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Photochemistry of some steroidal bicyclo[3.1.0]hexenones

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Abstract—The photochemistry of five 11-hydroxy-1,5-cyclopregn-3-en-2-ones ('lumi' products from the corresponding pregna-1,4-dien-3-ones) has been investigated. In all cases the photoproducts were 1,11-oxy derivatives, resulting from intramolecular attack of the hydroxyl group to the incipient positive charge at C-1. When a fluorine atom was present at C-6, HF elimination took place concurrently with the nucleophilic addition and led to linearly conjugated dienones, rather than the enones obtained in the other cases. Quantum yields were in the range 0.06–0.2, the lower values applying when a fluorine atom was present in position 6 (not in position 9). The results add new evidence on the role of zwitterionic intermediates in the photochemistry of cross-conjugated dienones and the corresponding lumi photoproducts.

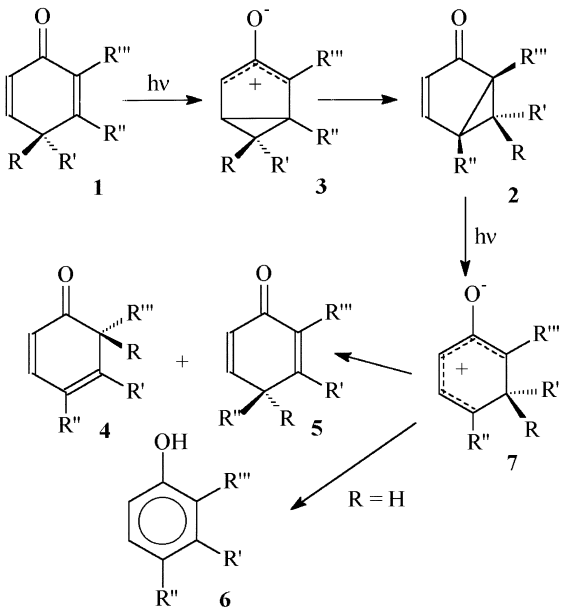
1. Introduction

The complex photochemical reactions of cross-conjugated cyclohexadienones (e.g., **1**, Scheme 1) have fascinated chemists over the past decades and many excellent reviews have been published on this topic.[1] Indeed, the light induced reactions occurring on natural sesquiterpene α-santonin have been among the first photochemical processes investigated[2] and the nature of the primary process occurring in neutral organic solvents has been recognized as rearrangement to bicyclo[3.1.0]hexenones (**2**, the so-called 'lumiproducts') in the 1950s.[3] The process has been envisaged as occurring via a zwitterionic intermediate (**3**)[4] and there is substantial evidence for such a path.[1]

The efficient photoreactions of lumiderivatives themselves complicate these studies. These compounds, in which a cyclopropane ring has replaced one of the double bonds of cross-conjugated dienones, share the high photoreactivity of their precursors. Sequential rearrangements involving a second, third and even fourth photoreactions are not uncommon, particularly with ring-fused cyclohexadienones, and have to be distinguished from thermal (usually acid-catalyzed) reactions. This further photochemistry leading, for example, to products **4**-**6** has been proposed[1a,b,e,g] to involve again a zwitterionic intermediate (**7**), the substitution pattern and the size of the fused ring affecting the course of the photoreaction.

Much work on cross-conjugated ketones has been carried on steroid derivatives,[5] including the exploration of secondary photoreactions. In this case, the rigid polycyclic skeleton further affects the course of the rearrangement and adds complexity. As an example, irradiation of lumidehydrotestosterone 21-acetate has been found to yield two cross-conjugated dienones, one of which with a spirocyclopentane moiety, along with further secondary and tertiary photoproducts, including four new bicyclohexenones, six phenols and three linearly conjugated cyclohexadienones. These arose through 17 different photochemical steps.[6]

Furthermore, intramolecular nucleophilic attack is also possible, as shown for the case of lumiprednisolone



Scheme 1.

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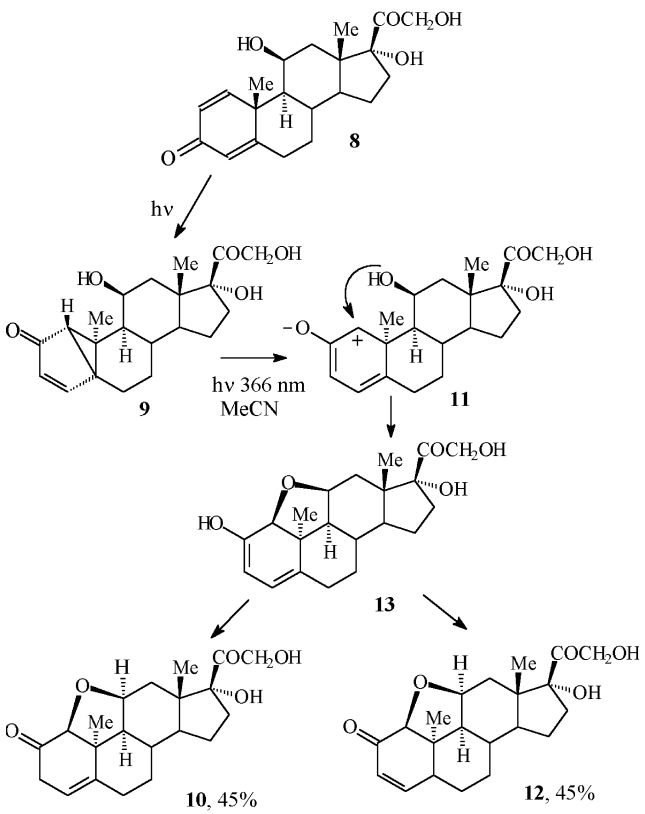
21-acetate **9** (formed in the primary photoreaction from **8**, Scheme 2). The 11β-hydroxyl group traps the (incipient) cation at C-1 (**11**) and yields the 1,11-oxy derivative **10**, while no such reaction occurs with the corresponding epimer, the 11α-hydroxy group apparently being too far away from the cationic site.[7]



Scheme 2.

We recently investigated[8] the photochemistry of a series of halogenated pregnadienones used as anti-inflammatory drugs and found that 'lumi' derivatives were the primary photoproducts, though, particularly at 366 nm, these further reacted at a rate comparable with that of the starting material. Such secondary photochemistry was not initially pursued, but further work that we report here evidenced that a novel photoreaction occurred with some of these derivatives, which supported the zwitterionic nature of the intermediate. In the following, product characterization and quantum yield for such derivatives are discussed.

2. Results and discussion

As mentioned above, the photochemistry of lumiprednisolone (**9**, 11β,17α,21-trihydroxy-16α-methyl-1,5-cyclopregna-3-ene-2,20-dione) had been previously shown to give **10** in dioxane and ethanol,[7a] although the quantum yield of the reaction had not been measured. In our hands, irradiation of **9** in argon-purged acetonitrile at 366 nm gave both product **10** and a further steroidal enone, each in 45% yield. The spectroscopic characteristics showed that the latter was isomeric with compound **10** and differed in containing a conjugated ketone moiety (structure **12**, Scheme 2).

Separate experiments, carried at low conversion in order to avoid secondary photoreactions, allowed measurement of a quantum yield of 0.2, under these conditions (Table 1). Product **12**, just as product **10**, arose from intramolecular OH addition, differing only for a different tautomerization from dienol **13**. The quantum yield was comparable to that for the rearrangement of the original pregnadienone **8** to the lumi derivative **9**. Furthermore, the latter absorbed more strongly at 366 nm, while the contrary was true at 254 nm. This explained why both with compound **8** and with related dienones[6,7] the best conditions for preparing the lumi derivative involved irradiation at 254 nm, while the use of a longer wavelength led to a mixture and, for a long irradiation time, led directly to the secondary photoproducts.

Table 1. Photoreaction quantum yield and products formed from the irradiation of lumi pregnadienone derivatives at 366 nm

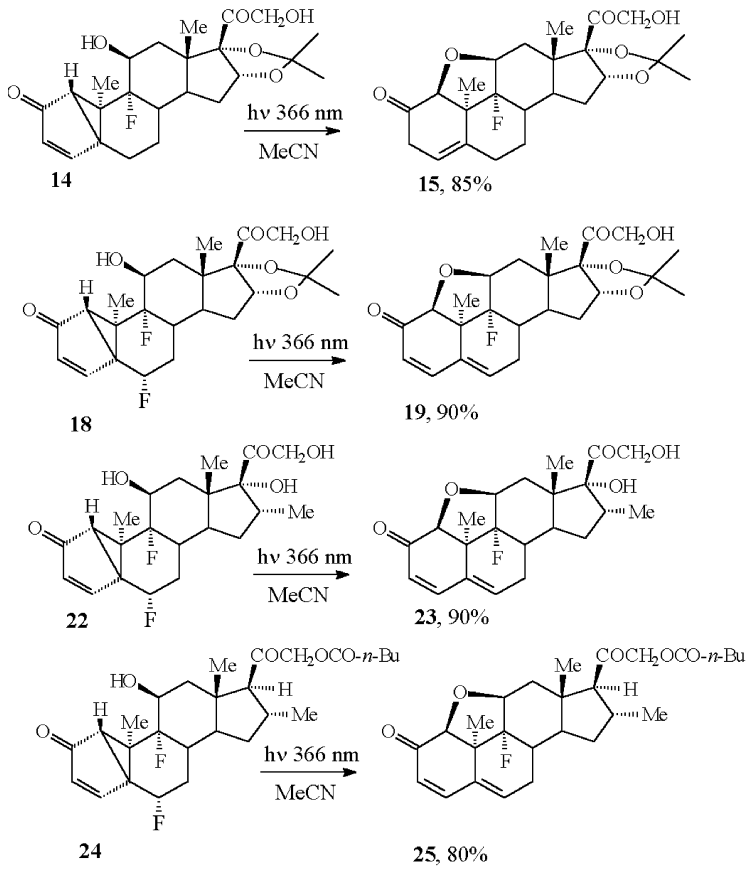
Reagent	Φ	Products (% yield)[a]	Φ (dienone)
9	0.2	**10** (45), **12** (45)	0.3[b]
14	0.2	**15** (85)	0.06[b]
18	0.06	**19** (90)	0.03
21	0.06	**22** (90)	0.03
23	0.06	**25** (80)	0.03[a]

[a] Isolated yield by chromatography calculated on the converted starting material (at ≥80% conversion).
[b] See Ref. 8b.

We next turned to the lumi derivatives of fluorinated pregnadienone drugs. Compound **14**, resulting from the irradiation of triamcinolone 16,17-acetonide, differed from **9** by bearing a fluorine atom in 9 and an acetonide group in 16, 17. This did not change the photochemical pattern and irradiation at 366 nm gave again a 1,11-oxy steroid (**15**, Scheme 3), as indicated by the analytical and spectroscopic properties. Examination of the irradiation mixture suggested that a small amount of an isomeric ketone, with conjugated structure corresponding to **12**, was also present, but the small amount did not allow complete characterization (see Section 3).

The quantum yield was the same as for **9** (0.2). This result can be contrasted with the strong difference in the quantum yield for the rearrangement of the respective pregnadienones (structure of the reactive moiety **16**, Scheme 4). In that case photochemical step a was less efficient in the fluoro derivative (**16**, X=F, Φ 0.06 rather than 0.3 for X=H), a phenomenon that was attributed to the electronegativity of the fluorine atom, which disfavored the positive charge developing during the reaction.[8b] In a structure such as **17**, however, the fluorine atom was too far away from the light-absorbing and reacting enone moiety and the same quantum yield was measured for photochemical step b for both X=H and F.

Lumifluocinolone 16,17-acetonide **18**, which differed from **14** by having a second fluorine atom again in ring B, was found to undergo a new reaction. A single photoproduct was formed, that was again a 1,11-oxy derivative but had lost the 6-fluorine atom and possessed a linearly conjugated dienone

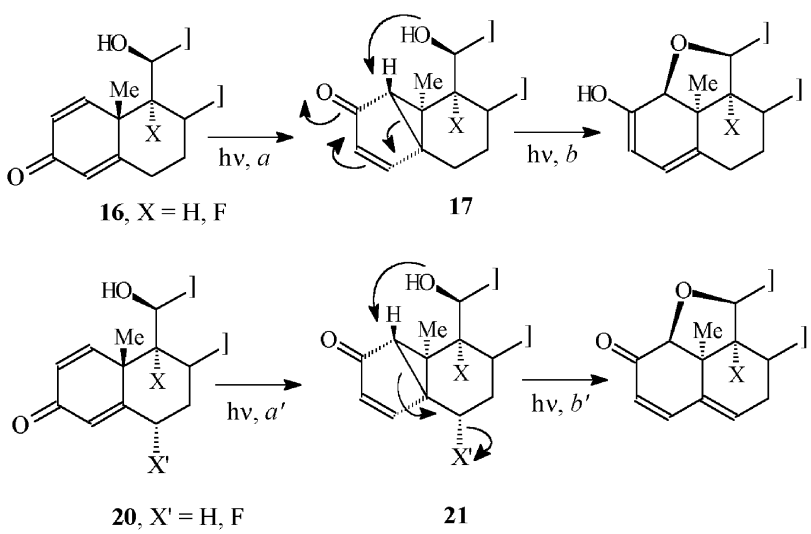


Scheme 3.

structure. Further analytical and spectroscopic evidence supported structure **19** for this compound and in particular NOESY experiments ascertained the stereochemistry. The reaction path was again consistent with an intramolecular attack onto the positive charge developing at C-1, but the presence of a suitably placed nucleofugal group diverted the reaction towards addition–elimination rather than mere addition (step b′ from **21**, Scheme 4).

In this case, the quantum yield was lower, 0.06, reasonably because the second fluorine atom (X′=F in formulae **20**, **21**) was much closer to the photoreacting enone moiety and both photochemical steps, a′ and b′, were affected. The corresponding dienone was in fact found to have a low quantum yield, Φ=0.003 (Table 1).

We then examined two further 6α,9-difluoro derivatives, differing for the substituents on ring D, viz. lumiflumetasone **22** (6α,9-difluoro-11β,17α,21-trihydroxy-16α-methyl-1,5-cyclopregna-3-ene-2,20-dione) and lumidiflucortolone **24**.



Scheme 4.

In both cases, 1,11-oxy monofluorinated dienones (formulae **23** and **25**) were formed in a high chemical yield. The quantum yield of both rearrangements had the same values as in **18** (0.06), in accord with the fact that the photoreacting moiety (compare formula **21**) remained the same in these derivatives, and the same held true for the rearrangement of the dienones (Table 1).

In conclusion, a clean photorearrangement was found on a series of 11-hydroxy-1,5-cyclopregn-3-en-2-ones. Chemical yields were good and NMR of the raw photolysate did not reveal side-products in substantial amounts. Thus, intramolecular nucleophilic attack by the 11β OH group always overcame other rearrangements from the excited bicyclohexenone (involving C–C bond migration, compare Scheme 1) that are normally observed in the absence of this group. This well fits the postulated development of a positive charge at C-1 upon excitation. Furthermore, a novel photochemical reaction of bicyclo[3.1.0]hexenone was found where nucleophilic attack at position 1 was coupled with elimination of a suitable nucleofugal group, a fluorine in 6, again consistent with the zwitterionic mechanism.

It was also found that a fluorine atom when adjacent to the enone moiety reduced the quantum yield of the bicyclohexenones, just as previously found when adjacent to a cross-conjugated dienone,[8b] while it had no effect when α to the three-membered ring in a cyclopropyl methyl ketone. As it appears from Table 1, the photoreaction of the lumiketones was either about as efficient as or, in most cases, more efficient than the primary photorearrangement of the cyclohexadienones. This made it difficult to avoid the second photochemical step particularly when irradiating above 310 nm, as in this wavelength region this is favored by the higher molar absorptivity of the lumi products. The photoreactivity in the UV–A region has also some bearing on the photostability and possible phototoxicity[9] of these steroids, that are used as topical drugs.

3. Experimental

3.1. Preparative photochemical reactions

Lumiproducts **9**, **14**, **18**, **21**, **23** were obtained by irradiation of the corresponding glucocorticosteroids as already reported.[8] Spectroscopic grade solvents were used for the irradiations.

Preparative irradiations were performed in an immersion well apparatus fitted with a Pyrex filtered 125 W medium pressure mercury arc lamp. Before irradiation argon was flushed under stirring for 30 min and a low gas flux was maintained during reactions. The course of the photoreactions was followed by HPLC (Hypersil ODS2. 4.6×25 mm, 5 μm column, eluting with acetonitrile–water mixtures) and TLC (eluting with cyclohexane–EtOAc mixtures). When the desired conversion was reached, the solvent was rotary evaporated and the products were purified by silica gel (0.040–0.063 mm) column chromatography.

The characterization of the new compounds was based on analytical and spectroscopic techniques, mainly IR and NMR (300 MHz). In every case, examination of the raw photolysate showed no evidence for other products in a significant amount (>5%), except when noted.

3.2. Irradiation of 11β,17α,21-trihydroxy-1,5-cyclopregna-3-en-2,20-dione (lumiprednisolone, 9)

A solution of compound **9** (60 mg, 0.1 mmol) in acetonitrile (100 mL) was irradiated for 20 min, and a 90% conversion was reached. Flash chromatography (cyclohexane–EtOAc (6/4)) gave a single product fraction (49 mg, 90% yield on the converted starting material) as a colorless glassy solid; IR (neat): ν_{max} 3430, 1710, 1660, 1104, 1043, 1011 cm^{-1}; the NMR analysis showed that two compounds were present. ^1H and ^{13}C NMR spectra and heterocorrelation analysis allowed the unambiguous assignment of the structure to the two isomers (ratio ca. 1/1), the first of which corresponded to the one isolated by Williams (only ^1H NMR reported in that case).[7a]

3.2.1. 21-Hydroxy-1β,11β-oxypregna-4-en-2,20-dione (10). ^1H NMR [$(CD_3)_2CO$]: δ, 0.77 (s, 3H), 1.38 (s, 3H), 1.2–2.75 (m, 12H), 2.50 (dd, J=16, 7.5 Hz, 1H), 3.19 (ddd, J=16, 4, 2 Hz, 1H), 4.08 (s, 1H), 4.23 (m, 1H), 4.42 (s, 1H, OH), 4.45 (broad s, 1H, OH), 4.23 and 4.62 (AB q, J=19 Hz, 2H), 5.46 (dt, J=7.5, 2 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$]: δ, 17.5 (CH_3), 23.2 (CH_2), 25.5 (CH_3), 26.8 (CH_2), 27.6 (CH_2), 32.0 (CH), 33.15 (CH_2), 34.9 (CH_2), 38.8 (CH_2), 48.9, 49.6 (CH), 54.1, 55.2 (CH), 67.7 (CH_2), 78.3 (CH), 87.2 (CH), 89.9, 117.3 (CH), 146.4, 204.6 (CO), 212.9 (CO).

3.2.2. 21-Hydroxy-1β,11β-oxypregna-3-en-2,20-dione (12). ^1H NMR [$(CD_3)_2CO$]: δ, 0.68 (s, 3H), 1.32 (s, 3H), 1.2–2.4 (m, 13H), 2.71 (m, 1H), 3.71 (s, 1H), 4.21 (m, 1H), 4.4 (m, 1H, OH), 4.4 (broad s, 1H, OH), 4.22 and 4.61 (ABq, J=19 Hz, 2H), 6.25 (dd, J=10 Hz, 1H), 6.74 (d, J=10 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$]: δ, 18.0 (CH_3), 23.4 (CH_2), 24.8 (CH_3), 27.1 (CH_2), 29.9 (CH), 32.5 (CH), 32.9 (CH_2), 34.9 (CH_2), 40.4 (CH_2), 49.4, 50.5 (CH), 53.9, 57.4 (CH), 67.7 (CH_2), 78.3 (CH), 87.0 (CH), 89.6, 132.4 (CH), 149.6 (CH), 195.1 (CO), 212.9 (CO).

3.3. Irradiation of 9α-fluoro-11β,21-dihydroxy-16α,17α-(1,1-dimethylmethylenedioxy)-1,5-cyclopregna-4-en-2,20-dione (lumitriamcinolone acetonide, 14)

A solution of compound **14** (200 mg, 0.46 mmol) in acetonitrile (120 mL) was irradiated for 2 h, and a 95% conversion was reached. A single main product was formed (162 mg, 85%, see below) and was isolated by flash chromatogrphy (cyclohexane–EtOAc (6/4)). However, examination of the crude photolysate evidenced signals at δ 6.33 (d, J=10 Hz) and 6.77 (d, J=10 Hz) which hinted to the presence of the corresponding pregna-3-en-2,20-dione. The small amount did not allow isolation and characterization.

3.3.1. 9α-Fluoro-21-hydroxy-16α,17α-(1,1-dimethylmethylenedioxy)-1α,11α-oxy-1,5-cyclopregna-4-en-2,20-dione (15). Colorless crystals, mp 157–159 °C; $[\alpha]_D^{17}$ −11.5 ($CHCl_3$); analysis, found: C, 66.70; H, 6.95;

$C_{24}H_{31}FO_6$ requires C, 66.34; H, 7.19; IR (KBr): ν_{max} 3490, 1725, 1710, 1105, 1045, 1003 cm^{-1}; ^1H NMR ($CDCl_3$): δ, 0.72 (s, 3H), 1.14 (s, 3H), 1.36 (d, J_{HF}=5 Hz, 3H), 1.47 (s, 3H), 1.3–2,5 (m, 10H), 2.75 (dd, J=16, 7 Hz), 3.09 (ddd, J=16, 4, 1.5 Hz, 1H), 4.17 (d, J=20 Hz, 1H), 4.20 (broad d, J=2 Hz, 1H), 4.21 (broad s, 1H), 4.25 (m, 1H), 4.68 (d, J=20 Hz, H-21), 5.01 (d, J=5 Hz, 1H), 5.45 (dt, J=7, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ, 16.2 (CH_3), 20.0 (d, J_{CF}=13 Hz, CH_3), 21.0 (d, J_{CF}=5 Hz, CH_2), 24.6 (CH_2), 25.2 (CH_3), 26.2 (CH_3), 30.6 (CH_2), 32.2 (CH_2), 33.1 (d, J_{CF}=21 Hz, CH), 37.5 (CH_2), 41.08 (CH), 45.9, 52.4 (d, J_{CF}=20 Hz), 66.8 (CH_2), 76.9 (d, J=30 Hz, CH), 81.8 (CH), 85.3 (d, J_{CF}=5 Hz, CH), 96.6, 98.5 (d, J=175 Hz), 111.1, 116.5 (CH), 143.3, 203.5 (CO), 210.4 (CO).

3.4. Irradiation of 6α,9α-difluoro-11β,21-dihydroxy-16α,17α-(1,1-dimethylmethylenedioxy)-1,5-cyclopregna-3-en-2,20-dione (lumifluocinolone 16,17-acetonide, 18)

A solution of compound **18** (200 mg, 0.44 mmol) in acetonitrile (120 mL) was irradiated for 6 h, and a 85% conversion was reached. Flash chromatographic separation (cyclohexane–EtOAc (6/4)) afforded 145 mg (90%) of a single product.

3.4.1. 9α-Fluoro-21-hydroxy-16α,17α-(1,1-dimethylmethylenedioxy)-1β,11β-oxy-pregna-3,5-dien-2,20-dione (19). Ligh yellow crystals, mp 142–144 °C; $[\alpha]_D^{17}$ −61.6 ($CHCl_3$); analysis: found: C, 66.70; H, 6.70; $C_{24}H_{29}FO_6$ requires C, 66.65; H, 6.76; IR (KBr): ν_{max} 3520, 2845, 1705, 1650 cm^{-1}; ^1H NMR [$(CD_3)_2SO$]: δ 0.54 (s, 3H), 1.1 (s, 3H), 1.23 (d, J_{H-F}=5 Hz, 3H), 1.24 (s, 3H), 1.40 (s, 3H), 1.2–2.5 (m, 9H), 4.02 (s, 1H), 4.11 (dd, J=19, 2 Hz, 2H), 4.50 (dd, J=19, 6 Hz, 1H), 4.17 (m, 1H), 4.9 (broad d, 1H, OH), 5.08 (broad t, J=6 Hz, 1H, OH), 5.91 (d, J=10 Hz, 1H), 6.44 (dd, J=19, 6 Hz, 1H), 7.41 (d, J=10 Hz, 1H); ^{13}C NMR [$(CD_3)_2SO$]: δ 16.7 (CH_3), 22.8 (d, J_{C-F}=5 Hz, CH_2), 23.9 (d, J_{C-F}=18 Hz, CH_3), 25.4 (CH_3), 26.6 (CH_3), 30.7 (CH_2), 32.2 (CH_2), 38.5 (CH), 39.4 (d, J_{C-F}=23 Hz, CH), 46.2 (d, J_{C-F}=20 Hz, CH), 46.7, 66.2 (CH_2), 77.4 (d, J_{C-F}=35 Hz, CH), 81.6 (CH), 84.9 (d, J_{C-F}=5 Hz, CH), 96.9, 98.7 (J_{C-F}=175 Hz), 110.7, 124.7 (CH), 134.5 (CH), 139.2, 148.2 (CH), 192.6 (CO), 210.6 (CO). NOESY experiments confirmed the stereochemical assignment by showing correlation between H-1 at δ 4.02 and Me-18 at 0.72, H-3 at 5.91 and H-11 at 4.17.

3.5. Irradiation of 6α,9α-difluoro-11β,17α,21-trihydroxy-16α-methyl-1,5-cyclopregna-3-en-2,20-dione (lumiflumetasone base, 22)

A solution of compound **22** (200 mg, 0.49 mmol) in acetonitrile (120 mL) was irradiated for 6 h, and a 85% conversion was reached. Flash chromatography of the residue (cyclohexane–EtOAc (6/4)) afforded 146 nm (90%) of a single photoproduct.

3.5.1. 6α-Fluoro-17α,21-dihydroxy-16α-methyl-1β,11β-pregna-3,5-dien-2,20-dione (23). Colorless crystals, mp 172–174 °C; $[\alpha]_D^{17}$ +29.4 ($CHCl_3$); analysis found: C, 67.70, H, 6.94; $C_{22}H_{27}FO_5$ requires C, 67.68, H, 6.97; IR (KBr): ν_{max} 3520, 1705, 1658, 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.82 (s, 3H), 0.96 (d, J=7 Hz, 3H), 1.32 (d, J=5 Hz, 3H), 1.25–3.1 (m, 8H), 3.31 (t, J=5 Hz, 1H, OH), 3.93 (s, 1H), 4.15, (m, 1H), 4.25 (dd, J=19, 5 Hz, 1H), 4.65 (dd, J=19, 5 Hz, 1H), 5.95 (d, J=10 Hz, 1H), 6.35 (dd, J=10, 1 Hz, 1H), 7.21 (d, J=10 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 17.0 (CH_3), 22.8 (d, J_{C-F}=5 Hz, CH_2), 24.1 (d, J_{C-F}=18 Hz, CH_3), 29.5 (CH_2), 30.8 (CH_2), 36.2 (CH), 40.3 (d, J_{C-F}=21 Hz, CH), 40.4 (CH), 46.4 (d, J_{C-F}=20 Hz), 50.1, 67.4 (CH_2), 78.2 (d, J_{C-F}=30 Hz, CH), 85.5 (d, J_{C-F}=5 Hz, CH), 89.8, 98.3 (d, J_{C-F}=175 Hz), 124.7 (CH), 134.2 (CH), 139.1, 147.8 (CH), 192.8 (CO), 211.8 (CO).

3.6. Irradiation of 6α,9α-difluoro-11β,21-dihydroxy-16α-methyl-1,5-cyclopregna-3-en-2,20-dione 21-pentanoate (lumidiflucortolone 21-valerate, 24)

A solution of compound **24** (200 mg, 0.42 mmol) in acetonitrile (120 mL) was irradiated for 6 h, and a 80% conversion was reached. Flash chromatographic separation (cyclohexane–EtOAc (7/3)) afforded 120 mg (80%) of a single photoproduct.

3.6.1. 9α-Fluoro-21-hydroxy-16α-methyl-1β,11β-oxy-pregna-3,5-dien-2,20-dione 21-pentanoate (25). Colorless crystals, mp 190 °C; $[\alpha]_D^{17}$ +20 ($CHCl_3$); analysis found: C, 70.67; H, 7.61; $C_{27}H_{35}FO_5$ requires C, 70.72; H, 7.69; IR (KBr): ν_{max} 1720, 1700, 1655, 1195, 1055 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (d, J=7 Hz, 3H), 0.93 (d, J=7 Hz, 3H), 0.98 (t, J=7 Hz, 3H), 1.44 (s, 3H), 3.13 (s, 1H), 4.25 (m, 1H), 5.92 (d, J=10 Hz, 1H), 6.31 (dd, J=10, 1 Hz, 1H), 7.23 (d, J=10 Hz, 1H) 1.0–2.5 all the other protons; ^{13}C NMR: δ 14.6 (CH_3), 15.3 (CH_3), 22.4 (d, J=5 Hz, CH_2), 23.6 (d, J_{C-F}=18 Hz, CH_3), 26.4 (CH_3), 26.8 (CH_2), 30.9 (CH), 31.0 (CH_2), 31.4 (CH_2), 33.2 (CH_2), 36.8(CH), 40.1 (d, J_{CF}=20 Hz, CH), 41.6 (CH_2), 44.3, 45.9 (d, J=20 Hz), 46.0 (CH), 68.2 (CH_2), 77.7 (d, J_{C-F}=20 Hz, CH), 85.1 (d, J_{C-F}=5 Hz, CH), 98.5 (d, J_{CF}=175 Hz), 124.2 (CH), 133.9 (CH), 138.6, 147.4 (CH), 172.4 (COO), 192.4 (CO), 202.7 (CO).

3.7. Quantum yield measurements

Quantum yields measurements were carried out on 3 mL samples of solutions (2.5×10^{-3} M) in spectrophotometric sealed cuvettes. The light source was a focalized 150 W high-pressure mercury arc lamp fitted with a 366 nm interference filter. The fraction of light absorbed was assessed by means of a photon counter. The extent of the reaction was determined by HPLC. The light flow was measured by ferrioxalate actinometry.

Acknowledgements

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