentane, 22299-70-3; succinimide, 123-56-8; (*S*)-1-(2-methylbutyl)succinimide, 95765-60-9; (*S*)-1-(3-methylpentyl)succinimide, 95765-61-0; 1,3-cycloocatdiene, 1700-10-3; *N*-methylsuccinimide, 1121-07-9; *cis*-*N*-methylcyclohexane-1,2-dicarboximide, 64090-28-4; 1,2-cyclohexanedicarboxylic anhydride, 85-42-7; triphenylene, 217-59-4.

Total Synthesis of the Novel Coenzyme Methoxatin

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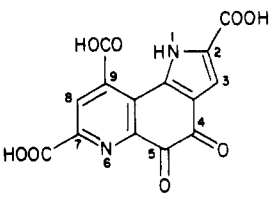
A convergent total synthesis of the novel coenzyme methoxatin (**1**) is described. This coenzyme is a pyrroloquinoline quinone tailored for efficient oxidation of methanol and formaldehyde in methylotrophic bacteria. The synthesis was achieved by joining pyrrole subunit **5a** with uvitonic acid ester **8b** followed by photocyclization of the resulting olefin **9** to deoxymethoxatin **10**. Conversion of **10** to methoxatin proceeded in five steps and led to some elaboration of the chemistry of the unusual pyrroloquinoline heterocycle. The overall yield is ~15% in 11 operations.

A number of bacteria, known as methylotrophs, can use methane or methanol as their sole source of energy and of carbon for synthesis. These organisms are currently of great interest as sources of single-cell protein for nutrition[2] and as a means of converting cheap raw materials such as methane and methanol into more complex structures. A crucial step in their metabolism is the conversion of methanol into formaldehyde and formic acid. The operative enzyme, methanol dehydrogenase[3] (EC 1.1.99.8), was found to be dependent on a coenzyme[4] not showing the usual spectroscopic characteristics of known redox coenzymes such as NADH/NADPH or flavins. Using ESR and ENDOR on the purified enzyme and on the isolated cofactor, Duine et al. established that the cofactor is a quinone containing two nitrogen atoms and three protons, one of which is exchangeable.[5] The actual structure (**1**) of the coenzyme was proposed by Forrest et al.[6] based upon



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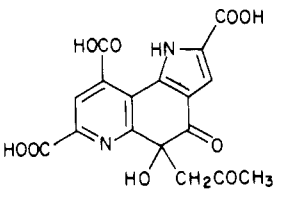

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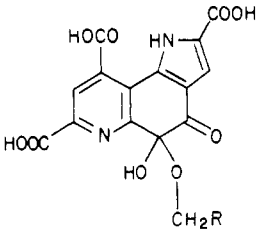

3

an X-ray study of its aldol adduct with acetone **2**, an artifact of the isolation. The structure was confirmed by ^{1}H NMR of the isolated cofactor and its trimethyl ester,[7] by four different total syntheses[8-11] (one of which[10] is our preliminary communication of this work), and by recon-

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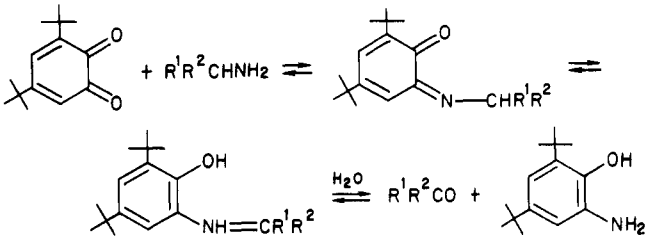
Scheme I



stitution of synthetic cofactor with the holoenzyme of glucose dehydrogenase, an enzyme also dependent on the same cofactor.[12] The names methoxatin[6] and pyrroloquinoline quinone[4] (PQQ) have been proposed for the cofactor.

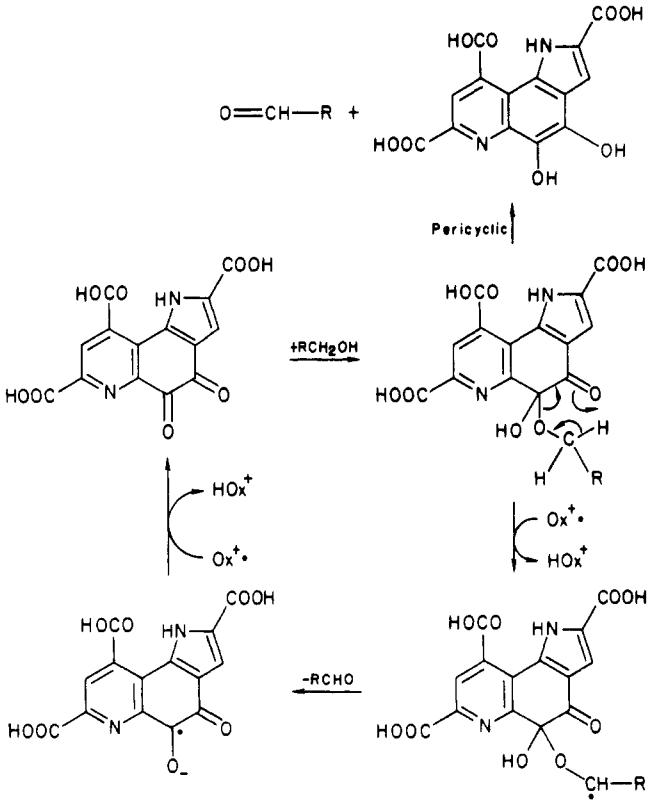
By use of the reconstitutional ability of the glucose dehydrogenase holoenzyme, the presence of methoxatin was established in several aerobic and anaerobic bacteria, where it serves as a cofactor for methanol dehydrogenase, alcohol dehydrogenase, glucose dehydrogenase, methylamine dehydrogenase, and lactate dehydrogenase.[4] Recently Duine was able to demonstrate the presence of methoxatin in bovine serum, indicating that occurrence of the cofactor is not confined to the bacterial realm.[13]

Both oxidized (quinone) and reduced (hydroquinone) forms of methoxatin seem to be present in methanol dehydrogenase, one molecule of each per enzyme molecule.[14] A one-to-one mixture of oxidized and reduced forms in an appropriate solvent system gives rise to an ESR signal, similar to that exhibited by the apoenzyme, and is probably caused by the semiquinone form.[14]

Alcohols, amines, and urea attack methoxatin at the 5-position, giving rise to hemiketal **3** and imine-type addition products.[15] Only in the presence of added one-electron oxidants such as phenazine methosulfate are primary alcohols oxidized to the aldehydes by methanol dehydrogenase in vitro. Alkylamines of the type RCH_2NH_2 are oxidized stoichiometrically to the corresponding aldehydes without added oxidant, even without enzyme. It was possible to reach turnover numbers up to 18 in the oxidation of primary amines of the type RCH_2NH_2 and $R^1R^2CHNH_2$ to the respective aldehydes and ketones with enzyme-free cofactor, using oxygen as external oxidant, if the reaction was performed in an aqueous solution of cationic surfactant.[16] Oxidation of amines with *o*-quinone has been described previously by Corey, who used 3,5-di-*tert*-butyl-*o*-quinone as a model system.[17] The mechanism he proposes seems applicable also to the enzymatic reaction (Scheme I).

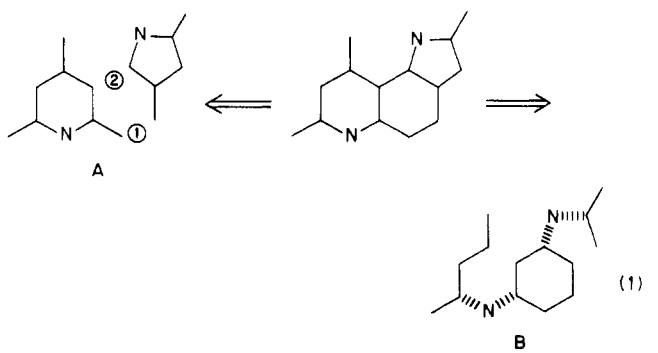
The mechanism of the oxidation of primary alcohols is still very unclear. Primary alcohols—secondary or tertiary alcohols are not substrates[18,19]—are not oxidized by methanol dehydrogenase (oxidized form) in vitro, unless a one-electron oxidant such as phenazine methosulfate is present.[19] One notable exception is cinnamyl alcohol, which is stoichiometrically oxidized to cinnamaldehyde.[20]

Scheme II



It is hard to fit all of the above data into a general reaction mechanism. In view of the high susceptibility of the 5-position of methoxatin toward nucleophilic attack,[15] it seems likely that the hemiketal **3** is an intermediate in the oxidation sequence. From there two pathways leading to product can be envisaged (Scheme II). First, a six-electron pericyclic collapse would lead directly to aldehyde and reduced form of methoxatin. In this mechanism there is no need for an external oxidant and hence it can apply only for the case of cinnamyl alcohol. With other alcohols the methylene proton of the hemiketal might not be acidic enough for the above reaction to occur at room temperature. On the other hand, hydrogen atoms α to an ether functionality are known to be relatively easily abstracted in a radical manner. The radical so produced then loses aldehyde and a proton, leading to highly stabilized semiquinone, which in turn is oxidized further to the quinone by release of an electron to the external oxidant.

Following our analysis of the greater efficiency of convergent synthesis,[21] we proposed to construct the methoxatin molecule following a convergent synthetic plan, based upon dissection A (eq 1), rather than a linear one



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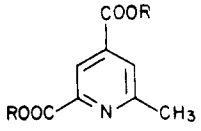
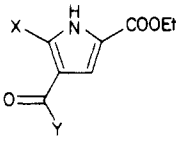
such as B, which implies sequential annelation of first one and then another heterocyclic ring onto a central aromatic ring. The left-hand unit in A is readily available with the correct functionality in the form of uvitonic acid (**4a**), made



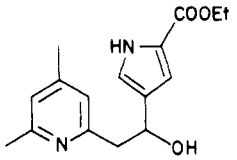
4a, R = H
b, R = CH_3
c, R = $C(CH_3)_3$



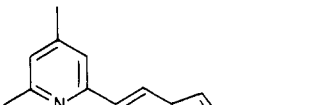
5a, X = H; Y = H
b, X = H; Y = OEt
c, X = Br; Y = OEt
d, X = Br; Y = H

by the interesting condensation of pyruvic acid with ammonia.[22] Given the methyl group of uvitonic acid as one element for the bond (bond 1 in A, eq 1) to be made, this demands an electrophilic carbon substituent at C-4 on the pyrrole unit as in **5**. Subsequent cyclization, forming bond 2 (A, eq 1), further requires a leaving group X on **5** if the cyclization is not be oxidative. The choice was ultimately settled on practical grounds since bromination of methyl pyrrole-2-carboxylate gives a 49:38 mixture of the 4- and 5-bromo derivatives, respectively (as well as 13% dibromo derivative[23]), and neither formylation nor acetylation of the separated 5-bromo ester could be achieved. The diester of pyrrole-2,5-dicarboxylic acid (**5b**) is readily obtained in one step from isocyanoacetate ester and formaldehyde with base (67%),[24] but its bromination with pyridinium hydrobromide perbromide gave a maximum yield of 10% of monobrominated product and mostly the dibromo derivative. Furthermore, the two carboxyl groups would have required discrimination, hence some refunctionalizing.

On the other hand, an uncommonly high regiospecificity (99%) was reported for the formylation of methyl pyrrole-2-carboxylate with dichloromethyl methyl ether and aluminum chloride (with added nitromethane in CH_2Cl_2) to create **5a** in 82% yield.[25] As bromination of **5a** under various conditions failed to produce **5d**, we elected to join the available starting materials and to seek an oxidative cyclization. In a model trial 2,4,6-trimethylpyridine was converted to its α-anion with *n*-BuLi, and this reacted without incident (87%) with **5a** to form **6** as an oil which

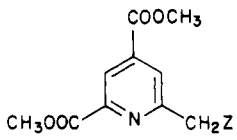


6

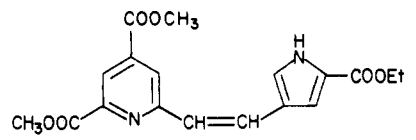


7

could be converted with mesyl chloride/pyridine to crystallize **7** (59%), apparently the pure trans isomer by NMR (J = 16 Hz). However, the same procedure applied to either the methyl or *tert*-butyl diesters of uvitonic acid (**4b** or **4c**) left **5c** unreacted and the uvitonic diester destroyed. Similarly, quenching the anion so formed with water did not recreate any uvitonic diester. Accordingly, the uvitonic diester **4b** was brominated first with *N*-bromosuccinimide and converted quantitatively to its triphenylphosphonium salt derivative **8b** for use in a Wittig coupling with **5a**,



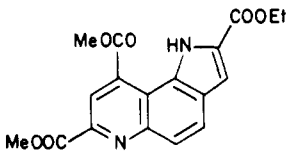
8a, Z = Br
b, Z = $PPh_3^+Br^-$



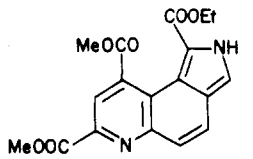
9

which afforded **9** in 84% yield. The olefin **9** was about 95% trans by NMR. The bromination of uvitonate to **8a** was plagued by dibromination, which was minimized by using only half of the equivalent amount of *N*-bromosuccinimide and recovering unreacted dimethyl uvitonate chromatographically.

The cyclization of *cis*-stilbenes to phenanthrenes has commonly been achieved by photolysis, usually with added external oxidants such as iodine, oxygen, etc.[26] The reaction has been carried out with a number of pyridine derivatives as well, but no such cyclizations involving pyrroles appear to have been examined. In the event, irradiation of **9** in benzene with a 550-W Hanovia lamp through a Pyrex filter for 2 h led only to smooth quantitative conversion to the *cis*-olefin, even with added oxidants such as sulfur or selenium. Much longer irradiation, however, with diphenyl diselenide present resulted in eventual disappearance of the *cis*-olefin and formation of deoxymethoxatin triester **10**, in 46% yield, as yellow



10



11

crystals, mp 174–176 °C. The alternate photocyclization product **11** was excluded on the NMR evidence of the hydrogen-bonded pyrrole NH, first observed[7b] in methoxatin itself as a peak downfield at δ 13.0. The *trans*-olefin **9** shows its pyrrole NH at δ 9.33, whereas in the photocyclization product **10** this peak appears at δ 12.42.

Our initial view had been that once the methoxatin skeleton had been created, the oxidation of the central ring would prove relatively simple by analogy with the oxidation of phenanthrene to phenanthraquinone. This proved not to be the case. A large number of different oxidants were examined for reaction with **10**, summarized as follows: CrO_3, $Na_2Cr_2O_7$, HIO_4, HIO_3, I_2O_5, $PhI(OAc)_2$, Cu^{II}/H_2O_2, $Co^{III}/HClO_4$, $AgO/HClO_4$, $Mn(OAc)_3/HOAc$, $Mn_2(SO_4)_3$, OsO_4 (and with *N*-methylmorpholine *N*-oxide or *t*-BuOOH), $Mo(CO)_6/t$-BuOOH, MCPBA, and Fenton's reagent. All of these oxidants resulted either in no reaction or in total destruction of the molecule.

Accordingly, the chemistry of aromatic substitution for this largely unexamined pyrrolo[2,3-*f*]quinoline heterocycle was explored.[27] The general result appears to be that the system reacts with electrophiles first exclusively at C-3 on the activated pyrrole ring and only afterward on the central ring at C-5. Nitration of **10** with nitric acid in acetic anhydride at 0 °C quantitatively affords the 3-nitro derivative **12a**, while nitration in sulfuric acid yields the 3,5-dinitro derivative **13a** (94%). The same results attended halo-

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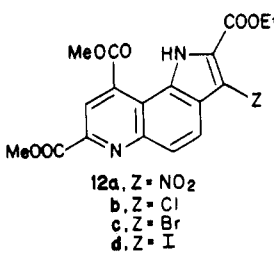
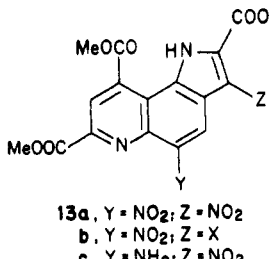
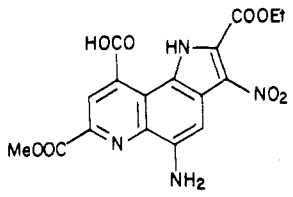
(27) The original synthesis of a pyrrolo[2,3-*f*]quinoline was by Dufton (Dufton, S. F. *J. Chem. Soc.* **1892**, *61*, 782), but virtually no reactions of this heterocycle have been reported except a recent account of a Chichibabin reaction: Akhvlediani, R. N.; Shabunova, V. P.; Motozova, I. A.; Volodina, T. A.; Suvorov, N. N. *Zh. Org. Khim.* **1981**, *17*, 1542.



12a, Z = NO_2
b, Z = Cl
c, Z = Br
d, Z = I



13a, Y = NO_2; Z = NO_2
b, Y = NO_2; Z = X
c, Y = NH_2; Z = NO_2
d, Y = NH_2; Z = NH_2
e, Y = Z = NHCOOEt
f, Y = NO_2; Z = NH_2



14

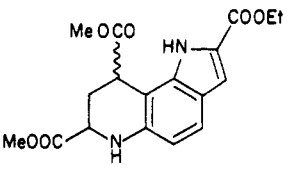
genation: chlorination with *tert*-butyl hypochlorite afforded the monochloro derivative **12b**, bromination (bromine and catalytic iron) yielded **12c**, and iodination with iodine and $PhI(OCOCF_3)_2$ yielded **12d**. Our hope of course was that the 3-position could thus be blocked with halogen in order to allow nitration on the central ring to form **13b**. However, the mildest nitration to afford any transformation on the halides **12b–d** yielded only the same dinitro derivative, **13a**. Oxidation of the C-3-blocked halides **12b–d** (after hydrolysis of the esters with LiOH in THF/H_2O) with oxygen and horseradish peroxidase afforded no reaction, and other oxidants (as above) led to either destruction or no reaction, as before.

The ready availability of the disubstituted derivative **13a** now demanded a selective reduction of the one nitro group on the central ring as an entree into its oxidation. For our purpose it is unimportant which position (C-4 or -5) bears the second nitro group introduced, but the rationale for the formulation of **13a** as the 3,5-derivative comes from hydrogenation to a diamino derivative. This compound (**13d**) on treatment with diethyl carbonate in refluxing $ClCH_2CH_2Cl$ formed a dicarbamate, i.e., **13e**, rather than the cyclic urea expected from a 3,4-diamino compound.

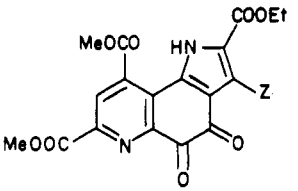
Selective reduction of dinitro aromatics has some tradition in the Zinin reaction,[28] and our presumption was that the 3-nitro group should be more stabilized by pyrrolic resonance so that reduction should proceed preferentially at C-5. In a variation of the Zinin reaction, much briefer and milder than the traditional, we found that **13a** was reduced nearly quantitatively and with complete regiospecificity by sodium disulfide hydrate in dimethylformamide for half an hour at room temperature. The immediate product was an acid diester **14**, convertible by diazomethane to **13c**. The C-9 ester is presumably very sensitive to hydrolysis because of the hydrogen bonding to the pyrrole NH observed in the NMR spectrum.

The presumption that the monoamine has structure **13c** instead of **13f** is supported by a shift of only 0.5 ppm in the NMR at C-4 on reduction of the C-3 nitro in **12a** and 0.6 ppm on its reduction in **13c** to **13d**, whereas the shift from **13a** to **13c** is fully 1.0 ppm when the reduction occurs at the neighboring 5-position. In any case, the further reactions to methoxatin confirm this assignment. After finishing the synthesis, detailed below, we examined the possibility of carrying the monoacid **14** through the same final steps, but while the distinctive color changes were duplicated, the spectral evidence indicated that a mixture of several compounds was produced. When full saponification of **14** to the corresponding triacid was similarly followed by the final synthetic steps, the resultant product was likewise judged to contain no more than 15% methoxatin.

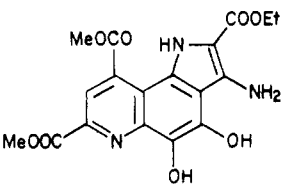
A concurrent examination of the reduction of deoxymethoxatin led to an interesting result for the chemistry of the pyrroloquinoline system. Reduction of deoxymethoxatin triester **10** with zinc in trifluoroacetic acid for half an hour at room temperature led to reduction of the pyridine ring, as did hydrogenation in trifluoroacetic acid over platinum, both in yields around 80%. The two diastereomeric ester products **15** were separated pure chro-



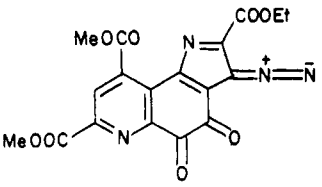
15



16a, Z = NO_2
b, Z = H



17



18

matographically in each case and assigned structures from the NMR spectra, which showed the aliphatic protons clearly. In one diastereomer the two protons α to carboxylate were very similar in chemical shift and coupling as were the two methylene protons at C-8, and this was assigned the cis configuration. In the other, trans, isomer the two protons α to carboxylate were quite different, one showing an axial coupling of 12.3 Hz with one methylene proton. The ratios of diastereomers differed in the two reductions, i.e., cis:trans = 93:7 for hydrogenation and 70:30 for zinc reduction. The reduced products were readily reoxidized, returning smoothly to deoxymethoxatin triester **10** with 3,5-dinitrobenzoyl *tert*-butyl nitroxide radical[29] and forming the dinitro compound **13a** on nitration.

With the amino group now established on the central ring (**13c**) the way was opened to its further oxidation to the quinone. Here, singlet oxygen photochemically generated led only to decomposition of **13c**, but thermally generated from an ozone/bicyclic phosphite complex,[30] it afforded a poor yield of **16**. Using 3,5-dinitrobenzoyl *tert*-butyl nitroxide as oxidant[29] also led to a poor yield of quinone, and Fremy's salt was unreactive with **13c**. Similar oxidations of the diamine **13d** failed completely. However, in a remarkably clean conversion, treatment of **13c** with activated manganese dioxide in sulfuric acid at 0 °C for 35 min gave a 92% yield of the nitroquinone **16a** as bright orange crystals. Hydrogenation of the nitro group over platinum quantitatively yielded the aminohydroquinone **17** as a black solid, and this in turn was diazotized to an orange diazoquinone, formulated as **18** in accord with its spectra, especially with the infrared peak at 2225 cm^{-1} and carbonyl absorption similar to that in **16a**. This diazoquinone (**18**) was directly reduced with excess hy-

(28) Porter, H. K. *Org. React. (N.Y.)* **1973**, *20*, 455.

(29) Alewood, P. F.; Calder, I. C.; Richardson, R. L. *Synthesis* **1981**, 121.

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

pophosphorus acid in acetic acid at room temperature. Some of the quinone was also reduced in this reaction but was readily restored by shaking with aqueous basic potassium ferricyanide in the working-up process.

In this way the methoxatin triester **16b** was produced in 82% yield as orange crystals from the nitroquinone **16a** without the necessity for any intervening purification of intermediates. Weinreb's procedure for saponification with lithium hydroxide[9] yielded methoxatin (**1**) as a red solid in 89% yield. Its spectral data agreed with those for natural[7b] and synthetic[8,9] methoxatin. For further comparison we converted the methoxatin to its aldol adduct with acetone **2**, and this was found to be identical spectroscopically[8] and in reverse-phase HPLC behavior with an authentic sample of the adduct.[31] The two samples mixed moved together in HPLC as a sharp peak.

Since we began our work, three other communications have appeared detailing separate syntheses of methoxatin.[8,9,11] All of these are linear syntheses (eq 1, B) and start from the central ring as a trisubstituted benzene. The most recent synthesis, from Rees,[11] is apparently the most efficient of these, affording some 24% overall yield of methoxatin from commercially available starting materials in 9 operations. In contrast our convergent synthesis affords 15% yield in 11 operations from uvitonic ester. The value of a convergent synthesis lies mainly in assembling the target from its two components *near the end of the synthesis*, and this criterion is largely vitiated in the present scheme by the five operations necessary to convert deoxymethoxatin triester **10** to the final methoxatin. Thus, if the deoxymethoxatin could be oxidized directly in the central ring, perhaps by delivering oxidant internally from the pyridine *N*-oxide, the value of convergency here would be realized and the synthesis substantially more efficient.

Experimental Section

Melting points were determined on a capillary tube melting point apparatus and are uncorrected. The denotion "mp dec" means that the compound gradually decomposed upon heating without melting. Infrared spectra (IR) were recorded on a Perkin-Elmer 137 spectrometer and ^{1}H NMR spectra were recorded on a Varian EM-390, a Bruker WH-90, or a Nicolet NT-200 NMR spectrometer. Tetramethylsilane (Me_4Si) was used as an internal standard; chemical shifts are denoted in ppm downfield to Me_4Si at δ 0. Splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained on an AEI MS-12 and absolute masses on an AEI MS-902 apparatus. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Solvents were purified by distilling from the appropriate drying agent under N_2: benzene and ether from Na/benzophenone; THF from $LiAlH_4/Ph_3CH$; CH_2Cl_2, EtOAc, and CCl_4 from P_2O_5; DMF and pyridine from CaH_2; CH_3OH from Mg. Hexane mixture was distilled and kept on molecular sieves (4 Å). **Uvitonic acid (4a)**[22] was synthesized from pyruvic acid and ammonia: ^{1}H NMR (Me_2SO-d_6) δ 8.28 (s, 1 H), 7.92 (s, 1 H), 7.48 (br s, 2 H), 2.69 (s, 3 H).

Dimethyl uvitonate (4b)[32] was prepared by Fischer esterification of uvitonic acid: ^{1}H NMR ($CDCl_3$) δ 8.43 (s, OH), 7.89 (s, 1 H), 4.00 (s, 3 H), 3.97 (s, 3 H), 2.71 (s, 3 H).

1-(4,6-Dimethyl-2-pyridyl)-2-[5-(ethoxycarbonyl)-3-pyrrolyl]ethene (7). To a solution of 2,4,6-trimethylpyridine (4.84 g, 40 mmol) in 70 mL of dry THF at −78 °C under N_2 a solution of *n*-BuLi in hexane (25.2 mL of a 1.59 M solution; 40 mmol) was added. The solution was allowed to come to room temperature, stirred for 1 h, and cooled down again to −78 °C. The orange solution of the collidine anion thus formed was added dropwise, over the course of 1 h, to a solution of ethyl 4-formylpyrrole-2-carboxylate[25] (3.34 g, 20 mmol) in 300 mL of dry THF at −78 °C through a double-ended needle by means of positive nitrogen pressure. During the first half of the addition the solution turned yellow but stayed clear; thereafter a yellow precipitate formed. After the mixture was stirred for another hour at −78 °C, excess NH_4Cl was added and the mixture was allowed to come to room temperature. Water was added and the layers were separated. The aqueous layer was extracted with ether (2×), and the combined organics were washed with brine and dried on Na_2SO_4. The solvents were evaporated to leave 7.69 g of a yellow oil. Purification over a silica gel column (220 g), eluting with 2:1 ether/hexane followed by ether, yielded 4.99 g (17.3 mmol, 87%) of alcohol **6** as a slightly yellow sticky gum: ^{1}H NMR ($CDCl_3$) δ 9.52 (1 H, br s), 6.92 (2 H, m), 6.83 (1 H, s), 6.76 (1 H, s), 5.10 (1 H, t, J = 6.2 Hz), 4.9 (1 H, br s), 4.29 (2 H, q, J = 7.0 Hz), 3.06 (2 H, d, J = 6.2 Hz), 2.50 (3 H, s), 2.28 (3 H, s), 1.34 (3 H, t, J = 7.0 Hz); IR (CH_2Cl_2) 3550, 3400, 3050, 1685, 1605 cm^{-1}.

A chilled solution of the alcohol **6** (1.15 g, 4 mmol) in 24 mL of CH_2Cl_2 was treated with pyridine (3 mL) followed by mesyl chloride (0.31 mL, 8 mmol). The resulting solution was allowed to come to room temperature and stirred overnight. The solution was evaporated at high vacuum (0.1–0.5 torr) to remove CH_2Cl_2 and pyridine. The residue was partitioned between aqueous $NaHCO_3$ and ether, and the aqueous layer was extracted once more with ether. The combined ether layers were washed with brine, dried on Na_2SO_4, and evaporated. The oily residue was kept under high vacuum overnight, which resulted in crystallization. The crystalline material (0.64 g, 2.37 mmol, 59%), mp 133–138 °C, was recrystallized from hexane CH_2Cl_2 to 0.47 g of **7** (1.74 mmol, 44%) of beige crystals: mp 138–142.5 °C; ^{1}H NMR ($CDCl_3$) δ 9.78 (1 H, br s), 7.43 (1 H, d, J = 16.0 Hz), 7.10 (2 H, m), 6.93 (1 H, s), 6.85 (1 H, d, J = 16.0 Hz), 6.75 (1 H, s), 4.20 (2 H, d, J = 7.0 Hz), 2.50 (3 H, s), 2.27 (3 H, s), 1.33 (3 H, t, J = 7.0 Hz); IR (KBr) 3270, 1695, 1645, 1600 cm^{-1}; MS, m/e 270 (97), 269 (42), 223 (49), 197 (100), 196 (88); absolute mass, calcd for $C_{16}H_{18}N_2O_2$ 270.137, found 270.135.

Bromination of Dimethyl Uvitonate. Dimethy uvitonate (**4b**) (22.30 g, 0.107 mol) was dissolved in 570 mL of dry CCl_4. NBS (9.60 g, 0.054 mol) was added, and the mixture was irradiated and kept at reflux by means of a Sylvania sunlamp. After 1.5 h the solution was cooled and filtered, the solvent was evaporated, and the residue was purified on a column of silica gel (700 g). The column was eluted first with ether/hexane (1:1), yielding 1.78 g (4.0 mmol, 5%) of dimethyl 6-(dibromomethyl)-2,4-pyridinedicarboxylate as white crystals, mp 68–71 °C after one crystallization from hexane: ^{1}H NMR ($CDCl_3$) δ 8.95 (2 H, m), 7.07 (1 H, s), 4.16 (6 H, s); IR (KBr) 1730 cm^{-1}; MS, m/e 369 (1), 367 (2), 365 (1), 288 (100), 286 (99); MS, calcd for $C_{10}H_9Br_2NO_4$ 364.890, found 364.891.

Further elution of the column with ether/hexane (5:4) yielded 10.03 g (34.9 mmol, 33%) of dimethyl 6-(bromomethyl)-2,4-pyridinedicarboxylate (**8a**) as slightly yellow crystals. Sublimation [100–105 °C (0.04 torr)] afforded an analytically pure sample, white crystals: mp 105.5–107 °C; ^{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); IR (KBr) 1725 cm^{-1}; MS, m/e 289 (4), 287 (4), 231 (59), 229 (100), 151 (41). Anal. Calcd for $C_{10}H_{10}BrNO_4$: C, 41.69; H, 3.50; Br, 27.74; N, 4.86. Found: C, 41.49; H, 3.40; Br, 27.90; N, 4.84.

Finally, elution with ether/hexane (4:1) afforded 12.81 g (57.3 mmol, 57%) of starting material. Reaction with 1.2 equiv of NBS yielded the three successive fractions in amounts of 18%, 42%, and 36%.

***trans*-Olefin 9.** Monobromide **8a** (5.33 g, 18.5 mmol) was dissolved in 90 mL of dry benzene. Triphenylphosphine (6.56 g, 25 mmol) was added, and the solution was refluxed for 3 h under a dry atmosphere. The off-white precipitate was filtered, washed with dry benzene, and dried under high vacuum overnight. This yielded 10.21 g (18.6 mmol, 100%) of the phosphonium bromide **8b**.

The phosphonium salt **8b** (8.25 g, 15 mmol) was dissolved in 80 mL of dry DMF. NaH (0.42 g, 18 mmol) was added and the solution was stirred at room temperature under nitrogen till hydrogen evolution ceased and another half hour after that, to-

(31) We thank Professor S. M. Weinreb for a sample of synthetic methoxatin and Professor H. S. Forrest for a sample of the acetone adduct **2** of native methoxatin.

(32) Pouteau-Thouvenot, M.; Padikkala, J.; Barbier, M. *Biochimie* **1972**, *54*, 115.

taling 2.5 h. The deep red solution of the ylide was transferred by dry syringe to a solution of aldehyde **5a**[25] (2.64 g, 15.8 mmol) in 40 mL of dry DMF under N_2, and the resulting solution was stirred at 65 °C for 4 h. The red color of the solution turned to yellow. After the mixture cooled to room temperature an equal volume of ice–water was added slowly, causing the appearance of a yellow crystalline precipitate. After 10 min of stirring, the precipitate was filtered off and washed several times with water. Drying under high vacuum overnight resulted in 4.5 g (12.6 mmol, 84%) of pure olefin **9** (>95% trans by NMR) uncontaminated by Ph_3PO or starting materials. Pure *trans*-olefin was obtained after one crystallization from benzene as yellow crystals: mp 201–204 °C; ^1H 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); IR (KBr) 3550, 3150, 1755, 1695, 1670, 1575 cm^{-1}; UV (EtOH) λ_{max} 231 (ϵ 21 000), 327 (28 000) nm; MS, m/e 358 (67), 329 (57), 311 (57), 149 (100). Anal. Calcd for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.28. Found: C, 60.46; H, 5.18; N, 7.76.

***cis*-Olefin 9.** A solution of 75 mg of the cis–trans mixture of olefins, prepared above, in 250 mL of dry benzene was irradiated with a 550-W medium-pressure Hg lamp (Hanovia) through a Pyrex cooling well. Nitrogen was sparged through the solution 15 min prior to irradiation and slowly throughout the reaction. After 2 h of irradiation the solvents were evaporated to yield 75 mg (100%) of *cis*-olefin **9**. One crystallization from CH_3OH gave yellow crystals: mp 176–180 °C; ^1H 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, dd, 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); IR (KBr) 3480, 3100, 1740, 1680, 1630, 1550 cm^{-1}; UV (EtOH) λ_{max} 325 (ϵ 17 300) nm; MS, m/e 358 (100), 329 (60), 311 (39), 149 (83). Anal. Calcd for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.29; H, 5.14; N, 7.77.

Deoxymethoxatin Triester 10. Olefin **9** directly from Wittig coupling (1.50 g, 4.19 mmol) and diphenyl diselenide (3.00 g, 9.61 mmol) were dissolved in 5 L of a mixture of dry benzene and dry ether (4:1). After N_2 was bubbled through for 20 min, the solution was irradiated with a 500-W medium-pressure Hg lamp (Hanovia) through a Pyrex cooling well. Irradiation was continued for 3–4 weeks. The course of the reaction was followed by TLC (silica, CH_2Cl_2/CH_3OH, 2%). After practically all starting material had been consumed the solvent was evaporated, and the residue was extracted with two 75-mL portions of hexane to remove most of the diphenyl diselenide. The residue was purified by flash chromatography (silica, CH_2Cl_2/CH_3OH, 2%) followed by medium-pressure LC (silica, CH_2Cl_2/dioxane, 3%). One crystallization from CH_3OH afforded 0.68 g (1.91 mmol, 46%) of deoxymethoxatin triester **10** as yellow crystals: mp 174–176 °C; ^1H NMR ($CDCl_3$) δ 12.47 (1 H, br 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 turns into two doublets: δ 8.05 (1 H, d, J = 9.0 Hz), 7.59 (1 H, d, J = 9.0 Hz)]; IR (KBr) 3450, 3050, 1730 cm^{-1}; UV EtOH) λ_{max} 212 (ϵ 24 000), 274 (14 000), 306 (47 000), 378 (7700) nm; MS, m/e 356 (100), 298 (70), 252 (69). Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.55; H, 4.59; N, 7.77.

3,5-Dinitrodeoxymethoxatin Triester 13a. To an ice-cooled mixture of fuming of HNO_3 (4 mL) and concentrated H_2SO_4 (4 mL) was added 400 mg (1.12 mmol) of deoxymethoxatin triester **10**. The flask was stoppered and shaken vigorously for 20 s and stirred for 10 min at 0 °C. The red solution was poured into ice, and the precipitate was filtered and washed several times with water. Drying under high vacuum over $CaCl_2$ overnight afforded 467 mg (1.06 mmol, 94%) of **13a** as a yellow solid, which was pure by TLC (silica, CH_2Cl_2/CH_3OH, 2%) and recrystallized from $ClCH_2CH_2Cl$/hexane: mp 244–248 °C; ^1H NMR (Me_2SO-d_6) δ 12.67 (1 H, br s), 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); IR (KBr) 3380, 3060, 1760, 1720, 1540, 1520 cm^{-1}; UV (EtOH) λ_{max} 261 (ϵ 86 000), 307 (66 000), 413 (52 000); MS; m/e 446 (82), 388 (100), 298 (53). Anal. Calcd for $C_{18}H_{14}N_4O_{10}$: C, 48.44; H, 3.16; N, 12.55. Found: C, 48.30; H, 3.17; N, 12.45.

3-Nitro-5-aminodeoxymethoxatin Triester 13c. 3,5-Dinitrodeoxymethoxatin **13a** (292 mg, 0.65 mmol) was dissolved in 22 mL of DMF. Upon addition of 900 mg of freshly prepared $Na_2S_2{\cdot}5H_2O$[33] the solution turned green. After the mixture was stirred for 30 min at room temperature the reaction was quenched by adding concentrated HCl dropwise till the solution turned pink. Ice and water were added to double the volume, and the resulting mixture was centrifuged. The supernatant was discarded and the remaining solid was washed with dilute HCl (pH 4). The centrifuging–washing sequence was repeated two times. A $NaHCO_3$ solution (4%) was then added, and after a brief stirring, the solution was centrifuged again. The basic solution was decanted and the procedure was repeated once more with the residue. The combined supernatants were acidified carefully with concentrated HCl, and the red precipitate was isolated by centrifuging and washing two times with dilute HCl (pH 4) as before. The precipitate was removed from the centrifuge tube with CH_3OH and after evaporation of the solvent dried under high vacuum overnight for a yield of 270 mg (0.67 mmol, 102%) of the red-brown product **14**: ^1H NMR (Me_2SO-d_6) δ 8.57 (1 H, s), 7.46 (1 H, s), 4.38 (2 H, q, J = 7.0 Hz), 4.07 (3 H, s), 1.37 (3 H, t, J = 7.0 Hz). The acid **14** was dissolved in 200 mL of a CH_2Cl_2/CH_3OH solution (3:2), and diazomethane was added as a solution in ether in small increments of 1 mL each. After each addition a TLC was taken (silica, CH_2Cl_2/CH_3OH, 4%) to ensure that no excess CH_2N_2 was added beyond the completion of the esterification since this led to methylation of the amino group. The solvent was evaporated and the product was purified on a column of silica gel eluting 224 mg (0.54 mmol, 92%) of **13c** as beautiful bordeaux red crystals: mp dec; ^1H NMR ($nCDCl_3/CD_3OD$) 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); IR (KBr) 3630, 3490, 3300, 3030, 1710, 1675 cm^{-1}; UV (EtOH) λ_{max} 215 (ϵ 27 600), 261 (14 000), 330 (28 800), 412 (11 000) nm; MS; m/e 416 (86), 326 (89), 266 (100), 235 (98), 208 (100). Anal. Calcd for $C_{18}H_{16}N_4O_8$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.75; H, 4.01; N, 13.24.

3-Nitromethoxatin Triester 16a. 3-Nitro-5-aminodeoxymethoxatin triester **13c** (100 mg, 0.24 mmol) was added to 8 mL of ice-cold concentrated H_2SO_4, and the mixture was stirred till all the starting material had dissolved (7 min). Activated MnO_2 (150 mg, 1.72 mmol) was added all at once, and the mixture was stirred at 0 °C for 30 min. The reaction mixture was poured on ice, and the resulting slurry was filtered through a pad of Celite. The Celite was then washed with H_2O (2×), CH_2Cl_2 (2×), CH_3OH (1×), and CH_2Cl_2 (2×). The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried on Na_2SO_4, and evaporated to give 97 mg (0.22 mmol, 92%) of **16a** as bright orange crystals, pure by TLC (silica, CH_2Cl_2/CH_3OH, 5%) and ^1H NMR. An analytically pure sample was prepared by crystallizing once from CH_2Cl_2/ether: mp 241–245 °C dec; ^1H 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); IR (KBr) 3570, 1730 cm^{-1}; UV (EtOH) λ_{max} 243 (ϵ 15 700), 280 (11 000), 344 (14 000); MS, m/e 431 (65), 399 (100), 254 (72). Anal. Calcd for $C_{18}H_{13}N_3O_{10}$: C, 50.13; H, 3.04; N, 9.74. Found: C, 49.99; H, 3.15; N, 9.56.

3-Aminohydroquinone Triester 17. 3-Nitroquinone triester **16a** (55 mg, 0.127 mmol) was dissolved in 10 mL of CH_3OH; 5 mg of PtO_2 was added, and the solution was hydrogenated for 3 h. After evaporation of the solvent 20 mL of CH_2Cl_2/CH_3OH (9:1) was added, and the solution was filtered over a pad of Celite. The Celite was washed repeatedly with the same solvent mixture till the filtrate was colorless. Evaporation of the filtrate gave a black solid, which was dissolved in 20 mL of CH_2Cl_2/CH_3OH (9:1). After filtration and evaporation 50 mg (0.124 mmol, 98%) of **17** as a black solid (CH_2Cl_2/hexane) was left, pure by ^1H NMR and TLC: mp dec; ^1H NMR ($CDCl_3$) δ 12.61 (1 H, br s), 8.85 (1 H, s), 6.14 (2 H, br s), 4.40 (2 H, q, J = 7.1 Hz), 4.14 (3 H, s), 4.05 (3 H, s), 1.64 (2 H, br s), 1.42 (3 H, t, J = 7.1 Hz); IR (KBr) 3630, 3510, 3340, 3070, 1730, 1700, 1670, 1620 cm^{-1}; UV (EtOH) λ_{max} 249 (ϵ 17 500), 340 (8000), 430 (8600); MS, m/e 403 (98), 357 (100), 314 (39), 297 (39); MS, calcd for $C_{18}H_{17}N_3O_8$ 403.

Methoxatin Triester 16b. Aminohydroquinone triester **17** (16.9 mg, 0.042 mmol) was dissolved in 3 mL of ice-cold concentrated HCl. An ice-cold solution of 25 mg of $NaNO_2$ in 1 mL

(33) Gabel, Y. O.; Shpeier, L. F. *J. Gen. Chem. USSR (Engl. Transl.)* **1947**, *17*, 2277.

of H_2O was added dropwise, and the resulting solution was stirred for another 20 min at 0 °C. The solution was extracted three times with CH_2Cl_2 and dried over Na_2SO_4. TLC (silica, $CH_2Cl_2CH_3OH$, 5%) shows one spot. Evaporation yielded 15.3 mg (0.037 mmol, 89%) of orange diazoquinone triester **18** as a solid: IR $(CH_2Cl)_2$ 2225 cm^{-1}. Of this material 14.6 mg (0.035 mmol) was added to 3 mL of HOAc, followed by 12 drops of 50% H_3PO_2. The diazoquinone triester gradually dissolved upon stirring at room temperature. The course of the reaction was followed by TLC (alumina, CH_2Cl_2/CH_3OH, 5%; the product appears as a fluorescent spot). After all the starting material had been consumed (25 min to 1 h) ice and water were added to the reaction mixture, and the resultant solution was extracted with CH_2Cl_2 till the aqueous layer was colorless. The CH_2Cl_2 solution was vigorously shaken with a solution of $K_3Fe(CN)_6$ in H_2O to which some $NaHCO_3$ had been added (pH 10). This was repeated once more after which the organic solution had turned from dark red to orange. The solution was dried (Na_2SO_4) and evaporated to yield 11.8 mg (0.031 mmol, 86%; 77% over the two steps) of methoxatin triester **16b** as an orange solid, pure by TLC (alumina, CH_2Cl_2/CH_3OH, 5%) and ^1H NMR. A sample was crystallized from CH_2Cl_2/ether, orange crystals: mp 199–205 °C; ^1H 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 (ϵ 15700), 313 (10900), 377 (5900) nm; IR (CH_2Cl_2) 3360, 3050, 1725, 1685 cm^{-1}; MS, m/e 388 (28), 386 (21), 358 (49), 344 (30), 342 (50), 300 (62), 286 (41), 282 (32), 254 (100) (calcd for $C_{18}H_{16}N_2O_8$: 388).

Methoxatin (1). Methoxatin triester **16b** (8.7 mg, 0.023 mmol) was dissolved in 1 mL of THF, and 1 mL of a 0.5 M solution of LiOH in H_2O was added. The solution was stirred under N_2 for 6.5 h, after which the THF was removed under vacuum to leave a green solution. Acidification with concentrated HCl to pH 3–4 yielded a red solution that was applied to a Waters C-18 Preppak. After the solution was washed with very dilute HCl (pH 2), methoxatin was eluted with 7:3 CH_3OH/H_2O. The resulting solution was evaporated to leave 6.6 mg (0.020 mmol, 89%) of methoxatin (1) as a red solid. TLC (cellulose, 2% aqueous 1:1 NH_4OAc/1-propanol) showed one fluorescent spot. R_f 0.35 (lit.[5a] R_f 0.33 for natural methoxatin). The material synthesized by Gainor and Weinreb[9,31] had the same R_f and fluorescent appearance in this system; a mixture of the two compounds moved as one peak: ^1H NMR (CD_3OD) δ 8.73 (1 H, s), 7.27 (1 H, s); UV (H_2O, pH 5) λ_{max} 250 (ϵ 19200), 327 (10300) nm.

4,5-Dihydro-5-hydroxy-4-oxo-5-(2-oxopropyl)-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylic Acid (2). Synthetic methoxatin (2.1 mg, 6.4 μmol) was dissolved in 0.5 mL of 10% acetone/H_2O, and the solution was brought to pH 9 with dilute NH_4OH. After 30 min the color of the solution had changed from orange-brown to yellow and concentrated HCl was added to pH 2.5. The solution was evaporated to give a yellow solid, which was purified further by HPLC using a Waters C-18 Bondapak with radial pressure. The solvent used for elution was 15.5 mM KH_2PO_4 in H_2O (brought to pH 2 with H_3PO_4) and CH_3OH (8:3).[7a] The fractions containing the pure acetone adduct were pooled, CH_3OH was evaporated, and the resulting solution was applied to a Waters Preppak C-18. After the solution was washed with dilute HCl (pH 2), the product was eluted with 7:3 CH_3OH/H_2O. Evaporation gave 1.7 mg (4.4 μmol, 68%) of **2** as a faintly yellow solid: ^1H NMR (Me_2SO-d_6) δ 13.43 (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 (ϵ 14300), 320 (4500) 363 (6200). Our synthetic acetone adduct was identical in HPLC behavior with an authentic sample;[7a] a mixture of the two compounds also appeared as a single peak. The two compounds also have an identical UV spectrum. Furthermore, the ^1H NMR spectrum of our compound matches exactly the spectrum reported by Gainor and Weinreb.[9]

3-Nitrodeoxymethoxatin Triester 12a. Ac_2O (2 mL) was cooled in ice, and 0.3 mL of fuming HNO_3 was added slowly dropwise. To this cold solution was added deoxymethoxatin triester **10** (73 mg, 0.21 mmol), and stirring was continued at 0 °C for 2 1/2 h. The orange solution was poured onto a mixture of ice and $NaHCO_3$, and the resulting suspension was extracted 3× with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine and dried over Na_2SO_4, and the solvent was evaporated. After some hours under high vacuum the residue crystallized to 83 mg (0.21 mmol, 100%) of yellow crystals, recrystallized (CH_2Cl_2/hexane) to mp 186–191 °C: ^1H NMR ($CDCl_3$) δ 13.23 (1 H, br s), 8.32 (1 H, d, J = 9.2 Hz), 7.99 (1 H, d, J = 9.2 Hz), 4.41 (2 H, q, J = 7.0 Hz), 4.11 (3 H, s), 4.05 (3 H, s), 1.41 (3 H, t, J = 7.0 Hz); IR 3350, 3170, 1760, 1730, cm^{-1}; MS, 402 (M + 1, 22), 401 (100), 343 (69), 253 (34); absolute mass, calcd for $C_{18}H_{15}N_3O_8$ 401.086, found 401.088.

3,5-Diaminodeoxymethoxatin Triester 13d. 3,5-Dinitrodeoxymethoxatin triester 13a (54 mg, 0.12 mmol) was dissolved in 4 mL of a 1:1 EtOAc/EtOH mixture. A small amount of PtO_2 was added and the solution was hydrogenated (1 atm) overnight. The solution was filtered over Celite, and the Celite was washed with CH_2Cl_2 till a clear solution resulted. The combined solutions were evaporated to leave 52 mg of a brown solid, which was crystallized from CH_2Cl_2/hexane, brown crystals: mp 194 °C dec; ^1H NMR ($CDCl_3$) δ 11.83 (1 H, br s), 8.68 (1 H, s), 6.98 (1 H, s), 4.31 (2 H, q, J = 7.0 Hz), 4.21 (4 H, br s), 4.12 (3 H, s), 4.05 (3 H, s), 1.45 (3 H, t, J = 7.0 Hz); IR (KBr) 3570, 3480, 3040, 1760, 1720, 1680 cm^{-1}; MS, m/e 386 (100), 340 (91), 297 (21). For further characterization the compound was converted into the dicarbamate **13e** by reaction with $(EtO)_2CO$ in refluxing $ClCH_2CH_2Cl$. The product was purified on a silica column (CH_2Cl_2/CH_3OH, 0–4%) and crystallized from CH_2Cl_2/ether, orange crystals: mp 245–251 °C; ^1H NMR ($CDCl_3$ + CD_3OD) δ 8.89 (1 H, s), 8.85 (1 H, s), 4.47 (2 H, q, J = 7.0 Hz), 4.32 (2 H, q, J = 7.0 Hz), 4.28 (2 H, q, J = 7.0 Hz), 4.17 (3 H, s), 4.12 (3 H, s), 1.51 (3 H, t, J = 7.0 Hz), 1.41 (3 H, t, J = 7.0 Hz), 1.34 (3 H, t, J = 7.0 Hz); IR (KBr) 3050–3730, 3000, 1715, 1260, 1215 cm^{-1}; MS, m/e 531 (M + 1, 25), 530 (86), 484 (90), 438 (100), 392 (79); absolute mass, calcd for $C_{24}H_{26}N_4O_{10}$ 530.165, found 530.166.

3-Chlorodeoxymethoxatin Triester 12b. To a solution of deoxymethoxatin triester **10** (36 mg, 0.1 mmol) in 2 mL of CH_2Cl_2 was added 7 drops of *tert*-butyl hypochlorite. The reaction mixture was stirred at room temperature for 20 min, followed by evaporation without external heating. The residue was redissolved in CH_2Cl_2, and the solution was washed with a $NaHSO_3$ solution followed by washings with H_2O and brine. After the solution was dried on Na_2SO_4, it was evaporated. The residue was purified by preparative TLC (silica, CH_2Cl_2/CH_3OH 1%) to yield a high R_f fraction (a dichloride, according to MS) and a low R_f fraction that was further purified by preparative TLC (silica, CH_2Cl_2) to give **12b** as a yellow powder (23 mg, 0.06 mmol, 60%), mp 189–194 °C. A sample was sublimed [190 °C (0.05 torr)] to mp 207–210 °C: ^1H NMR ($CDCl_3$) δ 12.53 (1 H, br s), 8.87 (1 H, s), 8.02 (2 H, s), 4.48 (2 H, q, J = 7.0 Hz), 4.16 (3 H, s), 4.11 (3 H, s), 1.48 (3 H, t, J = 7.0 Hz); IR (KBr) 1710 cm^{-1}; MS, m/e 392 (36), 391 (21), 390 (100), 288 (19), 286 (57); absolute mass, calcd for $C_{18}H_{15}N_2O_6Cl$ 390.062, found 390.061.

3-Bromodeoxymethoxatin Triester 12c. Deoxymethoxatin triester **10** (24 mg, 0.067 mmol) was dissolved in dry CH_2Cl_2 (1.5 mL). A solution of Br_2 in CCl_4 (0.1 mmol of Br_2) and a small amount of iron powder were added. The solution was refluxed for 1.5 h, followed by extraction with aqueous $NaHCO_3$, H_2O, and brine. The solution was dried over Na_2SO_4 and evaporated. The residue was purified by preparative TLC (silica gel, 1% CH_2Cl_2/CH_3OH). A high R_f fraction gave an almost negligible amount of a substance believed to be the dibromide (the same compound was the exclusive product from the reaction of deoxymethoxatin triester with excess Br_2 in refluxing CH_2Cl_2 catalyzed by $AlCl_3$) according to its MS. The main fraction consisted of **12c** (24 mg, 0.056 mmol, 84%) as a yellow powder of mp 218–221 °C, sublimed 206 °C: ^1H NMR ($CDCl_3$) δ 12.63 (1 H, br s), 8.74 (1 H, s), 7.98 (2 H, s), 4.49 (2 H, q, J = 7.0 Hz), 4.18 (3 H, s), 4.13 (3 H, s), 1.51 (3 H, t, J = 7.0 Hz); IR (KBr) 1710 cm^{-1}; *MS*, m/e 436 (100), 434 (100), 378 (20), 376 (22), 332 (54), 330 (53); absolute mass, calcd for $C_{18}H_{15}N_2O_6Br$ 434.011, found 434.010.

3-Iododeoxymethoxatin Triester 12d. To a solution of deoxymethoxatin triester **10** (36 mg, 0.10 mol) in 2 mL of CH_2Cl_2 were added I_2 (18 mg, 0.07 mmol) and $PhI(O_2CCF_3)_2$[34] (22 mg, 0.052 mmol). The solution was stirred at room temperature for 45 min followed by extraction with aqueous $NaHSO_3$, H_2O, and brine. The solution was dried over Na_2SO_4 and evaporated. The

(34) Merkushev, E. B.; Simakhina, N. D.; Koveshnikova, G. M. *Synthesis* **1980**, 486.

residue was purified by flash chromatography (silica, CH_2Cl_2/CH_3OH, 0–1%) to yield the title compound as a yellow crystalline solid (49.8 mg, 0.10 mmol, 100%), mp 215–220 °C dec. No diiodination product was ever found when this procedure was used. However, from the reaction of deoxymethoxatin triester with excess I_2O_5 in refluxing DMF a compound was isolated that on the basis of MS, is presumably the diiodo compound.

^1H NMR ($CDCl_3$) δ 12.78 (1 H, br s), 8.87 (1 H, s), 8.03 (1 H, d, J = 9.0 Hz), 7.90 (1 H, d, J = 9.0 Hz), 4.48 (2 H, q, J = 7.0 Hz), 4.17 (3 H, s), 4.10 (3 H, s), 1.50 (3 H, t, J = 7.0 Hz); IR (KBr) 3350, 3050, 1725 cm^{-1}; MS, m/e 483 (M + 1, 21), 482 (100), 378 (38); absolute mass, calcd for $C_{18}H_{15}N_2O_6I$ 481.998, found 481.998.

Reduction of Deoxymethoxatin Triester 10. Method A. Zn/CF_3COOH. To a stirred solution of deoxymethoxatin triester **10** (36 mg, 0.10 mmol) in 4 mL of CF_3COOH was added a liberal excess of Zn powder. Stirring was continued for 35 min, after which the reaction mixture was evaporated without external heating. CH_2Cl_2 and aqueous $NaHCO_3$ were added, and the liquids were decanted from the remaining zinc, which was thereafter washed twice with CH_2Cl_2. The layers were separated; the aqueous layers were extracted once with CH_2Cl_2, and the combined organic layers were washed with H_2O and brine. After the solution was dried over Na_2SO_4, it was evaporated. The residue was subjected to preparative TLC (silica, CH_2Cl_2/acetone, 5%) to yield two fractions.

High-R_f compound: 9 mg (0.024 mmol, 24%) of a white crystalline solid, mp 164–167 °C (CH_2Cl_2/hexane), which was identified as *trans*-6,7,8,9-tetrahydrodeoxymethoxatin triester **15**; ^1H NMR ($CDCl_3$) δ 9.16 (1 H, br s), 7.41 (1 H, d, J = 8.8 Hz), 7.12 (1 H, d, J = 2.0 Hz), 6.56 (1 H, d, J = 8.8 Hz), 4.75 (1 H, br s), 4.53 (1 H, dd, J = 12.3 Hz, J = 2.5 Hz), 4.38 (2 H, q, J = 7.1 Hz), 4.02 (1 H, dd, J = 5.8 Hz, J = 1.5 Hz), 3.86 (3 H, s), 3.76 (3 H, s), 2.75 (1 H, ddd, J = 13.1 Hz, J = 2.5 Hz, J = 1.5 Hz), 1.85 (1 H ddd, J = 13.1 Hz, J = 12.2 Hz, J = 5.8 Hz), 1.42 (3 H, t, J = 7.0 Hz); IR (KBr) 3400, 3290, 2940, 1730, 1705, 1685 cm^{-1}; MS, m/e 360 (100), 301 (38), 241 (39), 195 (82); absolute mass, calcd for $C_{18}H_{20}N_2O_6$ 360.132, found 360.133.

Low-R_f compound: 21 mg (0.058 mmol, 58%) of a white crystalline solid, mp 99–100 °C, which was identified as *cis*-6,7,8,9-tetrahydrodeoxymethoxatin triester **15**; ^1H NMR ($CDCl_3$) δ 9.00 (1 H, br s), 7.41 (1 H, d, J = 9.2 Hz), 7.11 (1 H, d, J = 2.0 Hz), 6.55 (1 H, d, J = 9.2 Hz), 4.56 (1 H, br s), 4.37 (2 H, q, J = 7.0 Hz), 4.11 (2 H, two almost identical, superimposed dd, J = 5.5 Hz, J = 1.0 Hz, for both protons), 2.65 (2 H, two almost identical superimposed ddd, J = 14.5 Hz, J = 7.0 Hz, J = 5.5 Hz for both protons) 1.40 (3 H, t, J = 7.0 Hz); IR (KBr) 3390, 2930, 1720, 1670 cm^{-1}; MS, m/e 360 (100), 301 (36), 241 (34), 195 (70); absolute mass, calcd for $C_{18}H_{20}N_2O_6$ 360.132, found 360.132.

Method B. H_2/PtO_2, CF_3COOH. Deoxymethoxatin triester **10** (36 mg, 0.1 mmol) was dissolved in 0.8 mL of CF_3COOH. A small amount of PtO_2 was added and the solution was hydrogenated at normal pressure during 72 h. The solution was evaporated and the residue partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed with H_2O and brine, dried on Na_2SO_4, and evaporated. The residue was purified on TLC as before to yield 27 mg (0.075 mmol, 75%) of the cis and 2 mg (0.006 mmol, 6%) of the trans tetrahydro compound **15**.

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Registry No. **1**, 72909-34-3; **2**, 73030-04-3; **4b**, 80721-35-3; **5a**, 7126-57-0; **6**, 95912-16-6; **7**, 95912-17-7; **8a**, 80721-36-4; **8a** (dibromide), 95912-26-8; **8b**, 80721-37-5; **8b** (ylide), 95912-18-8; (*E*)-**9**, 80721-38-6; (*Z*)-**9**, 80721-39-7; **10**, 80721-40-0; **12a**, 95912-19-9; **12b**, 95912-20-2; **12c**, 95912-21-3; **12d**, 95912-22-4; **13** (Y = Z = I), 95912-27-9; **13a**, 80721-41-1; **13c**, 80721-43-3; **13d**, 95912-23-5; **13e**, 95912-24-6; **14**, 80721-42-2; *cis*-**15**, 95912-25-7; *trans*-**15**, 95935-33-4; **16a**, 80721-44-4; **16b**, 80721-47-7; **17**, 80721-45-5; **18**, 80721-46-6; 2,4,6-trimethylpyridine, 108-75-8.

Stereospecific Intramolecular Diels–Alder Reaction of an *o*-Quinone Methide

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An *o*-quinone methide generated by the thermal dehydration of a functionalized 2-hydroxybenzyl alcohol was found to undergo the intramolecular Diels–Alder reaction. The presence of a remote chiral center on the dienophile resulted in complete sterocontrol during the transition state for cycloaddition. The synthesis of cyclized products **13** and **18** possessing the ring system and absolute configuration of naturally ocurring cannabinols is described.

In recent years there has been a great deal of interest in the intramolecular Diels–Alder reaction.[1] This interest stems from the fact that the intramolecular Diels–Alder reaction is both regioselective and stereospecific. As a consequence of its intramolecularity, this reaction may be employed to assemble complex polycyclic molecular structures in a single step. The use of *o*-quinodimethane derivatives as eneophilic partners in the intramolecular Diels–Alder reaction is well established.[2] We became interested in the chemistry of *o*-quinone methide in connection with another study in progress in our laboratories. We sought to determine whether a suitably functionalized *o*-quinone methide would participate as a diene in the intramolecular Diels–Alder reaction. Specifically, we were interested in the generation of substituted *o*-quinone methides by the thermal dehydration of *o*-hydroxybenzyl alcohol derivatives.

The intermolecular Diels–Alder cycloaddition of *o*-quinone methide has been known for some time.[3] Since

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