Structure elucidation and spectroscopic analysis of photodegradants of the *anti*-rhinitis drug fluticasone furoate

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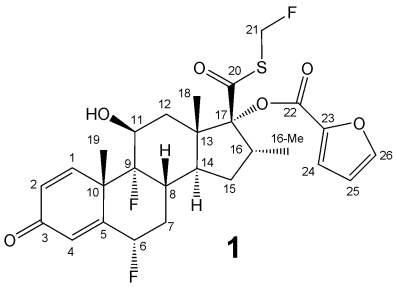
Fluticasone furoate is a novel glucocorticoid receptor agonist marketed as a treatment for seasonal and perennial allergic rhinitis. Forced degradation of fluticasone furoate under conditions of light led to a number of degradation products, the structures of which were elucidated using mass spectrometry and a range of one and two-dimensional NMR experiments. Three structures were derived, including two which involved a rearrangement of the steroid ring A to give cross-linked degradation products. The results demonstrate the applicability of a previously observed mechanism of photodegradation to fluticasone furoate.

Introduction

Fluticasone furoate[1] (**1**, Scheme 1) is a synthetic trifluorinated corticosteroid that possesses an enhanced affinity for the glucocorticoid receptor and has a potent anti-inflammatory action.[2] It was first approved for use in 2007 and is marketed as a treatment for seasonal allergic rhinitis and perennial allergic rhinitis in a number of countries as Veramyst™/Avamys™.[3] Structurally, it is related to fluticasone propionate which is marketed as flixotide™ and also as part of the combination therapy Seretide™/Advair™ for asthma.



Scheme 1 Structure of fluticasone furoate including numbering scheme.

During the development of this compound, degradation studies of the drug substance using a variety of forcing conditions were performed. Such studies are important in providing information to aid understanding of the degradation pathways of the drug and indicators to potential stability-critical impurities or potential phototoxicity issues with a given drug. Degradation under light was one of the forcing conditions studied for fluticasone furoate and this led to a number of degradation products. The structures of these photodegradation products were elucidated using a combination of NMR spectroscopy and mass spectrometry and demonstrate the key photochemical pathways associated with this compound and their relationship to photochemical degradation pathways of structurally similar steroid compounds which have been studied previously.[4–7]

Results and discussion

Exposure of fluticasone furoate to light led to differing results for the solid and solution states. In the solid state, the level of degradation after 30 h exposure was well below 10% and showed a single significant degradant (Fig. 1b) at a level of 0.5% area/area, with a polarity apparently greater than that of fluticasone furoate as indicated by its relative retention time of 0.76. In the solution state, exposure for a period of only 4 h led to a greater degree of degradation with three principal degradants now observed (Fig. 1a). One of these degradants corresponded to that seen in the solid state, with a relative retention time of 0.76 and at a level of 0.6% area/area, but two additional degradants, apparently less polar than fluticasone furoate with relative retention times of 1.04 and 1.20, were also observed at levels of 2.6 and 5.4% area/area, respectively. To understand the degradation occurring, it was necessary to elucidate the structures of the degradants.

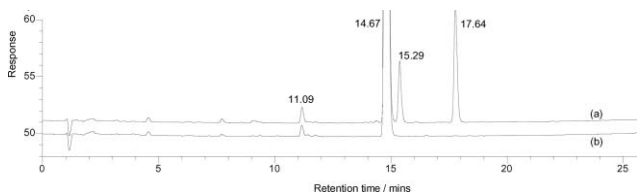


Fig. 1 HPLC chromatograms of fluticasone furoate degraded by light (a) in solution and (b) in solid form.

All HPLC-MS work was performed on the solution-degraded fluticasone furoate since the levels of all impurities were highest in these samples. The approach taken was first to obtain high resolution LC-MS data coupled with collision-induced dissociation to give fragment ions. It was not expected that fragmentation would give conclusive structural data due to the fused-ring steroid structure of fluticasone furoate which is known not to fragment significantly other than through loss of water and HF molecules.

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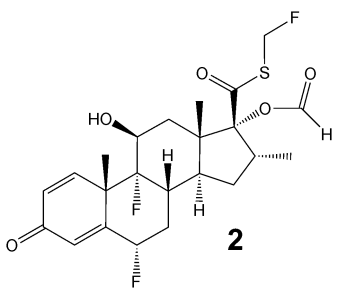
Table 1 Positive Ion Electrospray mass spectrometry data for **1**, **2**, **7** and **8**. Masses and molecular formulae presented are for the pseudo-molecular ions $[M+H]^+$

Compound	RRT	Accurate Mass (Da)	Molecular Formula	Mass error (ppm)
1	1.00	539.1715	$C_{27}H_{30}F_3O_6S$	1.8
2	0.76	473.1599	$C_{23}H_{28}F_3O_5S$	2.3
7	1.04	539.1708	$C_{27}H_{30}F_3O_6S$	1.3
8	1.20	519.1638	$C_{27}H_{29}F_2O_6S$	2.9

Fluticasone furoate ionises to give a molecular ion with a molecular formula of $C_{27}H_{30}F_3O_6S$. The peak at relative retention time (RRT) 0.76 ionised to give a molecular ion consistent with a molecular formula of $C_{23}H_{28}F_3O_5S$ (Table 1). This represents a loss of C_4H_2O relative to fluticasone furoate which would be consistent with loss of the furan ring. Additionally, hydrogen-exchange mass spectrometry was performed by substitution of water in the mobile phase with deuterium oxide (D_2O). This gave a mass spectrum with an increase in the measured mass, due to deuterium exchange, indicative of the presence of one exchangeable proton in the molecule. This is the same as the one exchangeable proton (11-hydroxyl proton) present in fluticasone furoate.

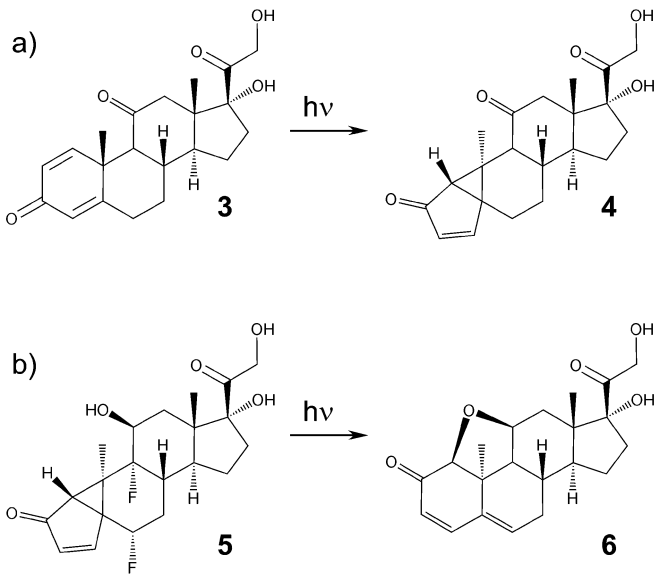
To confirm the structure of the impurity, a sample was isolated for NMR analysis by mass-directed preparative chromatography. The ^{1}H NMR spectrum of the resultant sample showed the presence of a singlet peak at 8.03 ppm, coupled in the HSQC spectrum to a carbon with a chemical shift of 159.2 ppm, consistent with a formyl group. Coupled with the loss of the three ^{1}H signals from the furan group observed in the spectrum of fluticasone furoate and the presence of all other signals analogous to those in fluticasone furoate, these data confirmed the loss of the furan group. The structure of the degradant at RRT 0.76 was therefore confirmed as the 17-*O*-formyl analogue of fluticasone furoate **2** (Scheme 2). The mechanism of formation of **2** was not determined although one possibility is that it may have formed *via* a radical-mediated process involving transfer of a proton from the furan ring to the adjacent carbonyl carbon.



Scheme 2 RRT 0.76 degradation product of fluticasone furoate.

HPLC-MS data obtained on the impurities with RRT 1.04 and 1.20 proved less conclusive. For the peak at RRT 1.04, a molecular ion was obtained consistent with a molecular formula of $C_{27}H_{30}F_3O_6S$ (Table 1). This is isomeric with fluticasone furoate. In addition, deuterium exchange mass spectrometry indicated the presence of one exchangeable proton, again in accordance with the one exchangeable proton observed in fluticasone furoate. MS/MS data did not provide any significant information to point to any specific isomeric structure and NMR analysis was therefore required to elucidate the structure.

For the peak at RRT 1.20, a molecular ion was obtained consistent with a molecular formula of $C_{27}H_{29}F_2O_6S$ (Table 1), representing a loss of HF relative to fluticasone furoate. In addition, deuterium exchange mass spectrometry showed, in this case, no exchangeable protons in the molecule thus suggesting a change had occurred in the 11-hydroxyl group. MS/MS data were once again inconclusive in pointing to any specific structure and NMR analysis was required for elucidation. Previous studies of systems such as prednisone and prednisone acetate, have shown that a rearrangement of the cyclohexadienone functionality occurs on exposure to light (Scheme 3a).[6] In addition, the products of these rearrangements, known as the 'lumi' products, have also been shown to eliminate HF when there is a fluorine present at C-6 (Scheme 3b).[7] As fluticasone furoate possesses a fluorine at C-6, it was therefore possible that a similar 'lumi' rearrangement followed by loss of HF may have occurred. Such an outcome would be consistent with the mass spectral data obtained on the peaks with RRT 1.04 and 1.20. ^{1}H NMR analysis showed significant differences between the spectra of the two impurities and the spectrum of fluticasone furoate suggesting significant structural differences potentially consistent with this type of change.



Scheme 3 (a) 'Lumi' rearrangement[5] of prednisone **3** to its 'lumi' product **4** and (b) photo-induced elimination of HF from 'lumi' product of flumethasone[7] **5** to its product **6**.

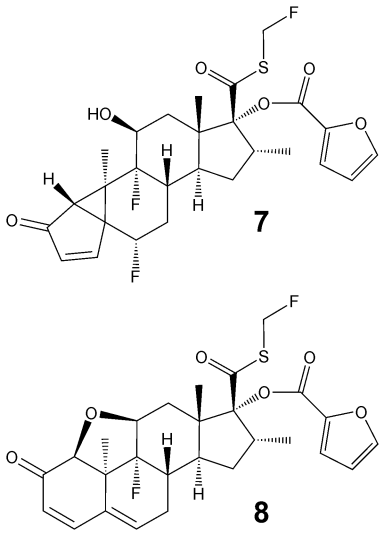
NMR analysis of the two samples coupled with the mass spectrometry data led to the confirmation of the structures of the RRT 1.04 peak as the 'lumi' rearrangement product **7** and the RRT 1.20 peak as the product of the elimination of HF from the 'lumi' compound **8** (Scheme 4).

Certain key spectral features were noted which helped characterise the structural changes. The ^{1}H NMR spectrum of **7** showed the presence of an aliphatic CH peak for H-1 at 2.36 ppm with a corresponding ^{13}C NMR shift for C-1 of 35.4 ppm. This contrasts with the olefinic H-1 proton in fluticasone furoate at 7.15 ppm with a corresponding ^{13}C NMR shift for C-1 of 150 ppm. Protons H-3 and H-4 showed chemical shifts of 6.11 and 7.68 ppm with a

Table 2 ^{19}F Chemical shifts and multiplicities for fluorine atoms at positions 6, 9 and 21 in compounds **1**, (a)**7** and (b) **8** in chloroform-*d* solution[a]

	F-6	F-9	F-21
1	187.3 dd (49)	165.6 dd (27)	192.0 t (50)
7	166.0 dd (52)	167.3 dm (25)	192.3 t (50)
8	—	194.1 dm (29)	192.3 t (50)

[a] ^{19}F Chemical shifts are given in ppm. Multiplicity is indicated with the following abbreviations: t (triplet), dd (doublet of doublets), dm (doublet of multiplets). The value of the largest coupling on each signal is indicated in brackets in Hz.



Scheme 4 (a) RRT 1.04 degradation product and (b) RRT 1.20 degradation product of fluticasone furoate.

^{3}**J** coupling constant of 5.5 Hz in comparison to the ^{3}**J** coupling constant of 10.2 Hz observed between H-1 and H-2 in fluticasone furoate. The lower value of the coupling constant in **7** is characteristic of the five-membered ring formed by the rearrangement, in contrast with the six-membered cyclohexadienone ring in fluticasone furoate. ^{19}F NMR data also showed changes consistent with the structures of **7** and **8**. Fluticasone furoate exhibits three signals in the ^{19}F NMR spectrum which could be assigned to F-6, F-9 and F-21 on the basis of their multiplicities and coupling constants (Table 2). Three ^{19}F signals were also observed for **7** but, as expected, only two ^{19}F signals were observed for **8** (Table 2) with the absent fluorine confirmed to be F-6.

One other feature of the rearrangement to the 'lumi' product is the change in conformation of the steroid structure compared to fluticasone furoate leading to some important changes in coupling constants and two-dimensional ROESY correlations. The stereochemistry of the methyl group H-19 was confirmed to be inverted through observation of ROESY correlations to H-11, H-3 and H-4, all located on the lower (α) face of the steroid structure (Fig. 2a). This contrasts with fluticasone furoate where strong ROESY correlations to functional groups on the upper (*β*) face, such as H-18, are observed from H-19. Proton H-6, also showed significantly different ^{1}H-^{1}H couplings compared to fluticasone furoate. In fluticasone furoate, H-6 exhibits couplings of 48 Hz to F-6, 11.4 Hz to H-7α, 6.6 Hz to H-7β and 1.4 Hz to H-4. In **7**, the analogous couplings are 52 Hz to F-6, 8.0 Hz to H-7α,

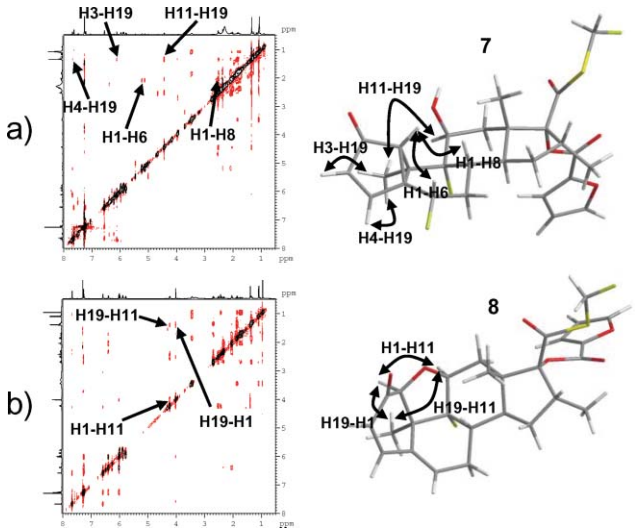


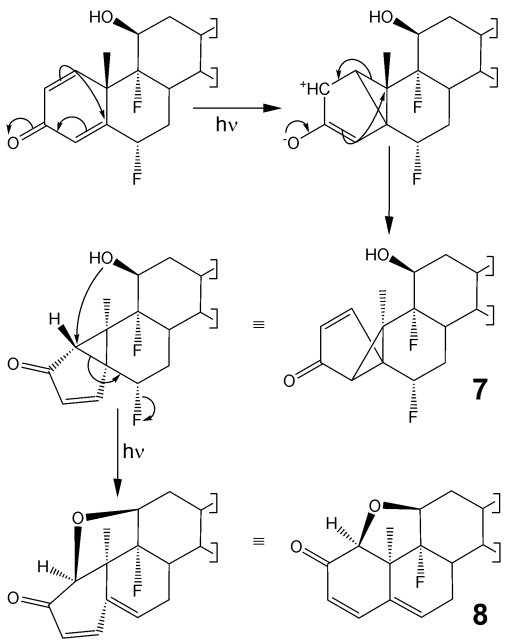
Fig. 2 Three dimensional conformations of (a) **7** and (b) **8** showing key ROESY correlations observed.

7.4 Hz to H-7β and no resolved coupling to H-4. The changes in relative couplings to H-7α and H-7β indicate the change from a pseudo-chair-like conformation of ring B in fluticasone furoate to a distorted ring B structure in **7**. One final significant spectral feature observed was the pair of ROESY correlations from H-1 to H-6 and H-8 (Fig. 2a). H-1 is located at the bridgehead carbon of the fused three and five-membered rings formed by the rearrangement. The correlations to H-6 and H-8, both located on the β-face of the steroid, confirm H-1 also to be on the β-face but also reflect the conformation adopted with this proton pointing inwards over ring B. The three-dimensional structure of **7** was modelled and confirmed these conformational features (Fig. 2a) and shows how the conformation brings C-1 much closer to the 11-hydroxyl group than it is in fluticasone furoate. This proximity between O-11 and C-1 therefore facilitates the cross-linking step required to eliminate HF and generate **8**. It has been previously noted that a developing positive charge at C-1 in **7**, leads to the susceptibility of C-1 to nucleophilic attack.[7] This developing positive charge along with the presence of two fluorine atoms in ring B as contributory factors to the HF elimination step and the three-dimensional structure of **8** show how this is facilitated by the proximity of the reacting centres.

As with **7**, the three-dimensional conformation of **8** (Fig. 2b) leads to some noteworthy spectral features. H-1 is a non-olefinic proton in **8** and its ^{1}H chemical shift of 3.99 ppm and corresponding ^{13}C chemical shift for C-1 of 85.7 ppm are consistent with the C–O–C linkage from C-11 to C-1. It was confirmed as C-1 based on the two-dimensional ^{1}H-^{13}C HMBC correlations to C-10, C-5 and C-19. Methyl group H-19 gave ROESY correlations to H-11 and H-1 (Fig. 2b) and, with H-11 known to be located on the α-face of the steroid ring, this confirmed H-19 also to be on the α-face, as was observed for **7** and in contrast to fluticasone furoate. H-1 also gave a ROESY correlation to H-11, which, combined with the ROESY correlation to H-19, confirms H-1 to be located on the α-face, unlike in **7** where it was noted as being located on the β-face. The nucleophilic cross-linking step from O-11 to C-1 thus leads, as expected, to an inversion of stereochemistry at C-1 supporting the elimination mechanism. One final point of interest

relating to the conformation of **8** is manifested in the appearance of the H-19 methyl group signal. In fluticasone furoate and **7** this signal appears as a singlet. However, in **8**, H-19 is observed as a doublet. This splitting of 5.8 Hz arises from a ^{4}J ^{1}H-^{19}F coupling to F-9, arising out of the conformational changes induced by the C–O–C cross-linking.

Previous studies of related compounds rationalise the formation of the degradants from fluticasone furoate and the mechanism is well-understood.[4–8] Initially, the molecule undergoes a stereoselective rearrangement to give the 'lumi' product **7**,[6,7] which is then subject to an intramolecular cross-linking elimination step to form **8** (Scheme 5).[7]



Scheme 5 Photo-rearrangement mechanism of fluticasone furoate.[7]

Unlike the solution state degradation, the solid phase degradation of fluticasone furoate did not lead to the formation of these similar rearrangement products but only to the degradation of the furoate group to give the 17-*O*-formyl product. It is not known why such a difference was observed but likely reflects the specific conditions required to induce the rearrangement.

Conclusions

The photochemistry and photodegradation of the *anti*-rhinitis drug fluticasone furoate have been studied and the principal photodegradation products identified. It has been found that these included a product of degradation of the furoate sidechain of the drug compound and two products arising from degradation of the ring A cyclohexadienone functionality with cross-linked structures formed by a light-induced rearrangement. Some unexpected NMR spectral features can be attributed to the subtle changes of conformation in the steroid structure induced by the cross-linkages. Whilst the differences in results for the solid and solution degradants indicate that the 17-*O*-formyl degradant may be of greatest relevance given the formulation of the drug as an intranasal suspension, the structures of this and the solution degradants provide an overall picture of the photodegradation pathways of the drug and may therefore have potential use for those studying this compound or class of compounds further.

Experimental section

Photodegradation conditions

Photodegradation was performed using an ATLAS CPS+ Suntest Cabinet with a lamp power of 500 W m^{-2}. This unit provides a source of high intensity lighting, similar in spectrum to that of natural sunlight, which may be used to simulate exposure to sunlight under controlled, accelerated conditions compliant with Option 1 of the ICH Guideline for Photostability Testing (Q1B). Solid samples were presented by spreading to a thickness of approximately 3 mm and covered with a glass lid in the light cabinet. Solution samples were prepared by dissolution in a 60% v/v acetonitrile in water mixture at a concentration of 4 mg mL^{-1}. The solid sample was placed in the light cabinet for 30 h and the solution samples for 1–4 h. The aim was for samples to degrade by a level of approximately 10–15% to ensure that primary rather than secondary degradants were most likely to be present.

HPLC conditions

Chromatographic analysis was performed using an Agilent 1100 HPLC system. A 150 × 4.6 mm Zorbax SB-C8 column with 3.5 μm particle size was used and employed mobile phases of (A) water + 0.05% v/v trifluoroacetic acid (TFA) and (B) 75 : 25 v/v acetonitrile : methanol with a linear gradient from 40–80% B over 30 min. The flow rate was 1.5 mL min^{-1}, UV detection wavelength was at 245 nm and the column temperature was 50 °C.

Mass spectrometry

HPLC-MS analysis of degraded solutions employed the same HPLC conditions as described above and a Waters Quadrupole-Time-of-Flight (QToF 1) mass spectrometer fitted with an electrospray (ESI) source for high resolution mass data and collision-induced fragmentation. Mass spectra were obtained in positive ion mode.

Analyses were performed using the following conditions: capillary voltage 3.5 kV; cone voltage 30 V; source temperature 120 °C; desolvation temperature 250 °C. Nitrogen was used as the desolvation gas at a flow rate of 450 L h^{-1}.

Mass-directed preparative chromatography

Samples for NMR analysis were isolated using a Waters ZQ mass-directed preparative chromatography system with collection triggered by the detection of ions with *m/z* 473, 539 and 519. The fractions of the desired degradant compounds were then prepared for NMR analysis by lyophilisation.

NMR spectroscopy

NMR analysis was performed on samples isolated by preparative chromatography using Bruker DRX500, AV400 and AV700 NMR spectrometers. Samples were dissolved in deuterated chloroform ($CDCl_3$). One-dimensional spectra were recorded at 27 °C with 32k data points, a spectral width of 20 ppm, a pulse width of 30° and a relaxation delay of 10 s. Full ^{1}H and ^{13}C assignments were made using two-dimensional COSY, multiplicity edited-HSQC, HMBC and ROESY spectra. These were performed using 4k data points in

Table 3 NMR chemical shift assignments for **1**, **2**, **7** and **8** in chloroform-*d* solution[a]

	Compound **1** (Fluticasone furoate)		Compound **2**		Compound **7**		Compound **8**	
Position	^{1}H parameters	^{13}C parameters	^{1}H parameters	^{13}C parameters[b]	^{1}H parameters	^{13}C parameters[b]	^{1}H parameters	^{13}C parameters[b]
1	7.15 d	150.4	7.10 dd	150.1	2.36 s	35.4	3.99 s	85.7
2	6.40 dd	130.4	6.38 dd	130.2	—	203.1	—	193.1
3	—	185.5	—	185.3	6.11 d	133.2	5.98 d	124.6
4	6.46 s	121.3 (J_{C-F} 12 Hz)	6.43 m	121.1	7.68 d	159.5	7.22 d	148.2
5	—	161.1 (J_{C-F} 14 Hz)	—	160.7	—	41.1	—	139.1
6	5.41 m	86.4 (J_{C-F} 185 Hz)	5.38 m	86.3	5.17 d	86.6	6.36 m	134.3
7α	1.80 m	33.7 (J_{C-F} 20 Hz)	1.75 m	33.5	1.85 m	27.7	2.30 m	22.8
7β	2.31 m	—	2.26 m	—	2.08 m	—	2.01 m	—
8	2.47 m	32.8 (J_{C-F} 11,19 Hz)	2.42 m	32.8	1.73 m	29.5	1.69 m	40.6
9	—	98.8 (J_{C-F} 177 Hz)	—	98.5	—	94.4	—	98.1
10	—	48.0 (J_{C-F} 24 Hz)	—	48.6	—	52.0	—	46.3
11	4.47 m	71.8 (J_{C-F} 38 Hz)	4.42 m	71.7	4.43 m	69.1	4.20 m	78.4
11-OH	1.84 t	—	1.62 t	—	ND	—	—	—
12α	2.53 dt	36.7	2.43 dt	36.6	2.02 m	34.1	2.49 dd	29.9
12β	1.96 d	—	1.87 d	—	2.52 m	—	2.39 d	—
13	—	49.0	—	48.0	—	48.8	—	50.2
14	2.40 m	43.3	2.28 m	42.9	2.49 m	41.8	2.66 td	40.0
15α	1.40 m	34.0	1.38 m	33.8	1.33 m	33.2	1.32 m	32.7
15β	1.93 q	—	1.90 m	—	1.83 m	—	1.83 q	—
16	3.48 m	36.7	3.41 m	36.3	3.46 m	36.2	3.42 m	37.2
16-Me	1.07 d	17.2	1.03 d	17.6	1.07 d	16.8	1.07 d	17.5
17	—	97.1	—	97.2	—	97.3	—	97.5
18	1.16 s	16.5	1.13 s	16.6	1.07 s	16.6	0.93 s	16.6
19	1.55 s	23.1	1.52 s	23.1	1.34 s	7.9	1.36 d	24.2
20	—	192.8	—	192.7	—	192.6	—	192.6
21	5.83, 5.93 m	81.0 (J_{C-F} 217 Hz)	5.87 m	80.5	5.83, 5.92 m	80.1	5.80, 5.90 m	80.3
22	—	157.0	8.03 s	159.2	—	ND	—	ND
23	—	143.5	—	—	—	143.6	—	143.5
24	7.16 s	119.2	—	—	7.22 d	118.4	7.24 s	118.8
25	6.52 dd	112.2	—	—	6.55 m	111.4	6.55 m	111.8
26	7.60 m	147.4	—	—	7.63 s	146.2	7.64 s	146.7

[a] ^{1}H Chemical shifts are given in ppm relative to either tetramethylsilane at 0 ppm or residual chloroform ($CHCl_3$) at 7.26 ppm. ^{13}C Chemical shifts are given in ppm relative to either tetramethylsiliane at 0 ppm or chloroform-*d* ($CDCl_3$) at 77.0 ppm. Multiplicity is indicated with the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets). [b] ^{13}C chemical shifts were obtained *via* ^{1}H-^{13}C HSQC and HMBC experiments. ND indicates no resonance or correlation to enable assignment was observed.

the directly-acquired dimension and either 128 or 256 increments in the indirect dimension. Standard Bruker pulse sequences were used for acquisition. The HMBC experiment was optimised for J-couplings of 8 Hz. ^{1}H and ^{13}C assignments are given in Table 3.

Molecular modelling

Molecular modelling was performed using CambridgeSoft Chem3D software with energy minimisation performed using MOPAC to generate low energy conformations.

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