catalyst and evaporation a white solid remained, which was recrystallized from ethyl acetate: yield, 16.6 g (66%); mp 116–120 °C.

The mixture was chromatographed on a silica gel column (Waters Prep LC-500 apparatus) with ethyl acetate. Two fractions with slightly different R_f values on TLC (ethyl acetate) were obtained. **8a**: eluting last; 10.5 g (46%); mp 143–145 °C. **8b**: eluting first; 4.8 g (19%); mp 162–165 °C. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H 7.80; N, 5.16. Found **8a**: C, 75.39; H, 7.87; N, 5.08. Found **8b**: C, 74.90; H, 7.68; N, 4.92.

***cis*-2-Benzoyl-1,2,3,4,4a,7,8,8a-octahydro-7-methyl-6-isoquinolone Phenylhydrazone (9a).** A mixture of **8a** (25 g, 92 mmol) and phenylhydrazine (10 g, 92 mmol) in ethanol (600 mL) was refluxed for 16 h. The solution was then concentrated to half the volume and chilled. The crystalline phenylhydrazone **9a** was recrystallized from ethanol to give 28.5 g (86%): mp 203–209 °C. Anal. Calcd for $C_{23}H_{27}H_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.36; H, 7.60; N, 11.35.

***trans*-2-Benzoyl-1,2,3,4,4a,7,8,8a-octahydro-7-methyl-6-isoquinolone Phenylhydrazone (9b).** **9b** was prepared analogously to the cis isomer: 72% yield; mp 176–182 °C. Anal. Calcd for $C_{23}H_{27}H_3O$: C, 76.42; H, 7.53; N, 11.63. Found: C, 76.15; H, 7.49; N, 11.43.

***trans*-2-Benzoyl-10b-methyl-1,2,3,4,4a,5,11,11a-octahydro-10b*H*-pyrido[4,3-*b*]carbazole (10b).** The trans-phenylhydrazone **9b** (3.6 g, 10 mmol) was dissolved in dichloromethane (70 mL); ether saturated with HCl (5 mL) was added to the solution and the mixture was stirred for 2 h at room temperature. The residue from evaporation of the solvents was dissolved in acetic acid (5 mL) and poured on ice/ammonia. The precipitate was filtered and crystallized from ethanol–ether: yield 1.3 g (38%); mp 204–206 °C. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02, N, 8.13. Found: C, 79.76; H, 7.03; N, 7.95.

***cis*-2-Benzoyl-10b-methyl-1,2,3,4,4a,5,11,11a-octahydro-10b*H*-pyrido[4,3-*b*]carbazole (10a).** This compound was prepared from **9a** analogously to **10b**: yield, 61%; mp 196–198 °C. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 79.80; H, 7.09; N, 8.00.

***cis*-10b-Methyl-1,2,3,4,4a,5,11,11a-octahydro-10b*H*-pyrido[4,3-*b*]carbazole (11a).** A mixture of **10a** (2.8 g, 8 mmol), ethanol (60 mL), and 50% KOH (6 mL) was refluxed for 3 h. After evaporation of the ethanol, the remaining oil was treated with water and ethyl acetate, and the organic extracts were washed, dried, and evaporated. From the residue a small amount of the free base **11a** could be crystallized from ether–ethanol: yield, 0.2 g (10%); mp 238–240 °C. Anal. Calcd for $C_{16}H_{20}N_2 \cdot H_2O$: C, 74.20; H, 8.39; N, 11.66. Found: C, 74.38; H, 8.15; N, 11.84.

The ether–ethanol filtrate was treated with ethereal HCl, which precipitated the dihydrochloride of **11a**, 1.2 g (48%), mp 248–251 °C, from ethanol. Anal. Calcd for $C_{16}H_{20}N_2 \cdot 2HCl$: C, 61.34; H, 7.07; N, 8.94; Cl, 22.63. Found: C, 61.15; H, 7.08; N, 8.53; Cl, 22.15.

***trans*-10b-Methyl-1,2,3,4,4a,5,11,11a-octahydro-10b*H*-pyrido[4,3-*b*]carbazole (11b).** A mixture of **10b** (2.3 g, 6.7 mmol) butanol (25 mL), and 50% KOH (12 mL) was refluxed for 3.5 h. After evaporation of the solvent the residue was treated with water and ethyl acetate and the oily base was converted to the hydrochloride with ethereal HCl. NMR analysis as discussed in the result section indicates the presence of two isomers: yield, 1.8 g (91%); mp 172–180 °C. Anal. Calcd for $C_{16}H_{20}N_2 \cdot H_2O \cdot HCl$: C, 65.18; H, 7.86; N, 9.50; Cl, 12.03. Found: C, 65.38; H, 7.75; N, 8.97; Cl, 12.04.

***cis*-3-Benzoyl-6-methyl-1,2,3,4,4a,5,6,11c-octahydropyrido[3,4-*c*]carbazole (12a).** The *cis*-hydrazone **9a** (1.0 g, 2.8 mmol) was added at ice bath temperature to 85% sulfuric acid (20 mL) and the mixture was stirred without further cooling until all hydrazone was dissolved. The solution was poured on ice/ammonia, and the solid was collected and purified on a silica gel column with dichloromethane/methanol (97/3) as eluant: yield, 0.4 g (42%); mp 218–226 °C. Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.17; H, 7.37; N, 7.90.

***cis*-6-Methyl-1,2,3,4,4a,5,6,11c-octahydropyrido[3,4-*c*]-carbazole (13a).** A mixture of the *cis*-benzoylindole derivative **12a** (0.45 g, 1.3 mmol), *n*-butanol (8 mL), and 50% KOH (1.5 mL) was refluxed for 18 h. The butanol was removed in vacuo and the remaining oil was treated with water and extracted with dichloromethane. The residue of the organic extract was purified by silica gel chromatography with dichloromethane/methanol (97/3) followed by dichloromethane/methanol (70/30) as eluant. The main fraction crystallized on evaporation: yield, 40 mg (12%); mp 225–227 °C. Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.52; H, 8.13; N, 11.78.

Acknowledgment. We wish to thank Christine Carter, Richard Kriwacki, and Scott Leonard for excellent technical assistance and Dr. Karl Hargrave for helpful discussion.

Synthesis of 3-Methyl-5,6-dihydro-3*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-ones

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The coupling of 2-(alkoxymethoxy)phenylcopper derivatives with the salt of ethyl chloroformate and ethyl 3-(pyridin-3-yl)propenoate was found to be an efficient method for the preparation of 4-(2-hydroxyphenyl)pyridines **13** substituted at C-3 with a propanoate side chain. N-Methylation and O-alkylation with ethyl bromoacetate gave salts **3** which when treated with base underwent an intramolecular enolate addition to the pyridinium nucleus to produce spiro[benzofuran-3(2*H*),4′(1′*H*)-pyridines] **4**. Prolonged base treatment of **4** yielded ethyl 3-methyl-7-hydroxy-5,7a-dihydro-3*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylates **5** by a Dieckmann reaction. Reduction of **5** led to predominately *trans*-3-methylhexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-ones, while reduction of **4** and then Dieckmann cyclization yielded mainly the cis isomers.

Recently derivatives of octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline have been found to be potent analgesics.[1] These tetracyclic compounds, of general structure **1**, are fragments of morphine **2** which possess the ACNO ring skeleton. Of particular interest are those compounds having the trans CN ring junction as in morphine. Importantly, compounds possessing the *N*-cyclopropylmethyl substituent exhibit both strong agonistic and antagonistic properties and are thus likely to have a low potential for

(1) (a) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261. (b) Ciganek, E. Eur. Pat. Appl. 9780, 1980; *Chem. Abstr.* **1980**, *93*, 220720*v*.

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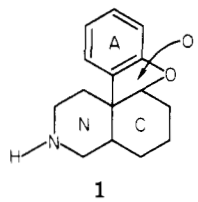

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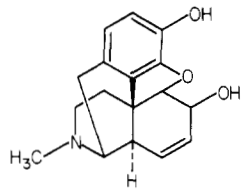
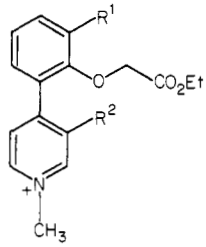
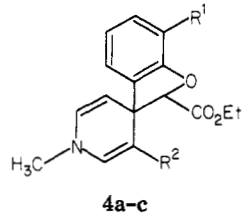


2

addiction.[1b] The earliest preparation of this ring system was reported by Schultz in 1976 by application of the heteroatom directed photoarylation sequence.[2] Ciganek's approach to this ring system utilized an intramolecular Diels–Alder reaction and led to either the cis or the trans ring junction stereoisomer by variation of the diene moiety in the Diels–Alder precursor.[1] Finally, Rapoport has prepared the ACNO system by extension of the versatile α-methylene lactam methodology.[3] We had previously shown that treatment of the *N*-methylpyridinium salt **3a**

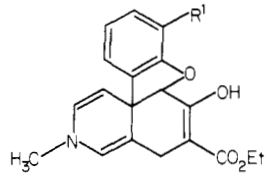


3a-c



4a-c

a, $R^1 = H$; $R^2 = H$
b, $R^1 = H$; $R^2 = CH_2CH_2CO_2Et$
c, $R^1 = OCH_3$; $R^2 = CH_2CH_2CO_2Et$

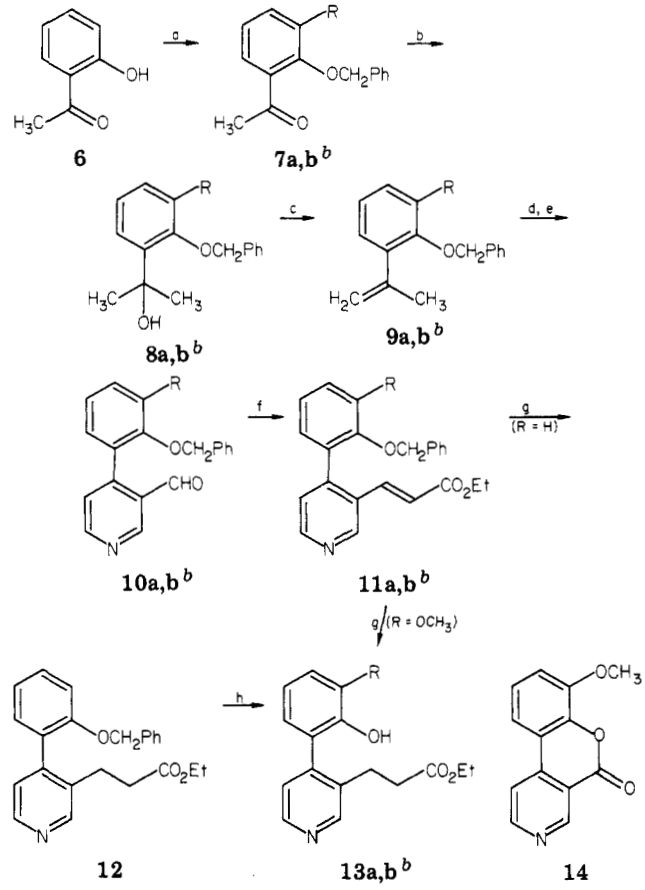


5a, R′ = H
b, R′ = OCH_3

with base generated an enolate which added intramolecularly to the 4-position of the pyridinium ring to yield the tricyclic spirobenzofuranopyridine **4a**.[4,5] When an ester-containing side chain was incorporated onto the β-position of the *N*-methylpyridinium salts, as in **3b**, enolate addition to give **4b** was followed by Dieckmann cyclization to give the tetracyclic ACNO model system **5a**.[6] We now report the details of this method and the application to the pharmacologically more interesting series **3c** → **5b** possessing an additional aromatic oxygen substituent.

In the construction of the model system **5a**, the 4-arylpyridinium salt **3b** was obtained by elaboration of the 4-arylpyridine-3-carboxaldehyde **10a**. This, in turn, was readily available from the corresponding α-methylstyrene **9a** (Scheme I). This sequence for the preparation of key intermediate **13a** proved to be much less attractive when applied to the synthesis of the methoxy analogue **13b**.

Scheme I[a]

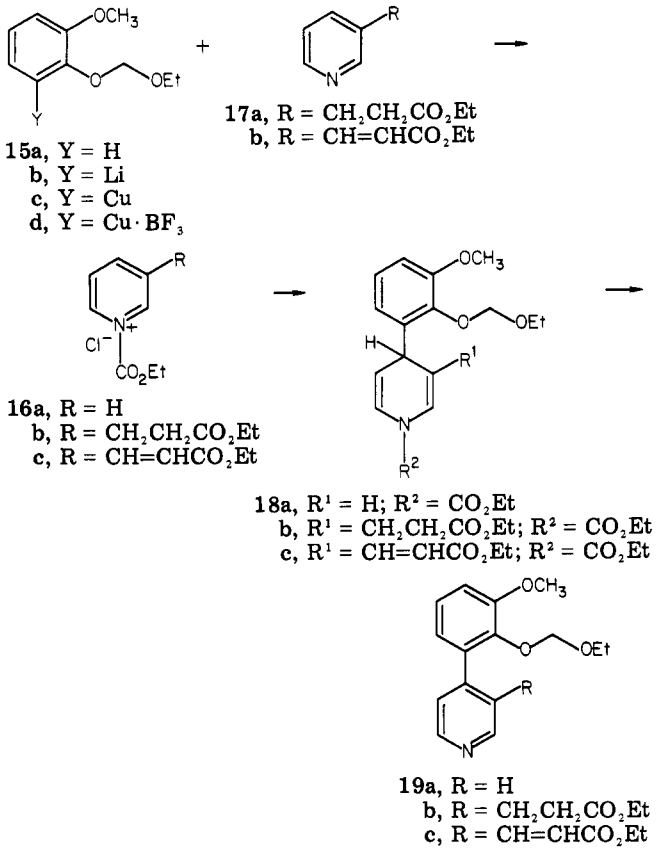


[a] (a) $PhCH_2I$, K_2CO_3, acetone, 56 °C; **7a**, 93%. (b) CH_3MgI, Et_2O, 34.5 °C; NH_4Cl, H_2O. (c) 200 °C, hydroquinone; **9a**, 94% (from **7a**); **9b**, 82% (from **7b**). (d) $(COCl)_2$, DMF, $ClCH_2CH_2Cl_2$, 90 °C. (e) HOAc, NH_4OAc, H_2O, 100 °C; **10a**, 78% (from **9a**); **10b**, 41% (from **9b**). (f) $CH_2(CO_2H)CO_2Et$, C_5H_5N, $C_5H_{11}N$, 100 °C; **11a**, 85%; **11b**, 60%. (g) H_2, Pd/C, EtOH; **12**, 91%, **13b**, 92%. (h) H_2, Pd/C, HCl/EtOH; **13a**, 95% (from **11a**). [b] a, R = H; b, R = OCH_3.

First, since the 3-methoxy analogue of **6** is not commercially available, extra steps were necessary to prepare the acetophenone **7b**. *o*-Vanillin was treated with benzyl iodide and potassium carbonate to give the corresponding benzyl ether. Addition of methyllithium, followed by pyridinium chlorochromate oxidation of the resulting alcohol, gave acetophenone derivative **7b** in 80% overall yield. As in the model series, Grignard reaction of **7b** with methylmagnesium iodide gave a carbinol which underwent thermal dehydration to yield 82% of α-methylstyrene **9b**. The yield for the Grignard/dehydration sequence was lower in this series than in the earlier case, apparently due to a competing debenzylation reaction. Second, although **9b** was converted to **10b** by the Vilsmeier formylation/cyclization procedure used to prepare **10a** from **9a**,[7] the yield was only 41%, presumably due to the added activation of the aromatic ring itself toward attack by the Vilsmeier reagent. Additionally, whereas **10a** could easily be purified by distillation, **10b** was found to be thermally labile and was instead isolated from the complex reaction mixture by chromatography. An attempted distillation of **10b** resulted in the isolation of a 1:1 mixture of **10b** and lactone **14**. Although the remaining steps in the conversion of **10b** into **13b** proceeded without incident, the overall

(2) (a) Schultz, A. G.; Lucci, R. D. *J. Chem. Soc., Chem. Commun.* **1976**, 925. (b) Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2162.
(3) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064.
(4) Weller, D. D.; Luellen, G. R.; *Tetrahedron Lett.* **1981**, *22*, 4381.
(5) Weller, D. D.; Luellen, G. R.; Weller, D. L. *J. Org. Chem.* **1983**, *43*, 3061.
(6) Weller, D. D.; Weller, D. L.; *Tetrahedron Lett.* **1982**, *23*, 5239.
(7) Jutz, C.; Muller, W.; Muller, E. *Chem. Ber.* **1966**, *99*, 2479.

Scheme II



yield from *o*-vanillin was only 15%.

An attractive and convergent alternative for the synthesis of **13b** would achieve a direct combination of the carbocyclic and heterocyclic aromatic rings. One method of accomplishing this procedure is the addition of organometallic reagents to pyridines, an often low-yield process due to the number of reactive sites on the pyridine and to the instability of the dihydropyridine product.[8] A general method for the introduction of alkyl and aryl groups at C-4 of pyridine was recently put forth by Akiba,[9] who found that alkyl- and arylcopper–boron trifluoride complexes add readily to the salt of pyridine and ethyl chloroformate. Comins has also described a similar procedure which was successful with β-picoline.[10] To investigate the applicability of this method, we briefly studied the reaction of **15d** with *N*-(ethoxycarbonyl)-pyridinium chloride (**16a**, Scheme II). Ether **15a** was selectively lithiated to **15b** with *n*-BuLi. Then treatment of **15b** with copper iodide gave **15c**, and addition of boron trifluoride etherate provided **15d**. When **15d** was added to a suspension of **16a**, formed from pyridine and ethyl chloroformate, dihydropyridine **18a** was obtained as an air-sensitive oil. Although Akiba's procedure called for air oxidation,[9] we found this to be inefficient, and, instead, immediate oxidation with *o*-chloranil gave the corresponding pyridine **19a** in 75% overall yield.

Extension of this methodology to the preparation of **13b** required the synthesis of the 3-substituted pyridine **17a**. This was readily available from pyridine-3-carboxaldehyde in 89% yield.[11] When this was reacted with **15d**, as above, dihydropyridine **18b** was obtained as part of a multicomponent mixture. Upon oxidation with *p*-chloranil, **19b** was obtained in 18% overall yield from **17a**. To enhance the reactivity of the substituted pyridine moiety, we carried out the reaction using pyridinium salt **16c**, which possesses an α,β-unsaturated ester side chain.[11] In the event, stable dihydropyridine **18c** was produced as a crystalline solid, but the yield was not much improved. By ^{1}H NMR, the reaction mixture contained significant amounts of byproducts which were apparently derived from the arylcopper reagent. To determine the origin of these byproducts, we undertook an investigation of the stability of the two intermediate arylcopper species, **15c** and **15d**. The first-formed derivative, **15c**, was found to be stable as a tetrahydrofuran solution at −20 °C. The boron trifluoride derivative **15d**, however, while stable at −78 °C, rapidly decomposed at −20 °C, and both **15c** and **15d** were converted to the unidentified reaction byproducts above this temperature. Addition of the more stable **15c** to pyridinium salt **16b** showed no marked improvement over results employing the derivative **15d**. However, addition of **15c** to **16c** proceeded at −20 °C over 2 h to give **18c** in 89% isolated yield, with only minimal byproduct formation. Best yields were obtained by using either freshly opened commercial copper iodide or the repurified salt.[12] The use of the copper bromide–dimethyl sulfide complex[13] in place of copper iodide or the use of catalytic copper iodide (5%)[10] with **15b** gave predominant formation of the aryl ether byproducts. While resistant to air oxidation, dihydropyridine **18c** was converted to the corresponding pyridine **19c** cleanly and efficiently with *o*-chloranil in benzene/toluene at 0 °C. Finally, catalytic hydrogenation of the pyridine side chain in **19c** over palladium on charcoal gave **19b** in 96% yield, and removal of the ethoxymethyl ether protecting group with *p*-toluenesulfonic acid in ethanol produced the desired phenol **13b** in 98% yield. By this route, **13b** was obtained in overall 69% yield from the 3-substituted pyridine **17b**, a marked improvement over construction of the 4-arylpyridine system by the α-methylstyrene sequence.

The formation of the remaining rings of the benzofuroisoquinoline system was initiated by N-alkylation of **13a** with methyl iodide to give **20a** and O-alkylation with ethyl bromoacetate to give the pyridinium salt **3b** in 98% yield (Scheme III). The conversion of **3b** into **4b** occurred instantaneously upon addition of 110 mol % of sodium ethoxide with dimethylformamide as the solvent. Compound **4b** was obtained in 92% yield as a mixture of syn and anti epimers (45/55). Although closure of the O ring was instantaneous and was not affected by the ethanol concentration, the Dieckmann reaction in dimethylformamide was very slow in the presence of added ethanol. However, treatment of **3b** as a 5% w/v solution in di-

(8) Eisner, V.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.

(9) Akiba, K.; Iseki, Y.; Wada, M. *Tetrahedron Lett.* **1982**, *23*, 429. See also: Piers, E.; Soucy, M. *Can. J. Chem.* **1974**, *52*, 3564.

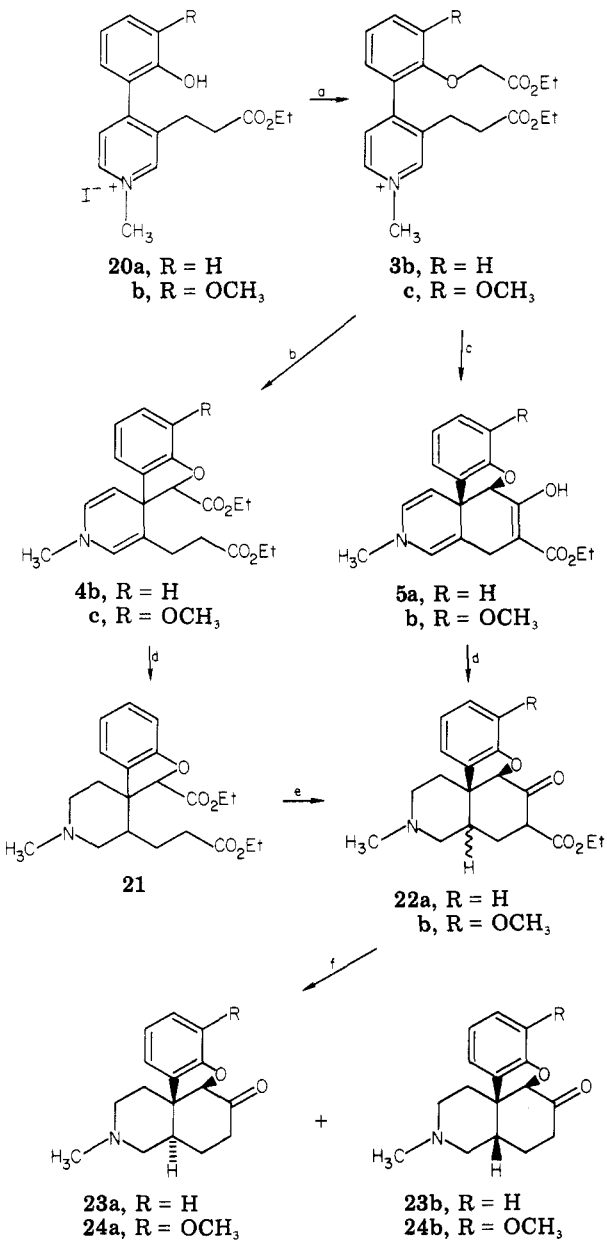
(10) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315.

(11) (a) From pyridine-3-carboxaldehyde was prepared **17b** by slight variations in the literature procedures[11b] in improved yields. A mixture of the aldehyde (4.41 mL, 46.7 mmol), malonic acid (9.58 g, 88.7 mmol), pyridine (15.0 mL, 187 mmol), and piperidine (0.11 mL, 1.11 mmol) was heated at 105 °C for 2.5 h. 3-(3-Pyridyl)propenoic acid was isolated as white crystals (6.72 g, 97%) by filtration and water washing: mp 235–236 °C (lit. mp 233 °C,[11b] 235.0–5.5 °C[11c]). The carboxylic acid derivative (22.3 g, 0.150 mol) and sulfuric acid (16.7 mL, 0.30 mol) in ethanol (280 mL) were heated at reflux for 2 h. Water was azeotroped off with ethanol (200 mL), fresh ethanol (200 mL) was added, and the mixture was heated 17 h longer. The solution was then concentrated, neutralized with 10% aqueous Na_2CO_3, and extracted with ether. Ester **17b** (25.00 g, 94%) was obtained as a colorless oil upon Kugelrohr distillation (0.5 mmHg, 90 °C) (lit.[11b] 14 mmHg, 156–158 °C). (b) Panizzon, L. *Helv. Chem. Acta* **1941**, *24*, 24E. (c) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 1209.

(12) (a) Kauffman, G. B.; Pinnell, R. P. *Inorg. Synth.* **1960**, *6*, 3. (b) Kauffman, G. B.; Teter, L. A. *Ibid.* **1963**, *7*, 9.

(13) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

Scheme III[a]



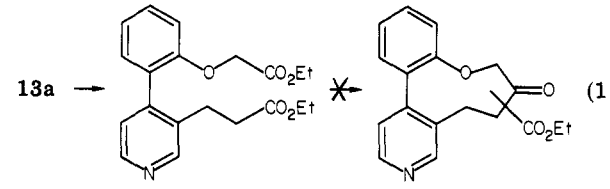
[a] (a) $BrCH_2CO_2Et$, K_2CO_3, DMF, 25 °C; **3b**, 98%; **3c**, 100%. (b) NaOEt/EtOH, DMF, 25 °C; **4b**, 92%; **4c**, 63%. (c) NaOEt, DMF, 25 °C; **5a**, 72%; **5b**, 69%. (d) H_2, PtO_2, EtOH; **22a**, 98%; **22b**, 100%; **21**, 96%. (e) NaOEt, DMF, 25 °C; **22a**, 64%. (f) 6 N HCl, 120 °C; **23a,b**, 76%; **24a,b**, 68%.

methylformamide, with 620 mol % of ethanol-free sodium ethoxide at 25 °C for 14 h gave sequential ring closures to yield 72% of the benzofuroisoquinoline derivative **5a**.

The conversion of **5a** into simpler members of the benzofuroisoquinoline series proceeded via catalytic hydrogenation over platinum to give a 98% yield of **22a** (Scheme III). A mixture of stereoisomers was produced, but these were not separated, and the reduction product was instead subjected to vigorous acidic hydrolysis to afford **23a** and **23b** in 76% yield in a ratio of 88:12. The trans isomer **23a** was readily obtained pure by recrystallization. Although the catalytic hydrogenation of **5a** was highly selective for the trans ring junction stereoisomer, the trans/cis ratio could be reversed by catalytic hydrogenation of the spirocyclic dihydropyridine **4b** prior to closure of the C ring. Thus, hydrogenation of **4b** over platinum gave a 96% yield of the spiro[benzofuran-3(2*H*),4′-piperidine] derivative **21** as an isomeric mixture. Subsequent Dieckmann condensation of **21** with sodium ethoxide in dimethylformamide yielded 64% of **22a**. Again, by ^1H NMR, one isomer appeared to predominate, but the major isomer in this case was the minor isomer obtained upon hydrogenation of **5a**. Decarboethoxylation of **22a**, as before, gave **23a** and **23b**, but in a ratio of 29:71, respectively.

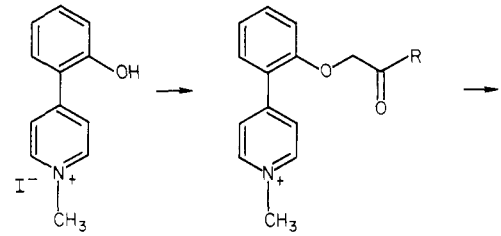
The synthesis of the benzofuroisoquinolines in the methoxy series was performed as above by treatment of salt **3c** with sodium ethoxide in ethanol/dimethylformamide, yielding 63% of the spiro[benzofuran-3(2*H*),4′-(1′*H*)-pyridine] **4c** (syn/anti ratio of 40:60). Prolonged reaction in ethanol-free dimethylformamide resulted in an overall conversion of **3c** to **5b** in 69%. Catalytic hydrogenation of **5b** over platinum gave a quantatitive yield of the mixture **22b**. Decarboethoxylation as above returned a 68% yield of **24a** and **24b** in an 88:12 ratio. Identification of the cis and trans isomers of **23** and **24** was based on spectral and chromatographic comparison of each isomer with the data reported by Rapoport et al.[3] for **24a** and **24b**. For these compounds, the trans isomer showed a methine proton in the ^1H NMR upfield from that of the cis isomer and an *N*-methyl group downfield from that of the cis isomer. Also consistent with Rapoport's results, the trans isomers were chromatographically less mobile on silica gel than the cis isomers.

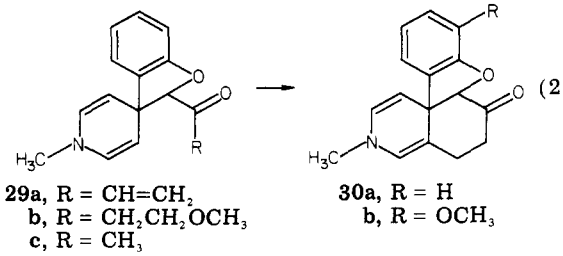
Several alternate O- and C-ring-closure schemes were attempted. The first alterntive for benzofuroisoquinoline formation would reverse the order of the Dieckmann and pyridinium/enolate addition steps. To this end, **13a** was selectively O-alkylated with ethyl bromoacetate to give **25** in moderate (63%) yield by using potassium carbonate in dimethylformamide (eq 1). However, all attempts to



(1)

achieve Dieckmann cyclization to the nine-membered ring **26** failed. In the second alternative, phenol **27** would be elaborated to **28a** (eq 2) which possesses a side-chain





(2)

consisting of the remaining carbons needed to construct the O and C rings. Treatment of **28a** with base would

result in dihydropyridine **29a**, and then intramolecular addition of the enamine moiety to the enone would provide the desired **30a**. Although this process proceeds from a readily available heterocyclic precursor[4] and is highly convergent, its success would depend heavily on the nucleophilicity of the 1-methyl-1,4-dihydropyridine system. Significantly, this system has been found much less reactive toward electrophilic attack than the corresponding 1-alkyl-1,4,5,6-tetrahydropyridine system, which behaved as a simple enamine.[14]

Although enones **28a** and **29a** were not available directly,[15] they were readily prepared in masked form. Alkylation of **27** with 1-chloro-4-methoxy-2-butanone afforded the intermediate salt **28b**, which gave dihydropyridine **29b** in 80% yield upon treatment with 4 N sodium hydroxide in dimethyl sulfoxide. Reaction with a catalytic amount of sodium ethoxide in dilute ethanol resulted in rapid consumption of **29b**. Workup provided an amorphous material, whose ^{1}H NMR spectrum was suggestive of polymerization of the unmasked enone, in preference to intramolecular Michael reaction with the dihydropyridine. Attempted thermal elimination of methanol by heating in dimethyl sulfoxide resulted in rapid decomposition at 80 °C. By comparison, simple dihydropyridines such as ketone **29c** were stable under these conditions until 120 °C. An authentic sample of **30a** was readily prepared in 74% yield by acidic hydrolysis of **5a** and treatment of the crude reaction mixture with sodium hydroxide. It could not be found among the products of either reaction above and was stable to the reaction conditions. Although these results were not conclusive in demonstrating the failure of this approach, the difficulty in the preparation of **28a** and the **29a** and the recorded low nucleophilicity of the 1,4-dihydropyridine system have discouraged further studies in this area.

In conclusion, we have developed a convergent, efficient synthesis of the benzofuroisoquinoline nucleus. The overall yield of **5b** from pyridine-3-carboxaldehyde is 44%, and it was readily converted into the perhydro series with the trans stereochemistry. Further, acidic hydrolysis of **5b** and base treatment provided **30b**, a candidate for further transformation into the 4,5-epoxymorphinan system of the morphine alkaloids.

Experimental Section

Low-resolution mass spectrometry was performed on a Varian MAT CH-7 or a Finnigan 3500. Infrared spectra were recorded on Perkin-Elmer spectrophotometers, Models 727B and 137. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ^{1}H NMR analyses were performed on Varian spectrometers, Model FT-80, HA-100, or EM-360. Chemical shifts (δ) are reported as parts per million downfield from tetramethylsilane as an internal standard. High-resolution mass spectra were obtained on a CEC-103B mass spectrometer by Richard Wielesek at the University of Oregon Micro-Analytical Laboratory. Combustion analyses were performed by Richard Wielesek at the University of Oregon Micro-Analytical Laboratory and by MicAnal, Tucson, AZ.

1-[2-(Phenylmethoxy)phenyl]ethanone (7a). Dried and finely ground K_2CO_3 (36.43 g, 0.264 mol) was added to a mechanically stirred solution of 2-hydroxyacetophenone (**6**; 15.9 mL, 0.132 mol) in acetone (180 mL), distilled from K_2CO_3). Benzyl chloride (22.8 mL, 0.198 mol) and NaI (32.67 g, 0.218 mol) were then added, and the reaction mixture was heated at reflux for 20 h. Additional K_2CO_3 (18.00 g) was added, and heating was continued for 23 h. The solids were filtered and washed well with ether. The solvents were evaporated, and the remaining benzyl iodide and **6** were removed by Kugelrohr distillation (2.5 mmHg, 120 °C). Finally, **7a** was distilled as an oil (0.1 mmHg, 130 °C; 27.64 g, 93%) which solidified upon standing. Recrystallization from MeOH gave the product: mp 39–41 °C (lit.[16] mp 40 °C); MS, m/z (relative intensity) 226 (M^+), 183, 121, 91 (100); IR (thin film) 1670, 1590, 1280, 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.56 (3 H, s), 5.09 (2 H, s), 6.86–7.79 (9 H, m).

2-(Phenylmethoxy)-α-methylstyrene (9a). To a solution of CH_3MgI (0.133 mol, 25 °C) was slowly added **7a** (15.00 g, 66.4 mmol) in ether (60 mL). The mixture was stirred at reflux for 5 h, the complex decomposed by the slow addition of aqueous NH_4Cl, and the carbinol **8a** extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and evaporated to give **8a** (16.56 g, crude) as a pale yellow oil: MS, m/z (relative intensity) 242 (M^+), 227, 134, 91 (100); IR (thin film) 3570, 1600, 1575 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.59 (6 H, s), 4.19 (1 H, s), 5.09 (2 H, s), 6.84–7.46 (9 H, m).

The carbinol **8a** (16.56 g) was heated at 200 °C in the presence of a trace amount of hydroquinone for 30 min. The sample was taken up with $CHCl_3$, washed with 2 N NaOH and brine, and dried (Na_2SO_4). The solvent was evaporated, and the resulting oil was purified by Kugelrohr distillation (0.05 mmHg, 120 °C) to give 13.96 g (94%) of α-methylstyrene **9a** as a colorless oil: MS, m/z (relative intensity) 224 (M^+), 209, 133, 105, 91 (100); IR (thin film) 1630, 1595, 898 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.15 (3 H, s), 5.08 (2 H, s), 5.02–5.18 (2 H, m), 6.82–7.47 (9 H, m); calcd for $C_{16}H_{16}O$ mol wt 224.120, found mol wt 224.120.

4-[2-(Phenylmethoxy)phenyl]pyridine-3-carboxaldehyde (10a). Oxalyl chloride (4.73 mL, 54.4 mmol) was added dropwise to a solution of $ClCH_2CH_2Cl$ (6.30 mL) and DMF (4.71 mL, 61.0 mmol). The reaction was vigorous, and a thick, white precipitate formed. To this was added, dropwise, a solution of **9a** (3.00 g, 13.4 mmol) in $ClCH_2CH_2Cl$ (2.70 mL). Additional $ClCH_2CH_2Cl$ (0.6 mL) was added to facilitate stirring. The mixture was brought to reflux, and the resulting red-brown solution was heated for 3 h. The $ClCH_2CH_2Cl$ was removed in vacuo, HOAc (5.0 mL), H_2O (1.25 mL), and NH_4OAc (4.19 g, 54.4 mmol) were added, and the resulting mixture was heated for 1 h at 100 °C. When cool, it was neutralized with 4 N NaOH and extracted with $CHCl_3$. The extracts were washed once with brine and dried (Na_2SO_4). The solvent was evaporated, and **10a** (3.02 g, 78%) was isolated as an oil by Kugelrohr distillation (0.005 mmHg, 190 °C): MS, m/z (relative intensity) 289 (M^+), 288, 261, 198, 91 (100); IR (thin film) 2970, 2890, 1690, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.06 (2 H, s), 7.04–7.55 (10 H, m), 8.79 (1 H, d, J = 4 Hz), 9.12 (1 H, s), 9.92 (1 H, s).

An analytical sample was prepared by preparative thin-layer chromatography on silica gel (5% acetone/$CHCl_3$): calcd for $C_{19}H_{15}NO_2$ mol wt 289.110, found mol wt. 289.108.

Ethyl 3-[4-[2-(Phenylmethoxy)phenyl]pyridin-3-yl]-propenoate (11a). A mixture of **10a** (100 mg, 0.346 mmol), ethyl hydrogen malonate (46.0 mg, 0.346 mmol),[17] pyridine (0.0275 mL, 0.346 mmol), and piperidine (0.5 μL) was stirred for 3 h at 100 °C. Pyridine and piperidine were removed in vacuo, and **11a** (104.8 mg, 84%) was isolated by Kugelrohr distillation (170 °C, 0.025 mmHg): MS, m/z (relative intensity) 359 (M^+), 358, 330, 182, 91 (100); IR (thin film) 1705, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz), 4.20 (2 H, q, J = 7 Hz), 5.04 (2 H, s), 6.38 (1 H, d, J = 16 Hz), 6.96–7.35 (10 H, m), 7.55 (1 H, d, J = 16 Hz), 8.59 (1 H, d, J = 4 Hz), 8.89 (1 H, s); calcd for $C_{23}H_{21}NO_3$ mol wt 359.152, found mol wt 359.156.

Ethyl 3-[4-[2-(Phenylmethoxy)phenyl]pyridin-3-yl]-propanoate (12a). A mixture of **11a** (53.7 mg, 0.150 mmol) and 10% Pd/C (5 mg) in EtOH (0.65 mL) was stirred under 1 atm of H_2 for 5 h. Additional catalyst (5 mg) in EtOH (0.4 mL) was added, and the mixture stirred under H_2 for 5 h longer. Catalyst was filtered off through Celite and washed with EtOH. The solvent was evaporated to give **12a**: 49.2 mg (91%); clear oil; MS, m/z (relative intensity) 361 (M^+), 360, 359, 284, 269, 175, 91 (100),

(14) (a) Saunders, M.; Gold, E. H.; *J. Org. Chem.* **1962**, *27*, 1439. (b) Kosower, E. M.; Sorenson, T. S.; *Ibid.* **1962**, *27*, 3764.

(15) See the supplementary material for details of the attempted preparation of **28a** and **29a**.

(16) (a) Priestly, H. M.; Moness, E. *J. Org. Chem.* **1940**, *5*, 355. (b) Schwenk, E.; Block, E. *J. Am. Chem. Soc.* **1942**, *64*, 3051.

(17) Strube, R. E. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 417.

79; IR ($CHCl_3$) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (3 H, t, J = 7 Hz), 2.25–2.55 (2 H, m), 2.76–3.06 (2 H, m), 4.01 (2 H, q, J = 7 Hz), 5.03 (2 H, s), 6.98–7.52 (10 H, m), 8.38–8.50 (1 H, br d) overlapping 8.50 (1 H, br s); calcd for $C_{23}H_{23}NO_3$ mol wt 361.168, found mol wt 361.170.

Ethyl 3-[4-(2-Hydroxyphenyl)pyridin-3-yl]propanoate (13a). A solution of **11a** (3.33 g, 9.28 mmol) in EtOH (34 mL) over 10% Pd/C (340 mg) was shaken on a Parr hydrogenator under 30 lbs of H_2. Additional catalyst (200 mg in 14 mL of EtOH) was added after 19 h. After another 12 h, TLC indicated complete double bond hydrogenation to give **12a**.

Additional 10% Pd/C (340 mg) in EtOH (10 mL) and HCl/EtOH (1.02 M, 10 mL) were added to the reaction vessel. The resulting mixture was shaken under 30 lbs of H_2 for 10 h at which time additional catalyst (200 mg in 10 mL of EtOH) was added, and reaction mixture was stirred under H_2 for 11 h longer. Catalyst was filtered off through Celite and washed well with EtOH. The ethanolic solution was poured into an excess of 10% aqueous $NaHCO_3$, and the resulting aqueous solution was extracted with ether. The ether extracts were washed once with brine, dried (Na_2SO_4), and evaporated to give **13a** (2.38 g, 95%) as a white, crystalline solid. An analytical sample was prepared by recrystallization from EtOH: mp 155–156 °C; MS, m/z (relative intensity) 271 (M^+), 180 (100); IR (KBr) 3000, 2720, 2600, 1730, 1610, 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.11 (3 H, t, J = 7 Hz), 2.24–2.91 (4 H, m), 3.95 (2 H, q, J = 7 Hz), 6.72–7.34 (5 H, m), 8.38 (1 H, d, J = 4 Hz), 8.43 (1 H, s), 9.60 (1 H, br s); calcd for $C_{16}H_{17}NO_3$ mol wt 271.121, found mol wt 271.121.

3-Methoxy-2-(phenylmethoxy)benzaldehyde (33). By use of the procedure for **7a**, *o*-vanillin (10.0 g, 65.8 mmol) was converted into **33** (14.5 g, 91%). Distillation (0.05 mmHg, 140–150 °C) afforded a pale yellow oil which crystallized upon standing. An analytical sample was recrystallized from MeOH: mp 43–44 °C (lit.[18] mp 45 °C); MS, m/z (relative intensity) 242 (M^+), 213, 150, 91 (100); IR (KBr) 1680, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (3 H, s), 5.15 (2 H, s), 7.04–7.48 (8 H, m), 10.21 (1 H, s).

1-[3-Methoxy-2-(phenylmethoxy)phenyl]ethanone (7b). To a solution of **33** (11.0 g, 46.2 mmol) in ether (76 mL) at 0 °C was added a 1.4 M solution of MeLi/LiBr complex in ether (34.1 mL, 47.7 mmol). The resulting mixture was stirred for 1 h at 0 °C, and then excess 10% aqueous $NaHCO_3$ was added to decompose the Li salt. Following extraction with ether, the extracts were washed once with brine, dried (Na_2SO_4), and evaporated to give 1-[3-methoxy-2-(phenylmethoxy)phenyl]ethanol: 11.8 g (99%); pale yellow oil; MS, m/z (relative intensity) 240 ($M - H_2O$)$^+$, 150, 121, 91, (100); IR (thin film) 3600, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (3 H, d, J = 6.5 Hz), 2.50 (1 H, s), 3.82 (3 H, s), 4.95–5.21 (1 H, m), 5.03 (2 H, s), 6.75–7.49 (8 H, m).

Pyridinium chlorochromate (14.8 g, 68.6 mmol) was added to a solution of the alcohol (11.8 g, 45.7 mmol) in dry CH_2Cl_2 (118 mL), and the mixture was stirred for 5 h at 25 °C. Ether (120 mL) was added, and the solid chromium species was removed by filtration. The filtrate was washed twice with 2 N HCl, once with brine, and dried (Na_2SO_4). Solvent was evaporated, and Kugelrohr distillation of the resulting oil (0.05 mmHg, 160 °C) gave **7b**: 10.41 g (89%); pale yellow oil; MS, (relative intensity) m/z 256 (M^+), 238, 214, 213, 151, 91 (100); IR (thin film) 1680, 1530 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (3 H, s), 3.88 (3 H, s), 5.08 (2 H, s), 7.00–7.51 (8 H, m); calcd for $C_{16}H_{16}O_3$ mol wt 256.110, found mol wt 256.110.

3-Methoxy-2-(phenylmethoxy)-α-methylstyrene (9b). By use of the procedure for **9a**, **7b** (5.00 g, 19.5 mmol) was converted to the carbinol **8b**: 5.10 g; pale yellow oil; MS, m/z (relative intensity) 254 ($M - H_2O$)$^+$, 239, 163, 91 (100); IR (thin film) 3540, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58 (6 H, s), 3.87 (3 H, s), 4.20 (1 H, s), 5.17 (2 H, s), 6.75–7.57 (8 H, m).

The carbinol **8b** (5.10 g) was then heated at 180–200 °C in the presence of a trace amount of hydroquinone for 30 min. The sample was taken up in $CHCl_3$, washed with 10% aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). The solvent was evaporated, and the resulting oil was purified by Kugelrohr distillation (0.05 mmHg, 130 °C) to give **9b**: 4.05 g (82% from **7b**); pale yellow oil; MS, m/z (relative intensity) 254 (M^+), 239, 163, 91 (100); IR (thin film) 1580, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (3 H, d, J = 1 Hz), 3.84 (3 H, s), 4.90 (2 H, s), 4.97–5.18 (2 H, m), 6.66–7.52 (8 H, m); calcd for $C_{17}H_{18}O_2$ mol wt 254.131, found mol wt 254.131.

Small amounts of the corresponding phenol were obtained along with **9b**: MS, m/z (relative intensity) 164 (M^+, 100); IR ($CHCl_3$) 3650, 1580, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (3 H, d, J = 1 Hz), 3.88 (3 H, s), 5.20 (2 H, d, J = 1 Hz), 5.85 (1 H, s), 6.77 (3 H, br s); calcd for $C_{10}H_{12}O_2$ mol wt 164.084, found mol wt 164.084.

4-[3-Methoxy-2-(phenylmethoxy)phenyl]pyridine-3-carboxaldehyde (10b). By use of the procedure for **10a**, **9b** (1.50 g, 5.91 mmol) was converted to **10b**. The crude product was flushed through a SiO_2 column (35 g) with 10% acetone/$CHCl_3$, and **10b** (780 mg, 41%) was obtained as an oil which crystallized upon standing. An analytical sample was recrystallized from EtOH and then sublimed (0.05 mmHg, 95 °C): mp 97.0–98.0 °C; MS, m/z (relative intensity) 319 (M^+), 290, 91 (100); IR (KBr) 2990, 2880, 1680, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.94 (3 H, s), 4.81 (2 H, s), 6.70–7.27 (9 H, m), 8.63 (1 H, d, J = 5 Hz), 8.99 (1 H, s), 9.68 (1 H, s). Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.20; H, 5.38; N, 4.39. Found: C, 75.10; H, 5.25; N, 4.41.

In one trial, Kugelrohr distillation (0.05 mmHg, 200 °C) was employed to purify the crude product isolated after extraction. The resulting distillate (520 mg) appeared as an approximately 1:1 mixture of two components by TLC (10% acetone/$CHCl_3$). With this solvent system it was chromatographed through a SiO_2 column (25 g). Compound **10b** (120 mg, 10%) was isolated along with lactone **14** (80 mg, 9%). An analytical sample of **14** was recrystallized from MeOH: mp 202.5–204 °C; MS, m/z (relative intensity) 227 (M^+), 213, 212, 91 (100); IR (KBr) 1730, 1580, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (3 H, s), 7.08–7.68 (3 H, m), 7.89 (1 H, d, J = 5 Hz), 8.93 (1 H, d, J = 5 Hz), 9.54 (1 H, s). Anal. Calcd for $C_{13}H_9NO_3$: C, 68.70; H, 4.00; N, 6.17. Found: C, 68.41; H, 4.10; N, 6.15.

Ethyl 3-[4-[3-Methoxy-2-(phenylmethoxy)phenyl]-pyridin-3-yl]propenoate (11b). As for **11a**, **10b** (720 mg, 2.26 mmol) was reacted with ethyl hydrogen malonate, and the resulting glass (760 mg) was chromatographed through a column of silica gel with 10% acetone/$CHCl_3$ to give **11b**: 530 mg (60%); amber oil; MS, m/z (relative intensity) 389 (M^+), 360, 212, 91 (100); IR ($CHCl_3$) 1720, 1640, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 3.92 (3 H, s), 4.16 (2 H, q, J = 7 Hz), 4.75 (2 H, s), 6.27 (1 H, d, J = 16 Hz), 6.54–7.30 (9 H, m), 7.23 (1 H, d, J = 16 Hz), 8.42 (1 H, d, J = 6 Hz), 8.77 (1 H, s). Calcd for $C_{24}H_{23}NO_4$ mol wt 389.163, found mol wt 389.162.

Ethyl 3-[4-(2-Hydroxy-3-methoxyphenyl)pyridin-3-yl]-propanoate (13b). Method 1. A solution of **11b** (330 mg, 0.85 mmol) in EtOH (20 mL) over 10% Pd/C (33 mg) was shaken on a Parr hydrogenator under 30 lbs of H_2. After 9 h, additional catalyst (33 mg) was added. After another 10 h, catalyst was filtered off through Celite, and the filtrate was evaporated to give **13b** (230 mg, 92%) as a white, crystalline solid. An analytical sample was prepared by recrystallization from EtOH: mp 108.0–108.5 °C; MS, m/z (relative intensity) 301 (M^+), 256, 227, 212, 210 (100); IR (KBr) 3000 (br), 1730, 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.11 (3 H, t, J = 7 Hz), 2.23–2.94 (4 H, m), 3.85 (3 H, s), 3.95 (2 H, q, J = 7 Hz), 6.54–7.12 (4 H, m), 8.37 (1 H, d, J = 5 Hz), 8.45 (1 H, s), 8.76 (1 H, br s). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.74; H, 6.37; N, 4.65. Found: C, 67.73; H, 6.45; N, 4.72.

Method 2. A solution of *p*-TsOH·H_2O [640 mg, 3.38 mmol; twice dissolved in EtOH (2.0 mL) and evaporated in vacuo] in EtOH (3.0 mL) was added to a solution of **19b** (1.1027 g, 3.07 mmol) in EtOH (8.0 mL). The reaction mixture was heated at 55 °C for 2 h and then added to a mixture of 10% aqueous $NaHCO_3$ (50 mL) and 20% acetone/$CHCl_3$ (30 mL). The aqueous layer was extracted further with 20% acetone/$CHCl_3$ (2 × 20 mL). The extracts were washed with brine (30 mL), dried (Na_2SO_4), and evaporated to give **13b** (906.1 mg, 98%) as an oil which crystallized upon standing.

2-(Ethoxymethoxy)anisole (15a). To a mixture of NaH (50% oil dispersion; 5.28 g, 0.110 mol; hexane washed) in DMF (60 mL) at 0 °C was slowly added guaiacol (11.00 mL, 0.100 mol). After the evolution of H_2 had ceased, chloromethyl ethyl ether (9.98 mL, 0.105 mol) was added dropwise at 25 °C, and the reaction mixture was stirred for 23 h at 25 °C. MeOH (6 mL) was added to quench excess NaH, followed by H_2O and benzene. The

(18) Richtzenhain, H. *Chem. Ber.* **1944**, *77B*, 1.

aqueous layer was extracted further with benzene, and the crude product obtained after washing with aqueous NaOH, H_2O, and brine was Kugelrohr distilled (1.0 mmHg, 100 °C) to give **15a**: 18.17 g (99%); colorless oil; MS, *m/z* (relative intensity) 182 (M^+), 59 (100); IR (thin film) 1590, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (3 H, t, *J* = 7 Hz), 3.76 (2 H, q, *J* = 7 Hz), 3.83 (3 H, s), 5.25 (2 H, s), 6.74–7.27 (4 H, m); calcd for $C_{10}H_{14}O_3$ mol wt 182.094, found mol wt 182.094.

4-[2-(Ethoxymethoxy)-3-methoxyphenyl]pyridine (19a). An *n*-BuLi/hexane solution (1.7 M, 3.24 mL, 5.50 mmol) was added to a solution of **15a** (500 mg, 2.75 mmol) in ether (2.0 mL) at 0 °C. The resulting slurry was stirred for 30 min at 18 °C. In situ, the lithio salt was filtered,[19] washed with hexane (5 × 1 mL), and transferred in THF (2.0 mL) to a suspension of CuI (520 mg, 2.75 mmol) in THF (6.0 mL) at −20 °C.[20] The resulting solution was stirred for 30 min at −20 °C and then cooled to −78 °C, and boron trifluoride etherate (0.34 mL, 2.75 mmol) was added. After 10 min at −78 °C, the dark brown solution was transferred to the slurry of **16a** formed upon addition of $ClCO_2Et$ (0.22 mL, 2.29 mmol) to pyridine (0.18 mL, 2.29 mmol) in THF (8.0 mL) at −78 °C. The reaction mixture was allowed to warm to 18 °C over a 2-h period and then stirred 2.5 h longer. Aqueous $NaHCO_3$ (5%, 20 mL) was added, the THF was evaporated, and the solids were removed by filtration. The filtrate was extracted with ether, and the extracts were washed once with brine, dried ($MgSO_4$), and evaporated to an amber oil. Filtration of the crude oil through SiO_2 (40 g) with 5% acetone/$CHCl_3$ gave **18a**: 760 mg (100%); air-sensitive, pale yellow oil; MS, *m/z* (relative intensity) 333 (M^+), 332, 59 (100); ^1H NMR ($CDCl_3$) δ 1.23 (3 H, t, *J* = 7 Hz), 1.30 (3 H, t, *J* = 7 Hz), 3.80 (2 H, q, *J* = 7 Hz), 3.82 (3 H, s), 4.26 (2 H, q, *J* = 7 Hz), 4.67–4.79 (1 H, m), 4.85–5.07 (2 H, m), 5.15 (2 H, s), 6.37–7.17 (5 H, m).

To a solution of **18a** (104.5 mg, 0.301 mmol) in benzene (1.0 mL) was added a solution of *o*-chloranil (74 mg, 0.301 mmol) in benzene (1.0 mL). After the mixture was stirred for 2 h at 20 °C, additional benzene was added, and the solution washed with 10% aqueous $NaHSO_3$, 0.1 N NaOH, and brine. It was dried (Na_2SO_4) and evaporated to give **19a** (58.4 mg, 75%) as an oil. An analytical sample was obtained by chromatography on SiO_2 (5% acetone/chloroform) as an amber oil which solidified upon standing: mp 67–70 °C; MS, *m/z* (relative intensity) 259 (M^+), 201, 200, 59 (100); IR (KBr) 3000, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, *J* = 7 Hz), 3.22 (2 H, q, *J* = 7 Hz), 3.88 (3 H, s), 4.93 (2 H, s), 6.88–7.19 (3 H, m), 7.45 (2 H, br d, *J* = 5 Hz), 8.35–8.85 (2 H, br); calcd for $C_{15}H_{17}NO_3$ mol wt 259.121, found mol wt 259.119.

Ethyl 3-(3-Pyridyl)propanoate (17a). A solution of **17b** (28.53 g, 0.161 mol) in EtOH (280 mL) over 9% Pd/C (2.85 g) was hydrogenated to give **17a** (28.23 g, 98%) as a colorless oil[11]. Final purification was effected by spinning-band distillation (0.05 mmHg, 72–74 °C): MS, *m/z* (relative intensity) 179 (M^+), 135 (100); IR (thin film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3 H, t, *J* = 7 Hz), 2.40–3.06 (4 H, m), 4.09 (2 H, q, *J* = 7 Hz), 7.14 (1 H, dd, *J* = 5, 8 Hz), 7.48 (1 H, br d, *J* = 8 Hz), 8.39 (1 H, dd, *J* = 5, 2 Hz), 8.43 (1 H, d, *J* = 2 Hz). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 66.99; H, 7.33; N, 7.82. Found: C, 66.70; H, 7.34; N, 7.87.

Ethyl 3-[4-[2-(Ethoxymethoxy)-3-methoxyphenyl]-pyridin-3-yl]propanoate (19b). Method 1. As for the formation of **19a**, ether **15a** (1.00 g, 5.50 mmol) was converted to its aryl–copper–BF_3 complex and reacted with the slurry of **16b** formed upon addition of $ClCO_2Et$ (0.44 mL, 4.58 mmol) to **17a** (820 mg, 4.58 mmol) in THF (16.0 mL) at −78 °C. The reaction mixture was allowed to warm to 18 °C over 1 h and then stirred 8 h longer. Workup, as before, gave crude **18b** as an amber oil. Chromatography on SiO_2 (75 g) with 5% acetone/$CHCl_3$ to remove the remaining **17a** and soluble Cu salts gave **18b** (2.08 g) in a pale yellow oil containing several materials which was carried on directly to the next step without further purification.

p-Chloranil (1.30 g, 5.29 mmol) was added to a solution of **18b** in benzene (20.0 mL), and the mixture stirred for 4 h at 18 °C. Excess aqueous $NaHSO_3$ was added, and the resulting benzene layer was washed with 0.1 N NaOH and brine, dried (Na_2SO_4), and evaporated to a dark oil (2.05 g). Chromatography on SiO_2 (75 g), first with 5% acetone/$CHCl_3$ to remove high-R_f impurities and then with 20% acetone/$CHCl_3$, gave **19b**: 290 mg (18%); pale yellow oil; MS, *m/z* (relative intensity) 359 (M^+), 342, 286, 59 (100); IR (thin film) 1730, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, *J* = 7 Hz), 1.18 (3 H, t, *J* = 7 Hz), 2.24–3.22 (4 H, m), 3.88 (3 H, s), 4.03 (4 H, q, *J* = 7 Hz), 4.87 (2 H, s), 6.63–7.32 (4 H, m), 8.47 (2 H, br s); calcd for $C_{20}H_{25}NO_5$ mol wt 359.173, found mol wt 359.171.

Method 2. A solution of **19c** (338.1 mg, 0.947 mmol) in EtOH (20 mL) over 9% Pd/C (34 mg) was hydrogenated to give **19b** (326.2 mg, 96%).

Ethyl 1,4-Dihydro-4-[2-(ethoxymethoxy)-3-methoxyphenyl]-3-(3-ethoxy-3-oxopropenyl)pyridine-1-carboxylate (18c). An *n*-BuLi/hexane solution (1.6 M, 3.44 mL, 5.50 mmol) was added to a solution of **15a** (500 mg, 2.75 mmol) in ether (2.5 mL) at 0 °C. The resulting slurry was stirred for 30 min at 18 °C. The lithio salt was filtered in situ, washed with hexane (4 × 1 mL), and transferred in THF (3.0 mL) to a suspension of CuI[20] (520 mg, 2.75 mmol) in THF (5.0 mL) at −20 °C. The resulting solution was stirred for 30 min at −20 °C, cooled to −78 °C, and transferred to the slurry of **16c** formed upon addition of $ClCO_2Et$ (0.22 mL, 2.29 mmol) to **17b** (410 mg, 2.29 mmol) in THF (8.0 mL) at −78 °C. The reaction mixture was warmed to −20 °C and stirred for 2 h. The solution was added to a mixture of benzene/hexane/10% aqueous $NaHCO_3$/brine (100 mL, 2:1:1:1). The solids were filtered off, and the aqueous layer was extracted with benzene/hexane (2:1). The extracts were washed with brine, dried (Na_2SO_4), and evaporated to an amber oil which crystallized upon standing. Chromatography on SiO_2 (35 g) with 5% acetone/$CHCl_3$ removed soluble Cu salts and gave a pale yellow oil which crystallized upon standing. Recrystallization from benzene/hexane gave white crystals of **18c**: 880 mg (89%); mp 111.5–112.0 °C; MS, *m/z* (relative intensity) 431 (M^+), 430, 371 (100); IR (KBr) 1720, 1670, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3 H, t, *J* = 7 Hz), 1.26 (3 H, t, *J* = 7 Hz), 1.35 (3 H, t, *J* = 7 Hz), 3.18–4.25 (4 H, m), 3.83 (3 H, s), 4.31 (2 H, q, *J* = 7 Hz), 4.89 (1 H, br d, *J* = 5 Hz), 5.11–5.34 [5.16 (1 H, d, *J* = 6 Hz), 5.25 (1 H, d, *J* = 6 Hz), overlapping 1 H, m], 5.65 (1 H, d, *J* = 16 Hz), 6.55–7.07 (4 H, m), 7.24 (1 H, d, *J* = 16 Hz), 7.43 (1 H, br s). Anal. Calcd for $C_{23}H_{29}NO_7$: C, 64.00; H, 6.79; N, 3.25. Found: C, 63.82; H, 6.57; N, 3.17.

Ethyl 3-[4-[2-(Ethoxymethoxy)-3-methoxyphenyl]-pyridin-3-yl]propenoate (19c). *o*-Chloranil (580 mg, 2.35 mmol) was added to a solution of **18c** (506.6 mg, 1.18 mmol) in benzene/toluene (5.0 mL, 1:1) at 0 °C. After 2 h at 0 °C, the reaction mixture was added to excess aqueous $NaHSO_3$ and benzene. The organic layer was washed with 0.5 N NaOH and brine, dried (Na_2SO_4), and evaporated to a dark oil. For removal of the remaining quinone derivatives, the crude oil was taken up in EtOH (4.0 mL) and treated with NaOEt/EtOH (1.69 M, 0.70 mL, 1.18 mmol). After 10 min, the solution was added to a mixture of benzene/0.5 N NaOH (40 mL, 1:1). The benzene layer was washed further with 0.5 N NaOH, and the aqueous layers were back-extracted with benzene. The combined benzene solutions were washed once with brine, dried (Na_2SO_4), and evaporated to give **19c** (381 mg) as a dark oil which crystallized upon standing. Traces of polar, highly colored impurities were removed by filtration through SiO_2 (15 g) with 20% acetone/$CHCl_3$ and gave **19c** (338.1 mg, 81%). An analytical sample was prepared by recrystallization from EtOH to give white crystals: mp 91.0–91.2 °C; MS, *m/z* (relative intensity) 357 (M^+), 328, 59 (100); IR (KBr) 1710, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3 H, t, *J* = 7 Hz), 1.27 (3 H, t, *J* = 7 Hz), 3.04 (2 H, q, *J* = 7 Hz), 3.89 (3 H, s), 4.18 (2 H, q, *J* = 7 Hz), 4.88 (2 H, s), 6.38 (1 H, d, *J* = 16 Hz), 6.60–7.34 (4 H, m), 7.53 (1 H, d, *J* = 16 Hz), 8.54 (1 H, br d, *J* = 5 Hz), 8.85 (1 H, br s). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.19; H, 6.50; N, 3.92. Found: C, 67.08; H, 6.40; N, 3.91.

4-(2-Hydroxyphenyl)-1-methyl-3-(3-oxo-3-ethoxypropyl)-pyridinium Iodide (20a). CH_3I (0.27 mL, 4.35 mmol) was added to a solution of **13a** (295 mg, 1.09 mmol) in DMF (3.0 mL), and the mixture was stirred for 1 h at 25 °C. DMF and excess CH_3I

(19) The lithiation of **18a** was performed in a 50-mL, three-necked flask constructed with a side-arm containing a fritted-glass disk. Under a nitrogen atmosphere, the ether/hexane solution could be filtered off with aspirator suction (dry ice/acetone trap), and the remaining solid successively washed with dry hexane and filtered to remove excess *n*-butyllithium. The lithio salt was then suspended in tetrahydrofuran and transferred from the flask under nitrogen pressure via cannula.

(20) CuI was from a freshly opened bottle (Fisher) or was purified as pure ref 12.

were removed in vacuo to give **20a**: 449 mg (100%); pale yellow oil; IR (thin film) 3550, 3400 (br), 1730, 1660 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.11 (3 H, t, J = 7 Hz), 2.41–3.06 (4 H, m), 4.00 (2 H, q, J = 7 Hz), 4.36 (3 H, s), 6.84–7.72 (4 H, m), 7.95 (1 H, d, J = 6 Hz), 8.85 (1 H, d, J = 6 Hz), 9.01 (1 H, br s).

4-[2-(2-Ethoxy-2-oxoethoxy)phenyl]-1-methyl-3-(3-oxo-3-ethoxypropyl)pyridinium Iodide (3b). To a solution of **20a** (450 mg, 1.09 mmol) in DMF (4.0 mL) was added dry, finely powdered K_2CO_3 (230 mg, 1.63 mmol). Ethyl bromoacetate (0.18 mL, 1.63 mmol) was then introduced to the red-orange mixture. After the mixture was stirred for 1 h at 25 °C, benzene (5 mL) was added to the now pale yellow reaction mixture. The solids were removed by filtration and washed with DMF/benzene (1:1). The solvents were removed in vacuo to give **3b** (534 mg, 98%) as an amber oil which crystallized upon standing. An analytical sample was prepared by recrystallization from EtOH: mp 135.0–135.5 °C; IR (KBr) 1750, 1730, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.13 (3 H, t, J = 7 Hz), 1.19 (3 H, t, J = 7 Hz), 2.40–3.06 (4 H, m), 3.98 (2 H, q, J = 7 Hz), 4.12 (2 H, q, J = 7 Hz), 4.40 (3 H, s), 4.83 (2 H, s), 7.00–7.63 (4 H, m), 7.93 (1 H, d, J = 6 Hz), 8.89 (1 H, d, J = 6 Hz), 9.07 (1 H, s). Anal. Calcd for $C_{21}H_{26}NO_5I$: C, 50.49; H, 5.26; N, 2.81. Found: C, 50.28; H, 4.96; N, 2.80.

Spiro[2-(ethoxycarbonyl)benzofuran-3(2*H*),4′(1′*H*)-1′-methyl-3′-(3-oxo-3-ethoxypropyl)pyridine] (4b). To a solution of **3b** (301.1 mg, 0.6030 mmol) in DMF (3 mL) was added 1.69 M NaOEt/EtOH (0.39 mL, 0.661 mmol). The resulting solution was stirred at 25 °C for 5 min and then poured into a mixture of benzene/10% aqueous $NaHCO_3$/hexane (25 mL, 2:2:1). The aqueous layer was extracted twice more with benzene/hexane (2:1). The extracts were washed once with 10% aqueous $NaHCO_3$ and once with 10% aqueous $NaHCO_3$/brine (1:1), dried (Na_2SO_4), and evaporated to give **4b** (219.1 mg, crude). Filtration through a column of neutral Al_2O_3 (10 g) with 5% acetone/$CHCl_3$ returned pure **4b**: 207.3 mg (92%); amber oil: MS, m/z (relative intensity) 371 (M^+), 298, 270 (100); IR (thin film) 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$; mixture of two isomers, 54.5/45.5) δ 1.10–1.34 (m, total intensity 6 H, 4 overlapping t), 1.79–2.42 (m, total intensity 4 H), 2.93 and 2.94 (each s, total intensity 3 H, relative intensity 1:1.2), 3.92–4.33 (m, 4 q, 2 H each, and a 1 H doublet), 4.43 (1 H, d, J = 8 Hz) (3.92–4.43, total intensity 5 H), 4.53 and 4.99 (each s, total intensity 1 H, relative intensity 1:1.2), 5.73 (1 H, br s), 5.81–5.96 (2 H, m), 6.12 (1 H, dd, J = 8, 2 Hz) (5.73–6.12, total intensity 2 H), 6.79–7.56 (m, total intensity 4 H); calcd for $C_{21}H_{25}NO_5$ mol wt 371.173, found mol wt 371.174.

Ethyl 3-Methyl-7-hydroxy-5,7a-dihydro-3*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate (5a). A solution of 1.69 M NaOEt/EtOH (1.55 mL, 2.62 mmol) was evaporated in vacuo. The residue was dissolved in DMF (2.0 mL) and added to a solution of **3b** (211.1 mg, 0.423 mmol) in DMF (2.0 mL). The reaction mixture was stirred at 25 °C for 12 h and then poured into a mixture of benzene/hexane/10% aqueous $NaHCO_3$ (30 mL, 2:1:2). The aqueous layer was extracted three times further with benzene/hexane (12 mL, 2:1), and the extracts were washed once with 10% aqueous $NaHCO_3$/brine (1:1), dried (Na_2SO_4), and evaporated to give **5a**: 98.1 mg (72%); amber oil; MS, m/z 325 (M^+), 197 (100), 169; IR ($CHCl_3$) 1720, 1690, 1660, 1610, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (3 H, t, J = 7 Hz), 2.74 (2 H, s), 2.91 (3 H, s), 4.18 (2 H, q, J = 7 Hz), 4.46 (1 H, d, J = 8 Hz), 4.74 (1 H, s), 5.77 (1 H, dd, J = 8,2 Hz), 6.06 (1 H, br s), 6.76–7.35 (4 H, m), 11.94 (1 H, s), resonance at δ 11.94 exchanges with D_2O; calcd for $C_{19}H_{19}NO_4$ mol wt 325.131, found mol wt 325.132.

Spiro[2-(ethoxycarbonyl)benzofuran-3(2*H*),4′-1′-methyl-3′-(3-oxo-3-ethoxypropyl)piperidine] (21). A mixture of **4b** (264.3 mg, 0.712 mmol) and PtO_2 (20 mg) in EtOH (20 mL) was hydrogenated to give **21**: 257.6 mg (96%); oil; MS, m/z (relative intensity) 375 (M^+, 100), 330, 302, 170; IR (thin film) 1730, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, mixture for four isomers) δ 4.63, 4.97, 5.04, and 5.09 (each 1 H, s); calcd for $C_{21}H_{29}NO_5$ mol wt 375.205, found mol wt 375.205.

Ethyl 3-Methyl-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate (22a). Method 1. A mixture of **5a** (121.6 mg, 0.374 mmol) and PtO_2 (6.1 mg) in EtOH (20 mL) was hydrogenated to give **22a** (120.3 mg, 98%) as an oil which solidified upon standing. The sample is a 12:88 mixture of cis/trans ring junction stereoisomers: MS, m/z (relative intensity) 329 (M^+, 100), 283, 282, 256, 255, 236; IR (thin film) 1720, 1650, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, total intensity 3 H),1.75–3.04 (m, total intensity 10 H), 2.34 and 2.44 (each s, total intensity 3 H), 4.16 (q, J = 7 Hz, total intensity 2 H), 4.76 and 4.96 (each s, total intensity 1 H; relative intensity 88:12), 6.77–7.58 (m, total intensity 4 H); calcd for $C_{19}H_{23}NO_4$ mol wt 329.163, found mol wt 329.163.

Method 2. By use of the procedure for the formation **5a**, **21** (257.6 mg, 0.687 mmol) was treated with NaOEt/DMF to yield **22a** (145.3 mg, 64%) after 5 h as an oil. ^1H NMR ($CDCl_3$) shows a mixture of cis/trans isomers (71:29, respectively): δ 1.25 (t, J = 7 Hz, total intensity 3 H), 1.71–3.01 (m, total intensity 10 H), 2.34 and 2.44 (each s, total intensity 3 H), 4.18 (q, J = 7 Hz, total intensity 2 H), 4.76 and 4.95 (each s, total intensity 1 H; relative intensity 29:71), 6.72–7.55 (m, total intensity 4 H).

3-Methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (23). Trial 1. A solution of **22a** (67.8 mg, 0.206 mmol; prepared via method 1) in 6 N HCl (2.0 mL) was refluxed for 3 h. When cool, the reaction mixture was basified with 4 N NaOH and extracted with benzene. The extracts were washed once with brine, dried (Na_2SO_4), and evaporated to give **23** (40.5 mg, 76%) as a white solid which was a mixture of cis and trans ring junction stereoisomers (12:88 **23b**/**23a** respectively). The trans isomer (**23a**) was isolated by recrystallization from benzene/hexane, and an analytical sample was then sublimed: mp 187.5–188.3 °C; IR (KBr) 1710 cm^{-1}; MS, m/z (relative intensity 257 (M^+, 100); ^1H NMR ($CDCl_3$) δ 1.43–2.99 (11 H, m), 2.43 (3 H, s), 4.37 (1 H, s), 6.69–7.43 (4 H, m). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.66; H, 7.46; N, 5.45. Found: C, 74.39; H, 7.43; N, 5.30.

Trial 2. As described above, **22a** (32.5 mg, 0.099 mmol; prepared via method 2) was dissolved in 6 N HCl (2.0 mL) and refluxed for 4 h. Upon workup, **23** (17.0 mg, 67%) was isolated as an oil which was a 29:71 mixture of trans/cis ring junction stereoisomers.

An analytical sample of the cis isomer (**23b**) was obtained by preparative TLC (5% MeOH/1% Et_3N/$CHCl_3$): IR (thin film) 1725 cm^{-1}; MS, m/z (relative intensity) 257 (M^+, 100); ^1H NMR ($CDCl_3$) δ 2.35 (3 H, s), 4.59 (1 H, s); calcd for $C_{16}H_{19}NO_2$ mol wt 257.142, found mol wt 257.143.

4-(2-Hydroxy-3-methoxyphenyl)-1-methyl-3-(3-oxo-3-ethoxypropyl)pyridinium Iodide (20b). CH_3I (0.600 mL, 0.960 mmol) was added to a solution of **13b** (72.2 mg, 0.240 mmol) in DMF (0.70 mL), and the mixture was stirred for 5 h at 25 °C. DMF and excess CH_3I were removed in vacuo to give **20b**: 106 mg (100%); pale yellow oil; IR (thin film) 3500, 1720, 1640 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.11 (3 H, t, J = 7 Hz), 2.40–3.03 (4 H, m), 3.85 (3 H, s), 3.97 (2 H, q, J = 7 Hz), 4.33 (3 H, s), 6.63–7.20 (3 H, m), 7.86 (1 H, d, J = 6 Hz), 8.80 (1 H, d, J = 6 Hz), 8.96 (1 H, s), 9.32 (1 H, br s).

4-[2-(2-Ethoxy-2-oxoethoxy)-3-methoxyphenyl]-1-methyl-3-(3-oxo-3-ethoxypropyl)pyridinium Iodide (3c). As for the preparation of **3b**, **20b** (90.7 mg, 0.205 mmol) gave **3c**: 108 mg (100%); pale yellow oil; IR (thin film) 3600, 1730, 1640, 1580 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.12 (6 H, t, J = 7 Hz), 2.40–3.02 (4 H, m), 3.84 (3 H, s), 3.97 (2 H, q, J = 7 Hz), 4.01 (2 H, q, J = 7 Hz), 4.35 (3 H, s), 4.57 (2 H, s), 6.72–7.30 (3 H, m), 7.91 (1 H, d, J = 6 Hz), 8.84 (1 H, d, J = 6 Hz), 9.03 (1 H, s).

Spiro[2-(ethoxycarbonyl)-7-methoxybenzofuran-3(2*H*),4′(1′*H*)-1′-methyl-3′-(3-oxo-3-ethoxypropyl)pyridine] (4c). As for **4b**, but with Me_2SO as the solvent, **3c** (94.4 mg, 0.178 mmol) was converted into **4c**: 44.7 mg (63%); isolated as an amber oil; MS, m/z (relative intensity) 401 (M^+), 328, 300 (100); IR (thin film) 1745, 1730 cm^{-1}; ^1H NMR ($CDCl_3$,[2] isomers) δ 1.11–1.33 (m, total intensity 6 H), 1.81–2.36 (m, total intensity 4 H), 2.94 (s, total intensity 3 H), 3.88 (s, total intensity 3 H), 3.91–4.36 (9 H, m) and 4.42 (1 H, d, J = 8 Hz) (total intensity 3.91–4.42, 5 H), 4.54 and 5.01 (each s, total intensity 1 H), 5.74 (1 H, br s) and 5.80–5.94 (2 H, m) and 6.10 (1 H, dd, J = 8,2 Hz) (total intensity 5.74–6.10, 2 H), 6.67–7.02 (m, total intensity 3 H); calcd for $C_{22}H_{27}NO_6$ mol wt 401.184, found mol wt 401.183.

Ethyl 9-Methoxy-3-methyl-7-hydroxy-5,7a-dihydro-3*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate (5b). As for the preparation of **5a**, **3c** (744.6 mg, 1.41 mmol) was converted into **5b**: 343.8 mg (69%); isolated as an amber oil; MS, m/z (relative intensity) 355 (M^+), 227 (100); IR (thin film) 1720, 1680, 1650,

1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz), 2.70–3.02 (2 H, m), 2.92 (3 H, s), 3.85 (3 H, s), 4.18 (2 H, q, J = 7 Hz), 4.46 (1 H, d, J = 8 Hz), 4.77 (1 H, s), 5.79 (1 H, dd, J = 8,2 Hz), 6.03 (1 H, br s), 6.64–6.99 (3 H, m), 11.81 (1 H, s, OH); calcd for $C_{20}H_{21}NO_5$ mol wt 355.142, found mol wt 355.144.

Ethyl 9-Methoxy-3-methyl-7-oxo-2,3,4,4a,5,6,7,7a-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate (22b). A mixture of **5b** (18.0 mg, 0.051 mmol) and PtO_2 (3.0 mg) in EtOH (20 mL) was hydrogenated to give **22b**: 18.2 mg (100%); oil; MS, m/z (relative intensity) 359 (M^+, 100), 313, 71, 70; IR (thin film) 1730, 1650, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, total intensity 3 H), 1.85–3.07 (m) and 2.47 (s) (total intensity 13 H), (s, total intensity 3 H), 4.16 (q, J = 7 Hz, total intensity 2 H), 4.83 and 4.99 (each s, total intensity 1 H, relative intensity 88:12), 6.72–7.17 (m, total intensity 3 H); calcd for $C_{20}H_{25}NO_5$ mol wt 359.173, found mol wt 359.171.

9-Methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (24). A solution of **22b** (323.4 mg, 0.901 mmol) in 6 N HCl (10.0 mL) was heated at reflux for 4 h. When cool, the reaction mixture was basified with 4 N NaOH and extracted with benzene. The extracts were washed once with brine, dried (Na_2SO_4), and evaporated to give **24** (175.1 mg, 68%) as an oil which solidified upon standing. The product is an 88:12 mixture of trans/cis ring junction stereoisomers.

The trans isomer (**24a**) was isolated by recrystallization from benzene/hexane, and an analytical sample was then sublimed: mp 139.5-140.0 °C; MS, m/z (relative intensity) 287 (M^+, 100); IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49–2.99 (11 H, m), 2.43 (3 H, s), 3.89 (3 H, s), 4.42 (1 H, s), 6.78–7.09 (3 H, m). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.03; H, 7.39; N, 4.88. Found: C, 70.97; H, 7.70; N, 4.84.

An analytical sample of the cis isomer (**24b**) was obtained by preparative TLC (5% MeOH/$CHCl_3$): MS, m/z (relative intensity) 287 (M^+, 100); IR (thin film) 1720, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67–2.94 (11 H, m), 2.33 (3 H, s), 3.89 (3 H, s), 4.60 (1 H, s), 6.62–7.00 (3 H, m); calcd for $C_{17}H_{21}NO_3$ mol wt 287.152, found mol wt 287.153.

3-Methyl-5,6-dihydro-3*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (30a). A solution of **5a** (65.5 mg, 0.202 mmol) in 6 N HCl (2.0 mL) was refluxed for 4 h. When cool, the reaction mixture was basified with 4 N NaOH and extracted with benzene. The extracts were washed once with 4 N NaOH/brine (1:1), dried (Na_2SO_4), and evaporated to give **30a**: 36.3 mg (71%); oil; MS, m/z (relative intensity) 253 (M^+), 197 (100), 196, 169; IR (thin film) 1720, 1680, 1610, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.22–2.87 (4 H, m), 2.97 (3 H, s), 4.43 (1 H, s), 4.50 (1 H, d, J = 8 Hz), 5.87 (1 H, dd, J = 8,2 Hz), 6.02 (1 H, br s), 6.82–7.17 (4 H, m); calcd for $C_{16}H_{15}NO_2$ mol wt 253.110, found mol wt 253.110.

9-Methoxy-3-methyl-5,6-dihydro-3*H*-benzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (30b). A solution of **5b** (111.2 mg, 0.313 mmol) in 6 N HCl (4.0 mL) was heated at reflux for 4 h. When cool, the solution was basified with 4 N NaOH and extracted with benzene. The extracts were washed once with 4 N NaOH/brine (1:1), dried (Na_2SO_4), and evaporated to give **30b**: 53.4 mg (60%); solid; mp 137–139 °C dec; MS, m/z (relative intensity) 283 (M^+), 227, 226 (100), 198; IR (KBr) 1720, 1680, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10–2.77 (4 H, m), 2.95 (3 H, s), 3.89 (3 H, s), 4.42 (1 H, s), 4.45 (1 H, d, J = 8 Hz), 5.86 (1 H, dd, J = 8, 2 Hz), 5.92 (1 H, s), 6.56–6.97 (3 H, m); calcd for $C_{17}H_{17}NO_3$ mol wt 283.121, found mol wt 283.121.

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Registry No. 3b, 85891-87-8; **3c**, 87307-96-8; *syn*-**4b**, 85891-90-3; *anti*-**4b**, 85891-89-0; *syn*-**4c**, 87307-97-9; *anti*-**4c**, 87308-12-1; **5a**, 85891-88-9; **5b**, 87307-98-0; **6**, 118-93-4; **7a**, 31165-67-0; **7b**, 87307-77-5; **7b**-ol, 87307-78-6; **8a**, 87307-75-3; **8b**, 87307-80-0; **9a**, 85891-82-3; **9b**, 87307-79-7; **9b**-ol, 87307-81-1; **10a**, 85891-84-5; **10b**, 87307-82-2; **11a**, 85891-85-6; **11b**, 87307-83-3; **12a**, 87307-76-4; **13a**, 85891-86-7; **13b**, 87307-84-4; **14**, 87308-11-0; **15a**, 79263-63-1; **15b**, 87307-86-6; **16a**, 63755-30-6; **16b**, 87307-89-9; **16c**, 87307-92-4; **17a**, 64107-54-6; **17b**, 28447-17-8; **18a**, 87307-87-7; **18b**, 87307-90-2; **18c**, 87307-91-3; **19a**, 87307-85-5; **19b**, 87307-88-8; **19c**, 87307-93-5; **20a**, 87307-94-6; **20b**, 87307-95-7; **21** (isomer 1), 87335-02-2; **21** (isomer 2), 87335-03-3; **21** (isomer 3), 87335-04-4; **21** (isomer 4), 87335-05-5; *cis*-**22a**, 85923-12-2; *trans*-**22a**, 85891-92-5; *cis*-**22b**, 87307-99-1; *trans*-**22b**, 87335-06-6; **23a**, 85891-93-6; **23b**, 85923-13-3; **24a**, 79619-24-2; **24b**, 79647-01-1; **25**, 87308-01-8; **27**, 81115-40-4; **29b**, 87308-02-9; **30a**, 85891-94-7; **30b**, 87308-00-7; **31a**, 87308-04-1; **31b**, 87308-05-2; **31d**, 86610-21-1; **31d**·BH_3, 87307-74-2; **31e**, 87308-06-3; **31f**, 87308-07-4; **31g**, 87308-08-5; **31g**·MeI, 87308-09-6; **32**, 87308-10-9; **33**, 2011-06-5; $PhCH_2I$, 620-05-3; $CH_2(CO_2H)CO_2Et$, 1071-46-1; $BrCH_2CO_2Et$, 105-36-2; $ClCH_2CN$, 107-14-2; CH_2=C-HLi, 917-57-7; CH_2=CHMgBr, 1826-67-1; *o*-vanillin, 148-53-8; guaiacol, 90-05-1; chloromethyl ethyl ether, 3188-13-4; pyridine-3-carboxaldehyde, 500-22-1; malonic acid, 141-82-2; 3-(3-pyridyl)propenoic acid, 1126-74-5; 1-chloro-4-methoxy-2-butanone, 87308-03-0; 4-(2-hydroxyphenyl)pyridine, 86610-20-0; piperidine, 110-89-4; chloroacetyl chloride, 79-04-9; *N*-(chloroacetyl)piperidine, 1440-60-4; allyl bromide, 106-95-6.

Supplementary Material Available: Attempted preparation of and experimental data for **26**, **28a**, **29a**, and **30a** (7 pages). Ordering information is given on any current masthead page.

Aryl Coupling Reactions of Pyrazolo[3,4-*d*]pyrimidin-4-yl Radicals

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4-Arylpyrazolo[3,4-*d*]pyrimidines (**4**) were the subjects of a synthetic investigation in order to evaluate their biological activity. Attempts to prepare **4** from 4-aminopyrazolo[3,4-*d*]pyrimidines (**5**) via classical Gomberg–Bachmann–Hey aryl coupling conditions failed. Conversion of **5** to **4** was accomplished by diazotiazation of **5** using alkyl nitrites with an acid catalyst in aromatic solvents. Isomer distribution of the aryl-coupled products **4** was that predicted for a radical intermediate (ortho > meta ≃ para); isomer structures were assigned by a detailed ^{1}H NMR analysis. Unusual fragmentation products **17** and **18** were isolated during the course of investigations. These oxadiazoles probably arise from collapse of intermediate pyrazolo[3,4-*d*]pyrimidin-4-yl radicals **15**.

Recent reports of the interesting anxiolytic properties of compounds such as **1**,[1] **2**,[2] and **3**[3] led us to investigate preparation of related 4-arylpyrazolo[3,4-*d*]pyrimidines (**4**) as potentially active pharmaceutical agents. A straight-

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