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A New Efficient Method for Conversion of Corticosteroid 17α,21-Cyclic Ortho Esters to 17α-Acyloxy-21-chloro-21-deoxy Derivatives

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The reaction of corticosteroid 17α,21-cyclic ortho esters (**2**) with various chloroformates (**3**) afforded the corresponding 17α-acyloxy-21-chloro-21-deoxy derivatives (**4**) in good yields. It was found that several new derivatives, 17α-acyloxy-21-chloro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-diones (**4a**—**g**), exhibited potent vasoconstrictive activities.

Keywords——corticosteroid 17α,21-cyclic ortho ester; chloroformate; 17α-acyloxy-21-chloro-21-deoxy corticosteroid; vasoconstrictive activity; tertiary amide; iminium chloride

Certain 17α-acyloxy corticosteroids in which the 21-hydroxy group is replaced a chlorine atom have recently been developed as potent topical antiinflammatory agents, among which 21-chloro-9α-fluoro-11β-hydroxy-16β-methyl-17α-(1-oxopropoxy)-1,4-pregnadiene-3,20-dione[1] is the most potent and is now being used clinically. We hoped to develop other useful antiinflammatory agents of similar types.

Direct conversions of the corticosteroid 17α,21-cyclic ortho esters (**2**) to the corresponding 17α-acyloxy-21-chloro-21-deoxy derivatives (**4**) have been attempted by using chlorinating reagents such as trialkylsilyl chloride[2] and triphenylmethyl chloride.[3] Reaction with triphenylmethyl chloride does not always give good results in the corticosteroid system (10—40% yields)[3] although it results in good yields (83—93%) in a simple dioxolane system.[4] The use of trialkylsilyl chloride affords 4 in poor (in CH_2Cl_2) or moderate (in *N,N*-dimethylformamide (DMF)) yields. It seems that the solvent used affects the yields, though no details have been given in the patent literature.[2]

In order to develop a useful and practical method for this direct conversion, we investigated the utilization of various chloroformates[5] (**3**) which are commercially available.

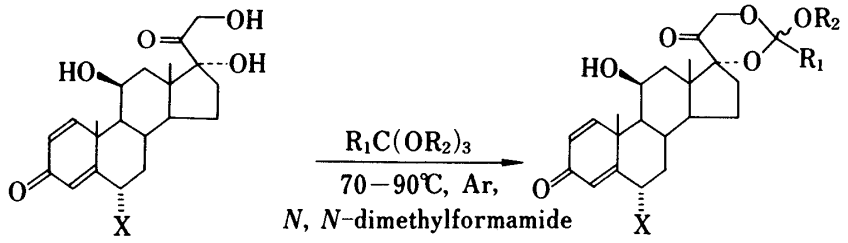
In this paper, we describe a new, efficient method for the conversion of the 17α,21-cyclic ortho esters (**2**) of corticosteroids to the corresponding 17α-acyloxy-21-chloro-21-deoxy derivatives (**4**) and report the vasoconstrictive activity[6] of some newly synthesized corticosteroid 17α-acyloxy-21-chloro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-diones (**4a**—**g**).

Results and Discussion

Synthesis

First, our improved synthetic method for the corticosteroid 17α,21-cyclic ortho esters (**2**) is described. In the known procedure,[2,3] the ortho esters are obtained in unsatisfactory yields. It is considered that the relatively severe reaction conditions used give rise to the formation of undesired products due to high reaction temperature (125°C) and prolonged reaction time (9 h). Several attempts to find better conditions and to optimize yields resulted in the corresponding ortho esters (**2**) in satisfactory yields by employing lower reaction temperatures (70—90°C) and shorter reaction times (1—2 h) than those in the known conditions. Under these conditions, most of the ortho esters (**2**) could be isolated easily by simple recrystallization from the crude reaction products. The results are shown in Table I.

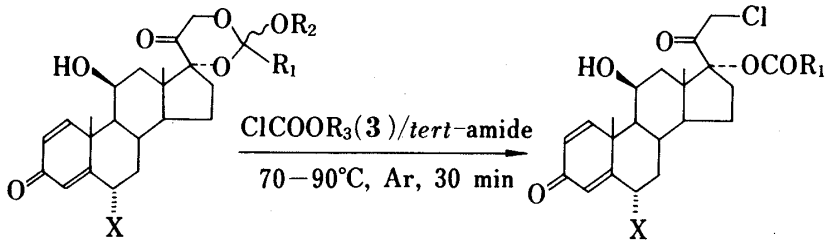
TABLE I. Corticosteroid 17α,21-Cyclic Ortho Esters (**2a**—**m**)



1 **2**

Compd. **2**	Yield[a] (%)	mp(°C)
2a	92.5	134.0—136.0
2b	91.2	160.0—164.0
2c	90.9	164.0—166.0
2d	93.9	172.0—175.0
2e	91.7[b]	Amorphous
2f	82.8	168.0—171.0
2g	66.4[b]	Amorphous
2h	89.9	186.0—189.5[c]
2i	93.1	187.5—189.5[d]
2j	84.7	217.5—219.5[e]
2k	84.0	146.0—147.0[f]
2l	88.4	180.5—182.5
2m	91.7	188.5—191.0

a) Isolated yield after recrystallization unless otherwise noted.
b) Isolated by silica-gel column chromatography.
c) Lit.[2b] mp 182.5—183.5°C.
d) Lit.[2b] mp 180.0—184.0°C.
e) Lit.[2b] mp 219.0—221.0°C.
f) Lit.[2b] mp 146.0—147.0°C.



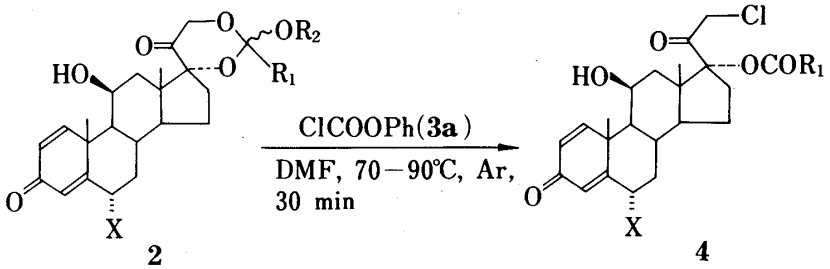
2 **4**

	R_1	R_2	X
2a	Me	Et	Me
2b	Et	Et	Me
2c	*n*-Pr	Et	Me
2d	iso-Pr	Me	Me
2e	*n*-Bu	Me	Me
2f	iso-Bu	Me	Me
2g	Ph	Me	Me
2h	Et	Et	H(1,2-dihydro)
2i	Et	Et	H
2j	Et	Et	H(9α-F-16α-Me)
2k	Et	Et	H(9α-Cl-16β-Me)
2l	Et	Et	H(1,2-dihydro-11-deoxy)
2m	Et	Et	H(11-oxo)

3a: R_3 = Ph
3b: R_3 = $PhCH_2$
3c: R_3 = CH_3CH_2

Chart 1

TABLE II. 17α-Acyloxy-21-chloro-21-deoxy Corticosteroids (**4a**—**m**)



2 **4**

Compd. **4**	Yield[a] (%)	mp(°C)
4a	47.3	242.0—246.0
4b	81.3(52.2)[b]	147.5—149.0
4c	68.9	121.5—123.0
4d	62.4	145.5—149.0
4e	53.4	110.0—112.0
4f	58.7	118.0—121.0
4g	51.2	156.0—158.0
4h	69.3	239.5—241.5[d]
4i	82.3	224.0—226.0[e]
4j	62.9	243.0—244.0[f]
4k	33.8[c]	229.0—230.0[g]
4l	84.1	177.0—178.5
4m	72.3	Amorphous[h]

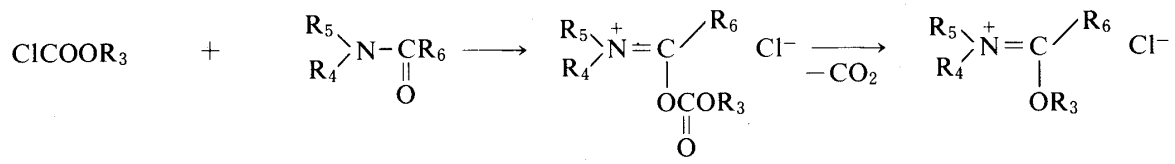
a) Isolated yield after recrystallization following preparative thin layer chromatography.
b) 1,2-Dichloroetnane was used as a solvent.
c) 9α-Chloro-11β-hydroxy-16-methyl-21-propanoyloxypregna-1,4,6-triene-3, 20-dione was obtained in 38.1% yield as a major product,[7] mp 203.0—206.0°C, *m/z* 448(M^++2), 447, 446(M^+).
d) Lit.[2b] mp 225.0—227.0°C.
e) Lit.[2b] mp 225.0—227.0°C.
f) Lit.[2b] mp 241.0—243.0°C.
g) Lit.[2b] mp 202.0—205.0°C.
h) Lit. mp 97.0—100.0°C (Boots Pure Drug Co., Ltd., Fr.Patent 1513708 (1968) [*cf. Chem. Abstr.*, **71**, P 13284*m*(1969)]).

The direct conversion of the ortho esters (**2**) according to the conventional methods[2,3] using triphenylmethyl chloride and trialkylsilyl chloride generally afforded the corresponding ring-opened compounds (**4**) in relatively low yields (20—50%). In order to improve this process, we tried to use a variety of chlorinating agents. The use of various chloroformates (**3**) with tertiary amides as solvents resulted in much improved yields. This reaction was usually carried out at 70—90°C for 30 min under an argon atmosphere, and the product was isolated by preparative thin layer chromatography (Chart 1). The yields and melting points of the products obtained in DMF are summarized in Table II.

In all cases, it was observed that chloroformates (**3**) reacted with the tertiary amides used as solvents to give the corresponding iminium compounds (**6**).[8] For example, phenyl chloroformate (**3a**) reacted immediately with DMF and *N*-formylmorpholine (NFM)[9] with vigorous generation of carbon dioxide at room temperature to afford the corresponding iminium compounds **6a** and **6b**, respectively, which could be isolated in crystalline forms, whereas the reaction of acetamide (DMA) or cyclic amides (*N*-methyl-2-pyrrolidone and *N*-methyl-2-piperidone) with **3** proceeded slowly with mild evolution of carbon dioxide at room temperature.

Hence, it could be considered that the resulting iminium compounds (**6**) or their precursors (**5**) might be the real chlorinating agents and react with **2** to afford **4**. It was further found that the ring-opening reactions of **2b** using isolated **6a** gave **4b** in 45.6% (in 1,2-dichloroethane) and 46.7% (in DMF)[10] yields. These results indicate that the iminium

compounds (**6**) play an important role in this reaction and probably are the actual chlorinating agents. The reaction scheme for the formation of the iminium salts (**6**) is illustrated in Chart 2.



3 **5** **6**

3a: R_3 = Ph
3b: R_3 = $PhCH_2$
3c: R_3 = CH_3CH_2

$R_4 = R_5 = CH_3$, R_6 = H
$R_4 = R_5 = O(CH_2CH_2)_2^-$, R_6 = H
$R_4 = CH_3$, $R_5 = R_6 = -(CH_2)_3-$
$R_4 = CH_3$, $R_5 = R_6 = -(CH_2)_4-$
$R_4 = R_5 = R_6 = CH_3$

6a: R_3 = Ph, $R_4 = R_5 = CH_3$, R_6 = H
6b: R_3 = Ph, $R_4 = R_5 = O(CH_2CH_2)_2^-$, R_6 = H

Chart 2

Among the tertiary amides the *N,N*-dialkylformamides (DMF and NFM) were more effective in the chlorination reaction, resulting in satisfactory formation of the corresponding ring-opened chloro derivatives (**4**) (Table III). This solvent effect correlates well with the ease of formation of the iminium salts (**6**). Furthermore, it seems that the reactivity of these iminium salts (**6**) for chlorination must be due to more favorable steric characteristics and the chemical nature (covalent or ionic bonding) of the chlorine atom.

In addition, among a variety of chloroformates (**3**), phenyl chloroformate (**3a**) was converted to the most moisture-insensitive iminium compounds (**6a** and **6b**), and the use of **3a** gave the best result in producing the corresponding product (**4**). The results are listed in Table IV.

TABLE III. Effect of Various *tert*-Amides

2b (0.1 mmol) —ClCOOPh (**3a**) 0.2—0.4 mmol, *tert*-amide 2 ml, Ar, 80—90℃, 30 min→ **4b**

tert-Amide	Yield[a] (%) of **4b**
N,N-Dimethylformamide (DMF)	81.3
N-Formylmorpholine (NFM)	92.3
N-Methyl-2-pyrrolidone	48.7
N-Methyl-2-piperidone	47.5
N,N-Dimethylacetamide	50.3

a) Isolated yield after recrystallization following preparative thin layer chromatography. All the reactions were carried out after formation of the corresponding iminium compound (**6**) from **3a** and *tert*-amides.

TABLE IV. Effect of Ester Moiety in the Reaction with Various Chloroformates (**3a—c**)

2b (0.1 mmol) —$ClCOOR_3$ (**3**) 0.4 mmol, DMF 2 ml, 85℃, Ar, 30 min→ **4b**

Compd. **3**	R_3 in **3**	Yield[a] (%) of **4b**
3a	Ph	81.3
3b	$PhCH_2$[b]	56.7
3c	CH_3CH_2	40.0

a) Isolated yield. All the reactions were carried out after formation of the corresponding iminium compound (**6**) from **3** and DMF.
b) A commercially available 30—35% toluene solution was used.

Thus, the present reaction using chloroformate (**3**) in *N,N*-dialkylformamides provides simple and efficient methodology for the direct conversion of corticosteroid 17α,21-cyclic ortho esters (**2**) to the 17α-acyloxy-21-chloro-21-deoxy corticosteroids (**4**), which are potentially useful as topical antiinflammatory agents.

Vasoconstrictive Activities

The newly synthesized 17α-acyloxy-21-chloro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-diones (**4a—g**) were tested for vasoconstrictive activities in humans by McKenzie's method.[6] This assay correlates well with the clinical efficacy of topical antiinflammatory corticosteroids.

Preparations of 0.01% (w/w) vaseline ointment of **4a—g**, 6α-methylprednisolone (MP) and betamethasone 17α-valerate (BMV) were applied to the flexor aspects of both forearms of ten healthy males and left undisturbed for 16 hr. After removal of the ointment, the vasoconstrictive activities were investigated at 2 and 6 h later. The results are summarized in Table V. All of the compounds (**4a—g**) were 2—4 times more active than the parent compound (MP). In particular, it was found that **4c** and BMV are equipotent.

TABLE V. Vasoconstrictive Activities of 17α-Acyloxy-21-chloro-21-deoxy Corticosteroids (**4a—4g**)

Compd. **4**	Vasoconstrictive activity[a]		Activity ratio[b]
	After 2 h	After 6 h	
4a	24.5	9.5	3.5
4b	25.5	13.0	3.6
4c	24.5	16.5	3.5
4d	25.5	13.5	3.6
4e	18.5	10.5	2.6
4f	16.5	7.0	2.4
4g	21.0	13.0	3.0
MP[c]	7.0	4.0	1
BMV[d]	26.5	17.0	3.8
Base(placebo)	3.0	2.0	—

a) Shown as total scores of ten males (maximum is 30). The ratios are as follows: 3 for the most potent vasoconstriction; 2 for moderate effect; 1 for slight effect; 0 for not effective.
b) Based on the activity after 2h.
c) 6α-Methylprednisolone.
d) Betamethasone 17α-valerate.

Experimental[11]

General Procedure for the Preparation of Corticosteroid 17α,21-Cyclic Ortho Esters (2a—m)——Ethyl or methyl ortho ester (2 mmol) was added to a solution of a corticosteroid (**1**; 1 mmol) dissolved in DMF (4ml) followed by the addition of *p*-toluenesulfonic acid (0.05—0.1 mmol), and the mixture was heated at 70—90°C with stirring for 1 or 2 h under an argon current. Then, ethyl acetate (50 ml) and 10% Na_2CO_3 aq. solution (0.5 ml) were added to the reaction mixture. The organic layer was separated and washed with water (30 ml×3). The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting product (**2**) was isolated by recrystallization from ether–hexane or by trimethylamine-moistened silica-gel column chromatography. The results are summarized in Table I. Spectral data for new compounds (**2**) are as follows.

6α-Methylprednisolone 17α,21-Ethyl Orthoacetate (2a)——IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1715 (C=O), 1650 (C=O). Mass spectrum (MS) *m/z*: 445 (M^++1), 444 (M^+), 427, 416, 399, 356, 297, 279, 161, 136, 135 (base peak), 121, 43.

6α-Methylprednisolone 17α,21-Ethyl Orthopropionate (2b)——IR ν_{max}^{KBr} cm^{-1}: 3350, (OH), 1720 (C=O), 1645 (C=O). MS *m/z*: 459 (M^++1), 458 (M^+), 441, 430, 395, 356, 297, 279, 161, 136, 135 (base peak), 121, 57.

6α-Methylprednisolone 17α,21-Ethyl Orthobutyrate (2c)——IR ν_{max}^{KBr} cm^{-1}: 3340 (OH), 1720 (C=O), 1645 (C=O). MS *m/z*: 473 (M^++1), 472 (M^+), 427, 356, 311, 297, 279, 161, 136, 135 (base peak), 121, 71.

6α-Methylprednisolone 17α,21-Methyl Orthoisobutyrate (2d)——IR ν_{max}^{KBr} cm^{-1}: 3320 (OH), 1715 (C=O), 1645 (C=O). MS *m/z*: 459 (M^++1), 458 (M^+), 427, 356, 325, 297, 279, 161, 136 (base peak), 135, 121, 71.

6α-Methylprednisolone 17α,21-Methyl Orthovalerate (2e)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1645 (C=O). MS *m/z*: 473 (M^++1), 472 (M^+), 454, 441, 356, 297, 279, 252, 203, 185, 161, 136, 135 (base peak), 121, 85.

6α-Methylprednisolone 17α,21-Methyl Orthoisovalerate (2f)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1715 (C=O), 1650 (C=O). MS *m/z*: 473 (M^++1), 472 (M^+), 458, 441, 356, 325, 297, 279, 264, 237, 171, 161, 136, 135 (base peak), 121,85.

6α-Methylprednisolone 17α,21-Methyl Orthobenzoate (2g)——IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1715 (C=O), 1645 (C=O). MS *m/z*: 493 (M^++1), 492 (M^+), 475, 461, 356, 297, 279, 264, 161, 149, 148, 136, 135, 121, 105 (base peak), 77.

11-Deoxyhydrocortisone 17α,21-Ethyl Orthopropionate (2l)——IR ν_{max}^{KBr} cm^{-1}: 1723 (C=O), 1658 (C=O). MS *m/z*: 431 (M^++1), 430 (M^+), 402, 385, 328, 283, 258, 227, 200, 124, 119, 103, 93, 57 (base peak).

Prednisone 17α,21-Ethyl Orthopropionate (2m)——IR ν_{max}^{KBr} cm^{-1}: 1723 (C=O), 1698 (C=O), 1658 (C=O). MS *m/z*: 443 (M^++1), 442(M^+), 414, 397, 368, 340, 295, 270, 242, 197, 147, 121, 103, 57 (base peak).

General Procedure for the Preparation of 17α-Acyloxy-21-chloro-21-deoxy Corticosteroids (4a—m)——A chloroformate (**3**; 0.2—0.4 mmol) was dissolved in DMF (2—4 ml) and the solution was heated at 80—90°C for 15 min in an argon atmosphere. Then, a corticosteroid 17α, 21-cyclic ortho ester (**2**; 0.1—0.2 mmol) was added to the solution and the reaction mixture was stirred for 30 min at the same temperature under an argon current. The reaction mixture was cooled, then ethyl acetate (50 ml) was added and the mixture was washed with water (30 ml×3), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. From the resulting residue, **4** was isolated by preparative thin-layer chromatography on silica gel and the product was recrystallized from ether–hexane. The results were as follows.

17α-Acetoxy-21-chloro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (4a)——IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1725 (C=O) 1715 (C=O), 1645 (C=O). ^{1}H-NMR δ ppm ($CDCl_3$): 0.98 (3H, s, C_{18}–CH_3), 1.12 (3H, d, *J*=6Hz, $C_{6\alpha}$–CH_3), 1.47 (3H, s, C_{19}–CH_3), 2.05(3H, s, $COCH_3$), 4.18 (2H, s, C_{21}–CH_2), 4.50 (1H, br, C_{11}–CH), 6.04 (1H, brs, C_4–CH), 6.28 (1H, d, *J*=10 Hz, C_2–CH), 7.37 (1H, d, *J*=10 Hz, C_1–CH). MS *m/z*: 436 (M^++2), 435, 434 (M^+), 297, 279, 239, 161, 137, 136 (base peak),135, 121, 43. $[\alpha]_D^{23}$ +61° (*c*=1.0, ethanol). *Anal.* Calcd for $C_{24}H_{31}ClO_5$: C, 66.27; H, 7.18; Cl, 8.15. Found: C, 66.12; H, 7.14; Cl, 8.08.

21-Chloro-11β-hydroxy-6α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4b)——IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1720 (C=O), 1710 (C=O), 1645 (C=O). ^{1}H-NMR δ ppm ($CDCl_3$): 1.00—1.20 (9H, m, $CH_2C\underline{H_3}$, C_{18}–CH_3 and $C_{6\alpha}$–CH_3), 1.47 (3H, s, C_{19}–CH_3), 4.14 (2H, s, C_{21}–CH_2), 4.50 (1H, br s, C_{11}–CH), 6.00 (1H, br s, C_4–CH), 6.25 (1H, d, *J*=10 Hz, C_2–CH), 7.37 (1H, d, *J*=10 Hz, C_1–CH). MS *m/z*: 450 (M^++2), 449, 448 (M^+), 374, 313, 297, 279, 161, 137, 136 (base peak), 135, 121, 57. $[\alpha]_D^{23}$ +46° (*c*=1.0, ethanol). *Anal.* Calcd for $C_{25}H_{33}ClO_5$: C, 66.88; H, 7.41; Cl, 7.90. Found: C, 67.14; H, 7.48; Cl, 7.69.

21-Chloro-17α-butyryloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione(4c)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1715 (C=O), 1645 (C=O). ^{1}H-NMR δ ppm ($CDCl_3$):0.93 (3H, m, $CH_2CH_2C\underline{H_3}$), 1.00 (3H, s, C_{18}–CH_3), 1.13 (3H, d, *J*=8 Hz, $C_{6\alpha}$–CH_3), 1.46 (3H, s, C_{19}–CH_3), 4.15 (2H, d, *J*=1.5 Hz, C_{21}–CH_2), 4.48 (1H, br, C_{11}–CH), 6.03 (1H, br s, C_4–CH), 6.26 (1H, d, *J*=10 Hz, C_2–CH), 7.33 (1H, d, *J*=10 Hz, C_1–CH). MS *m/z*: 464 (M^++2), 463, 462 (M^+), 374, 297, 279, 161, 137, 136 (base peak),135, 121, 71. $[\alpha]_D^{23}$ +50° (*c*=1.0, ethanol). *Anal.* Calcd for $C_{26}H_{35}ClO_5$: C, 67.45; H, 7.62; Cl, 7.66. Found: C, 67.33; H, 7.60; Cl, 7.82.

21-Chloro-11β-hydroxy-17α-isobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione (4d)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1715 (C=O), 1645 (C=O). ^{1}H-NMR δ ppm ($CDCl_3$): 1.02 (3H, s, C_{18}–CH_3), 1.16 (6H, d, *J*=6 Hz, –$CH(C\underline{H_3})_2$), 1.16 (3H, d, *J*=6 Hz, $C_{6\alpha}$–CH_3), 1.50 (3H, s, C_{19}–CH_3), 4.12 (2H, s, C_{21}–CH_2), 4.50 (1H, br, C_{11}–CH), 6.03 (1H, br s, C_4–CH), 6.27 (1H, d, *J*=10 Hz, C_2–CH), 7.35 (1H, d, *J*=10Hz, C_1–CH). MS *m/z*: 464 (M^++2), 463, 462 (M^+), 374, 297, 279, 161, 137, 136 (base peak), 135, 121, 71. $[\alpha]_D^{23}$ +56° (*c*=1.0, ethanol). *Anal.* Calcd for $C_{26}H_{35}ClO_5$: C, 67.45; H, 7.62; Cl, 7.66. Found: C, 67.12; H, 7.64; Cl, 7.73.

21-Chloro-11β-hydroxy-6α-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione (4e)——IR ν_{max}^{KBr} cm^{-1}:3400 (OH), 1720 (C=O), 1715 (C=O), 1650 (C=O). ^{1}H-NMR δ ppm ($CDCl_3$): 0.93 (3H, m, $CH_2CH_2CH_2C\underline{H_3}$), 1.02 (3H, s, C_{18}–CH_3), 1.16 (3H, d, *J*=6 Hz, $C_{6\alpha}$–CH_3),1.48 (3H, s, C_{19}–CH_3), 4.20 (2H, d, *J*=2 Hz, C_{21}–CH_2), 4.63 (1H, br, C_{11}–CH), 6.03 (1H, br s, C_4–CH), 6.28 (1H, d, *J*=10 Hz, C_2–CH), 7.30 (1H, d, *J*=10 Hz, C_1–CH). MS *m/z*: 478 (M^++2), 477, 476 (M^+), 374, 341, 297, 279, 181, 161, 137, 136 (base peak), 135, 121, 85. $[\alpha]_D^{23}$ +37° (*c*=1.0, ethanol). *Anal.* Calcd for $C_{27}H_{37}ClO_5$: C, 67.98; H, 7.82; Cl, 7.43. Found: C, 67.70; H, 7.76; Cl, 7.39.

21-Chloro-11β-hydroxy-17α-isovaleryloxy-6α-methyl-1,4-pregnadiene-3,20-dione (4f)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (C=O), 1710 (C=O), 1650 (C=O). ^{1}H-NMR δ ppm ($CDCl_3$): 1.00 (9H, m, $CH_2CH(C\underline{H_3})_2$ and C_{18}–CH_3), 1.14 (3H, d, *J*=6 Hz, $C_{6\alpha}$–CH_3), 1.46 (3H, s, C_{19}–CH_3), 4.16 (2H, s, C_{21}–CH_2), 4.50 (1H, br, C_{11}–CH), 6.07 (1H, br s, C_4–CH), 6.30 (1H, d, *J*=10 Hz, C_2–CH), 7.35 (1H, d, *J*=10 Hz, C_1–CH). MS *m/z*: 478 (M^++2), 477, 476 (M^+), 374, 341, 297, 279, 161, 137, 136 (base peak), 135, 121, 85. $[\alpha]_D^{23}$ +37° (*c*=1.0 ethanol). *Anal.* Calcd for $C_{27}H_{37}ClO_5$: C, 67.98; H, 7.82; Cl, 7.43. Found: C, 67.73; H, 7.58; Cl, 7.61.

17α-Benzoyloxy-21-chloro-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione (4g)——IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1715 (C=O), 1700 (C=O), 1650 (C=O). ^{1}H-NMR δ ppm ($CDCl_3$): 1.08 (3H, s, C_{18}–CH_3), 1.23 (3H, m, $C_{6\alpha}$–CH_3), 1.53 (3H, s, C_{19}–CH_3), 4.18 (2H, s, C_{21}–CH_2), 4.61 (1H, br, C_{11}–CH), 6.09 (1H, br s, C_4–CH), 6.29

(1H, d, J=10 Hz, C_2-CH), 7.25—8.10 (6H, m, C_1-CH and Ph). MS m/z: 498 (M^++2), 497, 496 (M^+), 401, 374, 361, 297, 279, 239, 161, 137, 136, 135, 122, 121, 105 (base peak),77. $[\alpha]_D^{23}$ +17° (c=1.0,ethanol). *Anal.* Calcd for $C_{29}H_{33}ClO_5 \cdot 1/2H_2O$: C, 68.83; H, 6.77; Cl, 7.01. Found: C, 68.96; H, 6.82; Cl, 6.98.

21-Chloro-11β-hydroxy-17α-propanoyloxy-4-pregnene-3,20-dione (4h)———IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1725 (C=O), 1715 (C=O), 1645 (C=O). MS m/z: 438 (M^++2), 437, 436 (M^+), 418, 401, 380, 362, 326, 286, 267, 163, 121, 105, 57 (base peak).

21-Chloro-11β-hydroxy-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4i)———IR ν_{max}^{KBr} cm^{-1}: 3360 (OH), 1725 (C=O), 1715 (C=O), 1645 (C=O). MS m/z: 436 (M^++2), 435, 434 (M^+), 416, 399, 360, 325, 284, 265, 223, 161, 135, 121, 57 (base peak).

21-Chloro-9α-fluoro-11β-hydroxy-16α-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4j)———IR ν_{max}^{KBr} cm^{-1}: 3270 (OH), 1730 (C=O), 1720 (C=O), 1655 (C=O). MS m/z: 468 (M^++2), 467, 466 (M^+), 446, 410, 372, 313, 295, 187, 135, 121, 57 (base peak).

9α,21-Dichloro-11β-hydroxy-16β-methyl-17α-propanoyloxy-1,4-pregnadiene-3,20-dione (4k)———IR ν_{max}^{KBr} cm^{-1}: 3460 (OH), 1730 (C=O), 1720 (C=O), 1660 (C=O). MS m/z: 486 (M^++4), 485, 484, 483, 482 (M^+), 446, 372, 358, 331, 295, 277, 187, 135, 121, 57 (base peak).

21-Chloro-17α-propanoyloxy-4-pregnene-3,20-dione (4l)———IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O), 1715 (C=O), 1660 (C=O). ^{1}H-NMR δ ppm ($CDCl_3$): 0.73 (3H, s, C_{18}-CH_3), 1.13 (3H, t, J=8 Hz, CH_2-$C\underline{H}_3$), 1.18 (3H, s, C_{19}-CH_3), 4.12 (2H, d, J=1.5 Hz,C_{21}-CH_2), 5.73 (1H, s, C_4-CH). MS m/z: 422 (M^++2), 421, 420 (M^+), 385, 371, 364, 346, 329, 297, 244, 147, 121, 105, 57 (base peak). $[\alpha]_D^{23}$ +63° (c=1.0, ethanol). *Anal.* Calcd for $C_{24}H_{33}ClO_5$: C, 68.47; H, 7.90; Cl, 8.42. Found: C, 68.56; H, 7.72; Cl, 8.29.

21-Chloro-17α-propanoyloxy-1,4-pregnadiene-3,11,20-trione (4m)———IR ν_{max}^{KBr} cm^{-1}: 1730 (C=O), 1725 (C=O), 1700 (C=O), 1660 (C=O). MS m/z: 434 (M^++2), 433, 432 (M^+), 397, 376, 358, 299, 281, 255, 161, 121, 57 (base peak).

Preparation of Phenoxymethyleneiminium Compounds (6a and 6b)

***N,N*-Dimethyl-*N*-phenoxymethyleneiminium Chloride (6a)**———Phenyl chloroformate (**3a**; 1.56 g, 10 mmol) was added to molecular sieves-dried DMF (1.46 g, 20 mmol) at room temperature and the mixture was stirred for 1 hr under an argon atmosphere. Dry ether (50 ml) was added to the reaction mixture to give crude crystals of **6a**, which were recrystallized from CH_2Cl_2-ether to afford **6a** in 83.2% yield. Very hygroscopic, light-brown crystals, mp 118.5—120.0°C. ^{1}H-NMR δ ppm ($CDCl_3$): 3.46 (3H, s, N-CH_3), 3.76 (3H, s, N-CH_3), 7.20—7.75 (5H, m, Ph), 10.50 (1H, s, =N=CH).

***N*-Phenoxymethylenemorpholinium Chloride (6b)**———According to the above method, the reaction of phenyl chloroformate (**3a**; 1.56 g, 10 mmol) and *N*-formylmorpholine (2.3 g, 20 mmol) afforded **6b** in 82.4% yield. See ref. 9.

Preparation of 4b using 6a———6α-Methylprednisolone 17α,21-ethyl orthopropionate (**2b**; 92 mg, 0.2 mmol) was added to DMF (2 ml) and the solution was heated at 80°C under an argon atmosphere. Then, **6a** (74 mg, 0.4 mmol) was added to the reaction mixture and the mixture was stirred for 30 min. After work-up as described in the general procedure for the preparation of **4**, **4b** was obtained in 46.7% yield. Similarly, the reaction of **6a** (74 mg, 0.4 mmol) and **2b** (92 mg, 0.2 mmol) in 1,2-dichloroethane (2 ml) afforded **4b** in 45.6% yield.

Preparation of 4b using 3a in 1,2-Dichloroethane———Phenyl chloroformate (**3a**; 62 mg, 0.4 mmol) was added to 1,2-dichloroethane (2 ml) and the mixture was stirred at 85°C under an argon atmosphere. Then, compound **2b** (92 mg, 0.2 mmol) was added to the solution and the mixture was stirred for 30 min. After work-up as described above, **4b** was obtained in 52.2% yield.

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9) The reaction of phenyl chloroformate (**3a**) and *N*-formylmorpholine afforded the corresponding iminium compound quantitatively, mp 170.0—171.5°C (dec.), hygroscopic, light-brown crystals, δ ppm 3.95 (4H, m, $O\begin{<}{CH_2-}{CH_2-}$), 4.25 (4H, m, $\begin{<}{-CH_2}{-CH_2}\overset{+}{N}=$), 7.20—7.82 (5H, m, Ph), 10.53 (1H, s, $=\overset{+}{N}=CH-$).

10) All the iminium compounds (**6**) are decomposed easily by moisture with the release of hydrogen chloride; this does not afford **4**, but the corresponding ring-opened 17α-acyloxy and 21-acyloxy compounds resulted from the decomposition of **2**. Hence, the iminium compounds (**6**) should be used in the reaction without isolation.

11) Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a JASCO IRA-I spectrophotometer. ^{1}H-NMR (δ ppm in $CDCl_3$) and mass spectra were taken on Hitachi R-24 and Hitachi RM-50 spectrophotometers, respectively. These spectra were consistent with the assigned structures.