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Asymmetric Synthesis of Trisubstituted *gem*-Difluorocyclohexanes by Intramolecular Trapping of Difluoroalkyl Radicals.

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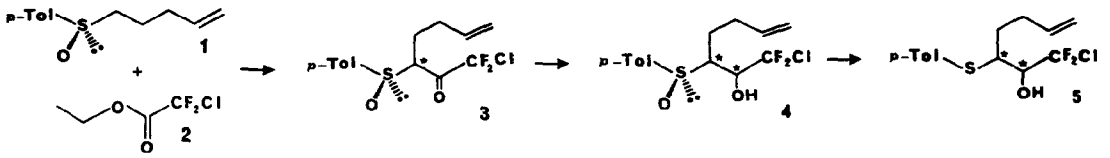
Abstract: *gem-Difluorocyclohexanols* **8** *bearing a methyl and a p-tolyl-sulphinyl substituent have been synthesized in optically pure form by intramolecular trapping of difluoroalkyl radicals on terminal double bonds. The radical intermediates have been generated by the tributyltin hydride method from 1-chloro-1,1-difluoro-3-[(4-methylphenyl)sulphinyl]hept-6-en-2-ols* (**4**), *obtained by acylating (R)-p-tolyl-ω-pentenyl sulphoxide* (**1**) *with ethyl chlorodifluoroacetate* (**2**) *and by reducing the carbonyl of the* β*-ketosulphoxide intermediate* **3**.

Chiral sulphoxides are versatile synthons which can be transformed to a large variety of functionalized products, and have been widely used in asymmetric synthesis[1]. As a part of a program directed towards developing an asymmetric approach to fluorosubstituted organic molecules we have prepared building blocks already possessing fluorine atoms and a sulphinyl group as chiral auxiliary[2]. Several optically pure fluorosubstituted and poly-functionalized open-chain compounds and a number of oxygen heterocycles have been obtained by properly elaborating those synthons[3]. In order to have access to highly functionalized and selectively fluorinated carbocyclic compounds in optically pure form we though that radical reactions on appropriate fluorosulphinyl chirons could be used. In fact it is known that cyclopentane and cyclohexane ring systems form predominantly from 5-hexenyl and 6-heptenyl radicals[4]. Therefore the chlorodifluoro compounds **4** and **5**, which could be useful substrates for generating difluoroalkyl radicals by halogen abstraction and for testing the asymmetric induction in radical promoted cyclizations to fluorosubstituted cyclohexanes[5], have been prepared as reported on Scheme 1.

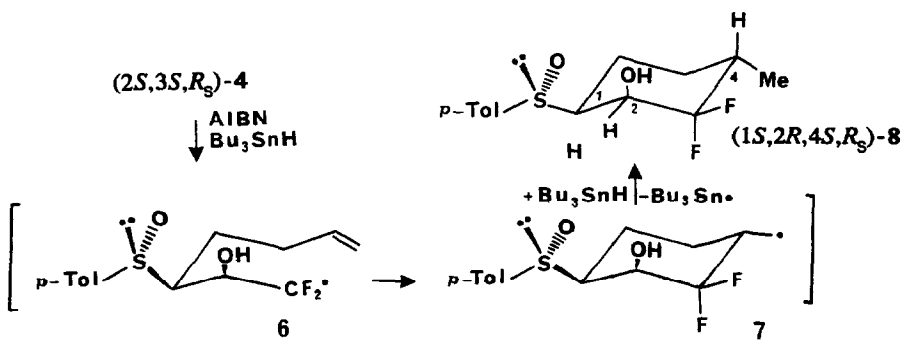
The lithium derivative of (*R*)-(4-methylphenyl)pent-4-en-5-yl sulphoxide (**1**), prepared following the Andersen procedure, was acylated with ethyl chlorodifluoroacetate (**2**) and gave 1-chloro-1,1-difluoro-3-[(4-methylphenyl)sulphinyl]hept-6-en-2-one (**3**) in fair yields but as a mixture of the keto and hydrate forms of the two ($3R,R_S$)- and ($3S,R_S$)- epimers. The crude β-ketosulphoxides **3** were reduced with sodium borohydride in methanol to give a mixture of the corresponding secondary alcohols **4**[6]. On flash chromatography of the reaction mixture ($2R,3R,R_S$)-1-chloro-1,1-difluoro-3-[(4-methylphenyl)sulphinyl]hept-6-en-2-ol (**4**) and the ($2S,3S,R_S$)-**4** epimer were separated in optically pure form by eluting with cyclohexane/ethyl acetate mixtures, while the ($2R,3S,R_S$)-**4** epimer was obtained by

eluting with chloroform/ethyl acetate[7]. The absolute configuration at the hydroxy-bearing carbon atom of the alcohols **4** was established through ^{1}H NMR analysis of the esters obtained by reacting the corresponding sulphenyl alcohols **5** with (*R*)- and (*S*)-2-phenylpropionic acids, as already done for related compounds[8,9]. The corresponding 1-chloro-1,1-difluoro-3-[(4-methylphenyl)sulphenyl]hept-6-en-2-ols (**5**)[10], having the (2*R*,3*R*), (2*S*,3*S*), and (2*R*,3*S*) configurations, were obtained in nearly quantitative yields by deoxygenating the corresponding sulphinyl derivatives **4** to the sulphur atom with sodium iodide and trifluoroacetic anhydride[11].



Scheme 1

Chlorodifluoro compounds **4** and **5** are suitable substrates for radical chemistry. Difluoroalkyl radicals can be easily generated by the tributyltin hydride method, because, as already known[12], the carbon-chlorine bond is quite reactive toward the nucleophilic tributyltin radical, and even more when electron-withdrawing groups are present close to it, as in the present case, while carbon-fluorine bonds are totally inert. The individual steps for the chain reaction when substrates **4** are submitted to radical cyclization (tributyltin hydride and azobisisobutyronitrile in oxygen-free benzene at 70°C) are reported on Scheme 2.



Scheme 2

Tributyltin radical selectively abstracts the chlorine atom from substrates **4** affording difluoroalkyl radical **6**, which attacks the terminal double bond in an *exo*-cyclization, forming the primary cyclohexylmethyl radical **7**. Intramolecular trapping by tributyltin hydride gives the final products **8** and tributyltin radical, which starts a new cycle. The reaction goes to completion over a period of about five hours at 70°C. Under those reaction conditions no racemization of the sulphinyl group, or extensive β-elimination occurred. Furthermore the cyclization step is fast enough in order to avoid reduction of the intermediate difluoroalkyl radical **6** by tributyltin hydride.

It is noteworthy that asymmetric induction for cyclization of sulphinyl heptenols (2*R*,3*R*,R_S)-**4** and (2*S*,3*S*,R_S)-**4** is very high; in fact cyclohexanes (1*R*,2*S*,4*R*,R_S)-**8** and (1*S*,2*R*,4*S*,R_S)-**8** were the only diastereoisomers isolated from the reactions. The high stereoselectivity may be explained by a particularly favorable geometry on the transition state, in which the incipient cyclohexane ring shows the bulkier polar

sulphinyl substituent in quasi-equatorial position, and contemporary the vicinal hydroxy group in quasi-axial position. That spatial arrangement is a particularly favourable one for vicinal sulphinyl and hydroxy substituents on six-membered ring systems[13]. Thus the methyl group would be equatorially disposed in order to avoid 1,3-diaxial interaction with the preexisting hydroxyl substituent. On the contrary, cyclization of the sulphinyl heptenol (2*R*,3*S*,R_S)-**4** afforded a 62 to 38 mixture of the two possible diastereoisomers, as a consequence of the absence of 1,3-diaxial interactions in an incipient cyclohexane ring having both vicinal substituents in equatorial position.

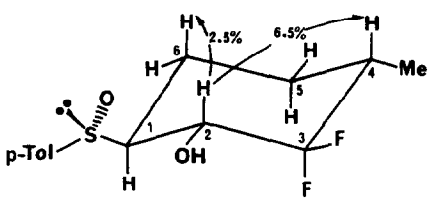
Yields, physical and selected ^{19}F NMR data of products **8** are reported on Table.

Table. Asymmetric cyclization of compounds **4**

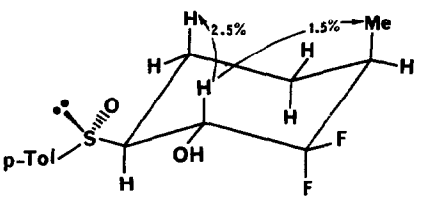
Substrate	Product	Yields (%)	$[\alpha]_D^{25}$	M. p. (°C) (solvent)[a]	Selected ^{19}F NMR data (δ_F, ppm)	
					F_{eq}	F_{ax}
(2*R*,3*R*,R_S)-**4**	(1*R*,2*S*,4*R*,R_S)-**8**	41	+245.1 (*c* 1.0, $CHCl_3$)	185-187 (A/B)	-113.6	-125.4
(2*S*,3*S*,R_S)-**4**	(1*S*,2*R*,4*S*,R_S)-**8**	52	+133.7 (*c* 1.0, $CHCl_3$)	204-205 (A/B)	-113.08	-125.01
(2*R*,3*S*,R_S)-**4**	(1*S*,2*S*,4*S*,R_S)-**8**	49	+217.3 (*c* 1.1, $CHCl_3$)	176-177 (B)	-113.94	-135.77
	(1*S*,2*S*,4*R*,R_S)-**8**	30	+190.5 (*c* 0.7, $CHCl_3$)	173-174 (B)	-113.24	-116.22

[a]Crystallization solvent: A, *n*-hexane; B, diisopropyl ether.

The structure and the preferred conformation of the title compounds were established by detailed ^1H, ^{13}C, and ^{19}F NMR studies, the relative configurations at C-2 and at the newly formed C-4 carbon atoms being determined by NOE difference experiments (see Figure).



(1*S*,2*S*,4*S*,R_S)-**8**



(1*S*,2*S*,4*R*,R_S)-**8**

Figure. Selected NOEs and preferred conformations for (1*S*,2*S*,4*S*,R_S)- and (1*S*,2*S*,4*R*,R_S)-**8** epimers.

The difluorocyclohexanols **8** are currently subjected to a number of transformations to investigate their synthetic potential. The results of this study will be published in due time.

References and Notes

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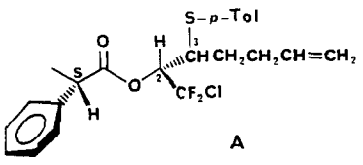
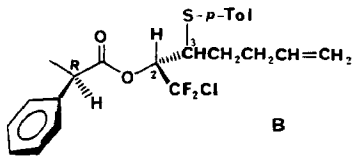
6. For a discussion on the asymmetric induction of the reduction of α-substituted-β-ketosulphoxides and of β-ketosulphoxides in the hydrate form see: Bravo, P., Piovosi, E., Resnati, G., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1201; Bravo, P., Frigerio, M., Resnati, G., *Synthesis*, **1988**, 955.
7. (2*R*,3*R*,R_S)-1-chloro-1,1-difluoro-3-[(4-methylphenyl)sulphinyl]hept-6-en-2-ol [(2*R*,3*R*,R_S)-**4**], liquid, $[\alpha]_D^{25}$ +148.7 (*c* 0.8, $CHCl_3$); (2*S*,3*S*,R_S)-**4**, liquid, $[\alpha]_D^{25}$ +74.6 (*c* 1.0, $CHCl_3$); (2*R*,3*S*,R_S)-**4**, $[\alpha]_D^{25}$ +109.6 (*c* 1.3, $CHCl_3$).
8. a) Bravo, P., Ganazzoli, F., Resnati, G., De Munari, S., Albinati, A., *J. Chem. Res. (S)*, **1988**, 216, *ibid.* (*M*), **1988**, 1701; b) Helmchen, G., *Tetrahedron Lett.*, **1974**, 1527; Helmchen, G., Schmierer, R., *Angew. Chem., Int. Ed. Engl.*, **1976**, *15*, 703.
9. In the esters **A**, obtained from (*S*)-2-phenylpropionic acid and sulphenyl secondary alcohols (2*R*,3*S*)- and (2*R*,3*R*)-**5**, the chemical shifts of the protons of the CH_2=$CHCH_2CH_2CH$ fragment were at higher fields ($\Delta\delta$ = 0.05-0.40) than the corresponding protons of the esters **B**, obtained from (*R*)-2-phenylpropionic acid. This is due to the shielding effect that the phenyl ring of the esterifying acid exerts on the facing protons of the secondary alcohol, according to the preferred conformations shown below. Therefore the (*R*) absolute configuration was assigned to the secondary alcohol. The opposite was true for the esters of alcohols having the (*S*) absolute configuration at C-2.



A



B

10. (2*R*,3*R*)-1-chloro-1,1-difluoro-3-[(4-methylphenyl)sulphenyl]hept-6-en-2-ol [(2*R*,3*R*)-**5**], liquid, $[\alpha]_D^{25}$ +21.5 (*c* 1.0, $CHCl_3$); (2*S*,3*S*)-**5**, liquid, $[\alpha]_D^{25}$ -22.4 (*c* 1.0, $CHCl_3$); (2*R*,3*S*)-**5**, liquid, $[\alpha]_D^{25}$ -22.7 (*c* 1.0, $CHCl_3$).
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12. Tedder, J. M., *Tetrahedron*, **1982**, *38*, 313.
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