

## Cyclization and Fluorination of 5-Hexenols with Boron Trifluoride Etherate. Stereoselective Synthesis of (Optically Active) Fluorinated Cyclohexane Derivatives by Cyclization of $\omega$ -Pentenyl Pentadienol Tricarbonyl Iron Complexes.

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**Abstract :** Monofluorinated cyclohexane derivatives are obtained by treatment of  $\omega$ -pentenyl pentadienol tricarbonyl iron complexes with boron trifluoride etherate. The reaction is stereoselective, so that optically active fluorocyclohexanes can be obtained from readily available enantiomerically pure starting complexes. This fluorocyclization reaction with the cheap reagent  $BF_3 \cdot Et_2O$  is not restricted to transition-metal coordinated substrates, working also with simple  $\omega$ -pentenyl benzylic alcohols.  
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A recent paper by A.J. Pearson *et coll.*,<sup>1</sup> dealing with the stereocontrolled cationic cyclization of secondary tricarbonyl iron pentadienols bearing an alkene functionality in the side chain, appeared when our work on cyclization with fluorination of similar alcohols, also mediated by  $BF_3 \cdot Et_2O$ , was nearly complete.<sup>2</sup> In view of small but significant differences between their results and ours, we have undertaken a thorough investigation of these reactions.

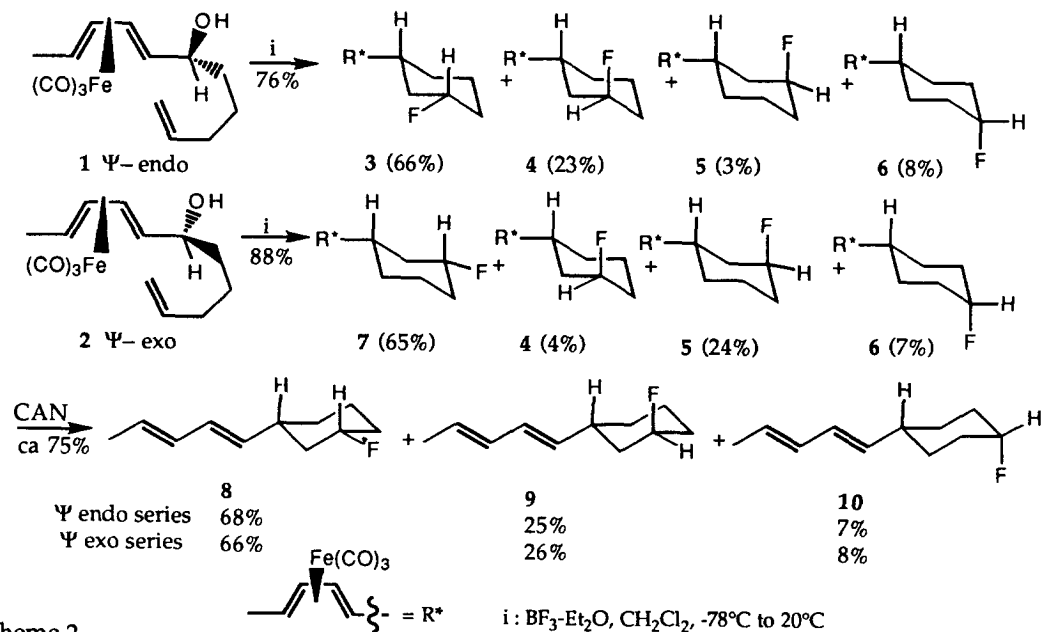
Treatment of the alcohols **1** and **2**<sup>3</sup> with  $BF_3 \cdot Et_2O$  in  $CH_2Cl_2$  at  $-78^\circ C$  (1-3 equiv), followed by warming to  $20^\circ C$  and rapid work-up (cooling to  $-78^\circ C$  and addition of water) gave in both cases a mixture of complexes consisting of four isomeric monofluorinated cyclohexanes (ca 75 % : **3-6** / respectively **4-7**).<sup>4,5</sup> By decomplexation ( $Ce^{IV}$  ammonium nitrate, MeOH/ $H_2O$ ,  $-40^\circ C$  then  $NaHCO_3$ ,  $H_2O$ ,  $-40^\circ C$  to  $20^\circ C$ ) the same three fluorocyclohexyldienes **8-10** were obtained. Careful examination of the  $^1H$ -NMR (400 MHz) and  $^{19}F$ -NMR (376 MHz) spectra ( $\delta$ ,  $J$  and integration) of these mixtures,<sup>6</sup> showed that in both series only one diastereomeric 1,3-disubstituted cyclohexane with the coordinated dienyl and fluorine substituents in equatorial positions was obtained (**3**, **7** stereospecific reaction), but that the same two diastereomeric cyclohexanes **4** and **5**, with an axial fluorine, also in position 3, were formed in reversed ratios, along with an isomeric fluorocyclohexane, **6**, with an axial fluorine, most probably in position 4<sup>7</sup> (scheme 1).

For biogenetic cationic cyclizations, tertiary carbocations are more suitable in view of the synthesis of precursors of natural products (steroids, polycyclic terpenes). So, we also investigated the cyclization reactions of the tertiary alcohols **11** and **12** obtained respectively as highly pure diastereoisomers, as expected,<sup>8</sup> by reaction in ether at  $-78^\circ C$  of pent-4-enyllithium with the known complex of hepta-2,4-dien-6-one (87 %), and of methylolithium with  $\omega$ -pentenyl pentadienone tricarbonyl iron (80 %).<sup>9</sup>

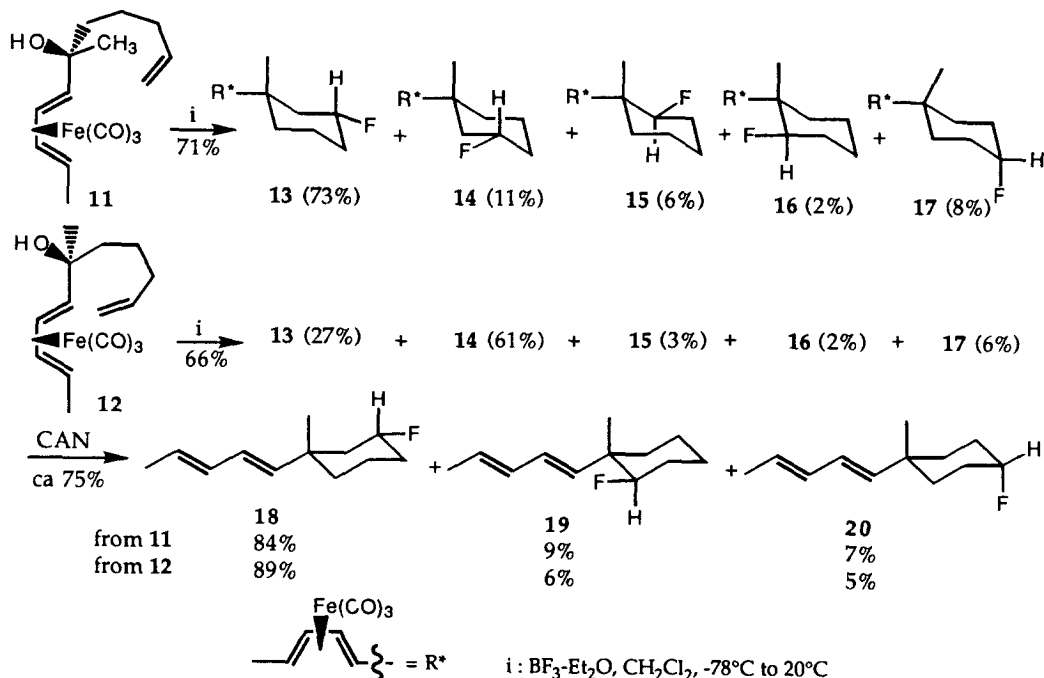
The reaction is more complex here, since five fluorocyclohexanes, **13-17**, were obtained in both series (ca 70 %, along with a small amount of cyclized elimination products), which reduced after decomplexation to three fluorocyclohexyldienes, **18-20**, two with an equatorial and one with an axial fluorine (scheme 2).

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Scheme 1



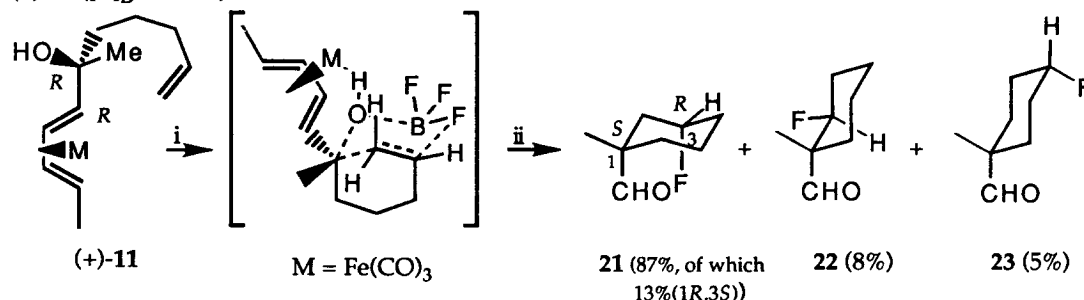
Scheme 2



Obviously, the cyclization reaction no longer proceeded with a high stereospecificity (13, 14) and was complicated by the formation of isomeric fluorides (diastereomeric 2-fluorocyclohexanes 15 and 16, and the "symmetrical" 4-fluorocyclohexane 17). However, the major product 13 from the complexed alcohol 11 could be isolated as single crystals after chromatographic enrichment,<sup>10</sup> allowing confirmation of the structure by

X-ray diffraction.<sup>11</sup> The cyclization proceeded therefore mainly with retention of configuration at the starting chiral centre.

From the nearly enantiomerically pure (5*R*)-(-)-hepta-2,4-dien-6-one complex ( $[\alpha]_D = -384$ , ee = 98 %),<sup>8,12</sup> optically active fluorocyclohexane derivatives are thus available, as shown by the following transformations (cyclization, decomplexation and cleavage by ozone to the aldehydes) of the chiral alcohol (+)-**11** ( $[\alpha]_D = +25.4$ ).

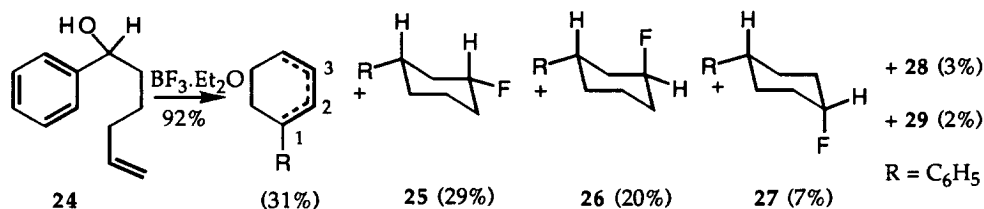


i)  $\text{BF}_3 \cdot \text{OEt}_2$  (1.1 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  to RT, (84%) ii) 1)  $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ ,  $\text{MeOH}/\text{H}_2\text{O}$ ,  $-60^\circ\text{C}$ , then  $\text{NaHCO}_3$ ,  $\text{H}_2\text{O}$ ,  $-60^\circ\text{C}$  to RT (75%) 2)  $\text{O}_3$ ,  $\text{MeOH}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  then  $\text{Me}_2\text{S}$ ,  $-78^\circ\text{C}$  to RT, (88%)

The formylfluorocyclohexanes **21-23**<sup>13</sup> could not be separated by simple column chromatography but the mixture of the products, which is mostly the major (1*S*)-formyl-(3*R*)-fluoromethylcyclohexane (-)-**21** (cyclization with retention of configuration), showed an  $[\alpha]_D$  of -2 ( $c = 0.5$ ,  $\text{CHCl}_3$ ). Before decomplexation, the mixture **13-17** corresponding to the major (3*R*)-fluoro-(1*S*)-tricarbonyliron pentadienylmethylcyclohexane (+)-**13** showed a larger rotation ( $[\alpha]_D = +34.4$ ,  $C = 0.71$ ,  $\text{CHCl}_3$ ).

Interestingly the major fluoro pentadienyl tricarboxyl iron complexes formed (**13** + **14**) are in a locked chair conformation with the bulky (diene)  $\text{Fe}(\text{CO})_3$  substituent and the fluorine in equatorial orientations, while the corresponding decomplexation and ozonolysis product **21** shows the reversed orientation with the formyl substituent and the fluorine in axial orientations (through-space coupling of the spatially close together nuclei H and F :  $J = 3.2$  Hz).

To verify if the metal plays a dominant role in the unusual fluorocyclization reaction of  $\omega$ -pentenyl carbinols, we investigated the reaction with the *non complexed*  $\omega$ -pentenyl benzylic analog **24** (1 eq.  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ). Cyclization with fluorination occurred, in competition with elimination reactions, yielding a mixture of the  $\Delta^1$ ,  $\Delta^2$  and  $\Delta^3$ -phenylcyclohexenes (overall 31 %, ca 3:1:2) and of five fluorocyclohexanes (overall 61 % ; equatorial F : **25**, **28** and **29**, axial F : **26** and **27**). Tertiary benzylic alcohols gave similar results.



By careful examination of the  $^1\text{H-NMR}$  and  $^{19}\text{F-NMR}$  spectra of the fluorocyclohexane fraction the structures of the fluorophenylcyclohexanes could be attributed, assuming that they are in locked chair conformations with the bulky phenyl substituent in an equatorial orientation. To increase the yield of

fluorinated products in the aromatic series, we used also up to 3 equivalents of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . However, with an excess of reagent, we obtained mainly cyclohexene derivatives. This result can be explained by easy ionization by the Lewis acid of the initially formed C-F bond, causing elimination.<sup>14</sup> The fluorocyclization reaction is, in consequence, not restricted to the complexed series, but is fairly general, however it is only observable if the fluorination reagent is not used in excess.

**Acknowledgment :** we are grateful to BASF for gifts of  $\text{Fe}(\text{CO})_5$ .

### References and notes :

- Pearson, A.J.; Alimardanov, A.; Pinkerton, A.A.; Fouchard, D.M.; Kirschbaum, K. *Tetrahedron Lett.* **1998**, *39*, 5919.
- Hanss, D. : Rapport de stage de Maîtrise de Chimie février-mai 1998, Université Louis Pasteur Strasbourg "Cyclisations cationiques de systèmes polyéniques coordonnés au greffon fer-tricarbonyle".
- The lithium alkyl reagent from 5-bromo-1-pentene was reacted with the known tricarbonyl iron complex of 2,4-hexadienal to give an easily separable mixture of the diastereomeric  $\psi$ -endo (less polar, 41 %) and  $\psi$ -exo (more polar, 46 %) alcohols **1** and **2**. These alcohols were also obtained by A.J. Pearson *et coll.*<sup>1</sup> For the definition of  $\psi$ -endo and  $\psi$ -exo cf. Clinton, N.A.; Lillya, C.P. *J. Am. Chem. Soc.* **1970**, *92*, 3058.
- Pearson, A.J. *et coll.*<sup>1</sup> mentioned the formation of only two fluorides, as single different diastereomers in each series.
- In the NMR spectra the F-C-H protons appear as two apparent heptuplets [ $J \sim 4.8$  Hz, when F is equatorial ( $2 \times 9.5$  Hz ax/ax and  $2 \times 5$  Hz ax/eq) and  $\sim 2.6$  Hz when F is axial ( $2 \times 5$  Hz ax/eq and  $2 \times 2.7$  Hz eq/eq)] with  $J_{\text{F-C-H}} \sim 49$  Hz. The fluorine appears as a relatively fine doublet ( $J_{\text{F-C-H}} \sim 49$  Hz,  $J_{\text{H-C-C-F}} \sim 7$  Hz) when equatorial ( $\delta \sim -168$  ppm) and an apparent broad quartet ( $J_{\text{F-C-H}} \sim 48$  Hz,  $J_{\text{H-C-C-F}} \sim 35$  Hz and 9 Hz) when axial ( $\delta < -182$  ppm), in good agreement with the expected values (S. Berger, S. Braun, H.O. Kalinowski, "NMR Spectroscopy of the Non-Metallic Elements", *John Wiley and Sons*, **1996**, pg 420-439 and 588-610).
- Chemical shifts ( $\delta^1\text{H}$  and  $\delta^{19}\text{F}$ ) of the CHF group : **3** [4.41, -168.6 (d)], **4** [4.88, -183.9 (q)], **5** [4.83, -182.8 (q)], **6** [4.76, -185.3 (m)], **7** [4.44, -168.6 (d)], **8** [4.48, -168.15 (d)], **9** [4.88, -182.9 (q)], **10** [4.79, -184.15 (m)], **13** [4.63, -172.55 (d)], **14** [4.63, -172.8 (d)], **15** [4.63, -174.8 (m)], **16** [4.63, -175.1 (m)], **17** [4.70, -183.0 (m)], **18** [4.70, -173.4 (d)], **19** [4.61, -172.1 (d)], **20** [4.57, -176.1 (m)],
- The fluorocyclohexane derivatives are in a locked chair conformation with the large diene- $\text{Fe}(\text{CO})_3$  substituent in an equatorial orientation. Our structure assignments based on  $^1\text{H-NMR}$  and  $^{19}\text{F-NMR}$  are supported by the X-ray crystal structure determinations of the products **7**<sup>1</sup> and **13** (this communication).<sup>11</sup>
- Cf. Franck-Neumann, M.; Chemla, P.; Martina, D. *Synlett* **1990**, 641.
- The  $\omega$ -pentenyl pentadienone- $\text{Fe}(\text{CO})_3$  complex was obtained in 85 % yield by oxidation with 1,1'-(azodicarbonyl)-dipiperidine<sup>15</sup> of the magnesium alcoholates resulting from the reaction of pent-4-enyl magnesium bromide with the complexed sorbic aldehyde.
- All diene  $\text{Fe}(\text{CO})_3$  complexes are easily identified in the IR by the characteristic (C=O) absorptions at 1973 and 2041  $\text{cm}^{-1}$ . **13** : mass peak 322 (FAB) ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) :  $\delta$  = 0.95 (3H, s), 1.05 (1H, m), 1.13 (1H, d,  $J = 10$  Hz), 1.41 (3H, d,  $J = 6.2$  Hz), 1.26-1.50 (4H, m), 1.66 (1H, m), 1.75 (1H, m), 1.85 (1H, broad t,  $J_{(1)} = 9.5$  Hz), 2.03 (1H, m), 4.63 (1H, dt,  $J = 49$  Hz, 9.5 Hz and 5 Hz), 4.99 (1H, dd,  $J = 5.1$  Hz and 8.8 Hz), 5.18 (1H, dd,  $J = 5.1$  Hz and 10 Hz) ;  $^{19}\text{F-NMR}$  (376 MHz,  $\text{CDCl}_3$ ) :  $\delta$  = -172.55 (d,  $J = 49$  Hz).
- The details of the X-ray structure determination will be given in the full paper. (Service Commun de rayons X de la Fédération de Recherche Chimie de l'ULP, June 1998).
- Franck-Neumann, M.; Bissinger, P.; Geoffroy, P. *Tetrahedron Lett.* **1997**, *38*, 4469.
- Chemical shifts ( $\delta^1\text{H}$  and  $\delta^{19}\text{F}$ ) of the CHF group : **21** [4.86, "hept" 2.8 Hz, -179.0 (q)], **22** [4.59, "hept" 4.2 Hz, -171.3 (d)], **23** [4.86, -177.2 (m)]
- Cf. Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769.
- Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn* **1977**, *50*, 2773.

