same solvent and ether resulted in the successive elution of pale yellow oil: total yield 757 mg; IR (neat) 3500–2500, 2950, 1730 (br), 1400, 1240, 1160, 1060 cm^{-1}; NMR ($CDCl_3$) δ 1.5–1.9 (m, 4), 2.2–2.5 (m, 2), 3.9–4.3 (m, 2).

Microbial Oxidation of Methyl 5-Hydroxypentanoate (9). *Gluconobacter roseus* IAM 1841 was grown in 100 mL of the medium contained in two 500-mL Erlenmeyer flasks. To each flask was added a 0.5-mL (502 mg, 3.94 mmol) portion of methyl 5-hydroxypentanoate (**9**), and they incubated on a rotary shaker for 4 days at 30 °C. After addition of hydrochloric acid to pH 3–4, the combined broth was extracted with three 100-mL portions of ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration followed by evaporation of the solvent under reduced pressure gave glutaric acid monomethyl ester (**10**) as a pale yellow oil: yield 938 mg (81%); IR (neat) 3300–2500, 1740–1700, 1440, 1380, 1240, 1200, 1160, 1040 cm^{-1}; NMR ($CDCl_3$) δ 1.9–2.1 (m, 2), 2.4 (m, 4), 3.63 (s, 3).

Hydrolysis of Glutaric Acid Monomethyl Ester (10) to Glutaric Acid (7). A mixture of methanol (15 mL), a 15% aqueous solution of sodium hydroxide (5 mL), and 535 mg (3.66 mmol) of glutaric acid monomethyl ester (**10**) was stirred at room temperature for 3 h. After removal of methanol under reduced pressure, 5 mL of water and concentrated hydrochloric acid were added to the reaction mixture. Extraction with a 20-mL portion of ethyl acetate for three times and a sequence of washing with brine, drying over anhydrous sodium sulfate, filtration, and evaporation of the solvent gave glutaric acid (**7**) as white crystals: mp 95–98 °C; yield 274 mg (54%).

Microbial Oxidation of 3-Methylpentane-1,3,5-triol (11). To six 500-mL Erlenmeyer flasks containing grown cells of *Gluconobacter scleroideus* IAM 1842 in 50 mL of the medium, 3 g of 3-methylpentane-1,3,5-triol (**11**) was added in equal protions. The flasks were shaken for 3 days at 30 °C. The broth was combined and extracted with three 300-mL portions of ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtation and evaporation of the solvent gave 1.33 g of colored oil. It was subjected to column chromatography on silica gel. Elution with ethyl acetate gave (+)-(*S*)-**12** as a colorless oil: yield 915 mg (32%); IR (neat) 3400, 2960, 2910, 1720, 1235, 1125, 1065, 1020, 930, 880, 800 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 3), 1.89 (m, 2), 2.55 (m, 2), 3.37 (br s, 1) and 4.2–4.8 (m, 2); $[\alpha]^{20}_D$ +18.14° (*c* 2.27, EtOH); mp of benzhydryl amide 97–98 °C (lit. mp 98–99 °C[14b]). Anal. Calcd for $C_{10}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47%. Found: C, 72.85; H, 7.54; N, 4.25.

Registry No. **1a**, 2163-42-0; **1b**, 2612-29-5; **1c**, 2612-27-3; **1d**, 1570-95-2; (−)-(*R*)-**2a**, 1910-47-0; (±)-**3a**, 64809-29-6; (−)-(*R*)-**3a**, 72657-23-9; (±)-**3b**, 81444-76-0; (−)-**3b**, 72604-81-0; (±)-**3c**, 81444-77-1; (−)-**3c**, 72604-82-1; (±)-**3d**, 81444-78-2; **4a**, 4457-71-0; **4b**, 61898-54-2; **4c**, 829-27-6; (+)-(*R*)-**5a**, 61898-55-3; (±)-**5b**, 21754-22-3; (+)-(*R*)-**5b**, 37147-17-4; (±)-**5c**, 61949-75-5; **6**, 111-29-5; **7**, 110-94-1; **8**, 542-28-9; **9**, 14273-92-8; **10**, 1501-27-5; **11**, 7564-64-9; (+)-(*S*)-**12**, 19022-60-7.

Routes to Mitomycins. Application of Iminium Salts to the Synthesis of 7-Methoxymitosene

Jay R. Luly and Henry Rapoport*

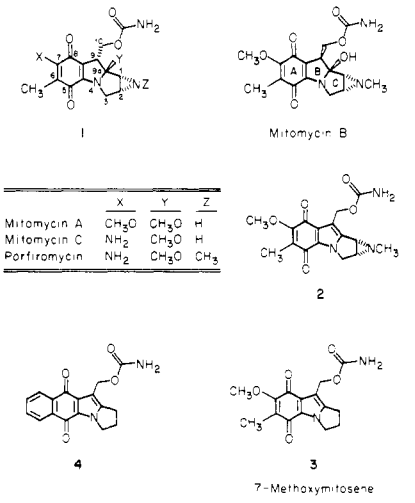
Department of Chemistry, University of California, Berkeley, California 94720

Received October 19, 1981

The synthesis of 7-methoxymitosene (**3**), a synthetic analogue of the mitomycins, is presented. Key steps include a regioselective addition of proline methyl ester to an unsymmetric benzoquinone, side-chain introduction through specific allylation, and an active methylene–iminium salt ring closure. Several methods for allylation of arenes and quinones were evaluated in building the pyrroloindole nucleus. The quinone function was incorporated in the educt, carried through as various hydroquinone derivatives, and regenerated in the very late stages by oxidative dealkylation.

The isolation, structure, chemistry, pharmacology, biosynthesis, and synthetic studies of the mitomycin antitumor antibiotics **1** and analogues have been thoroughly reviewed.[1] Further work in these areas has led to the recent isolation of new mitomycins[2] and to the preparation of mitomycin analogues with improved biological activity.[1b]

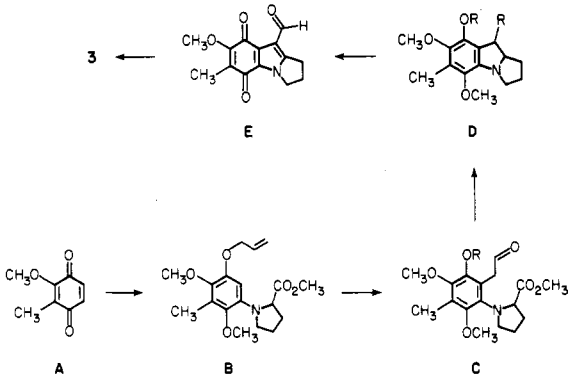
Chart I. Mitomycins and Mitosene Analogues



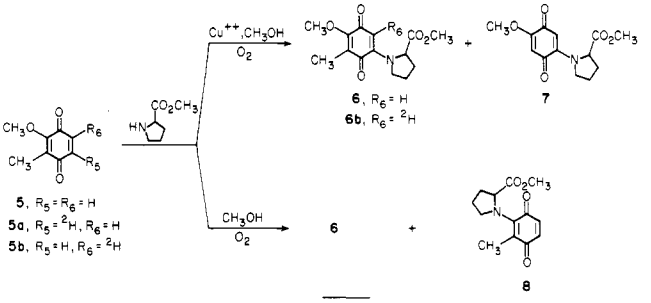
(1) (a) General: Franck, R. W. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 1. Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley: New York, 1979; Vol. 1, pp 221–76. Remers, W. A. "Mitomycin C: Current Status and New Developments"; Carter, S. K.; Crooke, S. T.; Alder, N. A., Eds.; Academic: New York, 1979. Nakano, K. *Hakko to Kogyo* **1979**, *37*, 1199. (b) Mitomycin analogues: Remers, W. A. "Medicinal Chemistry"; Academic: New York, 1980; Vol. 16, pp 131–46. Iyengar, B. S.; Lin, H.-J.; Cheng, L.; Remers, W. A. *J. Med. Chem.* **1981**, *24*, 975. Andreani, A.; Mungiovino, G. *Boll. Chim. Farm.* **1979**, *118*, 192. Andreani, A.; Mungiovino, G. *Ibid.* **1980**, *119*, 579. (c) Hornemann, U. "Antibiotics"; Corcoran, J. W., Ed.; Springer: New York, 1981; Part 4 (Biosynthesis), pp 295–312. Anderson, M. G.; Kibby, J. J.; Rickards, R. W.; Rothschild, J. M. *J. Chem. Soc., Chem. Commun.* **1980**, *24*, 1277. (d) Synthesis of pyrrolo[1,2-*a*]indoles and related systems: Kametani, T.; Takahashi, K. *Heterocycles* **1978**, *9*, 293. (e) Structure of mitomycin B: Yahashi, R.; Matsubara, I. *J. Anitibiot.* **1978**, *31*(6), correction, 78–67. (f) Total syntheses of mitomycins A, B, and C and porfiromycin: Kishi, Y. *J. Nat. Prod.* **1979**, *42*, 549. Nakatsubo, F.; Cocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835. Nakatsubo, F.; Fukuyama, T.; Cocuzza, A. J.; Kishi, Y. *Ibid.* **1977**, *99*, 8115. Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295.

0022-3263/82/1947-2404$01.25/0

Scheme I. Synthetic Plan



Scheme II. Amino Additions



The class of compounds known as mitosenes, obtained from the mitomycins by elimination of the functionality at C-9a, still possesses marked biological activity. A number of 1-substituted and 1,2-disubstituted mitosenes have antitumor and antibacterial activity,[3] and aziridinomitosene **2**, obtained from mitomycin B or *N*-methylmitomycin A, retains much of the strong antibiotic and antitumor activity of the parent compounds.[4] 7-Methoxymitosene (**3**) has important antibacterial activity in vitro and in mice (Chart I). In vitro it shows marked activity against a variety of Gram-positive organisms, including representative tetracycline- and penicillin-resistant species; however, it has only marginal activity against Gram-negative organisms.[5]

Due to their activity and simplified structures, the mitosenes have been common synthetic targets. A number of synthetic approaches to various mitosenes have been reported[6] recently, including the total synthesis of the naphthalenoid mitosene **4**.[7] The methods developed in the synthesis of this model system as well as the knowledge gained in our study of amine addition to unsymmetrical benzoquinones[8] provided the basis for the synthesis of indoloquinone aldehyde E (Scheme I), a convenient precursor to 7-methoxymitosene (**3**). The elaboration of this aldehyde to the carbamate proceeds in 60% yield and has been reported elsewhere.[5] Two previous syntheses of E[5,9] were in low yield (<1% and 6%) due in part to difficulty in introducing the quinone moiety late in the sequence. To avoid this problem, we incorporated the quinone function at an early stage and protected it as a hydroquinone dialkyl ether. This strategy allowed efficient generation of the quinone by oxidative dealkylation. It also enabled us to profit from the diverse reactivity of the quinone nucleus.

Examination of the carbon balance between quinones A and E (Scheme I) suggested that ring C could be attached by an amine addition of a proline derivative to A, and that C-9 and C-10 could be introduced by Claisen rearrangement of a corresponding hydroquinone allyl ether such as B followed by oxidative cleavage to C. Conversion of this tertiary amino acid ester to the corresponding iminium salt[10] followed by ring-B closure would provide indoline D and ultimately indoloquinone E after oxidation.

First we studied the addition of proline methyl ester to 2-methoxy-3-methyl-1,4-benzoquinone **5** (Scheme II). Unlike naphthoquinone, benzoquinone **5** has several potential sites for reaction: attack at either of the unsubstituted positions C-5 or C-6 via an addition–oxidation reaction to give **6** or its regioisomer, addition–elimination at the methoxyl C-2 position, or attack of the C-3 methyl group in an aminative-dealkylation reaction. When pyrrolidine was used as the aminating reagent, attack at C-5 was the predominant mode of addition,[8] and one would expect proline methyl ester, a more hindered and less nucleophilic amine, to give even more selective additions. This prediction was realized when a mixture of proline methyl ester, cupric acetate, and methanol under oxygen was treated with quinone **5**, and a 96% yield of **6** was obtained. Less than 1% of a side product, dealkylated aminoquinone **7**,[11] could be detected by reverse-phase HPLC (RPHPLC), the regiochemistry of which was assigned on the basis of spectral similarities with the corresponding pyrrolidine analogue isolated previously.[8]

Proline methyl ester was used in excess (usually 300 mol %); with less ester the reaction times were drastically increased, no doubt in part due to competing dioxopiperazine formation. Reactions were carried out with varying amounts of cupric salt (100–225 mol %) with no appreciable effect on the reaction, but when none was used a major side product was produced. The NMR spectrum of the product mixture showed the expected product **6** but also a characteristic C-5-H, C-6-H quinone splitting pat-

(2) Urakawa, C.; Tsuchiya, H.; Nakano, K.-I. *J. Antibiot.* **1981**, *34*, 243. Kasai, M.; Kono, M.; Shirahata, K.; Urakawa, C.; Tsuchiya, H.; Nakano, K.; Takahashi, I.; Mineura, K. *European Patent Application 8021* (Cl. C07D487/14), 20 Feb 1980, Japan Application 78/86, 748, 18 Jul 1978; *Chem. Abstr.* **1980**, *93*, P114493p.

(3) Leadbetter, G.; Fost, D. L.; Ekwuribe, N. N.; Remers, W. A. *J. Org. Chem.* **1974**, *39*, 3580. Remers, W. A.; Schepman, C. S. *J. Med. Chem.* **1974**, *17*, 729. Taylor, W. G.; Leadbetter, G.; Fost, D. L.; Remers, W. A. *Ibid.* **1977**, *20*, 138.

(4) Kinoshita, S.; Uzu, K.; Nakano, K.; Shimizu, M.; Takahashi, T.; Matsui, M. *J. Med. Chem.* **1971**, *14*, 103. Kinoshita, S.; Uzu, K.; Nakano, K.; Takahashi, T. *Ibid.* **1971**, *14*, 109. Patrick, J. P.; Williams, R. P.; Meyer, W. E.; Fulmor, W.; Cosulich, D. B.; Broschard, R. W.; Webb, J. S. *J. Am. Chem. Soc.* **1964**, *86*, 1889.

(5) Allen, G. R.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 3877; *J. Org. Chem.* **1965**, *30*, 2897.

(6) Rebek, J.; Shaber, S. *Heterocycles* **1981**, *15*, 161; *16*, 1173. Kametami, T.; Kigawa, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1607. Coates, R.; Hutchins, C. *J. Org. Chem.* **1979**, *44*, 4742. Okamoto, M.; Shunsaku, O. *Chem. Pharm. Bull.* **1980**, *28*, 1071.

(7) Falling, S. N.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 1260.

(8) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745.

(9) Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkins Trans. 1* **1976**, 389.

(10) For other examples of iminium salts generated from α-tertiary amino acids, see: Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448. Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43* 2115, 4183. Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259. Csendes, I. G.; Lee, Y. Y.; Padgett, H. C.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 4173.

(11) Dealkylations of this sort have ample precedent.[7,12] Additionally some of this side product may have resulted from a trace impurity in **5**. Commercial samples of 2-methylresorcinol, the educt for the synthesis of quinone 5,[8] obtained from Aldrich and Pfaltz and Bauer, were approximately 90% and 80% pure, respectively, containing up to 5% and 10% of resorcinol (RPHPLC, 40% CH_3CN/60% H_2O). Sublimation and recrystallization were not efficient in removing the impurity, and purification was best effected after conversion to 2,4-dimethoxy-3-methylphenol. Recrystallization (hexane/dichloromethane) at this stage provided the phenol in greater than 99% purity.

(12) Cameron, D. W.; Scott, P. M.; Todd, A. *J. Chem. Soc.* **1964**, 42; **1964**, 5569. Cameron, D. W.; Giles, R. G. G.; Titman, R. B. *J. Chem. Soc. C* **1969**, 1245.

tern. Additionally, an extra C-3 methyl and methyl ester were visible as well as a decrease in the integration of the C-2 methoxyl. These data suggest that the side product was addition–elimination adduct **8**, though chromatography on silica resulted in decomposition, and a pure sample could not be obtained. This observation is another example where a copper salt, originally used to assist oxidation of an intermediate hydroquinone,[13] plays a key role in regiochemical control.[8]

Deuterioquinones **5a** and **5b**[8] were indispensable tools in the evaluation of regiochemistry. Mass spectral comparison of the amine adducts obtained from **5** and from **5a** showed no evidence for a deuterioquinone, but to eliminate the possibility of exchange accounting for deuterium loss, we carried out the reaction with **5a** in CD_3OD. Again, only attack at C-5 occurred, though transesterification was shown by NMR and mass spectroscopy to have taken place. To prove unequivocally the mode of addition, we added proline methyl ester deuterioquinone **5b**. The proton NMR spectrum of the reaction product revealed the presence of approximately 99% $^2H_1$. It should be noted that aminoquinone **6b** does not exchange as readily as its pyrrolidinyl analogue,[8] and chromatography with 4% triethylamine/96% ether resulted in no detectable deuterium loss.

With aminoquinone **6** in hand we next sought to protect it as a hydroquinone dialkyl ether and to introduce the side chain necessary for ring closure. Protected quinone **14a** (Scheme III) was the target molecule since oxidative cleavage of the allyl group would give the desired acetaldehyde residue. If the allyl group were to be introduced into the aromatic nucleus by Claisen rearrangement of a hydroquinone allyl ether, it would be best to prepare regiospecifically only a monoallyl ether. A simple and effective monoallylation procedure proved to be reduction of aminoquinone **6** to hydroquinone **9**, lactonization to **10**, and allylation to **11**. This sequence was carried out in one flask in 75% yield.

At this point, the synthesis of **14a** was approached by two related routes which differed in the order of the steps. Path A, requiring one less step, was considered first and involves rearrangement and then methylation of the lactone hydrolysis product. The attempted rearrangement in acetic anhydride was an atmospheric pressure modification[7] of the sealed tube method[14] and was applied in an effort to trap the resulting phenol as acetate **12**. Several tries along these lines led to the formation of complex mixtures, only partial separation of which could be achieved. Rearrangement occurred, however, when **11** was refluxed in diethylaniline. The NMR spectrum of the crude crystalline reaction product showed loss of the aromatic proton in addition to an upfield shift of the allyl methylene protons from 4.5 to 3.4 ppm. Purification was postponed since a portion of the highly electron rich and air sensitive phenol **13** underwent partial decomposition to several products on silica TLC and during recrystallization. Instead, **13** was permethylated directly.[7,15] After chromatography, a moderate yield of a 7/3 mixture of **14a** and **15** was isolated. Phenol **10** was not detected in the rearrangement product mixture by NMR, due in part to the masking of the aromatic hydrogen by the highly split β-allyl proton of **13**, but the isolation of **15** demonstrated its presence and indicated that the substrate was undergoing partial loss of the allyl group during rearrangement.

To study this point more thoroughly, we considered the lactone opening/rearrangement route (Path B). It has been our experience that compounds in which the lactone has been opened and methylated (e.g., **16**) were more stable to air, distillation, and various chromatographic conditions than were those containing the lactone (e.g., **11**). Furthermore, the rearrangement products could be analyzed directly rather than after methylation. On changing the solvent to DMF, alkylations **10** → **11** → **16** could be carried out in one flask in 81% yield. When quinone **6** was incorporated into this essentially one-step (five transformations) sequence an improved overall yield of 88% (95% RPHLC purity) of **6** to **16** was achieved; purification was postponed until after the rearrangement.

Allyl ether **16** underwent rearrangement in refluxing diethylaniline to give a mixture of phenols **17** and **18**, and column chromatography led to isolated yields of 61% and 26%, respectively. As phenol **18** was of interest for C-alkylation studies described below, it was independently synthesized from **10** by benzylation to **19**, lactone opening and methylation, and hydrogenolysis of the *O*-benzyl group. Phenol **18** also could be recycled to **16** quantitatively by treatment with allyl bromide and alkali. Phenol **17**, obtained in 82% yield based on recycled **18**, was then methylated to afford the desired methyl ether **14a** in 88% yield. The loss of the allyl group and other mechanistic details of the rearrangement are presently under investigation.

Several alternative methods of side-chain introduction were considered. In principle, one should be able to prepare **14a** by dimethylating the hydroquinone of the corresponding *p*-quinone **25**. Two conceivable approaches to this quinone, aminating allylquinone **24** and allylating aminoquinone **6**, are outlined in Scheme IV. Allylquinone **24** was prepared by allylation of phenol **21**[16] with allyl bromide, rearrangement of the resulting allyl ether **22** to phenol **23** in refluxing diethylaniline, and oxidation of **23** with either argentic oxide[17] or nitric acid in dichloromethane.[8] This route to **24** is similar to a previously reported synthesis[1f] in which experimental details were not provided. The amine addition reaction of proline methyl ester and **24** was carefully monitored, but no useful product was obtained. It resulted in the formation of several colored products most of which were likely the result of amination of alkyl substituents.[12]

Due to the enormous interest in isoprenoid quinones, there have been a number of methods reported for the direct introduction of allylic side chains into aromatic and quinone nuclei. A variety of allylic units and quinones have been quite successfully coupled with use of trialkylallylstannanes which are prepared from the corresponding allylic Grignard reagent and trialkyltin chloride.[18] When quinone **6** was treated with tripropylallyltin, a low conversion took place not to the desired allylquinone **25** but to the addition–elimination product **26**. Because of this result and due to possible interference by the ester and by the vinylogous amide resonance of aminoquinones,[7] alternative allylating reagents for quinone **6**,[19] or for

(13) Baltzly, R.; Lory, E. *J. Am. Chem. Soc.* **1948**, *70*, 861. Crosby, A. H.; Lutz, R. E. *Ibid.* **1956**, *78*, 1233.
(14) Karanewsky, D. S.; Kishi, Y. *J. Org. Chem.* **1976**, *41*, 3026.
(15) Kuhn, R.; Trushman, H. *Chem. Ber.* 1961, *94*, 2258. Bondinell, W. E.; DiMari, S. J.; Frydman, B.; Matsumoto, K.; Rapoport, H. *J. Org. Chem.* **1968**, *33*, 4351.
(16) Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* 1974, 1353.
(17) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227; **1974**, *96*, 8046.
(18) (a) Naruta, Y. *J. Am. Chem. Soc.* **1980**, *102*, 3774. (b) Naruta, Y. *J. Org. Chem.* **1980**, *45*, 4097. (c) Naruta, Y.; Maruyama, K. *Ibid.* **1978**, *43*, 3796.
(19) (a) Allylsilanes: Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1977**, 4041. (b) π-Allylnickel halide complex: Hegedus, L. S.; Evans, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 3461.

masked quinones that might be derived from **6**,[20] were not considered.

Classically,[21] prenylated quinones have been prepared by treatment of the hydroquinone with the corresponding allylic alcohol in the presence of an acid catalyst, most commonly boron trifluoride etherate. Conversion to the quinone was then performed by mild oxidation. When hydroquinone **9** was allowed to react under these conditions, a sluggish reaction gave a substantial quantity of **6** and several other products. Lewis acid binding to the lone-electron pairs of the ring substituents no doubt deactivated **9** toward substitution. As the side products were probably derived in part from competitive mono- or di-O-alkylation, phenols **10** and **18** were considered next since spectral data for their O-allylation products (**11** and **16**) and for their C-allylation products (**13** and **17**) are available. Thus, NMR was used as a qualitative tool to see if enough C-allylation was realized to make the procedure a practical synthetic alternative.

Treatment of either phenol **10** or **18** with a sulfinylamine ester,[22] formed from the sulfinylamine of methyl anthranilate and allyl alcohol, gave O-alkylation and recovered starting material; no C-alkylation could be detected. Recently, a careful study of C-alkylation of phenol showed that best results were obtained by sequential treatment with sodium and the corresponding allylic chloride in ether.[23] Phenol **10** was subjected to these conditions, but only starting material was isolated. The absence of reactivity in our system can be explained in part by the heterogeneous nature of the reaction conditions, though it should be noted that heterogeneous alkylations, when they do occur, tend to favor C-alkylation.[24] One could further examine the dielectric constant[25] and the hydrogen-bonding capacity[26] of the solvent used, but the evidence indicates that even the best conditions result in significant O-alkylation.

As the preparative separation of allyl ether **16** and phenol **17** proved to be more difficult than that of phenol **18** and **17**, preparation of **17** by rearrangement seemed to be the efficacious route. Another rationale for pursuing path B is that it gives us added versatility in quinone protecting groups. Exemplary of this idea is benzyl ether **14b** obtained from the treatment of phenol **17** with benzyl bromide. When the quinone is needed, one could simply oxidatively dealkylate this hydroquinone mixed diether directly, or as an alternative one could debenzylate and oxidize the corresponding hydroquinone monomethyl ether, a process which in some cases has led to improved yields over the dialkyl ether oxidation.

The acetaldehyde side chain was then derived from **14** by a standard catalytic osmium tetraoxide/sodium metaperiodate procedure. In this way aldehydes **27a** and **27b** were both obtained in 85% crude yield. An attempt to remove polar impurities by column chromatography resulted in substantial decomposition of both aldehydes. We were encouraged, however, by subsequent preparations of **27a** in which the crude mixture was efficiently carried on in the next step without further purification.

The dimethyl acetal functionality, a source of enol ether in acidic media, provides the activation necessary for the iminium salt ring closure (Scheme V).[27] Conversion of aldehydes **27a** and **27b** to acetal esters **28a** and **28b** proceeds smoothly with excess trimethyl orthoformate and *p*-toluenesulfonic acid in dry methanol. The acetal can be isolated, but generally it is hydrolyzed directly to amino acid **29** with potassium hydroxide in aqueous methanol. Thus, when the acetalization and hydrolysis steps were performed on aldehydes **27a** and **27b**, yields of greater than 90% of the corresponding amino acids were realized.

Next, the iminium salt ring closure was carried out by heating the amino acid with excess phosphorus oxychloride followed by cooling and quenching the excess $POCl_3$ with methanol. A crude reaction mixture obtained in this way was examined by RPHPLC and indicated that the resulting indoline acetal **30** was greater than 85–90% pure. In addition to polar contaminants, 1–2% of the corresponding indole aldehyde **32** could be seen, the result of oxidation and deacetalization. Also, 5–10% of a compound which was only slightly less polar than **30** was evident. Conceivably, this product represents the minor diastereomer from ring closure, either *cis*-**30** or *trans*-**30**, although attempted purification of the reaction mixture by chromatography on Florisil gave only the major component and in poor recovery. Crude reaction mixtures have been subjected to vacuum drying in an effort to remove residual trimethyl phosphate generated in the isolation, but drying for extended periods or at an evelated temperature resulted in considerable decomposition. In view of these instabilities, indoline acetal is best carried on to the more stable indole aldehyde **32**. Treatment of **30** with DDQ in acetone/methylene chloride performed the oxidation to **31**, which under the reaction conditions was deacetalated to give **32**. Filtration of this crude material through a small column of neutral alumina provided **32b** in 61% overall yield from **27b**. Also, **32a** was obtained in 52% chromatographed yield when **14a** was carried through the entire sequence.

The relative stereochemistry of indoline **30** is not known; ring closure of enol ether/iminium salt **33** could proceed to either *cis*- or *trans*-**30** as shown in Scheme VI. The 90- and 250-MHz NMR spectra of the product isolated show proton H_b appearing as a broadened triplet centered at δ 3.58 (J_{ab} =3.7 Hz, J_{bc} = 3.1 Hz). Though molecular models suggest that the path leading to *trans*-**34** is less sterically encumbered, the use of transition state arguments in predicting the stereochemical outcome of the reaction is uninformative as *cis*- and *trans*-**34** could readily equilibrate through enol ether **35** under the reaction conditions.

Next, the oxidative dealkylation to indoloquinone **36** was examined. Treatment of **32a** with ceric ammonium nitrate

(20) (a) Cuprate of quinone bisketal alkylation: Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *J. Chem. Soc., Chem. Comm.* **1977**, 499. Chenard, B. L.; Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 378. (b) Grignard addition to cyanosilylated quinones: Evans, D. A.; Hoffman, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 1983. (c) Coupling of aryl bromides with π-allylnickel complexes: Inoue, S.; Yamagami, R.; Sato, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3098. Sato, K.; Inoue, S.; Saito, K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2289. (d) Coupling of metalloarenes with allylic halides or C-alkylation of hydroquinone derivatives: Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1974**, *96*, 8046.

(21) (a) Fieser, L. F. *J. Am. Chem. Soc.* **1939**, *61*, 3467. (b) Isler, O.; Doebel, K. *Helv. Chim. Acta* **1954**, *37*, 225. (c) Noll, H.; Ruegg, R.; Gloor, U.; Ryser, G.; Isler, O. *Ibid.* **1960**, *43*, 433. (d) Jackman, L. M.; Ruegy, R.; Ryser, G.; von Planta, C.; Gloor, U.; Mayer, H.; Schudel, P.; Koffer, M.; Isler, O. *Ibid.* **1965**, *48*, 1332. (e) For application of these conditions in the C-allylation of a phenol, see: Daves, G. D.; Moore, H. W.; Schwab, D. E.; Olsen, R. K.; Wilczynski, J. J.; Folkers, K. *J. Org. Chem.* **1967**, *32*, 1414.

(22) Sugihara, H.; Sasaki, M.; Kawamatsu, Y.; Morimoto, H. *Justus Liebigs Ann. Chem.* **1972**, *763*, 121.

(23) Yamada, S.; Ono, F.; Katagiri, T.; Tanaka, *Nippon* Kagaku Kaishi **1980**, *5*, 733; *Chem. Abstr.* **1980**, *93*, 167784r.

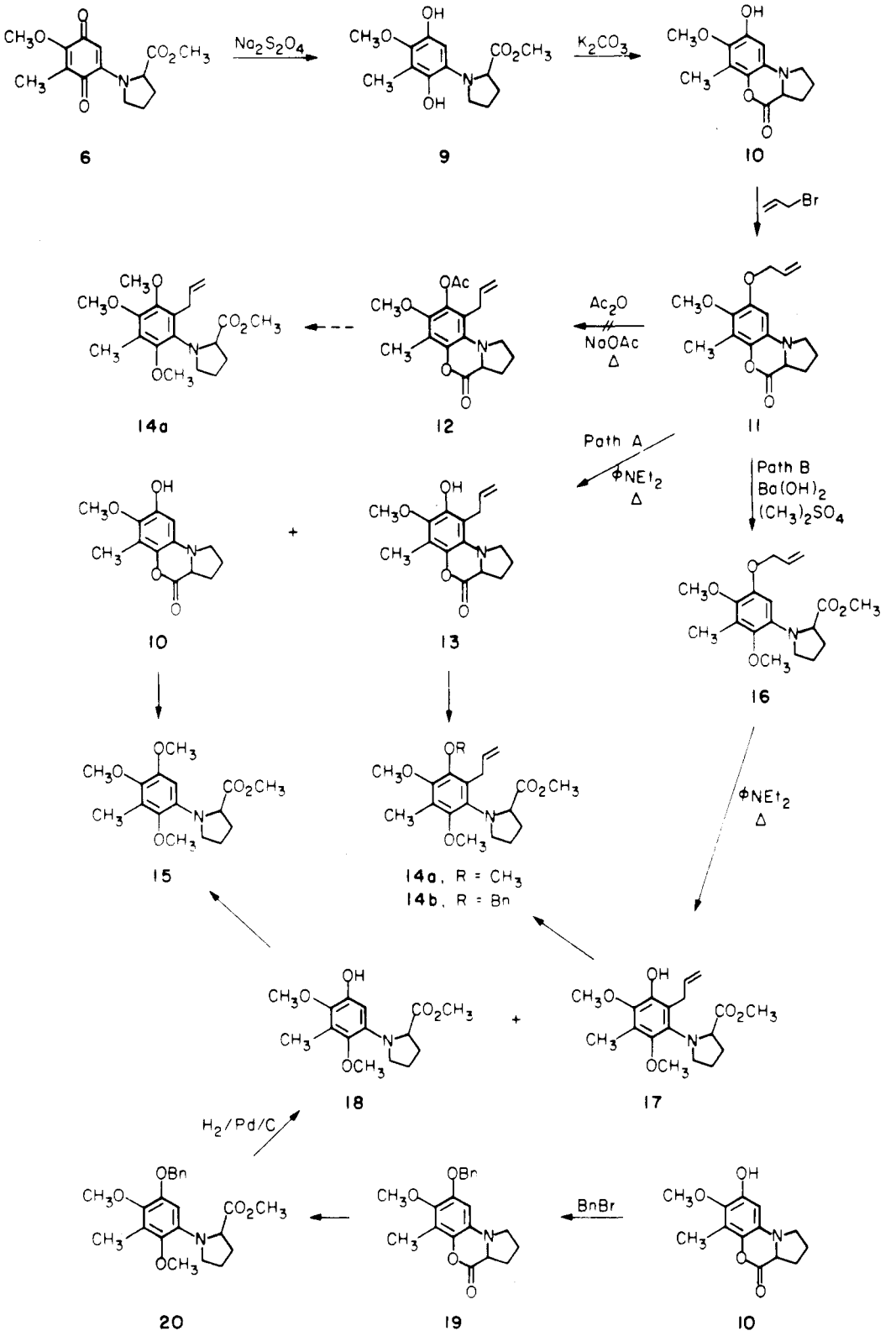
(24) Kornblum, N.; Lurie, A. *J. Am. Chem. Soc.* **1959**, *81*, 2705.

(25) Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* **1963**, *85*, 1148.

(26) Berrigan, P. J.; LeNoble, W. J.; Kornblum, N. *J. Am. Chem. Soc.* **1963**, *85*, 1141.

(27) For other examples of this type of activation, see: Wenkert, E.; Dave, K. G.; Stevens, R. V. *J. Am. Chem. Soc.* **1968**, *90*, 6177. Wenkert, E.; Chauncy, B.; Dave, K. G.; Jeffcoat, A. R.; Schell, M.; Schenck, H. P. *Ibid.* **1973**, *95*, 8427. Takano, S.; Ogawa, N.; Ogasawara, K. *Heterocycles* **1981**, *16*, 915.

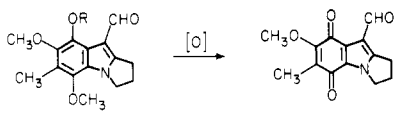
Scheme III. Aminoquinone Protection and Side-Chain Introduction



(CAN)[28] gave a sluggish and partial conversion to quinone **36**, along with a number of trace polar side products. When more CAN was added, substantial **32a** still remained, and more side products were formed. Though slightly cleaner, argentic oxide (AgO)[17] gave similar results. At this point pyridine-2,6-dicarboxylic acid *N*-oxide, an oxidation promoter popularized recently,[29] was prepared since both CAN and AgO have been stated to be more effective oxidizing agents, at least in some cases, in its presence. In our system the *N*-oxide offered no particular advantage; mixtures of comparable purity were isolated with either CAN or AgO, and the best yield of **36** was 20–25%. The poor yields for this transformation were surprising in light of the high yield precedent of this re-

(28) Peyton, J.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.

(29) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521.



32a, R = CH_3
32b, R = Bn
32c, R = H

36

action on the corresponding naphthalenoid model compound.[7] However, the model lacked a 7-methoxy which, in **32a**, is ortho to a methoxyl and para to an amino group, thereby potentially giving **32a** several competitive routes of oxidation.[30]

Since all six possible sites of nitration are blocked in indole aldehyde **32a**, we next examined nitric acid oxidations. Indoloquinone **36** was obtained in 46% yield when **32a** was treated with 6 M HNO_3 at room temperature. Better yields and purities were obtained when the reaction was performed at lower temperature and with less water. Thus, when cold concentrated HNO_3 was added dropwise to a slurry of aldehyde **32a** in glacial acetic acid at 0 °C, pure **36** was obtained in 83–88% yield. In light of this success the oxidation of **32b** or of phenol **32c**, which would result from hydrogenolysis of **32b**, was not actively pursued. Though the effect of various ethers on the outcome of oxidations of this sort has not been thoroughly investigated, the oxidation of benzyl ether **32b** with CAN proceeded cleanly and efficiently, unlike methyl ether **32a**, to give **36** in 87% yield.

Our synthesis of 7-methoxymitosene (**3**) ends with the preparation of indoloquinone aldehyde **36** since the transformation of **36** to **3** has been reported previously.[5,9] The overall yield from quinone **5** to aldehyde **36** is 20–25%.

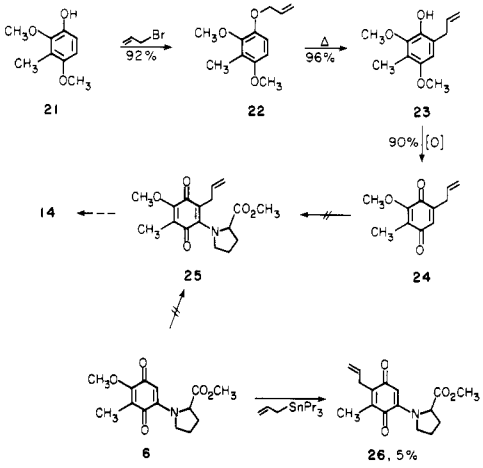
Experimental Section

The following reaction solvents were distilled from calcium hydride: methanol, acetonitrile, dimethylformanide (reduced pressure), and pyridine (after distillation from tosyl chloride). *N,N*-Diethylaniline was refluxed for 4 h with half its weight of acetic anhydride and then was fractionally distilled at reduced pressure. Allyl bromide was washed with $NaHCO_3$ solution and water, dried ($CaCl_2$), and fractionally distilled. Methyl iodide was purified by shaking with dilute aqueous $Na_2S_2O_3$, water, dilute aqueous Na_2CO_3, and water, drying ($CaCl_2$), and distilling.

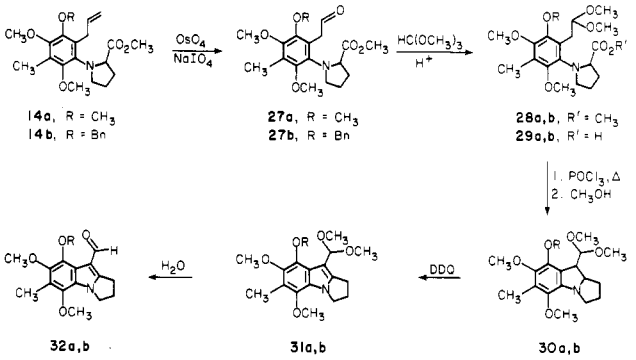
Melting points (Pyrex capillary) are uncorrected. IR spectra were determined with Perkin-Elmer Model 137 and 337 grating spectrophotometers with polystyrene film for calibration (1601.4-cm^{-1} absorption). ^1H NMR spectra were determined on Varian EM-390 (90 MHz) or Berkeley UCB 250 (250.80 MHz) spectrometers. For complex multiplets (m) the chemical shift is the center of the multiplet. ^{13}C NMR spectra were measured at 25 MHz (25.14 MHz) with a Nicolett TT-23 spectrometer. NMR spectra were taken in $CDCl_3$ and chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. UV spectra were determined in methanol with a Cary Model 219 spectrophotometer. Mass spectra were obtained with Atlas MS-12 and Consolidated 21-110 mass spectrometers at an ionizing voltage of 70 eV. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA. High-pressure liquid chromatography (HPLC) was done on an Altex analytical system consisting of two Model 110A pumps, a Model 115-10 UV–vis detector, and a Model 420 microprocessor controller/programmer using a Lichrosorb C_{18}, reverse-phase silica gel, 10 μm, 4.6 × 250 mm column. Unless otherwise noted, a flow rate of 1.0 mL/min was used, with monitoring at 280 nm, and with the following acetonitrile/water compositions: (A) 60/40, (B) 70/30, (C) 40/60, (D) 50/50 (isochratic). Preparative medium-pressure liquid chromatography (MPLC) was done with an Altex Model 110A pump equipped with a preparative liquid head and an Altex Model 151 UV detector, with monitoring at 280 nm. An Altex stainless-steel column packed with Spherisorb ODS reverse-phase silica gel (10 × 250 mm, 10 μm) was used. Column chromatography was performed with silica gel 60 (EM reagents, 63–200 μm) or neutral aluminum oxide (ICN). Analytical TLC was done with aluminum-backed silica plates (E. Merck). Unless otherwise noted, all reactions were conducted under a nitrogen atmosphere with magnetic stirring at room temperature, and final product solutions were dried over $MgSO_4$, filtered, and evaporated on a Berkeley rotary evaporator. Bulb-to-bulb distillations were carried out in a Kugelrohr-type apparatus.

2-Methoxy-3-methyl-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]-1,4-benzoquinone (6). Copper acetate monohydrate (12.0 g, 60.1 mmol) was partially dissolved in methanol (180 mL) under an oxygen atmosphere in the dark. Then freshly generated proline methyl ester[7] (9.94 g, 77.0 mmol) was added with rapid stirring. After 10 min quinone **5** (4.08 g, 26.8 mmol) dissolved in methanol (55 mL) was added dropwise over the course of 30 min. When TLC showed the absence of **5** (SiO_2/CH_2Cl_2; R_f 0.51), the reaction mixture was evaporated to a red paste which was shown to contain 1% **7** by RPHPLC (solvent C). Filtration through a short silica column with ether followed by evaporation

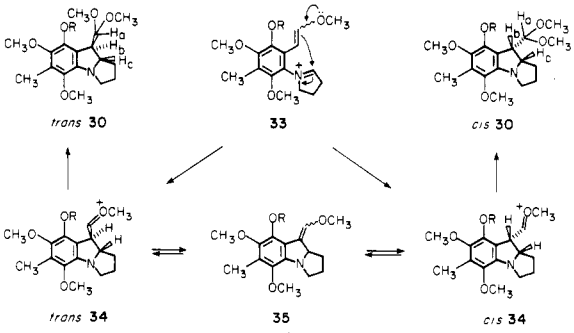
Scheme IV. Approaches to Allylquinone 25



Scheme V. Side-Chain Activation and Ring Closure



Scheme VI. Stereochemistry of Ring Closure



(30) Oxidation of a *p*-methoxyaniline to a quinone has recently been reported: Parker, K. A.; Kang, S.-K. *J. Org. Chem.* **1979**, *44*, 1536.

provided **6** as a purple oil: 7.18 g (96% yield); R_f (as above) 0.23; NMR (90 MHz) δ 1.84 (s, 3 H, CH_3), 2.07 (m, 4 H, $NCH_2CH_2CH_2$), 3.45 (m, 2 H, NCH_2), 3.71 (s, 3 H, CO_2CH_3), 4.05 (s, 3 H, OCH_3), 4.87 (dd, 1 H, NCH, J = 5, 6.5 Hz), 5.37 (s, 1 H, quinone H); ^{13}C NMR δ 8.0, 21.7, 30.8, 50.7, 51.7, 60.5, 62.1, 101.4, 123.4, 146.5, 156.6, 172.2, 180.6, 185.0; IR (neat) 3077, 2976, 1751, 1653, 1613, 1563, 1443, 1404, 1368, 1337, 1279, 1205, 1149, 1081, 1066, 1002, 806, 763 cm^{-1}; UV λ_{max} 502 nm (ϵ 1790), 316 (8690), 212 (15 890); mass spectrum, m/e (relative intensity) 281 (M + 2, 2.1), 280 (M + 1, 9.1), 279 (M^+, 52.8), 220 (100), 206 (21.0), 192 (83.0), 178 (45.3). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1; N, 5.0. Found: C, 60.1; H, 6.0; N, 5.0. Analogous reactions with quinone **5a**[8] were carried out in the same fashion.

2-Methoxy-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]-1,4-benzoquinone (7). Quinone **7** was isolated by chromatography of a large-scale preparation of **6** as described above: red crystals, mp 149–153 °C with decomposition; R_f (SiO_2/ether) 0.10; NMR (90 MHz) δ 2.02 (m, 4 H, $NCH_2CH_2CH_2$), 3.4 (m, 2 H, NCH_2), 3.63, 3.70 (2 s, 3 H each, 2 OCH_3), 4.83 (m, 1 H, NCH), 5.42, 5.55 (2 s, 1 H each, 2 quinone H); IR ($CHCl_3$) 3086, 1748, 1658, 1613, 1558, 1453, 1412, 1342, 1277, 1164, 1142 cm^{-1}; UV λ_{max} 215 nm (ϵ 17 610), 308 (14 420), 484 (2880). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.9; H, 5.7; N, 5.3. Found: C, 59.0; H, 5.7; N, 5.2.

2-Methoxy-3-methyl-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]-1,4-benzoquinone-*6-d* (6b). The amine addition on deuterioquinone **5b**[8] (0.20 g, 1.3 mmol) was carried out as described above, and the resulting crude product, suspended in a minimum amount of ether/triethylamine (96/4), was filtered through silica (0.80 g, equilibrated with that solvent). Evaporation provided **6b** (0.33 g, 92%). NMR analysis shows 99% deuterium incorporation; the only peak visible between 5 and 7 ppm was at 5.38 and corresponds to approximately 1% of **6**.

8-(Allyloxy)-6-methyl-7-methoxy-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one (11). To a flask topped with a molecular sieve filled Soxhlet extractor (16 g, 4 Å), a condenser, and an argon bubbler were added freshly degassed 3-pentanone (160 mL) and aminoquinone **6** (2.20 g, 7.88 mmol). Then an aqueous $Na_2S_2O_4$ solution (43 mL of 1 M solution adjusted to pH 7.0 with 2 M NaOH) was added and rapid stirring was initiated. After 15 min the organic phase turned from dark red to light yellow at which time the aqueous layer was removed by syringe, $Na_2S_2O_4$ powder (25 mg) was added, and heating to reflux was initiated. The mixture was heated at reflux with rapid stirring for 105 min after which it was allowed to cool to room temperature and anhydrous K_2CO_3 (2.19 g, 15.8 mmol, 200 M %) was added. The mixture was refluxed with rapid stirring for 90 min or until no visible red spot appeared on TLC (**9** → **6**, SiO_2, PhH/EtOAc, 1/1) at R_f 0.40 and a new spot appeared at R_f 0.47 (**10**). The mixture was then allowed to cool to 65–70 °C, allyl bromide (1.54 g, 12.7 mmol) was added, and rapid stirring was continued for 48 h. Cooling, rapid filtration, evaporation of solvent (45 °C, 1.5 mmHg), and vacuum drying (0.005 mmHg, 24 h, 20 °C) afforded **11** (air-sensitive white crystals, can be stored under argon, best reacted immediately): 1.71 g (75% yield); R_f (SiO_2, above solvent) 0.56; NMR (90 MHz) δ 2.15 (m, 4 H, $NCH_2CH_2CH_2$), 2.25 (s, 3 H, CH_3), 3.02 (m, 1 H), 3.38 (m, 2 H), 3.76 (s, 3 H, OCH_3), 4.52 (m, 2 H, OCH_2), 5.3 (m, 2 H, $CH{=}CH_2$), 6.00 (m, 1 H, $CH{=}CH_2$), 6.11 (s, 1 H, ArH); IR (Nujol) 1764, 1623, 1600, 1490, 1230, 1211, 1153, 1095, 1059, 990, 935, 782, 756 cm^{-1}; mass spectrum, m/e (relative intensity) 290 (M + 1, 7.4), 289 (M^+, 35.8), 220 (100), 192 (35.5). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.6; H, 6.6; N, 4.8.

8-Hydroxy-6-methyl-7-methoxy-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one (10). Lactone phenol **10** could be prepared as directed above by omitting the alkylation step: NMR (90 MHz) δ 2.2 (m, 4 H, $NCH_2CH_2CH_2$), 2.21 (s, 3 H, CH_3), 2.95 (m, 1 H), 3.33 (m, 2 H), 3.67 (s, 3 H, OCH_3), 6.13 (s, 1 H, ArH); IR (neat) 3509, 3195, 1754, 1603, 1490, 1374, 1168, 1106, 1073, 984, 928, 820 cm^{-1}.

Claisen Rearrangement of 11 and Methylation of Product Mixture. To degassed diethylaniline (15 mL) under argon was added lactone **11** (463 mg, 1.60 mmol) with stirring, and the resulting solution was brought to reflux over the course of 1 h and then heating was continued for 6.5 h. The solution was allowed to cool to room temperature, and the solvent was removed by bulb-to-bulb distillation (0.01 mm, 70 °C) giving a crude mixture of **10** and **13** which was used without further purification. RPHPLC (90% CH_3OH/10% H_2O) gave partial separation of **10** (t_R 7.6 min) from **13** (t_R 8.2 min) and indicated an approximate ration of 1/3. DMF (10 mL), methyl iodide (0.71 mL, 11.5 mmol), and barium hydroxide octahydrate (1.61 g, 5.10 mmol) were added to the crude phenols (369 mg of the above mixture), and the mixture was stirred under argon for 52 h. Filtration and evaporation provided an oil which was partitioned between water (20 mL) and ethyl acetate (6 mL). The aqueous phase was extracted with ethyl acetate (5 × 6 mL), and the combined organic phase was washed with saturated $NaHCO_3$ (2 × 6 mL) and saturated NaCl (6 mL) and was dried. Filtration, evaporation, and chromatography (50 g of SiO_2, ether/dichloromethane, 5/95 → 100/0) gave a 7/3 (NMR) mixture of **14a/15** (0.272 g). See below for specific spectral and physical properties.

3-(Allyloxy)-2,6-dimethoxy-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]toluene (16). A. From 6. Aminoquinone **6** (14.75 g, 52.8 mmol) was converted to hydroquinone **9** as directed above. The $Na_2S_2O_4$ solution was removed with a pipet and was extracted with 3-pentanone, and the extracts (3 × 50) were returned to the reaction flask. Solid $Na_2S_2O_4$ (150 mg) was added, an oil bath was applied (T_b 130 °C), and rapid stirring was initiated. After 2 h the mixture was allowed to cool briefly, anhydrous K_2CO_3 (14.68 g, 106 mmol) was added, and the heating bath was applied again. After 3 h, the reaction mixture was evaporated (1 mmHg). To the residue were added DMF (120 mL), allyl bromide (24.7 g, 158 mmol), and anhydrous K_2CO_3 (14.58 g, 105 mmol). A condenser was attached, rapid stirring with heating (T_b 65 °C) was continued for 24 h, the mixture was concentrated to one-fourth of the original volume (bulb-to-bulb distillation, 2 mm), and $(CH_3)_2SO_4$ (20.00 mL, 211 mmol), $Ba(OH)_2{\cdot}8H_2O$ (33.35 g, 106 mmol), and DMF (100 mL) were added. Stirring at 20 °C was continued for 10 h at which time the solvent was removed by distillation (as above), and the resulting light-brown paste was combined with 1 M HCl (480 mL, 0 °C). Water (600 mL) was added, the aqueous layer was extracted with $CHCl_3$, and the combined extracts were filtered through filter aid, dried, and evaporated to give **16** (15.60 g, 88% yield). RPHPLC (solvent A) showed 95% purity. A small sample was purified by preparative RPHPLC for analysis, but the remainder was used without further purification: t_R (RPHPLC, solvent A) 11.6 min; NMR (90 MHz) δ 2.08 (m, 4 H, $NCH_2CH_2CH_2$), 2.16 (s, 3 H, CH_3), 3.17 (m, 1 H, NCHH), 3.53 (s, 3 H, CO_2CH_3), 3.58 (m, 1 H, NCHH), 3.60, 3.70 (2 s, 3 H each 2 Ar OCH_3), 4.33 (dd, 1 H, NCH, J = 4, 8 Hz), 4.43 (split doublet, J = 6 Hz, 2 H, OCH_2), 5.2 (m, 2 H, $CH{=}CH_2$), 5.93 (m, 1 H, $CH{=}CH_2$), 6.19 (s, 1 H, Ar H); IR (neat) 2924, 1736, 1603, 1488, 1456, 1399, 1361, 1258, 1166, 1082, 1011, 931, 809 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.5; H, 7.5; N, 4.2. Found: C, 64.4; H, 7.5; N, 4.2.

B. From Phenol (18). To phenol **18** (55.0 mg, 0.19 mmol) and finely powdered anhydrous K_2CO_3 (77.1 mg, 0.56 mmol) in DMF (3.8 mL) was added allyl bromide (48.3 L, 0.56 mmol) with rapid stirring. A heating bath (T_b 65 °C) was applied for 10.5 h after which the reaction mixture was filtered and evaporated to give **16** (63.0 mg, 100%), which was pure by RPHPLC (solvent A). Spectra were identical with those obtained earlier.

Claisen Rearrangement of 16. Isolation of 6-Allyl-2,4-dimethoxy-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]-3-methylphenol (17) and 2,4-Dimethoxy-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]-3-methylphenol (18). Allyl ether **16** (2.50 g, 7.45 mmol) in diethylaniline (10 mL) was added to refluxing diethylaniline (75 mL) with rapid stirring over 2 min. Reflux was continued for 2.5 h and then the solvent was removed by bulb-to-bulb distillation (0.10 mm) to give an oil (2.60 g), which was chromatographed (150 g of SiO_2, degassed 40% hexane/60% ether). Combination of selected fractions gave **17** (1.52 g, 4.53 mmol, 61% yield) and **18** (0.56 g, 1.90 mmol, 26% yield). The yield of **17** was based on recovered **18** is 82%. RPHPLC (solvent A) showed a 7/3 ratio of **17** (t_R 10.6 min) to **18** (t_R 5.4 min).

17: R_f (SiO_2, ether/hexane, 1/1) 0.38; NMR (90 MHz) δ 2.0 (m, 4 H, $NCHCH_2CH_2$), 2.13 (s, 3 H, CH_3), 2.9 (m, 1 H, NCHH), 3.5 (m, 3 H, $ArCH_2$, NCHH), 3.49 (s, 3 H, CO_2CH_3), 3.60, 3.67 (2 s, 3 H each, OCH_3), 4.28 (dd, 1 H, NCH, J = 4, 8 Hz), 4.9 (m, 2 H, $CH{=}CH_2$), 5.33 (br, 1 H, OH), 5.92 (m, 1 H, $CH{=}CH_2$); IR (neat) 3509, 2967, 1733, 1639, 1605, 1451, 1401, 1264, 1199, 1189, 1159, 1068, 1014, 909 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.5;

H, 7.5; N, 4.2. Found: C, 64.1; H, 7.3; N, 4.2.

18: mp 98–102 °C; R_f (as above) 0.17; NMR (90 MHz) δ 1.9 (m, 4 H, $NCH_2CH_2CH_2$), 2.17 (s, 3 H, CH_3), 3.3 (m, 1 H, NCHH), 3.54 (s, 3 H, CO_2CH_3), 3.60, 3.67 (2 s, 3 H each; 2 OCH_3), 3.7 (m, 1 H, NCHH), 4.35 (dd, 1 H, NCH, J = 4, 7 Hz), 6.27 (s, 1 H, Ar H); IR (neat) 3425, 2941, 1727, 1592, 1486, 1445, 1429, 1379, 1348, 1205, 1075, 1001, 909, 826, 775; mass spectrum, m/e (relative intensity) 296 (M + 1, 3.6), 295 (M^+, 20.5), 280 (11.7), 236 (100), 206 (40.6); exact mass calcd for $C_{15}H_{21}NO_5$ m/e 295.1419, found m/e 295.1411 (M^+).

4-Allyl-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]-2,3,6-trimethoxytoluene (14a). To phenol **17** (1.52 g, 4.53 mmol) in DMF (15 mL) were added $(CH_3)_2SO_4$ (1.71 g, 13.6 mmol) and anhydrous barium hydroxide (0.78 g, 4.5 mmol) with stirring. After 5 h the solvent was evaporated and the residue was combined with 1 M HCl (4.5 mL). Water (25 mL) was added, the mixture was extracted with $CHCl_3$ (2 × 13 mL, 3 × 6 mL), and the combined organic phase was washed with water (6 mL) and brine (6 mL). Drying and evaporating provided **14a**: 1.39 g (88%); t_R (RPHPLC, solvent B, 1.5 mL/min) 8.3 min; NMR (90 MHz) δ 2.0 (m, 4 H, $NCH_2CH_2CH_2$), 2.10 (s, 3 H, CH_3), 2.88 (m, 1 H, NCHH), 3.45 (s, 3 H, CO_2CH_3), 3.5 (m, 3 H, NCHH, Ar CH_2), 3.63 (s, 3 H, Ar OCH_3), 3.70 (s, 6 H, 2 Ar OCH_3), 4.23 (dd, 1 H, NCH, J = 4, 8 Hz), 4.85 (m, 2 H, CH=CH_2), 5.95 (m, 1 H, CH=CH_2); IR (neat) 2959, 1736, 1642, 1456, 1395, 1335, 1256, 1193, 1161, 1086, 1025, 979, 948, 909, 800, 746 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.3; H, 7.8; N, 4.0. Found: C, 65.1; H, 7.6; N, 4.0.

4-Allyl-3-(benzyloxy)-2,6-dimethoxy-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]toluene (14b). To phenol **17** (400 mg, 1.2 mmol) in acetonitrile (12 mL) was added anhydrous K_2CO_3 (330 mg, 2.4 mmol) and benzyl bromide (224 mg, 1.31 mmol) with rapid stirring. The reaction mixture was heated (T_b 60 °C) for 24 h, and then it was cooled and filtered. The salts were extracted with acetonitrile and the combined extract and filtrate were evaporated to give **14b** as an oil: 0.43 g (84%); R_f (SiO_2, ether/hexane, 1/1) 0.46; NMR (90 MHz) δ 2.1 (m, 4 H, $NCH_2CH_2CH_2$), 2.17 (s, 3 H, CH_3), 2.95 (m, 1 H, NCHH), 3.50 (s, 3 H, CO_2CH_3), 3.55 (m, 3 H, Ar CH,2CH, NCHH), 3.67, 3.73 (2 s, 3 H each, OCH_3), 4.25 (dd, 1 H, NCH, J = 4, 8 Hz), 4.8 (m, 2 H, CH=CH_2), 4.89 (s, 2 H, Ar CH_2O), 5.9 (m, 1 H, CH=CH_2), 7.3 (m, 5 H, 5 Ar H); IR (neat) 2933, 1739, 1639, 1447, 1422, 1399, 1370, 1255, 1192, 1157, 1079, 1019 913, 736, 697 cm^{-1}.

5-[2-(Methoxycarbonyl)-1-pyrrolidinyl]-2,3,6-trimethoxytoluene (15). Methylation of the product mixture (as in **17** → **14a**) obtained from the Claisen rearrangement of **16** followed by chromatography (SiO_2/sample, 250/1, CH_2Cl_2) provided a sample of **15**: NMR (90 MHz) δ 2.1 (m, 4 H, $NCH_2CH_2CH_2$), 2.21 (s, 3 H, CH_3), 3.26 (m, 1 H, NCHH), 3.7 (masked m, 1 H, NCHH), 3.57 (s, 3 H, CO_2CH_3), 3.66, 3.74, 3.82 (3 s, 3 H each, 3 OCH_3), 4.43 (dd, 1 H, NCH, J = 4, 7 Hz), 6.31 (s, 1 H, Ar H); IR (neat) 2924, 1736, 1595, 1486, 1449, 1370, 1232, 1202, 1164, 1086, 1009, 962, 812, 757 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.1; H, 7.5; N, 4.5. Found: C, 61.8; H, 7.2; N, 4.4.

8-(Benzyloxy)-6-methyl-7-methoxy-1,2,3,3a-tetrahydro-4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-one (19). To the dry 3-pentanone solution of lactone phenol **10** (prepared on the same scale as described in the preparation of **11**) was added benzyl bromide (2.70 g, 15.8 mmol) with rapid stirring. Heat (T_b 75 °C) was applied for 41 h after which time the reaction mixture was cooled, filtered, and evaporated, providing **19** as a crystalline mass (2.88 g). This material was carried on in the next step without further purification (**19**, like **11**, is air and moisture sensitive and should be stored under an inert atmosphere in the cold). **19**: R_f (SiO_2, ethyl acetate) 0.67; NMR (90 MHz) δ 2.1 (m, 4 H, $NCH_2CH_2CH_2$), 2.24 (s, 3 H, CH_3), 2.98 (m, 1 H), 3.41 (m, 2 H), 3.76 (s, 3 H, OCH_3), 5.07 (s, 2 H, Ar CH_2), 6.18 (s, 1 H, Ar H), 7.41 (m, 5 H, Ar H); IR (neat) 2950, 1761, 1621, 1597, 1490, 1443, 1366, 1235, 1163, 1105, 1062, 1002, 849, 808, 7525, 697.

3-(Benzyloxy)-2,6-dimethoxy-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]toluene (20). To lactone benzyl ether **19** (2.69 g of above material) in DMF (90 mL) were added barium hydroxide octahydrate (8.38 g, 27 mmol) and methyl iodide (11.3 g, 80 mmol) with rapid stirring. After 32 h the reaction mixture was combined with 1 M HCl (18 mL) and extracted with $CHCl_3$ (3 × 25 mL), the combined extracts were washed with water (2 × 25 mL) and dried, and evaporation gave **20** as an oil: 2.39 g (83%); R_f (SiO_2, ethyl acetate/chloroform, 1/9) 0.65; NMR (90 MHz) δ 2.0 (m, 4 H, $NCH_2CH_2CH_2$), 2.16 (s, 3 H, CH_3), 3.2 (m, 1 H, NCHH), 3.6 (m, 1 H, NCHH), 3.54, 3.59, 3.74 (3 s, 3 H each, 3 OCH_3), 4.35 (dd, 1 H, NCH, J = 5, 7 Hz), 5.02 (s, 2 H, OCH_2), 6.31 (s, 1 H, Ar H), 7.4 (m, 5 H, Ar H); IR (neat) 2941, 1739, 1600, 1484, 1445, 1420, 1389, 1361, 1230, 1202, 1170, 1081, 1005, 913, 812, 739, 698 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.6; H, 7.1; N, 3.6. Found: C, 68.6; H, 7.0; N, 3.6.

2,4-Dimethoxy-5-[2-(methoxycarbonyl)-1-pyrrolidinyl]-3-methylphenol (18). To benzyl ether **20** (490 mg, 1.3 mmol) in methanol (6.4 mL) was added 5% Pd/C (49 mg). Shaking at 50 psi of H_2 was peformed for 18 h at which time more catalyst (49 mg) was added, and shaking was continued for 24 h. Filtration and evaporation provided **18**: 0.38 g (96%). Physical and spectral properties were identical with those reported above.

3-(Allyloxy)-2,6-dimethoxytoluene (22). To phenol **21**[16] (0.96 g, 5.7 mmol) and anhydrous K_2CO_3 (1.58 g, 11.4 mmol) in acetonitrile (11 mL) was added allyl bromide (0.76 g, 6.3 mmol) with rapid stirring. Heat (T_b 60 °C) was applied for 7 h. Filtration and evaporation afforded **22**: 1.10 g (92%); mp 30.5–32.5 °C; NMR (90 MHz) δ 2.10 (s, 3 H, CH_3), 3.67, 3.73 (2 s, 3 H each, 2 OCH_3), 4.41 (split d, 2 H, OCH_2, J = 4 Hz), 5.2 (m, 2 H, CH=CH_2), 6.0 (m, 1 H, CH=CH_2), 6.43, 6.67 (2 d, 1 H each, 2 Ar H, J = 9 Hz); IR (neat) 2933, 1595, 1477, 1250, 1111, 1070, 1028, 998, 930, 863, 792, 755 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7. Found: C, 68.9; H, 7.8.

6-Allyl-2,4-dimethoxy-3-methylphenol (23). Allyl ether **22** (3.73 g, 17.9 mmol) in diethylaniline (10 mL) was refluxed for 2 h. The mixture was cooled and diluted with ether (50 mL), and the resulting organic phase was washed with 2 M H_2SO_4 (4 × 50 mL), water (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). Drying and evaporating provided **23**: 3.60 g (96%); NMR (90 MHz) δ 2.07 (s, 3 H, CH_3), 3.30 (d, 2 H, CH_2), 3.67 (s, 6 H, 2 OCH_3), 5.1 (m, 2 H, CH=CH_2), 5.28 (br, 1 H, OH), 5.9 (m, 1 H, CH=CH_2), 6.44 (s, 1 H, Ar H); IR (neat) 3460, 2924, 1600, 1484, 1449, 1403, 1259, 1227, 1182, 1116, 1070, 1018, 916, 841 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7. Found: C, 68.8; H, 7.7.

6-Allyl-2-methoxy-3-methyl-1,4-benzoquinone (24). Dichloromethane (12 mL) and concentrated HNO_3 (3 mL) were mixed rapidly for 1 h. The layers were separated, and 1.0 mL of the organic phase was added to phenol **23** (37.7 mg, 0.18 mmol) in dichloromethane (1.0 mL) with rapid stirring. After 10 min, water (1 mL) was added followed by enough 10% $NaHCO_3$ to make the aqueous layer pH 7–8. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 1 mL). The combined organic layers were dried, filtered, and evaporated to **24** as a yellow oil: 31.2 mg (90%); R_f (SiO_2, dichloromethane) 0.19; NMR (90 MHz) δ 1.88 (s, 3 H, CH_3), 3.08 (br d, 2 H, CH_2CH, J = 7Hz), 3.90 (s, 3 H, OCH_3), 5.1 (m, 2 H, CH=CH_2), 5.7 (m, 1 H, CH=CH_2), 6.40 (t, 1 H, quinone H, J = 1.5 Hz); IR (neat) 2950, 1650, 1639 (sh), 1610, 1443, 1353, 1325, 1284, 1252, 1196, 1170, 1125, 1010, 926, 877 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3. Found: C, 68.7; H, 6.0.

6-Allyl-3-[2-(methoxycarbonyl)-1-pyrrolidinyl]-5-methyl-1,4-benzoquinone (26). To a rapidly stirring solution of aminoquinone **6** (107 mg, 0.38 mmol) in dichloromethane (3.8 mL) at −78 °C was added boron trifluoride etherate (142 μL, 1.15 mmol). Then tripropylallylstannane[31] (222 mg, 0.77 mmol) was added dropwise over the course of 5 min. The cold bath was removed 10 min later, and the reaction mixture was allowed to warm to 20 °C. After 1.5 h slight conversion to **26** was seen by TLC (SiO_2, ether; R_f **26**, 0.49; R_f **6**, 0.43). No further change was observed after a total of 11 h, at which time the reaction mixture was evaporaed to a red oil which was partitioned between 2 M HCl (12 mL) and ether (10 mL). The aqueous phase was further extracted with ether (2 × 10 mL), and the combined organic phase was washed with water and brine. Drying and evaporating provided a red oil (242 mg), which was chromatographed (10 g of SiO_2, ether/hexane, 9/1). Combination of selected fractions gave a 3-mg sample of pure **26**. Other fractions contained tin compounds or **6** contaminated with traces of **26**. **26**: NMR (90 MHz) δ 1.92 (s, 3 H, CH_3), 2.03 (m, 4 H, $NCH_2CH_2CH_2$), 3.17, (br d, 2 H, CH_2-CH=CH, J = 6 Hz), 3.37 (m, 2 H, NCH_2), 3.67 (s, 3 H, OCH_3),

(31) Abel, E. A.; Rowley, R. J. *J. Organomet. Chem.* **1974**, *84*, 199.

4.8 (m, 1 H, NCH), 4.9 (m, 2 H, CH=C**H**$_2$), 5.48 (s, 1 H, quinone H), 5.7 (br m, 1 H, C**H**=CH$_2$); IR (neat) 2967, 1754, 1672, 1650, 1618, 1577, 1414, 1383, 1359, 1276, 1212, 1174, 1010, 923 cm^{-1}; mass spectrum, *m/e* (relative intensity) 290 (M + 1, 6.5), 2.89 (M$^+$, 34.7), 274 (20.0), 230 (100), 202 (16.4), 161 (37.0); exact mass calcd for $C_{16}H_{19}NO_4$ *m/e* 289.1313, found *m/e* 289.1303 (M$^+$).

Sequence 14a → 27a → 28a → 29a → 30a → 32a. To allylbenzene **14a** (0.30 g, 0,86 mmol) in ether were added osmium tetraoxide (3.3 mL of a 1% aqueous solution, 0.13 mmol) and water (12 mL) with rapid stirring. Then $NaIO_4$ (0.40 g, 1.8 mmol) was added in one portion, and after 15 h, <1% of **14a** was detected by RPHPLC (solvent B). After the layers were separated, the aqueous phase was saturated with NaCl and extracted with ether. The combined organic phase was washed with saturated Na_2SO_3 solution and brine and was dried and evaporated to provide crude **27a** (0.30 g), which was used without further manipulation.

Aldehyde **27a**, methanol (10 mL), trimethylorthoformate (0.23 g, 2.2 mmol), and *p*-toluenesulfonic acid monohydrate (5 mg) were stirred rapidly for 12 h after which RPHPLC (as above) showed conversion to **28a**. The reaction mixture was evaporated to half-volume, and KOH (0.28 g of 85% KOH, 4.3 mmol) in water (2.8 mL) was added with heating at 95 °C and rapid stirring for 30 min. The mixture was evaporated, sodium hydroxide (4.0 mL, 1 M) was added, and the aqueous phase was washed with ether (3 × 6 mL). Phosphate buffer (7.8 mL, pH 7.4) was added, and the pH of the solution was carefully taken to 7.3 by dropwise addition of 1 M HCl with rapid stirring. The solution was saturated with solid NaCl and extracted with ethyl acetate (4 × 10 mL), and the combined organic phase was dried (Na_2SO_4, 0 °C) filtered, and evaporated to give **29a** (0.24 g).

Amino acid **29a** rapidly stirred in phosphorus oxychloride (0.96 mL, 10.6 mmol) was heated at 100 °C for 5 min after which the mixture was cooled to 0 °C. Methanol (6 mL) was then added dropwise over the course of 5 min, and after being stirred for 18 h at 20 °C, the solution was cooled to 0 °C and half-saturated Na_2CO_3 (50 mL) was added. Extraction with dichloromethane (4 × 7 mL) provided a combined organic phase, which was washed with saturated Na_2CO_3 (10 mL) and dried. Filtration and evaporation provided crude indoline acetal **30a**, which was seen by RPHPLC (as above) to contain less than 2% of **32a**. Traces of residual solvent were not removed so as to minimize decomposition, and **30a** was carried on to the next step without purification.

To a rapidly stirred solution of indoline acetal **30a** in dichloromethane (5.7 mL) and acetone (1.9 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.165 g, 0.73 mmol) in dichloromethane (11.3 mL). After 1.5 h RPHPLC (as above) showed complete conversion. The mixture was evaporated, and the solid residue was chromatographed on neutral alumina (activity III) with dichloromethane. Concentration of selected fractions provided crystalline **32a**, which was shown to be 99% pure by RPHPLC (as above): 0.130 g (52% from **14a**).

Properties for 6-[2-(Methoxycarbonyl)-1-pyrrolidinyl]-4-methyl-2,3,5-trimethoxyphenylacetaldehyde (27a), 6-[2-(Methoxycarbonyl)-1-pyrrolidinyl]-4-methyl-2,3,5-trimethoxyphenylacetaldehyde Dimethyl Acetal (28a), 6-(2-Carboxy-1-pyrrolidinyl)-4-methyl-2,3,5-trimethoxyphenylacetaldehyde Dimethyl Acetal (29a), 6-Methyl-2,3,9,9a-tetrahydro-5,7,8-trimethoxy-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde Dimethyl Acetal (30a), and 2,3-Dihydro-6-methyl-5,7,8-trimethoxy-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (32a). The same procedures as above were used to prepare the individual compounds. Unless otherwise noted, purification before analysis was achieved by preparative RPHPLC (solvent D), and samples were reexamined by analytical RPHPLC (retention times obtained at 1.5 mL/min, solvent B) to assure no loss of structural integrity.

27a: t_R 4.6 min; NMR (90 MHz) δ 2.1 (m, 4 H, NCH$_2$C**H**$_2$C**H**$_2$), 2.15 (s, 3 H, Ar CH$_3$), 3.0 (m, 1 H, NCH**H**), 3.25 (m, 1 H, NCH**H**), 3,53 (s, 3 H, CO$_2$CH$_3$), 3.68, 3.70, 3.75 (3 s, 3 H each, Ar OCH$_3$), 3.85 (m, 2 H, Ar CH$_2$), (dd, 1 H, NCH, *J* = 4, 8 Hz), 9.61 (t, 1 H, CHO, *J* = 2 Hz): IR (neat) 2941 cm^{-1}, 1724, 1460, 1401, 1261, 1203, 1155, 1089, 1028; mass spectrum, *m/e* (relative intensity) 352 (M + 1, 2.1), 351 (M$^+$, 10.9), 292 (100). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.5; H, 7.2; N, 4.0. Found: C, 61.3; H, 6.9; N, 4.0.

28a: t_R 5.6 min; NMR (90 MHz) δ 2.0 (m, 4 H, NCH$_2$C**H**$_2$C**H**$_2$), 2.13 (s, 3 H, Ar CH$_3$), 2.7–3.7 (m, 4 H, Ar CH$_2$, NCH$_2$), 3.25, 2.39 (2 s, 3 H each, CH(OC**H**$_3$)$_2$), 3.53 (s, 3 H, CO$_2$CH$_3$), 3.69 (s, 3 H, OCH$_3$), 3.73 (s, 6 H, 2 OCH$_3$), 4.12 (dd, 1 H, NCH, *K* = 4, 8 Hz), 4.62 (br t, 1 H, C**H**(OCH$_3$)$_2$, *J* = 6 Hz).

29a: t_R 3.4 min; NMR (90 MHz) δ 1.8–2.5 (br m, 4 H, NCH$_2$C**H**,2C**H**$_2$), 2.17 (s, 3 H, Ar CH$_3$), 3.28, 3.30 (2 s, 3 H each, CH(OC**H**$_3$)$_2$), 2.7–3.7 (m, 4 H, NCH$_2$, Ar CH$_2$), 3.77 (s, 6 H, 2 OCH$_3$), 3.79 (s, 3 H, OCH$_3$), 4.33 (dd, 1 H, NCH, *J* = 4, 8 Hz), 4.65 (t, 1 H, C**H**(OCH$_3$)$_2$, *J* = 5 Hz); IR (neat) 2933, 1724, 1462, 1403, 1357, 1264, 1193, 1124, 1093, 1043, 1025, 976, 922, 816, 735 cm^{-1}; mass spectrum, *m/e* (relative intensity) 384 (M + 1, 4.2), 3.83 (M$^+$, 18.8), 351 (49.7), 338 (4.0), 306 (82.5), 292 (57.4); exact mass calcd for $C_{19}H_{29}NO_7$ *m/e* 383.1943, found *m/e* 383.1933 (M$^+$).

30a (purified on Florisil, ether/hexane, 1/1): mp 34–35 °C; t_R 5.0 min; NMR (250 MHz) δ 1.38, 1.85, 1.98 (3 m, 1 H, 2 H, 1 H, NCH$_I$H$_H$CH$_G$H$_F$CH$_E$H$_D$CH$_C$), 2.15 (s, 3 H, CH$_3$), 3.23 (m, 1 H, NCH$_H$H$_I$), 3.27, 3.43 (2 s, 3 H each, CH(OC**H**$_3$)$_2$), 3.5 (m, 1 H, NCH$_H$H$_I$), 3.58 (overlapping dd, appears as br t, NCH$_C$H$_B$CH$_A$(OCH$_3$)$_2$, J_{AB} = 3.7 Hz, J_{BC} = 3.1 Hz), 3.74, 3.88 (2 s, 6 H, 3 H, 3 OCH$_3$), 4.04 (m, 1 H, NCH$_C$, J_{CD} = 9.3 Hz, J_{CE} = 6.2 Hz), 4.60 (d, 1 H, CH$_A$); NMR (90 MHz) irradiation of 3.58 resonance collapsed the 4.60 doublet to a singlet; IR (neat) 2950, 1608, 1466, 1441, 1403, 1366, 1248, 1189, 1080, 1019, 967, 731 cm^{-1}; UV λ_{max} 294 nm (ε 1728), 282 (1344), 248 (6387); mass spectrum, *m/e* (relative intensity) 338 (M + 1, 8.3), 337 (M$^+$, 42.4), 322 (16.0), 306 (8.3), 2.6 (88.8), 231 (43.8), 149 (47.2), 75 (100); exact mass calcd for $C_{18}H_{27}NO_5$ *m/e* 337.1890, found *m/e* 337.1884 (M$^+$).

32a: mp 138–139 °C; t_R 4.2 min; NMR (250 MHz) δ 2.30 (s, 3 H, CH$_3$), 2.68 (tt, 2 H, NCH$_2$C**H**$_2$), 3.30 (t, 2 H, NCH$_2$CH$_2$C**H**$_2$, *J* = 7.5 Hz), 3.83, 3.90, 3.97 (3 s, 9 H, 3 OCH$_3$), 4.32 (t, 2 H, NCH$_2$, *J* = 7.5 Hz), 10.34 (s, 1 H, CHO); IR (neat) 2915, 1647, 1520, 1490, 1445, 1416, 1383, 1355, 1101, 1030, 997, 983, 952, 867, 767, 740 cm^{-1}; UV λ_{max} 325 nm (ε 11 310), 254 (18 150). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.4; H, 6.6; N, 4.8.

2-(Benzyloxy)-3,5-dimethoxy-6-[2-(methoxycarbonyl)-1-pyrrolidinyl]-4-methylphenylacetaldehyde (27b). To benzyl ether **14b** (0.41 g, 0.96 mmol) in ether (17 mL) was added 1% aqueous osmium tetraoxide (2.46 mL, 10 mol%) and water with rapid stirring. After 5 min $NaIO_4$ (0.441 g, 2.06 mmol) was added, and the mixture was stirred for 16 h at which time TLC (SiO_2, ethyl acetate/hexane, 1/1) showed conversion of **14b** (R_f 0.45) to **27b** (R_f 0.28). The layers were separated, the aqueous phase was extracted with ether (2 × 5 mL), and the combined organic phase was washed with 10% aqueous $Na_2S{\cdot}9H_2O$ (2 × 5 mL, 3 mL) and water (5 mL). Drying and evaporating gave crude **27b** as a dark oil (0.38 g), which was resubjected to cleavage conditions ($Et_2O/H_2O/NaIO_4$) for 17 h. The layers were separated, the aqueous phase was extracted with ether, and the combined organic phase was dried and evaporated to give **27b** as a light-yellow oil (0.37 g). Two polar side products were removed by chromatography on Florisil (30 g, ether/isooctane, 1/1). Combination of selected fractions gave 0.14 g (33%) of **27b**: NMR (90 MHz) δ 2.0 (m, 4 H, NCH$_2$C**H**$_2$C**H**$_2$), 2.17 (s, 3 H, CH$_3$), 2.9 (m, 1 H, NCH**H**), 3.2 (m, 1 H, NCH**H**), 3.49 (s, 3 H, CO$_2$CH$_3$), 3.65, 3.73 (2 s, 3 H each, OCH$_3$), 3.7 (masked m, 2 H, ArC**H**$_2$CHO), 4.27 (dd, 1 H, NCH, *J* = 4, 8 Hz), 4.85 (s, 2 H, Ar CH$_2$O), 7.30 (m, 5 H, 5 Ar H), 9.57 (t, 1 H, CHO, *J* = 2 Hz); IR (neat) 2941, 1730, 1715, 1447, 1397, 1370, 1252, 1192, 1160, 1079, 1018, 913, 756, 735, 698 cm^{-1}.

Sequence 27b → 28b → 29b → 30b → 8-(Benzyloxy)-2,3-dihydro-5,7-dimethoxy-6-methyl-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (32b). To aldehyde **27b** (0.110 g, 0.26 mmol) in methanol (2.5 mL) was added trimethylorthoformate (0.15 mL, 1.4 mmol) and *p*-toluenesulfonic acid monohydrate (10.4 mg, 0.055 mmol) with rapid stirring. RPHPLC (solvent B, 2 mL/min) showed complete conversion to **28b** (t_R 6.6 min) after 17 h. The reaction mixture was evaporated to half-volume, and 85% KOH (0.082 g) in water (0.85 mL) was added with stirring. After being heated at 95 °C for 30 min, the reaction mixture was cooled, the solvent was evaporated, and 1 M NaOH (1.2 mL) and phosphate buffer (pH 7.3, 2.3 mL) were added. The resulting solution was acidified to pH 6.10 by dropwise addition of 1 M HCl with rapid stirring, the mixture was saturated with NaCl and extracted with

ethyl acetate (4 × 3 mL), and the combined extracts were dried (Na_2SO_4) and evaporated to provide **29b** as a light-yellow oil: 0.111 g (94%). RPHPLC (as above, t_R 4.2 min) showed >90% purity and the material was used without further purification.

A solution of crude amino acid **29b** in $POCl_3$ (0.36 mL, 4.0 mmol) was heated at 100 °C and rapidly stirred for 5 min. It was then cooled to 0 °C, and methanol (2.2 mL) was added dropwise over the course of 15 min. After being stirred at 20 °C for 11 h, the reaction mixture was cooled to 0 °C, and half-saturated Na_2CO_3 (18 mL) was added over the course of 25 min. Extraction with dichloromethane (4 × 2.5 mL) provided a combined organic phase which was washed with saturated Na_2CO_3 (2 mL), dried (Na_2SO_4), and evaporated to afford **30b** as an oil (0.27 g) contaminated with $(CH_3O)_3PO$. RPHPLC (as above, **30b**, t_R 11.6 min) showed less than 10% UV active impurity, approximately 2% of which was **32b**.

To crude indoline acetal **30b** in dichloromethane (2.2 mL) and acetone (0.7 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 63.1 mg, 0.28 mmol) in dichloromethane (4.3 mL) with rapid stirring. After 2 h the solvent was evaporated, and the residue was chromatographed (5 g of neutral Al_2O_3, activity III, dichloromethane). Combination of selected fractions gave **32b** as an oil which crystallized under vacuum: 57 mg (61% from **27b**); mp 145–148 °C; t_R (as above, 4.2 min); NMR (90 MHz) δ 2.26 (s, 3 H, CH_3), 2.54 (tt, 2 H, NCH_2CH_2), 3.17 (t, 2 H, $NCH_2CH_2CH_2$, J = 7 Hz), 3.73, 3.80 (2 s, 3 H each, OCH_3), 4.21 (t, 2 H, NCH_2, J = 7 Hz), 5.02 (s, 2 H, Ar CH_2), 7.32 (m, 5 H, 5 Ar H), 10.28 (s, 1 H, CHO); IR (Nujol) 1645, 1524, 1493, 1416, 1285, 1258, 1094, 1014, 845, 755, 700 cm^{-1}; mass spectrum, m/e (relative intensity) 366 (M + 1, 2.4), 365 (M^+, 7.4), 274 (91.6), 57 (100); exact mass calcd for $C_{22}H_{23}NO_4$ 365.1627, found m/e 365.1614 (M^+).

2,3-Dihydro-7-methoxy-6-methyl-5,8-dioxo-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (36). A. From 32a. Vacuum-dried indole aldehyde **32a** (31.2 mg, 0.11 mmol, 0.015 mm, 56 °C, 24 h) in glacial acetic acid (2.7 mL) was cooled with an ice/water bath for 20 min at which time concentrated HNO_3 (2.7 mL, 0 °C) was added dropwise to the pasty solid over the course of 3 min with rapid stirring. Water (10 mL, 5 °C) was added after 30 min followed by a 45-min dropwise addition of 10% $NaHCO_3$ (65 mL). The mixture was extracted with dichloromethane (4 × 15 mL), and the combined extracts were washed with brine. Drying and evaporation provided **36** as an orange solid: 23.2 mg (83% yield, pure by RPHPLC, solvent A, t_R 6.8 min); mp 226–228 °C (lit. mp 224–227 °C,[5] 222–224 °C[9]); R_f (SiO_2, ethyl acetate) 0.60; NMR (250 MHz) δ 2.01 (s, 3 H, CH_3), 2.68 (tt, 2 H, NCH_2CH_2), 3.14 (t, 2 H, $NCH_2CH_2CH_2$, J = 7 Hz), 4.06 (s, 3 H, OCH_3), 4.31 (t, 2 H, NCH_2, J = 7 Hz), 10.38 (s, 1 H, CHO) (lit.[5] NMR δ 1.99, 4.12, 4.34 (t, J = 7 Hz), 10.5); IR (Nujol) 1681, 1642, 1603, 1529, 1506, 1342, 1307, 1285, 1259, 1101, 1020, 995, 956, 922, 898, 806, 742 cm^{-1} (lit.[5] IR (KBr) 1689, 1672, 1647, 1104, 1022 cm^{-1}); UV λ_{max} 217 nm (ϵ 18 290), 246 (9740), 272 (10 430), 280 (10 960), 285 (10 940), 324 (5580), 370–530 (sh; 730 at 415 nm) (lit.[5] UV λ_{max} 216 (ϵ 25 200), 243 (14 900), 272 (14 250), 289 (13 870), 732 (7120)).

B. From 32b. To indole aldehyde **32b** (4.5 mg, 0.012 mmol) in acetonitrile (0.25 mL) was added ceric ammonium nitrate (19.7 mg, 0.036 mmol) in water (0.25 mL) over the course of 1 min. After 50 min water (2.0 mL) was added and the mixture was extracted with dichloromethane (3 × 1.0 mL). The combined organic extract was washed with water (1.0 mL), 10% $NaHCO_3$ (2 × 0.5 mL), water (1.0 mL), and brine (1.0 mL). Drying and evaporation provided crude **36** which was chromatographed (150 mg of SiO_2, ethyl acetate) to yield 2.7 mg (87%) of pure **36**.

Registry No. 5, 2207-57-0; **6**, 81457-00-3; **6b**, 81457-01-4; **7**, 81457-02-5; **9**, 81457-03-6; **10**, 81457-04-7; **11**, 81457-05-8; **13**, 81457-06-9; **14a**, 81457-07-0; **14b**, 81457-08-1; **15**, 81457-09-2; **16**, 81457-10-5; **17**, 81457-11-6; **18**, 81457-12-7; **19**, 81457-13-8; **20**, 81457-14-9; **21**, 19676-67-6; **22**, 81457-15-0; **23**, 81457-16-1; **24**, 81457-17-2; **26**, 81457-18-3; **27a**, 81457-19-4; **27b**, 81457-20-7; **28a**, 81457-21-8; **28b**, 81457-22-9; **29a**, 81457-23-0; **29b**, 81457-24-1; **30a**, 81457-25-2; **30b**, 81457-26-3; **31a**, 81457-27-4; **31b**, 81457-28-5; **32a**, 81457-29-6; **32b**, 81457-30-9; **36**, 3188-25-8; proline methyl ester, 2577-48-2.

Enones with Strained Double Bonds. 7. Precursors for Substituted Bicyclo[3.3.1]nonane Systems[1]

Herbert O. House,* Russell J. Outcalt, and Michael D. Cliffton

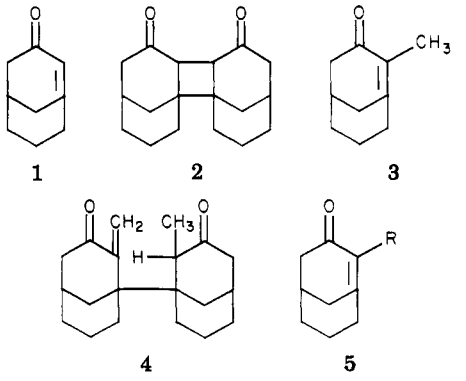
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received December 15, 1981

Compounds **11c**, **12**, and **13** have been synthesized as potential precursors for the 2-substituted bicyclo[3.3.1]non-1(2)-en-3-ones **5** (R = Ph and *t*-Bu). The lactone **34** and its derivatives **32** have also been synthesized as potential precursors for the parent bicyclo[3.3.1] enone **1**.

The rapid formation of dimeric 2 + 2 cycloadducts (e.g., **2**) has thus far frustrated our efforts to isolate the parent bicyclo[3.3.1] enone **1** (Scheme I) even when this enone **1** was generated in the absence of favorable reactants such as nucleophiles or dienes.[2] We reasoned that formation of dimeric cycloadducts such as **2** would be sterically impeded if the parent enone system contained α substituents such as the α-methyl enone **3**. In fact, no 2 + 2 cycloaddition products were isolated from solution of the enone **3**, and reaction of enone **3** with furan to form a Diels–Alder adduct was significantly slower than the corresponding reaction of enone **1** with furan.[3] Unfortunately, isolation

Scheme I



(1) A portion of this research has been supported by Public Health Service Grant R01-GM-20197 from the National Institute of General Medical Science. The execution of this research was also facilitated by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and an NMR spectrometer.

(2) (a) House, H. O.; Kleschick, W. A.; Zaiko, E. J. *J. Org. Chem.* **1978**, *43*, 3653. (b) House, H. O.; DeTar, M. B.; VanDerveer, D. *Ibid.* **1979**, *44*, 3793.

0022-3263/82/1947-2413$01.25/0