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A Concise Access to a New Class of Selective Anti-Inflammatory Steroid Derivatives

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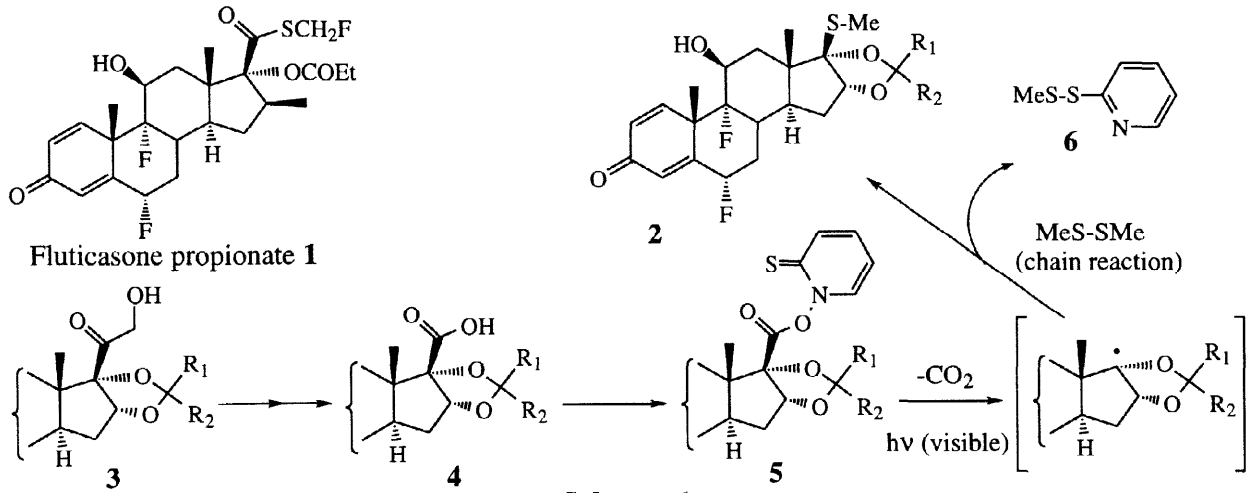
Abstract : The 17β-thiomethyl-16α,17α-ketal motif of a new class of selective anti-inflammatory androstane derivatives useful in the treatment of asthma is readily constructed by a new radical degradation of the corticosteroid side chain.

A number of potent anti-inflammatory glucocorticoids such as beclomethasone dipropionate, budesonide or, most recently, fluticasone propionate **1**, have been used in the alleviating the obstruction of airflow and other symptoms in patients suffering from asthma.[1] Unfortunately, the topical application of corticosteroids with high systemic bioavailability is associated with various undesirable side effects (Cushing's syndrome, bone erosion, alteration of circulating hormone levels, etc.). An important contribution to circumventing these difficulties has now emerged from a study in Rhône-Poulenc Rorer resulting in a new class of glucocorticoid derivatives, represented by **2**, where the functionality adorning ring D not only preserves a high potency in terms of anti-inflammatory activity but, being rapidly biodegraded by mono-oxygenases in the liver into inactive product, reduces significantly many of the adverse complications mentioned above.[2]



Scheme 1

Modification of the side chain of commercially available steroids appears to be the simplest entry into this family of promising antiasthma substances. The published synthesis[2] relies on a Barton decarboxylative chalcogenation[3] reaction as outlined in scheme 1. Thus, the radical produced following the decarboxylative step is captured with a vast excess of dimethyl disulfide to introduce the thiomethyl group with the desired stereochemistry, since the homolytic substitution has to occur from the least hindered β-face. Such an approach lacks a certain flexibility in that the substituent on the sulfur cannot be easily modified without

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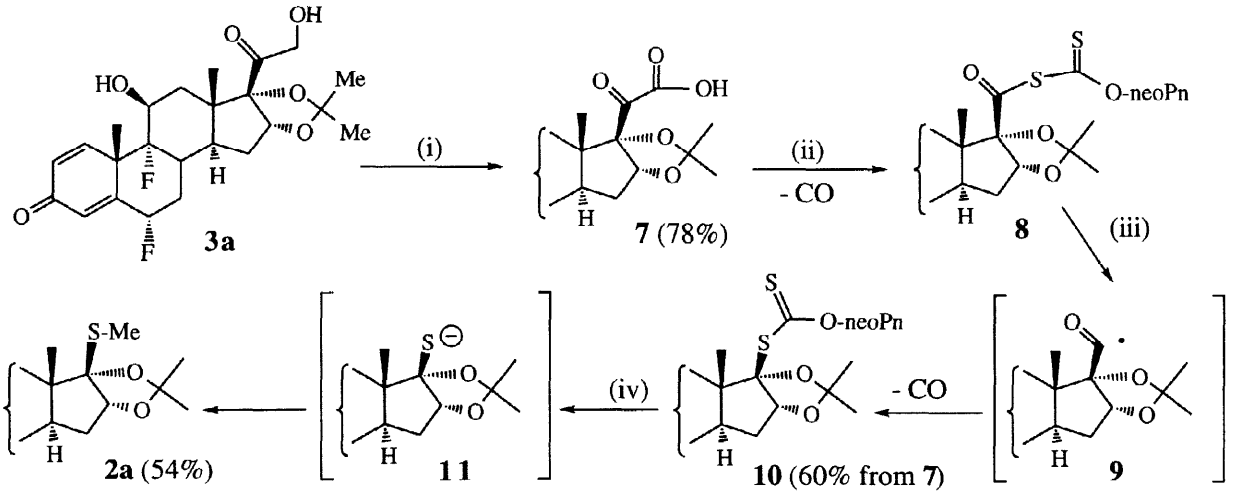
repetition of the whole sequence with the appropriate disulfide, and only a few are commercially available. In scale-up, the need to manipulate large quantities of the evil-smelling dimethyl disulfide as well as the practical problem of separating the unwanted unsymmetrical disulfide co-product **6** has to be addressed.



Reagents: (i) $Cu(OAc)_2$ / O_2 / MeOH; $NaClO_2$ / KH_2PO_4 / THF/t-BuOH / H_2O. (ii) $(COCl)_2$ / DMF / CH_2Cl_2; sodium O-neopentyl xanthate / acetone. (iii) hv (W; 500W) /toluene / reflux; (iv) NaOH / MeOH; MeI.

Scheme 2

We have shown over the past few years that xanthates constitute a convenient and cheap source of a variety of alkyl, acyl, alkoxycarbonyl, and other types of radicals that can be incorporated in a chain process.[4] In the case of acyl radicals, derived from S-acyl xanthates, our work confirms and extends an earlier observation by Barton and his colleagues,[5] whereby aliphatic S-acyl xanthates were found to undergo a radical decarbonylation upon irradiation with visible light.

Commercially available fluocinolone acetonide **3a** was first oxidised to the 21-aldehyde by exposure to oxygen in the presence of cupric acetate in methanol, and then to the 21-carboxylic acid **7** by further oxidation with sodium chlorite in buffered THF / t-butanol, in an overall yield of 78%. The carboxylic acid was converted by the action of oxalyl chloride to the nor-acid chloride by loss of one molecule of carbon monoxide.[6] This was not purified but treated with sodium O-neopentyl xanthate to give the desired acyl xanthate **8**. Irradiation with visible light (or initiation with lauroyl peroxide) of a refluxing toluene solution resulted in a smooth double decarbonylation of the intermediate radical **9** to give finally the desired xanthate **10** in 60% overall yield from carboxylic acid **7**. It finally remained to transform the xanthate group into a methyl sulfide group, and this was accomplished by saponification to the thiolate **11** and alkylation in one pot with methyl iodide. Compound **2a** was thus obtained in 54% yield from xanthate **10**.

We have thus established a viable and cheap route to this family of important anti-inflammatory steroids. None of the yields has been optimised; moreover, the fact that the penultimate intermediate is a thiolate should allow for an easy access to a variety of analogues by simply replacing methyl iodide with the plethora of other, commercially available, alkylating agents. Finally, this approach has served as a test for confirming the feasibility of a radical decarbonylation on a fragile steroid side chain. This process is certainly of more general synthetic utility.

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6. See for example: Tietze, L. F.; Schneider, C.; Pretor, M. *Synthesis* **1993**, 1079-1080.