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TETRAHEDRON

Novel Secosteroids Arising from Acid Catalysed Rearrangement of Fluocinonide Acetonide in the Presence of Tf_2O and TMSOTf

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Abstract Treatment of 6α,9α-difluoro-11β,21-dihydroxy-3,20-dioxo-16α,17α-isopropylidenedioxypregna-1,4-diene-21-yl acetate (fluocinonide acetonide) with trifluoromethanesulfonic anhydride in the presence of trimethylsilyl trifluoromethanesulfonate as catalyst gave the ketone **3** and furan **4** arising from cleavage of the C9-C10 bond and aromatisation of the A ring, and fluocinonide **5**. The ketone **3** was shown to be an intermediate in the formation of furan **4**.

Key words: rearrangement, steroid, aromatisation, cyclisation

Trifluoromethanesulfonate esters are extremely useful intermediates in organic synthesis, because of their ability to undergo facile nucleophilic substitution reactions. Almost invariably they are prepared by treatment of an alcohol with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of an amine base, usually pyridine, triethylamine or Hünig's base, in dichloromethane or chloroform and at low temperature, typically -20 to 0 °C. Recently Netscher and Bohrer[1] published a detailed account of unexpected side reactions observed during the preparation of trifluoromethanesulfonate esters. The side products range from trifluoromethanesulfinate esters, which could be the major product of the reaction, to a variety of amine cleavage products depending on the amine used, the substrate and the reaction temperature.

Recently, we have published[2] a very powerful new method for the acylation of alcohols by acid anhydrides catalysed by trimethylsilyl trifluoromethanesulfonate (TMSOTf). This method is very clean, extremely fast and high yielding. For example, the sterically hindered glucocorticoid fluocinonide acetonide (**1**) gave 6α,9α-difluoro-11β,21-dihydroxy-3,20-dioxo-16α,17α-isopropylidenedioxypregna-1,4-diene-11β,21-diyl diacetate (**2**) within 0.5 h, whereas acetylation using dimethylaminopyridine catalysis yielded the same product (**2**) in 8 h. As an extention of our esterification work we envisaged that reaction of alcohols with sulfonic anhydrides may also be catalysed by TMSOTf and provide an efficient route to sulfonate esters. Thus, treatment of 1-octadecanol with Tf_2O (1.25 equiv) and TMSOTf (0.05 equiv) in dichloromethane at room

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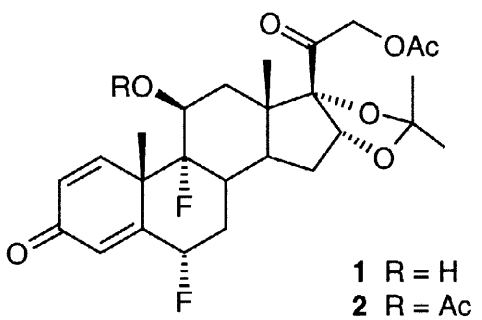
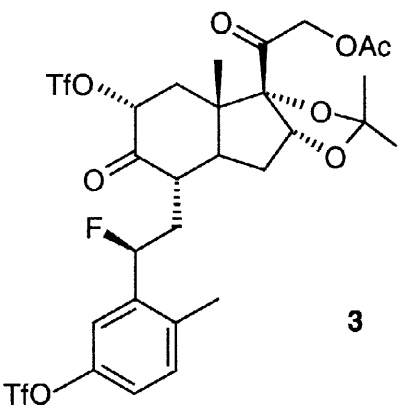
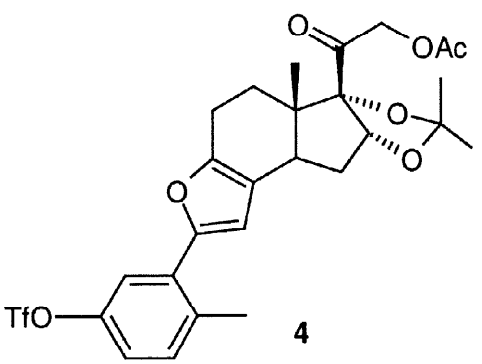
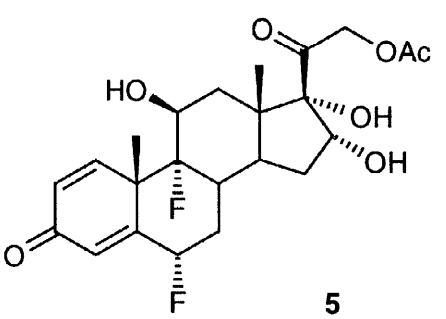
temperature gave, after aqueous sodium bicarbonate work-up, 1-octadecyl trifluoromethanesulfonate in 90% yield.

Having demonstrated the reaction with a simple alcohol we wanted to extend the reaction to a more complex and highly functionalised alcohol, such as the glucocorticoid **1**. Alcohol **1** was found not to react with Tf_2O (1 equiv) and excess pyridine in dichloromethane for 6 h. However, treatment of **1** with Tf_2O (1 equiv) and TMSOTf (0.05 equiv) gave after 15 min a less polar product plus starting material. More Tf_2O (0.25 equiv) was added and the reaction mixture was monitored by TLC and LCMS. A second less polar product together with a trace of a more polar product appeared plus unreacted starting material. After 3 h there was no change in the amount of starting material present and the reaction mixture was purified by column chromatography and preparative HPLC to give the products **3** (12%), **4** (5%) and fluocinonide (**5**) *vide infra* (1%), and recovered starting material **1** (51%).









Compound **3**, LCMS RT = 5.39 min, *m/z* 774, had a molecular formula of $C_{28}H_{31}F_7O_{12}S_2$, determined from its high resolution mass spectrum and the ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum indicated that the D ring, the 16,17-acetonide, C13-Me and the acetoxymethyl ketone at 17β were intact. The C10-Me was shifted downfield to 2.47 ppm, and the C6-H was simplified to two double doublets at 5.77 and 5.89. The A ring protons were shifted into the aromatic region and appeared at 7.13 (dd, J 8 and 2 Hz), 7.24 (d, J 8 Hz) and 7.28 (d, J 2 Hz). In addition there was a double doublet at 5.33 and a multiplet at 3.01 ppm. The ^{13}C NMR spectrum indicated the presence of an additional C=O at 201.2 ppm, 6 aromatic C atoms, two quaternary C atoms appearing as quartets at *ca* 119 ppm with a large F coupling, suggesting two TfO groups, a CH-F at 89.5, and a C-H at 86.1 ppm. The proton at 5.33 (dd) was attached to the C at 86.1 and was part of a $COCHCH_2$ group.

Clearly ring A had aromatised and was connected *via* $CHFCH_2$ to ring C at C8 which was in turn connected to the 201.2 ppm carbonyl. These data are compatible with structure **3** and this was confirmed by the HMBC spectrum. Long range ^{1}H - ^{13}C correlations are shown diagrammatically in Fig. 1. The configuration at C6 was assumed to be the same as in the starting material. The configuration at C11, however, was inverted as evidenced by the large coupling constant (12 Hz) due to diaxial coupling between 11β-H and 12α-H.

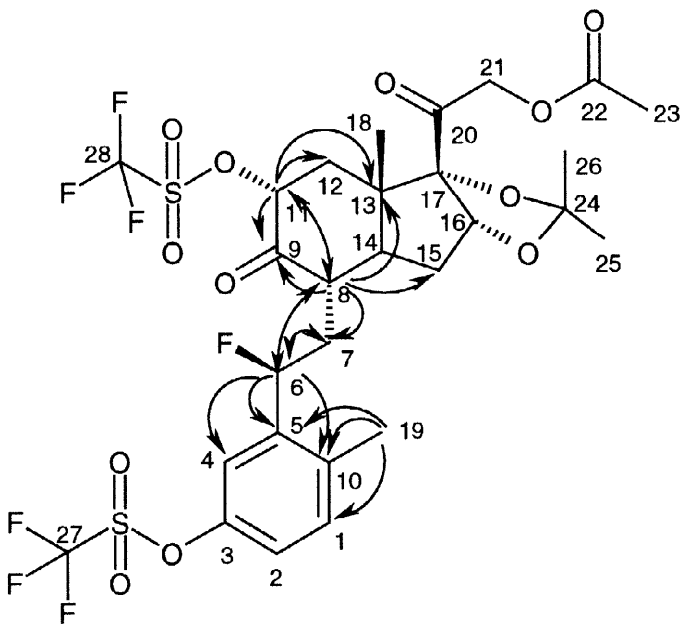


Fig. 1 Key long range ^{1}H - ^{13}C correlations for compound **3**

The minor product **4**, LCMS RT = 5.67 min, *m/z* 587, had a molecular formula of $C_{27}H_{29}F_3O_9S$ determined from its high resolution mass spectrum and the ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum indicated that the D ring, the 16,17-acetonide, C13-Me and the acetoxymethyl ketone group at C17 were again intact. The C10-Me was shifted downfield to 2.47 ppm. The A ring protons were shifted into the aromatic region and appeared at 7.03 (dd, J 8 and 2 Hz), 7.25 (d, J 8 Hz) and 7.60 (d, J 2 Hz). The C6-H had disappeared and a new singlet appeared at 6.43 ppm. The ^{13}C NMR spectrum indicated the presence of ten aromatic C atoms of which 6 were quaternary and 4 C-H (from the HMQC). The ^{19}F NMR spectrum indicated a singlet at -73.2 ppm, suggesting the presence of a triflate ester, and the UV spectrum indicated two maxima at 231 nm (ε 7600) and 302 nm (ε 11000), suggesting a conjugated aromatic system. From the above data it was clear that ring A had aromatised again to form a C3 triflate ester, but it was not clear as to what happened to ring B, although aromatisation was evident. From the HMQC and GHMBC structure **4** was proposed and this was confirmed by the following NOE's: C7-H→C4-H, C19-H→C1-H, and C19-H→C7-H. The key long range ^{1}H - ^{13}C correlations are shown in Fig. 2. It is noteworthy that in addition to the formation of the furan ring, C11 was deoxygenated.

The above described reaction of alcohol **1** with Tf_2O and TMSOTf does not take the same course in the absence of TMSOTf; extensive decomposition without any identifiable products occurs instead. As mentioned above, when **1** was reacted with Tf_2O (1.25 equiv) and TMSOTf (0.05 equiv) 51% of starting material was

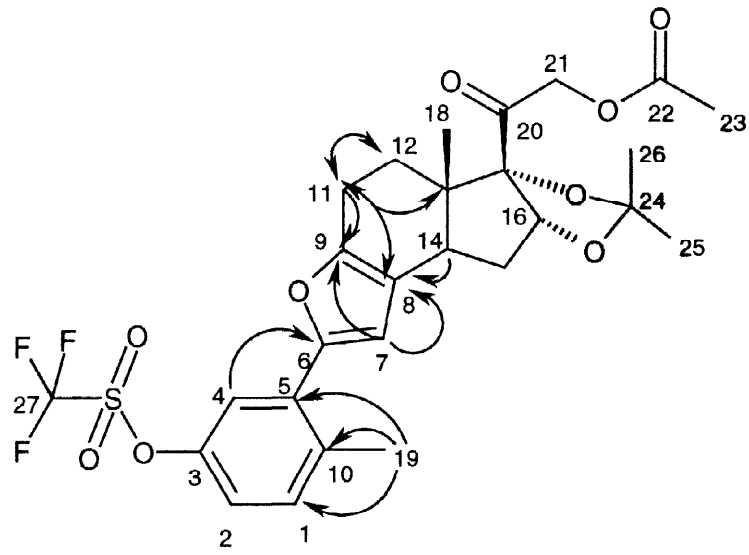
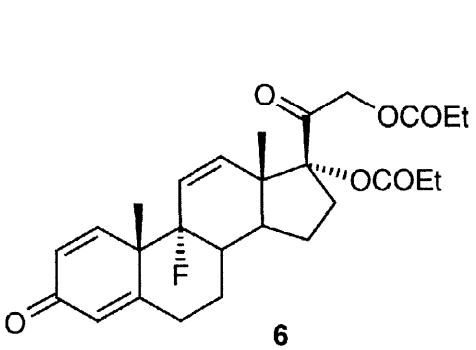


Fig. 2 Key long range ^{1}H - ^{13}C correlations for compound **4**

recovered unchanged. This is not surprising as two equivelants of Tf_2O are required per mole of **1** to form **3**. When the reaction was repeated in the presence of 2 equiv Tf_2O and TMSOTf (0.05 equiv, followed by extra 0.025 equiv after 1 h) the amount of unreacted starting material was reduced to 22% and the amount of products **3** and **4** was altered to 8% and 33% respectively. More importantly, HPLC indicated that the initial product formed was the ditriflate **3** (29%) and no furan **4** was present. However, as the reaction proceeded the ditriflate **3** was consumed, and the amount of furan **4** was increased to 33%. Additionally, fluocinonide (**5**) which was previously obtained only in trace amounts (< 1%), was now isolated in 8%. Furthermore, when the reaction was repeated with Tf_2O (1 equiv) and TMSOTf (0.05 equiv) HPLC indicated the presence of the unstable ditriflate **3** (45%) and fluocinonide acetonide (**1**) (27%), which were isolated in 12% and 21% respectively following column chromatography.

The aromatisation of the A ring of 1,4-diene-3-keto-steroids with concomitant migration of the C10 methyl group to C1 has been known for a long time and has been described by Djerassi as the dienone-phenol rearrangement.[3,4] More recently the rearrangement of the allylic fluoride **6** to enone **7** *via* cleavage of C9-C10 bond, rather than migration of the C10 methyl group has been reported.[5] This rearrangement is thought to arise by acid-catalysed (48% aqueous HF) solvolysis of the C9-F to a C9 carbonium ion.



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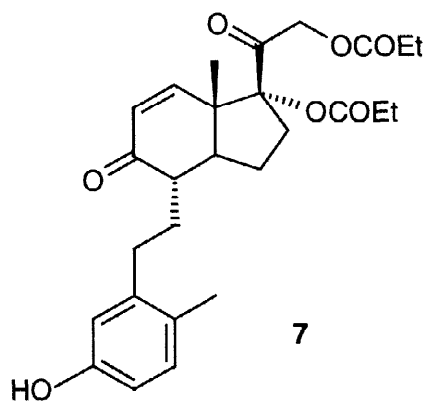

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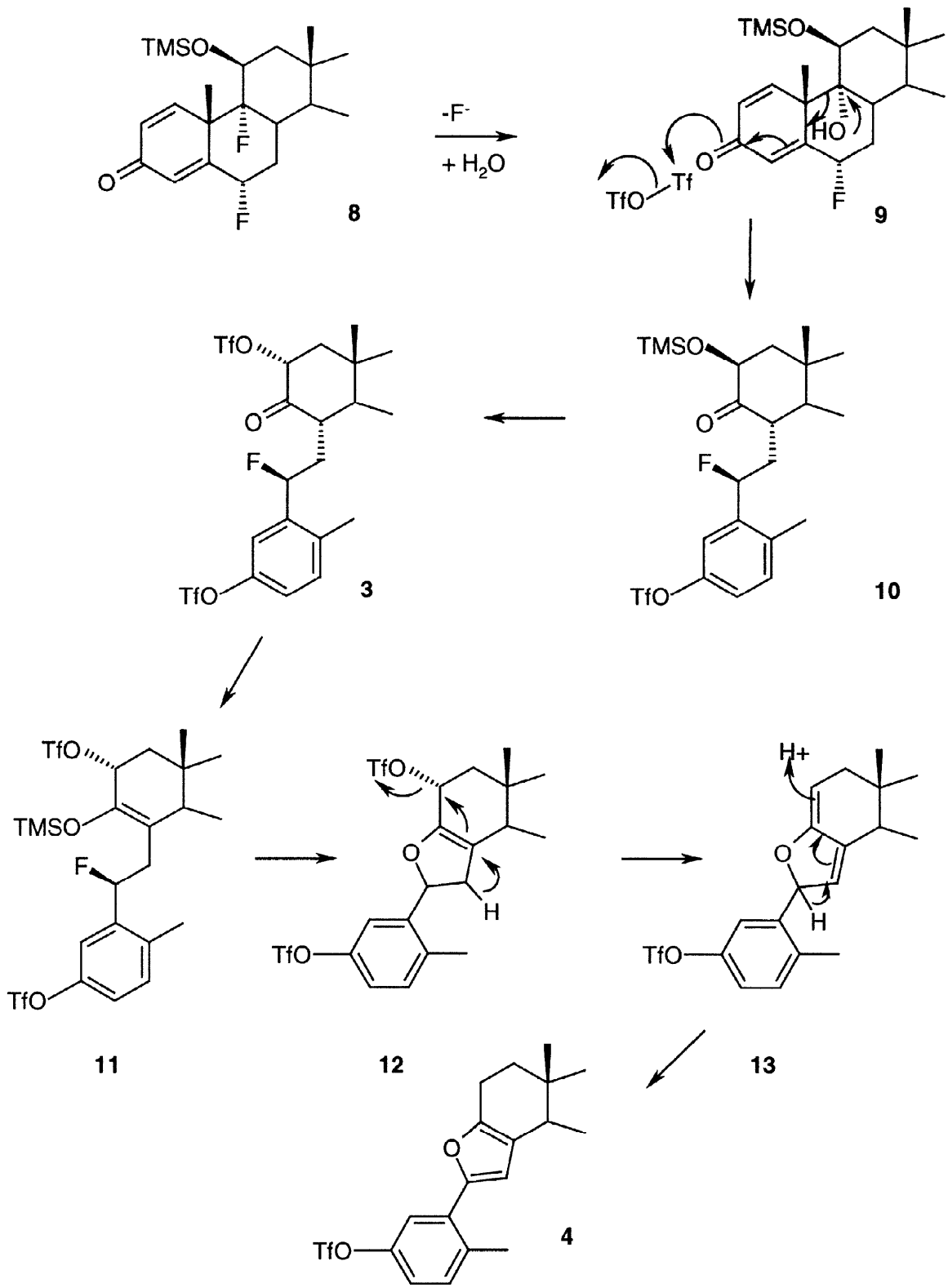

Scheme: Proposed mechanism for the formation of 3 and 4

In the present study the formation of **3** may be rationalised by conversion of the 11β-hydroxy to its TMS ether **8** brought about by the action of TMSOTf. The triflic acid that is generated during this conversion catalyses the formation of the carbonium ion at C9. Acid-catalysed solvolysis of *tert*-alkyl fluorides was studied by Chapman and Levy[6] and was shown to proceed by first order kinetics with respect to fluoride. The carbonium ion is then trapped by nucleophilic addition of adventitious water to form an intermediate alcohol **9**, which fragments to the C9-ketone with concomitant cleavage of the C9-C10 bond, aromatisation of ring A and sulfonylation at C3, as indicated in the Scheme. The C11 TMS ether **10** is now less sterically hindered following the breakdown of ring B, and reacts with Tf_2O to form compound **3**. The triflate at C11 assumes the more stable 11α equatorial position, presumably *via* enolisation of the C9 ketone. Only one diastereoisomer was detected by NMR spectroscopy (δ_H 5.33 and δ_C 86.1 ppm). The formation of **4** is postulated to arise from enolisation of the C9 carbonyl group of **3**, and cyclisation of the derived enolate **11** to the intermediate dihydrofuran **12**. Benzylic fluorides are known to undergo acid catalysed nucleophilic substitution reactions in contrast to the behaviour of the other benzyl halides.[7] This is thought to arise *via* hydrogen bonding of the acid catalyst leading on to an S_N1 mechanism. Elimination of the C11 triflate group of **12** gives the conjugated diene **13**, which upon acid catalysed rearrangement leads to furan **4**. Acid catalysed rearrangements of steroidal dienes were reported by Derek Barton nearly fifty years ago.[8] Clearly the amount of water present in the reaction mixture is critical for the formation of ketone **3**. However, we have not repeated the reaction in the presence of added water because we anticipated an increase in the rate of hydrolysis of the isopropylidene group.

In conclusion two interesting rearrangement products were identified during attempted trifluoromethanesulfonylation of the hydroxy group of **1** using the novel conditions of introducing a triflate group (Tf_2O/TMSOTf). The mechanism of their formation is also rationalised.

EXPERIMENTAL

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm × 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0 – 0.7 min 0% B, 0.7 – 4.2 min 100% B, 4.2 – 7.7 min 100% B, 7.7 – 8.0 min 0% B at a flow rate of 1 ml/min. The mass spectra were recorded on a Fisons VG Platform spectometer using electrospray positive and negative mode (ES + ve or ES – ve). Preparative HPLC was conducted on a Dynamax 60A column (30 cm × 5 cm) eluting with a gradient of 50% MeCN-water to 95% MeCN-water over 19 min, at a flow rate of 45 ml/min and detecting at 235 nm. The following NMR spectra were recorded ^1H, ^{13}C, ^{19}F, HMQC, gradient HMBC, COSY, and NOE difference on a Varian INOVA 400 MHz.

1-Octadecyl trifluoromethanesulfonate[9]:

A suspension of 1-octadecanol (518 mg, 1.9 mmol) in CH_2Cl_2 (6 ml) was treated at 20 °C with Tf_2O (0.4 ml, 2.37 mmol) and TMSOTf (1M in CH_2Cl_2; 0.1 ml). As soon as the TMSOTf was added complete solution was obtained. The mixture was partitioned between CH_2Cl_2 and aq. $NaHCO_3$ solution after stirring at 20 °C for 1 h. The organic phase was separated, washed with aq. $NaHCO_3$, dried ($MgSO_4$), and evaporated to give the title triflate (361 mg, 90%). NMR δ ($CDCl_3$) 0.88 (3H, t, J 7 Hz, CH_3CH_2), 1.77-1.89 (2H, m), 4.54 (2H, J 7 Hz, $TfOCH_2$).

Table

^{1}H and ^{13}C NMR data in $CDCl_3$ for compounds **3** and **4**.

Position	3		4	
	δ_H	δ_C	δ_H	δ_C
1	7.24 (d, 8)	132.6	7.25 (d, 8)	132.7
2	7.13 (dd, 8, 2)	121.1	7.03 (dd, 8, 2)	118.7
3	-	148.5	-	147.9
4	7.28 (d, 2)	117.9	7.60 (d, 2)	118.5
5	-	141.7	-	132.3
6	5.77 (dd, 11, 1) 5.89 (dd, 11, 1)	89.5 (d, 170)	-	149.8
7	1.6 (m) 2.2 (m)	35.6	6.43 (s)	110.0
8	3.01 (ddd, 14, 11, 2)	43.8	-	120.6
9	-	201.2	-	149.9
10	-	135.1	-	133.8
11	5.33 (dd, 12, 8)	86.1	2.89 (dd, 17, 7) 2.78 (m)	20.7
12	2.48 (m)	38.3	2.24 (dd, 12, 7) 1.98 (dd, 12, 6)	28.5
13	-	46.9	-	47.3
14	2.13 (m)	48.9	3.25 (m)	40.3
15	1.78 (m)	34.2	2.03 (dd, 13, 6) 1.80 (dt, 5, 13)	32.9
16	5.03 (m)	82.9	5.17 (d, 5)	83.8
17	-	96.0	-	97.0
18	1.12 (s)	15.2	0.64 (s)	13.3
19	2.47 (s)	18.8	2.47 (s)	21.8
20	-	203.8	-	204.0
21	4.89 (ABq, 17)	67.8	5.10 (d, 18) 4.94 (d, 18)	67.7
22	-	170.9	-	170.4
23	2.20 (s)	20.7	2.19 (s)	20.4
24	-	112.5	-	111.6
25	1.44[a] (s)	25.8[b]	1.29[c] (s)	25.6
26	1.24[a] (s)	26.7[b]	1.51[c] (s)	26.5
27	-	119.1[d] (q, 320)	-	118.8 (q, 320)
28	-	119.3[d] (q, 320)		

Chemical shifts superscripted with the same letter can be interchanged

Reaction of fluocinonide acetonide with Tf_2O and TMSOTf:

A solution of fluocinonide acetonide (**1**) (494 mg, 1 mmol) in CH_2Cl_2 (20 ml) was treated with Tf_2O (0.17 ml, 1 mmol) and a solution of TMSOTf in CH_2Cl_2 (1 M; 0.05 ml) at 20 °C. As soon as the Tf_2O was added the solution turned yellow and after 10 min darkened. Extra Tf_2O (0.04 ml, 0.25 mmol) was added and LCMS indicated a mixture RT = 3.95 min, *m/z* 455; RT = 4.53 min, *m/z* 495; RT = 5.39 min, *m/z* 774; RT = 5.67 min, *m/z* 587. The reaction mixture was stirred for 3 h and then aqueous $NaHCO_3$ solution was added. The organic phase was separated, washed with aq. $NaHCO_3$ (3 × 50 ml), dried ($MgSO_4$), and chromatographed on silica gel, eluting with ethyl acetate-cyclohexane (1:3) and further purified by preparative HPLC to give furan **4** (30 mg, 5%) as a colourless gum. Analytical HPLC RT = 5.67 min ; UV $\lambda_{max}(CH_3CN)$ 231 nm (ε 7600), 302 (11000); IR ν_{max}1754, 1729, 1423, 1210, 1141, 1080, 1039, 906 and 734 cm^{-1}; MS(ES + ve) *m/z* 587 [(M +

H)$^+$, 100%], 604 [(M + NH_4)$^+$, 30%]; HRMS(ES + ve) found: 587.1556 (M + H)$^+$ $C_{27}H_{30}F_3O_9S$ requires 587.1563. See table for NMR data.

Compound **3** (91 mg, 12%) a colourless gum. Anal. HPLC RT = 5.39 min; IR ν_{max} (KBr) 1747, 1731, 1494, 1415, 1235, 1140, 913 and 742 cm^{-1}; MS(ES + ve) *m/z* 774 (M + NH_4)$^+$; HRMS(ES + ve) found: 774.1505 (M + NH_4)$^+$ $C_{28}H_{35}F_7NO_{12}S_2$ requires 774.1489. See table for NMR data.

6α,9α-Difluoro-11β,16α,17α,21-tetrahydroxy-3,20-dioxopregnane-1,4-diene-21-yl acetate (fluocinonide)[10] (**5**). Anal. HPLC RT = 3.95 min; ^{1}H NMR δ (DMSO-d_6) 0.84 (3H, s, 18-H), 1.48 (3H, s, 19-H), 2.09 (3H, s, AcO), 4.17 (1H, m, 11αH), 4.71 (1H, br t, J 7 Hz, 16β-H), 4.80 (1H, dd, J 18 Hz, 21-H), 4.90 (1H, s, 17α-OH), 5.02 (1H, dd, J 18 Hz, 21-H), 5.43 (1H, d, J 6 Hz, OH), 5.50 (1H, d, J 5 Hz, OH), 5.58 and 5.70 (1H, 2m, 6β-H), 6.11 (1H, s, 4-H), 6.29 (1H, dd, J 10 and 2 Hz, 2-H), 7.25 (1H, d, J 10 Hz, 1-H); MS(ES +ve) *m/z* 455 [(M + H)$^+$, 100%], 909 [(2M + H)$^+$, 15%]; MS (ES – ve) *m/z* 453 [(M – H)$^-$, 100%], 907 [(2M – H)$^-$, 15%].

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***Dedication**: This paper is dedicated in loving memory to the grand master of chemistry, Sir Derek Barton, from his last Ph. D. student at Imperial College (1976-1979).*

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