Tetrahedron Vol. 48, No. 20, pp. 4239-4246, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

AN EFFICIENT SYNTHESIS OF FURANOCOUMARINS

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Abstract: An efficient synthesis of linear and angular furanocoumarins has been carried out starting from iodoumbelliferone derivatives. First synthesis of 6-iodoumbelliferone is described. The average yields are higher than those reported before.

(*Received in UK* 30 *March* 1992)

Furanocoumarins are natural products showing a wide range of biological properties, the most prominent of which are the photobiological effects that can exert upon irradiation with long-wavelength UV light. Thus, many furanocoumarins are potent photosensitizers of human skin with valuable applications in medicine, for the treatment of skin deseases.[1,2] They are also known to be phototoxic to insects, fungi, viruses and bacteria.[3-6] Great attention has been paid to the molecular bases of these properties, specially to photoreactions of furanocoumarins with DNA and RNA chains, and the derived carcinogenic and mutagenic effects.[1,6,7]

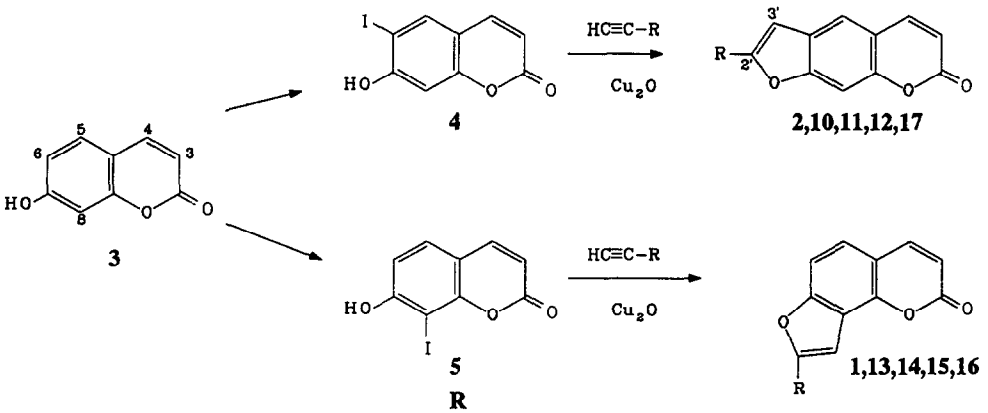
Synthesis of the furan ring of these compounds has usually implied several-step sequences and moderate yields. Thus, the most common synthetic route to angular furanocoumarins, as angelicin (**1**), involves the regioselective Claisen rearrangement on C-8 of 7-allyloxycoumarin to yield 8-allylumbelliferone, followed by oxidation and cyclization.[8]

Linear furanocoumarins, as psoralen (**2**), have been usually prepared through the same oxidation-cyclization sequence, from the corresponding 6-allyl-7-hydroxycoumarin. This has been obtained by Claisen rearrangement of 7-allyloxycoumarin, but blocking the C-8 with iodine.[9] It was also less efficiently prepared from the convenient 2-methoxy-4-hydroxybenzaldehyde, by O-allylation, rearrangement and pyrone ring formation.[10]

Total synthesis of psoralen (**2**) and angelicin (**1**) have been recently achieved, via an intramolecular Diels-Alder reaction[11] and by benzannulation reaction of carbene complexes with acetylenes,[12] respectively.

The relevant biological properties of furanocoumarins and the moderate yields in which they are obtained prompted us to work on alternative synthetic routes to this kind of compound.

Based on a recently reported synthesis of benzofurans,[13] we devised an one-step formation of the furan ring of furanocoumarins, by coupling of an acetylenic reagent with an *o*-iodohydroxycoumarin (scheme I). The key to the success of our synthesis was to prepare 6-iodoumbelliferone (**4**) in high yields. Because iodination of umbelliferone (**3**) under normal conditions yields regioselectively the C-8 isomer (**5**), a different iodination method had to be used. 6-iodoumbelliferone (**4**) was prepared from **3** through the route outlined in scheme II.



	R	
2	H	**1**
10	$(CH_3)_2(OH)C$-	**13**
11	$CH_2=C(CH_3)$-	**14**
12	$(CH_3)_2(NH_2)C$-	**15**
17	$CH_3CH_2O_2C$-	**16**

Scheme I

The strategy implies the coumarin lactone ring opening in order to modify the regioselectivity above mentioned as proposed by L.M. Harwood[14]. Thus, after protection of the hydroxyl group of **3** by methylation, the resulting methyl ether **6** was refluxed in dry methanol with an excess of freshly prepared MeONa. After neutralization and extraction **7** was obtained in almost quantitative yield. It is worth noting that rigorously anhydrous conditions are required to achieve this latter reaction.

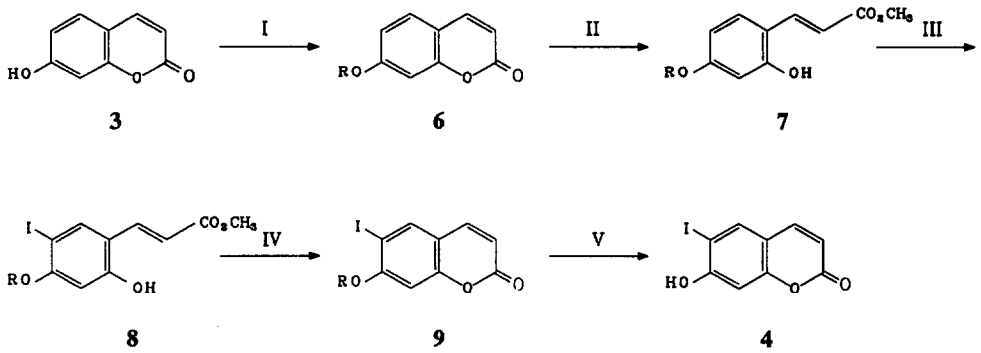
A convenient iodination of the cumarate ester **7** was carried out after investigating several conditions, by dropwise addition of I_2 dissolved in aq. KI to a solution of **7** in dioxane-NH_4OH. Work-up and purification of the mixture afforded **8** (59%) and **9** (12%). To relactonize **8** it was heated at 190°C in diphenyl ether, yielding **9** (80%).

Based on the well known efficiency of Lewis acids in the cleavage of ethers,[15] **9** was treated with an excess of BBr_3 in CH_2Cl_2 yielding 6-iodoumbelliferone (**4**) in 89% yield.

Similar results were obtained using a benzylic group to protect the hydroxyl on C-7 (scheme II, R=$PhCH_2$

The required starting material for angular furanocoumarins, 8-iodoumbelliferone (**5**) was readly available (82%) by iodination of umbelliferone (**3**).

Following the sequence of scheme I, the linear furanocoumarin 2'-hydroxyisopropylpsoralen (**10**) was prepared in 97% yield by treatment of **4** with 2-methyl-3-butyn-2-ol and cuprous oxide in refluxing pyridine. Similarly, by coupling of **4** with 2-methyl-1-buten-3-yne and 2-methyl-3-butyn-2-ylamine the coumarins arnocoumarin[16] (**11**) and prangosine[17] (**12**) were obtained in 89% and 86% yields, respectively.



$R=CH_3$

I) MeI, K_2CO_3, acetone; II)MeONa/MeOH; III)I_2/NH_4OH; IV)Ph_2O; V)BBr_3/CH_2Cl_2

Scheme II

The angular furanocoumarins oroselol[18-20] (**13**), oroselone [20] (**14**) and **15** were prepared (94%, 96% and 88% yields resp.) by treatment of **5** with the corresponding alkyne reagent and Cu_2O in refluxing pyridine.

The isopropenylfuranocoumarins **11** and **14** were also obtained through the corresponding alcohols **10** and **13**, by treatment of these with HCl in methanol.

Now that the efficiency of the route to isopropylfuranocoumarins was demonstrated, we tried to obtain the unsubstituted furanocoumarins **1** and **2**. Nevertheless, attempts to obtain angelicin (**1**) by coupling of **5** with acetylene were unsuccessful. When trimethylsilylacetylene instead of acetylene was used, **1** was obtained but only in 25% yield. These results seem to be a consequence of the instability of these acetylenic reagents in the reaction mixture, which in these cases turns to a dark gum. As mechanisms of cuprous oxide reactions are not yet clear the trivial explanation of a radical polymerization of the acetylenic reagent promoted by Cu_2O can not be ruled out.[21]

Investigating alternative alkyne reagents, **16** was prepared by reaction of **5** with ethyl propiolate and Cu_2O in DMF (77% yield). Alkaline hydrolysis of **16** and subsequent decarboxylation by treatment with copper powder in quinoline[22] yielded angelicin (**1**) (78%).

Treatment of **4** with ethyl propiolate and Cu_2O in DMF yielded **17** (76%), which after hydrolysis and decarboxylation in the same conditions above described, yielded psoralen (**2**) (81%).

Direct conversion, both of **16** in **1** and of **17** in **2**, was also achieved by treatment with copper powder in quinoline, although better overall yields are obtained through the two steps sequence.

Experimental

7-Methoxycoumarin (6): K_2CO_3 (2.0 g, 14.5 mmol) and MeI (1.5 ml, 24.1 mmol) were added to a solution of umbelliferone (**3**) (2.0 g, 12.3 mmol) in acetone (100 ml) and the mixture was refluxed for 5 h. After filtration and dilution with EtOAc, the resulting solution was washed with saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Evaporation afforded a crystalline solid which was purified by CC (hexane:EtOAc 7:3) yielding **6** (2.1 g, 97%): mp 115-116° C (hexane/EtOAc); **IR** (film): 1701, 1608, 1395, 1348, 1280, 1122, 1022 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$: 324, 204 nm. **^{1}H NMR** ($CDCl_3$) ∂ 7.63 (d, 1H, J=9.4 Hz, H-4), 7.37 (d, 1H, J=8.5 Hz, H-5), 6.84 (dd, 1H, J=8.5 and J=2.6 Hz, H-6), 6.80 (d, 1H, J=2.6 Hz, H-8), 6.24 (d, 1H, J=9.4 Hz, H-3), 3.87 (s, 3H, $-OCH_3$); **EIMS** (70 eV) *m/z* 176 (87), 148 (73), 133 (100), 105 (14), 91 (6), 77 (30).

Methyl 4-methoxy-*o*-coumarate (7): 20 ml of a solution of freshly prepared NaOMe (made from Na (1.0 g) and magnesium dried methanol (25 ml)) were added to a suspension of **6** (1.0 g, 5.7 mmol) in 15 ml of dry methanol under N_2, and the mixture was refluxed for 5 h. After cooling and neutralization with 2 N HCl the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated to yield **7** (1.1 g, 93%): mp 140-142°C (hexane/EtOAc); **IR** (film) 3321, 1671, 1604, 1435, 1323, 1279, 1033 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$ 330, 293, 240, 219 nm. **^{1}H NMR** (acetone-d_6) ∂ 7.95 (d, 1H, J=16.1 Hz, H-4); 7.55 (d, 1H, J=8.5 Hz, H-5); 6.54-6.51 (m, 2H, H-6 y H-8); 6.50 (d, 1H, J=16.1 Hz, H-3); 3.80 (s, 3H, $ArOCH_3$); 3.72 (s, 3H, $-CO_2CH_3$). **EIMS** (70 eV) *m/z* 208 (45), 177 (48), 176 (78), 149 (13), 148 (100), 133 (73), 121 (30), 77 (20).

Methyl 5-iodo-4-methoxy-*o*-coumarate (8): 12.5 ml of aqueous NH_4OH (20%) were added to a solution of **7** (0.6 g, 2.9 mmol) in dioxane (5 ml). Then a solution of iodine (0.79 g, 3.1 mmol) in 25 ml of aqueous KI (5% w/v) was added dropwise, with stirring and cooling in an iced water bath. After maintaining the agitation for 1 h the mixture was slightly acidified with 2.5 N H_2SO_4 and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Evaporation afforded a solid residue which after CC (hexane:EtOAc 8:2) yielded (i) an inseparable mixture 1:1 (226 mg) of **9** and **methyl 3-iodo-4-methoxy-*o*-coumarate. 9** (103 mg, 12% from **7**) was easily isolated converting methyl 3-iodo-4-methoxycoumarate into 8-iodo-7-methoxycoumarin by heating the mixture in diphenyl ether and purification in the same conditions described below; (ii) **8** (565 mg, 59%): mp 177-179° C (EtOAc); **IR** (film) 3322, 2948, 1670, 1620, 1593, 1435, 1392, 1305, 1271, 1205, 1168, 1042 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$ 339, 287, 232 nm; **^{1}HNMR** (acetone-d_6) ∂ 8.00 (s, 1H, H-5), 7.85 (d, 1H, J=16.2 Hz, H-4), 6.63 (s, 1H, H-8), 6.55 (d, 1H, J=16.2 Hz, H-3), 3.86 (s, 3H, Ar-OCH_3), 3.73 (s, 3H, $-CO_2CH_3$); **EIMS** (70 eV) *m/z* 334 (5), 303 (5), 259 (34), 231 (5), 176 (7), 160 (11), 148 (24), 133 (47), 119 (22), 105 (28), 89 (100).

6-Iodo-7-methoxycoumarin (9): a mixture of **8** (0.4 g, 1.2 mmol) and diphenyl ether (8 ml) was heated under N_2 at 195°C for 4 h. After cooling the solution was filtered through a silicagel column eluting with hexane until diphenyl ether was removed and then with hexane:EtOAc 9:1 to recover the desired product **9** (290 mg, 80%): mp 177-179°C (AcOEt); **IR** (film) 2922, 2854, 1730, 1593, 1367, 1260, 1213, 1143, 1033 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$ 330, 297, 236, 204 nm. **^{1}H NMR** ($CDCl_3$) ∂ 7.89 (s, 1H, H-5), 7.58 (d, 1H, J=9.5 Hz, H-4), 6.77 (s, 1H, H-8), 6.28 (d, 1H, J=9.5 Hz, H-3), 3.96 (s, 3H, $-OCH_3$). **EIMS** (70 eV) *m/z* 302 (100), 274 (34), 259 (33), 160 (4), 132 (7), 104 (4).

6-Iodoumbelliferone (4): a solution of **9** (260 mg, 0.86 mmol) in dry CH_2Cl_2 (15 ml) under N_2 was cooled at -22°C (CCl_4/N_2), and boron tribromide (0.3 ml, 3 mmol) was added. After stirring at -22°C for 2 h, the reaction mixture was allowed to warm up to room temperature and stirred for 36 h. Then it was quenched with ice cold water and diluted with EtOAc. The phases were separated and the aqueous layer was discarded. The organic layer was washed with saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Evaporation and purification by CC (hexane:EtOAc 8:2) yielded **4** (220 mg, 89%): mp 237-239°C (AcOEt); **IR** (film) 3167, 2925, 1680, 1606, 1385, 1228, 1150 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$ 334, 301, 234, 206 nm; **^{1}H NMR** (acetone-d_6) ∂ 8.07 (s, 1H, H-5), 7.88 (d, 1H, J=9.6 Hz, H-4), 6.87 (s, 1H, H-8), 6.22 (d, 1H, J=9.6 Hz, H-3). **EIMS** (70 eV) *m/z* 288 (100), 260 (51), 133 (16), 127 (3), 105 (19), 77 (14).

8-Iodoumbelliferone (5): was prepared as described previously.[22] Spectrocopic data agreed with those found in the literature.[23]

Isopropylfuranocoumarins (10 to 15), general procedure: the suitable alkyne reagent (0.8 mmol) and a solution of *o*-iodocoumarin (0.43 mmol) in dry pyridine (2 ml) were added to a suspension of Cu_2O (0.35 mmol) in dry pyridine (1 ml) under N_2, and the mixture was refluxed for 2 h. Work up was performed as follows: (i) In the synthesis of **10, 11, 13** and **14** the reaction mixture was filtered over a little silicagel column and diluted with EtOAc. The resulting solution was washed with 1 N HCl, saturated $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. After evaporation the crude solid obtained was purified by CC (hexane:EtOAc from 8:2 to 6:4) to obtain the desired pure coumarin; (ii) In the synthesis of **12** and **15** the reaction mixture was filtered through a silicagel column eluting with EtOAc until pyridine was removed, and then with EtOAc:MeOH 9:1 to collect the desired pure coumarin.

2'-(2-Hydroxyisopropyl)psoralen (10): reaction of **4** with 2-methyl-3-butin-2-ol yielded **10** (103 mg, 97%): mp 142-145°C (AcOEt); **IR** (film) 3434, 2986, 2938, 1721, 1626, 1570, 1446, 1386, 1287, 1127, 1081 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$ 330, 292, 250, 204 nm; **^{1}H NMR** ($CDCl_3$) ∂ 7.77 (d, 1H, J=9.6 Hz, H-4), 7.58 (s, 1H, H-5), 7.40 (s, 1H, H-8), 6.63 (s, 1H, H-3'), 6.36 (d, 1H, J=9.6 Hz, H-3); **EIMS** (70 eV) *m/z* 244 (23), 229 (100),

226 (18), 187 (17), 115 (8).

Arnocoumarin (11): reaction of **4** with 3-methyl-3-buten-1-yne yielded **11** (87 mg, 89%). Melting point and spectroscopic data agreed with those previously reported.[16]

Prangosine (12): reaction of **4** with 2-methyl-3-butyn-2-ylamine yielded **12** (91 mg, 86%): mp 131-132°C (AcOEt); **IR** (film) 3300, 1708, 1568 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$ 292, 249, 204 nm; **^{1}H NMR** (methanol-d_4) ∂ 8.00 (d, 1H, J=9.5 Hz, H-4), 7.75 (s, 1H, H-5), 7.43 (s, 1H, H-8), 6.70 (s, 1H, H-3'), 6.33 (d, 1H, J=9.5 Hz, H-3), 1.56 (s, 6H, -C(CH_3)$_2$); **EIMS** (70 eV) *m/z* 243 (8), 228 (100), 227 (17), 226 (55), 198 (27), 187 (3).

Oroselol (13): reaction of **5** with 2-methyl-3-butin-2-ol yielded **13** (100 mg, 94%): mp 149-151°C (hexane:EtOAc); (Lit.[20] 155-158°). Spectroscopic data agreed with those previously reported.[18-20]

Oroselone (14): reaction of **5** with 3-methyl-3-buten-1-yne yielded **14** (94 mg, 96%). mp 164-166°C (hexane:EtOAc); (Lit.[20] 178-180°). Spectroscopic data agreed with those previously reported.[20]

2'-(2-Aminoisopropyl)angelicin (15): reaction of **5** (0.17 mmol) and 2-methyl-3-butyn-2-ylamine (0.32 mmol) yielded **15** (37 mg, 88%): mp 143-144°C (MeOH); **IR** (film) 3373, 3315, 2984, 2939, 1706, 1608, 1442, 1270, 1118 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$ 300, 250, 204 nm. **^{1}H NMR** (methanol-d_4) ∂ 8.01 (d, 1H, J=9.5 Hz, H-4), 7.46 (ABq, 2H, H-5 and H-6), 6.92 (s, 1H, H-3'), 6.36 (d, 1H, J=9.5 Hz, H-3), 1.58 (s, 6H, -(CH_3)$_2$); **EIMS** (70eV) *m/z* 243 (7), 228 (100), 227 (4), 226 (10), 198 (5), 187 (3).

Oroselone (14) from oroselol (13): to a solution of **13** (50 mg, 0.21 mmol) in MeOH (2 ml) conc. HCl (0.7 ml) was added and the mixture was heated at 95°C for 30 min. After adding iced cold water the mixture was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Evaporation and purification by CC (hexane:EtOAc 8:2) afforded **14** (33 mg, 71%).

Arnocoumarin (11) from 10: to a solution of **10** (18 mg, 0.074 mmol) in MeOH (2 ml) conc. HCl (0.7 ml) was added and the mixture was heated at 95°C for 24 h. Work up of the reaction mixture as described above afforded a solid which after CC (CH_2Cl_2: MeOH 97.5:2.5) yielded: (i) **arnocoumarin (11)** (8 mg, 48%) and **2'-(2-Methoxyisopropyl)psoralen** (5 mg, 26%): mp 161-164°C (hexane:EtOAc); **IR** (film) 2984, 2932, 1722, 1627, 1572, 1446, 1378, 1285, 1173, 1124, 1072 cm^{-1}; **UV** (MeOH) $\lambda_{máx}$ 333, 291, 250, 204 nm; **^{1}H NMR** ($CDCl_3$) ∂ 7.79 (d, 1H, J=9.6 Hz, H-4), 7.61 (s, 1H, H-5), 7.46 (s, 1H, H-8), 6.67 (s, 1H, H-3'), 6.38 (d, 1H, J=9.6 Hz, H-3), 3.17 (s, 3H, -OCH_3), 1.64 (s, 6H, -C(CH_3)$_2$); **EIMS** (70 eV) *m/z* 258 (32), 243 (100), 227 (85), 213 (17), 199 (12), 185 (10), 171 (7).

2'-(Ethoxycarbonyl)angelicin (16): to Cu_2O (120 mg, 0.84 mmol) suspended in dry DMF (1 ml) under N_2 were added ethyl propiolate (0.25 ml, 2.5 mmol) and a solution of **5** (300 mg, 1.04 mmol) in dry DMF (7 ml). The mixture was heated at 110°C for 24 h. Work up as described in the synthesis of **10**, **11**, **13** and **14**, and purification by CC (CH_2Cl_2: EtOAc 99.5:0.5) yielded **16** (208 mg, 77%): mp 211-213°C (hexane:EtOAc); **IR** (film) 1735, 1611, 1289, 1208, 1107 cm^{-1}; **UV** (MeOH) λ_{max} 207, 220, 275 nm; **^{1}H NMR** ($CDCl_3$) ∂ 7.84 (s, 1H, H-3'), 7.83 (d, 1H, J=9.6 Hz, H-4), 7.54 (ABq, 2H, H-5 and H-6), 6.46 (d, 1H, J=9.6 Hz, H-3), 4.49 (q, 2H, J=14.3 and 7.2 Hz, $-CH_2-$), 1.47 (t, 3H, J=7.2, $-CH_3$); **EIMS** (70 eV) *m/z* 258 (100), 230 (29), 213 (28), 202 (55), 186 (13), 158 (12), 157 (12), 129 (11), 101 (10).

Angelicin (1): 5 ml of aqueous NaOH (20% w/v) were added to **16** (50 mg, 0.19 mmol) and the mixture was refluxed for 2 h. After cooling and acidification with conc. HCl, the mixture was vigorously stirred for 1 h and the precipitate collected by filtration. The crude solid obtained was solved in quinoline (2 ml), copper powder (5 mg, 0.08 mmol) was added and the mixture was heated under N_2 at 210°C for 1 h. After cooling, cold 1 N HCl was added and the mixture extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. Evaporation and purification by CC (CH_2Cl_2:EtOAc 99.9:0.1) yielded **1** (28 mg, 78%) identical in all respects with a natural sample of angelicin available in our laboratories.[25]

2'-(Ethoxycarbonyl)psoralen (17): to Cu_2O (100 mg, 0.70 mmol) suspended in dry DMF (1 ml) under N_2 were added ethyl propiolate (0.15 ml, 1.5 mmol) and a solution of **4** (300 mg, 1.04 mmol) in dry DMF (5 ml). The mixture was heated at 110°C for 48 h. Work up as described in the synthesis of **10**, **11**, **13** and **14**, and purification by CC (CH_2Cl_2: EtOAc 99.5:0.5) yielded **17** (170 mg, 76%): mp 217-218°C (hexane:EtOAc); **IR** (film) 1716, 1624, 1566, 1202, 1137; **UV** (MeOH) λ_{max} 215, 270, 335 nm; **^{1}H NMR** ($CDCl_3$) ∂ 7.80 (s, 1H, H-3'), 7.80 (d, 1H, J=9.6 Hz, H-4), 7.57 (s, 1H, H-5), 7.55 (s, 1H, H-8), 6.42 (d, 1H, J=9.6 Hz, H-3), 4.46 (q, 2H, J=14.3 and 7.1, $-CH_2-$), 1.44 (t, 3H, J=7.1 Hz, $-CH_3$); **EIMS** (70 eV) *m/z* 258 (100), 230 (27), 213 (20), 202 (35), 186 (12), 158 (8), 157 (8), 129 (8), 101 (4).

Psoralen (2): **17** (62 mg, 0.24 mmol) was subjected to alkaline hydrolysis and treatment with copper powder in quinoline as previously described for **16** yielding **2** (36 mg, 81%) identical in all respects with a natural sample of psoralen available in our laboratories.[26]

Acknowledgements

This research was supported by a grant from DGICYT (PB88-0570) and a cooperative project between Spain and Great Britain (Acciones integradas Hispano-Británicas, HB-225).

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