CONFORMATION STUDY OF A-RING IN 19β,28-EPOXY-2-FLUORO-18α-OLEANANES+

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Dedicated to Professor Jaroslav Podlaha on the occasion of his 70th birthday.

A series of 2-fluoro-substituted 19β,28-epoxy-18α-oleanane triterpenoids was prepared. Detailed NMR analysis (^{1}H, ^{13}C, ^{19}F) was used for independent determination of the configuration of substituents. Conformation of the A-ring was derived from coupling constants *J*(H,H), *J*(F,H), *J*(F,C) and NOE-contacts observed in 2D-H,H-NOESY spectra. It was found that A-ring in all 2α-fluoro derivatives **2**–**5** and 2β-fluoro-3β-OR derivatives **10** and **11** adopts chair-form, while in 2β-fluoro ketone **9** a boat-form is preferred. The chair–boat equilibrium of A-ring was found in 2β-fluoro-3α-OR derivatives **7** and **8**.

Keywords: Triterpenes; Triterpenoids; 18α-Oleanane; NMR spectroscopy; Coupling constants; Conformation analysis; NOESY.

Conformation study of the A-ring in 2-fluoro derivatives of 19β,28-epoxy-18α-oleanane is continuation of stereochemical research pursued in our laboratory. Previously, triterpenoids with bromine, chlorine, methyl and oxygen containing groups (oxo, OH, $OCOCH_3$, OCH_3, OC_2H_5) as substituents at C-2 and C-3 were investigated (see e.g. refs[2,3] and references therein). Similar compounds derived from 4,4-dimethyl steroids with fluorine atom at C-2 were also studied[4]. In some cases, it was proved that the A-ring existed completely or at least partly in the boat form. Destabilization of the chair-form of the A-ring was ascribed to the 1,3-*syn*-axial interactions between 4β- and 10β-methyl groups and the other substituent in the

+ Part CXII in the series Triterpenes; Part CXI see ref.[1]

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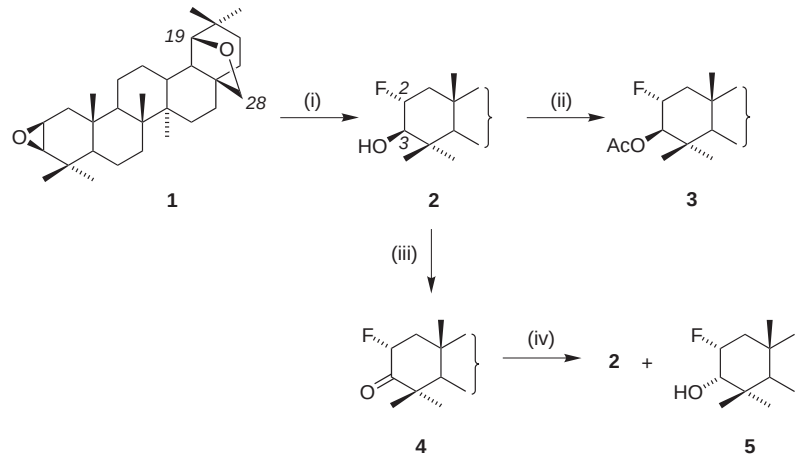
2β position. In comparison with 4,4-dimethyl steroids, the stability of the chair-form in triterpenoids was even lower because of additional diaxial interaction between methyl groups in the 10β and 8β positions. Therefore, in 2β-substituted triterpenoids, the A-ring existed mainly in a boat form and/or in chair–boat equilibrium where both forms were similarly abundant.

In 3-oxo derivatives with both polar and non-polar 2β substituents (Cl, Br, OCH_3, OC_2H_5, OAc, CH_3) the A-ring occurred almost exclusively in the boat form while in 2α derivatives the chair conformation was preferred.

Here we report on detailed stereochemical study of the A-ring conformation in 2-fluoro-substituted triterpenoids. To obtain reliable conclusions, we engaged ^1H, ^{13}C and ^{19}F NMR spectroscopy in combination with 2D NMR techniques in order to collect a complete and unambiguous set of *J*(H,H), *J*(F,H) and *J*(F,C) coupling constants.

Synthesis

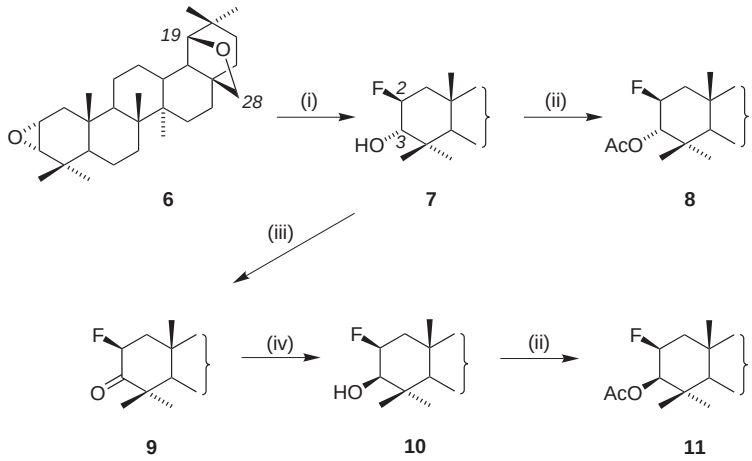
The studied fluoro derivatives were prepared using the common reactions with a known stereochemical course (Schemes 1 and 2). Compounds **2** and **7** with *trans*-configuration of the substituents in the 2 and 3 positions were obtained from epoxides[5,6] **1** and **6** by treatment with triethylamine trihydrofluoride. Subsequent oxidation of *trans*-fluorohydrins **2** and **7** afforded fluoro ketones **4** and **9** with a different configuration of fluorine atom in the 2 position. The products of the reduction of ketone **4** was



(i) $Et_3N.3HF$/pyridine; (ii) Ac_2O/pyridine; (iii) $Na_2Cr_2O_7$; (iv) $NaBH_4$

SCHEME 1

trans-fluorohydrin **2** and the *cis*-derivative **5**. The opposite *cis*-fluorohydrin **10** was prepared from ketone **9** under the same reductive conditions. Corresponding acetates **3**, **8** and **11** were prepared by acetylation of fluorohydrins. Configuration of the substituents in all the prepared compounds followed from the nature of the used reactions and, on the other hand, from analogy with the literature[4,7–10] and it was confirmed independently by detailed NMR analysis (see below).



(i) $Et_3N.3HF$/pyridine; (ii) Ac_2O/pyridine; (iii) $Na_2Cr_2O_7$; (iv) $NaBH_4$

SCHEME 2

*Configuration Determination of the Substituents in Fluoro Derivatives **2**–**5** and **7**–**11***

For determination of the configuration of the substituents of the A-ring it was necessary to assign all ^1H and ^{13}C NMR signals. In doing that, we considered the signals of the methyl groups and particularly of the quaternary carbon atoms 4 and 10 to be the most decisive. The chemical shifts of these quaternary carbon atoms were found to be similar (except the oxo derivatives **4** and **9**); however, the corresponding *J*(F,C) coupling constants were different. The HMBC spectra were proved to be extremely useful for the assignment of both ^{13}C signals. The protons of methyl groups in the 4α (H-23) and 4β (H-24) positions showed cross-peaks with C-3, C-4, C-5 and with each other, while the methyl group in position 10β (H-25) was correlated with C-1, C-9 and C-10. Thus, the careful analyses of these cross-peaks enabled us to distinguish both C-10 and C-4 resonances.

Having the A-ring assignment, we could carry on with investigating stereochemistry of the compounds. We intended to confirm the configuration of the substituents in positions 2 and 3 by NOESY technique regardless the stereochemistry of the reaction pathway. In oxo derivatives **4** and **9**, contacts of H-2 were of primary importance: in compound **4** (2α isomer) a spatial contacts between H-2β and methyl protons H-24 and H-25 were detected whereas in the case of 2β isomer **9** we found cross-peaks connecting H-28α with H-5α and 4α (H-23) methyl group. The configuration of the other compounds was determined in a similar way. A set of the crucial NOESY cross-peaks was summarized in Table I.

Coupling Constants

The complete set of all obtained coupling constants was presented in Table II.

^{3}J(H,H) Coupling Constants

By analyzing the ^{3}J(H,H) coupling constants it was possible to compare our results with many examples in literature.

For 2α-fluoro ketone **4** we found coupling constants J(1α,2β) = 12.2 Hz and J(1β,2β) = 6.6 Hz. A comparison with the data published for analogous derivatives[8–14] indicates that ketone **4** preferably adopts a chair conformation of the ring A. In a similar way a boat form of the A-ring was proposed for 2β-fluoro ketone **9** as the values of coupling constants (J(1α,2α) = 11.6 Hz and J(1β,2α) = 7.0 Hz) are close to related 2β-substituted 3-oxo derivatives known from literature[9,11–13].

TABLE I
Selected NOESY correlations of compounds **2**, **3**, **5**, **7**, **8**, **10** and **11**

Compound	NOESY correlations
2, **3**	H-2β/H-24, H-25; H-3α/H-1α, H-5α, H-23
5	H-2β/H-1β, H-3β, H-24, H-25; H-3β/H-23, H-24
7, **8**	H-2α/H-3β, H-5α, H-23; H-3β/H-23, H-24, H-25
10, **11**	H-2α/H-1α, H-1β, H-3α; H-3α/H-1α, H-5α, H-23

Inspecting the 2β-fluoro-3α-substituted derivatives **7** and **8** we obtained $J(2\alpha,3\beta)$ = 6.6 Hz, $\Sigma J(1,2)$ = 11.6 Hz and $J(2\alpha,3\beta)$ = 4.8 Hz, $\Sigma J(1,2)$ = 8.5 Hz. These values are significantly lower than could be ascribed to a pure boat conformation but, on the other hand, higher than typical chair-form values[11,15]. Hence, we suppose that both compounds exist in solution in equilibrium of both the forms. To estimate the chair/boat ratio, we took from literature typical values for the chair and a boat conformation as the reference: $J_c(2\alpha,3\beta)$ = 3 Hz and $\Sigma J_c(1,2)$ = 7 Hz for chair and $J_b(2\alpha,3\beta)$ = 12 Hz

TABLE II
The A-ring coupling constants (in Hz) of fluoro derivatives **2**–**5** and **7**–**11**

Coupling constants	**2**	**3**	**4**	**5**	**7**	**8**	**9**	**10**	**11**
	2α-F 3β-OH	2α-F 3β-OAc	2α-F 3-oxo	2α-F 3α-OH	2β-F 3α-OH	2β-F 3α-OAc	2β-F 3-oxo	2β-F 3β-OH	2β-F 3β-OAc
					Chair, %				
	100	100	100	100	60	80	0	100	100
					J(H,H)				
$^2J(1\alpha,1\beta)$	11.9	12.2	12.4	[a]	14.5	15.0	13.6	15.3	15.3
$^3J(1\alpha,2)$	11.4	11.3	12.2	11.9	6.6	4.8	11.6	3.2	3.2
$^3J(1\beta,2)$	5.0	5.0	6.6	5.0	5.0	3.7	7.0	3.2	3.2
$^3J(2,3)$	9.4	9.8	–	2.9	6.6	4.8	–	3.2	3.1
					J(F,H)				
$^2J(F,2)$	50.8	49.9	47.9	46.2	49.9	47.3	49.9	51.0	51.4
$^3J(F,3)$	13.4	12.4	–	8.7	9.5	8.2	–	33.0	33.3
$^3J(F,1\alpha)$	11.0	11.0	12.0	8.0	23.0	38.0	1.8	47.0	46.0
$^3J(F,1\beta)$	6.7	6.9	6.9	8.0	23.0	18.5	30.5	13.9	13.1
					J(F,C)				
$^1J(F,2)$	166	173	185	167	171	176	189	172	179
$^2J(F,1)$	16	16	16	16	17	17	18	17	17
$^2J(F,3)$	16	16	12	15	21	25	13	18	16
$^3J(F,4)$	8	7	~0	6	2	~0	~0	~0	~0
$^3J(F,10)$	11	10	9	11	2	~0	6	1	1
$^4J(F,23)$	~0	~0	2	~0	~0	~0	~0	~0	~0
$^4J(F,24)$	~0	~0	~0	~0	3	4	~0	3	4
$^4J(F,25)$	~0	~0	~0	~0	2	4	~0	6	6

[a] Not found.

and $\Sigma J_b(1,2)$ = 18.2 Hz for a boat form[15]. In the case of fluorohydrin **7**, the abundance of the boat form was 40% (calculated from both constants), whereas for compound **8** we found the value 20% from $J(2\alpha,3\beta)$ and 13% from $\Sigma J(1,2)$.

The population of the boat form in 2β-fluoro derivatives is lower than in the case of 2β-bromo derivatives where a boat is the preferable conformation (from more than 95%, cf. ref.[15]). It can be assumed that the origin of this difference lies in a lower van der Waals radius of fluorine atom than that of bromine, which is usually apparent from the lower energy of 1,3-*syn*-axial interaction between methyl group and corresponding halide atom ($-\Delta G^0(CH_3/F)$ = 1.67 kJ mol^{-1}, $-\Delta G^0(CH_3/Br)$ = 9.20 kJ mol^{-1}; cf. ref.[16]). Clearly, two 1,3-*syn*-axial interactions of 2β-fluorine with 4β- and 10β-methyl groups do not sufficiently increase the energy of chair conformation and, therefore, the equilibrium is shifted to the opposite one to 2β-bromo derivatives. As the abundance of the boat form in the case of fluorohydrin **7** is significantly higher than in acetate **8**, we presumed that this form could be stabilized by the intramolecular hydrogen bond between 2β-fluorine and 3α-hydroxy group.

In 2β-fluoro-3β-substituted derivatives **10** and **11**, values of the vicinal coupling constants ($J(1\alpha,2) = J(1\beta,2)$ = 3.2 Hz) parallel those of derivatives of 4,4-dimethyl-5α-cholestane[9] and 4,4-dimethyl-5α-estrane[10] and correspond to the chair-form of the ring A. Similarly, the value of $\Sigma J(1,2)$ = 6.4 Hz is close to the values published[11] for triterpenoid diols and their monoacetates of the same configuration with the chair-form of the ring A.

As was mentioned above, derivatives with 2α substituent known until now prefer a chair conformation of the ring A. The compounds with 2α-fluorine, **2**, **3** and **5** from our study, are not exceptional and the values of ^3J(H,H) (see Table II) are in full agreement with literature[11,12,15].

J(F,H) Coupling Constants

Geminal J(F,H). The values of ^2J(F,H) found for all the fluoro derivatives studied here are in accordance with the data published[4] for derivatives of 4,4-dimethyl-5α-cholestane and they agree with the rule shown by Levisalles[4]: in the case of fluorohydrins and their acetates the values of ^2J(F,H) are lower for axial OH (OAc) group (44–47 Hz) than for equatorial ones (49–52 Hz). A relatively high value obtained for 2β-fluoro-3α-hydroxy derivative **7** (49.9 Hz) with axial OH group is consistent with significant participation of the boat form where the hydroxy group have the equatorial character.

Vicinal J(F,H). In the case of ^3J(F,H), they follow the literature[4] values as well. For example, the value is about 33 Hz for 2β-fluoro-3β-hydroxy derivative **10** and its acetate **11**, which corresponds to the presence of the antiperiplanar orientation of the fluorine and hydrogen atoms. Concerning the synclinal arrangement, the constant is higher for the equatorial OR group on C-3 (about 13 Hz for compounds **2** and **3**) than for the axial one (about 9 Hz for **5**, **7** and **8**). The presence of the chair–boat equilibrium in the derivatives **7** and **8** could not be detected from this value obviously due to similar dihedral angles between C–F and C–H bonds in the both forms.

The values of *J*(F,H-1α) (12.0 Hz) and *J*(F,H-1β) (6.9 Hz) found for 2α-fluoro ketone **4** correspond to the chair-form of the ring A. In literature[17], similar values for simple derivatives of 2-fluorocyclohexanone are published where 13–13.5 Hz for equatorial-axial arrangement and 3–4 Hz for diequatorial one were presented. The distinction between both pairs of the mentioned values is likely caused by a slightly different geometry of the six-membered ring in polycyclic (steroids and triterpenoids) and monocyclic compounds.

The low value of *J*(F,H-1α) 1.8 Hz and high value of *J*(F,H-1β) 30.5 Hz found for 2β-fluoro ketone **9** agree with a boat slightly distorted from the pure form to a twist-boat conformation (about 90 and 0–30° for dihedral angles F–C2–C1–H1α and F–C2–C1–H1β, respectively).

Focused on 2α-fluoro derivatives **2**, **3**, **5** and compounds possessing 2β,3β configuration (**10**, **11**), coupling constants *J*(F,H-1α) and *J*(F,H-1β) resemble to a chair conformation of the ring A. A synclinal orientation of the C–F and C–H bonds sets the constants to the range 8–14 Hz which is rather similar to the case of simple fluorocyclohexane and fluorodecaline derivatives where the value about 10 Hz was reported[18,19]. Accordingly, in antiperiplanar arrangement (derivatives **10** and **11**), the obtained constant *J*(F,H-1α) was 46–47 Hz which parallels the axial fluorocyclohexane (46.6 Hz, lit.[18]) and fluorodecaline (46–47 Hz, lit.[19]) values.

For fluorohydrin **7** and its acetate **8** the chair–boat equilibrium of ring A was derived from *J*(H,H) constants (see above). This fact was confirmed independently by inspecting vicinal *J*(F,H) constants. The constant *J*(F,H-1α) was lower and *J*(F,H-1β) higher than can be expected for perfect chair conformation and, in addition, the corresponding constants for **7** and **8** differ (Table II). As before, we were able to calculate the population of boat conformation taking the values of 2β,3β derivatives **10** and **11** as limit values for chair arrangement (J_c(F,H-1α) = 46.5 Hz, J_c(F,H-1β) = 13.5 Hz). Unfortunately, the only non-optimal model of a boat, that could be used, was the

2β-fluoro ketone **9**: J_b(F,H-1α) = 1.8 Hz and J_b(F,H-1β) = 30.5 Hz. Based on these assumptions, the population of the boat conformation of fluorohydrin **7** was estimated on 56 and 53% from the constants *J*(F,H-1α) = 23.0 Hz and *J*(F,H-1β) = 23.0 Hz, respectively. In the case of acetate **8**, we found the constants values *J*(F,H-1α) = 38.0 Hz and *J*(F,H-1β) = 18.5 Hz. The corresponding calculated populations of boat form were 19 and 29%. Comparing these values with the populations obtained on the basis of *J*(H,H) (see above), we calculated average population of the boat conformation of the ring A for both compounds: 47% for fluorohydrin **7** and 20% for acetate **8**. It is worth to note that the populations calculated individually from coupling constants values show rather low deviations (about 10%) from the average values.

J(F,C) Coupling Constants

^1J(F,C). The values of the ^1J(F,C) coupling constants in the series of studied compounds lie in the range of 166–189 Hz (see Table II), namely, the values between 166 and 172 Hz were found for hydroxy derivatives, those between 173 and 179 Hz for acetoxy derivatives and the highest values (185 and 189 Hz) correspond to ketones. The particular values are influenced predominantly by electronic effects of the substituents of the A-ring.

Geminal J(F,C). The geminal coupling constants between C and F atom in position 1 (*J*(F,C-1)) in fluorohydrin derivatives are in a narrow range between 16 and 18 Hz. Nevertheless, some differences were detected in the case of interaction between fluorine atom and C-3. While the values in the range of 15–18 Hz were found for fluorohydrins and acetates **2**, **3**, **5**, **10** and **11**, in the case of ketones **4** and **9** the values were slightly lower (12–13 Hz). On the contrary, in derivatives with 2β,3α configuration (**7** and **8**), where the boat form is significantly populated, the corresponding values were somewhat higher (21–25 Hz). However, it seemed unlikely that these data represented any new information about A-ring conformation.

Vicinal J(F,C). Values of the vicinal coupling constants *J*(F,C-10) in all 2α-fluoro derivatives occurred in the range of 9–11 Hz, which agrees with those published for equatorial fluorocyclohexane, analogous fluoro derivatives of bicyclo[2,2,2]octane, bicyclo[2,2,1]heptane and adamantane as well as for related fluoro steroids[18,20,21]. In addition, the observed values correspond rather well with an antiperiplanar arrangement of the F and C-10 atoms with a dihedral angle around 180°. Only the value in 2β-fluoro ketone **9** was somewhat lower (6 Hz) which can indicate a lower dihedral angle (between 180 and 120°) of the boat conformation of the A-ring. In

fluorohydrins and their acetates with 2β-fluoro substituents the ^{3}J(F,C-10) are quite low (0–2 Hz).

In contrast, rather high values (J(F,C-4) = 6–8 Hz) were observed in fluorohydrins and acetates, which adopt α configuration of fluorine atom (**2**, **3**, **5**) with antiperiplanar orientation of coupled nuclei (F, C-4) i.e. a mutual orientation of the both studied atoms (F and C-4) is antiperiplanar. A low value of the J(F,C-4) constant (2 Hz) was found in 2β-fluoro-3α-hydroxy derivative **7**, which could be due to high abundance of the boat conformation. The orientation of the fluorine and C-4 atoms was almost antiperiplanar again. In corresponding acetate **8**, we were not able to measure any coupling at the C-4 atom, as the population of the boat form is too low.

Long-range J(F,C). In some cases, we observed a long-range coupling between carbon atom and fluorine through a four-bond distance at the maximum. In fluorohydrins **7** and **10** and their acetates **8** and **11** containing the fluorine atom in 2β position, the ^{13}C resonances of the axial 4β- and 10β-methyl groups (C-24, C-25) were split by interaction constants (^{4}J(F,C)) in the range of 2–6 Hz. We assumed that this is due to through-space spin–spin interaction, which can appear when a fluorine atom and a methyl group are in 1,3-*syn*-axial arrangement.

Interesting findings were revealed by comparison of ^{4}J(F,C-25) constants in 2β-fluoro derivatives: in compounds **10** and **11** with 2β,3β configuration we found 6 Hz, in 2β-fluoro-3α-acetoxy derivative **8** was observed 4 Hz, in the corresponding hydroxy derivative **7** the value 2 Hz was obtained. In the case of 2β-fluoro ketone **9** we observed no splitting at all. This observation can be explained by increasing population of the boat form (see above) of the A-ring along the stated series of compounds. The fluorine atom and 10β-methyl group (C-25) are far enough from each other to feel any steric interaction.

No splitting was also observed in compounds **2**, **3** and **5** with equatorial 2α-fluorine atom in contrast to 2α-fluoro ketone **4**, where 4α-methyl group (C-23) displayed C-F coupling.

^{1}H, ^{13}C and ^{19}F Chemical Shifts

As some differences between chair and boat conformations of the ring A can be traced also by looking at chemical shifts, we analyzed in detail also shifts of ^{1}H, ^{13}C and ^{19}F signals. The analyses of ^{1}H chemical shifts was carried out in 3-oxo derivatives, which differ in the conformation of their A-ring according to the values of coupling constants found there. As a measure can serve the chemical shift of H-25, which is typically lower for

boat conformation[3]. This can be ascribed to the influence of a magnetic anisotropy of the carbonyl group because both groups stick out at a β-side of a backbone in boat conformation. Subtracting the chemical shift for 2β and 2α isomers of 2-fluoro ketones **9** and **4** ($\Delta\delta = \delta(\text{H-25})_{2\beta\ \text{isomer}} - \delta(\text{H-25})_{2\alpha\ \text{isomer}}$) is –0.337, what is fully comparable with the difference presented in literature for 2-methyl ketones ($\Delta\delta$ = –0.442, ref.[3]).

Except for the 10β-methyl group (H-25), a connection was reported[22] between the conformation of A-ring and the chemical shift of hydrogen atom in position 1. There was shown that in 2α isomers of triterpenoid ketones bearing polar and/or non-polar substituents (Br, Cl, OCH_3, CH_3) on C-2 atom, the H-1α signal was shifted upfield (compared with H-1β) when they adopt a chair conformation of the A-ring. In corresponding 2β isomers, the situation is opposite. The very same trend was observed for fluoro ketone **4** (2α-F) (δ(H-1α) 1.43, δ(H-1β) 2.54) and **9** (2β-F) (δ(H-1α) 2.32, δ(H-1β) 1.79).

By comparing the ^{13}C chemical shifts of ring A in 2-fluoro and 2-methyl ketones we found that the values match with those presented in literature[2]. The differences of the 2β isomer chemical shifts (representing the boat ring conformation) and those of 2α isomer (chair conformation) coincide and confirm the boat conformation in fluoro ketone **9** (see also Table III). Ac-

TABLE III
The differences in the selected ^{13}C chemical shifts between 2β- and 2α-substituted 3-oxo derivatives of 19β,28-epoxy-18α-oleanane ($\Delta\delta = \delta_{2\beta\ \text{isomer}} - \delta_{2\alpha\ \text{isomer}}$)

Carbon	Δδ, ppm	
	2-fluoro ketones	2-methyl ketones[a]
1	+1.37	+1.26
2	–0.94	–0.69
3	+2.97	+2.77
4	–2.47	–1.72
5	–4.68	–4.91
6	+0.88	+0.80
7	–1.10	–1.06
10	–0.89	–0.66
23	+4.60	+4.22
24	–1.80	–2.27

[a] Ref.[2]

cording to the relevant literature[2], the highest difference can be found in C-4, C-5, C-23 and C-24 carbon signals: for boat conformation the C-4, C-5 and C-24 carbon resonances are diamagnetically shifted whereas C-6 and C-23 are shifted in paramagnetic direction.

2D-NOESY Spectra

The above results could be verified by NOESY spectra because on the basis of different spatial contacts observable between hydrogen atoms of ring A in the chair and boat conformations.

In 2α-fluoro ketone **4**, the chair conformation of ring A was ascertained by the presence of the cross-peaks connecting H-2β protons and 4β- (H-24), 10β- (H-25) methyl groups. Similar contacts were observed in the NOESY spectra of 2α-fluorohydrins **2** and **5** and acetate **3**, which also prefer chair conformation. Other typical contacts indicating a chair conformation in 2-fluoro-3β derivatives **2**, **3**, **10** and **11** are those one between H-3α protons and H-1α and H-5α ones. On the other hand, for 2β-fluoro ketone **9**, the observation of the cross-peaks H-2α with H-5α and 4α-methyl group (H-23) proved the boat arrangement.

Considering the equilibrium of forms for compounds **7** and **8**, contacts between H-2α and H-3β, H-5α and H-23 were found. In a chair conformation, H-2α and H-3β are spatially close to each other, whereas cross-peaks H-2α with H-5α and H-23 can be explained only by transition to a boat conformation. Similarly, contacts of H-3β with all methyl groups of the A-ring (H-23, H-24 and H-25) can support the presence of both form (the NOESY contacts are summarized in Table I).

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Optical rotation measurements were measured at 23 °C in chloroform (*c* 0.3–0.5) on an automatic polarimeter AUTOPOL III (Rudolph Research) with accuracy ±2; they are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded in chloroform on a Nicolet AVATAR 370 FT IR; wavenumbers are given in cm^{-1}. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian UNITY INOVA 400 FT spectrometer (^1H at 400 MHz, ^{13}C at 100.58 MHz, ^{19}F at 376.29 MHz) in deuteriochloroform with tetramethylsilane as the internal standard (in ^{13}C NMR, $\delta(CDCl_3)$ 77.00 ppm, in ^{19}F NMR $\delta(CFCl_3)$ 0 ppm). Chemical shift values (δ-scale, ppm) and coupling constants (*J*, Hz) were obtained by first-order analysis. For ^1H and ^{13}C NMR data see Tables IV–VII. Electron-impact mass spectra were measured on an INCOS 50 (Finnigan MAT) instrument (ionizing electron energy 75 eV, ion source temperature 150 °C). The samples were introduced by direct inlet at heating rate 10 mA s^{-1}. Column chromatography was carried out on silica gel Kieselgel 60 (Merck). The course of reactions and purity of the samples were

TABLE IV
^{1}H NMR chemical shifts and coupling constants (in parentheses) of compounds **2**–**5**

Proton	**2**	**3**	**4**	**5**
1α	1.06	1.16	1.43	1.48
1β	2.230 ddd (11.9, 6.7, 5.0)	2.286 ddd (12.2, 6.9, 5.2)	2.535 dt (12.4, 6.9)	1.90 m
2β	4.589 dddd (50.8, 11.4, 9.4, 5.0)	4.650 dddd (49.9, 11.3, 9.8, 5.0)	5.291 ddd (47.9, 12.2, 6.6)	4.911 dddd (46.2, 11.9, 5.0, 2.9)
3	3.257 dd (13.4, 9.5)[a]	4.782 dd (12.4, 9.8)[a]	–	3.649 dd (8.7, 2.9)[b]
5α	0.85	0.98	1.21	1.30
6a	1.44	1.40	1.52	1.30
6b	1.60	1.56	1.52	1.43
7a	1.39	1.43	1.40	1.42
7b	1.44	1.43	1.46	1.42
9α	1.42	1.46	1.46	1.53
11α	1.52	1.52	1.53	1.52
11β	1.30	1.32	1.36	1.29
12α	0.94	0.94	0.94	0.94
12β	1.67	1.67	1.67	1.67
13β	1.46	1.47	1.46	1.47
15α	1.09	1.10	1.09	1.09
15β	1.58	1.58	1.58	1.58
16α	1.40	1.40	1.40	1.40
16β	1.30	1.30	1.30	1.30
18α	1.45	1.48	1.47	1.47
19α	3.528 bs	3.529 bs	3.530 bs	3.530 bs
21α	1.21	1.22	1.22	1.22
21β	1.50	1.48	1.49	1.50
22α	1.34	1.33	1.33	1.32
22β	1.44	1.44	1.44	1.44
23	1.062 s	0.897 s	1.149 s	1.039 d (1.2)
24	0.825 s	0.856 s	1.085 s	0.857 s
25	0.919 s	0.933 s	1.164 s	0.897 bs
26	0.973 s	0.973 s	1.027 s	0.964 s
27	0.919 s	0.920 s	0.909 s	0.926 s
28(*pro-R*)	3.446 d (7.8)	3.448 d (7.8)	3.456 d (7.8)	3.443 d (7.8)
28(*pro-S*)	3.770 dd (7.8, 1.7)	3.768 dd (7.8, 1.5)	3.771 dd (7.8, 1.5)	3.771 dd (7.8, 1.7)
29	0.801 s	0.803 s	0.799 s	0.801 s
30	0.933 s	0.933 s	0.935 s	0.932 s
OH	2.278 bs	2.126 s	–	–

[a] 3α; [b] 3β.

TABLE V
^{1}H NMR chemical shifts and coupling constants (in parentheses) of compounds **7**–**11**

Proton	**7**	**8**	**9**	**10**	**11**
1α	1.64	1.38	2.323 bdd (13.6, 11.6)	1.15	1.21
1β	1.891 ddd (23.0, 14.5, 5.0)	2.073 ddd (18.5, 15.0, 3.7)	1.788 ddd (30.5, 13.6, 7.0)	2.382 ddd (15.3, 13.9, 3.1)	2.345 ddd (15.3, 13.1, 3.2)
2α	4.687 dtd (49.9, 6.6, 5.0)	4.624 dtd (47.3, 4.8, 3.7)	5.390 ddd (49.9, 11.8, 7.0)	4.867 dq (51.0, 3.2)	4.869 dq (51.4, 3.2)
3	3.744 ddd[a] (9.5, 6.7, 3.2)	4.979 bdd[a] (8.2, 4.7)	–	3.15 bd (33.0)[b]	4.532 dd[b] (33.3, 3.1)
5α	1.13	1.18	1.66	0.84	0.97
6a	1.44	1.46	1.44	1.52	1.56
6b	1.47	1.60	1.44	1.60	1.57
7a	1.42	1.43	1.42	1.38	1.42
7b	1.42	1.43	1.48	1.44	1.42
9α	1.39	1.38	1.52	1.30	1.35
11α	1.48	1.50	1.43	1.50	1.50
11β	1.38	1.36	1.32	1.30	1.33
12α	0.94	0.94	0.94	0.93	0.93
12β	1.66	1.67	1.67	1.66	1.66
13β	1.47	1.47	1.50	1.46	1.46
15α	1.09	1.10	1.12	1.09	1.09
15β	1.56	1.58	1.55	1.58	1.59
16α	1.40	1.40	1.40	1.40	1.40
16β	1.30	1.30	1.32	1.30	1.31
18α	1.47	1.47	1.50	1.46	1.47
19α	3.529 bs	3.532 bs	3.536 bs	3.526 bs	3.526 bs
21α	1.22	1.22	1.23	1.22	1.23
21β	1.51	1.50	1.49	1.52	1.52
22α	1.32	1.34	1.34	1.34	1.34
22β	1.44	1.44	1.44	1.44	1.44
23	0.961 s	0.891 s	1.141 s	1.039 s	0.903 s
24	1.011 d (1.5)	1.021 d (1.6)	1.111 s	0.943 d (1.2)	1.053 d (1.2)
25	1.057 s	1.082 bs	0.827 bs	1.057 s	1.110 bs
26	0.973 s	0.988 s	0.967 s	0.992 s	0.998 s
27	0.914 s	0.940 s	0.952 s	0.908 s	0.908 s
28(*pro-R*)	3.443 d (7.8)	3.448 d (7.8)	3.456 d (7.8)	3.445 d (7.8)	3.446 d (7.8)
28(*pro-S*)	3.771 dd (7.8, 1.7)	3.776 dd (7.8, 1.7)	3.772 dd (7.8, 1.5)	3.772 dd (7.8, 1.7)	3.771 dd (7.8, 1.7)
29	0.800 s	0.801 s	0.809 s	0.797 s	0.797 s
30	0.932 s	0.935 s	0.939 s	0.932 s	0.932 s
OH	1.842 d (4.0)	–	–	2.12 bs	–
OAc	–	2.098 s	–	–	2.153 s

[a] 3β; [b] 3α.

TABLE VI
^{13}C NMR chemical shifts and *J*(C,F) coupling constants (in parentheses) of compounds **2**–**5**

Carbon	**2**	**3**	**4**	**5**
1	44.18 d (16)	44.72 d (16)	47.26 d (16)	38.87 d (16)
2	93.28 d (166)	89.81 d (173)	89.20 d (185)	91.09 d (167)
3	81.12 d (16)	81.10 d (16)	210.27 d (12)	76.75 d (15)
4	39.64 d (8)	39.60 d (7)	48.60	38.59 d (6)
5	55.39	55.12	56.82	48.25
6	18.06	18.11	18.97	17.85
7	33.69	33.63	33.45	33.57
8	40.77	40.78	40.84	40.86
9	50.97	50.94	50.72	50.76
10	39.01 d (11)	38.74 d (10)	38.30 d (9)	39.03 d (11)
11	21.14	21.16	21.32	21.02
12	26.28	26.25	26.16	26.32
13	34.06	34.08	34.06	34.06
14	40.68	40.69	40.74	40.86
15	26.36	26.37	26.33	26.37
16	36.71	36.70	36.66	36.73
17	41.45	41.45	41.41	41.48
18	46.78	46.78	46.73	46.80
19	87.90	87.94	87.90	87.96
20	36.24	36.26	36.23	36.26
21	32.67	32.68	32.63	32.70
22	26.21	26.20	26.16	26.23
23	28.42	28.25	24.73 d (2)	28.31
24	16.61	17.52	21.15	21.72
25	17.63	17.68	17.23	17.55
26	15.69	15.67	15.77	15.71
27	13.47	13.44	13.40	13.57
28	71.21	71.23	71.18	71.25
29	24.53	24.52	24.49	24.54
30	28.78	28.78	28.75	28.80
OAc	–	21.03 170.91	–	–

TABLE VII
^{13}C NMR chemical shifts and *J*(C,F) coupling constants (in parentheses) of compounds **7**–**11**

Carbon	**7**	**8**	**9**	**10**	**11**
1	42.54 d (17)	41.37 d (17)	48.63 d (18)	43.38 d (17)	43.13 d (17)
2	93.16 d (171)	90.21 d (176)	88.26 d (189)	93.78 d (172)	90.48 d (179)
3	75.57 d (21)	76.01 d (25)	213.24 d (13)	77.82 d (18)	79.01 d (16)
4	37.05 d (2)	36.04	46.13	38.34	37.41
5	50.07	50.40	52.14	55.34	55.63
6	18.78	18.15	19.85	17.93	17.83
7	33.30	33.40	32.35	33.71	33.71
8	40.83	40.85	40.74	40.81	40.81
9	51.49	51.30	50.32	51.35	51.33
10	37.50 d (2)	36.98	37.41 d (6)	36.68 d (1)	36.75 d (1)
11	21.39	21.18	22.09	21.14	21.13
12	26.33	26.33	26.38	26.38	26.35
13	34.23	34.11	34.42	34.06	34.02
14	40.68	40.72	40.32	40.68	40.69
15	26.47	26.40	26.38	26.29	26.27
16	36.73	36.73	36.70	36.72	36.70
17	41.48	41.47	41.45	41.44	41.44
18	46.78	46.80	46.72	46.78	46.76
19	87.92	87.89	87.87	87.89	87.88
20	36.26	36.25	36.26	36.24	36.24
21	32.70	32.69	32.67	32.67	32.65
22	26.22	26.22	26.16	26.21	26.20
23	26.23	27.38	29.33	29.15	28.83
24	22.19 d (3)	21.56 d (4)	19.35	16.54 d (3)	17.53 d (4)
25	19.57 d (2)	18.37 d (4)	18.57	17.10 d (6)	17.15 d (6)
26	15.44	15.52	15.00	15.59	15.67
27	13.50	13.58	13.41	13.44	13.41
28	71.25	71.23	71.22	71.22	71.22
29	24.54	24.51	24.53	24.52	24.52
30	28.80	28.78	28.77	28.78	28.78
OAc	–	21.04 170.16	–	–	21.05 171.05

checked by thin-layer chromatography (TLC) on DC-Alufolien Kieselgel 60 foils (Merck). Spots were detected by spraying with 10% sulfuric acid and subsequent heating. Analytical samples were dried over phosphorus pentoxide at 100 °C under reduced pressure.

19β,28-Epoxy-2α-fluoro-18α-oleanan-3β-ol (**2**)

The starting epoxide[5] **1** (300 mg, 0.68 mmol) and triethylamine trihydrofluoride (10 g, 62 mmol) were dissolved in pyridine (5 ml). The reaction mixture was then refluxed for 21 h. The mixture was cooled to room temperature, 30 ml of water acidified with few drops of hydrofluoric acid was added to improve a separation of phases in subsequent extraction with chloroform (3 × 10 ml). The chloroform extracts were combined and evaporated to dryness. The crude yield was 280 mg, it was dissolved in 5 ml of chloroform and purified on silica gel column (25 g). Compound **2** was eluted with chloroform and a mixture of chloroform/ether (5:1). This purification procedure afforded a yield of 158 mg (50%) of the pure fluorohydrin **2**. Besides, small amount (5 mg) of the starting **1** was isolated. An analytical sample was obtained by recrystallization from a mixture chloroform/methanol. M.p. 264–266 °C, $[\alpha]_D$ +40. IR: 1029, 3638. For ^{1}H and ^{13}C NMR, see Tables IV and VI. ^{19}F NMR: –191.59 dddd (*J* = 51, 14, 11, 7). MS, *m/z* (%): 460 (M^+, 100), 440 (46), 431 (15), 429 (23), 422 (8), 409 (15), 389 (100), 225 (31). For $C_{30}H_{49}FO_2$ (460.7) calculated: 78.21% C, 10.72% H; found: 78.36% C, 10.86% H.

19β,28-Epoxy-2α-fluoro-18α-oleanan-3β-yl Acetate (**3**)

Fluorohydrin **2** (24.5 mg, 0.053 mmol) was dissolved in pyridine (0.4 ml) and acetic anhydride (0.6 ml) was added. During 5 days of staying at room temperature, acetate **3** crystallized from reaction mixture. The solid product was filtered, washed with acetic anhydride (1 ml) and dried at 110 °C. The yield was 19.8 mg (74%). M.p. 299–303 °C (decomp.), $[\alpha]_D$ +24. IR: 1034, 1244, 1734. For ^{1}H and ^{13}C NMR, see Tables IV and VI. ^{19}F NMR: –191.78 dtd (*J* = 50, 11, 7). MS, *m/z* (%): 502 (M^+, 95), 484 (17), 467 (10), 431 (65), 422 (80), 407 (11), 187 (45), 43 (100). For $C_{32}H_{51}FO_3$ (502.8) calculated: 76.45% C, 10.22% H; found: 76.57% C, 10.41% H.

19β,28-Epoxy-2α-fluoro-18α-oleanan-3-one (**4**)

Fluorohydrin **2** (180 mg, 0.39 mmol) and anhydrous sodium acetate (150 mg) was dissolved in glacial acetic acid (65 ml). In the following step, $Na_2Cr_2O_7 \cdot 2H_2O$ (335 mg, 1.12 mmol) was added while stirring. The resulting solution was left standing for 26 h and then the residue of the oxidation agent was quenched by an addition of ethanol (1 ml). After a few hours the greenish mixture was diluted with water (70 ml) and the product was extracted into chloroform. Evaporation of the chloroform extracts yield 176 mg (98%) of fluoro ketone **4**. A recrystallization from a chloroform/methanol mixture afforded analytical sample. M.p. 195–201 °C, $[\alpha]_D$ +52. IR: 1029, 1713. For ^{1}H and ^{13}C NMR, see Tables IV and VI. ^{19}F NMR: –195.83 ddd (*J* = 48, 12, 7). MS, *m/z* (%): 458 (M^+, 100), 440 (10), 438 (12), 429 (11), 427 (8), 387 (75), 367 (5), 223 (5). For $C_{30}H_{47}FO_2$ (458.7) calculated: 78.55% C, 10.33% H; found: 78.66% C, 10.43% H.

19β,28-Epoxy-2α-fluoro-18α-oleanan-3α-ol (**5**)

A solution of fluoro ketone **4** (95 mg, 0.21 mmol) in benzene (4 ml) and a solution of $NaBH_4$ (100 mg, 2.64 mmol) in methanol (16 ml) were mixed and the mixture was kept at room temperature without stirring. After 60 h, a solution of ammonium chloride (400 mg) in water (4 ml) was added. Then the mixture was stirred for 1 h which was followed by extraction with chloroform. The extracts were evaporated to yield 97 mg of crude product. This batch usually contained traces of starting fluoro ketone **4** and a mixture of isomeric fluorohydrins **5** and **2**. This mixture was subsequently chromatographically purified on a silica gel column (20 g) by elution with benzene and benzene/ether (4:1). To separate both isomers, 7 ml fractions were collected – isomer **2** (33 mg, 35%) was eluted first and then the target isomer **5** (R_F(**2**) 0.7, R_F(**5**) 0.45). The yield was 44 mg (46%). An analytical sample was obtained by recrystallization from benzene. M.p. 265–266 °C, $[\alpha]_D$ +39. IR: 1049, 3609. For ^{1}H and ^{13}C NMR, see Tables IV and VI. ^{19}F NMR: –191.13 dq (J = 46, 8). MS, *m/z* (%): 460 (M^+, 100), 440 (55), 431 (13), 429 (20), 422 (5), 409 (28), 389 (72), 225 (12), 205 (58).

19β,28-Epoxy-2β-fluoro-18α-oleanan-3α-ol (**7**)

A solution of epoxide[6] **6** (250 mg, 0.57 mmol) and triethylamine trihydrofluoride (10 g, 62 mmol) in dry pyridine (5 ml) was refluxed for 24 h. Then, the mixture was cooled and 30 ml of water acidified with few drops of hydrofluoric acid was added to improve phase separation in subsequent extraction with chloroform (3 × 10 ml). The chloroform extracts were unified and evaporated to dryness. Crude product (240 mg) was obtained, containing traces of starting epoxide **6**. In preparing a pure product, a chromatography on silica gel column (22 g) was used. A successive elution with chloroform and chloroform/ether (5:1) led to pure fluorohydrin **7** in the yield 113 mg (43%). An analytical sample was obtained after recrystallization from chloroform/methanol mixture. M.p. 270–272 °C, $[\alpha]_D$ +60. IR: 1028, 3640. For ^{1}H and ^{13}C NMR, see Tables V and VII. ^{19}F NMR: –180.40 bdtd (J = 49, 23, 9). MS, *m/z* (%): 460 (M^+, 100), 440 (39), 431 (11), 429 (33), 422 (11), 409 (8), 389 (50).

19β,28-Epoxy-2β-fluoro-18α-oleanan-3α-yl Acetate (**8**)

Into the solution of fluorohydrin **7** (100 mg, 0.22 mmol) in pyridine (2.5 ml) was dropped acetic anhydride (0.75 ml). Shortly, the acetate **8** started to precipitate in form of needle-shaped crystals. The solid was filtered off after 70 h, washed with 5 ml of acetic anhydride and dried at 105 °C. This first fraction yielded 52 mg (48%) of the product. A second portion (24 mg, 22%) was obtained when the filtrate was concentrated to one third of the original volume. Analytical sample was prepared by crystallization from chloroform/n-octane mixture. M.p. 246–248 °C, $[\alpha]_D$ +56. IR: 1030, 1258, 1735. For ^{1}H and ^{13}C NMR, see Tables V and VII. ^{19}F NMR: –178.08 dddd (J = 47, 38, 18, 8). MS, *m/z* (%): 502 (M^+, 100), 473 (3), 471 (7), 467 (7), 442 (9), 431 (30), 422 (32), 407 (15), 207 (60), 187 (77), 43 (85).

19β,28-Epoxy-2β-fluoro-18α-oleanan-3-one (**9**)

Fluorohydrin **7** (90 mg, 0.20 mmol) and anhydrous sodium acetate (70 mg) were dissolved in 99% acetic acid (35 ml), $Na_2Cr_2O_7 \cdot 2H_2O$ (165 mg, 0.55 mmol) was added while stirring. After 26 h, the remaining oxidation agent was quenched by addition of ethanol (1 ml); the color of the solution turned green during few following hours. Then the reaction mixture

was diluted by addition of water (40 ml) and the product was extracted with chloroform (3 × 5 ml). Combined organic fractions were extracted with fresh portion of water and sodium hydrogencarbonate and dried with anhydrous sodium sulfate. Evaporation of chloroform gave 78 mg (87%) of pure fluoro ketone **9**, which was recrystallized from a chloroform/methanol mixture to afford an analytical sample. M.p. 234–236 °C, $[\alpha]_D$ +121. IR: 1029, 1735. For ^{1}H and ^{13}C NMR, see Tables V and VII. ^{19}F NMR: –191.47 ddd (*J* = 50, 30, 2). MS, *m/z* (%): 458 (M^+, 100), 440 (4), 438 (6), 429 (12), 427 (11), 387 (76), 367 (4), 223 (12).

19β,28-Epoxy-2β-fluoro-18α-oleanan-3β-ol (**10**)

Solutions of fluoro ketone **9** (45 mg, 0.098 mmol) in benzene (2 ml) and $NaBH_4$ (50 mg, 1.32 mmol) in methanol (8 ml) were mixed. This mixture was left standing for 48 h and an aqueous solution of ammonium chloride was added (200 mg in 2 ml of water). The resulting solution was stirred for 1 h and then it was extracted with chloroform (3 × 10 ml). These extracts were combined, washed with water, dried with anhydrous sodium sulfate and evaporated to dryness. In such a way, 36 mg (80%) of fluorohydrin **10** was obtained. An analytical sample was prepared by recrystallization from a chloroform/methanol mixture. M.p. 216–218 °C, $[\alpha]_D$ +59. IR: 1029, 3620. For ^{1}H and ^{13}C NMR, see Tables V and VII. ^{19}F NMR: –195.67 dddd (*J* = 51, 47, 33, 14). MS, *m/z* (%): 460 (M^+, 100), 440 (36), 431 (17), 429 (30), 422 (11), 409 (6), 389 (44), 225 (48), 205 (68).

19β,28-Epoxy-2β-fluoro-18α-oleanan-3β-yl Acetate (**11**)

Fluorohydrin **10** (65 mg, 0.14 mmol) was dissolved in pyridine (2 ml) and acetic anhydride (1 ml) was added. This solution was left standing for 3 days and then it was neutralized with 10% hydrochloric acid followed by an extraction with chloroform. After an evaporation of the extract, 63 mg of crude acetate **11** was obtained. The purification was carried out on a silica gel column (15 g); the pure product (45 mg, 71%) was eluted with chloroform and recrystallized from a chloroform/n-octane mixture to obtain an analytical sample. M.p. 239–240 °C, $[\alpha]_D$ +73. IR: 1030, 1260, 1736. For ^{1}H and ^{13}C NMR, see Tables V and VII. ^{19}F NMR: –193.69 dddd (*J* = 52, 46, 33, 13). MS, *m/z* (%): 502 (M^+, 50), 473 (6), 471 (7), 467 (7), 442 (3), 431 (22), 422 (50), 407 (8), 207 (30), 187 (42), 43 (100).

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