Formylation of bile acid oxo derivatives - synthesis of new glucocorticoid precursors

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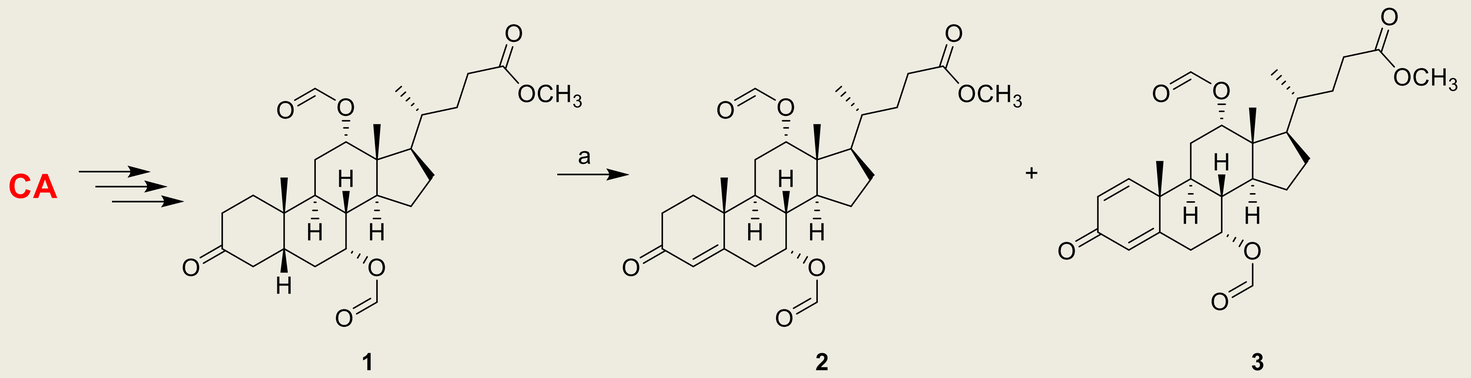
Introduction

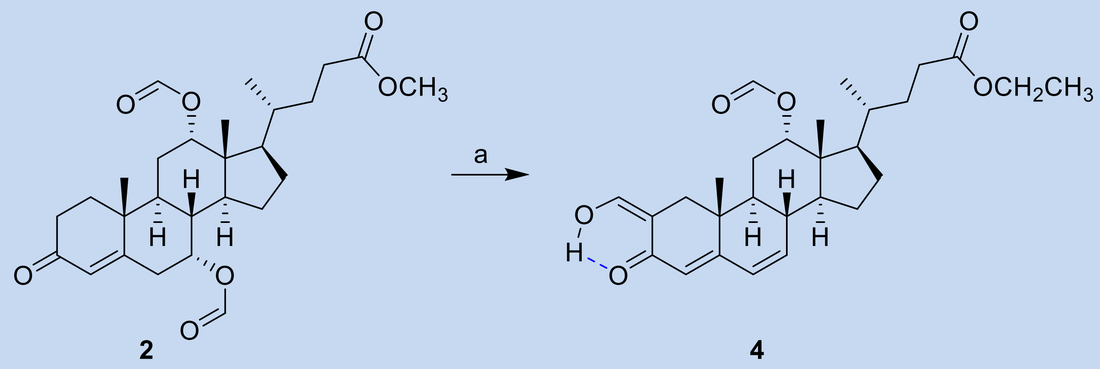
Glucocorticoids (GCs) are essential drugs for treating inflammatory diseases and immune system pathological conditions. Dexamethasone, a potent synthetic GC was the first successful treatment for severe COVID-19 patients. However, serious side effects, e.g., osteoporosis, Cushing's syndrome, high blood pressure, etc., limit the long-term and systematic use of these drugs. There is no alternative for GCs, and the search for GCs with better pharmacological properties is an urgent need. It is known that the carbonyl group at the C-3 steroid position is needed for recognition of some steroid hormones by an appropriate enzyme. This is also the case for GC; GCs have 4-en-3-one or 1,4-dien-3-one systems and by binding to GC receptor they mediate their physiological effect. Recent studies have shown that the ligand-binding domain of the GC receptor can accommodate *N*-phenyl pyrazole moieties attached to A steroid ring. A common way to fuse heterocycle on the steroid skeleton is the condensation of formyl, dicarbonyl steroid derivative with substituted hydrazines.

Results

Easily accessible and appropriately functionalized, cholic acid (CA) is promising starting compound for the development of potentially new GC. In a series of reactions CA is converted in ester-protected carbonyl compound **1**, which is upon treatment with IBX yielded enone **2** and dienone **3**.

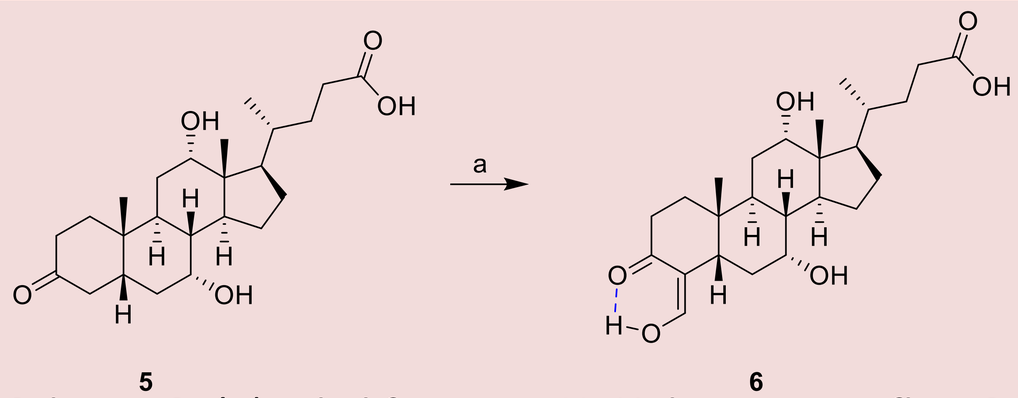


Scheme 1. (a) IBX, TFA, DMSO, 40 °C, 22 h.



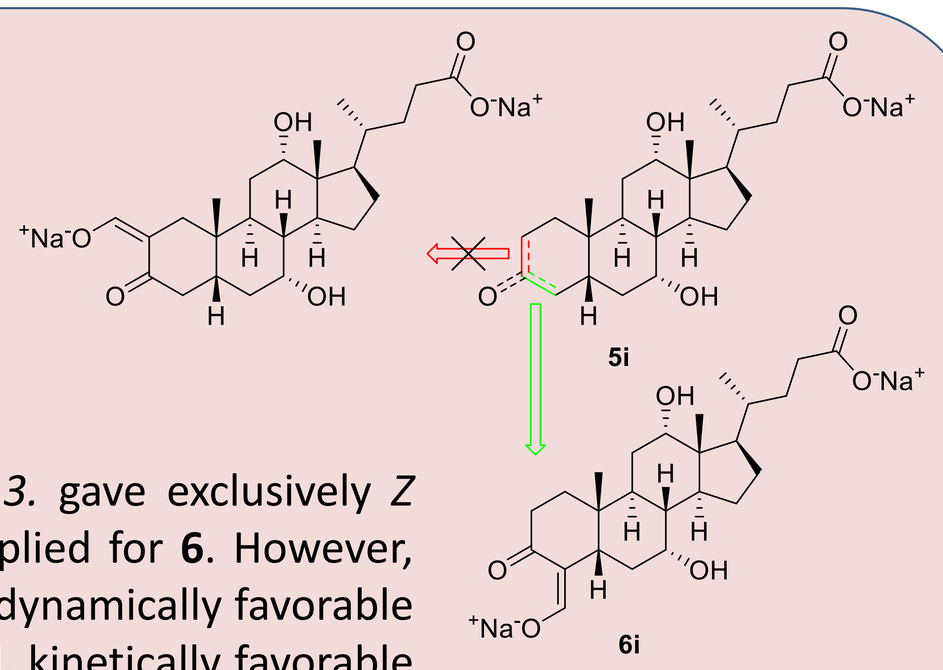
Scheme 2. (a) ethyl formate, NaH, benzene, reflux, 2.5 h.

When **2** was subjected to the reaction condition shown on *scheme 2*, compound **4** was obtained. Compound **4** is a result of three, one-pot reactions: Claisen condensation, elimination, and transesterification. Enol form of **4** is probably stabilized by conjugation with the dienone system and *Z* geometry of enol is likely a consequence of hydrogen bonding with the carbonyl group.



Scheme 3. (a) ethyl formate, NaH, benzene, reflux, 3 h.

The oxo bile acid derivate **5** in the reaction shown on *scheme 3.* gave exclusively *Z* hydroxymethylene **6**. The same explanation as for **4** could be applied for **6**. However, regioselectivity is different from known in the literature. A thermodynamically favorable C-2 isomer is not detected, but only the C-4 isomer. Firstly formed, kinetically favorable C-4 product (*scheme 4.*) is unable to isomerizes to C-2 isomer due to low solubility of ionic intermediate **6i** in benzene and practically his exception from the reaction.



Scheme 4.

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