Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 935–941

TETRAHEDRON: *ASYMMETRY*

2-Chloro and 2-fluoro ketones derived from the chiral-pool

Arlette Solladié-Cavallo * and Laëtitia Bouérat

Laboratoire de Stéréochimie Organométallique/ESA 7008, ECPM, 25 rue Becquerel, 67087 Strasbourg, France

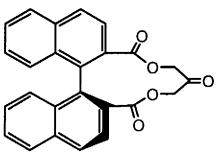
Received 29 November 1999; accepted 5 January 2000

Abstract

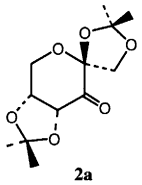
Both (2*R*,5*R*)- and (2*S*,5*R*)-isomers of 2-chloro-2-isopropyl-5-methyl-, 2-chloro-2-methyl-5-isopropyl- and 2-fluoro-2-methyl-5-isopropylcyclohexanones have been synthesized and fully characterized. It is shown that a rapid overview of the ^{1}H NMR spectrum allows an unambiguous assignment of the *axial* or *equatorial* position of the halogen atom and that the IR ν_{CO} absorption does not differ from one isomer to the other.

1. Introduction

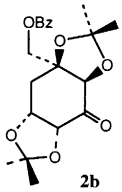
Since the first use, by Curci[1] in 1984, of chiral ketones as dioxirane precursors for the enantioselective epoxidation of olefins, important breakthroughs (yields ≥70%, ee ≥85%) have been achieved by Yang et al.[2] with type **1** ketones and by Shi et al.[3] with ketones **2**. However, ketone **1** (and analogues) are available only in low yield (~20%) from enantiomerically pure but expensive binaphthylamine, the fructose-derived ketone **2a** is inefficient in reactions with electron-poor olefins and ten steps are necessary for the preparation of ketone **2b** from (−)-quinic acid.



(*S*)-**1**



2a



2b

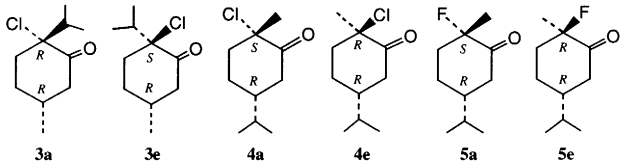
Based on the activating effects of halogen substitution observed by Curci et al.,[4] Yang et al.[2] and Denmark and Wu,[5] the syntheses of chiral ketones **3**–**5** having a halogen atom in position-2 either *axial* or *equatorial* and derived in a few steps (2 to 3) from natural compounds were envisaged.

Ketones **3** and **4** were first isolated in 1911,[6] then **4** was obtained in 43% yield through iron(III) chloride-catalyzed photo-oxidation of (*R*)-(+)-*p*-menthene in 1981[7a] and the *axial* orientation of the

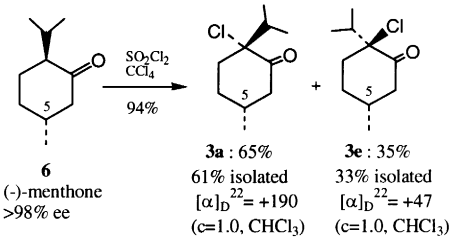
* Corresponding author. Tel: +33 3 88 13 69 79; fax: +33 3 88 13 69 49; e-mail: ascava@chimie.u-strasbg.fr

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00013-6

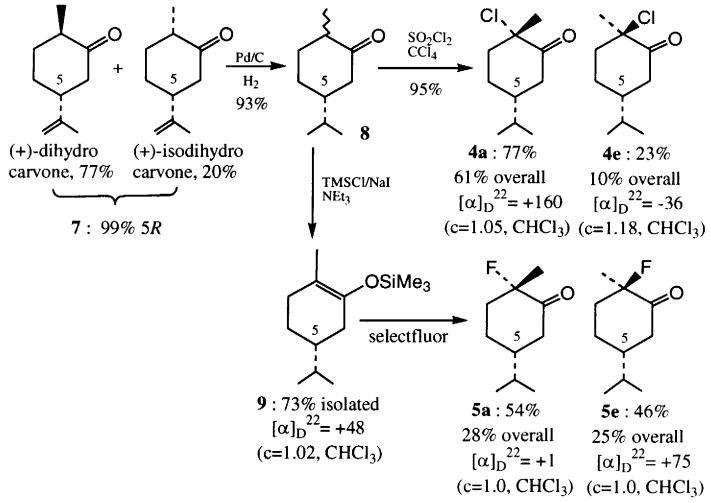
chlorine atom [leading to the (2*S*,5*R*)-configuration, **4a**] was deduced from the position of the IR ν_{CO}.[7b,c] Ketone **5** had been obtained from carvomenthene epoxide but the structure was not determined.[8]



We present here the syntheses of the 2-chloro ketones **3a**, **3e** and **4a**, **4e** and of the 2-fluoro ketones **5a** and **5e** from (2*S*,5*R*)-(−)-menthone (Scheme 1) and (+)-dihydrocarvone (77% for 2*R*,5*R* and 20% for 2*S*,5*R)* (Scheme 2), as well as their full characterization and the ^{1}H NMR pattern which allows rapid and unambiguous identification of the **a**- and **e**-isomers.



Scheme 1.



Scheme 2.

2. Results and discussion

The 2-chloro-2-isopropyl-5(*R*)-methylcyclohexanone was obtained as a 65:35 mixture of **3a** (65%) and **3e** (35%) from (2*S*,5*R*)-(−)-menthone **6** (>98% ee) (Scheme 1). After chromatographic separation, (2*R*,5*R*)-(+)-**3a** and (2*S*,5*R*)-(+)-**3e** were obtained and the overall yields were 61 and 33%, respectively. Because carbon-5 was not involved in the chlorination reaction, the enantiomeric purity of isomers **3a** and **3e** was thus assumed to be identical to that of the starting natural product, >98% ee.

The 2-chloro-2-methyl-5(*R*)-isopropylcyclohexanone was obtained as a 77:23 mixture of **4a** (77%) and **4e** (23%) in two steps from (+)-dihydrocarvone which contained 77% of (2*R*,5*R*)-(+)-dihydrocarvone and 20% of (2*S*,5*R*)-(+)-isodihydrocarvone with at least 98% ee at C5 (Scheme 2). Dihydrocarvone (+)-**7** was hydrogenated over Pd/C in EtOH under H_2 (1 atm)[9] *prior* to chlorination. After chromatographic separation (2*S*,5*R*)-(+)-**4a** and (2*R*,5*R*)-(−)-**4e** were obtained, the overall yields were 61 and 10%, respectively, and the enantiomeric purities identical to that of the starting compound **7** (98% ee).

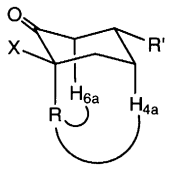
The 2-fluoro-2-methyl-5(*R*)-isopropylcyclohexanone was obtained as a 54:46 mixture of **5a** (54%) and **5e** (46%) in three steps from (+)-dihydrocarvone **7** (99% for *R* at C5) (Scheme 2).

The thermodynamic silylenolate **9** was obtained in satisfactory yield after modification of the literature work-up[10] and the fluorination was preformed with Selectfluor according to literature procedures.[11] After chromatographic separation (2*S*,5*R*)-(+)-**5a** and (2*R*,5*R*)-(+)-**5e** were obtained, the overall yields (three steps) were 28 and 25%, respectively, and the enantiomeric purities identical to that of the starting compound **7** at C5 (98% ee).

In all these ketones the signals of the H6-*axial* (H6a) proton and the H6-*equatorial* (H6e) proton are expected to be double-doublets with two large coupling-constants in the case of H6a (^2J ~12 Hz, $^3J_{180}$ ~11 Hz) but one large (^2J ~12 Hz) and one small ($^3J_{60}$ ~5 Hz) in the case of H6e. However, because of long range coupling(s) to H6e, H6a is, in fact, the only unambiguous signal. Therefore, in all cases, assignment of the signals was completed using H/C-correlation experiments (combined with predicted multiplicities).

An NOE-difference experiment demonstrated that, in ketone (+47)-**3e**, H6a and *i*Pr as well as *i*Pr and H4a were in close vicinity. Therefore, the (2*S*,5*R*) configuration, having the chlorine atom *equatorial*, was assigned to this ketone. The stability of the conformation having the large *i*Pr-group in the *axial* position is probably due to the fact that two substituents (Me and Cl) out of three adopt an *equatorial* position. As a consequence the other diastereomer **3a** was assigned the (2*R*,5*R*) configuration.

Similarly, positive NOEs were observed between Me, H6a and H4a for compounds **4e** and **5e** which were thus assigned the configuration (2*R*,5*R*). As a consequence, **4a** and **5a** were assigned the (2*S*,5*R*) configuration.



positive NOE R/H_{6a} and R/H_{4a} for
3e : X=Cl ; R=iPr ; R'=Me
4e : X=Cl ; R=Me ; R'=iPr
5e : X=F ; R=Me ; R'=iPr

However, for standard and/or daily use a rapid identification of isomers-**a** (halogen *axial*) versus isomers-**e** (halogen *equatorial*) is necessary. This can be done by a rapid overview of the ^{1}H NMR spectra, as shown in Fig. 1.

It indeed appears that the well recognizable H6a signal, a double-doublet or a triplet (with only two large coupling-constants in the cases of ketones **3a**, **3e**, **4a**, **4e** and **5e**) and a double-triplet (with two large coupling-constants and one extra, but smaller, due to a $^4J_{HF}$ in the case of ketone **5a**), is significantly deshielded in isomers having the halogen in the axial position (**3a**, **4a** and **5a**) and is the most deshielded signal in these isomers (Fig. 1A, C and E) while it is shielded in all **e**-isomers (**3e**, **4e** and **5e**) (Fig. 1B, D and F).

Therefore, both (2*R*,5*R*)- and (2*S*,5*R*)-diastereomers of 2-chloro and 2-fluoro cyclohexanones **3**, **4** and **5** with enantiomeric purities of 98% have been obtained pure and fully characterized. They can, now, be easily identified through a rapid overview of their ^{1}H NMR.

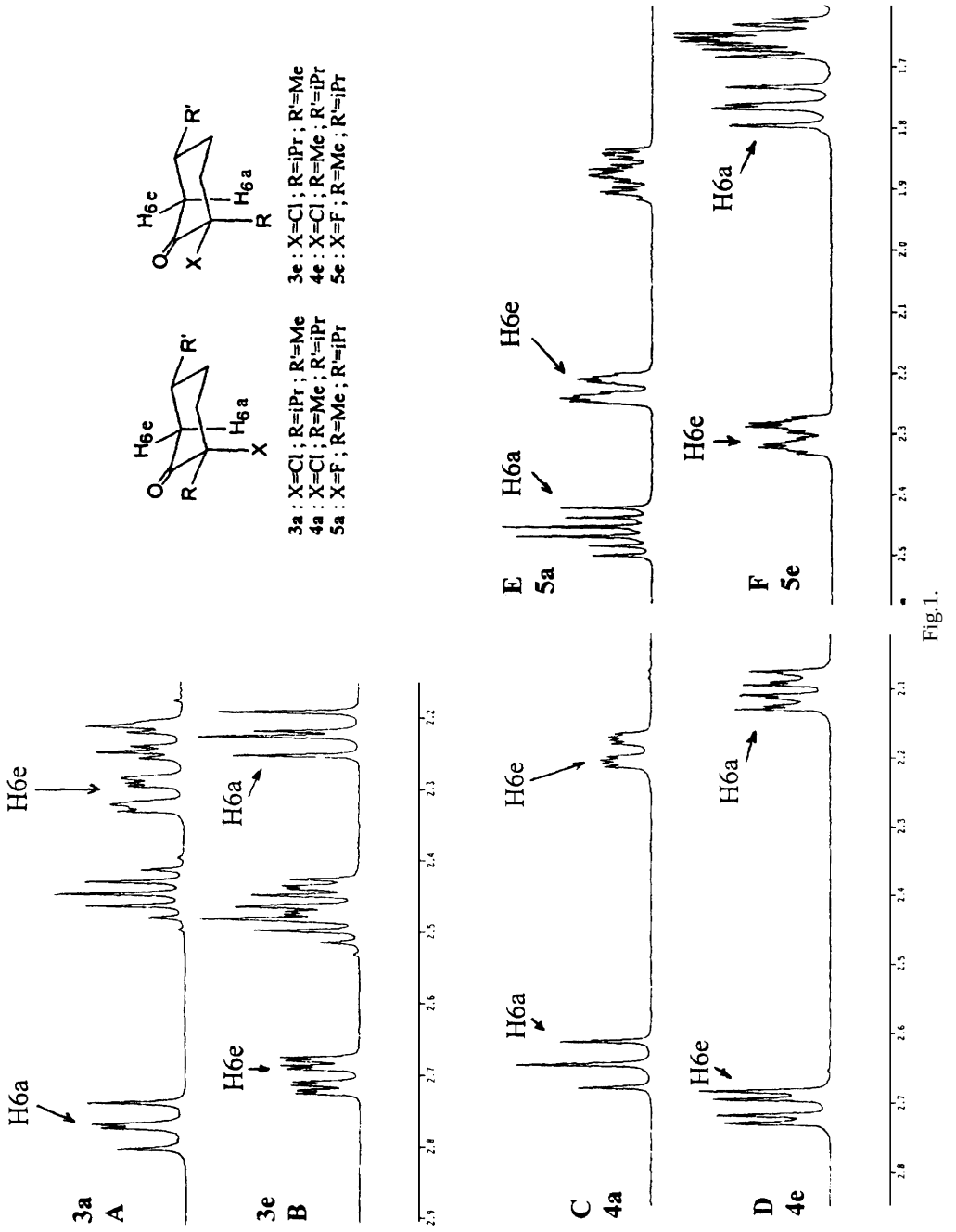

H6a
H6e
3a
A
H6e
H6a
3e
B
H6a
H6e
C
4a
H6e
H6a
D
4e
H6a
H6e
E
5a
H6e
H6a
F
5e
H6e
H6a
3a : X=Cl ; R=iPr ; R'=Me
4a : X=Cl ; R=Me ; R'=iPr
5a : X=F ; R=Me ; R'=iPr
3e : X=Cl ; R=iPr ; R'=Me
4e : X=Cl ; R=Me ; R'=iPr
5e : X=F ; R=Me ; R'=iPr

Fig.1.

3. Experimental

^{1}H 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 the solvent. Chemical shifts (δ) are given in ppm downfield from TMS as an internal standard. Optical rotation measurements were carried out with a Perkin–Elmer 241 MC polarimeter. TLC was performed on Merck's glass plates with silica gel 60 F_{254}. Silica gel for column chromatography (Merck) was used for the chromatographic purifications. (2*S*,5*R*)-(−)-Menthone, purchased from Fluka, was claimed to be >98% ee by GC. (+)-Dihydrocarvone, purchased from Fluka, was a 77% (2*R*,5*R*) and 20% (2*S*,5*R*) mixture, having the enantiomeric purity of the starting (−)-carvone, 99% *R* (98% ee).

3.1. Chlorination of menthone: *3a*, *3e*

A solution of (−)-menthone **6** (4 g, 26 mmol, 1 equiv.) in CCl_4 (45 ml) was stirred at 0°C in a 250 ml two-necked flask equipped with a gas trap (10% NaOH). Then a solution of freshly distilled SO_2Cl_2 (2.53 ml, 31.2 mmol, 1.2 equiv.) in CCl_4 (15 ml) was added dropwise within 45 min. The reaction mixture was further stirred for 7 h and then poured on ice (100 ml). The two phases were separated and the aqueous phase was extracted with CH_2Cl_2. The organic phases were washed with saturated $NaHCO_3$ and dried over Na_2SO_4. After filtration and evaporation, the crude product was purified by column chromatography using a gradient of pentane:CH_2Cl_2, from 80:20 to 40:60, to afford 3.015 g of **3a** (61%) and 1.304 g of **3e** (33%), respectively.

3.1.1. (2R,5R)-(+)-2-Chloro-2-isopropyl-5-methylcyclohexanone *3a*

$[\alpha]_D^{22}$=+190 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95 (d, *J*=6.5 Hz, 3H, Me isopropyl), 1.04 (d, *J*=6 Hz, 3H, Me10), 1.06 (d, *J*=6.5 Hz, 3H, Me isopropyl), 1.80 (m, 4H, H4a, H4e, H5, H3a), 2.25 (dt, ^3J=^3J=3.5 Hz, ^2J =14 Hz, 1H, H3e), 2.3 (dd, ^3J=4 Hz, ^2J=14 Hz, 1H, H6e), 2.47 (sept, *J*=6.5 Hz, 1H, H7), 2.77 (dd, ^3J=12 Hz, ^2J=14 Hz, 1H, H6a); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.3 (C8 and C9), 22.3 (C10), 29.6 (C4), 33.8 (C7), 34.5 (C5), 35.2 (C3), 46.2 (C6), 78.3 (C2), 204.9 (C1). IR ($CHCl_3$): ν=3620, 2960, 2920, 2880, 1715, 1450, 1390, 1370, 1260–1180, 1050, 880 cm^{-1}. Anal. calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 63.30; H, 9.07.

3.1.2. (2S,5R)-(+)-2-Chloro-2-isopropyl-5-methylcyclohexanone *3e*

$[\alpha]_D^{22}$=+47 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.90 (d, *J*=6.5 Hz, 3H, Me isopropyl), 1.02 (d, *J*=6.5 Hz, 3H, Me10), 1.07 (d, *J*=6.5 Hz, 3H, Me isopropyl), 1.53 (qd, ^3J=4 Hz, ^3J=^3J=^2J=13 Hz, 1H, H4a), 1.87 (dqd, ^4J=1.5 Hz, ^3J=^3J=^3J=4 Hz, ^2J=13 Hz, 1H, H4e), 2.05 (m, 2H, H3a, H5), 2.22 (dd, ^3J=11 Hz, ^2J=13.5 Hz, 1H, H6a), 2.48 (m, 1H, H3e), 2.5 (sept, *J*=6.5 Hz, 1H, H7), 2.71 (ddd, ^4J=1.5 Hz, ^3J=4.5 Hz, ^2J=13.5 Hz, 1H, H6e); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.9 (C8 or C9), 17.7 (C9 or C8), 21.5 (C10), 30.2 (C4), 32.7 (C7), 34.4 (C5), 38.0 (C3), 47.0 (C6), 83.0 (C2), 205.2 (C1). IR ($CHCl_3$): ν=3620, 2970 , 2930, 2890, 1720, 1450, 1390, 1375, 1260–1180, 1050, 875 cm^{-1}. Anal. calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 63.84; H, 9.16.

3.2. Chlorination of tetrahydrocarvone: *4a*, *4e*

The chlorination was carried out following the same procedure. After column chromatography, using CCl_4 as eluant, **4a** and **4e** were isolated pure with 69 and 11% yield, respectively.

*3.2.1. (2*S,*5*R*)-(+)-2-Chloro-2-methyl-5-isopropylcyclohexanone **4a***

$[\alpha]_D^{22}$=+160 (*c* 1.05, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.65 (d, *J*=6.5 Hz, 3H, Me isopropyl), 0.66 (d, *J*=6.5 Hz, 3H, Me isopropyl), 1.08 (m, 1H, H5), 1.19 (oct, *J*=6.5 Hz, 1H, H7), 1.25 (m, 2H, H4e, H3a), 1.55 (s, 3H, Me10), 1.6 (qd, ^3J=3 Hz, ^3J=^3J=^{2}J=12 Hz, 1H, H4a), 1.92 (m, 1H, H3e), 2.19 (ddd, ^4J=2 Hz, ^3J=4 Hz, ^2J=13.5 Hz, 1H, H6e), 2.65 (t, ^3J=^2J=13.5 Hz, H6a); ^{13}C NMR (C_6D_6, 100 MHz): δ 19.4 (C8 or C9), 19.5 (C9 or C8), 24.9 (C4), 26.7 (C10), 32.8 (C7), 40.4 (C6), 41.8 (C3), 45.7 (C5), 70.2 (C2), 204.0 (C1). IR ($CHCl_3$): ν=3630, 2980, 2940, 2890, 1720, 1450, 1400, 1250–1200, 1100–1020, 865 cm^{-1}. Anal. calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 64.02; H, 9.00.

*3.2.2. (2*R,*5*R*)-(−)-2-Chloro-2-methyl-5-isopropylcyclohexanone **4e***

$[\alpha]_D^{22}$=−36 (*c* 1.18, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.56 (d, *J*=6.5 Hz, 3H, Me isopropyl), 0.65 (d, *J*=6.5 Hz, 3H, Me isopropyl), 1.06 (oct, *J*=6.5 Hz, 1H, H7), 1.2 (m, 2H, H5, H4), 1.45 (s, 3H, Me10), 1.65 (m, 2H, H4, H3), 1.80 (m, 1H, H3), 2.11 (ddd, ^4J=3 Hz, ^3J=9 Hz, ^2J=14 Hz, 1H, H6a), 2.71 (dd, ^3J=4.5 Hz, ^2J=14 Hz, 1H, H6e); ^{13}C NMR (C_6D_6, 100 MHz): δ 20.1 (C8 or C9), 20.3 (C9 or C8), 24.7 (C4), 27.0 (C10), 29.4 (C7), 40.2 (C3), 40.7 (C6), 44.2 (C5), 72.0 (C2), 203.3 (C1). IR ($CHCl_3$): ν=3620, 2960, 2880, 1720, 1450, 1390, 1270–1180, 1090, 1050, 875 cm^{-1}. Anal. calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 63.19; H, 9.12.

*3.3. Fluoration of tetrahydrocarvone: **5a**, **5e***

*3.3.1. Preparation of silylenol ether **9***

To a solution of (+)-tetrahydrocarvone **8** (4.55 g, 29 mmol, 1 equiv.) in acetonitrile (125 ml) under an argon atmosphere was added rapidly anhydrous NaI (8.2 g, 53 mmol, 1.8 equiv.). Then triethylamine (7.3 ml, 53 mmol, 1.8 equiv.) and freshly distilled trimethylsilyl chloride (6.7 ml, 53 mmol, 1.8 equiv.) were added, respectively, to the reaction mixture. After stirring at room temperature for 2 h, the mixture was rapidly poured into a cold NaOH solution[10] (2.2 g, 53 mmol, 1.8 equiv. NaOH in 200 ml H_2O). Then pentane (100 ml) was added. The two phases were separated and the aqueous phase was extracted with pentane (3×120 ml). The organic phases were dried over $MgSO_4$ and the solvent was evaporated to give **9** as a pure yellow oil (4.82 g, 73%).

2-Methyl-5-(*R*)-isopropyl-1-trimethylsiloxycyclohexene **9**: $[\alpha]_D^{22}$=+48 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.18 (s, 9H, Me de TMS), 0.89 (d, *J*=6.5 Hz, 3H, Me isopropyl), 0.90 (d, *J*=6.5 Hz, 3H, Me isopropyl), 1.15 (qd, ^3J=4 Hz, ^2J=^3J=^3J=12 Hz, 1H, H4a), 1.3 (m, 2H), 1.49 (oct, *J*=6.5 Hz, 1H, H7), 1.56 (bs, 3H, Me10), 1.71 (d, ^2J=12 Hz, 1H, H4e), 1.82 (ddm, ^3J=12 Hz, ^2J=13 Hz, 1H, H6a), 1.97 (bm, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 1.1, 16.5, 20.1, 20.3, 26.9, 30.7, 32.5, 34.4, 34.5, 42.0, 111.8, 143.1. IR ($CHCl_3$): ν=2880, 1680, 1450–1400, 1360, 1320, 1160, 910, 890, 830 cm^{-1}.

*3.3.2. Fluoration: **5a**, **5e***

To a solution of **9** (1.5 g, 6.62 mmol, 1 equiv.) in dry DMF (25 ml) under an argon atmosphere was added dropwise a solution of Selectfluor (3.29 g, 9.3 mmol, 1.4 equiv.) in DMF (40 ml). The mixture was stirred at 0°C for 2 h. Then water (50 ml) was poured into the reaction mixture, the different phases were separated and the aqueous phase was 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 a pentane:ether gradient [96:4 (for **5a**), 10:90 (for starting material), 15:85 (for **5e**)] to afford 0.478 g of **5a** (42%) and 0.411 g of **5e** (36%).

(2*S*,5*R*)-(+)-2-Fluoro-2-methyl-5-isopropylcyclohexanone **5a**: $[\alpha]_D^{22}$=+1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.63 (d, *J*=6.5 Hz, 3H, Me isopropyl), 0.64 (d, *J*=6.5 Hz, 3H, Me isopropyl), 1.06

(dddd, ^3J=4 Hz, ^3J=13 Hz, ^2J=15 Hz, $^3J_{HF}$=40 Hz, 1H, H3a), 1.15 (m, 3H, H4e, H5, H7), 1.34 (d, $^3J_{HF}$=22 Hz, 3H, Me10), 1.49 (qd, ^3J=4.5 Hz, ^2J=^3J=^3J=13 Hz, 1H, H4a), 1.89 (dddd, ^3J=2 Hz, ^3J=4.5 Hz, $^3J_{HF}$=10 Hz, ^2J=15 Hz, 1H, H3e), 2.22 (dtd, $^4J_{HF}$=$^4J_{HH}$= 2 Hz, ^3J=4 Hz, ^2J=12 Hz, 1H, H6e), 2.48 (td, $^4J_{HF}$=6 Hz, ^2J=^3J=12 Hz, 1H, H6a); ^{13}C NMR (C_6D_6, 100 MHz): δ 19.3 (C8 or C9), 19.5 (C9 or C8), 20.3 (d, $^2J_{CF}$=24 Hz, C10), 24.0 (d, $^3J_{CF}$=9 Hz, C4), 32.7 (C7), 38.5 (d, $^2J_{CF}$=23 Hz, C3), 41.9 (d, $^3J_{CF}$=2 Hz, C6), 46.4 (C5), 95.5 (d, $^1J_{CF}$=171 Hz, C2), 206.5 (d, $^2J_{CF}$=25 Hz, C1). IR ($CHCl_3$): ν=2920, 2850, 1720, 1420, 1360, 1310, 1150, 1130, 1090, 1070, 980, 890, 880 cm^{-1}. Anal. calcd for $C_{10}H_{17}FO$: C, 69.73; H, 9.95. Found: C, 69.22; H, 10.01.

(2*R*,5*R*)-(+)-2-Fluoro-2-methyl-5-isopropylcyclohexanone **5e**: $[\alpha]_D^{22}$=+75 (*c* 1.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.58 (d, *J*=6.5 Hz, 3H, Me isopropyl), 0.60 (d, *J*=6.5 Hz, 3H, Me isopropyl), 0.9 (m, 1H, H4a), 1.06 (oct, *J*=6.5 Hz, 1H, H7), 1.10 (m, 1H, H5), 1.17 (d, $^3J_{HF}$=21.5 Hz, 3H, Me10), 1.32 (bd, ^2J=14 Hz, 1H, H4e), 1.65 (m, 2H, H3a and H3e), 1.78 (dd, ^3J=11 Hz, ^2J=14 Hz, 1H, H6a), 2.30 (dtd, ^4J=2 Hz, ^3J=$^4J_{HF}$=3 Hz, ^2J=14 Hz, 1H, H6e); ^{13}C NMR (C_6D_6, 100 MHz): δ 19.6 (C8 or C9), 19.7 (C9 or C8), 22.1 (d, $^2J_{CF}$=25 Hz, C10), 25.8 (d, $^3J_{CF}$=9 Hz, C4), 31.5 (C7), 37.9 (d, $^2J_{CF}$=22 Hz, C3), 42.6 (C6), 45.0 (C5), 96.0 (d, $^1J_{CF}$=184 Hz, C2), 205.6 (d, $^2J_{CF}$=17 Hz, C1). IR ($CHCl_3$): ν=2920, 2850, 1720, 1450, 1370, 1310, 1125, 1090, 980, 970, 950, 890 cm^{-1}. Anal. calcd for $C_{10}H_{17}FO$: C, 69.73; H, 9.95. Found: C, 69.17; 10.02.

Acknowledgements

This work was supported by Dr. A. Wick and the Sylachim/Synthelabo Groupe as well as by the MENRT, France with a grant to L.B. M. M. Schmitt (Laboratoire de Stéréochimie Organométallique) is acknowledged for the 2D NMR studies and Mme A. Klein for technical participation.

References

1. Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun*. **1984**, 155.
2. Yang, D.; Wang, X. C.; Wong, M. K.; Yip, Y. C.; Tang, M. W. *J. Am. Chem. Soc*. **1996**, *118*, 11311 and included references.
3. Wang, Z. X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem*. **1999**, *64*, 6443, and references cited therein.
4. Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett*. **1995**, *36*, 5831.
5. Denmark, S. G.; Wu, Z. *Synlett* **1999**, 847, and references cited therein.
6. Kötz, A.; Steinhorst, H. *Justus Leibig Ann. Chem*. **1911**, *379*, 25.
7. (a) Kohda, A.; Sato T. *J. Chem. Soc., Chem. Commun*. **1981**, 951. (b) Kohda, A.; Nagayoshi, K.; Maemoto, K.; Sato T. *J. Org. Chem*. **1983**, *48*, 425. (c) It must be noted that no difference was observed between the IR ν_{CO} of ketone **4a** with an *axial*-Cl and ketone **4e** with an *equatorial*-Cl, which were 1720 cm^{-1} in both cases.
8. Farges, G.; Kergomard, A. *Bull. Soc. Chim*. **1963**, 51.
9. Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Org. Chem*. **1982**, *47*, 1200.
10. The work-up as described in the following reference leads to the starting material (100% recovery): Wenkert, E.; Arrhenius, T. S.; Bookser, B.; Guo, M.; Mancini, P. *J. Org. Chem*. **1990**, 55, 1185.
11. Denmark, S. E.; Zhiai, W.; Crudden, C. M.; Matsukashi, H. *J. Org. Chem*. **1997**, *62*, 8288.