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NEW 9,10-SECO-STEROIDS FROM 11ß-HYDROXY-8ß,9-EPOXY-DERIVATIVES

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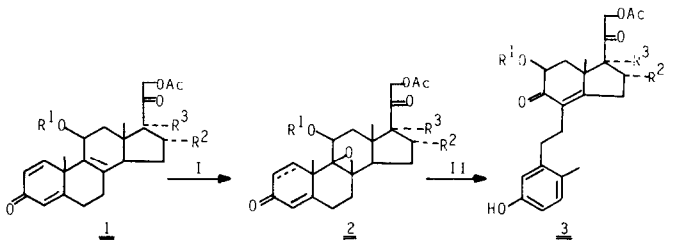
Summary: Reaction of readily available 11ß-hydroxy-8ß,9-epoxy-steroids with hydrogen fluoride-pyridine gave the corresponding 9.10-seco-derivatives in good yields.

Ring cleavages between C-9 and C-10 of steroids by micro-organisms[1] or photochemical methods[2] are well known and often used. In contrast, we found only a few reports about mild and selective chemical methods of skeleton cleavage in the literature. Three representative examples are mentioned: a) the radically initiated opening of a 9α,11-epoxy-hecogenin derivative followed by cleavage between C-9 and C-10 recently described by Barton, et al.[3] b) under similar conditions Magnus, et al.[4] treated 11α-xanthates of 1-dehydroprogesterone with Samarium diiodide and obtained the corresponding 9,10-secosteroids c) the ionic cleavage of the 9,10-bond is reported by Lythgoe, et al.[5] and is achieved by treatment of 9α,11-epoxy-cholesta-1,4-dien-3-one with lithium aluminium hydride accompanied by a dienone-phenol rearrangement.



1 2 3

	Δ	R^1	R^2	R^3
1a, 2a	1.4	H	H	$-OCOC_2H_5$
1b, 2b	1.4	H	-O O- H_3C CH_3	
2c	4	H	H	$-OCOC_2H_5$
2d	1.4	$-OCOCH_3$	H	$-OCOC_2H_5$

	R^1	R^2	R^3
a	H	H	$-OCOC_2H_5$
b	H	-O O- H_3C CH_3	
c	H	-OH	-OH
d	$-OCOCH_3$	H	$-OCOC_2H_5$

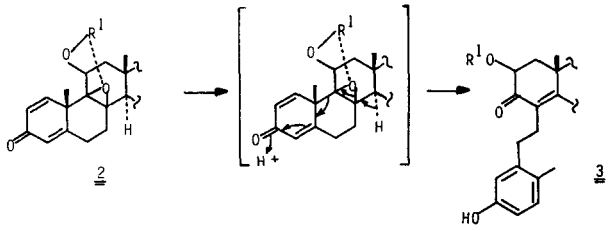
I R^1=H; MCPA (4 equiv) / CH_2Cl_2-phosphate buffer[9] = 1:1 (r.t./ 3d / yield 75%

II R^1=H; $-COCH_3$; $(HF)_n$·Py/30 min / -30°C / yield 65%

In conjunction with our studies in the area of corticosteroids, we have recently succeeded in stereoselective epoxidation of biologically active Δ^8-steroids 1a[6,17] and 1b[7] to 2a and 2b.

Influenced by the presence of the 11ß-hydroxy-group[8], the epoxidation of 1 with m-chloroperbenzoic acid in a buffered system[9] proceeds exclusively from the sterically more hindered ß-face of the molecule[10]. Subsequent treatment of the epoxide 2a with hydrogen fluoride-pyridine[11] gave the 9,10-secosteroid 3a in high yield. Under similar conditions, opening of the epoxide 2b afforded the 9,10-secosteroid 3b as major product and the diol 3c as minor product. The 11ß-acetoxy-derivative 2d prepared from the α,ß-epoxy-alcohol 2a with acetic anhydride and catalytic amounts of 4-dimethylaminopyridine[12] gave the corresponding fragmentation product 3d when the same acidic reaction conditions were employed.

While cleavage of the epoxide ring in several steroidal epoxides with various reagents yields diaxial products[13], we assume that the different behaviour of compounds 2 may be related to two factors: a) the tendency of ring A to undergo dienone-phenol rearrangement[14] under acidic conditions supported by b) the polar influence of the hydroxy or acetoxy group[15] at C-11 leading to reinforcement of the nearly C(8)-O bond.



2 3

R^1 = H; $-COCH_3$

Based on this assumption, treatment of the 4-en-3-one 2c with hydrogen fluoride-pyridine afforded in contrast to 2a, 2b, 2d a complex mixture of products. The educt 2c was obtained by selective hydrogenation of 2a catalysed by tris(triphenylphosphine)chlororhodium(I)[16].

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17)All new compounds gave satisfactory spectral and analytical properties. Selected data are as follows:

1a: IR(KBr) νmax: 3460 (OH); 1750 (C=O); 1730 (C=O); 1660 (3-Oxo); 1617; 1600; 1225 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 0.96 (s, 3H, CH_3-18); 1.13 (t, J = 7 Hz, 3H, -$COCH_2CH_3$); 1.62 (s, 3H, CH_3-19); 2.17 (s, 3H, 21-OAc); 4.54 (m, 1H, 11α-H), 4.67 and 4.96 (AB-system, J = 16 Hz, 2H, 21-H); 6.09 (m, 1H, 4-H); 6.29 (dd, J = 10 Hz and 2 Hz, 1H, 2-H); 7.63 (d, J = 10 Hz, 1H, 1-H) ppm.
2a: IR(KBr) νmax: 3340 (OH); 1755 (C=O); 1735 (C=O); 1660 (3-Oxo); 1615; 1605; 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.00 (s, 3H, CH_3-18); 1.11 (t, J = 7 Hz, 3H, -$COCH_2CH_3$); 1.63 (s, 3H, CH_3-19); 2.18 (s, 3H, 21-OAc); 2.36 (q, J = 7 Hz, 2H, -$\overline{CO}CH_2CH_3$); 4.54 (dd, J = 6 Hz and 2 Hz, 1H, 11α-H); 4.62 and 4.94 (AB-system, J = 17 Hz, 2H, 21-H); 6.06 (m, 1H, 4-H); 6.33 (dd, J = 10 Hz and 2 Hz, 1H, 2-H); 7.68 (d, J = 10 Hz, 1H, 1-H) ppm. 2b: IR(KBr) ν

max: 3365 (OH); 1747 (C=O); 1730 (C=O); 1660 (3-Oxo); 1620; 1605; 1235; 1055 cm^{-1}; ^{1}H-NMR (C_5D_5N) δ = 1.27 (s, 3H, CH_3-18); 1.28 and 1.43 (s, 6H, $>C(CH_3)_2$); 1.76 (s, 3H, CH_3-19); 2.12 (s, 3H, 21-OAc); 4.82 (m, 1H, 11α-H); 5.00 and 5.31 (AB-system, J = 18 Hz, 2H, 21-H); 5.20 (m, 1H, 16-H); 6.31 (m, 1H, 4-H); 6.56 (dd, J = 10 Hz and 2 Hz, 1H, 2-H); 8.10 (d, J = 10 Hz, 1H, 1-H) ppm. 2c: IR(KBr) ν max: 3460 (OH); 1734 (C=O); 1665 (3-Oxo); 1620; 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.0 (s, 3H, CH_3-18); 1.14 (t, J = 7 Hz, 3H, $-COCH_2CH_3$); 1.59 (s, 3H, CH_3-19); 2.20 (s, 3H, 21-OAc); 4.58 (m, 1H, 11α-H); 4.63 and 4.97 (AB-system, J = 16 Hz, 2H, 21-H); 5.76 (s, 1H, 4-H) ppm. 2d: IR(KBr) ν max: 1740 (C=O); 1665 (3-Oxo); 1630, 1608; 1235 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 0.89 (s, 3H, CH_3-18); 1.12 (t, J = 7 Hz, 3H, $COCH_2CH_3$); 1.42 (s, 3H, CH_3-19); 2.13 (s, 3H, 11-OAc); 2.22 (s, 3H, 21-OAc); 4.37 and 4.88 (AB-system, J = 16 Hz, 2H, 21-H); 5.48 (dd, J = 5 Hz and 2 Hz, 1H, 11-H); 6.04 (m, 1H, 4-H); 6.30 (dd, J = 10 Hz and 2 Hz, 1H, 2-H); 6.81 (d, J = 10 Hz, 1H, 1-H) ppm. 3a: IR(KBr) ν max: 3440 (OH); 1750 (C=O); 1735 (C=O); 1645, 1235; 1055 cm^{-1}; ^{1}H-NMR (C_5D_5N) δ = 1.02 (t, J = 7 Hz, 3H, $-COCH_2CH_3$); 1.78 (s, 3H, CH_3-18); 2.10 (s, 3H, 21-OAc); 2.36 (s, 3H, Ar-CH_3); 2.38 (q, J = 7 Hz, 2H, $-COCH_2CH_3$); 4.61 (dd, J = 6 Hz and 2 Hz, 1H, 11α-H); 5.14 and 5.28 (AB-system, J = 17 Hz, 2H, 21-H); 6.93 - 7.19 (m, 3H, 1-H, 2-H, 4-H) ppm; MS ^{m}/e: 472 (M^+); 121. 3b: IR(KBr) ν max: 3430 (OH); 1750 (C=O); 1725 (C=O); 1665; 1230; 1070 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 1.02 and 1.27 (s, 6H, $>C(CH_3)$; 1.33 (s, 3H, CH_3-18); 2.20 (s, 3H, 21-OAc); 2.24 (s, 3H, $ArCH_3$); 4.37 (t, J = 7.5 Hz, 1H, 11-H); 4.93 and 5.14 (AB-system, J = 18 Hz, 2H, 21-H); 4.99 (m, 1H, 16-H); 6.54 (m, 1H, 4-H); 6.58 (dd, J = 8 Hz and 2.5 Hz, 1H, 2-H); 6.97 (d, J = 8 Hz, 1H, 1-H) ppm; MS ^{m}/e: 472 (M^+); 121. 3c: IR(KBr) ν max: 3430 (OH); 1745 (C=O); 1725 (C=O); 1640; 1235; 1070 cm^{-1}; ^{1}H-NMR (C_5D_5N) δ = 1.80 (s, 3H, CH_3-18); 2.09 (s, 3H, 21-OAc); 2.29 (s, 3H, Ar-CH_3); 4.69 (m, 1H, 16-H); 5.36 and 5.50 (AB-system, J = 18 Hz, 2H, 21-H); 5.63 (t, J = 8 Hz, 1H, 11-H); 6.92 - 7.18 (m, 3H, 1-H, 2-H, 4-H) ppm; MS ^{m}/e: 432 (M^+); 121. 3d: IR(KBr) ν max: 3450 (OH); 1740 (C=O); 1670; 1645; 1235; 1055 cm^{-1}; ^{1}H-NMR (C_5D_5N) δ = 1.03 (t, J = 7 Hz, 3H, $-COCH_2CH_3$); 1.49 (s, 3H, CH_3-18); 1.99 (s, 3H, 11-OAc); 2.07 (s, 3H, 21-OAc); 2.32 (s, 3H, Ar-CH_3); 5.18 (s, 2H, 21-H); 5.79 (dd, J = 6 Hz and 2.5 Hz, 1H, 11-H); 6.90 - 7.16 (m, 3H, 1-H, 2-H, 4-H) ppm; MS ^{m}/e: 514 (M^+); 121.

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