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Conformation of tri- and tetra-substituted 2-fluoro cyclohexanones: proton non-equivalence, F–H and F–C coupling constants, conformational dependence of $^3J_{FH}$ and $^4J_{FH}$

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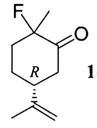
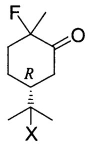
Abstract—The main conformation in solution (C_6D_6) of monofluorinated 2,2′,5-tri- and 2,2′,5,5′-tetra-substituted cyclohexanones have been studied using 1D and 2D NMR. It has been shown that for tri-substituted ketones the two possible diastereomers differ by the orientation of the fluorine atom which is axial or equatorial and that, similarly, the diastereomers of the tetra-substituted ketones having a methyl and a benzyl at C5 differ by the axial or equatorial position of the fluorine atom (the benzyl group remaining equatorial). However, the diastereomers of the tetra-substituted ketone having a methyl and a phenyl at C5 differ by the orientation of the phenyl group which is either axial or equatorial while the fluorine atom is axial in both cases. A conformational dependence of $^3J_{FH}$ (with $^3J_{FH}$ axial/axial=35–40 Hz>$^3J_{FH}$ equatorial/axial=13–13.5 Hz>$^3J_{FH}$ axial/equatorial=10–12 Hz≫$^3J_{FH}$ equatorial/equatorial=3–4 Hz) and $\Delta\delta_{6e-6a}$ (positive when the fluorine atom is equatorial but negative when the fluorine atom is axial) has been found for ketones 1–5 as well as a clear geometrical dependence of $^4J_{FH}$ (with $^4J_{FH}$ axial/axial=6 Hz>$^4J_{FH}$ equatorial/equatorial=3–4 Hz>$^4J_{FH}$ axial/equatorial=1.5 Hz>$^4J_{FH}$ equatorial/axial=0 Hz) for ketones 1–4. © 2002 Elsevier Science Ltd. All rights reserved.

During work on asymmetric catalytic epoxidation of olefins via chiral dioxiranes generated in situ from chiral ketones and oxone[1,2] we have synthesized the tri- and tetra-substituted 2-fluoro cyclohexanones **1–6**. Both diastereomers (**I** and **II**) of ketones **1–4** have been isolated enantiopure from (+)-dihydrocarvone (99% *R* configured at C5) while those of ketones **5** and **6** have been isolated racemic and resolved.[3,4]


1(I, II)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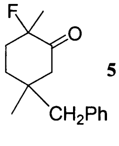
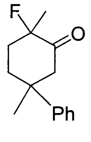
3 (I, II): X= Cl
4 (I, II): X= F


5 (I, II)


6 (I, II)

We present here non-equivalences of protons at C3 and C6, the F–H and F–C coupling constants which have been determined on these ketones, as well as a geometrical dependence of $^3J_{FH}$ and $^4J_{FH}$ which could then be used for identification of the axial or equatorial position of the fluorine atom.

1. F–H coupling constants and geometrical dependence of $^3J_{FH}$ and $^4J_{FH}$

In the cases of tri-substituted ketones **1–4**, the AB parts of the ABX systems (CH_2–CH in blue on Scheme 1) are easily identified at first sight and principally proton H6a. In all cases H6a exhibits two large coupling constants ($^2J_{66}$ and $^3J_{65}$) indicating that H5 is axial and the '*i*Pr'-group equatorial. Assignment of all other protons signals has, then, been done using 2D H/C correlation and nOe experiments.

Considering also that the configuration at C5 is known (*R*), it was concluded, from the presence in diastereomers **I** (**1I–4I**) of a positive nOe between the Me-doublet at C2 and proton H6a (easily identified) and a positive $H5_{axial}/H3_{axial}$ nOe, that the configurations of **1I–4I** were (2*R*,5*R*) and the main conformation as shown in Scheme 1 (with the Me at C2 axial and the '*i*Pr'-group equatorial). Similarly the two large coupling constants for H6, the absence of such C2–Me/H6 nOe in diastereomers **1II–4II** together with the presence of a positive $H5_{axial}/H3_{axial}$ nOe indicated that the configurations of **1II–4II** were (2*S*,5*R*) and the main conformation as shown in Scheme 1.

Keywords: fluoro cyclohexanones; conformation cyclohexanones; NMR F–H coupling constants; NMR F–C coupling constants.

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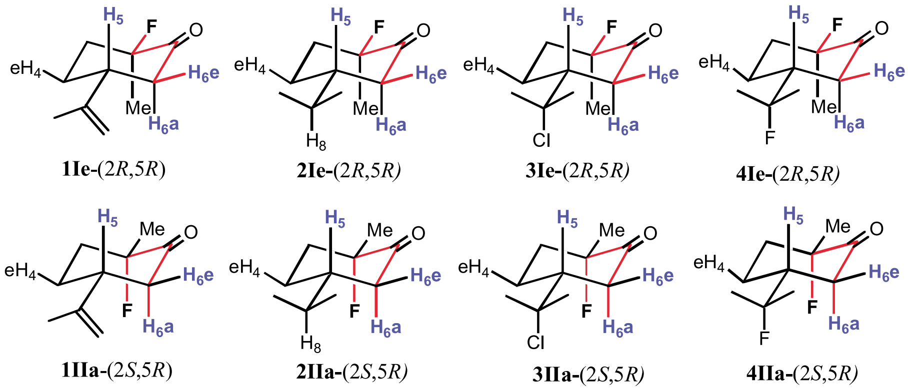


Scheme 1. Both diastereomers of tri-substituted ketones **1**–**4** in their main conformation in C_6D_6 solution (**Ie** for equatorial fluorine and **IIa** for axial fluorine).

Table 1. ^{1}H chemical shifts, J_{HH} and J_{FH} coupling constants for diastereomers **Ie** of tri-substituted ketones (equatorial fluorine) in their main conformation in C_6D_6 solution: CH_2 at C6

	δH_6a	$^2J_{66}$	$^3J_{65}$(aa)	$^4J_{FH}$(ea)	δH_6e	$^2J_{66}$	$^3J_{65}$(ea)	$^4J_{FH}$(ee)	$^4J_{64}$(ee)	$\Delta\delta_{6e-6a}$
1Ie	2.08	13.5	10	0	2.41	13.5	4	4	1.5	+0.33
2Ie	1.78	14	11	0	2.30	14	3	3	2	+0.52
3Ie	2.10	12.5	12.5	0	2.39	12.5	3.5	3.5	3.5	+0.29
4Ie	1.92	13	13	0	2.36	13	4	4	2.5	+0.44

Table 2. ^{1}H chemical shifts, J_{HH} and J_{FH} coupling constants for diastereomers **IIa** of tri-substituted ketones (axial fluorine) in their main conformation in C_6D_6 solution: CH_2 at C6

	δH_6a	$^2J_{66}$	$^3J_{65}$(aa)	$^4J_{FH}$(aa)	δH_6e	$^2J_{66}$	$^3J_{65}$(ea)	$^4J_{FH}$(ae)	$^4J_{64}$(ee)	$\Delta\delta_{6e-6a}$
1IIa	2.72	13	13	6	2.29	13	3	1.5	1.5	−0.43
2IIa	2.48	12	12	6	2.22	12	3	1.5	1.5	−0.26
3IIa	2.67	13	13	6	2.45	13	3.5	1.5	1.5	−0.22
4IIa	2.54	13	13	6	2.37	13	3	1.5	1.5	−0.17

Diastereomers (2*R*,5*R*)-**I**, having an equatorial fluorine, will be noted **Ie**, while diastereomers (2*S*,5*R*)-**II** with an axial fluorine will be noted **IIa**.

A complete patterns analysis of the ABX systems (CH_2–CH in blue on Scheme 1) of ketones **1Ie**–**4Ie** and **1IIa**–**4IIa** (without and with decoupling of H4e) allowed determination and assignment of the coupling constants. The results are gathered in Tables 1 and 2.

It must be noted that in some cases, ketones **1IIa**, **2IIa** and **4IIa**, the H6e signals is difficult to analyze. When the values of the small coupling constants are such that $J=2J'$ the pattern is a double-12221 multiplet, which must not be confused with a double-pentuplet.[5] However, usually H6e gives a classical double double triplet (ddt) pattern with three different values of coupling constants (one large, ^2J, and two small among which one is acting twice, ketone **3IIa**).

Examination of Tables 1 and 2 showed that the geometrical dependence of $^4J_{FH}$ was of significant amplitude with $^4J_{FH}$(aa)=6 Hz and $^4J_{FH}$(ee)=3–4 Hz in accord with the values estimated from half-height width measurements of the protons signals by Cantacuzène[6] on 2-fluoro-4-tbutyl cyclohexanone and 2,6-difluoro cyclohexanones ($^4J_{FH}$(aa) = 5.5 Hz and $^4J_{FH}$(ee)=3.7 Hz). Moreover it appeared that, when the fluorine is axial, the axial/equatorial, $^4J_{FH}$, is larger than when the fluorine is equatorial: $^4J_{FH}$(ae)=1.5 Hz> $^4J_{FH}$(ea)=0 Hz. This could be due to the larger hyperconjugative interaction $\pi_{C=O}\cdot\sigma^*_{C-F}\pi^*_{C=O}\cdot\sigma_{C-F}$ when the C–F bond is coplanar with the $\pi_{C=O}$ system leading to a better delocalization of the electrons and to a better transmission of the coupling information.

One must note also that when the fluorine is axial (Table 2) proton H6a is deshielded compared to proton H6e with negative values of $\Delta\delta$(6e–6a), while the contrary occurs when the fluorine is equatorial (Table 1).

The data obtained from analysis of the protons-H3 signals are gathered in Tables 3 and 4.

In ketones **1Ie** and **2Ie** the non-equivalences between protons H3e and H3a, $\Delta\delta$(3e–3a), were too small to allow a rapid analysis (second order spectra) while the analysis was easy for all the other ketones (**1IIa**, **2IIa**, **3Ie**, **3IIa**, **4Ie** and **4IIa**). Examination of the estimated (**1Ie**, **2Ie**) and/or measured (all others) $\Delta\delta$(3e–3a) showed that the non-equivalences were almost 10 times larger when the fluorine atom is axial (diastereomers **IIa**) than when the fluorine is equatorial (diastereomers **Ie**). Moreover the geometrical dependence of $^3J_{H3/F}$ is still more significant than the geometrical dependence of $^4J_{FH}$ with: $^3J_{HF}$ *trans* **aa**=39 to

Table 3. ^{1}H chemical shifts, J_{HH} and J_{FH} coupling constants for diastereomers **Ie** of tri-substituted ketones (equatorial fluorine) in their main conformation in C_6D_6 solution: CH_2 at C3

	δH_3a	$^2J_{33}$	$^3J_{3F}$(ae)	δH_3e	$^2J_{33}$	$^3J_{3F}$(ee)	$\Delta\delta$(3e−3a)
1Ie	~1.60	nd	nd	~1.6	nd	nd	<0.05
2Ie	~1.65	nd	nd	~1.65	nd	nd	<0.05
3Ie	1.58	13	13	1.66	13	3	+0.08
4Ie	1.59	13.5	13.5	1.69	13.5	4	+0.10

nd, not determined.

Table 4. ^{1}H chemical shifts, J_{HH} and J_{FH} coupling constants for diastereomers **IIa** of tri-substituted ketones (axial fluorine) in their main conformation in C_6D_6 solution: CH_2 at C3

	δH_3a	$^2J_{33}$	$^3J_{3F}$(aa)	δH_3e	$^2J_{33}$	$^3J_{3F}$(ea)	$\Delta\delta$(3e−3a)
1IIa	1.04	14	39	1.90	14	10	+0.86
2IIa	1.06	15	40	1.89	15	10	+0.83
3IIa	0.92	14.5	40	1.81	14.5	12	+0.89
4IIa	0.95	15	40	1.80	15	10	+0.85

40 Hz, $^3J_{HF}$ *gauche* **ae** or **ea**=10–13.5 Hz and $^3J_{HF}$ *gauche* **ee**=3–4 Hz.

It is thus easy and rapid to assign the axial position for the fluorine atom in all these tri-substituted ketones **1–4** either from the CH_2 at C6 or from the CH_2 at C3.

The behavior of tetra-substituted ketones **5** and **6** is more ambiguous, in these cases H5, the proton able to provide the $^3J_{trans}$ with one of the H6 which allows the H5a/H6a assignment, is absent, Fig. 1.

Nevertheless the AB patterns of protons H6a and H6e (CH_2 in blue on Scheme 2) are easily located on the spectra, then, all other protons and the carbons signals have been assigned by 2D H/C correlation experiments.

Positive nOe's between the Me-singlet (at C5) and protons H3a, H4e and H6e were observed in both diastereomers **5I**

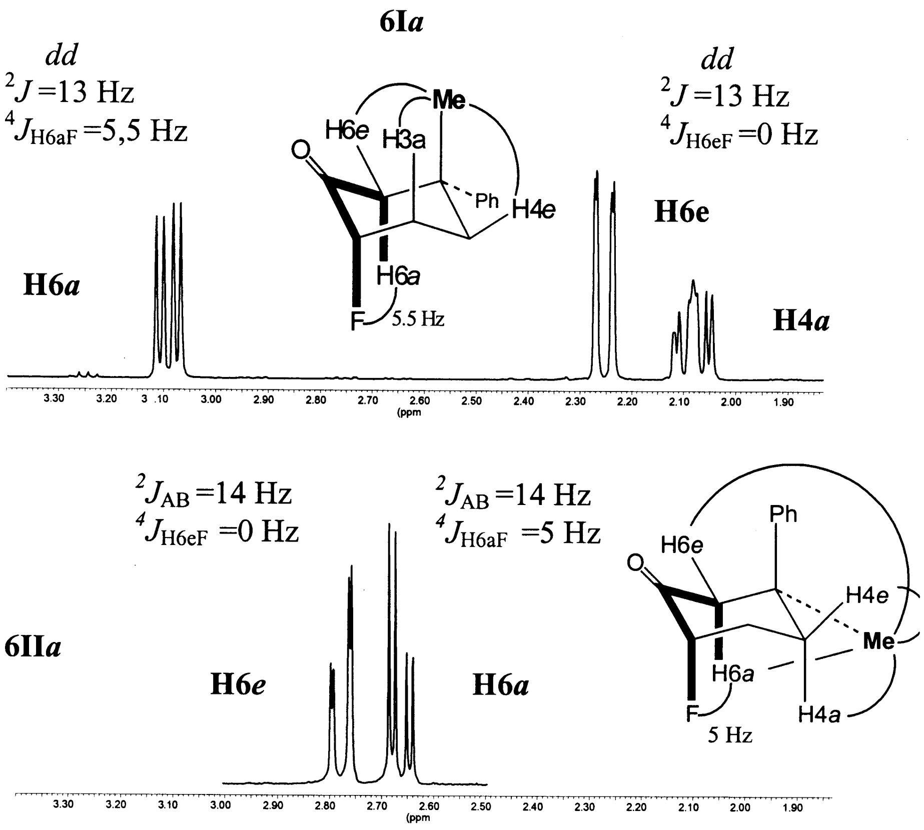
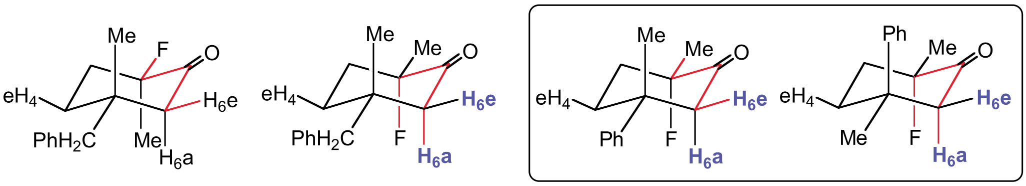


Figure 1.



5Ie-(2*R*,5*S*/2*S*,5*R*) **5IIa**-(2*S*,5*S*/2*R*,5*R*) **6Ia**-(2*S*,5*R*/2*R*,5*S*) **6IIa**-(2*S*,5*S*/2*R*,5*R*)

Scheme 2. Tetra-substituted ketones **5**, **6** in their main conformation in solution.

Table 5. ^{1}H chemical shifts, J_{HH} and J_{FH} coupling constants for tetra-substituted ketones having an equatorial and/or axial fluorine in their main conformation in C_6D_6 solution: CH_2 at C6

	δH_6a	$^2J_{66}$	$^4J_{FH}$(ea)	$^4J_{FH}$(aa)	δH_6e	$^2J_{66}$	$^4J_{FH}$(ee)	$^4J_{FH}$(ae)	$^4J_{64}$(ee)	$\Delta\delta_{6e-6a}$
5Ie	2.09	13	0	–	2.33	13	5.5	–	1.5^{a}	+0.24
5IIa	2.67	12.5		6	1.90	12.5		0	1^{a}	−0.77
6Ia	3.09	13		5.5	2.25	13		0	2^{a}	−0.84
6IIa	2.65	14		5	2.77	14		0	1.5^{a}	+0.12

[a] Assigned through H4e decoupling.

Table 6. ^{1}H chemical shifts, J_{HH} and J_{FH} coupling constants for tetra-substituted ketones having an equatorial and/or axial fluorine in their main conformation in C_6D_6 solution: CH_2 at C3

	δH_3a	$^2J_{33}$	$^3J_{3F}$(aa)	$^3J_{3F}$(ae)	δH_3e	$^2J_{33}$	$^3J_{3F}$(ea)	$^3J_{3F}$(ee)	$\Delta\delta$(3e–3a)
5Ie	1.80^{a}	?	–	13	1.55^{b}	?	–	?	−0.25
5IIa	1.32^{a}	15	35	–	1.78	15	12	–	+0.46
6Ia	1.40	15	31^{c}	–	1.76	15	12^{c}	–	+0.36
6IIa	1.25^{a}	?	30	–	1.75^{d}	?	12^{c}	–	+0.50

[a] Assigned by NOESY as axial.
[b] Overlapped with H4e.
[c] Determined on ^{19}F NMR.
[d] Overlapped with one of the two H4.

and **5II** indicating that the Me at C5 was axial in both diastereomers.

Attempt to use the $^4J_{FH}$ geometrical dependence (cf. above for tri-substituted ketones **1**–**4**) to assign the axial or equatorial position of the fluorine atom to **5I** or **5II** failed because the $^4J_{FH}$ value (5.5 Hz) observed on one of the H6 proton for one diastereomer was too close to the $^4J_{FH}$ value (6 Hz) observed on one of the H6 proton of the other diastereomer. However, the values of the $^3J_{FH}$ determined on proton H3a being 13 Hz in diastereomer **5I** and 35 Hz in diastereomer **5II**, one could reasonably conclude that the fluorine atom is axial in diastereomer **5II** (**5IIa**) and equatorial in diastereomer **5I** (**5Ie**).

In diastereomer **6I** the positive nOe's observed between the Me-singlet (at C5) and protons H3a, H6e and H4e (which is overlapped with the Me-doublet) indicated that this Me at C5 is axial. The same Me-singlet in diastereomer **6II** exhibited positive nOe's with protons H4a, H4e, H6a and H6e indicating that this Me is equatorial. The values of the $^3J_{FH}$ determined on the proton H3a are similar: 31 Hz in diastereomer **6I** and 30 Hz in diastereomer **6II** suggesting that the fluorine atom is axial in both cases (**6Ia**, **6IIa**).

Table 7. F–C coupling constants in ketones **1**–**6** (C_6D_6 solution)

	$^1J_{FC2}$	$^2J_{FMe}$	$^2J_{FC1}$	$^2J_{FC3}$	$^3J_{FC4}$	$^3J_{FC6}$
1Ie	182	25	18	22	8	0
1IIa	172	24	24	22	2	2
2Ie	184	25	17	22	9	0
2IIa	171	25	25	23	2	2
3Ie	186	26	16	22	10	0
3IIa	172	24	25	23	0	0
4Ie	185	26	17	21	10	0
4IIa	171	23	25	23	2	2
5Ie	177	24	21	23	0	0
5IIa	173	24	23	23	0	0
6Ia	173	24	23	22	3	0
6IIa	175	24	22	23	3	0

The fluorine atom being axial in both cases, **6Ia** and **6IIa**, assignment of H6a is straightforward on the basis of $^4J_{FH}$ values (cf. Tables 1 and 2).

It thus appeared that the most populated conformer of both diastereomers of ketone **6** have a fluorine axial (**Ia** and **IIa**) while the phenyl group is equatorial in **6Ia** and axial in **6IIa**, Scheme 2.

It is worth noting that inversion of the non-equivalence ($\Delta\delta_{6e-6a}>0$) with H6a more shielded than H6e in **6IIa** (Table 5, line 4), instead of what is generally observed with an axial fluorine (H6a more deshielded than H6e) is due to the fact that, in **6IIa**, proton H6e is in the deshielding cone of the phenyl ring (Table 6).

Moreover, the preference of equatorial phenyl and axial methyl (at C-5) is not in opposition with Eliel's results concerning phenyl-methyl-disubstituted cyclohexane.[7] In the case of ketones **6**, we are dealing with tetrasubstituted compounds and α-disubstituted cyclohexanones where at C2 (α to the carbonyl) a fluorine atom is in competition with a methyl group for the equatorial position, and hyperconjugative $\sigma^*\cdot\pi/\sigma\cdot\pi^*$ interactions between the carbonyl and the axial C-halogen (C–F) or C–C (C–Me) bond are present and could be responsible of the fluorine adopting the axial position.[8]

2. F–C coupling constants

From Table 7, it appeared that, concerning F–C coupling constants, tetra-substituted ketones **5** and **6** behave also differently from tri-substituted ketones **1**–**4**.

In the case of tri-substituted ketones **1**–**4**, the one-bond coupling constant between F and C2 ($^1J_{FC2}$) reflects the equatorial or axial position of C–F with a 10–14 Hz smaller value when the fluorine is axial ($^1J_{FC2}$=171–172 Hz) than when the fluorine is equatorial ($^1J_{FC2}$=182–186 Hz), Table 7 (compare lines 2, 4, 6, 8 with 1, 3, 5, 7). Similarly the two-bonds coupling constant between F and C1 ($^2J_{FC1}$) reflects also the equatorial or axial position of C–F with a smaller value of $^2J_{FC1}$ (16–18 Hz) when the fluorine is equatorial than when the fluorine is axial (24–25 Hz), Table 7 (lines 1–8).

No significant variation was observed between equatorial (**5Ie**) and axial (**5IIa**, **6Ia**, **6IIa**) fluorine in the case of tetra-substituted ketones **5** and **6**.

3. Conclusion

It has been found in solution (C_6D_6) that for tri-substituted ketones **1**–**4** the two possible diastereomers differ by the orientation of the fluorine atom which is axial or equatorial and that, similarly, the diastereomers of the tetra-substituted ketone **5** having a methyl and a benzyl at C5 differ by the axial or equatorial position of the fluorine atom (the benzyl group being equatorial in both cases). However the diastereomers of the tetra-substituted ketone **6** having a methyl and a phenyl at C5 differ by the orientation of the phenyl group which is either equatorial or axial while the fluorine atom is axial in both cases.

Moreover the tri-substituted ketones **1**–**4** and the tetra-substituted ketone **5** behave similarly concerning:

The geometrical dependence of $^3J_{FH}$:

> $^3J_{FH}$ axial/axial=35–40 Hz (fluorine axial)>$^3J_{FH}$ equatorial/axial=13–13.5 Hz (fluorine equatorial)>$^3J_{FH}$ axial/equatorial=10–12 Hz (fluorine axial)≫$^3J_{FH}$ equatorial/equatorial=3–4 Hz (fluorine equatorial).

The non-equivalence $\Delta\delta_{6e-6a}$ *(between H6e and H6a)*

> $\Delta\delta_{6e-6a}$ is positive when the fluorine atom is equatorial (+0.24 to +0.52 ppm) but negative when the fluorine atom is axial (−0.17 to −0.77 ppm).

The tri-substituted ketones **1**–**4** exhibit clear geometrical dependence of $^4J_{FH}$ between F and protons H6 (with significantly different values of $^4J_{FH}$):

> $^4J_{FH}$ axial/axial=6 Hz>$^4J_{FH}$ equatorial/equatorial=3–4 Hz>$^4J_{FH}$ axial/equatorial=1.5 Hz>$^4J_{FH}$ equatorial/axial=0 Hz.

Tetra-substituted ketone **6** is a special case, having a phenyl group on the ring, and $\Delta\delta_{6e-6a}$ is positive in one case (**6Ia**, phenyl ring equatorial) although the fluorine atom is axial but $^3J_{FH}$ axial/axial=31 Hz and $^3J_{FH}$ axial/equatorial=12 Hz in both cases (**6Ia** and **6IIa**) in consistency with the other ketones.

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