Simple and Convenient Method for the Synthesis of $\Delta^{9(11)}$-3-Hydroxy, $\Delta^{1,4}$- and $\Delta^{1,4,9(11)}$-3-Ketosteroids by Selective Dehydrogenation of 3-Hydroxy-12-Ketosteroids

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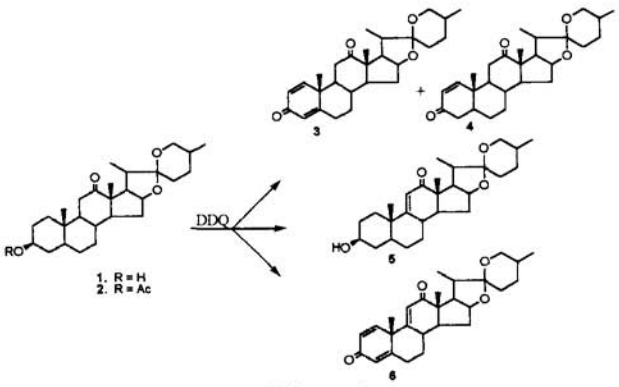
(Received August 21, 1998; CL-980646)

Hecogenin can be selectively dehydrogenated to the corresponding $\Delta^{9(11)}$-3-hydroxysteroid, $\Delta^{1,4}$- and $\Delta^{1,4,9(11)}$-3-ketosteroids by the treatment of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) with a variety of solvents.

Corticosteroids contained $\Delta^{1,4}$-3-keto group at ring A are known to have high anti-inflammatory, antirheumatic properties and also reduce the sodium-retaining effect. Moreover the presence of oxygen at C-11 position and halogen at C-9 position in the molecule is necessary for significant glucocorticoid activity but not for mineralocorticoid activity.[1] The generation of the important 1,4-diene-3-one unit could be achieved by a conventional bromination-debromination method[2] or by dehydrogenation of 3-keto or 4-ene-3-ketosteroids. The commonly used reagents in the dehydrogenation method were 2,3-dichloro-5,6-dicyanobenzoquinone(DDQ),[3] chloranil,[4] selenium dioxide[5] and diphenyl diselenide.[6] The steroids containing hydroxy group at C-11 and halogen at C-9 were normally generated from the corresponding 9(11)-dehydrogenated compounds.[7,8] Therefore, the 9(11)-dehydrosteroids constitute an important group of intermediates in the synthesis of steroid drugs. They can easily be transformed into steroids with 9-halogen and 11-hydroxy substituents. Although a number of methods for dehydrogenation of steroids have been intensively studied in the last decade, to the best of our knowledge the construction of 1,4-diene-3-one unit and 9(11) double bond in the steroid molecules is still required several reaction steps. Herein we wish to demonstrate that it is possible to achieve selective dehydrogenation of steroids at ring A and/or ring C from 3-hydroxy-12-ketosteroids using DDQ to give 9(11)-ene-3-hydroxysteroid, 1,4-diene and 1,4,9(11)-triene-3-ketosteroids (Scheme 1). In this work, hecogenin has first been investigated because of its potential uses as starting material for the partial synthesis of corticosteroid drugs and it is also found to be the most abundant naturally occuring 12-ketosteroid sapogenin.

The reactions were performed using an excess of DDQ at refluxing temperature of dioxane or methanol. The experimental results are summarized in Table 1. Treatment of hecogenin(**1**) with 5.0 mole equivalent of DDQ in refluxing dioxane (entry 1) gave a moderated yield of a 2:1 mixture of $\Delta^{1,4}$-22-isoallospirosten-3,12-dione(**3**) and Δ^{1}-22-isoallospirosten-3,12-dione(**4**) in 16 h. Under this reaction condition hecogenin acetate(**2**) failed to react with DDQ even after 16 h. only a starting material was recovered. When methanol was used as solvent both hecogenin and hecogenin acetate (entries 2 and 3) produced a similar yield of $\Delta^{9(11)}$-22-isoallospirosten-3β-ol-12-one(**5**) after refluxing for 5 h. Then a mixture of dioxane and methanol(1:3) was employed in the dehydrogenation of hecogenin, again $\Delta^{9(11)}$-22-isoallospirosten-3β-ol-12-one(**5**) was obtained together with staring material after refluxing for 8 h. However when this condition was carried out by refluxing in dioxane for 16 h and then triple volume of methanol was added and refluxed for additional 5 h (entry 4), $\Delta^{1,4,9(11)}$-isoallospirosten-3,12-dione(**6**) was obtained in 36% isolated yield.

In conclusion, we have demonstrated that 3-hydroxy-12-ketosteroids could be transformed selectively to either $\Delta^{1,4}$-3-keto or $\Delta^{9(11)}$-3-hydroxysteroids. In addition, the one-step preparation of $\Delta^{1,4,9(11)}$-3-ketosteroids, an important intermediate



Scheme 1.

Table 1. Dehydrogenation of hecogenin and it's acetate by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) at refluxing temperature

Entry	Substrate	Conditions[c]	Products[a] and yield/%[b]
1	**1**	Dioxane,16 h	**3** + **4** (ratio:2:1) (38)
2	**2**	Methanol,5 h	**5**(48)
3	**1**	Methanol, 5 h	**5**(43)
4	**1**	Dioxane,16 h then add Methanol(1:3), 5 h	**6**(36)

[a] All products obtained were fully characterised by spectrometric means(IR, ^{1}H and ^{13}C NMR and MS). [b]Isolated yield after column chromatography. [C] 5.0 mol-equiv. of DDQ was used.

for the synthesis of corticosteroids drugs from the coresponding 3-hydroxy-12-keto compounds was established for the first time. The extension of the reaction to more functionalized steroids is underway in our laboratory.

General procedure: To a solution of the steroid (0.22 mmol) in dioxane(10 ml) was added 2,3-dichloro-5,6-dicyano-benzoquinone(DDQ) (1.1 mmol). The mixture was stirred at refluxing temperature for the time indicated in Table1. The solvent was evaporated to dryness under reduce pressure without heating then methylene chloride was added to precipitate out hydroquinone. The precipitate was filtered and the filtrate was concentrated. The crude product was purified on a silica gel chromatographic column and recrystalization.

We thank the Chulabhorn Research Institute (CRI), Thailand and the Bioresources Research Unit, National Center for Genetic Engineering and Biotechnology, Thailand for providing 400 MHz and 200 MHz NMR and mass spectral data. We also wish to thank the Thailand Research Fund(TRF) for financial support.

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8 Compound **3**: H^1NMR (400 MHz,$CDCl_3$) δ : 0.9(d, J=8 Hz, 3H, CH_3), 1.05(s,3H, CH_3), 1.1(d, J=10 Hz, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.8-2.6(m, 17H), 3.3(t, J=11.2 Hz,2H), 3.4(m, 1H), 4.3 (m,1H), 6.09(s,1H), 6.2(dd,J=9.6,1.9 Hz, 1H), 6.81 (d,J=9.6 Hz,1H).

9 Compound **4**: H^1NMR (400 MHz,$CDCl_3$) δ : 0.9(d, J=8 Hz, 3H, CH_3), 1.05(s,3H,CH_3), 1.1(d, J=10 Hz, 3H, CH_3), 1.62 (s,3H, CH_3), 1.8-2.6(m,17H), 3.3(t, J=11.0 Hz,2H), 3.4(m, 1H), 5.8 (d,1H), 6.85(d, 9.5 Hz,1H), 6.9(d, 9.5 Hz,1H).

10 Compound **5**: H^1NMR(400 MHz,$CDCl_3$) δ:0.75(d, J=8 Hz, 3H, CH_3), 0.85(s,3H,CH_3), 102(d, J=9.6 Hz,3H, CH_3), 1.08 (s, 3H,CH_3), 1.45-1.9(m,17H), 2.0(m,1H), 2.4(t, J=10 Hz, 1H), 3.35 (t, J=11.0 Hz, 2H), 3.4(m,1H), 3.6(m,1H), 5.5(d, J=2.4 Hz,1H).

11 Compound **6**: H^1NMR(400 MHz,$CDCl_3$) δ:0.8(d,J=8 Hz, 3H, CH_3), 1.01(s, 3H,CH_3), 1.1(d, J=10 Hz,3H, CH_3), 1.25-1.50(m,2H),1.58(s,3H,CH_3),1.55-1.85(m,6H), 2.2-2.32 (m,2H), 2.4 (dd, J=10 Hz, 8 Hz,1H), 2.5(dq, J=8.4,0.8 Hz, 1H), 2.75 (m,2H), 3.35(t, J=11.2 Hz,1H), 3.5(m, 1H), 4.4(q, J=11.2 Hz, 1H), 5.83(d, J=2.4 Hz,1H), 6.17(t, J=1.9 Hz,1H), 6.33 (dd, J=9.6, 1.9 Hz, 1H), 7.13(d, 9.6 Hz,1H).