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A facile approach to steroidal 20-hydroxy-17(20)-en-21-aldehydes: important intermediates in the biological 17-dehydroxylation of C-17 dihydroxyacetone steroids

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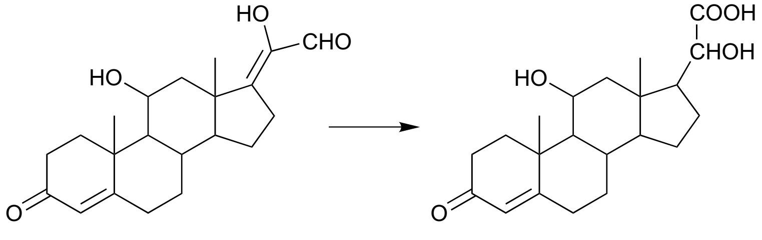
Abstract—A novel and straightforward route to steroidal *Z*- and *E*-enol aldehydes is presented. Acid-catalysed treatment allows formal dismutation of corticosteroids, affording good yields of the related enol compounds which can be easily separated and purified. © 2001 Elsevier Science Ltd. All rights reserved.

Steroidal carboxylic derivatives are the larger part of cortisol metabolites.[1] For example the radioactive metabolite 11β,20-dihydroxy-3-oxo-4-pregnen-21-oic acid was separated and isolated from the urine of some patients to which was given a radiotracer dose of cortisol.[2] 11β,20-dihydroxy-3-oxo-4-pregna-4-17,(20)-dien-21-al (**1**), a compound with a C-17 enol aldehyde side chain, has been proposed as the key intermediate in the formation of 11β,20-dihydroxy-3-oxo-4-pregnen-21-oic acid (**2**, Scheme 1).

The enol aldehyde was synthesized and used as a mixture of *E* and *Z* isomers, and not as a single isomer, to investigate in vitro its role in the biosynthesis of 11β,20-dihydroxy-3-oxo-4-pregnen-21-oic acid. The experiment showed that only the *cis*-isomer is converted to give the corresponding carboxylic acids.[3] The poor availability of the proposed enol aldehyde intermediates has not made possible a comprehensive study of the 17-dehydroxylation reaction of cortisol and related steroidal systems having a C-17 dihydroxyacetone side-chain.

Previously reported chemical syntheses[4,5] of steroidal enol aldehydes were unsatisfactory because all tested procedures provided low yields of the desired products. Moroever enol aldehydes were obtained as a mixture of their *E* and *Z* isomers which were not fully characterised. Very low yields of enol aldehydes were also obtained by refluxing suitable substrates with zinc acetate in glacial acetic acid.[6] Furthermore both isomers of thus prepared enol aldehydes were separated by time



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Scheme 1.

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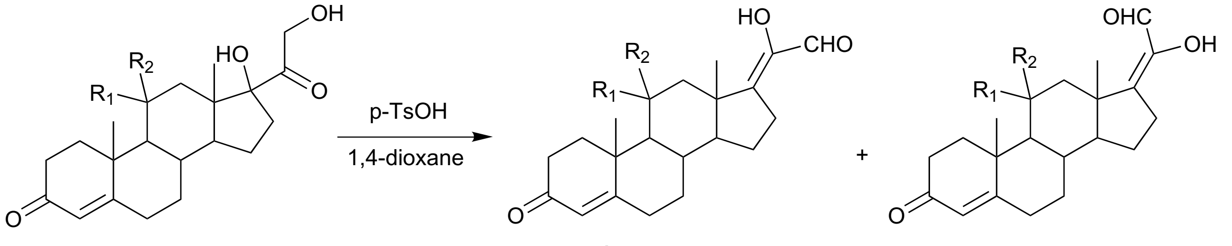


3a-c **4a-c** **5a-c**

Scheme 2.

consuming and difficult to reproduce purification procedures.

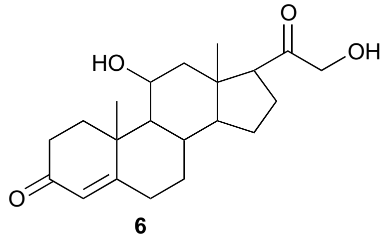
We repeated the 17-dehydroxylation reaction of cortisol adopting the above cited synthetic approach.[6] The corresponding enol aldehyde was recovered as a mixture of its *E* and *Z* isomers in 20% total yield. In a second experiment, cortisol was treated with glacial acetic acid without zinc acetate to afford the same products in similar yields (25%). These results provided evidence that the presence of zinc acetate is unnecessary and the acid is the only one required reagent. As a consequence, it seemed to be of great interest to realise the conversion of C-17 dihydroxyacetone side-chain steroids into the corresponding enol aldehydes by carrying the reaction in an inert ethereal solvent under acid catalysis conditions. To achieve this aim, model compounds **3a**–**c** were allowed to react with a catalytic amount of *p*-toluenesulfonic acid (Scheme 2). Treatment afforded the *Z*-enol aldehydes **4a**–**c** in very high overall yield (71–78%) and the *E*-enol aldehydes **5a**–**c** in 10–13% yields (Table 1), after chromatographic purification of the crude reaction mixtures.[7] In a typical experimental protocol, a mixture of cortisol **3a** (1.49 mmol) and *p*-toluenesulfonic acid monohydrate (2 mg) in dry 1,4-dioxane (25 ml) was refluxed under inert atmosphere for 1.5 h. After this time, TLC showed nearly total conversion of the starting material into the corresponding enol aldehydes. A saturated aqueous Na_2CO_3 solution was then added and the basified aqueous solution (pH 10) was extracted with chloroform (4×15 ml). The combined organic extracts were washed with distilled water, then dried (Na_2SO_4) and evaporated to dryness. The resulting residue was purified by short column flash chromatography using light petroleum/diethyl ether as eluent (8:2) to afford *Z*-enol aldehyde **4a** (73% yield) and *E*-enol aldehyde **5a** (13% yield). When a solution of cortisol in dry 1,4-dioxane, not containing the acid catalyst, was refluxed for 1.5 h, the starting reactant was recovered unchanged. This experiment showed that the acid catalysis is essential to convert the steroidal substrate into the enol aldehydes. The catalyst is probably involved in enolization equilibria and in the dehydroxylation at the C-17 position.

Table 1.

	R_1	R_2	Yield (4) %	Yield (5) %
a	OH	H	73	13
b	H	H	71	10
c	$R_1=R_2=O$		78	13

In order to evaluate the structural characteristics of substrates that could be converted in enol aldehydes, we planned further experiments using steroids containing modified side chains as starting materials. Corticosterone **6** and 17-hydroxyprogesterone **7** (Fig. 1) have their side chains characterised by lacking the hydroxyl group on the C-21 and C-17 positions, respectively, compared to cortisol. These two compounds were treated with *p*-toluenesulfonic acid under the same conditions used for cortisol but after 1.5 h the starting reactants were recovered unchanged. This result suggested that the presence of hydroxyl group on the C-17 and C-21 positions is essential for the reaction to proceed.

The formal dismutation of the dihydroxyacetone side chain by acid catalysis represents a good strategy to prepare the corresponding enol aldehydes. The chemical transformation of steroids into enol aldehydes by general acid catalysis can be related to the conditions of the corresponding biological process.



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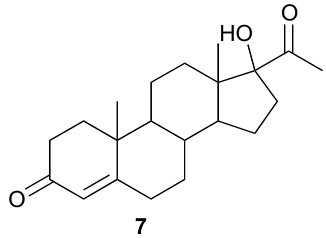

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Figure 1.

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6. Lewbart, M. L.; Monder, C.; Boyko, W. J.; Singer, C. J.; Iohan, F. *J. Org. Chem.* **1989**, *54*, 1332–1338.
7. Selected spectroscopic data:

   Compound **4a**. Mp: 149–152°C, IR (KBr): 3520, 3360, 1670, 1636 cm^{-1}, ^{1}H NMR δ (300 MHz, CDCl$_3$): 9.57 (1H, s, CHO), 5.69 (1H, s, H-4), 5.63 (1H, s, OH-20; disappears in D$_2$O), 4.45 (1H, m, H-11), 1.47 (3H, s, 19-CH$_3$), 1.25 (3H, s, 18-CH$_3$), 2.97–0.99 (24H, m), ^{13}C NMR δ (75 MHz, CDCl$_3$): 199.57, 186.14, 172.07, 146.98, 141.58, 122.27, 68.47, 56.48, 55.47, 45.38, 44.93, 39.23, 34.72, 33.73, 32.58, 31.91, 30.80, 24.77, 24.65, 20.91, 17.82, ESI-TOF MS: calcd for (C$_{21}$H$_{28}$O$_4$+H)$^+$ 345.2066, found 345.2048.

   Compound **5a**. Mp: 171–174°C, IR (KBr): 3420, 1654, 1638 cm^{-1}, ^{1}H NMR δ (300 MHz, CDCl$_3$): 9.74 (1H, s, CHO), 5.86 (1H, s, OH-20; disappears in D$_2$O), 5.59 (1H, s, H-4), 4.42 (1H, m, H-11), 1.42 (3H, s, 19-CH$_3$), 1.24 (3H, s, 18-CH$_3$), 2.75–0.90 (24H, m), ^{13}C NMR δ (75 MHz, CDCl$_3$): 199.26, 183.84, 171.56, 150.58, 142.69, 122.43, 65.78, 57.15, 56.07, 52.39, 48.84, 41.31, 34.95, 33.73, 32.46, 31.89, 29.02, 28.70, 27.63, 22.53, 15.19, ESI-TOF MS: calcd for (C$_{21}$H$_{28}$O$_4$+H)$^+$ 345.2066, found 345.2048.

   Compound **4b**. Mp: 166–170°C, IR (KBr): 3416, 1663, 1640 cm^{-1}, ^{1}H NMR δ (300 MHz, CDCl$_3$): 9.52 (1H, s, CHO), 5.68 (1H, s, H-4), 5.57 (1H, s, OH-20; disappears in D$_2$O), 1.18 (3H, s, 19-CH$_3$), 0.98 (3H, s, 18-CH$_3$), 2.90–0.90 (25H, m), ^{13}C NMR δ (75 MHz, CDCl$_3$): 199.27, 186.02, 170.67, 146.98, 141.88, 123.75, 53.95, 53.57, 46.05, 38.50, 33.45, 34.88, 34.62, 33.73, 32.54, 31.75, 25.02, 24.71, 20.81, 17.11, 15.35, ESI-TOF MS: calcd for (C$_{21}$H$_{28}$O$_3$+H)$^+$ 329.2117, found 329.2100.

   Compound **5b**. Mp: 147–150°C, IR (KBr): 3422, 1666, 1640 cm^{-1}, ^{1}H NMR δ (300 MHz, CDCl$_3$): 9.76 (1H, s, CHO), 5.94 (1H, s, OH-20; disappears in D$_2$O), 5.75 (1H, s, H-4), 1.23 (3H, s, 19-CH$_3$), 1.12 (3H, s, 18-CH$_3$), 3.00–0.90 (25H, m), ^{13}C NMR δ (75 MHz, CDCl$_3$): 199.17, 183.72, 170.19, 150.33, 142.79, 123.87, 55.33, 52.94, 45.99, 39.15, 33.45, 34.88, 34.62, 33.69, 32.44, 31.55, 23.80, 21.28, 20.31, 17.15, 15.31, ESI-TOF MS: calcd for (C$_{21}$H$_{28}$O$_3$+H)$^+$ 329.2117, found 329.2100.

   Compound **4c**. Mp: 188–192°C, IR (KBr): 3422, 1704, 1665, 1648 cm^{-1}, ^{1}H NMR δ (300 MHz, CDCl$_3$): 9.54 (1H, s, CHO), 5.70 (1H, s, H-4), 5.65 (1H, s, OH-20; disappears in D$_2$O), 1.39 (3H, s, 19-CH$_3$), 1.19 (3H, s, 18-CH$_3$), 3.20–0.85 (23H, m), ^{13}C NMR δ (75 MHz, CDCl$_3$): 208.60, 199.52, 185.67, 168.29, 142.69, 142.14, 124.57, 63.21, 54.03, 53.22, 38.22, 35.47, 34.70, 33.63, 32.15, 32.07, 29.59, 25.28, 24.55, 17.15, 156.77, ESI-TOF MS: calcd for (C$_{21}$H$_{26}$O$_4$+H)$^+$ 343.1909, found 343.1891.

   Compound **5c**. Mp: 146–149°C, IR (KBr): 3424, 1702, 1664, 1646 cm^{-1}, ^{1}H and ^{13}C NMR analyses were unsuccessful because compound decomposed in deuteriochloroform, ESI-TOF MS: calcd for (C$_{21}$H$_{26}$O$_4$+H)$^+$ 343.1909, found 343.1891.