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Synthesis of Atropoisomeric Fluorocyclohexadienones by *Ipso*-fluorination of Binaphthol Derivatives

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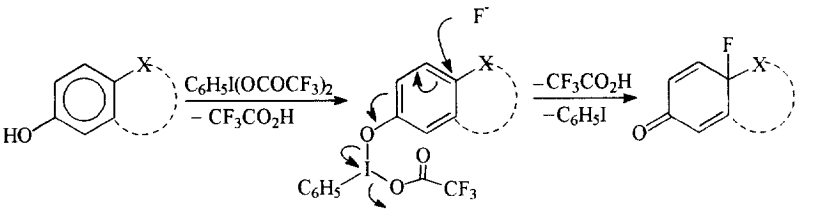
Abstract : *Nucleophilic para-fluorination of (R,S)-1,1'-Bi-5,6,7,8-tetrahydro-2-naphthol (and its monoacetate) with $C_6H_5I(OCOCF_3)_2$- pyridinium polyhydrogen fluoride yields atropoisomeric fluorocyclohexadienones.* Copyright © 1996 Elsevier Science Ltd

We recently reported a novel synthesis of 4-fluorocyclohexa-2,5-dienones from 4-alkylphenols using phenyliodine bis(trifluoroacetate) (PIFA) with pyridinium polyhydrogen fluoride (PPHF) [1].

The mecanism implies reaction of the reagent PIFA on the phenolic group and trapping of the resulting intermediate by a nucleophilic fluoride.



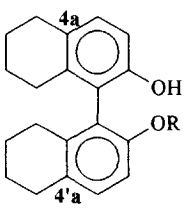
We now wish to report, on account of the importance of fluoroderivatives in organic and bioorganic chemistry[2], the synthesis of atropoisomeric fluorocyclohexadienones, starting from (R,S)-1,1'-Bi-5,6,7,8-tetrahydro-2-naphthol **1a** (and its monoacetate **1b**) prepared by hydrogenation of the commercially available (R,S)-1,1'-Bi-2-naphthol.

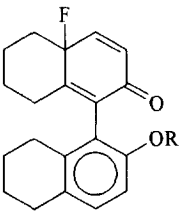
The reaction was carried out as previously described, pyridinium polyhydrogen fluoride, then $C_6H_5I(OCOCF_3)_2$ being added to a solution of the phenol in dichloromethane.

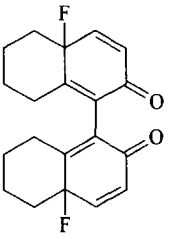
Table 1 shows that with 1.2 equivalent of PIFA fluorination of phenol **1a** yields a complex mixture of mono and difluoroderivatives and of the starting material. Phenols acetates being unreactive, reaction of monoester **1b** gives only racemic cyclohexadienones **2b** and **3b**.

In these compounds the configuration R or S of the newly created asymmetric center 4a, coupled with the atropoisomeric system (indicated as Ra or Sa), accounts for the formation of these products. Structure of dienone **2b** has been determined by X-ray analysis (Scheme 1), implying for dienone **3b** the proposed structure.

Mild hydrolysis ($NaHCO_3$ / H_2O) of esters **2b** and **3b** yields the corresponding phenols **2a** and **3a**. Entries 3 and 4 show that fluorination of these phenols leads to racemic ketones **5** and **6**, and **4** and **5**, respectively, confirming that the configuration of atropoisomers has been maintained during alkaline hydrolysis of esters **2b** and **3b**.







(R,S)-1 **a R=H** **2 (RSa, SRa)** **4 ($R^*R^*Ra^*$)**

b R=Ac **3 (RRa, SSa)** **5 ($R^*S^*Ra^*$)**

6 ($R^*R^*Sa^*$)

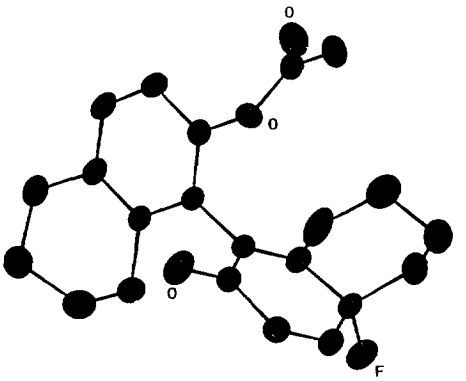
Table 1

Entry	Substrate	PIFA (equiv.)	Products [3](%)
1	**1a**	1.2	**1a** + **2a** + **3a** + **4** + **5** + **6**
2	**1b**	1.2	**2b** + **3b** (65)(molar ratio 40/60)
3	**2a**	1.2	**5** + **6** (42)(molar ratio 28/72)
4	**3a**	1.2	**5** + **4** (48)(molar ratio 83/17)
5	**1a**	2.4	**4** + **5** + **6** (45)(molar ratio 18/65/17)

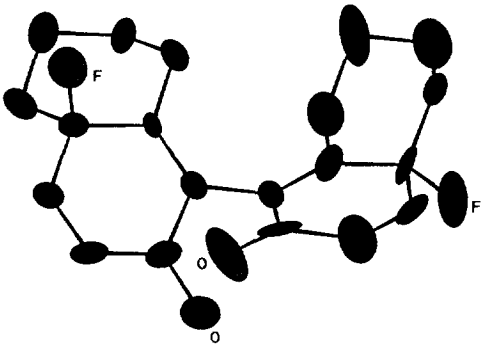
Ketones **4**, **5** and **6** are obtained directly when the reaction is carried out on phenol **1a** (entry 5). The second fluorination creates a second asymmetric center at C-4'a, identical with the first one. Six isomers could be formed and are effectively obtained, corresponding to racemic ketones **4**, **5** and **6**.

Formation of a commun difluorodienone **5** starting either from phenol **2a** or from phenol **3a** was expected and its structure has been confirmed by X-ray analysis (Scheme 1). Structures of isomers **4** and **6** follow from those of their respective precursors **3a** and **2a**.

Scheme 1 : X-Ray Structures



(RSa)-2b

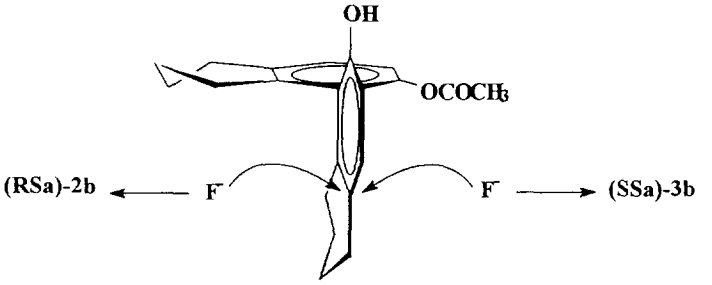


(RSSa)-5

It should be noticed that whereas ketones **4** and **6** exhibit only ten different carbon signals in ^{13}C-NMR, twenty signals are observed for ketone **5**, in concordance with different configurations for the asymmetric carbons.

These results deserve several comments:

- Fluorination of monoester **1b** appears to be poorly stereoselective (**2b/3b** molar ratio 40/60). This reflects, according to the conformation of the substrate, a slight preference for nucleophilic fluorination on the face occupied by the acetoxy group.



(Sa)-1b

On the other hand, from the results of entries 3, 4, 5 we can infer that fluorination of **1a** is much more selective , with a pronounced preference for the face occupied by the hydroxyl group (**2a/3a** calculated molar ratio 22/78).

This selectivity might be due to an anchimeric assistance through an hydrogen bond between the hydroxyl group and the solvated fluoride $F(HF)_n^-$. A similar effect was observed previously in the addition of hydrogen fluoride on unsaturated alcohols in the steroid series [4].

- A complete reversal of selectivity is observed in the second fluorination (entries 3 and 4). The reaction occurs preferentially on the face of the phenol opposite to the carbonyl group (selectivity 28/72 with **2a**, and 17/83 with **3a**) and this is probably due to a repulsive interaction between the solvated fluoride and the oxygen atom of the carbonyl group.

In summary we have demonstrated that the nucleophilic *para*-fluorination of *para*-alkyl phenols by $C_6H_5I(OCOCF_3)_2$ and pyridinium polyhydrogen fluoride represents a useful method for the preparation of atropoisomeric fluorocyclohexadienones. Further applications of this methodology is in progress and will be reported in due course.

References and notes

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3. Relative yields have been determined by HPLC:
   Chromatographic conditions: Column: Spherisorb 5µm Silica, 4.6-250mm, HPLC Technology LTD; eluent: AcOEt / Hexane 1:9 (v/v); Flow rate: 1mL/min; Detection λ=280nm; HPLC System: WATERS.
   The products have been separated using preparative TLC (Plates Kieselgel 60 F_{254} MERCK).
   The new products gave satisfactory spectral data (MS, ^1H and ^{13}C NMR) and the expected analytical (HRMS or microanalysis) results.

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