Synthetic Approaches to 3-Substituted-5'-(N-pyridiniummethyl)-4',5'-dihydropsoralen [1]

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New synthetic approaches to 3-substituted-5'-(N-pyridiniummethyl)-4',5'-dihydropsoralens are described. The novel pathways presented utilize appropriately substituted coumarins and 4',5'-dihydropsoralens. The compounds proposed represent potential therapeutic agents for psoralen uv radiation treatment.

Psoralens (linear furocoumarins) are naturally occurring compounds which have been known for their medicinal purposes for thousands of years. The systematic investigation of the biological effects of these agents began in 1938 and continues to this day [2]. These compounds, especially 8-methoxypsoralen, are utilized with uv radiation in the treatment of various proliferative skin diseases such as vitiligo, psoriasis, mycosis fungoides and eczema. Recent years have seen their application to cancer (T cell lymphoma), autoimmune disease and viral inhibition [3].

Regarding their photobiological activity, it is well known that psoralens can cross the cell membrane, intercalate and subsequently photo-crosslink nuclear DNA by forming mono- and bis-cyclobutane adducts generated from the 3,4-double bond and the 4',5'-double bond to double bonds in the pyrimidine rings [2]. Earlier papers from our group on the synthesis [4,5,6] and phototherapy of psoralens derivatives have concentrated on the proposition that an alternative mechanism of action (not involving DNA) is responsible for the biological activity of psoralens [7]. We have shown that psoralens can also bind to a specific membrane receptor (a 22,000 Da protein) which was identified in the cytoplasmic membrane of epidermal target cells. When this receptor is covalently modified by psoralens in the presence of uv light, the binding of the epidermal growth factor is prevented [7,8,9].

A severe limitation to the clinical acceptance of psoralen-based photochemotherapy has been that the natural cellular level repair process of bi-functional DNA-crosslinks are highly error prone. Consequently, this represents a significant post-treatment risk of cancer induction. In earlier papers, we have explored the photobiology of psoralens using analogs which would be structurally unable to photo-crosslink with DNA. As a result, we have shown that the

unsaturation in the furan ring, and also that the furan ring itself, are unnecessary for the photoactivity of psoralens [4,8]. Similarly, the use of water-soluble salts such as quaternary amines which will be unable to penetrate the cell, will increase cell surface effects and minimize the mutagenic/carcinogenic events [3]. Earlier results in our group have shown that nucleophilic displacement of the bromine of 5'-bromomethyl-4,8-dimethylpsoralen with pyridine gave a water-soluble and yet highly active quaternary salt [3,10]. IC_{50} measurements on psoralens and coumarins in our photoactivated Hela cell assay have shown that an electron withdrawing group such as a nitro or a carboethoxy group at C_3 normally enhances photoactivity [10,11]. Consequently, we have outlined pathways which lead to 4',5'-dihydropsoralens bearing a N-pyridiniummethyl group at $C_{5'}$ and an electron withdrawing substituent at C_3 (Figure I).

Figure I
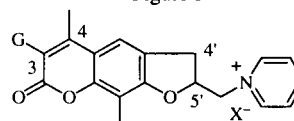
G = electron wtihdrawing group

Results and Discussion.

This work has been aimed at producing 4',5'-dihydro-5'-(N-pyridiniummethyl)psoralens substituted at the 3-position with electron withdrawing groups such as nitro, bromo, cyano or fluoro. In addition, the synthesis of the 3-hydro compound was undertaken in order to compare its biological activity with the 3-substituted analogs.

Preparation of 3-Hydro and 3-Nitropsoralen Derivatives.

Our synthesis involves 4,8-dimethyl–6-(2,3-dibromopropyl)-7-acetoxycoumarin **1** as intermediate (Scheme I),

this compound was prepared in 5 steps from 2-methyl-resorcinol as described by Kaufman [12]. The last steps of the Kaufman reported synthesis consist in acetylation of 4,8-dimethyl–6-allyl-7-hydroxycoumarin 7 in order to avoid bromination on C$_3$ during the addition of bromine to the allyl double bond. In the Kaufman process, the 4,8-dimethyl–6-(2,3-dibromopropyl)-7-acetoxycoumarin 1 was then ring-closed by uncapping the 7-acetoxy group with sodium ethoxide with concomitant cyclisation and double dehydrobromination yielding 4,5',8-trimethylpsoralen in 48% yield. This reaction obviously involves the loss of two molar equivalents of HBr and might occur in two separable distinct steps in which one HBr loss follows a second through a potential intermediate such as 4,8-dimethyl-5'-bromomethyl-4',5'-dihydropsoralen 2. As noted above, our aim was to prepare 5'-(N-pyridinium-methyl)-4',5'-dihydropsoralen derivatives, so 5'-bromomethyl-4',5'-dihydropsoralens were valuable target compounds since the bromo on the C$_5$· methyl site could be accessible to nucleophilic displacement with pyridine. Careful duplication, however, of Kaufman's synthesis revealed no trace of the desired compound 2 as a possible transient.

Pure target compound 6 was obtained in 53% yield from the 81:19 mixture of psoralen 2 and its pyrano isomer 3 by selective precipitation during reaction with refluxing pyridine. It is also possible that nucleophilic displacement proceeded exclusively with the more accessible primary bromine of 2 rather than with the secondary bromine of 3, thus using our work-up conditions 6 was the only product isolated.

Nitration at the C$_3$ position was then achieved with concentrated nitric acid in glacial acetic acid giving 3-nitro-4,8-dimethyl-5'-bromomethyl-4',5'-dihydropsoralen 4 and nitration product(s) of 3. Through recrystallisation of the mixture, pure 4 was obtained in 66% yield. One can note that nitration of 2 at the C$_5$ position seems to not proceed. Finally, the bromide salt 5 was prepared in 69% yield by refluxing 4 in anhydrous pyridine (Scheme I).

Preparation of 3-Bromopsoralen Derivatives.

Like the nitro group, the bromo substituent was introduced at C$_3$ directly from a coumarin/psoralen precursor. 4,8-Dimethyl-6-allyl-7-hydroxycoumarin 7 [12] was treated with bromine in chloroform affording 3-bromo-4,8-dimethyl-6-(2,3-dibromopropyl)-7-hydroxycoumarin

Scheme I

(ratio 81:19 in favor of 2)
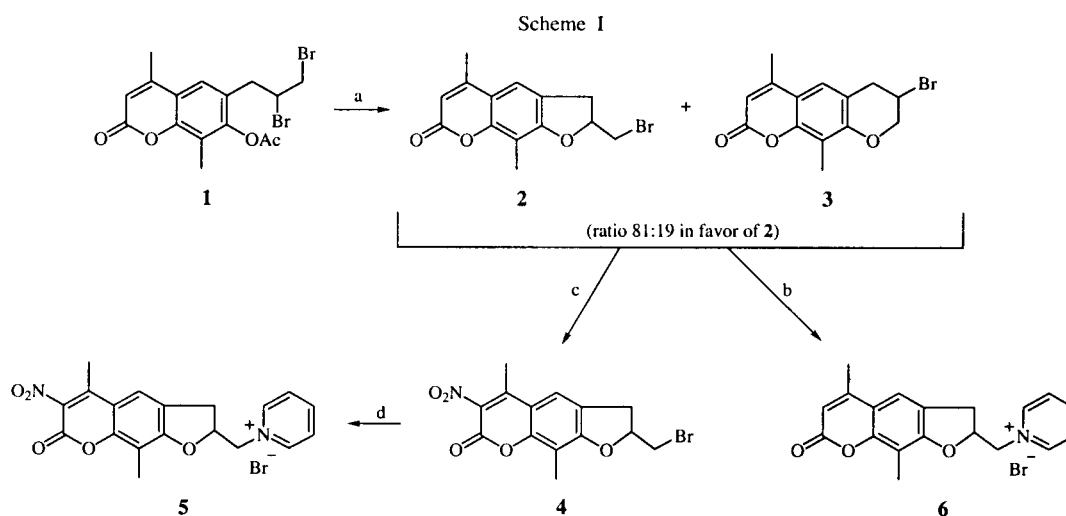
Reagents and conditions: (a) sodium borohydride, ethyleneglycol dimethyl ether, 45°, 88% yield (mixture 81:19 respectively of 2 and its isomer 3); (b) anhydrous pyridine, reflux, 53% yield; (c) nitric acid, acetic acid, rt, 66% yield; (d) anhydrous pyridine, reflux, 69% yield.

We have discovered that treating coumarin derivative 1 with sodium borohydride in ethyleneglycol dimethyl ether affords the desired product 2 in 88% yield. All attempts to deblock the acetoxy group prior to ring closure gave lower combined yields. Examination of the ^{1}H nmr spectra revealed that cyclisation of 1 yielded an 81:19 mixture of psoralen 2 and its undesired six-membered bromoben-zodipyranone isomer 3. Chromatographic separation of these isomers is possible but unnecessary in order to obtain pure final products as noted below.

8 in 75% yield. Bromination-addition of the allyl double bond without concomitant bromination-substitution at C$_3$ was not successful. Earlier results from our laboratory have shown that 3-unsubstituted coumarins bearing oxygenated functions at C$_7$ (hydroxyl, alkoxyl or acetoxy) possess psoralen-like beneficial photopharmacology [13]. Therefore, for comparison with our 3-substituted electron withdrawing analogs (reported herein), we sought to characterize and submit for screening these novel coumarins. As a result, 7-acetoxycoumarin 11 was prepared from 8 in

90% yield. Removal of the two vicinal bromine atoms of **8** with zinc dust in ethanol was conducted in order to obtain the 6-allyl candidates, thus coumarin derivative **9**, and afterward its 7-acetoxy derivative **10**, were obtained in 80% and 64% yield respectively. The furan-ring closure of coumarin derivative **8** was performed with sodium carbonate in acetone in 74% yield. This milder base allowed us to obtain the ring closed mono-dehydrohalogenated product **12** without subsequent transformation, as was reported by Kaufman by the use of sodium ethoxide, to fully aromatic psoralen. As in the preparation of 3-hydro derivatives (see above), ^{1}H nmr spectra revealed that a mixture 81:19 of psoralen **12** derivative and its six-membered bromobenzodipyranone isomer **13** was obtained. This 81:19 mixture was treated with refluxing anhydrous pyridine leading, by selective precipitation, to pure target compound **14** in 81% yield (Scheme II).

Knoevenagel condensation and subsequent ring closure did proceed, affording 3-cyanocoumarin **17**. Traditionally aldehydes not ketones are most often used as starting material for this type of Knoevenagel condensation [14]. In our case, prolonged reaction (*i.e.* 6 days) gave an acceptable conversion (see Experimental) with our ketonic precursor **16** (Scheme III).

A Claisen rearrangement of 3-cyanocoumarin **17** in refluxing *N,N*-diethylaniline gave 76% yield of 7-hydroxycoumarin **18**. Purging with argon during the reaction proved necessary to obtain acceptable yields. In a similar fashion to the preparation of the 3-bromopsoralen derivatives (Scheme II), their 3-cyano counterparts were obtained by initial bromination of the allyl double bond (92% of **19**) and subsequent cyclisation of **19** with sodium carbonate in acetone to a 78% yield of a 90:10 mixture of 3-cyano-5'-bromomethyldihydropsoralen **21** and its pyrano

<div align="center">Scheme II</div>
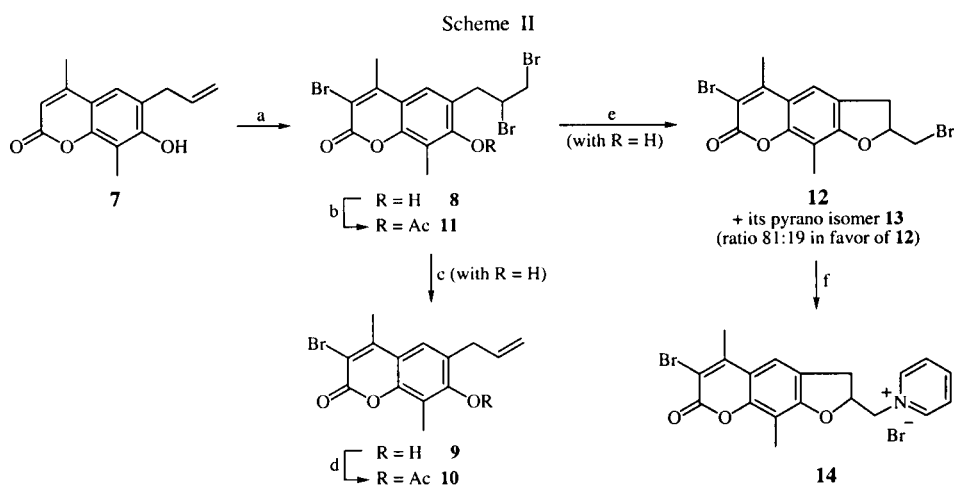
Reagents and conditions: (a) bromine, chloroform, rt, 75% yield; (b) sodium acetate, acetic anhydride, rt, 90% yield; (c) zinc dust, ethanol (95%), reflux, 80% yield; (d) sodium acetate, acetic anhydride, rt, 64% yield; (e) sodium carbonate, acetone, reflux then rt, 74% yield (mixture 81:19 respectively of **12** and its isomer **13**); (f) anhydrous pyridine, reflux, 81% yield.

Preparation of 3-Cyanopsoralen Derivatives.

While the nitro and the bromo substituents were introduced directly from coumarin or psoralen precursors (see above), the cyano group was incorporated at an earlier stage in the synthetic design. In a projected synthesis of **21**, the plausible Knoevenagel condensation of 2,4-dihydroxy-3-methylacetophenone **15** and ethyl cyanoacetate returned only starting material. However, protection of the 4-hydroxy moiety as an allyloxy led to **16** which underwent the Knoevenagel condensation in 65% yield with ethyl cyanoacetate as the co-reactant. We have discovered that the synthesis of this requisite 4-allyloxy compound **16** can be driven to high yield (86%) with an excess of allyl bromide because the *ortho* hydroxyl function is unreactive (hydrogen bonding) under these alkylation conditions. With **16** as the starting material, the

isomer **22**. Pure target compound **23** was obtained in 88% yield (Scheme III) from the 90:10 mixture of **21:22** by selective precipitation with pyridine as previously mentioned in synthesis of the 3-hydro pyridinium salt.

Preparation of 3-Fluoropsoralen Derivatives.

Direct electrophilic fluorination of coumarin and psoralen derivatives **1** and **2** was attempted utilizing three commercial electrophilic fluorinating "N-F" reagents belonging to three different reagent classes: *N*-fluorobenzenesulfonimide, *N*-fluoropyridinium triflate and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate). Monitoring of the reactions by gc-ms revealed that expected fluorinated products were formed in each case with the three different "N-F" reagents. However, fluorinated products could be isolated only when 1-chloromethyl-4-fluoro-1,4-diazoniabicy-

Scheme III
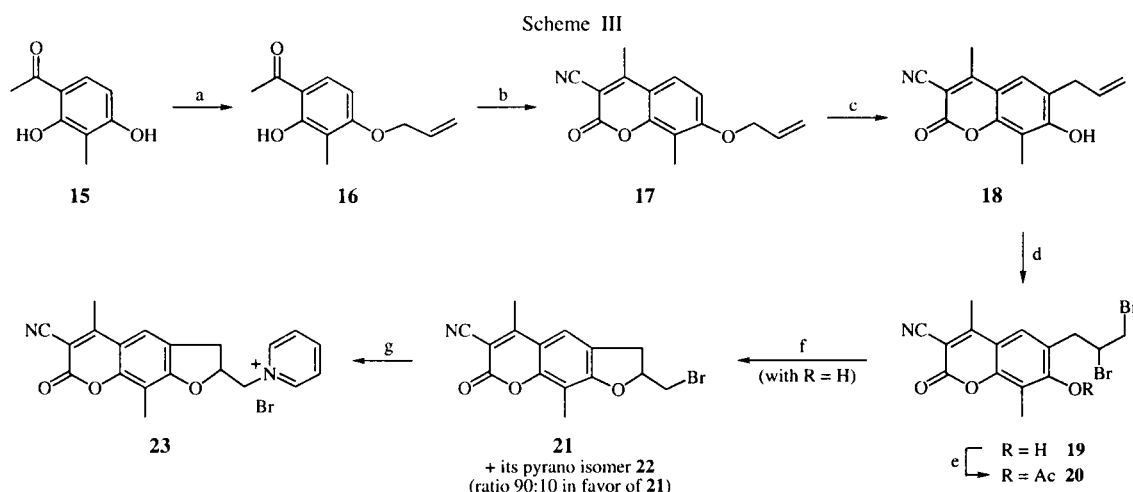
Reagents and conditions: (a) allyl bromide, potassium carbonate, acetone, rt, 86% yield; (b) ethyl cyanoacetate, acetic acid, ammonium acetate, benzene, reflux, 65% yield; (c) N,N-diethylaniline, reflux, 76% yield; (d) bromine, chloroform, rt, 92% yield; (e) sodium acetate, acetic anhydride, rt, 72% yield; (f) sodium carbonate, acetone, rt, 78% yield (mixture 90:10 respectively of 21 and its isomer 22); (g) anhydrous pyridine, reflux, 88% yield.

Scheme IV
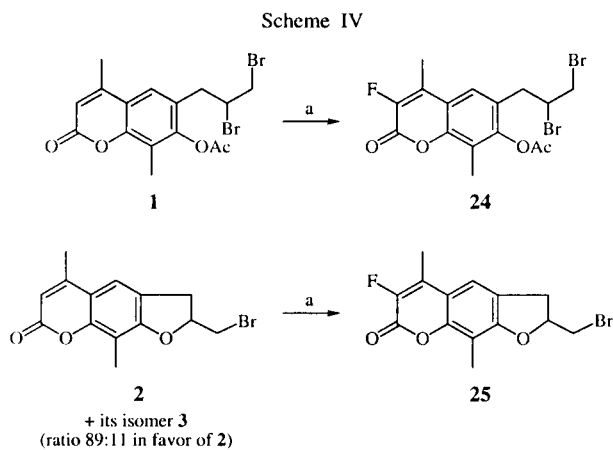
Reagents and conditions: (a) 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate), acetonitrile (anhydrous), reflux, 12-14% yield.

clo[2.2.2]octane bis(tetrafluoroborate) was used as the fluorinating agent. One can suppose that higher conversions are possible with the more reactive 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) enabling the isolation of the products. Nevertheless, even with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate), fluorinated products 24 and 25 were isolated in very low yields (12% and 14% respectively) and unreacted starting material was mostly recovered (Scheme IV).

Attempts to increase the conversion by the use of an excess of 4 molar equivalents of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) and prolonged reaction time were also unsuccessful. Alternatively, we decided to follow an indirect pathway, similar to that used for the preparation of the 3-cyano deriv-

Scheme V
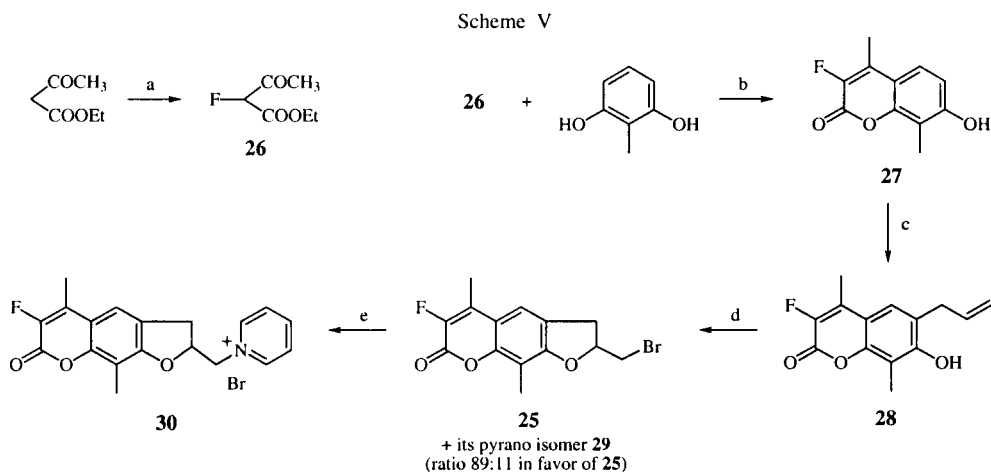
Reagents and conditions: (a) lit [15], 76% yield; (b) 2-methylresorcinol, 1,4-dioxane, concentrated sulfuric acid, 0°, 84% yield; (c) (i) allyl bromide, potassium carbonate, acetone, rt, 78% yield, (ii) N, N-diethylaniline, reflux, 55% yield; (d) (i) bromine, chloroform, rt, 85% yield, (ii) sodium carbonate, acetone, rt, 78% yield (mixture 89:11 respectively of 25 and its isomer 29); (e) anhydrous pyridine, reflux, 73% yield.

atives (Scheme III), by incorporating the fluorine atom during the formation of the pyrone moiety (Scheme V).

To obtain a 3-fluoroderivative, the Pechmann coumarin synthesis requires ethyl 2-fluoro-acetoacetate **26** as the fluorine carrier. This latter was prepared from ethyl acetoacetate [15] (using 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) as the fluorinating reagent) in 76% yield. The Pechmann reaction of 2-methylresorcinol with **26** afforded 3-fluoro-7-hydroxycoumarin **27** in 84% yield. Alkylation with allyl bromide of the 7-hydroxy group of **27** followed by a Claisen rearrangement yielded 3-fluoro-6-allyl-7-hydroxycoumarin **28** in 43% overall yield. Ring closure was achieved in two steps in a 66% overall yield following the same route employed with the 3-cyano derivatives giving a mixture 89:11 (in favor of the expected psoralen **25**) of the 3-fluoro-5'-bromomethyl-dihydropsoralen **25** and its minor pyrano isomer **29**. Finally, this 89:11 mixture was reacted with refluxing anhydrous pyridine affording, by selective precipitation, pure target compound **30** in 73% yield.

These 3-unsubstituted, 3-nitro, 3-bromo, 3-cyano and 3-fluoropsoralens and coumarins have been submitted for screening in a photoactivated antiproliferative bioassay employing epidermal cells in culture.

EXPERIMENTAL

The ^{1}H and ^{13}C nmr spectra were recorded at 360 and 90 MHz respectively. Chemical shifts for hydrogen and carbon resonances are reported in ppm (δ) relative to tetramethylsilane. Thin-layer chromatographies (tlc) were performed with plates (0.25 mm) precoated with fluorescent silica gel. Reaction components were then visualized under uv light and/or with iodine. Preparative tlc were performed with plates precoated with fluorescent silica gel. Silica gel (230-400 mesh) was used for flash chromatography separations. Gas chromatography-mass spectrometry (gc-ms) was performed with a Hewlett-Packard 5890 GC apparatus linked to a Model 5972 EIMS. Uncorrected melting points (mp) were determined with a Thomas Hoover capillary melting point apparatus. Combustion analyses were provided by Quantitative Technologies Inc., P.O. Box 470, Whitehouse, NJ, 08888. 2,4-Dihydroxy-3-methylacetophenone and anhydrous solvents were purchased from Aldrich (except anhydrous acetonitrile which was distilled from P_2O_5). 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) was purchased from Fluka. All extractions were usually followed by water and saturated NaCl aqueous solution washings, magnesium sulfate drying, filtration and evaporation.

Preparation of 3-Hydro and 3-Nitropsoralen Derivatives.

4,8-Dimethyl-6-(2,3-dibromopropyl)-7-acetoxycoumarin (**1**).

This compound was prepared as described by Kaufman [12].

4,8-Dimethyl-5'-bromomethyl-4',5'-dihydropsoralen (**2**).

A mixture of coumarin derivative **1** (1.00 g, 2.31 mmoles), 50 ml of anhydrous ethyleneglycol dimethyl ether and 1.00 g of sodium borohydride was stirred and heated at 45° for 12 hours.

The reaction mixture was chilled in ice, decomposed by dropwise addition of saturated ammonium chloride solution, 100 ml of dichloromethane were added and the layers separated. The aqueous layer was washed with dichloromethane and the organic phases combined and washed with a solution of saturated ammonium chloride. After the usual work-up a pale yellow solid was isolated and recrystallised from methanol. Thus 0.631 g (88% yield) of the mixed isomers **2** and **3** was obtained; ir (nujol): 1709 cm^{-1}; ^{1}H nmr (methanol-d$_4$): δ 2.22 (s, 3H), 2.31 (s, 3H), 3.27 (dq, J_1 = 16.0 Hz, J_2 = 9.1 Hz, J_3 = 6.9 Hz, 2H), 3.54 (dq, J_1 = 10.5 Hz, J_2 = 6.9 Hz, J_3 = 4.4 Hz, 2H), 5.06 (m, 1H), 6.03 (s, 1H), 7.19 (s, 1H).

Within the mixture of isomeric closure products generated herein, integration of the C$_3$-H resonances in the respective products revealed an 81:19 relative ratio favoring the furano psoralen **2** over the benzodipyranone **3**. The ^{1}H nmr (methanol-d$_4$) of that minor isomer **3** was: δ 2.23 (s, 3H), 2.33 (s, 3H), 2.81 (dd, J_1 = 8 Hz, J_2 = 6.5 Hz, 2H), 3.32 (dd, J_1 = 8.0 Hz, J_2 = 6.5 Hz, 2H), 4.97 (m, 1H), 6.01 (s, 1H), 7.15 (s, 1H). Furthermore, this 81:19 ratio of **2** to **3** is labile to the dehydrohalogenation of **2** to 4,5',8-trimethylpsoralen, a process which begins during the very isolation of these brominated materials and which can be readily recognized by the appearance of an additional methyl signal at 2.20 ppm. In freshly isolated product the nmr integration revealed a 20% contamination by the 4,5',8-trimethylpsoralen which is further substantiated by the combustion analysis. This dehydrobrominated byproduct was inseparable by tlc as demonstrated by overlapping of the components, Rf's = 0.59 on silica gel plates with 1% methanol: 99% methylenechloride. The brominated material should be employed directly for further synthesis since dehydrobromination is a continuous process.

Anal. Calcd. for an 80:20 mixture of (**2** + **3**)/trimethylpsoralen: C, 57.29; H, 4.40; Br, 21.96. Found: C, 56.98; H, 4.58; Br, 21.64.

4,8-Dimethyl-5'-(N-pyridiniummethyl)-4',5'-dihydropsoralen Bromide Salt (**6**).

The above mixture (0.10 g, 0.32 mmole) of psoralen derivative **2** and its isomer **3** was dissolved in 2 ml of anhydrous pyridine. This solution was heated at reflux under an inert atmosphere for 16 hours, while being protected by a calcium chloride drying tube. The resulting precipitate was collected by suction filtration giving 0.066 g (53% yield) of the pyridinium salt **6** as a grey solid, mp 295-295.5° dec; ^{1}H nmr (methanol-d$_4$): δ 2.20 (s, 3H), 2.42 (d, J = 0.8 Hz, 3H), 3.26 (dd, J_1 = 16.8 Hz, J_2 = 6.3 Hz, 1H), 3.66 (dd, J_1 = 16.4 Hz, J_2 = 10.2 Hz, 1H), 4.88 (dd, J_1 = 13.6 Hz, J_2 = 9.1 Hz, 1H), 5.11 (dd, J_1 = 13.7 Hz, J_2 = 2.7 Hz, 1H), 5.37-5.47 (m, 1H), 6.15 (d, J = 0.8 Hz, 1H), 7.50 (s, 1H), 8.20 (dd, $J_1 \approx$ 7 Hz, $J_2 \approx$ 7 Hz, 2H), 8.68 (dd, $J_1 \approx$ 8 Hz, $J_2 \approx$ 8 Hz, 1H), 9.09 (d, J = 5.5 Hz, 2H).

Anal. Calcd. for $C_{19}H_{18}BrNO_3$ x 0.7 H_2O: C, 56.93; H, 4.88; N, 3.49; Br, 19.93. Found: C, 56.91; H, 4.55; N, 3.29; Br, 19.83.

3-Nitro-4,8-dimethyl-5'-bromomethyl-4',5'-dihydropsoralen (**4**).

The above mixture (0.201 g, 0.650 mmole) of psoralen derivative **2** and its isomer **3** was dissolved in 3.5 ml of glacial acetic acid and a solution of concentrated nitric acid:glacial acetic acid (25:75; v:v) was added dropwise. The reaction mixture was stirred at room temperature under an inert atmosphere for 5 hours. Water (80 ml) was added, the resulting yellow precipitate was collected by suction filtration and washed with water.

Recrystallisation from methanol gave 0.153 g (66% yield) of the 3-nitropsoralen **4** as a yellow solid: mp 187-188°; ir (nujol): 1719 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.27 (s, 3H), 2.44 (s, 3H), 3.37 (dq, J_1 = 16.2 Hz, J_2 = 9.2 Hz, J_3 6.3, 2H), 3.62 (dq, J_1 = 10.7 Hz, J_2 = 6.3 Hz, J_3 = 4.4 Hz, 2H), 5.19 (m, 1H), 7.36 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 8.6, 14.5, 14.5, 82.5, 82.8, 108.6, 111.3, 119.2, 124.3, 145.6, 152.1, 153.7, 163.1.

Anal. Calcd. for C$_{14}$H$_{12}$BrNO$_5$: N, 3.95. Found: N, 3.83.

3-Nitro-4,8-dimethyl-5'-(*N*-pyridiniummethyl)-4',5'-dihydropso-ralen Bromide Salt (5).

5'-Bromomethylpsoralen **4** (0.105 g, 0.296 mmole) was reacted as for **6** using 2 ml of anhydrous pyridine. The resulting precipitate was collected by suction filtration giving 0.089 g (69% yield) of the pyridinium salt **5** as a yellow solid: mp 250-251° dec; ir (nujol): 3490-3270, 1718 cm^{-1}; ^{1}H nmr (methanol-d$_4$): δ 2.23 (s, 3H), 2.48 (s, 3H), 3.29-3.30 (m, 1H), 3.70 (dd, J_1 = 16.5 Hz, J_2 = 9.3 Hz, 1H), 4.82-4.92 (m, 1H), 5.12 (dd, J_1 = 13.8 Hz, J_2 = 2.7 Hz, 1H), 5.45-5.55 (m, 1H), 7.70 (s, 1H), 8.21 (dd, J_1 ≈ 7 Hz, J_2 ≈ 7 Hz, 2H), 8.69 (dd, J_1 ≈ 8 Hz, J_2 ≈ 8 Hz, 1H), 9.10 (d, J = 5.6 Hz, 2H).

Anal. Calcd. for C$_{19}$H$_{17}$BrN$_2$O$_5$•0.25 H$_2$O: C, 52.13; H, 4.03; N, 6.40. Found: C, 52.13; H, 3.93; N, 6.31.

Preparation of 3-Bromopsoralen Derivatives.

4,8-Dimethyl-6-allyl-7-hydroxycoumarin (7).

This compound was prepared as described by Kaufman [12].

3-Bromo-4,8-dimethyl-6-(2,3-dibromopropyl)-7-hydroxy-coumarin (8).

Compound **7** (2.31 g, 10.03 mmoles) was dissolved in 40 ml of chloroform. To this stirred solution at room temperature and under an inert atmosphere was slowly added bromine (1.18 ml, 22.90 mmoles) dissolved in 40 ml of chloroform. After the addition was complete, the reaction mixture was stirred overnight. The resulting precipitate was collected by suction filtration, washed with chloroform and dried *in vacuo*. Thus, 3.54 g (75% yield) of **8** was obtained as a white solid: mp 202-204° dec; ir (nujol): 3600-3200, 1701 cm^{-1}; ^{1}H nmr (dimethyl-d$_6$ sulfoxide): δ 2.23 (s, 3H), 2.55 (s, 3H), 3.14 (dd, J_1 = 14.3 Hz, J_2 = 9.4 Hz, 1H), 3.46 (dd, J_1 = 14.3 Hz, J_2 = 4.9 Hz, 1H), 3.96 (d, J = 5.6 Hz, 2H), 4.67-4.77 (m, 1H), 7.52 (s, 1H), 9.83 (s, 1H); ^{13}C nmr (dimethyl-d$_6$ sulfoxide): δ 8.8, 8.9, 19.4, 53.3, 53.6, 107.9, 111.3, 111.9, 122.7, 125.1, 150.0, 152.0, 156.6, 156.9.

Anal. Calcd. for C$_{14}$H$_{13}$Br$_3$O$_3$: C, 35.85; H, 2.79. Found: C, 36.38; H, 2.99.

3-Bromo-4,8-dimethyl-6-allyl-7-hydroxycoumarin (9).

A mixture of coumarin derivative **8** (0.628 g, 1.339 mmoles) and 0.40 g of zinc dust in solution in 35 ml of 95% ethanol was stirred and heated at reflux under an inert atmosphere for 20 minutes. The excess zinc was removed by filtration through a Millipore membrane (0.22 μm filter unit) and the ethanol evaporated under reduced pressure. The resulting solid was recrystallised from a mixture of methanol:water affording 0.330 g (80% yield) of **9** as a white solid: mp 158-160°; ir (nujol): 3500-3080, 1692 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.32 (s, 3H), 2.57 (s, 3H), 3.47 (d, J = 6.2 Hz, 2H), 5.18-5.25 (m, 2H), 5.55 (s, 1H), 5.96-6.04 (m, 1H), 7.24 (s, 1H); ms: (EI) m/z (relative intensity) 310 (M$^+$, 97), 308 (M$^+$, base), 201 (51), 173 (58), 128 (57), 115 (76), 77 (47).

Anal. Calcd. for C$_{14}$H$_{13}$BrO$_3$•0.2 H$_2$O: C, 53.76; H, 4.32. Found: C, 53.75; H, 4.00.

3-Bromo-4,8-dimethyl-6-allyl-7-acetoxycoumarin (10).

A mixture of compound **9** (0.123 g, 0.398 mmole) and a few crystals of fused sodium acetate in 1.5 ml of acetic anhydride was stirred at room temperature for 16 hours. The resulting precipitate was collected by suction filtration, washed with cold acetic anhydride and dried *in vacuo*. Recrystallisation from a mixture of methanol:water gave 0.089 g (64% yield) of **10** as a white solid: mp 162-163°; ir (nujol): 1746, 1726 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.24 (s, 3H), 2.35 (s, 3H), 2.60 (s, 3H), 3.32 (d, J = 6.3 Hz, 2H), 5.07-5.14 (m, 2H), 5.80-5.90 (m, 1H), 7.35 (s, 1H); ms: (EI) m/z (relative intensity) 352 (M$^+$, 5), 350 (M$^+$, 5), 310 (67), 308 (69), 43 (base).

Anal. Calcd. for C$_{16}$H$_{15}$BrO$_4$: C, 54.72; H, 4.30. Found: C, 54.44; H, 4.03.

3-Bromo-4,8-dimethyl-6-(2,3-dibromopropyl)-7-acetoxy-coumarin (11).

Coumarin derivative **8** (3.30 g, 7.04 mmoles) was reacted as for **10** using 26 ml of acetic anhydride. Recrystallisation from a mixture of 95% ethanol:water gave 3.22 g (90% yield) of **11** as a white solid: mp 156-157°; ir (nujol): 1760, 1718 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.26 (s, 3H), 2.41 (s, 3H), 2.62 (s, 3H), 2.85 (dd, J_1 = 14.8 Hz, J_2 = 9.6 Hz, 1H), 3.64-3.70 (m, 2H), 3.90 (dd, J_1 = 10.4 Hz, J_2 = 3.8 Hz, 1H), 4.26-4.34 (m, 1H), 7.50 (s, 1H).

Anal. Calcd. for C$_{16}$H$_{15}$Br$_3$O$_4$: C, 37.61; H, 2.96. Found: C, 37.48; H, 2.95.

3-Bromo-4,8-dimethyl-5'-bromomethyl-4',5'-dihydropsoralen (12).

A mixture of coumarin derivative **8** (1.22 g, 2.60 mmoles) and approximately 11 g of oven-dried sodium carbonate in 80 ml of dry acetone was stirred under an inert atmosphere at reflux for 1 hour, then at room temperature overnight. The carbonate salt was removed by suction filtration washed with cold acetone and the solvent evaporated under reduced pressure to yield a pale yellow solid which was recrystallised from methanol giving 0.75 g (74% yield) of the mixed isomers **12** and **13**: ir (nujol): 1709 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.21 (s, 3H), 2.59 (s, 3H), 3.59 (dq, J_1 = 9.3 Hz, J_2 = 1.3 Hz, J_3 = 1.3 Hz, 2H), 3.82 (dq, J_1 = 10.9 Hz, J_2 = 5.0 Hz, J_3 = 4.9 Hz, 2H), 5.25 (m, 1H), 7.55 (s, 1H).

Anal. Calcd. for C$_{14}$H$_{12}$Br$_2$O$_3$: C, 43.33; H, 3.12; Br, 41.18. Found: C, 43.30; H, 3.09; Br, 41.17.

Within the mixture of isomeric closure products generated herein, integration of their respective C$_5$-H resonances in the furano isomer **12** and in the pyrano isomer **13** revealed an 81:19 ratio favoring the expected 4',5'-dihydropsoralen **12**. The ^{1}H nmr (deuteriochloroform) of that minor isomer **13** was: δ 2.22 (s, 3H), 2.60 (s, 3H), 4.42 (dq, J_1 = 5.5 Hz, J_2 = 1.8 Hz, J_3 = 1.8 Hz, 2H), 4.58 (dq, J_1 = 2.5 Hz, J_2 = 1.4 Hz, J_2 = 1.3 Hz, 2H), 4.84 (m, 1H), 7.48 (s, 1H).

3-Bromo-4,8-dimethyl-5'-(*N*-pyridiniummethyl)-4',5'-dihydrop-soralen Bromide Salt (14).

The above mixture (0.204 g, 0.526 mmole) of psoralen deriv-ative **12** and its isomer **13** was dissolved in 4 ml of anhydrous pyridine. This solution was heated at reflux for 1.5 hours. The pyridine was evaporated under reduced pressure and the result-ing solid washed on a filter with anhydrous ether. The product, 0.198 g (81% yield), was recrystallised from methanol with the assistance of charcoal decolorization, to yield the pyridinium

salt **14** as a white solid: mp 270-270.5° dec; ir (nujol): 3700-3200, 1698 cm⁻¹; ¹H nmr (methanol-d₄): δ 2.22 (s, 3H), 2.61 (s, 3H), 3.24-3.31 (m, 1H), 3.68 (dd, J_1 = 16.3 Hz, J_2 = 9.3 Hz, 1H), 4.82-4.92 (m, 1H), 5.10 (dd, J_1 = 13.7 Hz, J_2 = 2.7 Hz, 1H), 5.42-5.61 (m, 1H), 7.58 (s, 1H), 8.20 (dd, J_1 ≈ 7 Hz, J_2 ≈ 7 Hz, 2H), 8.68 (dd, J_1 ≈ 8 Hz, J_2 ≈ 8 Hz, 1H), 9.09 (d, J = 5.5 Hz, 2H).

Anal. Calcd. for $C_{19}H_{17}Br_2NO_3$•0.5 H_2O: C, 47.93; H, 3.81; N 2.94; Br, 33.56. Found: C, 47.89; H, 3.86; N, 2.88; Br, 33.53.

Preparation of 3-Cyanopsoralen Derivatives.

3-Cyano-4,8-dimethyl-7-allyloxycoumarin (**17**).

Allyl bromide (2.82 ml, 32.59 mmoles) was added to a mixture of 2,4-dihydroxy-3-methylacetophenone **15** (4.92 g, 29.61 mmoles), approximately 24 g of potassium carbonate, 60 ml of dry acetone and the reaction mixture stirred under an inert atmosphere at room temperature for 16 hours. Then, excess allyl bromide (0.51 ml, 5.89 mmoles) was added, and the reaction mixture was stirred for another 16 hours. The carbonate salt was removed by suction filtration, washed with acetone and the solvent evaporated under reduced pressure. Water (20 ml) was added and the residue was extracted with ether followed by the usual work-up. The crude compound was purified by flash chromatography (mixture hexane:ethyl acetate; 90:10; v:v; as the eluent) giving 5.25 g (86% yield) of the intermediate, 2-hydroxy-3-methyl-4-allyloxyacetophe-none (**16**), as a colorless liquid [16] used directly in the subsequent Pechmann Condensation: ¹H nmr (deuterio-chloroform): δ 2.11 (s, 3H), 2.54 (s, 3H), 4.57-4.62 (m, 2H), 5.28 (ddd, J_1 = 9.2 Hz, J_2 = 1.4 Hz, J_3 = 1.4 Hz, 1H), 5.40 (ddd, J_1 = 17.2 Hz, J_2 = 1.4 Hz, J_3 = 1.4 Hz, 1H), 5.96-6.09 (m, 1H), 6.40 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H), 12.76 (s, 1H); ms: (EI) m/z (relative intensity) 206 (M⁺, 63), 191 (99), 137 (46), 91 (31), 43 (base), 41 (99), 39 (82). A solution of the acetophenone derivative **16** (5.60 g, 27.15 mmoles), ethyl cyanoacetate (5.78 ml, 54.31 mmoles), and glacial acetic acid (2.48 ml, 43.32 mmoles) in 30 ml of benzene was heated at reflux in a Dean-Stark apparatus under an inert atmosphere for 6 days. During this time, ammonium acetate (2.10 g, 27.24 mmoles) was added by small portions to the hot solution. The reaction mixture was analysed by gc-ms (oven temperature: 90° for 2 minutes, then 25°/minute to 300°), signals were observed at 6.89 minutes (20%, unreacted starting material **16**) and 10.01 minutes (80%, product **17**). Thus assuming an 80% conversion, the reaction was cooled at room temperature. After benzene removal under reduced pressure, chloroform was added and the mixture was washed with water followed by the usual work-up. The crude compound was purified by recrystallisation from a mixture of ethanol:water, affording 4.54 g (65% yield) of the coumarin derivative **17** as a pale brown solid: mp 172-173.5°; ir (nujol): 2225, 1712 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.30 (s, 3H), 2.69 (s, 3H), 4.68 (dd, J_1 = 3.5 Hz, J_2 = 1.5 Hz, 2H), 5.33 (d, J = 10.5 Hz, 1H), 5.43 (d, J = 17.3 Hz, 1H), 5.97-6.10 (m, 1H), 6.89 (d, J = 8.9 Hz, 1H), 7.52 (d, J = 9.9 Hz, 1H); ¹³C nmr (deuteriochloroform): δ 7.9, 17.8, 69.1, 108.6, 108.8, 111.7, 113.8, 114.6, 117.9, 124.2, 131.6, 152.2, 157.2, 161.7, 161.9; ms: (EI) m/z (relative intensity) 255 (M⁺, 94), 214 (27), 41 (base), 39 (39).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.29; H, 5.06; N, 5.62.

3-Cyano-4,8-dimethyl-6-allyl-7-hydroxycoumarin (**18**).

A solution of compound **17** (1.27 g, 4.97 mmoles) in 14 ml of N,N-diethylaniline was deoxygenated with argon for 30 minutes, and then was heated at reflux for 6 hours, while being purged by bubbling argon through the solution. The reaction mixture was chilled in ice, the resulting precipitate was collected by suction filtration and dried *in vacuo*. Recrystallisation from a mixture of benzene:methanol gave 0.97 g (76% yield) of **18** as a pale brown solid, mp 234-235°; ir (nujol): 3500-3000, 2224, 1694 cm⁻¹; ¹H nmr (acetone-d₆): δ 2.30 (s, 3H), 2.72 (s, 3H), 3.51 (d, J = 6.4 Hz, 2H), 5.02-5.14 (m, 2H), 5.96-6.10 (m, 1H), 7.61 (s, 1H), 8.90 (broad s, 1H).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.77; H, 4.93; N, 5.46.

3-Cyano-4,8-dimethyl-6-(2,3-dibromopropyl)-7-hydroxy-coumarin (**19**).

To a stirred solution of coumarin derivative **18** (0.656 g, 2.570 mmoles) in 15 ml of chloroform, at room temperature and under an inert atmosphere, was slowly added bromine (0.14 ml, 2.70 mmoles) dissolved in 15 ml of chloroform. After the addition was complete, the reaction mixture was stirred for 4 hours, then chilled in ice. The resulting precipitate was collected by suction filtration, washed with cold chloroform and dried *in vacuo* yielding 0.977 g (92% yield) of **19** as a pale brown solid. An analytical sample of **19** was obtained by recrystallisation from a mixture of benzene:methanol: mp 221-223°; ir (nujol): 3500-3100, 2232, 1734 cm⁻¹; ¹H nmr (dimethyl-d₆ sulfoxide): δ 2.22 (s, 3H), 2.66 (s, 3H), 3.15 (dd, J_1 = 14.4 Hz, J_2 = 9.5 Hz, 1H), 3.47 (dd, J_1 = 14.5 Hz, J_2 = 4.5 Hz, 1H), 3.95-4.02 (m, 2H), 4.69-4.80 (m, 1H), 7.66 (s, 1H), 10.43 (s, 1H); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 8.7, 8.9, 18.2, 53.1, 53.4, 96.5, 110.8, 111.5, 114.9, 123.4, 126.55, 151.9, 157.5, 160.0, 163.6.

Anal. Calcd. for $C_{15}H_{13}Br_2NO_3$: C, 43.40; H, 3.16; N, 3.37. Found: C, 43.67; H, 2.92; N, 3.33.

3-Cyano-4,8-dimethyl-6-(2,3-dibromopropyl)-7-acetoxy-coumarin (**20**).

A mixture of compound **19** (0.167 g, 0.402 mmole) and a few crystals of fused sodium acetate in 2 ml of acetic anhydride was stirred at room temperature under an inert atmosphere for 16 hours. The solvent was removed under reduced pressure and the resulting solid was recrystallised from a mixture of methanol:water, affording 0.132 g (72% yield) of **20** as a white solid: mp 170-171°; ir (nujol): 2230, 1749, 1731 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.24 (s, 3H), 2.43 (s, 3H), 2.75-2.83 (s and m, 4H), 3.62-3.80 (m, 2H), 3.95 (dd, J_1 = 10.2 Hz, J_2 = 3.3 Hz, 1H), 4.20-4.32 (m, 1H), 7.56 (s, 1H).

Anal. Calcd. for $C_{17}H_{15}Br_2NO_4$: C, 44.67; H, 3.31; N, 3.06. Found: C, 44.55; H, 2.97; N, 2.93.

3-Cyano-4,8-dimethyl-5'-bromomethyl-4',5'-dihydropsoralen (**21**).

A mixture of compound **19** (0.593 g, 1.429 mmoles) and 5.6 g of oven-dried sodium carbonate in 50 ml of dry acetone was stirred under an inert atmosphere at room temperature for 24 hours. The carbonate salt was removed by suction filtration washed with acetone and the solvent evaporated under reduced pressure to yield a solid which was recrystallised from a mixture of benzene:methanol. Thus, 0.371 g (78% yield) of a mixture of **21** and its minor isomer **22** was obtained as a pale brown solid:

mp 204-206°; ir (nujol): 2227, 1733 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.26 (s, 3H), 2.67 (s, 3H), 3.25 (dd, J_I = 16.2 Hz, J_2 = 6.3 Hz, 1H), 3.45 (dd, J_I = 15.7 Hz, J_2 = 9.3 Hz, 1H), 3.55-3.69 (m, 2H), 5.15-5.25 (m, 1H), 7.35 (s, 1H).

Anal. Calcd. for $C_{15}H_{12}BrNO_3$: C, 53.91; H, 3.62; N, 4.19. Found: C, 54.03; H, 3.38; N, 4.05.

Within the mixture of isomeric closure products generated herein, integration of their respective C_5-H resonances in the furano isomer **21** and in the pyrano isomer **22** revealed a 90:10 ratio favoring the expected 4',5'-dihydropsoralen **21**. The ¹H nmr (CDCl₃) of that minor isomer **22** was: δ 2.31 (s, 3H), 2.73 (s, 3H), 4.30-4.40 (m, 2H), 4.45-4.60 (m, 4H), 7.23 (s, 1H).

3-Cyano-4,8-dimethyl-5'-(N-pyridiniummethyl)-4',5'-dihydropsoralen Bromide Salt (**23**).

A solution of the above mixture (0.142 g, 0.425 mmole) of 5'-bromomethylpsoralen **21** and its isomer **22** was reacted as for **6** using 2.5 ml of anhydrous pyridine. The resulting precipitate was collected by suction filtration, dried *in vacuo*, affording 0.155 g (88% yield) of the pyridinium salt **23** as a pale grey solid: mp 303-305° dec; ir (nujol): 3415 (broad), 2229, 1714 cm⁻¹; ¹H nmr (methanol-d₄): δ 2.21 (s, 3H), 2.70 (s, 3H), 3.29-3.34 (m, 1H), 3.70 (dd, J_I = 16.6 Hz, J_2 = 9.5 Hz, 1H), 4.95 (dd, J_I = 13.8 Hz, J_2 = 9.3 Hz, 1H), 5.09 (dd, J_I = 13.7 Hz, J_2 = 2.6 Hz, 1H), 5.43-5.55 (m, 1H), 7.69 (s, 1H), 8.21 (dd, J_I ≈ 7 Hz, J_2 ≈ 7 Hz, 2H), 8.69 (dd, J_I ≈ 8 Hz, J_2 ≈ 8 Hz, 1H), 9.10 (d, J = 6.2 Hz, 2H).

Anal. Calcd. for $C_{20}H_{17}BrN_2O_3$: C, 58.13; H, 4.15; N, 6.78. Found: C, 57.74; H, 4.13; N, 6.71.

Reaction of coumarin and psoralen derivatives with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

In a typical experiment, a solution of coumarin or psoralen derivative (0.23 mmole), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (0.25 mmole) in anhydrous acetonitrile (4 ml) was stirred and heated at reflux under an inert atmosphere for 16 hours. The reaction was monitored by tlc, besides the unreacted starting material (major spot) a less polar product was visualized. The solvent was removed under reduced pressure and the crude compound purified by preparative tlc (mixture of hexane:ethyl acetate; 70:30; v:v as the eluent) yielding pure crystalline 3-fluoro product (12-14% yield). The products (**24** and **25**) arising from the two compounds fluorinated in this fashion were isolated in trace quantities and although they had nmr spectra in accord with their anticipated structures, they were not employed in further synthesis. Compound **25** was obtained by ring closure of **32** in adequate yield for future syntheses.

Preparation of 3-Fluoropsoralen Derivatives.

Ethyl 2-Fluoroacetoacetate (**26**).

This compound was prepared as described by Banks [15].

3-Fluoro-4,8-dimethyl-7-hydroxycoumarin (**27**).

A solution of 2-methylresorcinol (3.23 g, 26.02 mmoles), ethyl 2-fluoroacetoacetate **26** (3.85 g, 25.99 mmoles) in 0.5 ml of 1,4-dioxane was added dropwise, at 0° and under an inert atmosphere, to 25 ml of concentrated sulfuric acid. The reaction mixture was stirred for 1.5 hours, while the temperature was increased to 25°. Cold water (100 ml) was added, the reaction

mixture was stirred for 15 minutes and the resulting precipitate was collected by suction filtration, dried *in vacuo*, affording 4.56 g (84% yield) of 3-fluorocoumarin **27** as a white solid. An analytical sample was obtained by recrystallisation from methanol:water: mp 260-262° dec; ir (nujol): 3400-3100, 1706 cm⁻¹; ¹H nmr (dimethyl-d₆ sulfoxide): δ 2.15 (s, 3H), 2.31 (d, J = 2.7 Hz, 3H), 6.91 (d, J = 8.7 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 10.40 (s, 1H); ms: (EI) m/z (relative intensity) 208 (M⁺, base), 180 (29), 179 (17), 152 (22), 151 (13).

Anal. Calcd. for $C_{11}H_9FO_3$: C, 63.46; H, 4.36. Found: C, 63.14; H, 4.31.

3-Fluoro-4,8-dimethyl-7-allyloxycoumarin (**31**).

Allyl bromide (1.08 ml, 12.48 mmoles) was added to a mixture of coumarin derivative **27** (1.73 g, 8.31 mmoles), approximately 5 g of potassium carbonate and 45 ml of dry acetone. The reaction mixture was stirred under an inert atmosphere at room temperature for 28 hours. During this time, excess allyl bromide (1.44 ml, 16.64 mmoles) was added in two portions. The carbonate salt was removed by suction filtration washed with acetone and the solvent evaporated under reduced pressure yielding a solid, which was purified by recrystallisation from a mixture of methanol:water. Thus, 1.60 g (78% yield) of **31** was obtained as a white solid: mp 117-118°; ir (nujol): 1718 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.32 (s, 3H), 2.34 (d, J = 2.7 Hz, 3H), 4.61 (d, J = 4.9 Hz, 2H), 5.30 (d, J = 10.5 Hz, 1H), 5.42 (dd, J_I = 17.3 Hz, J_2 = 1.2 Hz, 1H), 5.97-6.13 (m, 1H), 6.86 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H); ms: (EI) m/z (relative intensity) 248 (M⁺, base), 208 (30), 207 (79), 179 (56), 41 (63), 39 (25).

Anal. Calcd. for $C_{14}H_{13}FO_3$: C, 67.73; H, 5.28. Found: C, 67.47; H, 5.26.

3-Fluoro-4,8-dimethyl-6-allyl-7-hydroxycoumarin (**28**).

A solution of compound **31** (1.56 g, 6.28 mmoles) in 20 ml of N,N-diethylaniline was deoxygenated with argon for 30 minutes and then was heated at reflux for 4 hours, while being purged by bubbling argon through the solution. The reaction mixture was chilled in ice, the resulting precipitate was collected by suction filtration and dried *in vacuo*. Recrystallisation from a mixture of methanol:water gave 0.859 g (55% yield) of **28** as a white solid: mp 163-164°; ir (nujol): 3500-3100, 1724 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.31 (s, 3H), 2.35 (d, J = 2.8 Hz, 3H), 3.47 (d, J = 6.1 Hz, 2H), 5.18-5.27 (m, 2H), 5.47 (s, 1H), 5.95-6.10 (m, 1H), 7.14 (s, 1H); ms: (EI) m/z (relative intensity) 248 (M⁺, base), 233 (18), 205 (18), 177 (21), 27 (19).

Anal. Calcd. for $C_{14}H_{13}FO_3$: C, 67.73; H, 5.28. Found: C, 67.57; H, 5.21.

3-Fluoro-4,8-dimethyl-6-(2,3-dibromopropyl)-7-hydroxycoumarin (**32**).

Coumarin derivative **28** (0.211 g, 0.850 mmole) was dissolved in 6 ml of chloroform. To this stirred solution, at room temperature and under an inert atmosphere, was slowly added bromine (0.046 ml, 0.89 mmole) dissolved in 4 ml of chloroform. After the addition was complete, the reaction mixture was stirred for 16 hours, and the solvent removed under reduced pressure. Recrystallisation from a mixture of methanol:water gave 0.295 g (85 % yield) of **32** as a white solid: mp 175-176°; ir (nujol): 3500-3100, 1717 cm⁻¹; ¹H nmr (dimethyl-d₆ sulfoxide): δ 2.23 (s, 3H), 2.33 (d, J = 2.5 Hz, 3H), 3.15 (dd, J_I = 14.3 Hz, J_2 = 8.0 Hz, 1H), 3.46 (dd, J_I = 14.4 Hz, J_2 = 4.9 Hz, 1H), 3.96 (d, J = 5.2 Hz, 2H), 4.69-4.78 (m, 1H), 7.42 (s, 1H), 9.65 (s, 1H).

Anal. Calcd. for $C_{14}H_{13}Br_2FO_3$: C, 41.21; H, 3.21. Found: C, 41.06; H, 2.97.

3-Fluoro-4,8-dimethyl-5'-bromomethyl-4',5'-dihydropsoralen (**25**).

A mixture of compound **32** (0.231 g, 0.566 mmole) and 2.2 g of oven-dried sodium carbonate in 15 ml of dry acetone was stirred under an inert atmosphere at room temperature for 16 hours. The carbonate salt was removed by suction filtration, washed with acetone and the solvent evaporated to yield a solid which was recrystallised from a mixture of methanol:water giving 0.145 g (78% yield) of a mixture of **25** and its minor isomer **29** as a white solid: mp 143-144°; ir (nujol): 1717 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.25 (s, 3H), 2.34 (d, $J = 2.9$ Hz, 3H), 3.22 (dd, $J_1 = 16.0$ Hz, $J_2 = 6.4$ Hz, 1H), 3.45 (dd, $J_1 = 16.0$ Hz, $J_2 = 9.2$ Hz, 1H), 3.55 (dd, $J_1 = 10.6$ Hz, $J_2 = 6.7$ Hz, 1H), 3.63 (dd, $J_1 = 10.6$ Hz, $J_2 = 4.5$ Hz, 1H), 5.06-5.15 (m, 1H), 7.18 (s, 1H).

Anal. Calcd. for $C_{14}H_{12}BrFO_3$: C, 51.40; H, 3.70. Found: C, 51.23; H, 3.38.

Within the mixture of isomeric closure products generated herein, integration of their respective $C_{5'}$-H resonances in the furano isomer **25** and in the pyrano isomer **29** revealed an 89:11 ratio favoring the expected 4',5'-dihydropsoralen **25**. The ^{1}H nmr (deuteriochloroform) of minor isomer **29** was: δ 2.25 (s, 3H), 2.34 (s, 3H), 4.15-4.25 (m, 2H), 4.25-4.50 (m, 4H), 7.04 (s, 1H).

3-Fluoro-4,8-dimethyl-5'-(N-pyridiniummethyl)-4',5'-dihydropsoralen Bromide Salt (**30**).

A solution of the above 89:11 mixture (0.100 g, 0.306 mmole) of psoralen derivative **25** and its minor isomer **29** was reacted as for **6** using 2 ml of anhydrous pyridine. The resulting precipitate was collected by suction filtration and dried *in vacuo*, affording 0.091 g (73% yield) of the pyridinium salt **30** as a white solid: mp 289-290° dec; ir (nujol): 3490 (broad), 1717 cm^{-1}; ^{1}H nmr (methanol-d_4): δ 2.21 (s, 3H), 2.38 (d, $J = 2.9$ Hz, 3H), 3.25-3.30 (m, 1H), 3.67 (dd, $J_1 = 16.2$ Hz, $J_2 = 9.3$ Hz, 1H), 4.78-4.92 (m, 1H), 5.09 (dd, $J_1 = 13.8$ Hz, $J_2 = 2.6$ Hz, 1H), 5.35-5.46 (m, 1H), 7.48 (s, 1H), 8.19 (dd, $J_1 \approx 7$ Hz, $J_2 \approx 7$ Hz, 2H), 8.68 (dd, $J_1 \approx 8$ Hz, $J_2 \approx 8$ Hz, 1H), 9.08 (d, $J = 6.2$ Hz, 2H).

Anal. Calcd.for $C_{19}H_{17}BrFNO_3$: C, 56.17; H, 4.22; N, 3.45. Found: C, 55.82; H, 3.93; N, 3.38.

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