Lactone 4e.[22] A mixture of enol ether **3e** (0.432 g, 2 mmol), PCC (1.72 g, 8 mmol), and Celite (1.7 g) in CH_2Cl_2 (10 mL) was treated as earlier for 2.5 h to afford the lactone **4e**[22] (0.312 g, 82%). IR (neat): 3080, 3060, 3020, 1770, 1600 cm^{-1}. NMR ($CDCl_3$): δ 1.44 (s, 3 H), 1.91-2.15 (m, 2 H), 2.16-2.27 (m, 1 H), 2.35-2.50 (m, 1 H), 2.94 (d, 2 H, J = 3.75 Hz), 7.21-7.35 (m, 5 H). MS (m/e): 190 (M^+).

Lactone 4f.[17,23a-d] Enol ether **3f** (0.404 g, 2 mmol) was treated with PCC (1.7 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 1.5 h as described earlier to give lactone **4f**[17,23a-d] (0.264 g, 75%). IR (neat): 3080, 3060, 1775, 1600 cm^{-1}. NMR ($CDCl_3$): δ 1.72 (s, 3 H), 2.35-2.69 (m, 4 H), 7.3 (s, 5 H). MS (m/e): 176 (M^+).

Lactone 4g.[16b,24c] Enol ether **3g** (0.420 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) as described earlier to give the lactone **4g**[16b,24c] (0.290 g, 79%). IR (neat): 1780 cm^{-1}. NMR ($CDCl_3$): δ 0.90 (t, 3 H), 1.35 (s, 3 H), 1.2-1.6 (br s, 10 H), 1.71-2.13 (m, 2 H), 2.47-2.60 (m, 2 H). MS (m/e): 184 (M^+).

Lactone 4h.[23d,24a-d] A mixture of enol ether **3h** (0.304 g, 2 mmol), PCC (1.72 g, 8 mmol), and Celite (1.7 g) in CH_2Cl_2 (10 mL) was stirred for 1.5 h to give the lactone **4h**[23d,24a-d] (0.203 g, 66%) after flash chromatography. IR (neat): 1780 cm^{-1}. NMR ($CDCl_3$): δ 1.2-1.9 (m, 10 H), 2.04 (t, 2 H, J = 8 Hz), 2.62 (t, 2 H, J = 8 Hz). MS (m/e): 154 (M^+).

Lactone 4i.[23d,24b] Enol ether **3i** (0.276 g, 2 mmol) was treated with PCC (1.72 g, 8 mmol) and Celite (1.7 g) in CH_2Cl_2 (10 mL) for 1 h as described earlier to afford lactone **4i**[23d,24b] (0.157 g, 56%). IR (neat): 1770 cm^{-1}. NMR ($CDCl_3$): δ 1.5-2.0 (m, 8 H), 2.12-2.53 (t, 2 H), 2.51-2.75 (t, 2 H). MS (m/e): 140 (M^+).

Lactone 4j.[23c,26] Enol ether **3j** (0.276 g, 2 mmol), PCC (1.72 g, 8 mmol), and Celite (1.7 g) in CH_2Cl_2 (10 mL) were allowed to react for 1.5 h as described earlier to give the lactone **4j**[23c,26] (0.143 g, 51%). IR (neat): 1780 cm^{-1}. NMR ($CDCl_3$): δ 1.1-2.12 (m, 8 H), 2.13-2.7 (m, 3 H), 3.82-4.06 (m, 1 H). MS (m/e): 140 (M^+).

Lactone 4k.[9] Enol ether **3k** (0.248 g, 1 mmol) was treated with PCC (0.86 g, 4 mmol) and Celite (0.86 g) in CH_2Cl_2 (7 mL) for 1.5 h as described earlier to afford the lactone **4k**[9] (0.115 g, 52%) after chromatographic purification. IR (neat): 2200, 1780 cm^{-1}. NMR ($CDCl_3$): δ 0.87 (t, 3 H), 1.26 (m, 12 H), 2.21-2.63 (m, 6 H), 5.06-5.35 (m, 1 H). MS (m/e): 222 (M^+).

(±)-(Z)-5-Tetradecen-4-olide 9.[9c] Palladium on barium sulfate (50 mg, 5%) and quinoline (1 drop) were added to a solution of (±)-**4k** (0.111 g, 0.5 mmol) in 25 mL of ether. The mixture was stirred under a hydrogen atmosphere at room temperature for 12 h. The concentrated filtrate was subjected to column chromatography on silica gel to afford (±)-**9**[9c] (0.106 g, 95%) as a colorless oil. IR (neat): 3020, 2940, 2860, 1785, 1660, 1460, 1220, 1180, 1015, 980, 720 cm^{-1}. NMR ($CDCl_3$): δ 0.89 (t, 3 H), 1.0-1.48 (br s, 12 H), 1.5-2.5 (m, 6 H), 5.08 (m, 1 H), 5.20-5.66 (m, 2 H). MS (m/e): 224 (M^+).

Acknowledgment. We wish to express our thanks to the Ministry of Defence, New Delhi, and CSIR, New Delhi, for financial assistance.

Registry No. **1b**, 124099-62-3; **1d**, 2270-57-7; **1e**, 124099-61-2; **1f**, 124099-68-9; **1g**, 121402-96-8; **1h**, 1773-40-6; **1i**, 53544-43-7; **1j**, 111268-65-6; **1k**, 72130-70-2; **2a** (stereoisomer 1), 124152-05-2; **2a** (stereoisomer 2), 124152-06-3; **2b** (stereoisomer 1), 124099-63-4; **2b** (stereoisomer 2), 124099-64-5; **2c** (stereoisomer 1), 124099-89-4; **2c** (stereoisomer 2), 124099-93-0; **2d** (stereoisomer 1), 124099-65-6; **2d** (stereoisomer 2), 124099-66-7; **2e** (stereoisomer 1), 124099-67-8; **2e** (stereoisomer 2), 124099-87-2; **2f** (stereoisomer 1), 124099-69-0; **2f** (stereoisomer 2), 124099-70-3; **2g** (stereoisomer 1), 124099-71-4; **2g** (stereoisomer 2), 124099-72-5; **2h**, 124099-90-7; **2i**, 124099-91-8; **2j** (stereoisomer 1), 124099-92-9; **2j** (stereoisomer 2), 124099-94-1; **2k** (stereoisomer 1), 124099-73-6; **2k** (stereoisomer 2), 124099-88-3; **3a**, 124099-83-8; **3b**, 124099-74-7; **3c**, 124099-75-8; **3d**, 124099-76-9; **3e**, 124099-77-0; **3f**, 124099-78-1; **3g**, 124099-79-2; **3h**, 124099-80-5; **3i**, 124099-81-6; **3j**, 124099-82-7; **3k**, 124125-59-3; **4a**, 40478-72-6; **4b**, 124099-84-9; **4c**, 124099-85-0; **4d**, 1193-36-8; **4e**, 61520-92-1; **4f**, 69854-29-1; **4g**, 124099-86-1; **4h**, 699-61-6; **4i**, 33448-80-5; **4j**, 61248-46-2; **4k**, 72130-77-9; (±)-**9**, 72151-71-4; **10**, 110-93-0.

(23) (a) Hoppe, D.; Hanko, R.; Bronneke, A. *Chem. Ber.* **1985**, *118*, 2822. (b) Giordano, C.; Belli, A.; Casagrande, F.; Guglielmetti, G. *J. Org. Chem.* **1981**, *46*, 3149. (c) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10. (d) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

(24) (a) Gupta, T. K. D.; Felix, D.; Kempe, U. M.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2198. (b) Canonne, P.; Belanger, D.; Lemay, G.; Foscolos, G. B. *J. Org. Chem.* **1981**, *46*, 3091. Canonne, P.; Foscolos, G. B.; Belanger, D. *J. Org. Chem.* **1980**, *45*, 1828. (c) Trost, B. M.; Bogdanowicz, M. T. *J. Am. Chem. Soc.* **1973**, *95*, 5321. (d) Jacobson, R. M.; Lahm, G. P.; Clader, J. W. *J. Org. Chem.* **1980**, *45*, 395.

(25) Eaton, P. E.; Cooper, G. F.; Johnson, R. C.; Mueller, R. H. *J. Org. Chem.* **1972**, *37*, 1947.

(26) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4111. Herz, W.; Glick, L. A. *J. Org. Chem.* **1963**, *28*, 2970.

Azapsoralens. Synthesis of 8-Azapsoralens

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The synthesis of some *N*-methyl-8-azapsoralen salts **1** is described for use as water-soluble analogues of psoralens. A key intermediate is the furopyridine carboxaldehyde **16** prepared in four steps from simple acyclic precursors. The pyrone ring is fused on by first extending the carbon chain via a Reformatsky or Doebner condensation followed by deprotection and ring closure. Since stability of this ring system in water is crucial to its potential use as a nucleic acid cross-linking reagent, rates of pyrone hydrolysis for the *N*-methylazapsoralens were measured. Sufficient stability in the necessary pH range was found for several analogues.

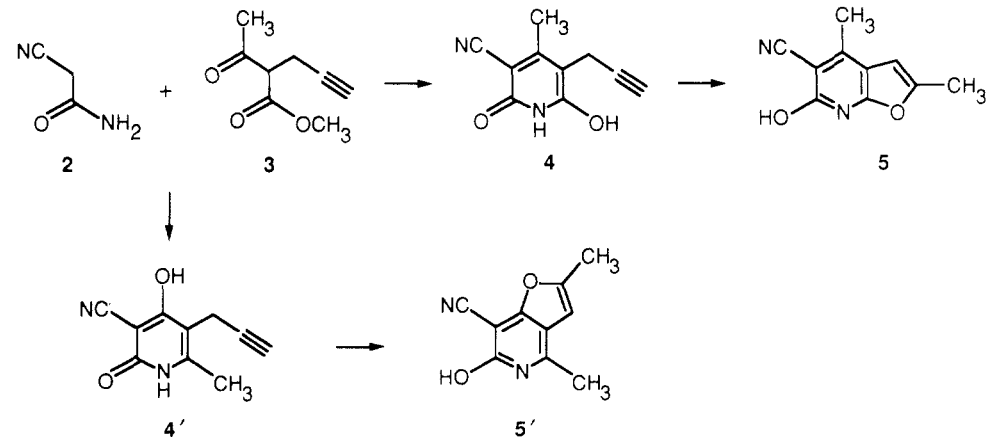
Linear furocoumarins, commonly named psoralens, have proved useful as drugs for the treatment of skin diseases and also as reagents for the biophysical study of nucleic acids.[1] They have been shown to intercalate nucleic acids and undergo photochemically induced [2 + 2] cycloadditions to adjacent pyrimidine bases.[2] Work toward increasing the yields of photoadducts has led to a number of analogues having hydrophilic side chains that confer

(1) Cimino, G. D.; Gamper, H. B.; Isaacs, S. T.; Hearst, J. E. *Annu. Rev. Biochem.* **1985**, *54*, 1151.

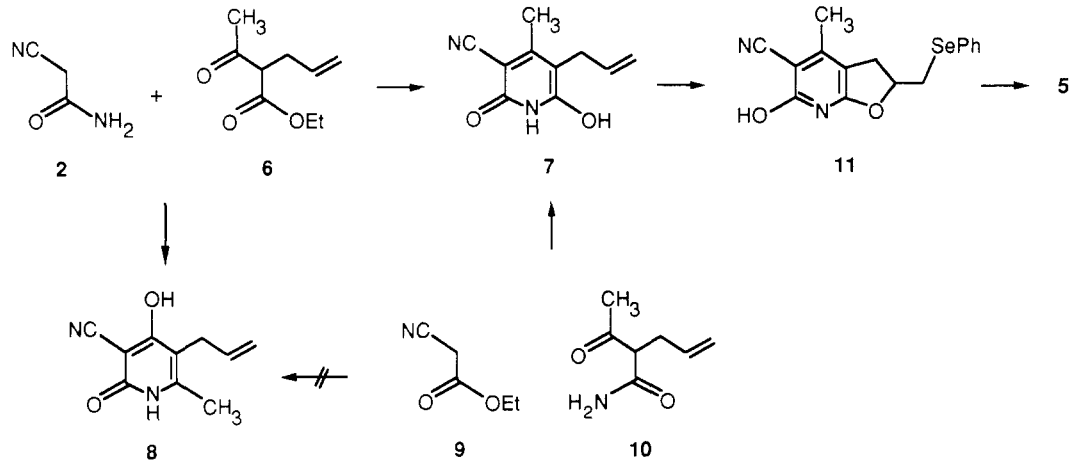
(2) Hearst, J. E.; Isaacs, S. T.; Kanne, D.; Rapoport, H.; Straub, K. *Q. Rev. Biophys.* **1984**, *17*, 1.

0022-3263/90/1955-0895$02.50/0

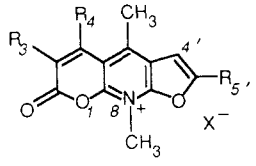
Scheme I. Synthesis of Substituted Furo[2,3-*b*]pyridine Ring System



Scheme II. Structure Proof of Allylpyridine 7 and Its Conversion to Furopyridine 5



both higher water solubility and enhanced noncovalent binding to DNA in the absence of light.[3] Another structural variant of psoralen that warrants investigation is the azapsoralen 1 in which the quaternary amine salt



1, X = $CF_3SO_3^-$

incorporated into the central ring would provide solubility in water. The methyl substituent para to the nitrogen is desired because it would allow the elaboration of more complex side chains and potential activation with longer wavelength light. To obtain such an azapsoralen, we have investigated the synthesis of the 8-azafuro[3,2-*g*]coumarin ring system.

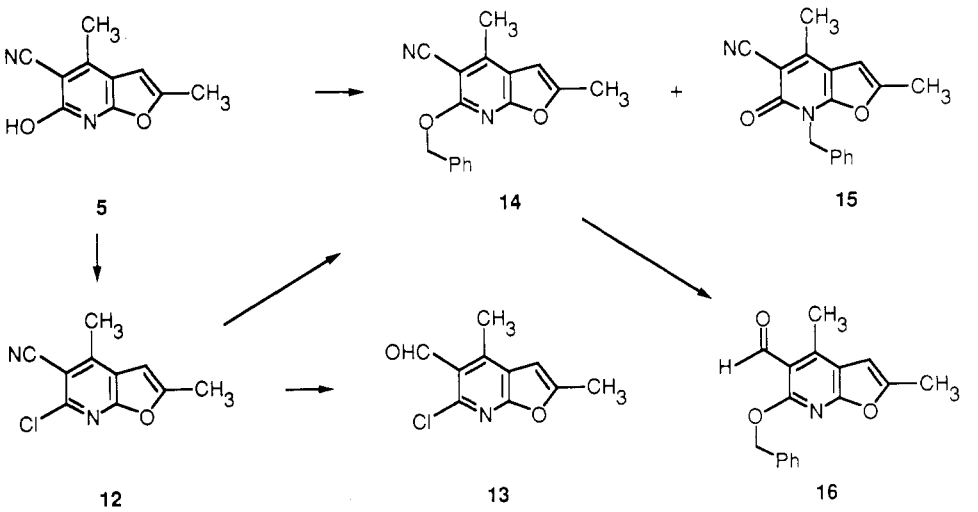
Our synthetic strategy called for the preparation of a pyridine having appropriate substituents for the annulation of furan and pyrone rings. Previous syntheses of 8-azacoumarins, for example, have relied on this strategy with the pyrone ring being added initially to a pyridone by the von Pechmann reaction.[4] Most furo[2,3-*b*]pyridines have been based on annulation of the furan onto a substituted pyridine[5] although the method of annulation has varied greatly. The known furopyridine 5[6] was an attractive intermediate because it offered the 6-hydroxy and 5-cyano functions, which could be elaborated for construction of the pyrone ring. The methyl group present at C-2 was of no concern since a methyl in that position of the psoralens has been shown to have a negligible effect on their photochemistry.[7]

Furopyridine 5 was synthesized by a modification of the reported[6] procedure (Scheme I). Condensation of cyanoacetamide and methyl 2-acetyl-4-pentynoate[8] in concentrated aqueous NH_3 gave the propargylpyridine 4, which crystallized from the reaction mixture as its ammonium salt in 74%. Heating this salt in trifluoroacetic acid gave the furopyridine 5 in 76% yield. This synthesis, however, is not unambiguous. Condensation of the ester at the methylene carbon and the ketone at the amide nitrogen woud lead to the regioisomeric furopyridine 5′.

To establish its structure, we invoked an alternate synthesis of 5 based on the allylpyridine 7 (Scheme II). This pyridine was synthesized in two ways. The first involved condensation of cyanoacetamide and ethyl 2-acetyl-4-pentenoate (6)[9] in piperidine to give the free pyridine in 51%. Although 7 is the expected product of

(3) (a) Isaacs, S. T.; Shen, C. J.; Hearst, J. E.; Rapoport, H. *Biochemistry* **1977**, *16*, 1058. (b) Isaacs, S. T.; Chun, C.; Hyde, J. E.; Rapoport, H.; Hearst, J. E. *Trends in Photobiology*; Helene, C., Laustriat, G., Eds.; Plenum: 1982; p 274.
(4) Atkins, R. L.; Bliss, D. E. *J. Org. Chem.* **1978**, *43*, 1975.
(5) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: 1984; Vol. 4, p 974.
(6) Reisch, J. *Arch. Pharm.* **1964**, 297, 754.
(7) Kanne, D.; Rapoport, H.; Hearst, J. E. *J. Med. Chem.* **1984**, *27*, 531.
(8) Dötz, K. H.; Popall, M. *Tetrahedron* **1985**, *41*, 5797.
(9) Wolff, C. *Liebigs Ann. Chem.* **1880**, *201*, 45.

Scheme III. Protection of Pyridinol 5 and Reduction to Aldehyde 16



the reaction, the possibility still exists that the product had the structure of regioisomer **8**. Spectroscopic evidence did not appear to offer an unambiguous identification of the product. However, by changing the components to ethyl cyanoacetate (**9**) and 2-acetyl-4-pentenamide (**10**) and carrying out the condensation in sodium ethoxide–ethanol, the same allylpyridine resulted. Since these latter components can only produce pyridine **7**, the structure of the product from the former condensation (**2** plus **6**) is established. Treatment of allylpyridine **7** with benzeneselenenyl bromide gave the selenide **11** in 92% yield. Oxidation of **11** to the selenoxide ($NaIO_4$) followed by pyrolysis (15 h in boiling dioxane/H_2O) gave furopyridine **5** (50%) plus recovered selenide **11** (20%). Presumably the vigorous conditions necessary for the selenoxide elimination result from the presence of an ether oxygen adjacent to the site of proton abstraction.

To complete the synthesis of the pyrone ring, we planned to first convert nitrile **5** to an aldehyde (Scheme III). Methods of reduction using Raney Ni in acidic or buffered media[10] led to destruction of the molecule while treatment with DiBAlH led only to recovered nitrile. Presumably the sterically congesting ortho substituents and the acidic proton of the pyridinol conspire to inhibit delivery of hydride to the nitrile. In order to eliminate deprotonation of the hydroxyl by hydride reagents, we sought to mask this function as the chloropyridine, which could be unmasked by hydrolysis later in the synthesis.

Chlorodehydroxylation of **5** proved difficult. Treatment of **5** in the usual way with $POCl_3$ or phenylphosphonic dichloride[11] under a variety of conditions led to phosphate adducts, but displacement of the phosphate by chloride did not occur to any appreciable extent. Oxalyl chloride and thionyl chloride also gave adducts with **5** but none of the chloropyridine. More vigorous conditions involving PCl_5 at temperatures >150 °C produced some chlorodehydroxylation but electrophilic chlorination of other sites in the molecule was a competing reaction. There are reports that yields of chlorodehydroxylation products have been improved by the addition of chloride ion via tetrabutylammonium chloride,[12] thus increasing the rate of displacement of the phosphorus leaving group. For the reaction of furopyridine **5**, adding 500 mol % Et_4NCl did lead to some success in producing chloropyridine **12** (18% yield) with $POCl_3$ (180 °C) and with $PhPOCl_2$ (30% yield, 258 °C). The low solubility of the ammonium salt seemed to limit the amount of chloride that could be delivered by this reagent.

Conceivably the ultimate extension of this technique would be to use a source of chloride ion that could also serve as the solvent. Pyridine hydrochloride seemed ideal because of its ready availability and good solvent properties.[13] Hydroxypyridine **5** was first converted to the phosphorodichloridate in $POCl_3$. Dissolving this crude intermediate in pyridine hydrochloride at 180 °C readily gave the chloropyridine **12** in an improved yield of 51%. The nitrile of chloropyridine **12** could be easily reduced with DiBAlH to give aldehyde **13** (45%). Although our strategy of masking the pyridine's hydroxyl as a chloride was effective, the overall yield of 25% led us to investigate an alternate method of protection.

For this purpose we considered the use of benzyl as a protecting group because of its stability to the DiBAlH reduction and subsequent acidic isolation as well as the variety of deprotection methods available. Alkylation of **5** with benzyl chloride and triethylamine in DMF gave O- and N-alkylated products in yields of 58% and 28%, respectively (Scheme III). Identification of the *O*-benzyl isomer **14** was made by comparison with a sample of **14** obtained from chloropyridine **12** and potassium benzyloxide. The reactivity of the benzylating agent in the alkylation had no effect on the ratio of isomers; benzyl chloride, tosylate,[14] triflate,[15] and phenyldiazomethane[16] all gave O/N ratios of 2/1. The ratio was significantly affected, however, by using silver carbonate as the base.[17] Reaction of **5** with Ag_2CO_3[18] and benzyl bromide gave almost exclusively the *O*-benzyl isomer **14**, which could be obtained pure in 88% yield after one crystallization. Reduction of the nitrile in **14** with DiBAlH gave a 67% yield of aldehyde **16**. A similar reduction on the *N*-benzyl isomer **15** gave many polar products, which were not characterized. Conversion of **16** to *trans*-acrylic acid **17**

(10) (a) Backeberg, O. G.; Staskun, B. *J. Chem. Soc.* **1962**, 3961. (b) van Es, T.; Staskun, B. *J. Chem. Soc.* **1965**, 5775.
(11) Robison, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 5481.
(12) Robins, M. J.; Uznanski, B. *Can. J. Chem.* **1981**, *59*, 2601.
(13) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; J. Wiley and Sons, 1967; Vol. 1, p 964.
(14) Tipson, R. S. *J. Org. Chem.* **1944**, *9*, 235.
(15) Lemieux, R. U.; Kondo, T. *Carbohydr. Res.* **1974**, *35*, C4–C6.
(16) Anselme, J.-P. *Org. Prep. Proced.* **1969**, *1*, 73.
(17) Hopkins, G. C.; Jonak, J. P.; Minnemeyer, H. J.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 4040.
(18) Poyer, L.; Fielder, M.; Harrison, H.; Bryant, B. E. *Inorg. Synth.* **1957**, *5*, 18.

Scheme IV. Synthesis of Azapsoralen Triflates

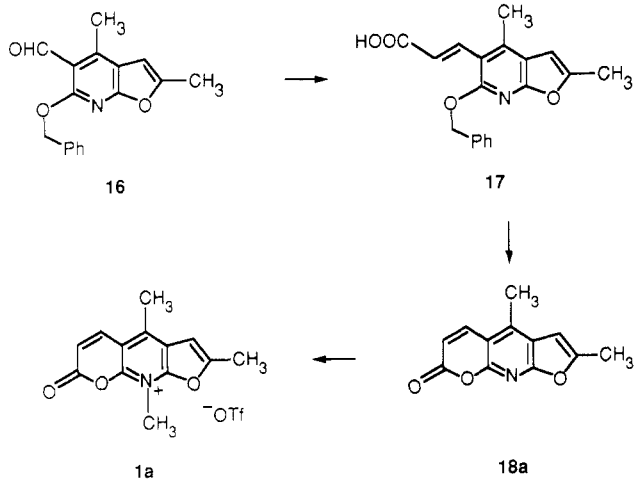
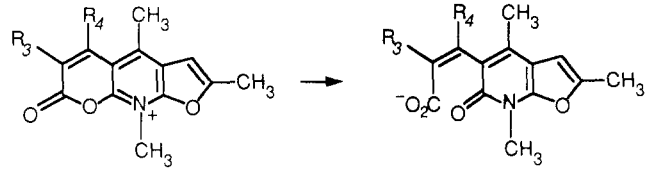


Table I. Half-Lives (in hours) for *N*-Methylazapsoralen Salts in Phosphate-Buffered Deuterium Oxide



substrate	pD 6.4 $t_{1/2}$	pD 7.4 (neutral) $t_{1/2}$	pD 7.7 $t_{1/2}$
1a ($R_3 = R_4 = H$)	9.6	4.4	0.2
1b ($R_3 = CH_3$, $R_4 = H$)	9.8	3.1	0.4
1c ($R_3 = H$, $R_4 = CH_3$)	1.5	0.6	0.4
1d ($R_3 = R_4 = CH_3$)	1.6	1.0	0.4

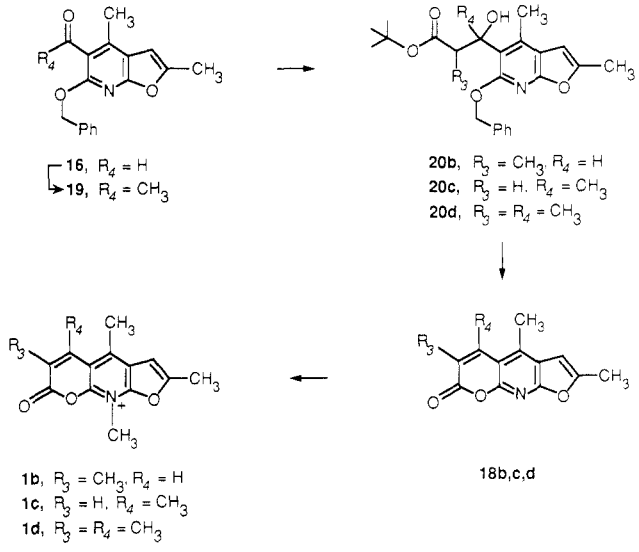
(Scheme IV) was accomplished in 89% yield under standard Doebner reaction conditions (malonic acid, piperidine, pyridine).

At this point it became necessary to remove the benzyl group, isomerize the *trans*-acrylic acid, and close the pyrone ring. Our plan had called for deprotection and ring closure in separate steps but a report[19] on the conversion of a methoxycinnamic acid to the coumarin with acetyl chloride prompted us to attempt this same one-step technique on our system. While acetyl chloride alone did not lead to ring closure, treatment of **17** with boiling acetyl chloride containing phenyltrimethylammonium iodide gave the azapsoralen **18a** in 75%. When the solvent/reagent was changed to acetyl bromide, no source of iodide was required and the yield of **18a** increased to 98%. Methylation of **18a** was unsuccessful with CH_3I but with methyl triflate, **18a** gave the quaternary amine salt **1a** in 94%.

Since biophysical investigations using psoralens are done in aqueous medium, a determination of the stability of the quaternized pyrone under those conditions became important. Our initial attempts to monitor ring opening by UV spectroscopy were foiled by the small changes in absorbance during the course of the reaction. ^1H NMR spectroscopy, however, easily established that ring opening, to form initially the *cis*-acrylate ($J_{H2,3} = 12$ Hz) pyridone was taking place readily. Half-lives for **1a** in phosphate buffered D_2O under acidic (pD 6.4), neutral (pD 7.4), and alkaline (pD 7.7) conditions are presented in Table I. The half-life of **1a** under these neutral and acidic conditions is more than adequate for the time span (15 min) used in the usual psoralen photochemistry. On the other hand,

(19) Mitter, P. C.; Paul, P. K. *J. Indian Chem. Soc.* **1931**, *8*, 271.

Scheme V. Synthesis of Azapsoralens Substituted on the Pyrone Ring



the high rate of hydrolysis in alkaline medium makes the compound's usefulness doubtful at higher pH's.

To investigate the effect of substituents on pyrone ring stability, we decided to synthesize the 3-methyl-, 4-methyl-, and 3,4-dimethyl-substituted azapsoralens **1b**, **1c**, and **1d**. Our thought was that the substituted pyrones would show greater resistance to hydrolysis under mildly alkaline conditions. Such compounds would also prove useful because substitution on the pyrone ring of psoralens influences the ratios of photochemical products.[7] Furthermore, the compounds offered the challenge of broadening the scope of our azafurocoumarin synthesis. Since the Doebner reaction is generally inapplicable for the preparation of cinnamic acids substituted on the alkene function, another method was needed to make precursors for the pyrone-forming reaction.

The carbon framework for a 3-methyl analogue was seen as coming from the aldehyde **16** and a propionic ester enolate (Scheme V). For this purpose, aldehyde **16** and *tert*-butyl 2-bromopropionate[20] were treated with zinc. In THF under standard Reformatsky conditions no adduct was formed, but at 100 °C in diglyme a 34% yield of **20b** was obtained. The use of magnesium[21] instead of zinc facilitated the reaction, which now proceeded at 50 °C in 85% yield to give a 3/2 mixture of diastereomers **20b**. Treatment of this mixture with acetyl bromide converted it directly to azapsoralen **18b** in 87% yield.

The 4-methylazapsoralens were seen to come from a two- or three-carbon enolate plus ketone **19**. Attempts to make this ketone by the addition of methyl anions to nitrile **14** were unsuccessful. Instead we resorted to the two-step sequence of adding CH_3MgBr to aldehyde **16** followed by oxidizing the resulting alcohol with pyridinium dichromate. Treating ketone **19** with magnesium turnings and *tert*-butyl bromoacetate[20] gave **20c** in 88% yield. In a similar manner, ketone **19**, *tert*-butyl α-bromopropionate, and magnesium gave **20d** of which only one diastereomer (31% based on recovered educt) could be obtained pure enough for further transformations. These adducts **20** were converted as before with acetyl bromide to give the azapsoralens **18c** (75%) and **18d** (87%). All three of the pyrone-substituted azapsoralens were converted to the *N*-

(20) Prepared by the method of McCloskey, A. L.; Fonken, G. S.; Kluiber, R. W.; Johnson, W. S. *Org. Synth.* **1954**, *34*, 26.
(21) Moriwake, T. *J. Org. Chem.* **1966**, *31*, 983.

methyl salts with methyl triflate.

Table I lists the half-lives of the methyl-substituted pyrones in D_2O. Immediately obvious is the destabilizing effect of the 4-methyl group under neutral and acidic conditions. A possible source of this destabilization could be steric interactions between peri methyl groups at positions 4 and 5. The 3-methyl group has a negligible effect at pH 6.4 and 7.4. However, the 2-fold increase in ring stability it imparts at pD 7.7 is sufficient to make **1b** a feasible substrate for future studies of its photochemical interaction with nucleic acids. The relative instabilities of 4-methyl derivatives **1c** and **1d** plus their more difficult syntheses make them less attractive than **1a** and **1b**.

Experimental Section

General Methods. THF was distilled from potassium/benzophenone, dioxane from $LiAlH_4$, CH_2Cl_2 from P_2O_5, Et_3N from CaH_2, and pyridine from NaOH. Dimethylformamide, benzyl bromide, benzyl chloride, benzyl alcohol, and piperidine were vacuum distilled from freshly activated 4-Å molecular sieves. Malonic acid was recrystallized from acetone, cyanoacetamide from EtOH. Pyridine hydrochloride was recrystallized from $CHCl_3$/EtOAc and isolated by filtration under an N_2 atmosphere. Methyl trifluoromethanesulfonate[22] was distilled immediately before use. All other reagents were made as referenced or used directly from commercial suppliers. Reactions were conducted under an N_2 atmosphere and final extracts were dried over $MgSO_4$. Unless otherwise noted, 70–230-mesh silica gel (EM Reagents) was used for column chromatography and analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (E. Merck).

Melting points are uncorrected. ^1H NMR spectra are referenced to Me_4Si unless otherwise noted and coupling constants, J, are in hertz. ^{13}C NMR spectra are referenced to the solvent used; carbon multiplicity (CH, CH_2, CH_3) was determined by the ^{13}C NMR DEPT experiment. IR spectra are referenced to polystyrene film. Mass spectra and elemental analyses were done by the Analytical Laboratory, College of Chemistry, University of California, Berkeley.

3-Cyano-2,6-dihydroxy-4-methyl-5-(propyn-3′-yl)pyridine (4) Ammonium Salt. Cyanoacetamide (27.3 g, 0.33 mol) and methyl 2-acetyl-4-pentynoate (**3**)[8] (50.6 g, 0.33 mol) were dissolved in concentrated aqueous ammonia (350 mL) in a 1-L Morton flask and the reaction mixture was stirred mechanically at room temperature for 5 days. The precipitated solid was isolated by filtration and dried under vacuum (75 °C, 0.05 Torr) to give 49.6 g, 74% yield: mp 272–275 °C dec (lit.[6] mp 274 °C); ^1H NMR (200 MHz, Me_2SO-d_6) δ 9.88 (s, 1 H), 7.13 (s, 4 H), 3.14 (d, J = 2.6, 2 H), 2.57 (t, J = 2.6, 1 H), 2.08 (s, 3 H); ^{13}C NMR (50 MHz, Me_2SO-d_6) δ 164.1, 163.5, 150.2, 121.8, 103.3, 84.2, 76.1, 68.9, 17.7, 14.4. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.5; H, 5.4; N, 20.5. Found: C, 58.6; H, 5.4; N, 20.4.

5-Cyano-2,4-dimethyl-6-hydroxyfuro[2,3-*b*]pyridine (5). From 4. A solution of **4** (44.5 g, 0.22 mol) in trifluoroacetic acid (130 mL) was heated at reflux for 6 h. Solvent was evaporated and the remaining solid was recrystallized from acetic acid, removing the last traces of acetic acid by azeotropic distillation with hexane: 30.9 g of **5**, 76% yield; mp 259–261 °C dec (lit.[6] mp 295 °C); ^1H NMR (250 MHz, MeOH-d_4) δ 6.51 (q, J = 1.2, 1 H), 2.59 (s, 3 H), 2.41 (d, J = 1.2, 3 H); ^{13}C NMR (50 MHz, Me_2SO-d_6) δ 162.1, 160.4, 153.3, 147.5, 115.7, 113.3, 100.9, 90.4, 17.2, 13.7; IR (KBr) 2240 cm^{-1}; UV (MeOH) λ_{max} (log ϵ) 212 (4.41), 232 (4.32), 318 (3.88). Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9. Found: C, 63.7; H, 4.2; N, 14.7.

From Phenyl Selenide 11. An aqueous solution of $NaIO_4$ (0.35 mL of 0.125 M, 0.044 mmol) was added to **11** (15 mg, 0.043 mmol) in 40% water/dioxane (5 mL) at 0 °C. TLC of the reaction mixture after 3.5 h at 0 °C indicated that **11** had been consumed. The solution was then heated under reflux for 15 h. After evaporation of the solvent the crude product was adsorbed on silica (0.5 g) and chromatographed on silica (230–400 mesh, 5 g, EtOAc) to give **11**, 20% recovery, and the product **5** in 50% yield.

2-Acetyl-4-pentenamide (10). A solution of 3-oxobutanamide[23] (1.00 g, 9.9 mmol) in THF (7 mL) was added dropwise to a solution of lithium diisopropylamide (9.4 mmol) in THF (10 mL) at room temperature. The solution was heated to 60 °C and allyl bromide (1.14 g, 9.4 mmol) in THF (10 mL) was added dropwise over 30 min. The reaction mixture was then heated at reflux 4 h. After cooling, solids were removed by filtration, the filtrate was evaporated, and the residue was chromatographed (silica, 230–400 mesh, EtOAc/$CHCl_3$, MeCN/EtOAc) and separated into three components: (1) Dialkylated compound, R_f 0.5 (EtOAc), 0.23 g (13%); mp 112–113 °C; ^1H NMR (250 MHz, CD_3CN) δ 5.7–5.55 (m, 2 H), 5.2–5.05 (m, 4 H), 2.55 (br d, 4 H), 2.11 (s, 3 H). (2) Monoalkylated compound **10**, R_f 0.3 (EtOAc), 0.48 g (34%); mp 106–107 °C; ^1H NMR (250 MHz, CD_3CN) δ 6.5 (br s, 1 H), 6.0 (br s, 1 H), 5.8–5.6 (m, 1 H), 5.15–4.95 (m, 2 H), 3.45 (t, 1 H), 2.48 (m, 2 H), 2.16 (s, 3 H); IR (KBr) 1720, 1660 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.6; H, 7.8; N, 9.9. Found: C, 59.4; H, 7.9; N, 9.8. (3) Starting material, R_f 0.1 (EtOAc), 0.19 g (19%).

3-Cyano-2,6-dihydroxy-4-methyl-5-(propen-3′-yl)pyridine (7). Ethyl 2-acetyl-4-pentenoate[9] (1.17 g, 6.87 mmol), cyanoacetamide (1.79 g, 2.13 mmol), and piperidine (2 mL) were heated at reflux for 5.5 h. Solvent was removed and the resulting syrup was dissolved in H_2O (10 mL). Addition of concentrated HCl (0.5 mL) and cooling the solution in an ice bath precipitated **7**, 0.66 g (51%). A crystalline sample was obtained by recrystallization from H_2O: mp 174–175 °C (lit.[24] mp 172–173 °C); ^1H NMR (200 MHz, Me_2SO-d_6) δ 8.0 (s), 5.79 (m, 1 H), 4.95 (m, 2 H), 3.18 (m, 2 H), 2.23 (s, 3 H); ^{13}C NMR (125 MHz, Me_2SO-d_6) δ 162.3, 162.1, 153.6, 135.6, 117.1, 114.9, 110.2, 84.6, 29.3, 17.7; IR (KBr) 2200 cm^{-1}.

Pyridine 7 from 10. Amide **10** (0.20 g, 4.2 mmol) was added to a solution of ethyl cyanoacetate (0.48 g, 4.2 mmol) in sodium ethoxide–ethanol (0.2 M, 20 mL). The reaction mixture was heated under reflux for 12 h, followed by removal of solvent. The residue crystallized from dilute HCl (aq) to give **7** (0.07 g, 30%) with identical mp and ^1H NMR as above.

2-[(Phenylseleno)methyl]-5-cyano-6-hydroxy-4-methyl-1,2-dihydrofuro[2,3-*b*]pyridine (11). Phenyl diselenide[25] (0.10 g, 0.32 mmol) was added to a solution of bromine (0.050 g, 0.031 mmol) in THF (4 mL) and the solution was stirred for 2 h. A solution of **7** (0.12 g, 0.63 mmol) in THF (4 mL), dried with 4-Å molecular seives, was added to the benzeneselenenyl bromide solution and the solution was stirred for 21 h. The entire reaction mixture was adsorbed on silica (2 g) and chromatographed on silica (20 g, 0.25% AcOH/EtOAc) to give 0.20 g (92%) of **11** as a white solid: mp 233–235 °C dec; ^1H NMR (250 MHz, pyridine-d_5) δ 7.66 (m, 2 H), 7.29 (m, 3 H), 5.14 (m, 1 H), 3.48 (dd, 1 H), 3.31 (dd, 1 H), 3.11 (dd, 1 H), 2.84 (dd, 1 H), 2.20 (s, 3 H); IR (KBr) 2215 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O_2Se$: C, 55.7; H, 4.1; N, 8.1. Found: C, 55.8; H, 4.0; N, 8.1.

6-Chloro-5-cyano-2,4-dimethylfuro[2,3-*b*]pyridine (12). Pyridinol **5** (0.50 g, 2.7 mmol) and freshly distilled $POCl_3$ (20 mL) were heated at reflux 0.5 h. Removal of solvent by Kugelrohr distillation left a white powder, which was mixed with pyridine hydrochloride (7.0 g) under a N_2 atmosphere. This mixture was heated at 180 °C under Ar for 7 h. After cooling the reaction mixture, it was dissolved in THF/H_2O and extracted with Et_2O. The Et_2O was washed with $NaHCO_3$ and brine, and evaporation of solvent left 0.28 g of slightly yellow **12**: TLC R_f 0.25, 1/2 EtOAc/Hex; 51% yield; mp 157–158 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 6.51 (q, 1 H), 2.70 (s, 3 H), 2.54 (d, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 158.0, 147.1, 146.6, 120.4, 114.8, 106.1, 100.9 (CH), 18.1 (CH_3), 14.4 (CH_3); MS (EI) m/z 206. Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.1; H, 3.4; N, 13.6. Found: C, 57.9; H, 3.4; N, 13.5.

6-Chloro-2,4-dimethylfuro[2,3-*b*]pyridine-5-carboxaldehyde (13). Diisobutylaluminum hydride (1 M in hexane, 1.2 mL, 1.2 mmol) was added to a solution of **12** (0.11 g, 0.53 mmol)

(22) Beard, C. D.; Baum, K.; Grakauskas, V. *J. Org. Chem.* **1973**, *38*, 3673.

(23) Kato, T.; Yamanaka, H.; Shibata, T. *Chem. Pharm. Bull.* **1967**, *15*, 921.

(24) Guareschi, I. *Chem. Zentralbl.* **1905**, II, 683.

(25) Reich, H. J.; Cohen, M. L.; Clark, P. S. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 533.

in THF (4 mL) at room temperature. After 8 h the reaction was quenched with MeOH (1 mL), poured into H_2SO_4 (0.5 M, 25 mL), and extracted with Et_2O. The Et_2O was washed with $NaHCO_3$ and brine, dried, and evaporated to give a yellow solid, which was purified by chromatography on silica (1/7 EtOAc/Hex): 0.05 g of **13**, 45% yield: mp 97–100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1 H), 6.52 (q, 1 H), 2.76 (s, 3 H), 2.51 (d, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0 (CH), 160.7, 156.9, 149.9, 145.9, 123.2, 122.3, 101.3 (CH), 17.6 (CH_3), 14.4 (CH_3); MS (EI) m/z 211, 210, 209 (M^+), 208, 180, 173, 145; MS (EI) m/z 209.0244 (209.0244 calcd for $C_{10}H_8ClNO_2$).

6-(Benzyloxy)-5-cyano-2,4-dimethylfuro[2,3-*b*]pyridine (14) and 7-Benzyl-5-cyano-6,7-dihydro-2,4-dimethyl-6-oxofuro[2,3-*b*]pyridine (15). Pyridinol **5** (2.00 g, 10.6 mmol), DMF (30 mL), and Et_3N (4.5 mL, 32 mmol) were stirred together and cooled in an ice bath as benzyl chloride (2.0 mL, 17 mmol) was added dropwise. After the addition, the mixture was heated at 60 °C for 3 h, then diluted with H_2O, and extracted with Et_2O. The Et_2O was washed with brine, dried, and evaporated. Chromatography of the residue (1/9 EtOAc/Hex) gave two compounds. **14**: 1.72 g, 58% yield; R_f 0.45 (1/2 EtOAc/Hex); mp 148–149 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.4 (m, 5 H), 6.35 (q, 1 H), 5.51 (s, 2 H), 2.61 (s, 3 H), 2.45 (d, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 160.5, 154.4, 147.6, 136.1, 128.4, 127.9, 127.7, 115.1, 114.8, 100.5, 92.7, 68.7, 17.5, 14.1; UV (CH_3OH) λ_{max} 212, 231, 311, 395 nm. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.1; N, 10.1. Found: C, 73.4; H, 5.1; N, 10.1. **15**: 0.82 g, 28% yield; R_f 0.14 (1/2 EtOAc/Hex); mp 176–178 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.4 (m, 5 H), 6.26 (q, 1 H), 5.35 (s, 2 H), 2.52 (s, 3 H), 2.41 (d, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 152.8, 151.5, 134.9, 128.9 (CH), 128.7 (CH), 128.3 (CH), 115.8, 106.0, 102.3 (CH), 98.4, 45.9 (CH_2), 18.3 (CH_3), 13.6 (CH_3); UV (CH_3OH) λ_{max} (log ϵ) 206 (4.41), 241 (4.28), 355 (4.10). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.1; N, 10.1. Found: C, 73.2; H, 5.1; N, 10.0.

(Benzyloxy)furopyridine 14 from Chlorofuropyridine 12. Potassium (0.06 g, 2 mmol) was dissolved in benzyl alcohol (2 mL). After addition of **11** (0.03 g, 0.1 mmol), the reaction mixture was heated at 80 °C for 3 h. The solution was cooled to room temperature, diluted with ether, and washed with water, saturated aqueous K_2CO_3, and brine. After drying, the solvent was removed and the yellow oil was chromatographed (1/4 EtOAc/Hex) to give 0.02 g (50%) of **14**.

6-(Benzyloxy)-5-cyano-2,4-dimethylfuro[2,3-*b*]pyridine (14) via the Silver Carbonate Procedure. To a solution of **5** (5.34 g, 28.4 mmol) and benzyl bromide (5.83 g, 34.1 mmol) in THF (250 mL) was added silver carbonate[18] (4.69 g, 17.0 mmol). The mixture was stirred mechanically in the dark while the solvent was heated at reflux for 5 h; then it was cooled to room temperature and the solids were removed by filtration. Evaporation of the supernatent and recrystallization of the residue from absolute EtOH gave 6.88 g (87%) of **14** with identical spectroscopic data as above.

6-(Benzyloxy)-2,4-dimethylfuro[2,3-*b*]pyridine-5-carboxaldehyde (16). Diisobutylaluminum hydride (40 mL, 1 M in hexane, 40 mmol) was added over 1 h by syringe pump to a stirred 50 °C mixture of **13** (10.00 g, 35.9 mmol) in dioxane (60 mL). After stirring 2 h more, an additional portion of DiBAlH (15 mL, 15 mmol) was added over 20 min. The reaction was stirred 1 h more and then pipetted into 2 M H_3PO_4 (400 mL), and the mixture was heated gently on a steam bath for 45 min. Extraction with Et_2O (3 × 250 mL), followed by washing the Et_2O solution with H_2O (250 mL), $NaHCO_3$ (250 mL), and brine (250 mL), drying ($MgSO_4$), and evaporation left an orange oil. Column chromatography (1/9 EtOAc/hexane) gave 6.80 g (67%) of aldehyde **16** as a white solid, which turns pink on standing: mp 110–111 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 10.63 (s, 1 H), 7.4 (m, 5 H), 6.39 (q, J = 1.1, 1 H), 5.52 (s, 2 H), 2.74 (s, 3 H), 2.45 (d, J = 1.1, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0 (CH), 163.3, 161.0, 153.5, 146.2, 136.4, 128.4 (CH), 127.9 (CH), 127.8 (CH), 116.3, 113.6, 100.9 (CH), 68.5 (CH_2), 17.5 (CH_3), 14.0 (CH_3). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.6; H, 5.4; N, 5.0. Found: C, 72.7; H, 5.1; N, 5.0.

3-[6′-(Benzyloxy)-2′,4′-dimethylfuro[2,3-*b*]pyrid-5′-yl]-propenoic Acid (17). A mixture of **16** (2.10 g, 7.47 mmol), pyridine (8 mL), piperidine (0.64 g, 7.5 mmol), and malonic acid (3.89 g, 37.3 mmol) was heated at 80 °C for 15 h. After cooling to room temperature, it was poured into NaOH (0.5 M, 300 mL) and the yellow solution was extracted with Et_2O (5 × 100 mL). The aqueous phase was acidified to pH 2 with 85% H_3PO_4 and the precipitate collected and dried to yield 2.16 g (89%) of **17**: mp 118–120 °C; ^1H NMR (500 MHz, Me_2SO-d_6) δ 12.21 (s, 1 H), 7.63 (d, J = 16.1, 1 H), 7.2 (m, 5 H), 6.51 (q, J = 1.0, 1 H); 6.41 (d, J = 16.1, 1 H), 5.31 (s, 2 H), 2.36 (s, 3 H), 2.25 (d, J = 1.0, 3 H); ^{13}C NMR (125 MHz, Me_2SO-d_6) δ 168.2, 158.2, 158.1, 152.6, 142.8 136.9 (CH), 136.3, 128.4 (CH), 127.8 (CH), 127.7 (CH), 122.4 (CH), 115.2, 111.6, 101.3 (CH), 67.9 (CH_2), 16.6 (CH_3), 13.7 (CH_3). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.3; N, 4.3. Found: C, 70.5; H, 5.5; N, 4.3.

5,5′-Dimethyl-8-azapsoralen (18a). Acetyl bromide (15 mL) was distilled from red phosphorous into a flask containing **17** (1.00 g, 3.09 mmol) and the mixture was heated at reflux under N_2 for 1 h. Evaporation of solvent and drying (50 °C, 0.1 Torr) gave an orange solid. Purification by chromatography (1/9 EtOAc/$CHCl_3$) gave 0.65 g (98%) of off-white **18a**: mp 244 °C dec; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 9.7, 1 H), 6.46 (q, J = 1.1, 1 H), 6.42 (d, J = 9.7, 1 H), 2.66 (s, 3 H), 2.49 (d, J = 1.1, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 160.5, 156.3, 155.7, 139.6 (CH), 139.2, 119.5, 114.7 (CH), 100.6 (CH), 15.0 (CH_3), 14.4 (CH_3); UV (H_2O) λ_{max} (log ϵ) 251 (4.34), 265 (sh), 295 (3.96), 355 (4.02). Anal. Calcd for $C_{12}H_9NO_3$: C, 67.0; H, 4.2; N, 6.5. Found: C, 66.7; H, 4.3; N, 6.5.

5-Acetyl-6-(benzyloxy)-2,4-dimethylfuro[2,3-*b*]pyridine (19). Methylmagnesium bromide (3M in Et_2O, 4.6 mL, 14 mmol) was added by syringe to **16** (3.78 g, 13.6 mmol) in THF (40 mL), cooled in an ice–salt bath. The rate of addition was controlled to keep the internal temperature between −10 and 0 °C. Following the addition, the solution was stirred at 0 °C for 15 min, then poured into NH_4Cl (2 M, 400 mL), and extracted with Et_2O. The Et_2O extract was washed with brine, dried, and evaporated to give the alcohol (4.03 g, 100%) as a slightly yellow oil [^1H NMR (500 MHz, $CDCl_3$) δ 7.4 (m, 5 H), 6.30 (s, 1 H), 5.49 (d, 2 H), 5.14 (m, 1 H), 3.7 (br d, 1 H), 2.42 (s, 6 H), 1.52 (d, 3 H)], which was used directly in the oxidation step. The alcohol (3.22 g, 10.8 mmol), pyridinium dichromate (10.2 g, 27.1 mmol), and DMF (100 mL) were stirred together at 5 °C for 4 h. The solution was then poured into 1 L of H_2O and extracted with Et_2O (4 × 200 mL), and the Et_2O was washed with H_3PO_4 (0.1 M, 2 × 500 mL) and brine (2 × 500 mL). Drying and evaporating the solvent gave a residue, which was chromatographed on silica (200 g, 1/9 Et_2O/Hex) to give 2.13 g (67%) of ketone **19** as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 6.31 (q, J = 1.2, 1 H), 5.45 (s, 2 H), 2.53 (s, 3 H), 2.42 (d, J = 1.1, 3 H), 2.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 158.9, 157.5, 152.9, 141.0, 136.7, 128.3 (CH), 127.84 (CH), 127.79 (CH), 120.3, 115.1, 100.8 (CH), 68.3 (CH_2), 32.0 (CH_3), 16.2 (CH_3), 14.0 (CH_3). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.2; H, 5.8; N, 4.7. Found: C, 73.2; H, 5.9; N, 4.7.

***tert*-Butyl 3-[6′-(Benzyloxy)-2′,4′-dimethylfuro[2,3-*b*]-pyrid-5′-yl]-3-hydroxy-2-methylpropanoate (20b).** *tert*-Butyl 2-bromopropanoate[20] (1.15 g, 5.50 mmol) in THF (4 mL) was added dropwise over 2 h to a mixture of **16** (1.50 g, 5.33 mmol) and magnesium (0.15 g, 6.2 mmol) in THF (35 mL) heated to 50 °C. The mixture was stirred at 50 °C for a further 2 h and then pipetted into ice-cold AcOH (0.5 M, 100 mL) and extracted into Et_2O (2 × 50 mL). The Et_2O phase was washed with H_2O, $NaHCO_3$, and brine, dried, and evaporated to give an orange oil. Purification by chromatography (silica, 1/19 EtOAc/Hex) gave recovered **16** (0.06 g, 4%) plus **20b** (1.86 g, 85%) as a colorless oil. ^1H NMR indicated a 3/2 mixture of diastereomers: ^1H NMR (500 MHz, $CDCl_3$) major isomer δ 7.4 (m, 5 H), 6.32 (q, J = 1.2, 1 H), 5.500 (s, 2 H), 5.11 (t, J = 10.5, 1 H), 3.59 (d, J = 10.5, 1 H), 3.14 (m, 1 H), 2.50 (s, 3 H), 2.44 (d, J = 1.1, 3 H), 1.48 (s, 9 H), 0.85 (d, J = 7.1, 3 H); minor isomer δ 7.4 (m, 5 H), 6.30 (q, J = 1.1, 1 H), 5.497 (s, 2 H), 4.87 (dd, J = 11.4, 9.3, 1 H), 3.37 (d, J = 11.5, 1 H), 3.14 (m, 1 H), 2.45 (s, 3 H), 1.33 (d, J = 6.8, 3 H), 1.06 (s, 3 H). Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.1; H, 7.1; N, 3.4. Found: C, 69.8; H, 7.2; N, 3.5.

***tert*-Butyl 3-[6′-(benzyloxy)-2′,4′-dimethylfuro[2,3-*b*]-pyrid-5′-yl]-3-hydroxybutanoate (20c)** was prepared by the same procedure as for **20b** above. Ketone **19** (0.83 g, 2.8 mmol), magnesium (0.20 g, 8.3 mmol), and *tert*-butyl bromoacetate[20] (1.1 g, 5.6 mmol) in THF gave 1.01 g of **20c** (88%) as a clear oil: ^1H NMR (250 MHz, $CDCl_3$) δ 7.4 (m, 5 H), 6.32 (m, 1 H), 5.52 (d,

J = 12.2, 1 H), 5.31 (d, J = 12.2, 1 H), 4.57 (d, J = 0.9, 1 H), 3.64 (d, J = 15.0, 1 H), 2.74 (s, 3 H), 2.54 (d, J = 15.1, 1 H), 2.42 (d, J = 1.1, 3 H), 1.60 (d, J = 0.9, 3 H), 1.21 (s, 9 H). Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.1; H, 7.1; N, 3.4. Found: C, 70.0; H, 7.1; N, 3.4.

***tert*-Butyl 3-[6′-(Benzyloxy)-2′,4′-dimethylfuro[2,3-*b*]pyrid-5′-yl]-3-hydroxy-2-methylbutanoate (20d).** Ketone **19** (0.81 g, 2.7 mmol) and magnesium (0.20 g, 8.3 mmol) in THF (5 mL) were heated to 50 °C and *tert*-butyl 2-bromopropanoate[20] (1.26 g, 6.03 mmol) in THF (4 mL) was added via syringe pump over 4 h. After three additional hours at 50 °C, the reaction mixtue was poured into cold AcOH (0.5 M, 100 mL) and extracted with Et_2O (2 × 50 mL). The Et_2O was washed with H_2O, $NaHCO_3$, and brine and dried. Evaporation gave an orange oil, which was chromatographed on silica (230–400 mesh, 1/9 EtOAc/Hex) to give recovered ketone **19** (0.34 g, 42%) plus a diastereomeric mixture of **20d** as a clear oil (0.30 g). Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.6; H, 7.3; N, 3.3. Found: C, 70.4; H, 7.4; N, 3.1. Subjecting a portion (0.23 g) to MPLC (240 g of silica, 230–400 mesh, 1/19 EtOAc/Hex) separated the mixture into two fractions. The faster moving one (0.16 g, 31% based on recovered **19**) was a single diastereomer of **20d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (m, 5 H), 6.29 (q, J = 1, 1 H), 5.50 (d, J = 12.3, 1 H), 5.34 (d, J = 12.3, 1 H), 4.24 (s, 1 H), 3.79 (q, J = 7.1, 1 H), 2.71 (s, 3 H), 2.40 (d, J = 0.8, 3 H), 1.56 (s, 3 H), 1.17 (d, J = 7.1, 3 H), 1.07 (s, 9 H); IR ($CHCl_3$) 3490, 2980, 2975, 1725, 1690 cm^{-1}.

3,5,5′-Trimethyl-8-azapsoralen (18b). Acetyl bromide (20 mL) was distilled from red phosphorous into a flask containing **20b** (1.37 g, 3.34 mmol). The yellow solution was stirred at room temperature for 1 h and then heated at reflux for 3 h. Volatile material was removed from the green reaction mixture and the residue was chromatographed on silica ($CHCl_3$) to give **18b** (0.67 g, 87%) as a light yellow solid: mp 289–291 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 1.3, 1 H), 6.45 (d, J = 1.1, 1 H), 2.65 (s, 3 H), 2.50 (d, J = 1.0, 3 H), 2.26 (d, J = 1.3, 3 H); UV (CH_3CN) λ_{max} (log ϵ) 250 (4.31), 265 (sh, 4.02), 288 (3.91), 332 (4.07). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.1; H, 4.8; N, 6.1. Found: C, 67.7; H, 4.9; N, 5.9.

4,5,5′-Trimethyl-8-azapsoralen (18c) was prepared by the same method as for **18b**. Ester **20c** (0.71 g, 1.7 mmol) was converted to **18c**, a grey solid (0.30 g, 75% yield): mp 238–240 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.46 (s, 1 H), 6.20 (s, 1 H), 2.85 (s, 3 H), 2.67 (s, 3 H), 2.50 (s, 3 H); UV (CH_3CN) λ_{max} (log ϵ) 204 (4.19), 250 (4.27), 285 (3.87), 292 (3.85), 331 (3.99). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.1; H, 4.8; N, 6.1. Found: C, 67.9; H, 4.7; N, 6.0.

3,4,5,5′-Tetramethyl-8-azapsoralen (18d). Furopyridine **20d** (0.30 g, 0.71 mmol) was stirred with acetyl bromide (10 mL) at room temperature for 1 h followed by heating at reflux for 1 h. Solvent was evaporated and the residue purified by chromatography on silica (1/19 EtOAc/CH_2Cl_2) to give 0.15 g (87%) of **18d** as a white solid, which crystallized from acetonitrile as clear needles: mp 269–272 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.45 (s, 1 H), 2.85 (s, 3 H), 2.61 (d, J = 0.8, 3 H), 2.49 (d, J = 1.0, 3 H), 2.22 (d, J = 0.6, 3 H); UV (CH_3CN) λ_{max} (log ϵ) 208 (4.17), 249 (4.23), 285 (3.90), 331 (4.08). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.1; H, 5.4; N, 5.8. Found: C, 69.1; H, 5.4; N, 5.6.

Quaternization of Azapsoralens with Methyl Triflate. The azapsoralen and methyl trifluoromethanesulfonate[22] (200 mol %) were heated in CH_2Cl_2 (5 mL) at reflux for 3 h. Volatile material was removed by evaporation (aspirator) and the remaining solid was dried at 78 °C and 0.1 Torr for 20 h to give the pure product.

5,5′,8-Trimethyl-8-azapsoralen Triflate (1a) was obtained from azapsoralen **18a** (0.20 g, 0.93 mmol) as an off-white solid (0.33 g, 94%): mp 178–180 °C; ^{1}H NMR (250 MHz, D_2O, referenced to HDO = δ 4.65) δ 8.29 (d, J = 10.0, 1 H), 6.89 (q, J = 1.2, 1 H), 6.62 (d, J = 10.0, 1 H), 4.18 (s, 3 H), 2.74 (s, 3 H), 2.47 (d, J = 1.0, 3 H); UV (H_2O) λ_{max} (log ϵ) 257 (4.30), 300 (3.85), 337 (4.12). Anal. Calcd for $C_{14}H_{12}F_3NO_6S$: C, 44.3; H, 3.2; N, 3.7. Found: C, 44.2; H, 3.2; N, 3.7.

3,5,5′,8-Tetramethyl-8-azapsoralen triflate (1b) was obtained from azapsoralen **18b** (0.20 g, 0.87 mmol) as a tan solid (0.33 g, 96% yield): mp 214–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (q, J = 1.4, 1 H), 6.79 (q, J = 1.2, 1 H), 4.36 (s, 3 H), 2.85 (s, 3 H), 2.62 (d, J = 1.1, 3 H), 2.32 (d, J = 1.4, 3 H); UV (CH_3CN) λ_{max} (log ϵ) 209 (4.10), 255 (4.22), 298 (3.81), 336 (4.10). Anal. Calcd for $C_{15}H_{14}F_3NO_6S$: C, 45.8; H, 3.6; N, 3.6. Found: C, 45.8; H, 3.6; N, 3.6.

4,5,5′,8-Tetramethyl-8-azapsoralen triflate (1c) was obtained from azapsoralen **18c** (0.11 g, 0.48 mmol) as an orange solid (0.17 g, 89% yield): mp 221–225 °C dec; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.82 (d, J = 1.1, 1 H), 6.42 (d, J = 0.8, 1 H), 4.37 (s, 3 H), 3.06 (s, 3 H), 2.78 (d, J = 1.0, 3 H), 2.65 (d, J = 0.7, 3 H); UV (CH_3CN) λ_{max} (log ϵ) 211 (4.05), 233 (4.10), 253 (4.18), 289 (3.77), 299 (3.78), 335 (4.04). Anal. Calcd for $C_{15}H_{14}F_3NO_6S$: C, 45.8; H, 3.6; N, 3.6. Found: C, 45.6; H, 3.6; N, 3.6.

3,4,5,5′,8-Pentamethyl-8-azapsoralen triflate (1d) was obtained from azapsoralen **18d** (0.10 g, 0.41 mmol): 0.17 g, 94% yield, mp 133–136 °C dec; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.81 (d, J = 1.0, 1 H), 4.31 (s, 3 H), 3.01 (s, 3 H), 2.65 (d, J = 0.6, 3 H), 2.60 (s, 3 H), 2.25 (d, J = 0.3, 3 H); UV (CH_3CN) λ_{max} (log ϵ) 216 (4.14), 237 (4.10), 255 (4.20), 291 (3.83), 301 (3.83), 337 (4.13). Anal. Calcd for $C_{16}H_{16}F_3NO_6S$: C, 47.2; H, 4.0; N, 3.4. Found: C, 47.1; H, 4.0; N, 3.4.

Determination of the Half-Life of 1a–d in Deuterium Oxide. Phosphate buffers (0.2 M) of pD 6.5, 7.5, and 7.8 were prepared by dissolving weighed amounts of KH_2PO_4 and Na_2HPO_4 in 10 mL of D_2O, adjusting the pD measured with a standard glass electrode pH meter by adding one or the other phosphate, evaporating the D_2O, adding 5 mL more of D_2O and evaporating, then finally dissolving the residue in 10 mL of D_2O and rechecking the pD. The azapsoralen triflate (5 μmol) was dissolved in 0.7 mL of the buffer and the ^{1}H NMR spectrum was taken at 20 °C, using a presaturation pulse to eliminate residual HDO. The integration of the *N*-methyl protons of starting material (δ 4.1) and the product (δ 3.5) was followed as a function of time. Following the collection of NMR data, the acidity of the NMR sample was again measured to determine the pD change during the reaction. This change was −0.2 pD unit in all cases. The median pD's are recorded in Table I.

Registry No. **1a**, 124098-52-8; **1b**, 124125-51-5; **1c**, 124098-54-0; **1d**, 124098-56-2; **3**, 101413-11-0; **4**, 1013-16-7; **5**, 1013-42-9; **7**, 124098-59-5; **10**, 124098-58-4; **11**, 124098-57-3; **12**, 124098-60-8; **13**, 124098-61-9; **14**, 124098-62-0; **15**, 124098-63-1; **16**, 124098-64-2; **17**, 124098-65-3; **18a**, 124098-66-4; **18b**, 124098-73-3; **18c**, 124125-53-7; **18d**, 124125-54-8; **19**, 124098-68-6; (*R**,*S**)-**20b**, 124098-69-7; (*R**,*R**)-**20b**, 124098-70-0; **20c**, 124125-52-6; (*R**,*S**)-**20d**, 124098-72-2; (*R**,*R**)-**20d**, 124098-71-1; $NCCH_2CONH_2$, 107-91-5; $H_2NCOCH_2COCH_3$, 5977-14-0; $NCCH_2CO_2Et$, 105-56-6; $CH_2(CO_2H)_2$, 141-82-2; *t*-$BuOCOCH(Br)CH_3$, 39149-80-9; $BrCH_2CO_2Bu$-t, 5292-43-3; 2-acetyl-2-(2-propen-3-yl)-4-pentenamide, 100132-11-4; ethyl 2-acetyl-4-pentenoate, 610-89-9; 5-(1-hydroxyethyl)-6-(benzyloxy)-2,4-dimethylfuro[2,3-*b*]pyridine, 124098-67-5.