Efficient Total Synthesis of 5-Methoxypsoralen

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Abstract: A rapid and efficient synthesis of 5-methoxypsoralen, furocoumarin commonly used in dermatology for the treatment by PUVA therapy of skin diseases, is described using cheap and easily available starting materials. An alternative method to synthesize 7-(2-oxoethoxy)coumarin, the key step to generate the furan ring, is suggested.

Key words: furocoumarin, psoralen, medicinal chemistry, total synthesis, furan ring

Bergapten or 5-methoxypsoralen (5-MOP, **1**) is a naturally occurring furocoumarin isolated from *citrus bergamia* oil by Kalbrunner in 1834 (Figure 1).[1]

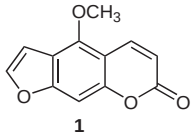
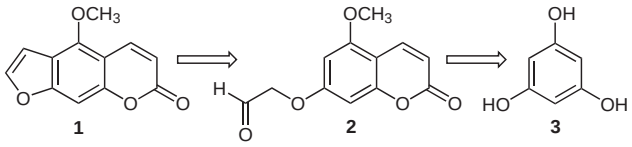


Figure 1

Psoralen and its derivatives are commonly used in dermatology for the treatment by PUVA therapy (psoralen + ultraviolet light A) of skin diseases such as vitiligo and psoriasis.[2] Among furocoumarins utilized at present in therapy, 5-MOP was reported to have several advantages compared with 8-MOP, especially for reducing the phototoxic response.[3] Moreover, 5-MOP has a chemopreventive role in the human hepatocellular carcinoma cell line[4] and show inhibitory activity of monoamine oxidase.[5]

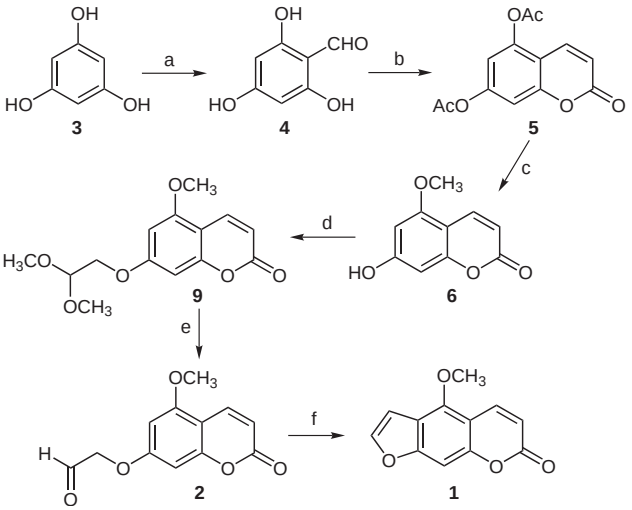
Several research groups have reported synthetic pathways for psoralens but most of these methods result in low yield or numerous steps and no really satisfactory synthesis of 5-methoxypsoralen has yet been reported.[6] MacLeod[7] and recently Chimichi[8] described a convenient methodology to obtain linear furanocoumarins by alkaline treatment of 7-(2-oxoethoxy)coumarin. On this basis, the development of a simple and efficient synthesis of 5-methoxypsoralen was undertaken. In addition to this result, we are reporting here a method easily accessible to synthesize 5-methoxy-7-(2-oxoethoxy)coumarin (**2**) which was the intermediate



Scheme 1 Retrosynthetic analysis

of the key step of the formation of the furan ring (Scheme 1).

To begin with, 2,4,6-trihydroxybenzaldehyde (**4**) was obtained by a Wilsmeier formylation of phloroglucinol (**3**) with $POCl_3$ in DMF in a 84% yield (Scheme 2). In Perkin's classical reaction, compound **4** was heated with acetic anhydride and sodium acetate to generate 5,7-diacetoxycoumarin (**5**) in a quantitative yield.[9] According to the similar reactivity of the 5- and 7-hydroxy groups, the partial alkylation of 5,7-dihydroxycoumarin was difficult. Accordingly, methylation of the per-O-acetylated compound **5**, followed by hydrolysis, was effected to obtain 7-hydroxy-5-methoxycoumarin (**6**) as the major product (61%).



Scheme 2 *Reagents and conditions*: (a) $POCl_3$ (1.4 equiv), DMF, 0 °C to r.t., 1 h, 84%; (b) NaOAc, Ac_2O, 190 °C, 14 h, 100%; (c) CH_3I (4 equiv), K_2CO_3, acetone, reflux, 15 h, then 10% aq NaOH, MeOH, reflux, 5 min, 61%; (d) $C_4H_9BrO_2$ (2 equiv), NaH (1.5 equiv), DMF, reflux, 10 h, 71%; (e) TFA, H_2O–CH_2Cl_2, 0 °C to 10 °C, 48 h, 90%; (f) NaOH, reflux, 4 h, 40%.

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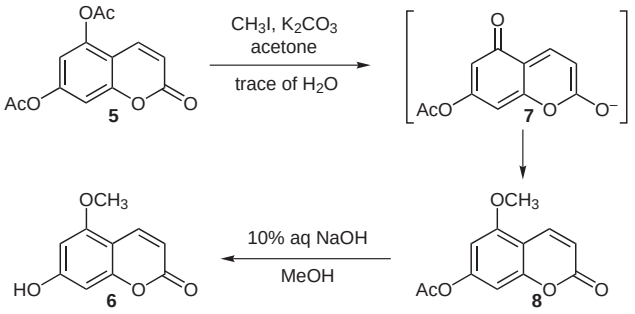
Under normal methylation conditions (CH_3I, K_2CO_3, acetone, reflux), we think that traces of water in the reaction medium may hydrolyze chemoselectively the 5-acetyl group leading to the intermediate **7** stabilized by conjugating effect of the pyrone ring (Scheme 3), whose methylation gave the product **8**. Without further purification, product **8** was deacetylated (10% aq NaOH, MeOH, reflux) to provide the desired product **6**.



Scheme 3

In order to generate the furan ring of 5-MOP, 5-methoxy-7-(2-oxoethoxy)coumarin (**2**) was synthesized by a two-step synthesis (Scheme 2). Coumpound **2** resulted from O-alkylation of the 7-hydroxy group of compound **6** with bromoacetaldehyde dimethyl acetal using sodium hydride as a base[10] followed by hydrolysis of the acetal functionality of **9** to the corresponding aldehyde with trifluoroacetic acid in a biphasic system.[11]

Finally, 5-MOP (**1**) was obtained by the cyclization of the aldehydic compound **2** to form the furan ring according to the procedure described by Chimichi.[8] Repeated modifications of this general procedure for synthesis of the psoralens did not allow us to obtain a yield better than 40% of the linear furocoumarin **1** due to the increase in angular furocoumarin's proportion which was a result of a thermodynamically controlled process faced with the 5-methoxy group.

In conclusion, this work provides an interesting synthetic route to bergapten with few and easily workable steps and an overall yield comparable with the one of the total synthesis of bergapten via a photochemical aromatic annulation strategy described by Danheiser and Trova.[6d] This study allows us to suggest the possibility of a chemoselective O-alkylation of numerous diphenolic coumarins based on conjugating effect of the pyrone ring. This result allows us to continue with the synthesis of other derivatives and biological evaluation of all the resulting linear furocoumarins with the intention of reducing undesirable symptoms for patients after PUVA therapy.

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