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# Synthesis of Optically Pure Fluoro- and *gem*-Chlorofluoro-cyclohexane Derivatives by Intramolecular Trapping of Dihaloalkyl Radicals.

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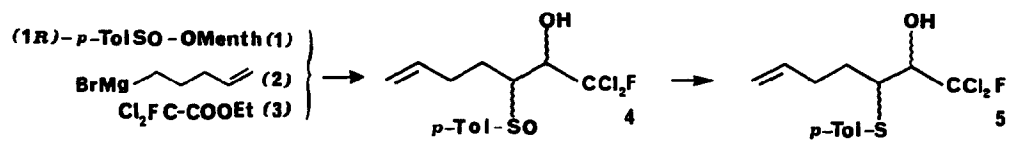
**Abstract:** *gem-Chlorofluorocyclohexanols* **8** *bearing a methyl and a p-tolylsulphinyl substituent have been obtained in optically pure form by radical cyclization of the corresponding halo-alkenes* **4**. *Reductive dechlorination of both (6R)- and (6S)-***8** *gave fluoroderivative (6R)-***9**, *which through functional group elaborations gave the hydroxyfluoro- and trihydroxyfluoro-cyclohexane derivatives* **12** *and* **15**.

As part of our ongoing program on the synthesis of optically pure fluorinated heterocycles and carbocycles[2] we were interested in preparing selectively fluorinated highly hydroxylated cyclohexanes related to *pseudo*-sugars. Because of conformational resemblance to the parent sugars, those compounds may act as substrates for specific enzymes and thus exhibit interesting biological properties[3]. Recently we reported on the synthesis of a few *gem*-difluorocyclohexanes, isolated in optically pure form[4], and of some 2,4-disubstituted-3,3-difluorotetrahydrofurans[5], obtained by intramolecular trapping of difluoroalkyl radicals generated through the tributyltin hydride method respectively from 1-chloro-1,1-difluorohept-6-en-2-ols and allyl ethers of 1-chloro-1,1-difluoropropan-2-ols, all bearing a sulphinyl group as a chiral auxiliary.

We thought that 1,1-dichloro-1-fluoro olefins 4 could be prepared and transformed into chlorofluorocyclohexane derivatives 8 through the same radical-mediated cyclization procedure. A wide range of optically active fluorinated products would arise from those versatile intermediates by properly elaborating the different functionalities.

In the present paper we report preliminary results on the subject. The open-chain precursors 4 have been synthesized from (1*R*)-menthyl sulphinate (1), pent-1-en-5-yl magnesium bromide (2) and ethyl dichlorofluoroacetate (3) through a reaction sequence already described for similar products[6] (Scheme 1).

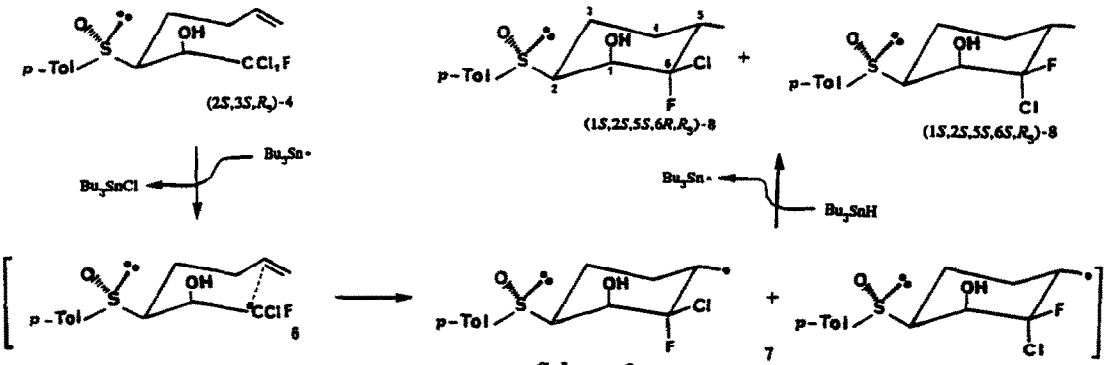



**Scheme 1**

Single diastereoisomers have been isolated in optically pure form by flash chromatography and the absolute configurations at the hydroxy-bearing carbons have been established through $^1$H NMR analyses of the esters of the corresponding thio derivatives *5* with (*R*)- and (*S*)-phenylpropionic acids[7].

(2*S*,3*S*,$R_S$)-4 Was submitted to radical promoted cyclization with tributyltin hydride and azobisisobutyronitrile in

oxygen-free benzene[8]. The required energy for bond breaking was supplied by heating (benzene at reflux) or by irradiating (mercury discharge lamp with significant emission at 350 nm). Preferential generation of free radical intermediate 6 (see Scheme 2) occurs *via* selective homolytic cleavage of one of the weaker C-Cl σ bonds by the mild nucleophilic tributyltin radical[8,9]. Electrophilic chlorofluoroalkyl radical attacks intramolecularly the terminal double bond through a chair-like transition state, forming by an *exo* cyclization the primary cyclohexylmethyl radicals 7. Hydrogen abstraction from a tributyltin hydride molecule gives final products 8 and a stannyl radical which starts a new cycle of radical reactions.




**Scheme 2**

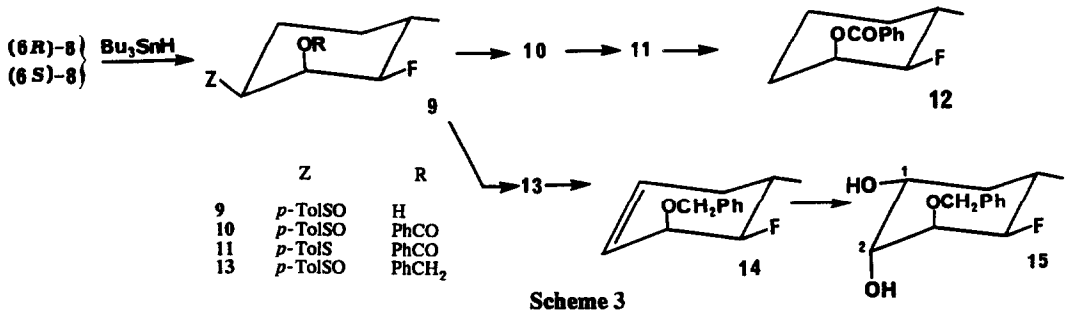
The product compounds 8 still contain a chlorine atom and could undergo further reaction in the presence of stannyl radicals. However it is known that the reactivity of halogen atoms competing towards abstraction by stannyl radicals reflects the bond energies at the possible abstraction sites. In our case the chlorine in substrate 4, activated by the two adjacent halogens, is more reactive than the chlorine present geminally to the fluorine in cyclohexane derivatives 8, and of course much more reactive than fluorine in both substrate 4 and products 8. The difference in reactivity between halogens and the efficient propagation steps in the single chain reaction provided in Scheme 2 make it possible to efficiently transform substrate 4 into desired products 8, thus avoiding secondary reactions. Indeed, when 1.2 molar ratio of tributyltin hydride is used and the reaction is quenched immediately after the substrate (2*S*,3*S*,$R_S$)-4 has disappeared (tlc monitoring), (1*S*,2*S*,5*S*,6*R*,$R_S$)-8 and (1*S*,2*S*,5*S*,6*S*,$R_S$)-8 could be isolated in pure form in about 60% yield[10]

It can be noted that only two of the four possible diastereoisomers formed during cyclization. The exclusive formation of compounds (5*S*)-8, having the methyl equatorially disposed, may be attributed to the fact that in the reaction intermediate 1,3-diaxial interaction between incipient methyl radical and hydroxyl groups is avoided, thus allowing a better electronic interaction between the radical and the π bond[11]. The preference for equatorially *versus* axially disposed fluorine is on the contrary quite small [(6*S*)-8:(6*R*)-8 about 2.0 to 1.0]. No significant differences in yields and diastereoisomers ratio were noticed when using photolytically *versus thermally induced reactions.*

Both diastereoisomeric *gem*-chlorofluorocyclohexanes 8 can be reductively dechlorinated under the same reaction conditions used for the cyclization process (AIBN, tributyltin hydride). Reductive dechlorination of (6*S*)-8 isomer gives exclusively (6*R*)-9 with retention of configuration. On the contrary dechlorination of (6*R*)-8 is quite slow and gives the same (6*R*)-9 epimer with neat inversion of configuration[12]. The corresponding (6*S*)-9 could be detected only in small amount by NMR analysis of the crude product of the reaction[13]. These observations are quite interesting, and consequently (1*R*,2*S*,5*S*,6*R*,$R_S$)-6-fluoro-5-methyl-2-[(4-methylphenyl)sulphinyl]cyclohexan-1-ol (9) was obtained as the only product of the reaction from the open-chain substrate (2*S*,3*S*,$R_S$)-4, when a two molar excess of tributyltin hydride was used for a longer reaction time, formally by a completely stereoselective process.

Some functional group elaborations on compound 9 are reported on Scheme 3. The chiral auxiliary was removed reductively as follows: the hydroxy group was protected through benzoylation to give 10, which was firstly deoxygenated at sulphur (11), then submitted to Raney-Nickel treatment to give (1*S*,2*R*,3*S*)-1-benzoyloxy-2-fluoro-3-methylcyclohexane (12). Thermal elimination of the chiral auxiliary on benzyl derivative 13 (ethylene glycol, reflux, 5 h) gave the (1*S*,5*S*,6*R*)-1-benzyloxy-6-fluoro-5-methylcyclohex-2-ene (14) which, upon dihydroxylation with trimethylamine-N-oxide in the presence

of catalytic amounts of osmium tetroxide[14], gave (1*R*,2*R*,3*S*,4*R*,5*S*)-3-benzyloxy-4-fluoro-5-methylcyclohexan-1,2-diol (15); the latter compound can be considered a 5,6-dideoxy hexose having the ring oxygen replaced by the CHF grouping which, along with the $CF_2$ one, constitutes the best isoster and isopolar replacement for oxygen to be used in biologically active molecules[15].

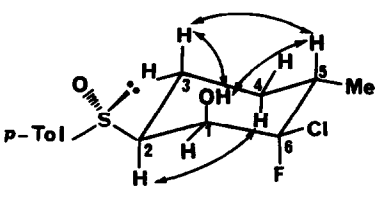



| | Z | R |
|---|---|---|
| 9 | *p*-TolSO | H |
| 10 | *p*-TolSO | PhCO |
| 11 | *p*-TolS | PhCO |
| 13 | *p*-TolSO | $PhCH_2$ |

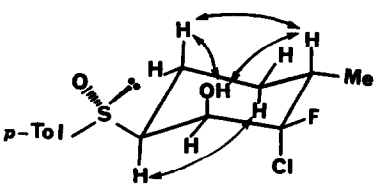
**Scheme 3**

**Structural and Conformational Determination.** The structure, relative configuration and preferred conformation of the cyclic compounds reported below followed from the analysis of the corresponding $^1H$, $^{13}C$ and $^{19}F$ NMR spectra and NOE difference experiments, the absolute configuration at C-1 for compounds **8** deriving from that established for the precursor (2*S*,3*S*,$R_S$)-**4**.

| Product | M.p., °C | Crystallization solvent | $[\alpha]_D^{20}$ (*c*, $CHCl_3$) | $^{19}F$ NMR chemical shifts (ppm) |
|---|---|---|---|---|
| (2*S*,3*S*,$R_S$)-**4** | liquid | | +57.4 (0.9) | -65.65 (F-1) |
| (2*S*,3*S*)-**5** | liquid | | -45.2 (0.8) | -64.85 (F-1) |
| (1*S*,2*S*,5*S*,6*S*,$R_S$)-**8** | 210-211 | ethyl acetate | +112.7 (0.7) | -116.01 (F-6) |
| (1*S*,2*S*,5*S*,6*R*,$R_S$)-**8** | 168-170 | diisopropyl ether | +97.3 (0.7) | -130.12 (F-6) |
| (1*R*,2*S*,5*S*,6*R*,$R_S$)-**9** | 190-192 | diisopropyl ether | +120.0 (0.7) | -190.71 (F-6) |
| (1*S*,2*R*,3*S*)-**12** | liquid | | +58.1 (1.2) | -189.50 (F-2) |
| (1*S*,5*S*,6*R*)-**14** | liquid | | +173.1 (0.2) | -196.44 (F-6) |
| (1*R*,2*R*,3*S*,4*R*,5*S*)-**15** | 63-65 | pentane | -16.2 (0.5) | -202.90 (F-4) |




(1*S*,2*S*,5*S*,6*R*,$R_S$)-**8**




(1*S*,2*S*,5*S*,6*S*,$R_S$)-**8**

**Figure**

For the C-6 epimers **8**, the magnitude of the vicinal coupling constants observed between H-2, assumed as α, and H-3β, and H-4α and H-5β (12-14 Hz) points to a *trans* diaxial configuration for each pair of protons while the couplings of 2.2 and 2.3 Hz exhibited by the axially disposed H-2α and H-1α require a *cis* orientation. The NOEs observed between H-2α and H-4α (2-3%) and H-3β, H-5β and OH-1 (1-5%) confirmed the above findings indicating that both the epimers **8** preferentially adopt the chair-like conformations shown in the Figure. The values of 30.5 and 7.2 Hz observed for the coupling constants between F-6 and H-5β for the C-6 epimers **8** are consistent with axial-axial and axial-equatorial interactions thus allowing the assignment of the chirality at C-6 as *R* and *S*, respectively. The absolute configuration at C-6 for the dechlorinated isomer (6*R*)-**9** was assigned as *R* since the value of 10.7 Hz observed for the coupling between H-5β and H-6α indicates a *trans* relationship between these protons. Finally, the absolute configuration at the two hydroxylated carbons C-1 and C-2 for compound **15** was established as *R,R* since the coupling of 3.2 Hz observed between H-1β and H-2β is indicative of a *cis* relationship, being H-1β axially disposed in the preferred chair conformation shown in Scheme 3 because of a coupling of 10.0 Hz with H-6α.

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