General and facile method for determination of configuration of steroid-17-yl methyl glycolates at C-20 based on kinetic examination

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Plots of the amount of the isomeric steroid-17-yl methyl glycolate produced by a reaction of the corresponding steroids, prednisolone, dexamethasone and hydrocortisone with cupric acetate in absolute methanol, and kinetic examination of methoxycarbonylation of their products provide a general and facile method for determination of the configuration of the steroid-17-yl methyl glycolates at C-20.

To obtain steroidal compounds with strong sustained action as agents for treating inflammation and allergy, many natural and semi-synthetic steroids have been studied. At present, steroidal drugs are considered essential for treating chronic rheumatism, dermatological disorders, inflammation and allergy. However, therapeutic use of antiinflammatory steroids has been limited by the diverse systemic and adverse effects such as decrease of adrenal secretion, immunological competence, osteoporosis, full moon-like face due to defective lipid or protein metabolism, fatty liver and infantile growth disturbance. To overcome this limitation, efforts toward discovery of steroidal compounds demonstrating separation of topical antiinflammatory activity from potentially harmful side effects have increased.[1–9]

Our most recent efforts toward this goal include the syntheses of the various types of steroidal methyl glycolates from common steroids such as prednisolone, dexamethasone and hydrocortisone, and we found some of the compounds possessing extremely strong vasoconstrictive activity without pituitary–adrenal expression.[10]

In spite of many studies on the biological activities of the compounds derived from prednisolone and dexamethasone acid esters, precise mechanisms for the formation of steroid-17-yl methyl glycolates from their corresponding steroids, and general methods for determining the ambiguous configuration of their steroid-17-yl methyl glycolates at C-20, have not been reported yet.

It is already known that methanolic cupric acetate catalyzes the transformation of steroid glyoxal (20-keto-21-aldehydes) to the corresponding methyl glycolates (20-hydroxy-21-acid methyl ester) as an epimeric mixture at C-20.[11] The configuration at C-20 of a pair of epimeric 20-acetoxy pregnanes can be established by comparing their molecular rotations. A simple rule, formulated by Fieser *et al.*,[12] states that a (20*S*)-acetoxy compound of any type is more dextrorotary than its (20*R*)-acetoxy epimer. However, this rule is empirical and not applicable to 5β-pregnan-21-oic acid derivatives, where the results are entirely opposite to Fieser's rule.

After extensive studies on the rate of disappearance of the glyoxals derived from the steroids possessing an α-ketol functional group at C-17 in various solvents, Lewbart *et al.*[11] postulated the mechanism of this conversion, which involves transfer of a hydride ion at C-21 to C-20 in the glyoxal hemiacetal formed by nucleophilic addition of methanol to the glyoxals, and characterized each product (epimeric mixture at C-20, ratio being 1 : 1).

Results and discussion

Each steroid (prednisolone, dexamethasone or hydrocortisone) was treated with 0.5 equivalent of cupric acetate in dry methanol at room temperature to provide the corresponding methyl glycolates as diastereomers at C-20. Attempts to separate the isomers by silica gel column chromatography met with little success. However, good separation was achieved with the corresponding acetylated compounds **8** and **9**, **10** and **11**, and **12** and **13**. Mild hydrolysis of each compound with potassium carbonate in dry methanol provided the pure methyl glycolates **1** and **2**, **3** and **4**, and **5** and **6**, respectively.

In order to find the optimal conditions for these transformations, the time courses of the formation of methyl 20-dihydroprednisolonates **1** and **2**, methyl 20-dihydrodexamethasonates **3** and **4** and methyl 20-dihydrohydrocortisonates **5** and **6** from the corresponding prednisolone, dexamethasone and hydrocortisone, respectively, were followed by high pressure liquid chromatography (HPLC) until 24 to 29 days under various conditions in the molar ratio of cupric acetate : steroid of 0.1, 0.2, 1.0 and 2.0. The results are shown in Fig. 1. In the formation of the methyl prednisolonates under various conditions, we observed the preferential formation of the less polar compound **1** (20*S*) over the more polar compound **2** (20*R*) in the presence of sufficient catalyst (more than 0.5 mole equivalents of cupric acetate : steriod), in contrast to the results reported by Lewbart *et al.*[11] in which they described the ratio of 1 : 2 as simply 1 : 1. This was also recognized in the conversion of dexamethasone and hydrocortisone to their corresponding methyl glycolates **3** and **4**, and **5** and **6**, respectively. Thus, the less polar compounds (**3** and **5**) as well as compound **1** are also the preferentially formed. Based on these results, we tentatively assigned the compounds **3** and **5** as being 20*S* configuration, and the compounds **4** and **6** as having 20*R* configuration.

Preferable formation of (20*S*)-methyl glycolates can be explained based on the conformations of the acetal intermediates (**7a** and **7b**) whose bonds between C-17 and C-20 are possibly fixed by the chelation of copper with the carbonyl group at C-20 and the hydroxy group at C-17α. The migration of a hydride ion from C-21 to C-20 thus proceeds *via* the more stable intermediate **7a** whose acetal group is located far from the methyl group at C-18, to provide (20*S*)-methyl glycolates **1**, **3** and **5** as the main products.

A more reliable determination of the configuration at C-20 has been achieved by conformational analyses of the transformation of the dimethyl esters (**14**, **16** and **18**) and their

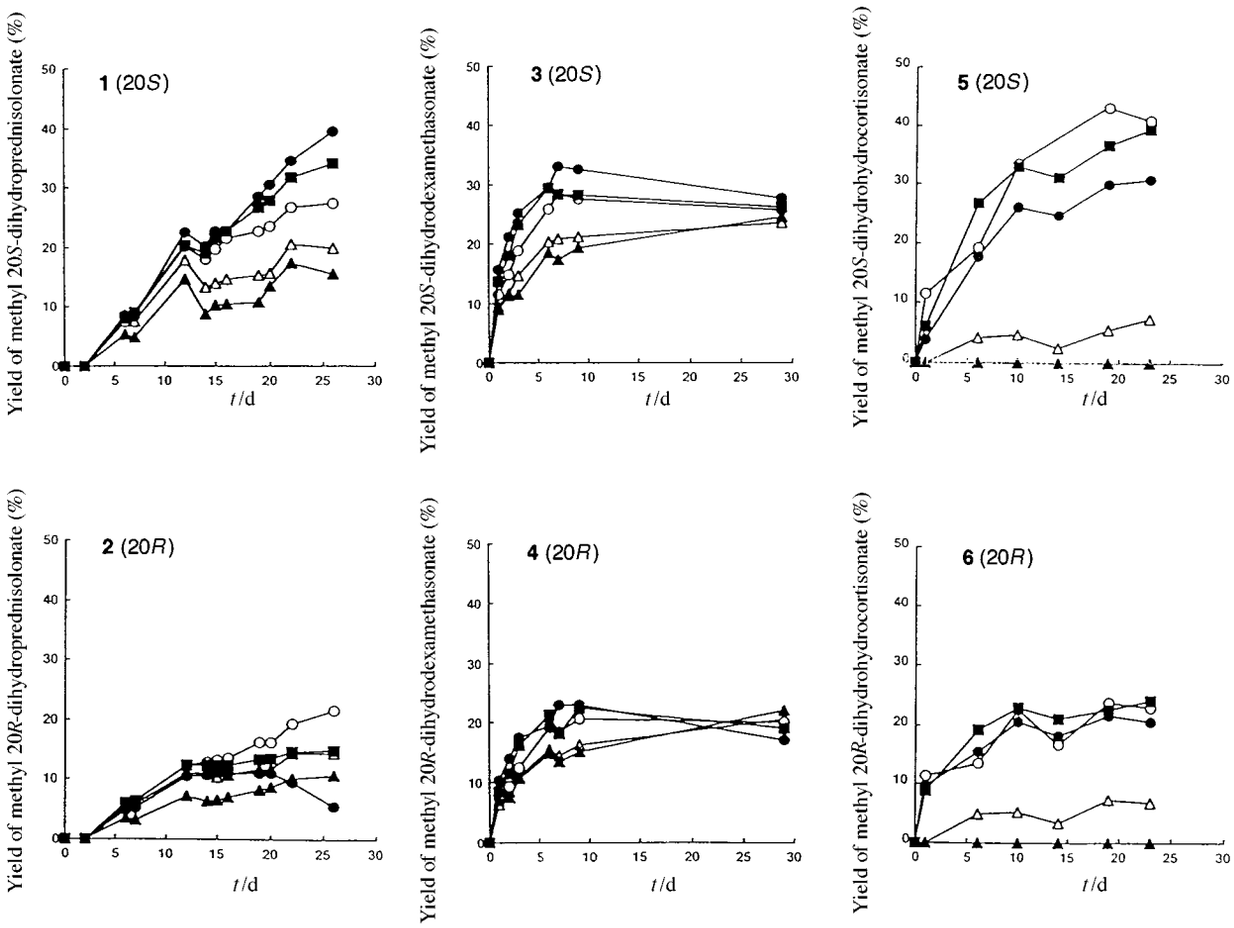
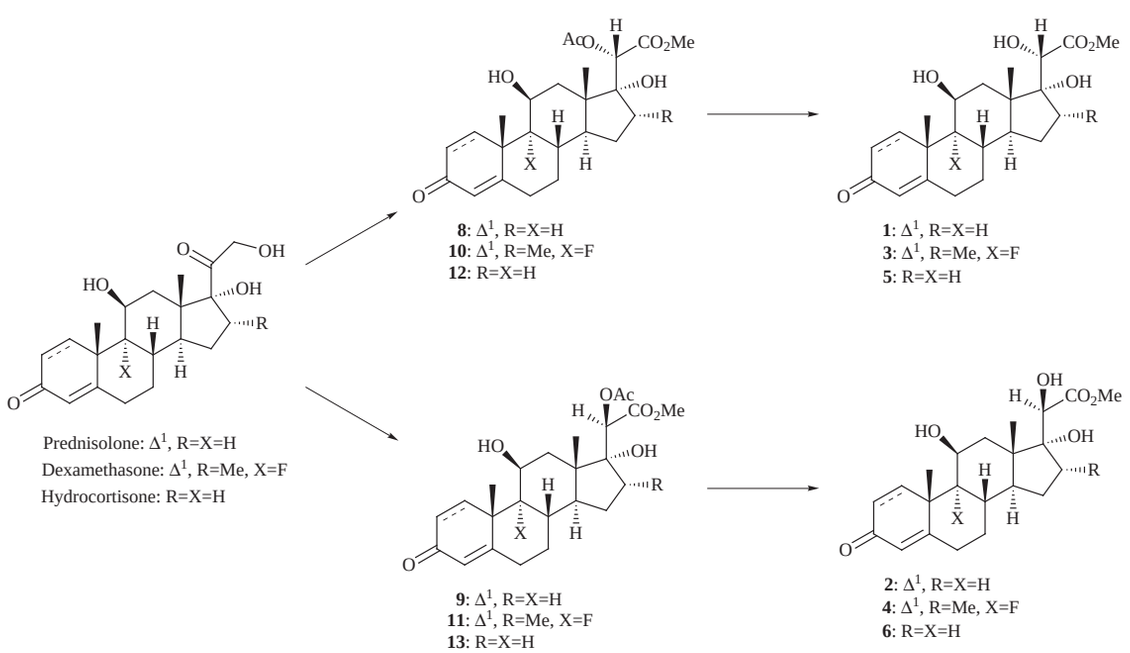


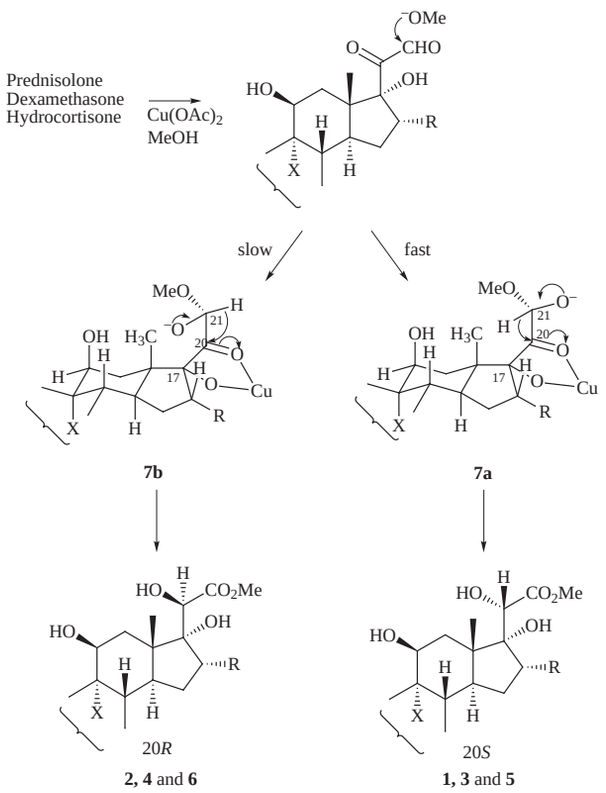
Fig. 1 Time courses for the formation of methyl glycolates (20*S* and *R*) from steroids. All reactions were performed by stirring a mixture of each steroid and $Cu(OAc)_2$ in dry methanol at room temperature. $Cu(OAc)_2$/steroid (molar ratio); 0.1, ▲; 0.2, △; 0.5, ○; 1.0, ■; 2.0, ●.



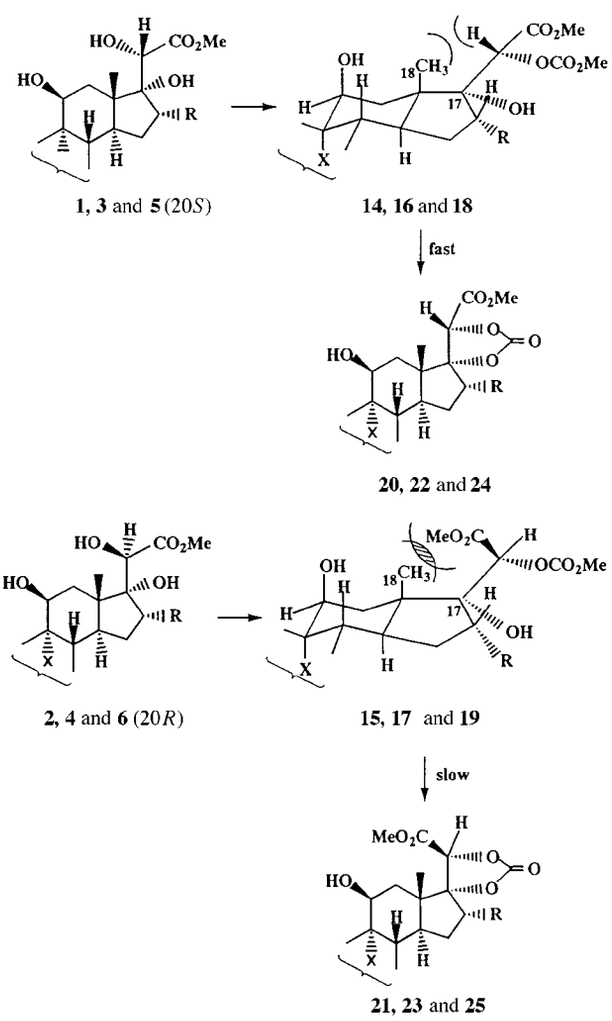
Scheme 1

epimers (**15**, **17** and **19**) to the corresponding dioxolanones (**20**, **22** and **24**, and **21**, **23** and **25**). More intense interactions exist between the C-18 methyl group and the C-20 methoxycarbonyl group in the intermediates **15**, **17** and **19** than between the C-18 methyl and the C-20 proton in **14**, **16** and **18**. Hence we predicted that the reaction rate for the cyclization of **14**, **16** and **18** (20*S*) would be faster than that of **15**, **17** and **19** (20*R*).

Based on this speculation, methoxycarbonylations of each pair of epimers **1** and **2**, **3** and **4**, and **5** and **6** were examined, and the results are shown in Table 1. The rates of formation, k_2, of each of the dioxolanones **20**, **22** and **24** derived from the preferred intermediates (less polar) which are supposed to possess the 20*S* configuration are 2.53, 1.87 and 2.23 times faster than those of the dioxolanones **21**, **23** and **25** derived



Scheme 2



Scheme 3

from the corresponding isomeric compounds (more polar), as we predicted.

These results suggest that our speculation and discussion on the C-20 configurations are reliable and provide a general and facile method to determine the configuration at C-20 of the steroid derivatives possessing the same type of functional groups at C-17.

Experimental

All reactions were performed under a nitrogen atmosphere. Melting points were determined with a Yazawa BY-1 melting point apparatus and are uncorrected. Specific rotations were measured with a PM-101 polarimeter. ^{1}H NMR spectra were taken for solutions in deuteriochloroform (tetramethylsilane as an internal standard) on JEOL JNM-PMX-60 and JEOL JNM-EX-270 instruments. IR spectra were recorded on a JASCO IR-810 spectrophotometer. Mass spectra were obtained on a JEOL JMS-OISG-2 spectrometer. The HPLC system used was a Waters 600E pump with Waters 484 Tunable Absorbance Detector. All products described in the Experimental section were homogeneous by TLC and HPLC.

Methyl (20*S*)- and (20*R*)-acetoxy-11β,17α-dihydroxy-3-oxopregna-1,4-dien-21-oates 8 and 9

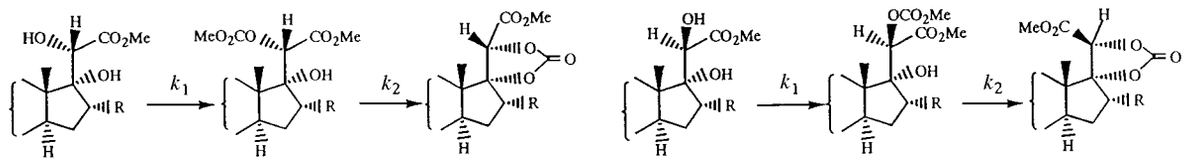
A solution of prednisolone (5 g, 13.9 mmol) in dry methanol (350 ml) was added dropwise to a stirred solution of cupric acetate (1.2 g, 7.5 mmol) in dry methanol (350 ml) and the mixture was stirred for 26 days. After addition of a solution of ethylenediaminetetraacetic acid disodium salt dihydrate (2.89 g, 7.5 mmol) in water (70 ml), the solvent was evaporated to leave a residue which was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and then evaporated to leave a residue (5.5 g) which was chromatographed on silica gel (250 g) with $CHCl_3$–MeOH (99 : 1, v/v) as eluant to give methyl prednisolonates (**1** and **2**) as a mixture of the diastereomers at C-20. This mixture was used in the next reaction without further purification.

A mixture of methyl prednisolonates (**1** and **2**, 1 g) and acetic anhydride (3 ml) in dry pyridine (3 ml) was stirred for 20 h at room temperature. The reaction was quenched by addition of water, and excess acetic acid and pyridine were evaporated *in vacuo* to leave a residue which was extracted with chloroform. The extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent left a residue which was chromatographed on silica gel (30 g). The first elution with $CHCl_3$–MeOH (99 : 1, v/v) provided **9** (303 mg, 16.2% from prednisolone), mp 236–238 °C, $[\alpha]_D$ +69.3 (*c* 0.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3550–3200(OH), 1746, 1660(C=O), 1619, 1605(C=C); δ_H (60 MHz; $CDCl_3$) 1.23 (3H, s, Me), 1.47 (3H, s, Me), 2.15 (3H, s, COMe), 3.75 (3H, s, CO_2Me), 4.28–4.67 (1H, m, 11-H), 5.07 (1H, s, 20-H), 5.98 (1H, d, *J* 2 Hz, 4-H), 6.12 (1H, dd, *J* 10, 2 Hz, 2-H), 7.20 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 432.2142. $C_{24}H_{32}O_7$ requires *M*, 432.2147), and the second elution with the same solvent gave **8** (380 mg, 20.3% from prednisolone), mp 203–204 °C, $[\alpha]_D$ +44.7 (*c* 0.3, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3550–3200(OH), 1746, 1660(C=O), 1619, 1605(C=C); δ_H (60 MHz; $CDCl_3$) 1.05 (3H, s, Me), 1.45 (3H, s, Me), 2.17 (3H, s, COMe), 3.73 (3H, s, CO_2Me), 4.30–4.53 (1H, m, 11-H), 5.08 (1H, s, 20-H), 5.97 (1H, br s, 4-H), 6.12 (1H, dd, *J* 10, 2 Hz, 2-H), 7.20 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 432.2142. $C_{24}H_{32}O_7$ requires *M*, 432.2147).

Methyl (20*S*)- and (20*R*)-acetoxy-11β,17α-dihydroxy-9α-fluoro-16α-methyl-3-oxopregna-1,4-dien-21-oates 10 and 11

The (20*R*)-acetate **11** (171.9 mg, 17.1% from dexamethasone), mp 235–238 °C (colorless needles, MeOH–hexane); $[\alpha]_D$ +30.6 (*c* 0.22, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3550–3300(OH), 1744, 1665(C=O), 1624, 1605(C=C); δ_H (270 MHz; $CDCl_3$) 1.10 (3H,

Table 1 Reaction rates on transformation of methyl glycolates into dioxolanones



1, **3** and **5** (20*S*) **14**, **16**, and **18** **20**, **22** and **24** **2**, **4** and **6** (20*R*) **15**, **17** and **19** **21**, **23** and **25**

	Methyl prednisolonates		Methyl dexamethasonates		Methyl hydrocortisonates	
Reaction rate constants	**1** (20*S*)	**2** (20*R*)	**3** (20*S*)	**4** (20*R*)	**5** (20*S*)	**6** (20*R*)
k_1 (min)$^{-1}$	1.26×10^{-2}	3.10×10^{-2}	1.0	0.62	—[a]	—[a]
k_2 (min)$^{-1}$	5.57×10^{-4}	2.20×10^{-4}	3.67×10^{-3}	1.96×10^{-3}	4.15×10^{-4}	1.86×10^{-4}
20*S* k_2/20*R* k_2	2.53		1.87		2.23	

[a] The rate of this reaction was so fast that k_1 could not be calculated. All reactions were performed by treatment of the methyl glycolate with methyl chloroformate (3 equiv.) and 4-dimethylaminopyridine (4 equiv.) in dry dichloromethane at room temperature.

d, *J* 7 Hz, Me), 1.27 (3H, s, Me), 1.55 (3H, s, Me), 2.14 (3H, s, COMe), 3.76 (3H, s, CO_2Me), 4.26–4.34 (1H, m, 11-H), 5.12 (1H, s, 20-H), 6.03 (1H, d, *J* 1.6 Hz, 4-H), 6.23 (1H, dd, *J* 9.9, 1.6 Hz, 2-H), 7.13 (1H, d, *J* 9.9 Hz, 1-H) (Found: M^+, 465.2283. $C_{25}H_{34}O_7$ requires *M*, 465.2288), and the (20*S*)-acetate **10** (239.7 mg, 23.8% from dexamethasone), mp 263–265 °C (colorless needles, MeOH–hexane); $[\alpha]_D$ +49.4 (*c* 0.24, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3550–3300(OH), 1740, 1665(C=O), 1625, 1605(C=C); δ_H (270 MHz; $CDCl_3$) 0.83 (3H, d, *J* 7 Hz, Me), 1.10 (3H, s, Me), 1.55 (3H, s, Me), 2.08 (3H, s, COMe), 3.76 (3H, s, CO_2Me), 4.30–4.45 (1H, m, 11-H), 4.97 (1H, s, 20-H), 6.03 (1H, d, *J* 1.6 Hz, 4-H), 6.23 (1H, dd, *J* 9.9, 1.6 Hz, 2-H), 7.13 (1H, d, *J* 9.9 Hz, 1-H) (Found: M^+, 465.2285. $C_{25}H_{34}O_7$ requires *M*, 465.2288) were obtained from dexamethasone (1 g, 2.55 mmol) under the same conditions as described above.

Methyl (20*S*)- and (20*R*)-acetoxy-11β,17α-dihydroxy-3-oxopregn-4-en-21-oates 12 and 13

The (20*R*)-acetate **13** (376 mg, 16.5% from hydrocortisone), $[\alpha]_D$ +112.6 (*c* 0.888, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3602, 3500–3400(OH), 1745, 1663(C=O), 1618 (C=C); δ_H (270 MHz; $CDCl_3$) 1.20 (3H, s, Me), 1.44 (3H, s, Me), 2.16 (3H, s, COMe), 3.78 (3H, s, CO_2Me), 4.37–4.43 (1H, m, 11-H), 5.10 (1H, s, 20-H), 5.77 (1H, s, 4-H) (Found: M^+, 434.2298. $C_{24}H_{34}O_7$ requires *M*, 434.2303), and the (20*S*)-acetate **12** (603.7 mg, 25.2% from hydrocortisone), $[\alpha]_D$ +72.6 (*c* 1.12, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600–3400(OH), 1749, 1663(C=O), 1619 (C=C); δ_H (270 MHz; $CDCl_3$) 1.04 (3H, s, Me), 1.44 (3H, s, Me), 2.19 (3H, s, COMe), 3.77 (3H, s, CO_2Me), 4.43–4.48 (1H, m, 11-H), 5.12 (1H, s, 20-H), 5.68 (1H, s, 4-H) (Found: M^+, 434.2310. $C_{24}H_{34}O_7$ requires *M*, 434.2305), were obtained from hydrocortisone (2 g, 5.52 mmol) under the same conditions as described above.

Methyl (20*S*)- and (20*R*)-11β,17α,20-trihydroxy-3-oxopregna-1,4-dien-21-oates 1 and 2

A mixture of the acetate **8** (1 g, 2.31 mmol) and K_2CO_3 (100 mg) in absolute MeOH (11 ml) was stirred for 30 min at room temperature. After the solvent was evaporated, the residue was diluted with chloroform. It was washed with brine, dried ($MgSO_4$) and then evaporation of the solvent left a residue whose recrystallization from MeOH provided **1** (805 mg, 89.2%), mp 176–178 °C (lit.,[8d] 171–173 °C), $[\alpha]_D$ +20.0 (*c* 0.3, $CHCl_3$) (lit.,[8d] $[\alpha]_D$ +17.7); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3575–3200(OH), 1730, 1660(C=O), 1620, 1605(C=C); δ_H (60 MHz; $CDCl_3$) 1.15 (3H, s, Me), 1.45 (3H, s, Me), 3.75 (3H, s, CO_2Me), 4.20–4.53 (2H, m, 11-H and 20-H), 5.98 (1H, d, *J* 2 Hz, 4-H), 6.23 (1H, dd, *J* 10, 2 Hz, 2-H), 7.32 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 390.2049. $C_{22}H_{30}O_6$ requires *M*, 390.2044).

A mixture of the acetate **9** (982 mg) and K_2CO_3 (98 mg) in dry MeOH (10 ml) was stirred for 10 min at room temperature. After work-up, the crystalline residue was recrystallized from MeOH to give **2** (750 mg, 84.6%), mp 263–264 °C (lit.,[8d] 254–255 °C), $[\alpha]_D$ +36.7 (*c* 0.3, $CHCl_3$) (lit.,[8d] +38.4); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3575–3200(OH), 1727, 1660(C=O), 1620, 1605(C=C); δ_H (60 MHz; $CDCl_3$) 1.13 (3H, s, Me), 1.45 (3H, s, Me), 3.80 (3H, s, CO_2Me), 4.00–4.67 (2H, m, 11-H and 20-H), 6.00 (1H, d, *J* 2 Hz, 4-H), 6.22 (1H, dd, *J* 10, 2 Hz, 2-H), 7.18 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 390.2036. $C_{22}H_{30}O_6$ requires *M*, 390.2044).

Methyl (20*S*)- and (20*R*)-9α-fluoro-16α-methyl-11β,17α,20-trihydroxy-3-oxopregna-1,4-dien-21-oates 3 and 4

A mixture of the acetate **10** (163.6 mg) and K_2CO_3 (22 mg) in dry MeOH (4 ml) was stirred for 30 min at room temperature. After work-up, the crystalline residue was recrystallized from MeOH–hexane to give **3** (145 mg, 97.7%), mp 145–147 °C, $[\alpha]_D$ +20.2 (*c* 0.22, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3550–3300(OH), 1732, 1668(C=O), 1624, 1605(C=C); δ_H (270 MHz; $CDCl_3$) 0.87 (3H, d, *J* 7 Hz, Me), 1.20 (3H, s, Me), 1.53 (3H, s, Me), 3.73 (3H, s, CO_2Me), 4.29 (1H, s, 20-H), 6.07 (1H, d, *J* 1.6 Hz, 4-H), 6.27 (1H, dd, *J* 9.9, 1.6 Hz, 2-H), 7.17 (1H, d, *J* 9.9 Hz, 1-H) (Found: M^+, 422.2113. $C_{23}H_{31}O_9F$ requires *M*, 422.2105).

A mixture of the acetate **11** (76.3 mg) and K_2CO_3 (10 mg) in dry MeOH (4 ml) was stirred for 40 min at room temperature. After work-up, recrystallization of the resultant residue from MeOH–hexane afforded **4** (63.3 mg, 91.4%), mp 245–247 °C, $[\alpha]_D$ +29.6 (*c* 0.22, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3550–3300(OH), 1731, 1667(C=O), 1628, 1611(C=C); δ_H (270 MHz; $CDCl_3$) 1.07 (3H, d, *J* 7 Hz, Me), 1.10 (3H, s, Me), 1.57 (3H, s, Me), 3.77 (3H, s, CO_2Me), 4.25 (1H, s, 20-H), 6.07 (1H, d, *J* 1.6 Hz, 4-H), 6.28 (1H, dd, *J* 9.9, 1.6 Hz, 2-H), 7.17 (1H, d, *J* 9.9 Hz, 1-H) (Found: M^+, 422.2109. $C_{23}H_{31}O_6F$ requires *M*, 422.2104).

Methyl (20*S*)- and (20*R*)-11β,17α,20-trihydroxy-3-oxopregn-4-en-21-oates 5 and 6

A mixture of the acetate **12** (337 mg) and K_2CO_3 (45 mg) in absolute MeOH (4 ml) was stirred for 3 h at room temperature. After work-up, elution with $CHCl_3$–MeOH (99 : 1, v/v) afforded **5** (261 mg, 85.7%), $[\alpha]_D$ +36.6 (*c* 0.67, MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3575–3350(OH), 1733, 1663(C=O), 1620(C=C); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, Me), 1.45 (3H, s, Me), 3.81 (3H, s, CO_2Me), 4.18 (1H, s, 20-H), 4.39–4.45 (1H, m, 11-H), 5.68

(1H, s, 4-H) (Found: M^+, 392.2196. $C_{22}H_{32}O_6$ requires *M*, 392.2197).

A mixture of the acetate **13** (373 mg) and K_2CO_3 (50 mg) in dry MeOH (4 ml) was stirred for 3 h at room temperature. After work-up, elution with $CHCl_3$–MeOH (99:1, v/v) afforded **6** (270 mg, 80.1%), $[\alpha]_D$ +69.2 (*c* 0.60, MeOH); $\nu_{max}(CHCl_3)$/cm^{-1} 3600, 3550–3350(OH), 1727, 1664(C=O), 1620(C=C); δ_H (270 MHz; $CDCl_3$) 1.12 (3H, s, Me), 1.44 (3H, s, Me), 4.20 (1H, s, 20-H), 3.80 (3H, s, CO_2Me), 4.33–4.39 (1H, m, 11-H), 5.68 (1H, s, 4-H) (Found: M^+, 392.2200. $C_{22}H_{32}O_6$ requires *M*, 392.2199).

Methyl (20*S*)- and (20*R*)-11β,17α-dihydroxy-20-methoxycarbonyloxy-3-oxopregna-1,4-dien-21-oates 14 and 15

Methyl chloroformate (59.4 µl, 0.77 mmol) was added dropwise to a solution of **1** (100 mg, 0.26 mmol) and DMAP (94 mg, 0.77 mmol) in dry dichloromethane (2 ml) and the mixture was stirred for 10 min at room temperature. After quenching the reaction by addition of water, the mixture was extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$) and then evaporation of the solvent left a residue which was passed though a short silica gel pad with $CHCl_3$ as eluant to provide **14** (114 mg, quantitative yield) as a colorless syrup: $[\alpha]_D$ +45.7 (*c* 0.93, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1751, 1660(C=O), 1620, 1600(C=C); δ_H (270 MHz; $CDCl_3$) 1.07 (3H, s, Me), 1.43 (3H, s, Me), 3.63 (3H, s, CO_2Me), 3.80 (3H, s, CO_2Me), 4.30–4.50 (1H, m, 11-H), 5.0 (1H, s, 20-H), 5.93 (1H, d, *J* 2 Hz, 4-H), 6.17 (1H, dd, *J* 2, 10 Hz, 2-H), 7.23 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 448.2095. $C_{24}H_{32}O_8$ requires *M*, 448.2095).

Compound **15** (112 mg, quantitative yield) as a colorless syrup was obtained from **2** (100 mg) under the same conditions except reaction time (2 h) as described above: $[\alpha]_D$ +44.4 (*c* 0.93, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1750, 1660(C=O), 1620, 1600(C=C); δ_H (270 MHz; $CDCl_3$) 1.20 (3H, s, Me), 1.62 (3H, s, Me), 3.73 (3H, s, CO_2Me), 3.77 (3H, s, CO_2Me), 4.27–4.50 (1H, m, 11-H), 5.0 (1H, s, 20-H), 5.97 (1H, d, *J* 2 Hz, 4-H), 6.20 (1H, dd, *J* 10, 2 Hz, 2-H), 7.27 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 448.2096. $C_{24}H_{32}O_8$ requires *M*, 448.2095).

Methyl (20*S*)- and (20*R*)-9α-fluoro-16α-methyl-11β,17α-dihydroxy-20-methoxycarbonyloxy-3-oxopregna-1,4-dien-21-oates 16 and 17

Compound **16** (2.5 mg, 68.2%): $[\alpha]_D$ +52.2 (*c* 0.023, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3608, 3550–3350(OH), 1746, 1663(C=O), 1620, 1607(C=C); δ_H (270 MHz; $CDCl_3$) 0.83 (3H, d, *J* 6.9 Hz, Me), 1.12 (3H, s, Me), 1.54 (3H, s, Me), 3.78 (3H, s, CO_2Me), 3.84 (3H, s, CO_2Me), 4.31–4.38 (1H, m, 11-H), 4.93 (1H, s, 20-H), 6.11 (1H, d, *J* 1.7 Hz, 4-H), 6.33 (1H, dd, *J* 10, 1.7 Hz, 2-H), 7.17 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 480.2163. $C_{25}H_{33}O_8F$ requires *M*, 480.2160) was obtained along with its dioxolanone **22** (1.0 mg, 27.5%) from **3** (3.2 mg) under the same conditions (reaction time; 10 min) as described above.

Compound **17** (4.0 mg, 76.4%): $[\alpha]_D$ +58.3 (*c* 0.024, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3608, 3550–3350(OH), 1750, 1660(C=O), 1620, 1600(C=C); δ_H (270 MHz; $CDCl_3$) 1.10 (3H, d, *J* 6.9 Hz, Me), 1.27 (3H, s, Me), 1.53 (3H, s, Me), 3.79 (3H, s, CO_2Me), 3.82 (3H, s, CO_2Me), 4.26–4.34 (1H, m, 11-H), 5.05 (1H, s, 20-H), 6.10 (1H, d, *J* 2 Hz, 4-H), 6.32 (1H, dd, *J* 10, 2 Hz, 2-H), 7.23 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 480.2165. $C_{25}H_{33}O_8F$ requires *M*, 480.2160) was obtained along with its dioxolanone **23** (2.8 mg, 23.5%) from **4** (4.6 mg) under the same conditions (reaction time; 2 h) as described above.

Methyl (20*S*)- and (20*R*)-11β,17α-dihydroxy-20-methoxycarbonyloxy-3-oxopregn-4-en-21-oates 18 and 19

Compound **18** (13.3 mg, 43.9%): $[\alpha]_D$ +78.1 (*c* 0.064, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3604, 3500–3300(OH), 1748, 1660(C=O), 1615(C=C); δ_H (270 MHz; $CDCl_3$) 1.14 (3H, s, Me), 1.44 (3H, s, Me), 3.79 (3H, s, CO_2Me), 3.85 (3H, s, CO_2Me), 4.47–4.52 (1H, m, 11-H), 5.06 (1H, s, 20-H), 5.68 (1H, s, 4-H) (Found: M^+, 450.2249. $C_{24}H_{34}O_8$ requires *M*, 450.2252) was obtained along with its dioxolanone **24** (8.6 mg, 30.5%) from **5** (26.4 mg) under the same conditions (reaction time; 10 min) as described above.

Compound **19** (42.1 mg, quantitative yield) was obtained from **6** (36.5 mg) under the same conditions (reaction time; 2 h) as described above: $[\alpha]_D$ +74.6 (*c* 0.421, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3500–3300(OH), 1749, 1663(C=O), 1610(C=C); δ_H ($CDCl_3$) 1.21 (3H, s, Me), 1.44 (3H, s, Me), 3.81 (3H, s, CO_2Me), 3.83 (3H, s, CO_2Me), 4.35–4.42 (1H, m, 11-H), 5.02 (1H, s, 20-H), 5.68 (1H, s, 4-H) (Found: M^+, 450.2251. $C_{24}H_{34}O_8$ requires *M*, 450.2252).

Conversion of (20*S*)- and (20*R*)-methyl glycolates 1 and 2 into dioxolanones 20 and 21

Methyl chloroformate (160 µl, 2.1 mmol) was added dropwise to a solution of the methyl glycolate **1** (270 mg, 0.69 mmol) and DMAP (338 mg, 2.8 mmol) in dry dichloromethane (5 ml) at 0 °C and the mixture was stirred for 25 h at room temperature. After dilution of the mixture with chloroform, it was washed with brine, dried ($MgSO_4$) and then evaporation of the solvent left a residue which was chromatographed on silica gel with hexane–ethyl acetate (1:1, v/v) to give **20** (217 mg, 87.6%), mp 255–256 °C, $[\alpha]_D$ +55.0 (*c* 0.20, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1815, 1753, 1660(C=O), 1620, 1605(C=C); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, Me), 1.45 (3H, s, Me), 3.80 (3H, s, CO_2Me), 4.43–4.63 (1H, m, 11-H), 4.90 (1H, s, 20-H), 5.97 (1H, d, *J* 1.7 Hz, 4-H), 6.18 (1H, dd, *J* 10, 1.7 Hz, 2-H), 7.17 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 416.1834. $C_{23}H_{28}O_7$ requires *M*, 416.1834).

Dioxolanone **21** (288 mg, quantitative yield) was obtained from **2** (270 mg) under the same condition described above, mp 278–279 °C, $[\alpha]_D$ +32.0 (*c* 0.20, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1815, 1753, 1660(C=O), 1620, 1605(C=C); δ_H (270 MHz; $CDCl_3$) 1.17 (3H, s, Me), 1.44 (3H, s, Me), 3.86 (3H, s, CO_2Me), 4.45–4.50 (1H, m, 11-H), 4.85 (1H, s, 20-H), 6.02 (1H, d, *J* 1.7 Hz, 4-H), 6.27 (1H, dd, *J* 10, 1.7 Hz, 2-H), 7.19 (1H, d, *J* 10 Hz) (Found: M^+, 416.1831. $C_{23}H_{28}O_7$ requires *M*, 416.1834).

Conversion of (20*S*)- and (20*R*)-methyl glycolates 3 and 4 into dioxolanones 22 and 23

Dioxolanone **22** (51.6 mg, quantitative yield) was obtained from **3** (24 mg) as a colorless caramel under the same conditions described above, $[\alpha]_D$ +27.7 (*c* 0.56, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1811, 1745, 1665(C=O), 1625, 1610(C=C); δ_H (270 MHz; $CDCl_3$) 0.92 (3H, d, *J* 7 Hz, Me), 1.19 (3H, s, Me), 1.52 (3H, s, Me), 3.77 (3H, s, CO_2Me), 4.17–4.50 (1H, m, 11-H), 4.87 (1H, s, 20-H), 6.03 (1H, d, *J* 1.7 Hz, 4-H), 6.22 (1H, dd, *J* 10, 1.7 Hz, 2-H), 7.20 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 448.1890. $C_{24}H_{29}O_7F$ requires *M*, 448.1895).

Dioxolanone **23** (26.4 mg, 98.0%) was obtained from **4** (24 mg) under the same conditions described above, mp 263–264 °C, $[\alpha]_D$ +21.4 (*c* 0.16, MeOH); $\nu_{max}(KBr)/cm^{-1}$ 1810, 1752, 1660(C=O), 1610(C=C); δ_H (270 MHz; $CDCl_3$) 1.13 (3H, d, *J* 7 Hz, Me), 1.19 (3H, s, Me), 1.54 (3H, s, Me), 3.87 (3H, s, CO_2-Me), 4.18–4.28 (1H, m, 11-H), 4.87 (1H, s, 20-H), 6.08 (1H, d, *J* 2 Hz, 4-H), 6.28 (1H, dd, *J* 10, 2 Hz, 2-H), 7.25 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 448.1890. $C_{24}H_{29}O_7F$ requires *M*, 448.1895).

Conversion of (20*S*)- and (20*R*)-methyl glycolates 5 and 6 into dioxolanones 24 and 25

Dioxolanone **24** (28.1 mg, quantitative yield) was obtained from **5** (25.9 mg) under the same conditions described above. $[\alpha]_D$ +60.0 (*c* 0.05, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3550–-3300(OH) 1811, 1747, 1662(C=O), 1619(C=C); δ_H (270 MHz; $CDCl_3$) 1.14 (3H, s, Me), 1.45 (3H, s, Me), 3.85 (3H, s, CO_2Me), 4.40–4.53 (1H, m, 11-H), 4.96 (1H, s, 20-H), 5.69 (1H, s, 4-H) (Found: M^+, 418.1992. $C_{23}H_{30}O_7$ requires *M*, 418.1992).

Dioxolanone **25** (9.3 mg, 96.0%) was obtained from **6** (9.1 mg) under the same conditions described above: $[\alpha]_D$ +57.1 (*c* 0.056, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3600, 3550–3300(OH), 1812, 1750, 1662(C=O), 1618(C=C); δ_H (270 MHz; $CDCl_3$) 1.15 (3H, s, Me), 1.43 (3H, s, Me), 3.86 (3H, s, CO_2Me), 4.38–4.46 (1H, m, 11-H), 4.86 (1H, s, 20-H), 5.66 (1H, s, 4-H) (Found: M^+, 418.1993. $C_{23}H_{30}O_7$ requires *M*, 418.1992).

Quantitative analysis on the formation of the methyl glycolates 1 and 2, 3 and 4, and 5 and 6 from corresponding prednisolone, dexamethasone and hydrocortisone under various conditions

A solution of the appropriate steroid (each 20 mg) in dry methanol was added dropwise to a solution of cupric acetate in dry methanol at the molar ratios cupric acetate : steroid of 0.1, 0.2, 0.5, 1.0 and 2.0, and the mixture was stirred at room temperature for the time shown in Fig. 1. Time courses for the formation of the products (**1** and **2**), (**3** and **4**) and (**5** and **6**) were followed by HPLC. Thus, a reaction mixture (50 ml) was diluted with dichloromethane (10 ml) from which a solution (6 ml) was taken and subjected to the analysis. The yields of the products (**1** and **2**), (**3** and **4**) and (**5** and **6**) were determined by calculating the area under the curve of the corresponding peaks A (retention time, 4.3 min for **1**, 6.2 min for **3** and 4.5 min for **5**) and B (3.9 min for **2**, 5.7 min for **4** and 4.0 min for **6**) which were detected at 245 nm in the HPLC system developed with acetonitrile–water (55 : 45, v/v) as a mobile phase.

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