Synthetic Approaches to 4,8-Dimethyl-5'-(*N*-pyridiniummethyl)- 4',5'-dihydropsoralens and 4,8-Dimethyl-5'- (*N*-aminomethyl)- 4',5'-dihydropsoralens [1,2]

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Received November 10, 2000

New synthetic approaches to 4,8-dimethyl-5'-(*N*-pyridiniummethyl)-4',5'-dihydropsoralens and 4,8-dimethyl-5'-(*N*-aminomethyl)-4',5'-dihydropsoralens are described. The 5'-halomethyl-4',5'-dihydropsoralen precursors are formed by electrophilic ring closures of 4,8-dimethyl-6-allyl-7-hydroxycoumarin. The ring-closure reactions may also be applied to the synthesis of 5'-halomethyl-4-methyl-4',5'-dihydroangelicins. The compounds are potential therapeutic agents for improved psoralen ultraviolet A radiation treatment.

J. Heterocyclic Chem., **38**, 909 (2001).

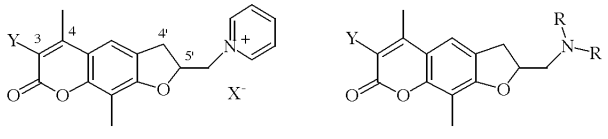
Psoralens (linear furocoumarins) are useful, in combination with uv radiation, in the treatment of psoriasis, eczema and mycosis fungoides [3]. These are naturally occurring with extracts having been used for thousands of years. Recent years have seen their application to cancer (T cell lymphoma), autoimmune diseases, and viral inhibition by modification of the techniques through which psoralen and light are co-administered to the offending condition [4].

The accepted mode of phototherapeutic action for psoralens has been the penetration of the target cell's membrane, intercalation of DNA followed by photoactivated crosslinking the double helix through cyclobutanes generated at the 3,4-double bond and the 4',5'-double bond of the psoralen to double bonds in the DNA pyrimidine bases [3]. With the DNA unable to unravel, it cannot function as a template for new gene expression and the cell becomes non-viable. Though considered the most effective treatment for some diseases, concerns exist about genetic mutations induced by DNA damage [5].

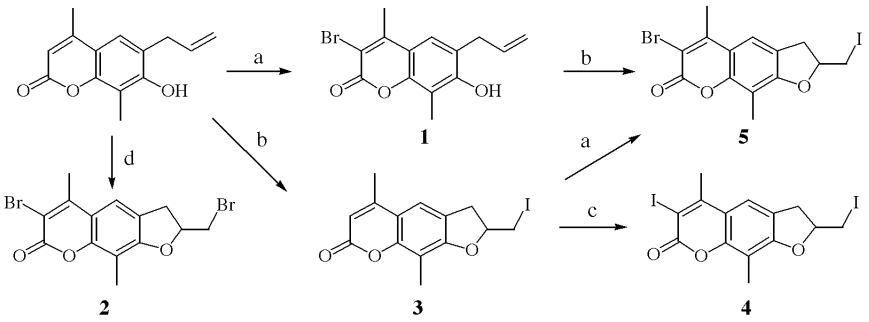
In an alternative mechanism of action, a 22,000 Da protein present in the cell membrane of psoralen-sensitive cells has been found to be a specific binding site for psoralens [6]. When psoralens bind to this receptor, followed by exposure to uv light, the binding of the epidermal growth factor is prevented [6,7,8]. Previous syntheses from our laboratories have shown that psoralens can retain phototherapeutic activity and can anchor to the target membrane receptor even after major structural alteration to the furan ring [9,10,11]. It was found that unsaturation of the furan ring is not necessary for the photoactivity of psoralens. Saturation of the furan ring would eliminate the possibility of DNA crosslink formation. Use of water-soluble salts or hydrophilic amine functionalities would limit passage through cell membranes, thereby increasing cell surface effects and minimizing mutagenic/carcinogenic effects [4].

A previous synthesis in our labs generated 4',5'-dihydro-5'-bromomethyl moieties as precursors to the pyridinium derivatives [12]. Improvements to the molecular bromine route include: no bromopyran formation resulting from the ring closure, improved nucleophilic displacement upon an iodomethyl moiety, and reduced dehydrohalogenation during synthetic manipulations. IC_{50} measurements of

Figure 1



Scheme 1



Reagents and conditions: (a) 1 mole NBS, chloroform, room temperature, 77% yield (b) 1.5 moles NIS, CH_2Cl_2, 92% yield or I_2, $SnCl_4$ and CH_2, 82% yield, (c) ICl, glacial acetic acid, 85% yield, (d) 3 moles NBS, tetrahydrofuran, room temperature, 85% yield.

psoralens and coumarins in the photoactivated keratinocyte assay have shown impressive activity by quaternary compounds and amines [13].

Results and Discussion.

The 4,8-dimethyl-5'-halomethyl-4',5'-dihydropsoralens were valuable synthetic targets for the preparation of 4,8-dimethyl-5'-*N*-pyridiniummethyl-4',5'-dihydropsoralens and 4,8-dimethyl-5'-*N*-aminomethyl-4',5'-dihydropsoralens, some with substitution at the C_3 with groups such as bromo, iodo, and cyano (Figure 1).

Our synthesis began with the precursor, 4,8-dimethyl-7-hydroxycoumarin, generated by a von Pechmann reaction from methyl resorcinol and ethyl acetoacetate in trifluoroacetic acid in high yield as described by Woods [14]. The 7-allyloxy-4,8-dimethylcoumarin, formed by the addition of allyl bromide with potassium carbonate in acetone, was converted to the Claisen product, 4,8-dimethyl-6-allyl-7-hydroxycoumarin in refluxing diethylaniline as described by Kaufman. The presence of the C_8 methyl prevented rearrangement of the allyl to the C_8 position, which in ring closure would yield the angular angelicin derivative [15].

Allyl phenol ring closures offer many possibilities for electrophiles that were useful in catalyzing the closure of 4,8-dimethyl-6-allyl-7-hydroxycoumarin to substituted dihydropsoralens [16-19]. Electrophiles explored in the halocyclization reaction to form the dihydrofuran portion of the psoralen ring gave the Markovnikov products with higher regioselectivity than the molecular bromine facilitated cyclization route that lead to 10 to 20% benzopyran by-product formation [12].

Bromine Based Cyclizations.

Natural products with significant biological properties containing unsaturated furan ring systems have been generated synthetically by *N*-bromosuccinimide ring closure of alkenols [20,21]. The *N*-bromosuccinimide cyclization of alkenols was applied to generation of 3-bromo-4,8-dimethyl-5'-bromomethyl-4',5'-dihydropsoralen **2**, selectively brominating the C_3 and ring closing to the dihydrofurocoumarin in 85% yield using three molar equivalents of NBS (Scheme 1). Variations in temperature (from -80° to 25°) and the presence or absence of light did not appear to affect this reaction. No tetrahydropyran formation was detected in the ^1H nmr of the crude mixture. Use of one mole of *N*-bromosuccinimide in chloroform or one mole of pyridinium hydrobromide perbromide in acetic acid selectively gave 3-bromo-4,8-dimethyl-6-allyl-7-hydroxycoumarin **1** in high yields [13]. Ring closures did not occur under these conditions when the electrophile concentration was only equi-molar, rather substitution at the C_3 occurred more readily.

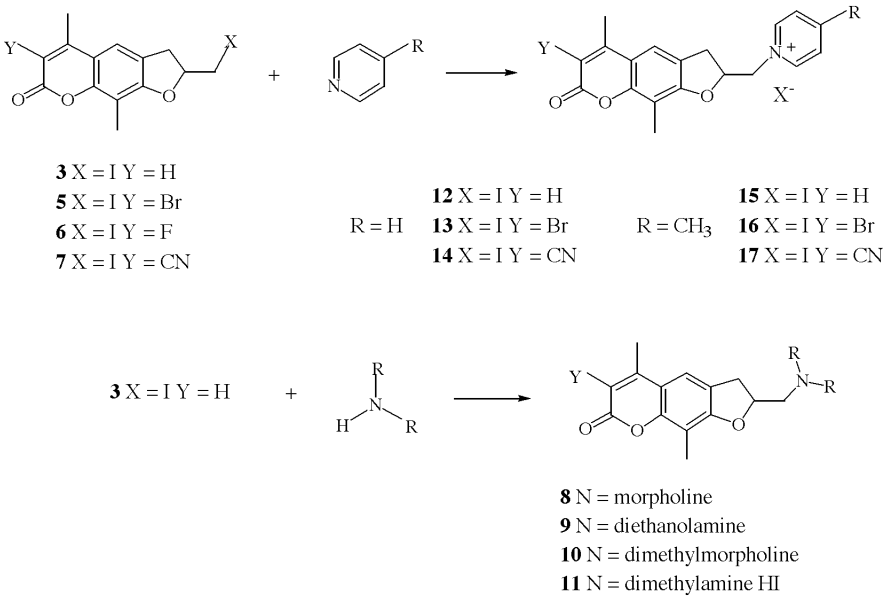
Iodine Based Cyclizations.

The 5'-iodomethylpsoralens proved very useful for the iodomethyls were generated regioselectively in a 5-*exo*-Trig type cyclization in the absence of C_3 substitution or benzofuran formation. The formation of the 5'-iodomethyl derivative facilitated the formation of the tertiary amine and quaternary derivatives. One route employed *N*-iodosuccinimide, to selectively ring close 4,8-dimethyl-6-allyl-7-hydroxycoumarin (Claisen product) in a single step to 4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen **3** in 92% yield (Scheme 1).

Initial reactions showed trace iodination at the C_3 position but further attempts to isolate 3-iodo-4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen **4** by this route were not successful. Use of a two-fold excess of *N*-iodosuccinimide yielded only 4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen **3** with no C_3 substitution. When C_3 substitution was desired, 3-iodo-4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen **4** was generated in 85% yield by reacting 4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen **3** with ICl in acetic acid at 50° overnight. Bromination at the C_3 position may be accomplished with *N*-bromosuccinimide.

A second route to **3** by tin (IV) chloride assisted iodocyclization was based on the synthesis of the 5-iodomethylbenzofurans from 2-allylphenol by Orito [19]. Applied to psoralen synthesis, this route gave the similar advantage of the *N*-bromosuccinimide and *N*-iodosuccinimide cyclizations in that reactions proceed in high yield with no

Scheme 2



competing benzopyran formation, as determined by ^{1}H nmr (Scheme 1). Additional iodinating reagents used to successfully ring close include iodine /sodium bicarbonate / acetonitrile, iodine monochloride /methylene chloride (prone to halogen exchange and to multiple reaction products) and iodine monobromide/methylene chloride (prone to multiple products). Attempts to ring close using *N*-chlorosuccinimide failed.

The bromine and iodine based cyclization reactions offer alternative methods for the synthesis of readily substituted dihydropsoralen precursors to tertiary amines or quaternary compounds (Scheme 1). The above discussed pathways were applied to the synthesis of various C_3 substituted dihydropsoralens *via* the 3-*R*-5'-bromomethyl-4',5'-dihydropsoralens or *via* the highly reactive 3-*R*-5'-iodomethyl-4',5'-dihydropsoralens. Substitution at the C_3 position by bromine, iodine, fluorine or cyano did not significantly affect nucleophilic displacement of the halide by pyridine, morpholine, diethanolamine or dimethylamine.

Amine Substitution.

The pyridinium iodide or bromide derivatives of the 4,8-dimethyl-5'-halomethyl-4',5'-dihydropsoralens were synthetic targets designed to limit cell membrane penetration by the presence of a charged functionality (Scheme 2). Refluxing 4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen **3** in anhydrous pyridine overnight followed by collection of the crystals by filtration recovered 80% yield of 4,8-dimethyl-5'-(*N*-pyridiniummethyl)-4',5'-dihydropsoralen iodide salt **12**. Reactions of **3** with 4-methylpyridine gave **15** in 94% yield after recrystallization. The 3-bromo and 3-cyano substituted 5'-iodomethylpsoralens gave similar yields with pyridine and 4-methylpyridine. Purification of the quaternary compounds was afforded by alcohol recrystallization. The resulting pure compounds were hydroscopic.

Increasing water solubility would also favor membrane effects, thereby targeting the psoralen receptor. Amino derivatives included morpholino, dimethylmorpholino, dimethylamino hydroiodo and *N*,*N*-β-(hydroxyethyl)-amino psoralens. 4,8-Dimethyl-5'-morpholinomethyl-4',5'-dihydropsoralen **8** was generated in 70% yield by refluxing the 5'-iodomethyl-dihydropsoralen **3** in morpholine for three hours, followed by removal of excess morpholine *in vacuo*. 4,8-Dimethyl-5'-(2,6-dimethyl-morpholino)methyl-4',5'-dihydropsoralen **10** was generated similarly and recovered in 74% yield. Due to the high boiling point of diethanolamine, the reaction of the 5'-iodomethyl-dihydropsoralen **3** required a different work up and generated a 23% yield of 4,8-dimethyl-5'-[*N*,*N*-β-(hydroxyethylamino)methyl]-4',5'-dihydropsoralen **9**. The 4,8-dimethyl-5'-[(*N*,*N*-dimethylamino)methyl]-4',5'-dihydropsoralen hydroiodide salt **11** was formed in a Teflon lined metal reactor due to the volatility of the dimethyl amine. The product mixture contained 50% 4,8,5'-trimethylpsoralen, readily separated by refluxing in chloroform with the desired product separated by filtration.

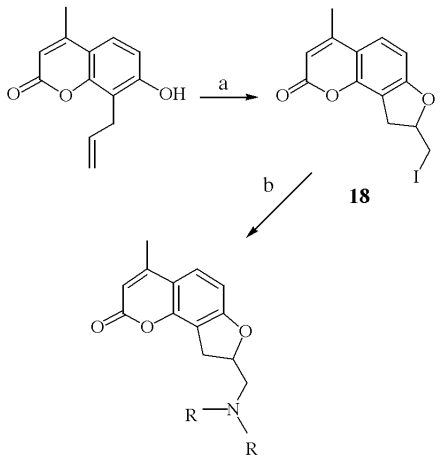
Some limitations are seen in that the quaternary amine from triethylamine could not be prepared and attempts to react the 5'-iodomethyl-dihydropsoralen **3** with dodecyl amine proved to be unsuccessful. Elimination dominated over substitution when more basic nucleophiles were employed. The elimination product, 4,8,5'- trimethylpsoralen

was recovered when displacements were attempted with the 5'- iodomethyl-dihydropsoralen **3** and imidazole, diisopropanolamine, piperidine, dodecyl morpholine or an amine in the presence of a strong base when attempting to force the alkylation of that amine.

Angelicin Synthesis.

The ring closure methods pursued in the formation of 4,8-dimethyl-5'-halomethyl-4',5'-dihydropsoralens were applied to the synthesis of 5'-halomethyl-4',5'-dihydroangelicins from 4-methyl-8-allyl-7-hydroxycoumarin (purchased from Lancaster) (Scheme 3). The iodine, tin (IV) chloride ring closure of 4-methyl-8-allyl-7-hydroxycoumarin gave 88% yield of 4-methyl-5'-iodomethyl-4',5'-dihydroangelicin **18**. Amine substitutions similar to the 4,8-dimethyl-5'-halomethyl-4',5'-dihydropsoralen substitutions gave 4-methyl-5'-pyridiniummethyl-4',5'-dihydroangelicin iodide salt **19** in 62% yield and 4-methyl-5'-morpholiummethyl-4',5'-dihydroangelicin **20** was recovered in 43% yield from refluxing 4-methyl-5'-iodomethyl-4',5'-dihydroangelicin **18** with the amine.

Scheme 3



19 N = pyridinium iodide
20 N = morpholine

Reagents and conditions: (a) I_2, $SnCl_4$, in CH_2Cl_2 rt, 88% yield; (b) refluxing pyridine or morpholine.

EXPERIMENTAL

The ^1H and ^{13}C nmr spectra were recorded on a Bruker AC 250 operated at 250.13 MHz and 62.89 MHz in the FT mode. Chemical shifts for hydrogen and carbon resonances were reported in ppm (δ) relative to tetramethylsilane. Structural determination also included COSY, DEPT and HETCOR experiments. Thin-layer chromatographies were performed with fluorescent silica gel plates. Silica gel (230-400 mesh) was used for flash chromatography separations. Melting points were determined on a Mettler FP 81 MBC cell with a Mettler FP 80 central processor or a Thomas Hoover capillary melting point apparatus. Elemental analyses were determined by Oneida Research Services, Whitesboro, NY and by Quantitative Technologies Inc., P. O. Box 470, Whitehouse, NJ. Gas chromatography/mass spectrometry was run on a Varian gas chromatograph 3300 model in series with a Finnegan ITS 40™ Magnum Ion Trap Mass Spectrometer. High performance liquid chromatography analyses were run on a Hewlett Packard HP 1050 Series model. Solvents and materials were purchased from Aldrich. All extractions were followed by water and saturated NaCl aqueous solution washings, drying over magnesium sulfate, filtration and evaporation.

Synthesis of 3-Bromocoumarins and 3-Bromo-4',5'-Dihydropsoralens.

3-Bromo-4,8-dimethyl-6-allyl-7-hydroxycoumarin (**1**).

A mixture of 4,8-dimethyl-6-allyl-7-hydroxycoumarin (1.25 g, 5.43 mmoles) and *N*-bromosuccinimide (1.12 g, 6.20 mmoles) was added to 50 ml dry tetrahydrofuran and stirred in the dark at room temperature for 1.5 hours. Saturated aqueous potassium sulfite was added and stirring was continued for an additional ten minutes. The tetrahydrofuran was evaporated, and solids were taken up in chloroform, washed with brine and dried over magnesium sulfate. The chloroform was evaporated *in vacuo* to give pale yellow crystals. The product was purified on a silica column using 30% ethyl acetate/70% hexanes, with a yield of 1.29 g (77% yield) 3-bromo-4,8-dimethyl-6-allyl-7-hydroxycoumarin. The product was further purified by column chromatography with 5% methanol/95% chloroform yielding white crystals: mp 175.4-175.8 °C; ^1H-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 $C_{14}H_{13}BrO_3 \cdot 0.2H_2O$: C, 53.76; H, 4.32. Found: C, 53.75; H, 4.35.

3-Bromo-4,8-dimethyl-5'-bromomethyl-4',5'-dihydropsoralen (**2**).

4,8-Dimethyl-6-allyl-7-hydroxycoumarin (2.00 g, 8.68 mmoles) was dissolved in 200 ml of anhydrous tetrahydrofuran before the addition of *N*-bromosuccinimide (4.68 g, 26.3 mmoles) with stirring in the dark at room temperature for 1.5 hours. The gc-ms indicated no starting material remained. Saturated aqueous sodium bisulfite was added, and stirring continued for ten minutes. The tetrahydrofuran layer was evaporated and solids were taken up in chloroform, washed with sodium chloride solution, water, and dried over magnesium sulfate. Evaporation of the chloroform layer yielded mustard yellow crystals that were recrystallized from methanol. The yield was 2.88 g (85% yield). The compound was purified by column chromatography with elution by 5% methanol/ 95% chloroform to yield tan crystals. Thin layer chromatography using the same solvent showed one spot with an Rf of 0.72. Further recrystallization from methanol gave white crystals: mp 182.3-182.5 °C; ^1H-nmr (dimethyl sulfoxide-d_6): 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). ^{13}C-nmr (dimethyl sulfoxide-d_6): 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; ms: (EI) m/z (relative intensity) 390 (M^+, 51), 389 (M^+, 18), 388 (M^+, Base) 387 (48), 309 (12), 307 (13), 228 (13).

Anal. Calcd. for $C_{14}H_{12}Br_2O_3$: C, 43.33; H, 3.12. Found: C, 43.16; H, 3.06.

Synthesis of 4,8-Dimethyl-5'-Iodomethyl-4',5'-Dihydropsoralens.

4,8-Dimethyl-5'-iodomethyl-4',5'-dihydropsoralen (**3**).

Route One .

To 4,8-dimethyl-6-allyl-7-hydroxycoumarin (2.00 g, 8.68 mmoles) in 50 ml methylene chloride was added *N*-iodosuccinimide (2.92 g, 13.0 mmoles). Stirring continued at room temperature overnight. The gc-ms indicated conversion was complete. Saturated aqueous bisulfite was added, after 10 minutes the usual workup followed. Recrystallization from ethanol gave 2.84 g (92% yield) white crystals: mp 137.4-138.2 °C; ^{1}H-nmr (deuteriochloroform): δ 2.19 (s, 3H), 2.28 (s, 3H), 3.04 (dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz, 1H), 3.33 (dd, J_1 = 9.9 Hz, J_2 = 7.6, 1H), 3.40 (dd, J_1 = 15.8 Hz, J_2 = 6.7, 1H), 3.44 (dd, J_1 = 9.9, J_2 = 4.9, 1H), 4.84-4.92 (m, 1H), 6.01 (s, 1H), 7.13 (s, 1H). ^{13}C-nmr (deuteriochloroform): δ 8.5, 8.6, 19.0, 35.8, 82.6, 108.1, 111.2, 114.0, 117.4, 122.0, 152.8, 153.2, 160.9, 161.6; ms: (EI) m/z (relative intensity) 358 (M^+, 13), 357 (M^+, base) 356 (20), 229 (13), 115 (12).

Anal. Calcd. for $C_{14}H_{13}IO_3$: C, 47.21; H, 3.68. Found: C, 47.27; H, 3.77.

Route Two.

4,8-Dimethyl-6-allyl-7-hydroxycoumarin (5.02 g, 21.8 mmoles), 12 ml 1 *M* tin tetrachloride and iodine (5.50 g, 22.6 mmoles) were added to 50 ml of methylene chloride, with stirring at room temperature overnight. Ice water was added and mixture was washed with saturated aqueous sodium bicarbonate, 0.5 *N* sodium hydroxide, 5% sodium hydrogen sulfide and water before drying over magnesium sulfate. Methylene chloride was removed *in vacuo* with a yield of 6.37 g (82% yield). Recrystallization from ethanol or purification on a silica column with 1% acetone / 99% methylene chloride afforded pure product.

3-Iodo-4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen (**4**).

The mixture of **3** (100 mg, 0.28 mmoles), iodine monochloride (72 mg, 0.42 mmoles) and 1 ml of glacial acetic acid was heated at 50 °C overnight. Excess iodine monochloride was destroyed by aqueous sodium bisulfite. Tan crystals were collected by filtration and washed with ether. The yield was 114 mg (85% yield) after recrystallization from ethanol, with white crystals: mp 213-214 °C; ^{1}H-nmr (deuteriochloroform): δ 2.29 (s, 3H), 2.65 (s, 3H), 3.14 (dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz, 1H), 3.35-3.54 (m, 3H), 4.92-4.99 (m, 1H), 7.31 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 8.5, 8.6, 25.8, 35.8, 82.8, 88.1, 107.9, 113.6, 117.9, 118.1, 152.3, 156.6, 158.3, 161.2; ms: (EI) m/z (relative intensity) 484 (M^+, 24), 483 (M^+, base) 356 (14), 229 (12), 200 (23), 172 (10).

Anal. Calcd. for $C_{14}H_{12}I_2O_3$: C, 34.88; H, 2.51. Found: C, 35.09; H, 2.61.

3-Bromo-4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen (**5**).

Route One .

A mixture of **1** (200 mg, 0.645 mmoles), *N*-iodosuccinimide (217 mg, 0.967 mmoles) and 15 ml methylene chloride was stirred overnight at room temperature. Saturated aqueous bisulfite was added and after 10 minutes the methylene chloride layer was extracted with water. Unreacted starting material was removed by a base extraction. The organic layer was dried over magnesium sulfate, and evaporated to give a pale mustard colored solid. The product may be recrystallized from ethanol or purified by column chromatography using 5% methanol/95% chloroform. The yield of white crystals was 271 mg (77% yield): mp 188.7-189.4 °C; ^{1}H-nmr (deuteriochloroform): δ 2.30 (s, 3H), 2.56 (s, 3H), 3.16 (dd, J_1 = 15.9 Hz, J_2 = 6.7 Hz, 1H), 3.40 (dd, J_1 = 9.3 Hz, J_2 = 7.6 Hz, 1H), 3.47 (dd, J_1 = 15.9 Hz, J_2 = 6.7 Hz, 1H), 3.51 (dd, J_1 = 9.3 Hz, J_2 = 4.9, 1H), 4.93-5.30 (m, 1H), 7.28 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 8.5, 8.6, 19.8, 35.8, 82.7, 108.0, 109.2, 113.8, 117.8, 122.9, 151.3, 151.5, 157.5, 161.1; ms: (EI) m/z (relative intensity) 437 (M^+, 21), 437 (M^+, 99) 435 (M^+, base) 309 (11), 307 (13), 115 (10).

Anal. Calcd. for $C_{14}H_{12}BrIO_3$: C, 38.65; H, 2.78. Found: C, 38.57; H, 2.88.

Compound **5** may also be generated by the iodine/tin tetrachloride ring closure of **1**.

Route Two.

To Compound **3** (75 mg, 0.21 mmoles) in methylene chloride was added *N*-bromosuccinimide (56 mg, 0.31 mmoles), with stirring continued in the dark at room temperature overnight. The solvent was evaporated *in vacuo*, solids were extracted with chloroform and the organic layer was washed with aqueous bisulfite and water. The organic layer was dried and solvent removed *in vacuo* to recover 76 mg (84% yield) product. Recrystallization from ethanol afforded white crystals: mp 188.9-189.5 ° C.

3-Fluoro-4,8-dimethyl-5'-iodomethyl-4',5'-dihydrofurocoumarin (**6**).

For 3 hours at room temperature 3-fluoro-4,8-dimethyl-6-allyl-7-hydroxycoumarin [12] (200 mg, 0.804 mmoles) was stirred with *N*-iodosuccinimide (271 mg, 1.20 mmoles) in enough methylene chloride to dissolve. Saturated aqueous sodium bisulfite was added to decolorize followed by washing twice with 1.5 ml portions of water. Yield was 277 mg crystals (91% yield). Further purification was achieved by chromatography on silica gel with 30% ethyl acetate/70% hexane to give white crystals: ^{1}H-nmr (deuteriochloroform): δ 2.30 (s, 3H), 2.56 (s, 3H), 3.16 (dd, J_1 = 15.9 Hz, J_2 = 6.7 Hz, 1H), 3.40 (dd, J_1 = 9.3 Hz, J_2 = 7.6 Hz, 1H), 3.47 (dd, J_1 = 15.9 Hz, J_2 = 6.7 Hz, 1H), 3.51 (dd, J_1 = 9.3 Hz, J_2 = 4.9, 1H), 4.93-5.25 (m, 1H), 7.28 (s, 1H). ^{13}C-nmr (deuteriochloroform): δ 8.9, 9.1, 10.8, 36.3, 83.0, 108.6, 113.5, 117.7, 123.5, 132.0, 142.5, 150.1, 155.7, 160.6; ms: (EI) m/z (relative intensity) 375 (M^+, 17), 374 (M^+, base) 247 (30), 207 (16), 73 (21).

Anal. Calcd. for $C_{14}H_{12}FIO_3$: C, 44.94; H, 3.23. Found: C, 45.05; H, 3.26.

3-Cyano-4,8-dimethyl-5'-iodomethyl-4',5'-dihydropsoralen (**7**).

3-Cyano-4,8-dimethyl-6-allyl-7-hydroxycoumarin [12] (69 mg, 0.27 mmoles), *N*-iodosuccinimide (91 mg, 0.41 mmoles) and 2 ml deuteriochloroform were stirred at room temperature overnight. Saturated aqueous bisulfite was added and stirring was continued for 10 minutes. The organic layer was washed with water and dried over magnesium sulfate. The solvent was evaporated *in vacuo*. Purification by column chromatography using 5% methanol/95% chloroform on silica gel recovered 70.0 mg (71% yield) bright yellow crystals: mp 234.7-234.9 °C;

^{1}H-nmr (deuteriochloroform): 2.28 (s, 3H), 2.70 (s, 3H), 3.16 (dd, $J_1 \cong 15$ Hz, $J_2 \cong 6$ Hz, 1H), 3.42-3.56 (m, 3H), 5.00-5.08 (m, 1H), 7.36 (s, 1H). ^{13}C-nmr (deuteriochloroform): δ 8.4, 8.6, 18.5, 35.7, 83.4, 96.5, 108.9, 112.7, 114.5, 119.2, 122.0, 153.7, 157.8, 162.3, 164.2; ms: (EI) m/z (relative intensity) 382 (M^+, 17), 381 (M^+, base) 254 (33), 226 (10), 127 (10), 83 (18), 73 (17).

Anal. Calcd. for $C_{15}H_{12}INO_3$: C, 47.21; H, 3.17. Found: C, 47.08; H, 3.29.

Synthesis of 4,8-Dimethyl-5'-Aminomethyl-4',5'-Dihydropsoralens.

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

Compound **3** (500 mg, 1.40 mmoles) was heated at reflux in dry morpholine (4 ml) for 3 hours. The mixture was evaporated *in vacuo* to remove excess morpholine and the product was taken up in methylene chloride and washed with water. The organic layer was dried and evaporated *in vacuo* to recover tan crystals, 306 mg (70% yield). The product was purified by column chromatography on silica gel with 30% ethyl acetate/70% hexane to give white crystals: mp 159.8-160.9 °C; ^{1}H-nmr (deuteriochloroform): δ 2.17 (s, 3H), 2.27 (s, 3H), 2.40-2.70 (m, 6H), 2.99 (dd, 1H), 3.25 (dd, J_1 = 15.3 Hz, J_2 = 9.2 Hz, 1H), 3.63 (t, J = 4.8 Hz, 4H), 4.87-4.96 (m, 1H), 5.98 (s, 1H), 7.13 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 8.49, 19.00, 33.60, 54.34 (2 carbons), 62.87, 66.93 (2 carbons), 82.8, 107.7, 110.9, 113.5, 117.2, 122.6, 152.8, 153.1, 160.7, 161.6; ms: (EI) m/z (relative intensity) 317 (M^+, 20), 316 (M^+, base) 101 (21), 100 (97), 99 (34), 98 (22), 70 (17).

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.38; H, 6.73; N, 4.34.

4,8-Dimethyl-5'-[*N*,*N*-β-(hydroxyethylamino)methyl]-4',5'-dihydropsoralen (**9**).

Compound **3** (235 mg, 0.660 mmoles) in 3 ml diethanolamine was heated at 80 °C for eight hours. Recovery of pure product was difficult because of the high boiling point of diethanolamine. The reaction mixture was refluxed in methanol and allowed to stand overnight. Crystals were removed by filtration and identified by nmr as 4,8,5'-trimethylpsoralen. Methanol was removed *in vacuo* and the mixture was taken up in chloroform. Unreacted diethanolamine separated as the upper layer and was removed. The chloroform layer was washed with dilute HCl and water to remove residual diethanolamine. Purification by column chromatography using 2% methanol/98% chloroform, yielded pink crystals, decolorized by an ether rinse, which weighed 50 mg (23% yield): ^{1}H-nmr (acetone-d_6): δ 2.19 (s, 3H), 2.40 (s, 3H), 2.79 (t, 4H), 2.91 (t, 2H), 3.08 (dd, 1H), 3.37 (dd, 2H), 3.57 (t, 4H), 5.01-5.09 (m, 1H), 6.04 (s, 1H), 7.40 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 8.7, 19.3, 33.4, 57.6 (2 carbons), 60.0, 60.2 (2 carbons), 83.6, 108.2, 111.1, 114.0, 117.8, 123.1, 153.3, 153.5, 161.2, 162.1.

Anal. Calcd. for $C_{18}H_{23}NO_5 \cdot 2.9H_2O$: C, 63.65; H, 7.02; N, 4.12. Found: C, 63.67; H, 6.91; N, 4.22.

4,8-Dimethyl-5'-(2,6-dimethylmorpholino)methyl-4',5'-dihydropsoralen (**10**).

Compound **3** (250 mg, 0.700 mmoles) in 2 ml 2,6-dimethylmorpholine (a mixture of isomers) was heated at reflux overnight. Excess dimethylmorpholine was removed *in vacuo*. Crystals recovered weighed 142 mg (74% yield). Thin layer chromatography using 5% methanol/ 95% chloroform showed two spots with Rf 0.82 and 0.46. Purification on silica gel column using the same solvent afforded white crystals: mp 167.2-169.0 °C; ^{1}H-nmr (deuteriochloroform): δ 1.17 (d, J_1 = 6.3 Hz, 6H), 1.94 (q, J_1 = 11 Hz, 2H), 2.27 (s, 3H), 2.38 (s, 3H), 2.49 - 2.68 (m, 3H), 2.76 (d, J_1 = 11 Hz, 1H), 2.92 (dd, J_1 = 15.8 Hz, J_2 = 7.3 Hz, 1H), 3.30 (dd, J_1 = 9.1 Hz, J_2 = 6.3, Hz 1H), 3.54 - 3.72 (m, 2H), 4.92 - 5.13 (m, 1H), 6.09 (s, 1H), 7.23 (s, 1H); ^{13}C-nmr (dimethyl sulfoxide-d_6): δ 8.3, 18.6, 19.0 (2 carbons), 32.9, 59.3, 59.7, 61.8, 70.9 (2 carbons), 82.5, 106.0, 109.9, 113.0, 118.4, 123.3, 152.3, 153.9, 160.3, 160.8.

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.82; H, 7.35; N, 4.07.

4,8-Dimethyl-5'-[(*N*,*N*-dimethylamino)methyl]-4',5'-dihydropsoralen Hydroiodide Salt (**11**).

Compound **3** (216 mg, 0.606 mmoles) was added to a Teflon lined metal reactor with dimethylamine (2 ml dimethylamine in methanol, 2 *M* solution). The reactor was flushed with nitrogen then sealed before heating to 95 °C for 3 hours. ^{13}C nmr indicated trimethylpsoralen mixed with the desired 4,8-dimethyl-5'-[(*N*,*N*-dimethylamino)methyl]-4',5'-dihydropsoralen (1:1). Recovered weight was 206 mg. The mixture was purified by refluxing in chloroform to solubilize the trimethylpsoralen, and the 4,8-dimethyl-5'-[(*N*,*N*-dimethylamino)methyl]-4',5'-dihydropsoralen hydroiodide salt was collected by filtration as a white solid; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.22 (s, 3H), 2.39 (s, 3H), 2.5 (s, 6H), 3.02 (dd, J_1 = 16 Hz, J_2 = 7 Hz, 1H), 3.42-3.58 (m, 3H), 3.91-4.13 (m, 1H), 5.30-5.46 (m, 1H), 6.21 (s, 1H), 7.54 (s, 1H); ^{13}C-nmr (dimethyl sulfoxide-d_6): δ 9.6, 18.5, 32.6, 43.9 (2), 60.5, 81.3, 106.6, 110.3, 118.5, 122.3, 123.5, 152.7, 153.6, 153.8, 160.2.

Anal. Calcd. for $C_{16}H_{20}NIO_3$: C, 47.90; H, 5.02; N, 3.49. Found: C, 48.21; H, 5.03; N, 3.33.

4,8-Dimethyl-5'-(*N*-pyridiniummethyl)-4',5'-dihydropsoralen Iodide Salt (**12**).

Compound **3** (200 mg, 0.560 mmoles) was refluxed in 4 ml pyridine overnight. Crystals were collected by suction filtration and washed with ether. The yield was 196 mg (80% yield). Recrystallization from methanol was required to obtain buff yellow crystals: mp 295-300 °C; ^{1}H-nmr (methanol-d_4): δ 2.36 (s, 3H), 2.48 (s, 3H), 3.19 (dd, J_1 = 16.5 Hz, J_2 = 5.5 Hz 1H), 3.57-3.63 (m, 1H), 4.82 (dd, J_1 = 14 Hz, J_2 = 10.3 Hz 1H), 5.04 (d, J_1 = 12.2 Hz, 1H), 5.36-5.44 (m, 1H), 6.19 (s, 1H), 7.51 (s, 1H), 8.21 (t, J_1 = 6.1 Hz, 2H), 8.65 (t, J_1 = 8.5 Hz, 1H), 9.10 (d, J = 6.1 Hz, 2H); ^{13}C-nmr (dimethyl sulfoxide-d_6): δ 8.4, 18.6, 31.8, 63.2, 82.1, 107.0, 110.6, 113.8, 118.7, 122.3, 128.1 (2 carbons), 145.5 (2 carbons), 146.4, 152.4, 153.9, 159.5, 160.2.

Anal. Calcd. for $C_{19}H_{18}INO_3$: C, 52.43; H, 4.17; N, 3.22. Found: C, 52.46; H, 4.31; N, 3.14.

3-Bromo-4,8-dimethyl-5'-(*N*-pyridiniummethyl)-4',5'-dihydropsoralen Iodide Salt (**13**).

Compound **5** (200 mg, 0.460 mmoles) was refluxed in 3 ml pyridine overnight. Crystals were collected by filtration, washed with ether, and recrystallized from ethanol to obtain tan crystals with a weight of 100 mg (57% yield), decomposed above 270 °C: ^{1}H-nmr (methanol-d_4): δ 2.36 (s, 3H), 2.48 (s, 3H), 3.19 (dd, J_1 = 16.5 Hz, J_2 = 5.5 Hz, 1H), 3.57-3.63 (m, 1H), 4.82 (dd, J_1 = 14 Hz, J_2 = 10.3 Hz, 1H), 5.04 (d, J = 12.2 Hz, 1H), 5.36-5.44 (m, 1H), 7.51 (s, 1H), 8.21 (t, J = 6.1 Hz, 2H), 8.65 (t, J = 8.5 Hz, 1H), 9.10 (d, J = 6.1 Hz, 2H).

Anal. Calcd. for $C_{19}H_{17}BrINO_3$: C, 44.39; H, 3.33; N, 2.72. Found: C, 44.39; H, 3.24; N, 2.68.

3-Cyano-4,8-dimethyl-5'-(*N*-pyridiniummethyl)-4',5'-dihydropsoralen Iodide Salt (**14**).

Pyridine (3 ml) was added with **7** (175 mg, 0.458 mmoles) and refluxed for 5 hours. Crystals were collected by filtration and washed with ether. Recrystallization from ethanol gave 168 mg (78% yield) pale orange crystals: mp above 300 °C; ^{1}H-nmr (methanol-d_4): δ 2.21 (s, 3H), 2.70 (s, 3H), 3.29-3.34 (m, 1H), 3.70 (dd, J_1 = 16.3 Hz and J_2 = 9.3 Hz, 1H), 4.92-4.98 (m, 1H), 5.09 (dd, J_1 = 13.7 Hz and J_2 = 2.6 Hz, 1H), 5.43-5.53 (m, 1H), 7.69 (s, 1H), 8.21 (dd, J_1 = 7 Hz and J_2 = 7 Hz, 2H), 8.69 (dd, J = 7 Hz, 1H) 9.10 (d, J = 5.5 Hz, 2H); ^{13}C-nmr (dimethyl sulfoxide-d_6): δ 8.2, 18.4, 31.4, 63.1, 83.0, 96.5, 107.3, 112.5, 114.8, 120.7, 124.1, 128.1 (2 carbons), 145.4 (2 carbons), 146.4, 152.7, 157.4, 162.4, 163.7.

Anal. Calcd. for $C_{20}H_{17}IN_2O_3 \cdot H_2O$: C, 49.75; H, 4.24; N, 5.81. Found: C, 49.75; H, 4.15; N, 5.68.

4,8-Dimethyl-5'-(*N*-4''-methylpyridiniummethyl)-4',5'-dihydropsoralen Iodide Salt (**15**).

Compound **3** (148.5 mg, 0.417 mmoles) was dissolved in 2 ml of anhydrous 4-methylpyridine and the mixture was reacted up to 115-120 °C under inert atmosphere for 2 hours. After cooling to room temperature, the 4-methylpyridine was removed by evaporation under reduced pressure. The crude solid was recrystallized from a mixture of chloroform (70%)/hexane (20%)/methanol (10%), with the assistance of charcoal decolorization, to yield to the pyridinium salt **15** as a yellow solid (175.5 mg, 94% yield); IR (KBr) : 1698 (CO), 3100-3650; ^{1}H nmr (methanol-d_4): δ 2.18 (s, 3H), 2.40 (d, J = 1.1 Hz, 3H), 2.71 (s, 3H), 3.23 (dd, J_1 = 16.5 Hz, J_2 = 6.6 Hz, 1H), 3.65 (dd, J_1 = 16.5 Hz, J_2 = 9.4 Hz, 1H), 4.82 (dd, J_1 = 13.9 Hz, J_2 = 9.3 Hz, 1H), 5.04 (dd, J_1 = 13.9 Hz, J_2 = 1.7 Hz, 1H), 5.36-5.45 (m, 1H), 6.12 (d, J = 0.9 Hz, 1H), 7.49 (s, 1H), 8.01 (d, J = 6.5 Hz, 2H), 8.92 (d, J = 6.5 Hz, 2H). ^{13}C nmr (deuteriochloroform): δ 8.51, 19.13, 22.17, 33.27, 64.47, 83.55, 109.01, 111.55, 115.71, 119.67, 123.72, 129.84 (2 carbons), 145.62 (2 carbons), 154.04, 156.09, 161.14, 162.37, 163.45.

Anal. Calcd for $C_{20}H_{20}NO_3I \cdot H_2O$: C, 49.68; H, 4.96; N, 2.90. Found: C, 49.72; H, 4.43; N, 2.71.

3-Bromo-4,8-dimethyl-5'-(*N*-4''-methylpyridiniummethyl)-4',5'-dihydropsoralen Iodide Salt (**16**).

Compound **16** was prepared in the same way as **15** using compound **5** (136 mg, 0.312 mmoles) in 2.5 ml of 4-methylpyridine. The crude product was recrystallized from chloroform to yield 120 mg (73% yield) of the pyridinium salt **16** as a yellow solid; IR (KBr): 1699 (CO), 3160-365; ^{1}H nmr (methanol-d_4): δ 2.21 (s, 3H), 2.60 (s, 3H), 2.71 (s, 3H), 3.26 (dd, J_1 = 16.5 Hz, J_2 = 5.9 Hz, 1H), 3.67 (dd, J_1 = 16.5 Hz, J_2 = 9.6 Hz, 1H), 4.82-4.87 (m, 1H), 5.02 (dd, J_1 = 13.9 Hz, J_2 = 2.7 Hz, 1H), 5.38-5.46 (m, 1H), 7.57 (s, 1H), 8.02 (d, J = 6.3 Hz, 2H), 8.90 (d, J = 6.3 Hz, 2H); ^{13}C nmr (deuteriochloroform): δ 8.71, 20.17, 22.42, 33.09, 64.01, 83.13, 108.74, 109.26, 114.87, 119.51, 123.79, 129.57 (2 carbons), 145.06 (2 carbons), 151.78, 153.04, 158.46, 160.29, 161.64.

Anal. Calcd for $C_{20}H_{19}BrNO_3I \cdot H_2O$: C, 43.98; H, 3.88; N, 2.56. Found: C, 43.94; H, 3.83; N, 2.41.

3-Cyano-4,8-dimethyl-5'-(*N*-4''-methylpyridiniummethyl)-4',5'-dihydropsoralen Iodide Salt (**17**).

Compound **17** was prepared in the same way as **15** using compound **7** (71 mg, 0.19 mmoles) in 1.5 ml of 4-methylpyridine. The crude product was recrystallized from a mixture of chloroform (90%)/hexane (10%) to yield 82.5 mg (82% yield) of the pyridinium salt **17** as a yellow solid; IR (KBr): 1731 (CO), 2228 (CN), 3150-3640; ^{1}H nmr (methanol-d_4): 2.20 (s, 3H), 2.68 (s, 3H), 2.72 (s, 3H), 3.27-3.33 (m, 1H), 3.69 (dd, J_1 = 16.4 Hz, J_2 = 9.5 Hz, 1H), 4.90 (dd, J_1 = 13.9 Hz, J_2 = 9.5 Hz, 1H), 5.06 (dd, J_1 = 13.9 Hz, J_2 = 2.6 Hz, 1H), 5.45-5.53 (m, 1H), 7.69 (s, 1H), 8.03 (d, J = 6.4 Hz, 2H), 8.92 (d, J = 6.4 Hz, 2H); ^{13}C nmr (deuteriochloroform) δ : 8.51, 19.13, 22.17, 33.27, 64.47, 83.55, 109.01, 111.55, 115.71, 119.67, 123.72, 129.8 (2 carbons), 145.62 (2 carbons), 154.04, 156.09, 161.14, 162.37, 163.45.

Anal. Calcd for $C_{21}H_{19}N_2O_3I \cdot 1.85H_2O$: C, 49.69; H, 4.51; N, 5.52. Found: C, 49.69; H, 4.14; N, 5.31.

Synthesis of Angelicins.

4-Methyl-5'-iodomethyl-4',5'-dihydroangelicin (**18**).

4-Methyl-8-allyl-7-hydroxycoumarin (purchased from Lancaster) (300 mg, 1.38 mmoles) was added to 20 ml methylene chloride and treated to the dropwise addition of tin (IV) chloride (0.759 ml 1 *M* solution in methylene chloride, 0.759 mmoles). Iodine (353 mg, 1.38 mmoles) was dissolved in methylene chloride and was added with stirring continuing overnight. The methylene chloride layer was washed with aqueous bisulfite, brine and water. The solvent was evaporated and 413 mg crystals (88% crude yield) were recovered from the organic layer. Purification on silica gel with 5% methanol/95% chloroform gave white crystals: mp 141.3-141.6°C; ^{1}H (dimethyl sulfoxide-d_6): δ 2.39 (s, 3H), 2.50 (d, J = 2.2 Hz, 2H), 3.01 (dd, J_1 = 15.3 Hz, J_2 = 6 Hz, 1H), 3.62 (dd, J_1 = 15.3 Hz, J_2 = 6 Hz, 1H), 4.98-5.11 (m, 1H), 6.19 (s, 1H), 6.87 (d, J = 8.5 Hz, 1H), 7.59 (d, 8.5 Hz, 1H). ^{13}C (dimethyl sulfoxide-d_6): δ 8.7, 19.3, 33.6, 83.3, 107.0, 111.8, 112.1, 124.8, 126.2, 153.8, 159.9, 160.6, 162.7; ms: (EI) m/z (relative intensity) 343 (M^+, 39), 342 (M^+, base) 215 (26), 115 (12).

Anal. Calcd. for $C_{13}H_{11}IO_3$: C, 45.64; H, 3.24. Found: C, 45.92; H, 3.23.

4-Methyl-5'-pyridiniummethyl-4',5'-dihydroangelicin Iodide Salt (**19**).

Compound **18** (100 mg, 0.292 mmoles) was added to 2 ml dry pyridine and the mixture was heated at reflux for 2 hours. Precipitation formed after 30 minutes. The pyridine was removed by evaporation *in vacuo* and residual pyridine was removed on a vacuum pump overnight. To solubilize the 4,5'-dimethylangelicin that was formed as the major product, 8 ml chloroform was added. Crystals were recovered by filtration and washed with ether. Recrystallization by methanol recovered tan crystals weighing 22 mg (17% yield): ^{1}H-nmr (methanol-d_4): δ 2.44 (s, 3H), 3.70 (dd, J = 16.5, 10 Hz, 1H), 4.90-4.98 (m, 2H), 5.14 (dd, 1H), 5.43-5.57 (m, 1H), 6.16 (s, 1H), 6.84 (d, J = 8.5 Hz, 1H), 7.62 (d, 8.5 Hz, 1H), 8.18 (t, 2H), 8.68 (t, 1H), 9.07 (d, 2H).

Anal. Calcd. for $C_{18}H_{16}INO_3$: C, 51.33; H, 3.83; N, 3.33. Found: C, 51.12; H, 3.89; N, 3.45.

4-Methyl-5'-morpholiummethyl-4',5'-dihydroangelicin (**20**).

Compound **18** (40 mg, 0.12 mmoles) and 2 ml dry morpholine were refluxed for three hours. White precipitation began to form within 30 minutes. The solids were filtered while the solution was still warm and the morpholine layer was evaporated to dryness *in vacuo*. The recovered glassy solid was taken up in chloroform and washed with dilute hydrochloric acid. After evaporation of solvent, solids were taken up in methanol/ether with a drop of water added. After 4 days, crystals formed which were filtered and washed with ether to dry. The recovered weight was 15 mg (43% yield) tan sharp crystals: mp 115-116° C; ^{1}H-nmr (deuteriochloroform): δ 2.30 (s, 3H), 2.52 (s, 4H), 2.68 (dd, J_1 = 13 Hz, J_2 = 8 Hz, 2H), 3.02 (dd, J_1 = 15 Hz, J_2 = 8 Hz, 1H), 3.36 (dd, J_1 = 15 Hz, J_2 = 8 Hz, 1H), 3.66 (s, 4 H), 4.98-5.13 (m, 1H), 6.01 (s, 1H), 6.67 (d, 8.5 Hz,1H), 7.31 (d, 8.5 Hz, 1H); ms: (EI) m/z (relative intensity) 303 (M^+, 3), 302 (M^+, 18) 101 (6), 100 (base), 99 (8).

Anal. Calcd. for $C_{17}H_{19}NO_4$•0.1 H_2O: C, 67.48; H, 6.73; N, 4.63. Found: C, 67.48; H, 6.73; N, 4.37.

Acknowledgements.

This study was supported, in part, by NIH grant ES 03647 and ES 06897.

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