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TETRAHEDRON: *ASYMMETRY*

Tri- and tetrasubstituted α-fluorocyclohexanones with enantiomeric excesses in the range of 97–100%

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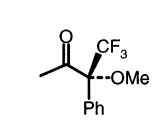
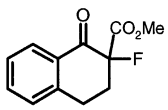
Abstract—The α-fluorinated trisubstituted ketones (2*S*,5*R*)-(−)-**7-I*a***, (2*R*,5*R*)-(+)-**7-II*e***, (2*S*,5*R*)-(−)-**8-I*a*** and (2*R*,5*R*)-(+)-**8-II*e*** were synthesised from (+)-dihydrocarvone (99% (*R*)-configuration at C-5) and fully characterised. α-Fluorinated tetrasubstituted ketones (−)-**9-I*a***, (+)-**9-I*a***, (+)-**9-II*a*** and (+)-**10-I*a*** having e.e.s of ≥97% were synthesised as racemates from 3-methyl cyclohexenone then resolved into the pure enantiomers using chiral HPLC and fully characterised. © 2001 Published by Elsevier Science Ltd.

1. Introduction

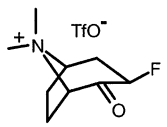
Since the first use by Curci et al.[1] in 1989 of trifluoromethyl acetone as a dioxirane precursor for the epoxidation of olefins, the observed activating effect of fluorine substitution has been extended to the asymmetric epoxidation of olefins and chiral ketones **1**–**6** have been reported.[2–7]



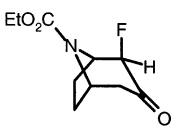
1 Curci
β-methylstyrene
77% conv., 18% e.e.



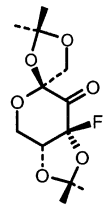
2 Marples
β-methylstyrene
100% conv., 0% e.e.



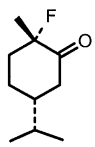
3 Denmark
β-methylstyrene
100% conv., 35% e.e.



4 Armstrong
Stilbene
88% yield, 76% e.e.



5 Shi
Stilbene
3% conv., 11% e.e.



6 Solladié-Cavallo
Stilbene
68% conv., 60% e.e.

The observation that a fluorine atom at C-(2)[7,8] and replacement of the proton of the *iso*-propyl group located at C-(5) by a halogen increased the enantioselectivity,[9] and led to the synthesis and full characterisation of ketones **7** and **8**. Ketones **9** and **10** have been envisaged to desymmetrise the axial face and thereby check whether or not axial approaches to the corresponding dioxiranes made significant contributions during epoxidations.[7,10]

Herein, we present the synthesis of both diastereomers of ketones **7** and **8** from commercially available (+)-dihydrocarvone (79% (2*R*,5*R*) and 21% (2*S*,5*R*)). Because carbon C-(5) in this natural product is 99% (*R*)-configured, the desired ketones **7-I*a***, **7-II*e***, **8-I*a*** and **8-II*e*** will similarly have e.e.s of ≥98%.

Ketones **9-I*a***, **9-II*a***, **10-I*a*** and **10-II*e***, synthesised from 3-methyl cyclohexenone, were obtained in racemic form. The most promising ketones having *axial* fluorine and either *axial* methyl as in **9-I*a*** and **10-I*a*** or axial phenyl as in **9-II*a***, were subsequently resolved using chiral chromatography.

2. Results and discussion

2.1. Synthesis

As shown in Scheme 1, the 2-fluoro-2-methyl-5-(*R*)-(chloro-isopropyl) cyclohexanone **7** was obtained (72% isolated) as a 43:57 mixture of **7-I*a*** (43%) and **7-II*e*** (57%) in three steps, from (+)-dihydrocarvone **11**. Hydrochlorination was performed following the literature procedure.[11] The thermodynamic silylenolate **13**

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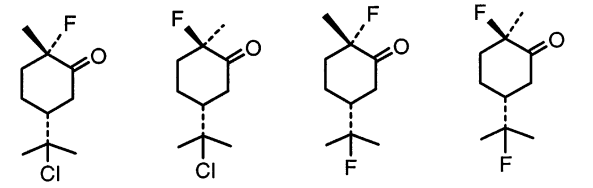
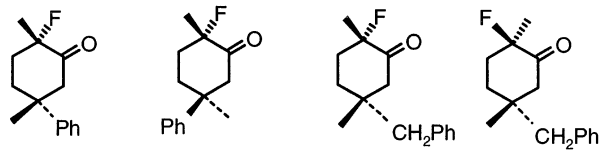


(2*S*,5*R*)-**7-Ia** (2*R*,5*R*)-**7-IIe** (2*S*,5*R*)-**8-Ia** (2*R*,5*R*)-**8-IIe**



Rac-**9-Ia** resolved into (-) and (+) | *Rac*-**9-IIa** resolved into (-) and (+) | *Rac*-**10-Ia** resolved into (-) and (+) | *Rac*-**10-IIe**

was obtained in quantitative yield after modification of the literature work-up[12] and the fluorination was performed with Selectfluor according to the literature procedure.[13] After chromatographic separation (2*S*,5*R*)-**7-I*a*** and (2*R*,5*R*)-**7-II*e*** were obtained in 31 and 41% overall yields, respectively, with enantiomeric excesses of $\geq$98%, identical to that of the starting dihydrocarvone.

The 2-fluoro-2-methyl-5-(*R*)-(fluoro-*iso*-propyl) cyclohexanone **8** was also obtained from **11** in three steps (Scheme 1). The thermodynamic silylenolate **14** was obtained in quantitative yield after modification of the literature work-up[12] and the fluorination, performed with Selectfluor according to the literature procedure,[13] provided a near 1:1 mixture of **15-I** (51%) and **15-II** (49%) which were separated by chromatography. Fluorination of the double bond was carried out on **15-I** and/or **15-II**, with pyridinium hydrofluoride 70% HF following a literature method.[14] (2*S*,5*R*)-**8-I*a*** and (2*R*,5*R*)-**8-II*e*** were obtained over the three steps, in 27% and 24% overall yield, respectively, with enantiomeric purities of $\geq$98%, identical to that of the starting (+)-dihydrocarvone.

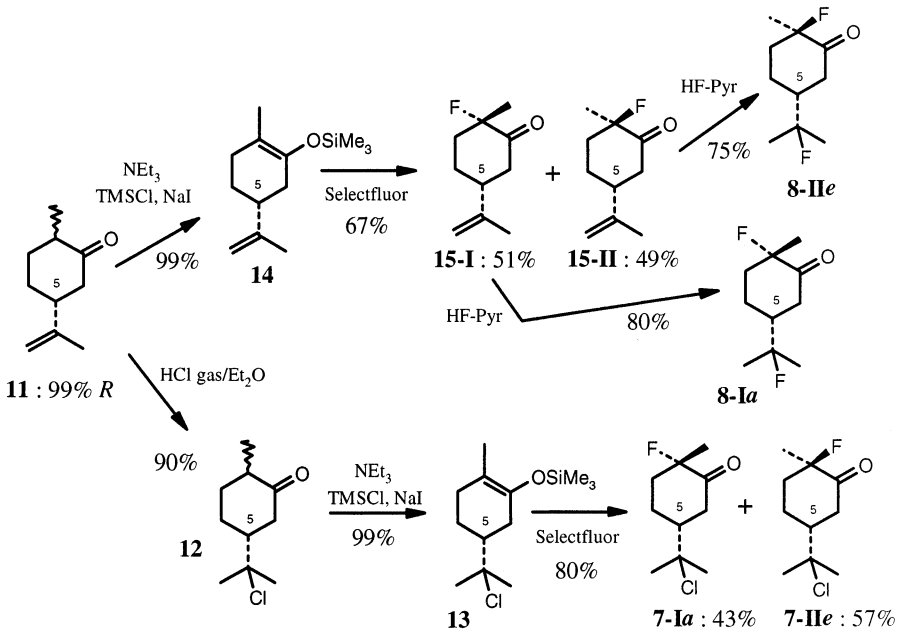
As shown in Scheme 2, racemic 2-fluoro-2-methyl-5-methyl-5-phenylcyclohexanone **9** was also obtained (61% isolated yield) as a 46/54 mixture of **9-I*a*** (46%) and **9-II*a*** (54%) in four steps from 3-methylcyclohexenone **16**. Conjugate addition of phenyl Grignard reagent was performed in the presence of $CuBr/Me_2S$[15] affording **18** in 84% isolated yield. The thermodynamic silylenolate **20** was subsequently obtained in 90% yield.[16] Fluorination was performed with Selectfluor analogously to the synthesis of **7** and **15**. After chromatographic separation (±)-**9-I*a*** (2*S*,5*R*/2*R*,5*S*) and (±)-**9-II*a*** (2*S*,5*S*/2*R*,5*R*) were obtained in overall yields of 28 and 33%, respectively.

(±)-2-Fluoro-2-methyl-5-methyl-5-benzylcyclohexanone **10** was obtained (38% isolated) as a mixture of **10-I*a*** (72%) and **10-II*e*** (28%) in four steps from 3-methylcyclohexenone **16**.

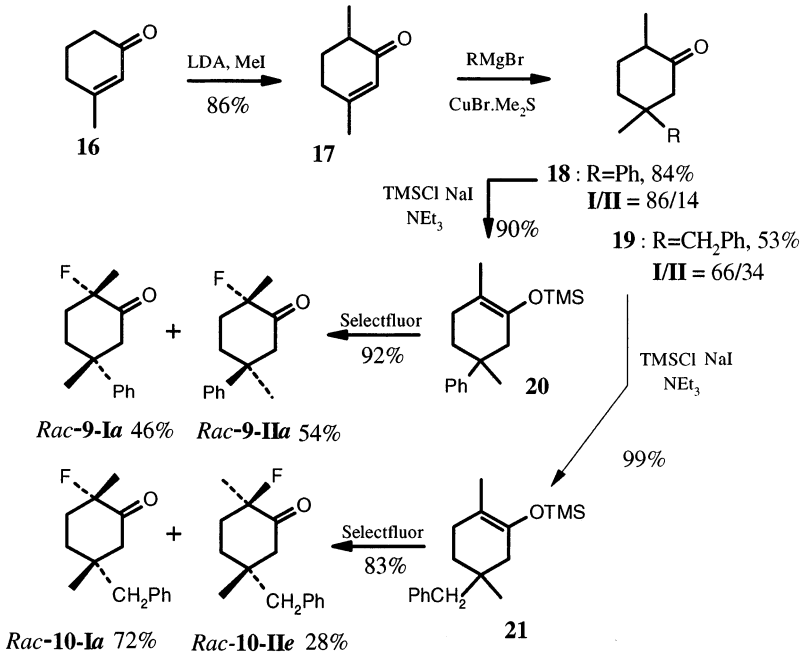
Conjugate addition of the commercial benzyl Grignard reagent in the presence of $CuBr/Me_2S$[15] gave, as expected, a lower isolated yield of 53%. The thermodynamic silylenolate **21** was obtained in quantitative yield after modification of the literature work-up[12] and fluorination was also effected with Selectfluor. After chromatographic separation (±)-**10-I*a*** (2*S*,5*S*/2*R*,5*R*) and (±)-**10-II*e*** (2*R*,5*S*/2*S*,5*R*) were obtained with an overall yield of 27 and 11%, respectively.

2.2. Structural determination of ketones 7, 8, 9 and 10 by NMR

For all ketones full assignment of the 1H signals was done using 2D C/H correlations, COSY and analysis of the multiplicity.



Scheme 1.



Scheme 2.

The well recognisable H-(6a) signals (two large coupling constants of about 11–12 Hz, a ^{2}J and a $^{3}J_{180}$) can be easily assigned in the ^{1}H NMR spectra of ketones **7-I*a***, **7-II*e***, **8-I*a*** and **8-II*e*** (Fig. 1). From our previous results,[17] which showed that the H-(6a) signal is deshielded compared to H-(6e) signal when the fluorine atom at C-(2) is axial, it was concluded (see Fig. 1) that in ketones **7-I*a*** and **8-I*a*** the fluorine atom is axial (which is also supported by the $^{4}J_{HF}$ coupling constant value of about 5 Hz as already observed[17]) and that in ketones **7-II*e*** and **8-II*e*** fluorine is equatorial. This assignment was confirmed by NOESY experi-

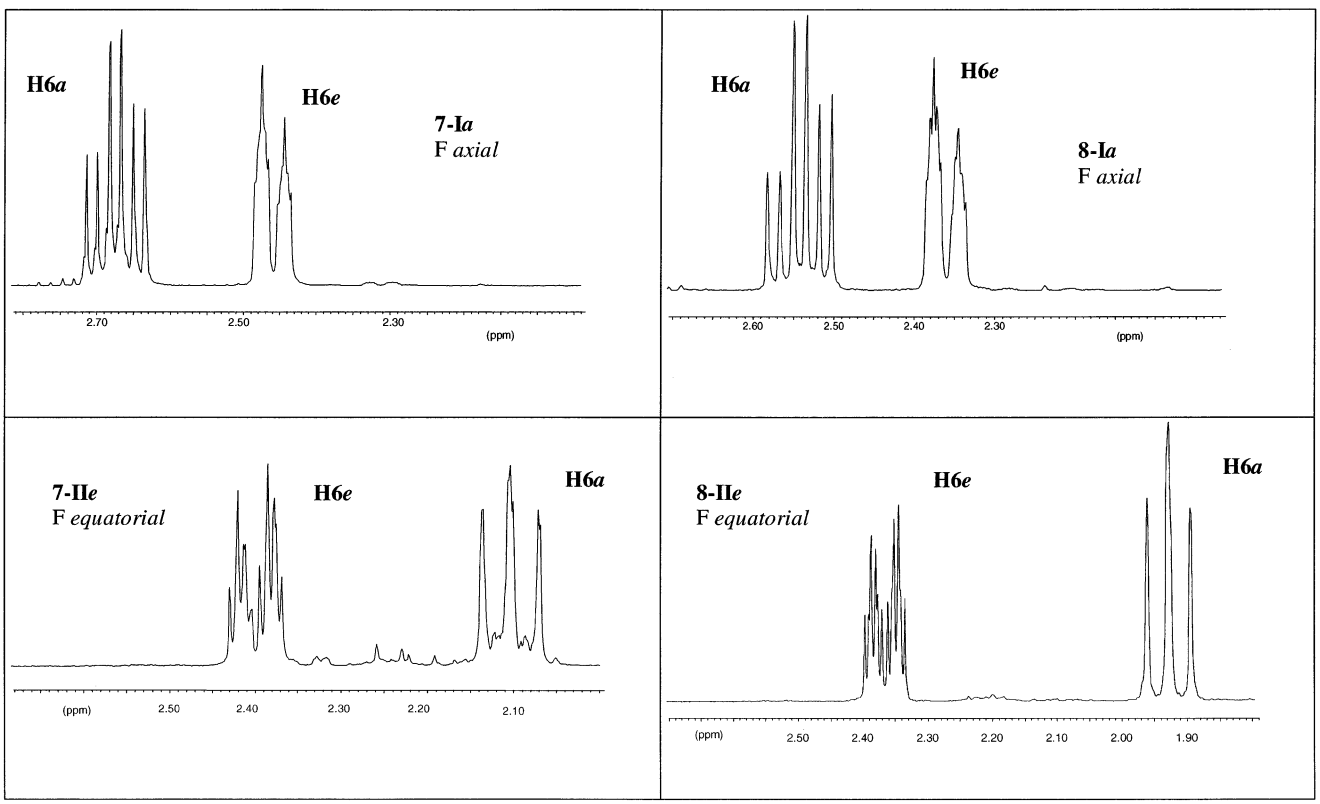


Figure 1. ^{1}H NMR 400 MHz (C_6D_6/TMS): AB part (CH_2 at C6) of the ABX system for ketones **7-I*a***, **7-II*e***, **8-I*a*** and **8-II*e***.

ments on isomers **7-II*e*** and **8-II*e*** which exhibited, in both cases, correlation spots between the H-(6a) multiplet and the doublet of the, thus axial, methyl at C-(2).

In ketones **9** and **10** the two protons at C-(6) give an AB system having long range couplings with the fluorine atom and assignment to H-(6a) or H-(6e) is less obvious. A NOESY experiment on isomer **9-I*a*** showed that the singlet for the C-(5) methyl group was correlated with one proton at C-(6), one proton at C-(4) and one proton at C-(3). It can thus be concluded that the C-(5) methyl group is axial (otherwise it would have been correlated with the two protons at C-(6) and the two protons at C-(4) but not with any C-(3) protons), as a consequence, the H-(6), H-(4) and H-(3) signals were assigned to H-(6e), H-(4e) and H-(3a). Moreover, the doublet for the C-(2) methyl group had no correlation spot with H-(6a) indicating its equatorial position and the axial position of fluorine, in accord with the $^4J_{HF}$ value of 5.5 Hz found for H-(6a).[17] Although in 1-methyl-1-phenylcyclohexane axial phenyl orientation is preferred by 0.32 kcal/mol,[18] it appears that the conformer having axial fluorine at C-(2) and axial methyl at C-(5) is the most populated for diastereomer **9I*a*** in C_6D_6, probably due to the absence of *syn*–axial interactions between the methyl and the carbonyl groups and possible C-F/C=O hyperconjugative interactions ($\sigma^*.\pi/\sigma.\pi^*$) favouring axial fluorine.[19]

A differential-NOE experiment on isomer **9-Ii*a***, irradiating the C-(5) methyl group showed that this methyl group, being correlated to the two protons at C-(6) and the two protons at C-(4), was equatorial. Assignment of H-(6a) was done by irradiation of H-(4a) and was consistent with the 5 Hz value found for $^4J_{HF}$ for the H-(6a) signal, leading to the conclusion that the fluorine atom was axial. Thus, both **9-I*a*** and **9-II*a*** have an axial fluorine (see Fig. 2).

The inversion of the H-(6a) and H-(6e) chemical shifts, with H-(6a) more shielded than H-(6e) in **9-II*a***, instead of what is generally observed when the fluorine is axial, is due to the fact that in **9-II*a*** H-(6e) is in the deshielding cone of the phenyl ring.

A NOESY experiment on isomer **10-I*a*** showed that the methyl singlet at C-(5) was correlated with one proton at C-(6), one proton at C-(4) and one proton at C-(3). It can thus be concluded that the C-(5) methyl is axial, as a consequence, the H-(6), H-(4) and H-(3) signals were assigned to H-(6e), H-(4e) and H-(3a). Moreover, the doublet of the C-(2) methyl group had no correlation spot with H-(6a) indicating its equatorial position and the axial position of the fluorine, in accord with the 6 Hz value of the $^4J_{HF}$ found for H6a.

A NOESY experiment on isomer **10-II*e*** showed that the methyl group at C-(5) correlated with one proton at C-(6), one proton at C-(4) and one proton at C-(3). It can thus be concluded that the methyl group at C-(5) is axial. As a consequence, the H-(6), H-(4) and H-(3) signals were assigned to H-(6e), H-(4e) and H-(3a). Moreover, the doublet for the methyl group at C-(2) was correlated with H-(6a) indicating its axial position and the equatorial position of the fluorine, in accord with the 5.5 Hz value of the $^4J_{HF}$ found for H-(6e).

It thus appeared that in the most populated conformers in C_6D_6 the benzylic group is equatorial in isomers

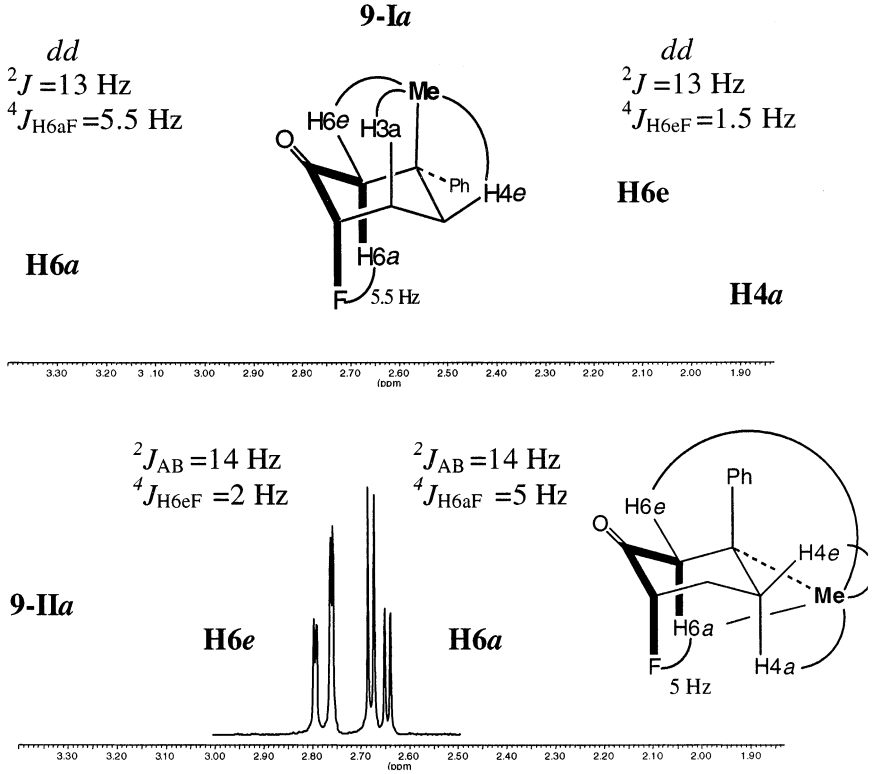
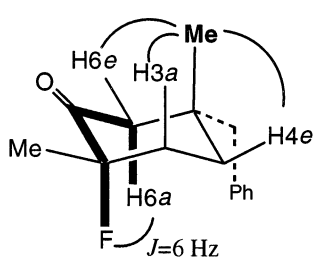
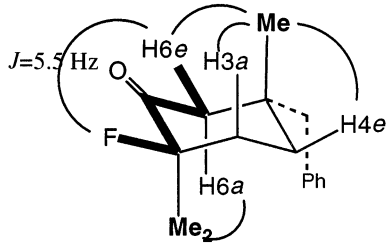


Figure 2. ^{1}H NMR 400 MHz (C_6D_6/TMS): AB system (at C-(6) methylene) for ketones **9-I*a*** and **9-II*a***.



10-I*a*
Me correlated to H-(6*e*), H-(4*e*), H-(3*a*)



10-II*e*
Me correlated to H-(6*e*), H-(4*e*), H-(3*a*)
Me_2 correlated to H-(6*a*)

Figure 3. NOE (from NOESY, 400 MHz, C_6D_6) and $^4J_{HF}$.

10-I*a* and **10-II*e*** while the fluorine is axial in **10-I*a*** and equatorial in **10-II*e*** (Fig. 3). Although from known conformational energies (calculated for monosubstited cyclohexane) one would expect axial benzyl,[18] it is known that deviations from additivity occur for disubstitution which could reverse the equilibrium and it thus appears that the 1-methyl-1-benzyl analogue behaves differently to the monobenzyl analogue.

2.3. Resolution of 9-I*a*, 9-II*a* and 10-I*a*

Preparative resolution of (±)-**9-I*a*** (0.500 g) was performed on a (200×5, 20 μm) Chiralpak AD column through 20 injections of 0.025 g using heptane/ethanol (98.5/1.5) as mobile phase (5 mL/min). Detection, 210–550 nm. Two samples were obtained: (**9-I*a*)-1**, rt = 4.7 min; 0.150 g, e.e. = 99.1%; $[\alpha]_D = -55$ ($c = 1.02$, $CHCl_3$) and (**9-I*a*)-2**, rt = 5.8 min; 0.150 g, e.e. = 100%; $[\alpha]_D = +56$ ($c = 1.03$, $CHCl_3$).

Preparative resolution of (±)-**9-II*a*** (0.600 g) was performed on a (250×5, 20 μm) Chiralcel OD column through 25 injections of 0.024 g using MeOH/H_2O (90/10) as mobile phase (100 mL/min). Detection, 210 nm. Two samples were obtained: (**9-II*a*)-1**, rt = 6.9 min; 0.270 g, e.e. = 91.8%; $[\alpha]_D = -13.5$ ($c = 1.1$, $CHCl_3$) and (**9-II*a*)-2**, rt = 8.4 min; 0.180 g, e.e. = 97%; $[\alpha]_D = +16$ ($c = 1.05$, $CHCl_3$).

Preparative resolution of (±)-**10-I*a*** (0.900 g) was performed on a (250×20, 5 μm) Chirose C1 column through three injections of 0.250, 0.300 and 0.350 g using heptane/$CHCl_3$ (90/10) as mobile phase (10 mL/min). Detection, 254 nm. Two samples were obtained: (**10-I*a*)-1**, rt = 11.4 min; 0.290 g, e.e. = 100%; $[\alpha]_D = +4$ ($c = 1$, $CHCl_3$) and (**10-I*a*)-2**, rt = 12.5 min; 0.096 g, e.e. = 91%; $[\alpha]_D = -3.5$ ($c = 1$, $CHCl_3$). Three other samples having lower e.e. have been obtained (0.350 g).

3. Conclusion

In conclusion, α-fluorinated ketones trisubstituted, (2*S*,5*R*)-(−)-**7-I*a***, (2*R*,5*R*)-(+)-**7-II*e***, (2*S*,5*R*)-(−)-**8-I*a*** and (2*R*,5*R*)-(+)-**8-II*e***, as well as tetrasubstituted, (−)-**9-I*a***, (+)-**9-I*a***, (+)-**9-II*a*** and (+)-**10-I*a***, having e.e. of ≥97% were obtained and fully characterised.

4. Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz) or a Bruker Avance (400 MHz) spectrometer with $CDCl_3$ or C_6D_6 as solvent. Chemical shifts (δ) are given in ppm downfield from TMS. Optical rotations were determined with a Perkin–Elmer 341 polarimeter. TLC was performed on Merck's glass plates with silica gel 60 F_{254}. Silica gel Si 60 (40–60 μm) from Merck was used for the chromatographic purifications. (+)-Dihydrocarvone was purchased from Fluka. Grignard reagents in THF solution were purchased from Aldrich.

4.1. 3,6-Dimethylcyclohexenone 17

Compound **17** was prepared by methylation of 3-methylcyclohexen-1-one following a known literature procedure.[20] Isolated as a colourless oil; $R_f = 0.48$ (hexane/ether, 1:1); ^1H NMR ($CDCl_3$, 400 MHz): δ 1.14 (d, $^3J = 6.5$ Hz, 3H, CH_3), 1.72 (m, 1H), 1.94 (s, 3H, CH_3), 2.06 (qt, $^2J = 12$ Hz, $^3J = {}^3J = {}^3J = 4$ Hz, 1H, H5e), 2.32 (m, 3H, H4a, H4e and H6), 5.85 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.5, 24.6, 31.0, 31.1, 40.8, 126.6, 161.9, 202.5. IR ($CHCl_3$): $\nu_{C=O}$, $\nu_{C=C} = 1660$ (broad, strong) cm^{-1}.

4.2. General procedure for Grignard addition

To a stirred suspension of CuBr:$S(Me)_2$ (0.12 equiv.) in anhydrous THF (0.75 mL for 75 mg) under argon, was added at −20°C a solution of 3,6-dimethylcyclohexen-1-one (1 equiv.) in THF (0.6 mL for 400 mg). A 2 M solution of the desired Grignard in THF (1.4 equiv.) was then added dropwise. After stirring at −20°C for 3 h, the reaction mixture was poured into a cold solution of hydrochloric acid 2N and ice (4 mL) and extracted with ether (4×6 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography.

4.3. 2,5-Dimethyl-5-phenylcyclohexanone 18

Eluent: pentane/Et_2O (100/0–85/15), colourless oil, 84%, two diastereomers, **I**/**II** = 86/14. ^1H NMR ($CDCl_3$, 400 MHz): **I** (major), δ 0.96 (d, $^3J = 6.5$ Hz, 3H, CH_3),

1.14 (qd, $^2J=^3J_{aa}=^3J_{aa}=13$ Hz,$^3J_{ae}=3$ Hz, s,1H, H3a), 1.38 (s, 3H, CH_3), 1.87 (ddt, $^2J=13$ Hz, $^3J_{ee}=6$ Hz, $^3J_{ea}=^3J_{ea}=3.5$ Hz, 1H, H3e), 1.97 (td, $^2J=^3J_{aa}=13$ Hz, $^3J_{ae}=3.5$ Hz, 1H, H4a), 2.35 (m, 2H), 2.42 (dd, $^2J=14.5$ Hz, $^4J=1$ Hz, 1H, H6e), 3.06 (dd, $^2J=14.5$ Hz, $^4J=3$ Hz, 1H, H6a), 7.20 (m, 1H, Harom.), 7.35 (m, 4H, Harom.). **II** (minor): overlapped with **I** but δ 1.12 (d, $^3J=6.5$ Hz, 3H, CH_3), 1.26 (s, 3H, CH_3), 2.10 (m, 3H), 2.60 (A from ABX, $^2J_{AB}=13$ Hz, $^3J_{AX}=2.5$ Hz, 1H, H6a), 2.75 (B from ABX, $^2J_{AB}=13$ Hz, 1H, H6e). ^{13}C NMR ($CDCl_3$, 100 MHz), **I**: δ 14.8 (CH_3), 31.2 (CH_2), 33.6 (CH_3), 39.1 (CH_2), 44.5 (CH), 45.0 (Cq), 52.7 (CH_2), 126.6 (CHarom.), 128.6 (CHarom.), 146.7 (Cq), 212.9 (CO). **II**: δ 15.0 (CH_3), 26.2 (CH_3), 31.8 (CH_2), 37.5 (CH_2), 43.4 (Cq), 44.8 (CH), 53.5 (CH_2), 125.3 (CHarom.), 126.6 (CHarom.), 149.6 (Cq), 213.2 (CO).

4.4. 2,5-Dimethyl-5-benzylcyclohexanone 19

Eluent: pentane/Et_2O (9/1), colourless oil, 53%, two diastereomers, **I**/**II**=66/34. ^{1}H NMR ($CDCl_3$, 400 MHz), **I** (major): δ 0.95 (s, 3H, CH_3), 1.11 (d, $^3J=6.5$ Hz, 3H, CH_3), 1.70 (m, 3H), 2.08 (m, 1H), 2.15 (A from ABX, $^2J_{AB}=13$ Hz, 1H), 2.33 (B from ABX, $^2J_{AB}=13$ Hz, $^4J_{HF}=2$ Hz, 1H), 2.42 (m, 1H), 2.47 (A from AB, $^2J_{AB}=13.5$ Hz, 1H), 2.55 (B from AB, $^2J_{AB}=13.5$ Hz, 1H), 7.16 (m, 2H, Harom.), 7.30 (m, 3H, Harom.). **II** (minor), signals overlapped with **I** but: δ 0.88 (s, 3H, CH_3), 1.01 (d, $^3J=6.5$ Hz, 3H, CH_3), 1.56 (m, 2H, CH_2), 2.01 (m, 1H), 2.63 (AB, $^2J_{AB}=12$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz), **I**: δ 15.1 (CH_3), 28.3 (CH_3), 31.6 (CH_2), 36.4 (CH_2), 41.1 (Cq), 44.3 (CH_2), 44.8 (CH), 52.8 (CH_2), 126.5 (CH arom.), 128.3 (CH arom.), 131.1 (CH arom.) 138.3 (Cq), 213.9 (CO). **II**: δ 14.7 (CH_3), 23.7 (CH_3), 31.7 (CH_2), 36.3 (CH_2), 40.9 (Cq), 44.8 (CH), 51.1 (CH_2), 53.2 (CH_2), 126.7 (CH arom.), 128.3 (CH arom.), 131.1 (CH arom.) 137.9 (Cq arom), 213.6 (CO). IR ($CHCl_3$), **I** and **II**: $\nu_{C=O}=1705$ cm^{-1}.

4.5. General procedure for the preparation of silylenol ethers

To a solution of the desired ketone (1 equiv.) in dry pentane (7 mL for 9 mmol) was added, under argon, NEt_3 (2 equiv.), TMSCl (2 equiv.) followed by a solution of anhydrous NaI (2 equiv.) in dry CH_3CN (20 mL).[12] After stirring for 3–4 h at room temperature, stirring was stopped and the upper organic layer (pentane) transferred into a dry flask. The remaining mixture was extracted with dry pentane until no trace of silylenol ether was detected by TLC.[12] The pentane phases were gathered and evaporated to afford a colourless oil, pure by NMR analysis.

4.6. (5*R*)-(+)-[5-(1-Chloro-1-methyl-ethyl)-2-methylcyclohexenyloxy]-trimethylsilane 13

Colourless liquid, $[\alpha]_D^{20}=+61.5$ ($c=1.1$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.20 (s, 9H, MeSi), 1.32 (m, 1H), 1.55 (s, 6H, 2 Me), 1.58 (s, 3H, Me), 1.98 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 1.1 ($3CH_3Si$), 16.4 (CH_3), 25.2 (CH_2), 30.5 (CH_2), 30.55 (CH_3), 30.9 (CH_3), 32.7 (CH_2), 48.1 (CH), 74.1 (Cq), 111.9 (Cq), 142.3 (Cq).

4.7. (5*R*)-(+)-(5-Iso-propenyl-2-methyl-cyclohexenyloxy)-trimethylsilane, 14

Colourless liquid, $[\alpha]_D^{20}=+72$ ($c=1.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.18 (s, 9H, 3MeSi), 1.39 (qd, $^2J=^3J_{aa}=^3J_{aa}=12$ Hz, $^3J_{ae}=5.5$ Hz, 1H, H4a), 1.57 (s, 3H, Me), 1.74–1.75 (s, 3H, Me and m, 1H), 2.02 (m, 4H), 2.23 (m, 1H), 4.72 (bs, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 1.1 ($3CH_3Si$), 16.5, 21.2, 28.3 (CH_2), 30.5 (CH_2), 36.0 (CH_2), 42.8, 109.1 (CH_2), 111.7 (Cq), 142.7 (Cq), 149.8 (CO). IR ($CHCl_3$): $\nu_{C\text{-}H}=3050$, 2900, $\nu_{C=C}=1690$ cm^{-1}.

4.8. (±)-(2,5-Dimethyl-5-phenyl-cyclohexenyloxy)-trimethylsilane 20

Colourless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.23 (s, 9H, $3CH_3Si$), 1.30 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.75 (m, 1H), 1.87 (m, 2H), 2.30 (m, 1H), 2.15 (A from AB, $^2J_{AB}=16.5$ Hz, 1H, H6), 2.49 (B from AB, $^2J_{AB}=16.5$ Hz, 1H, H6), 7.20 (m, 1H, Harom.), 7.35 (m, 4H, Harom.); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 1.2 ($3CH_3Si$), 16.4 (CH_3), 28.1 (CH_3), 28.1 (CH_2-4), 35.2 (CH_2-3), 38.5 (Cq), 43.1 (CH_2-6), 111.2 (Cq), 125.9 (CHarom.), 126.1 (CHarom.), 128.5 (CHarom.), 142.0 (Cq), 149.8 (Cq).

4.9. (±)-(5-Benzyl-2,5-dimethyl-cyclohexenyloxy)-trimethylsilane 21

Colourless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.19 (s, 9H, $3CH_3Si$), 0.89 (s, 3H, CH_3), 1.38 (m, 2H), 1.59 (s, 3H, CH_3), 1.70 (A from AB, $^2J_{AB}=15$ Hz, 1H), 2.03 (bm, 2H overlapped with B of AB, 1H), 2.58 (s, 2H), 7.17 (m, 2H, Harom.), 7.23 (m, 1H, Harom.), 7.30 (m, 2H, Harom.); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 1.2 ($3CH_3$), 16.4 (CH_3), 24.5 (CH_3), 27.9 (CH_2), 33.8 (CH_3), 35.2 (Cq), 42.8 (CH_2), 48.7 (CH_2), 110.5 (Cq), 126.3 (CHarom.), 128.1 (CHarom.), 131.1 (CHarom.), 139.2 (Cq), 142.0 (Cq).

4.10. General procedure for fluorination reactions with Selectfluor

To a solution of the desired silylenol ether (1 equiv.) in dry DMF (25 mL for 7 mmol) was added dropwise, under argon, a solution of Selectfluor (1.4 equiv.) in DMF (40 mL). The mixture was stirred at 0°C for 2 h. Then water (50 mL) and ether (50 mL) was poured into the reaction mixture, the phases were separated and the aqueous phase extracted with ether (3×100 mL). The organic phases were dried over $MgSO_4$. After filtration and evaporation, the residue (containing DMF) was directly purified by column chromatography with an appropriate pentane/ether gradient.

4.11. (±)-2-Fluoro-2,5-dimethyl-5-phenylcyclohexanone 9

A colourless oil, 92%, two racemic diastereomers, **9-I*a***/**9-II*a*** = 46/54. After separation: **9-I*a*** (minor): Anal.

calcd for $C_{14}H_{17}FO$: C, 76.33; H, 7.78. Found: C, 75.96; H, 7.26. R_f=0.17 (pentane/ether, 95/5); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.93 (s, 3H, Me), 1.30 (d, $^3J_{HF}$=22 Hz, 3H, Me), 1.37 (m, 1H, H4e), 1.41 (dddd, ^2J=15 Hz, $^3J_{HF}$=31 Hz, $^3J_{aa}$=11.5 Hz, $^3J_{ae}$=4.5 Hz, 1H, H3a), 1.76 (ddt, ^2J=15 Hz, $^3J_{HF}$=12.5 Hz, $^3J_{ea}$=$^3J_{ae}$=4.5 Hz, 1H, H3e), 2.08 (ddd, ^2J=15 Hz, $^3J_{aa}$=11.5 Hz, $^3J_{ae}$=4.5 Hz, 1H, H4a), 2.25 (dd, ^2J=13 Hz, $^4J_{HF}$=1.5 Hz, 1H, H6e), 3.09 (dd, ^2J=13 Hz, $^4J_{HF}$=5.5 Hz, 1H, H6a), 7–7.2 (m, 5H, Harom.); ^{13}C NMR (C_6D_6, 100 MHz): δ 20.8 (d, $^2J_{CF}$=24 Hz, CH_3), 26.4 (CH_3), 33.9 (d, $^3J_{CF}$=4 Hz, CH_2-4), 35.3 (d, $^2J_{CF}$=23 Hz, CH_2-3), 43.0 (Cq), 49.8 (CH_2-6), 95.4 (d, $^1J_{CF}$=175 Hz, Cq-2), 125.4 (CHarom.), 126.6 (CHarom.), 128.8 (CHarom.), 148.2 (Cq), 205.6 (d, $^2J_{CF}$=23 Hz, CO). IR ($CHCl_3$): $\nu_{C=O}$=1730 cm^{-1}. Resolution by preparative HPLC: Chiralpak AD 20 μm (25×200); 98.5% heptane+1.5% EtOH; 30°C; 5.0 mL/min: rt of **9-I*a*-**(−)=4.7 min; 99.1% e.e., $[\alpha]_D^{20}$=−55 (c=1.02, $CHCl_3$) and rt of **9-I*a*-**(+)=5.8 min; 100% e.e., $[\alpha]_D^{20}$=+56 (c=1.03, $CHCl_3$).

Compound **9-II*a*** (major): colourless oil. Anal. calcd for $C_{14}H_{17}FO$: C, 76.33; H, 7.78. Found: C, 76.46; H, 7.37. R_f=0.31 (pentane/ether, 95/5); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.97 (s, 3H, Me), 1.14 (d, $^3J_{HF}$=22 Hz, 3H, Me), 1.23 (m, 1H, H3a), 1.70 (m, 1H, H4e), 1.71 (m, 1H, H3e), 1.89 (m, 1H, H4a), 2.65 (A from ABX, $^2J_{AB}$=14 Hz, $^4J_{HF}$=5 Hz, 1H, H6a), 2.77 (B from ABX, $^2J_{AB}$=14 Hz, $^4J_{HF}$=2 Hz, 1H, H6e), 7.00 (m, 1H, Harom.), 7.1–7.2 (m, 1H, Harom.); ^{13}C NMR (C_6D_6, 100 MHz): δ 20.5 (d, $^2J_{CF}$=24 Hz, CH_3), 32.3 (CH_3), 33.9 (d, $^3J_{CF}$=3 Hz, CH_2-4), 35.2 (d, $^2J_{CF}$=22.5 Hz, CH_2-3), 43.8 (Cq), 49.1 (CH_2-6), 95.0 (d, $^1J_{CF}$=173 Hz, Cq-2), 126.2 (CHarom.), 126.6 (CHarom.), 128.0 (CHarom.), 146.0 (Cq), 204.4 (d, $^2J_{CF}$=22 Hz, CO). IR ($CHCl_3$): $\nu_{C=O}$=1730 cm^{-1}.

Resolution by preparative HPLC: Chiralcel OD 20 μm (250×5); 90% MeOH+10% H_2O; 0°C; 100 mL/min Detection, 210 nm: rt of **9-II*a*-**(−)=6.9 min; 91.8% e.e., $[\alpha]_D^{20}$=−13.5 (c=1.1, $CHCl_3$) and rt of **9-II*a*-**(+)=8.4 min; 97% e.e., $[\alpha]_D^{20}$=+16 (c=1.05, $CHCl_3$).

4.12. (±)-2-Fluoro-2,5-dimethyl-5-benzylcyclohexanone, 10

A colourless oil; 83%, two racemic diastereomers, **10-I*a*/10-II*e***=72/28. After separation, **10-I*a*** (major): Anal. calcd for $C_{15}H_{19}FO$: C, 76.89; H, 8.17. Found: C, 77.11; H, 7.72. R_f=0.41 (benzene); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.56 (s, 3H, Me), 0.93 (bd, ^2J=12.5 Hz, 1H, H4e), 1.27 (d, $^3J_{HF}$=22 Hz, 3H, Me), 1.32 (dddd, ^2J=12 Hz, $^3J_{HF}$=35 Hz, $^3J_{aa}$=14 Hz, $^3J_{ae}$=5 Hz, 1H, H3a), 1.75 (m, 2H, H3e and H4a), 1.90 (A from ABX, J_{AB}=12.5 Hz, $^4J_{HF}$=1 Hz, 1H, H6e), 2.24 (AB system, J_{AB}=13 Hz, 2H, H9), 2.67 (B from ABX, J_{AB}=12.5 Hz, $^4J_{HF}$=6 Hz, 1H, H6a), 6.86 (m, 2H, H aromatic), 7.11 (m, 3H, H aromatic); ^{13}C NMR (C_6D_6, 100 MHz): δ 20.6 (d, $^2J_{CF}$=24 Hz, CH_3), 22.7 (CH_3), 32.1 (d, $^3J_{CF}$=3 Hz, CH_2-4), 35.1 (d, $^2J_{CF}$=23 Hz, CH_2-3), 40.3 (Cq-5), 49.7 (CH_2-6), 49.8 (CH_2Ph), 95.6 (d, $^1J_{CF}$=173 Hz, Cq-2), 126.4 (CHarom.), 128.2 (CHarom.), 130.9 (CHarom.), 137.5 (Cq), 205.9 (d, $^2J_{CF}$=23.5 Hz, CO). IR ($CHCl_3$): $\nu_{C=O}$=1735 cm^{-1}. Resolution by preparative HPLC on Chirose C1 5 μm (250×20); 90% heptane+10% $CHCl_3$; 10 mL/min: rt of **10-I*a*-**(+)=11.4 min; 100% e.e., $[\alpha]_D^{20}$=+4 (c=1, $CHCl_3$) and rt of **10-I*a*-**(−) =12.5 min, 91% e.e., $[\alpha]_D^{20}$=−3.2 (c=1, $CHCl_3$).

Compound **10-II*e*** (minor): colourless oil. Anal. calcd for $C_{15}H_{19}FO$: C, 76.89; H, 8.17. Found: C, 77.13; H, 8.28. R_f=0.25 (benzene); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.61 (s, 3H, Me), 1.10 (m, 1H, H4a), 1.24 (d, $^3J_{HF}$=24 Hz, 3H, Me), 1.48 (m, 1H, H4e), 1.55 (m, 1H, H3e), 1.80 (m, 1H, H3a), 2.09 (A from ABX overlapped with A from AB, 2H, H6a and H), 2.24 (B from AB, $^2J_{AB}$=13 Hz, 1H), 2.34 (B from ABX, $^2J_{AB}$=13 Hz, $^4J_{HF}$=5.5 Hz, 1H, H6e), 6.95 (m, 2H, Harom.), 7.10 (m, 3H, Harom.). ^{13}C NMR (C_6D_6, 100 MHz): δ 21.1 (d, $^2J_{CF}$=24 Hz, CH_3), 26.3 (CH_3), 32.8 (d, $^3J_{CF}$=5 Hz, CH_2-4), 35.1 (d, $^2J_{CF}$=23 Hz, CH_2-3), 40.4 (Cq-5), 45.5 (CH_2Ph), 46.2 (CH_2-6), 95.6 (d, $^1J_{CF}$=177 Hz, Cq-2), 126.7 (CHarom.), 131.0 (CHarom.), 131.2 (CHarom.), 137.8 (Cq), 206.0 (d, $^2J_{CF}$=21 Hz, CO). IR ($CHCl_3$): $\nu_{C=O}$=1735 cm^{-1}.

4.13. 2-Fluoro-5-iso-propenyl-2-methylcyclohexanone 15

A colourless liquid; 67%, two diastereomers, **15I**/**15II**=51/49. After separation, **15I-**(−)-(2*S*,5*R*): Anal. calcd for $C_{10}H_{15}FO$: C, 70.49; H, 8.81. Found: C, 69.85; H, 8.74. $[\alpha]_D^{20}$=−3 (c=1.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): δ 1.03 (dddd, ^2J=15 Hz, $^3J_{HF}$=39 Hz, $^3J_{aa}$=13.5 Hz, $^3J_{ae}$=4.5 Hz, 1H, H3a), 1.23 (bd, ^2J=13.5 Hz, 1H, H4e), 1.31 (d, $^3J_{HF}$=22 Hz, 3H, Me), 1.42 (s, 3H, Me), 1.72 (qd, ^2J=$^3J_{aa}$=$^3J_{aa}$=13.5 Hz, $^3J_{ae}$=4 Hz, 1H, H4a), 1.82 (ddt, $^3J_{aa}$=13.5 Hz, $^3J_{aa}$=13 Hz, $^3J_{ae}$=$^3J_{ae}$=3.5 Hz, 1H, H5), 1.93 (bt, ^2J=$^3J_{HF}$=15 Hz, 1H, H3e), 2.29 (d, ^2J=13 Hz, 1H, H6e), 2.72 (td, ^2J=$^3J_{aa}$=13 Hz, $^4J_{HF}$=6 Hz, 1H, H6a), 4.59 (bs, 1H), 4.63 (bs, 1H). ^{13}C NMR (C_6D_6, 100 MHz): δ 20.2 (CH_3), 20.4 (d, $^2J_{CF}$=24 Hz, CH_3), 26.1 (d, $^3J_{CF}$=2 Hz, CH_2-4), 38.3 (d, $^2J_{CF}$=22.5 Hz, CH_2-3), 43.5 (d, $^3J_{CF}$=2.5 Hz, CH_2-6), 46.9 (CH-5), 95.6 (d, $^1J_{CF}$=172 Hz, Cq-2), 110.5 (CH_2), 147.1 (Cq), 205.6 (d, $^2J_{CF}$=24.5 Hz, CO). IR ($CHCl_3$): $\nu_{C=O}$=1700, $\nu_{C=C}$=1610 cm^{-1}.

Compound **15II**-(+)-(2*R*,5*R*): $[\alpha]_D^{20}$=+103 (c=1.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): δ 1.11–1.15 (m, 1H, H4 overlapped with d, $^3J_{HF}$=22 Hz, 3H, Me), 1.37 (s, 3H, Me), 1.48 (m, 1H, H4), 1.64 (m, 2H, H3), 1.86 (m, 1H, H5), 2.08 (dd, ^2J=13.5 Hz, $^3J_{aa}$=10 Hz, 1H, H6a), 2.41 (dtd, ^2J=13.5 Hz, $^3J_{ea}$=$^4J_{HF}$=4.5 Hz, ^4J=2 Hz, 1H, H6e), 4.55 (bs, 1H), 4.65 (bs, 1H). ^{13}C NMR (C_6D_6, 100 MHz): δ 20.9 (CH_3), 21.9 (d, $^2J_{CF}$=25.5 Hz, CH_3), 26.8 (d, $^3J_{CF}$=8.5 Hz, CH_2-4), 37.2 (d, $^2J_{CF}$=22 Hz, CH_2-3), 43.6 (CH_2-6), 44.7 (CH-5), 96.0 (d, $^1J_{CF}$=182.5 Hz, Cq-2), 110.9 (CH_2), 146.5 (Cq), 204.8 (d, $^2J_{CF}$=18 Hz, CO). IR ($CHCl_3$): $\nu_{C=O}$=1735, $\nu_{C=C}$=1650 cm^{-1}.

4.14. 5-(1-Chloro-1-methyl-ethyl)-2-fluoro-2-methyl-cyclohexanone, 7

A colourless liquid; 80%, two diastereomers, **7-I*a*/7-II*e*** = 43/57. Anal. calcd for $C_{10}H_{16}ClFO$: C, 58.91; H, 7.74. Found: C, 57.79; H, 7.51. After separation, **7-I*a*-**(2*S*,5*R*)-(−): $[\alpha]_D^{20} = -3$ ($c = 1.0$, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz): δ 0.93 (dddd, $^2J = 15$ Hz, $^3J_{HF} = 40$ Hz, $^3J_{aa} = 13.5$ Hz, $^3J_{ae} = 4$ Hz, 1H, H3a), 1.14 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.32 (d, $^3J_{HF} = 22$ Hz, 3H, Me), 1.38 and 1.43 (m, 2H, H4e and H5), 1.71 (qd, $^2J = {}^3J_{aa} = {}^3J_{aa} = 13.5$ Hz, $^3J_{ae} = 4$ Hz, 1H, H4a), 1.81 (m, 1H, H3e), 2.45 (bd, $^2J = 13$ Hz, H6e), 2.67 (td, $^2J = {}^3J_{aa} = 13$ Hz, $^4J_{HF} = 6$ Hz, 1H, H6a); ^{13}C NMR (C_6D_6, 100 MHz): δ 20.1 (d, $^2J_{CF} = 24$ Hz, CH_3), 22.3 (d, $^3J_{CF} = 2$ Hz, CH_2-4), 30.0 (CH_3), 30.3 (CH_3), 37.4 (d, $^2J_{CF} = 23$ Hz, CH_2-3), 40.3 (d, $^3J_{CF} = 2.5$ Hz, CH_2-6), 51.3 (CH-5), 72.1 (Cq), 95.0 (d, $^1J_{CF} = 172$ Hz, Cq-2), 205.3 (d, $^2J_{CF} = 25$ Hz, CO). IR ($CHCl_3$): $\nu_{C=O} = 1715$ cm^{-1}.

Compound **7-II*e*-**(+)-(2*R*,5*R*): white solid, mp = 49°C; $[\alpha]_D^{20} = +73$ ($c = 1.0$, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz): δ 1.06 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.14 (d, $^3J_{HF} = 21.5$ Hz, 3H, Me), 1.21 (m, 2H, H5 and H4a), 1.40 (m, 1H, H4e), 1.58 (qd, $^2J = {}^3J_{HF} = {}^3J_{aa} = 13$ Hz, $^3J_{ae} = 4$ Hz, 1H, H3a), 1.66 (dq, $^2J = 13$ Hz, $^3J_{ea} = {}^3J_{ea} = {}^3J_{ee} = 3$ Hz, 1H, H3e), 2.10 (dd, $^2J_{HH} = 14$ Hz, $^3J_{aa} = 12.5$ Hz, 1H, H6a), 2.39 (qd, $^2J_{HH} = 14$ Hz, $^4J_{HF} = {}^3J_{ea} = {}^4J_{H6eH4} = 3$ Hz, 1H, H6e); ^{13}C NMR (C_6D_6, 100 MHz): δ 22.1 (d, $^2J_{CF} = 26$ Hz, CH_3), 24.3 (d, $^3J_{CF} = 10$ Hz, CH_2-4), 30.6 (CH_3), 30.8 (CH_3), 36.9 (d, $^2J_{CF} = 22$ Hz, CH_2-3), 41.5 (d, $^3J_{CF} = 1.5$ Hz, CH_2-6), 49.6 (CH-5), 72.2 (Cq), 95.8 (d, $^1J_{CF} = 186.5$ Hz, Cq-2), 204.7 (d, $^2J_{CF} = 16$ Hz, CO). IR ($CHCl_3$): $\nu_{C=O} = 1715$ cm^{-1}.

4.15. 5-(1-Fluoro-1-methyl-ethyl)-2-fluoro-2-methylcyclohexanone 8

Hydrofluorination was completed following a literature procedure.[14]

Compound **8-I*a*-**(−)-(2*S*,5*R*)- (from **15I**): colourless liquid; $[\alpha]_D^{20} = -10$ ($c = 1.0$, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz): δ 0.93 (d, $^3J_{HF} = 21.5$ Hz, 3H, CH_3), 0.94 (d, $^3J_{HF} = 21.5$ Hz, 3H, CH_3), 0.95 (dddd, $^2J = 15$ Hz, $^3J_{HF} = 40$ Hz, $^3J_{aa} = 13$ Hz, $^3J_{ae} = 4.5$ Hz, 1H, H3a), 1.26 (m, 1H, H4e) overlapped with 1.30 (d, $^3J_{HF} = 22$ Hz, 3H, Me), 1.50 (bq, 1H, H5) overlapped with 1.56 (qd, $^2J = {}^3J_{aa} = {}^3J_{aa} = 13$ Hz, $^3J_{ea} = 3.5$ Hz, 1H, H4a), 1.81 (ddt, $^2J = 15$ Hz, $^3J = 10$ Hz, $^3J_{ea} = {}^3J_{ee} = 3.5$ Hz, 1H, H3e), 2.37 (bd, $^2J = 13$ Hz, 1H, H6e), 2.54 (td, $^2J = {}^3J_{aa} = 13$ Hz, $^4J_{HF} = 6$ Hz, 1H, H6a); ^{13}C NMR (C_6D_6, 100 MHz): δ 20.2 (d, $^2J_{CF} = 23.5$ Hz, CH_3), 21.5 (dd, $^3J_{CF} = 5.5$ Hz, $^3J_{CF} = 2$ Hz, CH_2-4), 24.1 (d, $^2J_{CF} = 25$ Hz, CH_3), 24.2 (d, $^2J_{CF} = 25$ Hz, CH_3), 37.9 (d, $^2J_{CF} = 23$ Hz, CH_2-3), 39.5 (dd, $^3J_{CF} = 5.5$ Hz, $^3J_{CF} = 2$ Hz, CH_2-6), 48.8 (d, $^2J_{CF} = 23$ Hz, CH-5), 95.4 (d, $^1J_{CF} = 171$ Hz, Cq-2 and Cq), 205.3 (d, $^2J_{CF} = 25$ Hz, CO). IR ($CHCl_3$): $\nu_{C=O} = 1730$ cm^{-1}.

Compound **8-II*e*-**(+)-(2*R*,5*R*) (from **15II**): white solid, mp = 65°C. Anal. calcd for $C_{10}H_{16}F_2O$: C, 63.49; H, 8.45. Found: C, 63.04; H, 8.08. $[\alpha]_D^{20} = +134$ ($c = 0.3$, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz): δ 0.88 (d, $^3J_{HF} = 21.5$ Hz, 3H, CH_3), 0.89 (d, $^3J_{HF} = 21.5$ Hz, 3H, CH_3), 1.03 (qm, $^3J_{HF} = {}^3J_{aa} = {}^3J_{aa} = 15$ Hz, 1H, H5), 1.12 (d, $^3J_{HF} = 21.5$ Hz, 3H, Me), 1.36 (m, 2H, H4a and H4e), 1.59 (qd, $^2J = {}^3J_{HF} = {}^3J_{aa} = 13.5$ Hz, $^3J_{ae} = 4$ Hz, 1H, H3a), 1.69 (m, 1H, H3e), 1.92 (t, $^2J = {}^3J_{aa} = 14$ Hz, 1H, H6a), 2.36 (dtd, $^2J = 14$ Hz, $^3J_{ae} = {}^4J_{HF} = 4$ Hz, $^4J_{HF} = 2.5$ Hz, 1H, H6e); ^{13}C NMR (C_6D_6, 100 MHz): δ 22.1 (d, $^2J_{CF} = 26$ Hz, CH_3), 23.5 (d, $^3J_{CF} = 4.5$ Hz, $^3J_{CF} = 10$ Hz, CH_2-4), 24.5 (d, $^2J_{CF} = 25$ Hz, CH_3), 24.6 (d, $^2J_{CF} = 25$ Hz, CH_3), 37.4 (d, $^2J_{CF} = 21.5$ Hz, CH_2-3), 40.1 (d, $^3J_{CF} = 5$ Hz, CH_2-6), 47.1 (d, $^2J_{CF} = 22.5$ Hz, CH-5), 95.2 (d, $^1J_{CF} = 170$ Hz, Cq), 95.9 (d, $^1J_{CF} = 185$ Hz, Cq), 204.6 (d, $^2J_{CF} = 16.5$ Hz, CO). IR ($CHCl_3$): $\nu_{C=O} = 1730$ cm^{-1}.

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