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EPC Synthesis of *gem*-Difluorocyclopentane Derivatives§

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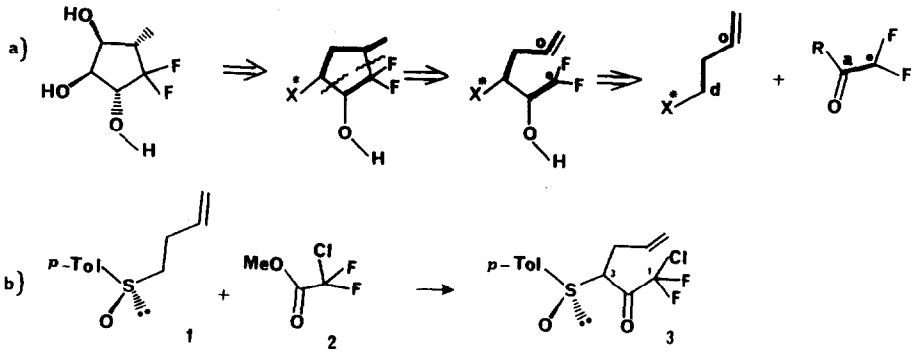
Abstract: *gem-Difluorooyclopentane derivatives were obtained in optically pure form by thermal or photochemical radical cyclization of the corresponding haloalkenes. Reductive or thermal elimination of the chiral auxiliary and appropriate elaborations afforded some difluoromethyl-cyclopentanols and -cyclopentantriols. The structure of the compounds was elucidated on the basis of ^{1}H, ^{13}C and ^{19}F NMR data and of NOE difference experiments.*

Introduction

The synthesis of organofluorine compounds in optically pure form is becoming increasingly important [1] in view of their growing role in medicinal[2] and agricultural[3] chemistry, and for the construction of novel ferroelectric devices[4]. Introduction of fluorine at a late stage in synthesis often produces technical and economic problems[5]. Although fluorine itself is an unexpensive available element it is too reactive to be used on sensitive functionalized molecules. On the other hand fluorinating agents[6], like popular diethylamino sulfur trifluoride (DAST), are quite expensive and not devoid of selectivity problems.

A different approach to the synthesis of complex organofluorine compounds starts from easily available fluorinated molecules, and fluorine atoms are held in place through all stages of the synthetic plan. Our latest achievements in the asymmetric synthesis of optically pure fluorinated molecules by the second approach provided new routes to mono- and geminally di-fluorinated tetrahydrofuran and cyclohexane derivatives[7]. The key step in the construction of those compounds consists in a free radical cyclization of fluoroalkyl radical intermediates generated from mixed haloalkyl groups deriving from the corresponding methyl or ethyl esters of halogenated acetic acids as inexpensive fluorinated starting materials.

In the present paper we wish to report the asymmetric synthesis of a number of *gem*-difluorocyclopentane derivatives whose carbon backbone is obtained by linking together, *via* ionic and radical carbon-carbon forming reactions, two fragments like those outlined in the retrosynthetic Scheme 1a[8].



Scheme 1

Specifically, the ω-sulfinyl-1-butene **1** (see Scheme 1b) furnishes the three-carbon fragment having in place the chiral auxiliary (**X***) needed for transferring the chirality on carbons, a potentially donor (**d**) carbon, and a radical accepting carbon (**o**) for the connections[9]. The methyl chlorodifluoroacetate **2** gives the remaining two-carbon unit having the geminally placed fluorine atoms along with an "acceptor" carbon atom (**a**), and a potentially radical donor carbon atom (•). A difluorinated chiron is furnished first by assembling the two fragments through the ionic reaction, *i.e.* the acylation of the α-lithium derivative of the ω-sulfinyl-1-butene **1** by methyl chlorodifluoroacetate **2**. The transfer of chirality from the sulfinyl chiral auxiliary group to carbon follows by the reduction of the carbonyl of the β-ketosulfoxide **3**. The second connection to form the cyclopentane ring is obtained by generating a difluoroalkyl radical (through chlorine abstraction by the tributyltin method), which attacks intramolecularly the olefinic double bond. Finally some functional group elaboration on the sulfinyl compounds allows to isolate optically pure *gem*-difluoro monohydroxy-cyclopentane and *gem*-difluoro vicinal trihydroxy-cyclopentane derivatives.

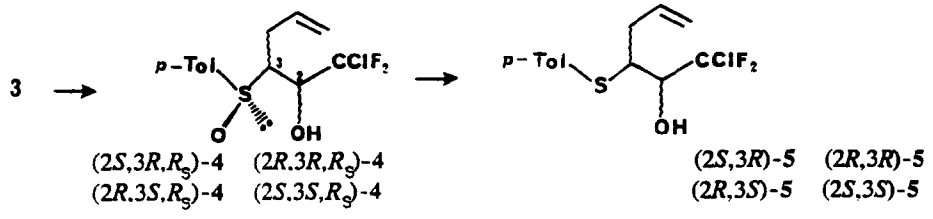
Results and Discussion

The (*R*)-4-[(4-methylphenyl)sulfinyl]but-1-ene (**1**) was prepared from (-)-(1*R*,2*S*,5*R*)-menthyl 4-methylphenyl-(*S*)-sulfinate and but-1-ene-4-magnesium bromide by the Mikolajczyk improved procedure of the Andersen synthesis[10,11] in 98% yield.

The lithium derivative of (**1**), obtained with lithium diisopropylamide (LDA) in tetrahydrofuran (THF), was acylated with methyl chlorodifluoroacetate (**2**). The ketone (**3**) was obtained in high yield as a mixture of the two (3*R*,R_S)- and (3*S*,R_S)-**3** diastereoisomers both in their keto form.

Because of their lability the two diastereoisomers could not be isolated as optically pure compounds by chromatographic separation. The crude mixture was reduced[12] with sodium borohydride in methanol/aqueous ammonia or with diisobutylaluminium hydride in tetrahydrofuran, and the four diastereoisomeric secondary alcohols (2*S*,3*R*,R_S)-**4**, (2*R*,3*S*,R_S)-**4**, (2*R*,3*R*,R_S)-**4** and (2*S*,3*S*,R_S)-**4** (Scheme 2) were separated by two successive flash chromatographies on silica gel by using chloroform/ethyl acetate and cyclohexane/ethyl acetate mixtures, giving the following yields of optically pure products: 30.8%, 8.8%, 13.3% and 17.2%, respectively, when sodium borohydride was used, and 0.7%, 3.9%, 44.1% and 29.4%, respectively, when diisobutylaluminium hydride was used as the reducing agent.

The absolute configuration at the hydroxy-bearing carbon atom of the four diastereoisomeric alcohols **4** was determined by ^{1}H NMR studies carried out on the esters **6** obtained by reacting the corresponding sulfenyl alcohols **5** with (*R*)- and (*S*)-2-phenylpropionic acids[13], while the configuration at carbon C-3 follows from that established onward for the corresponding cyclic compounds.

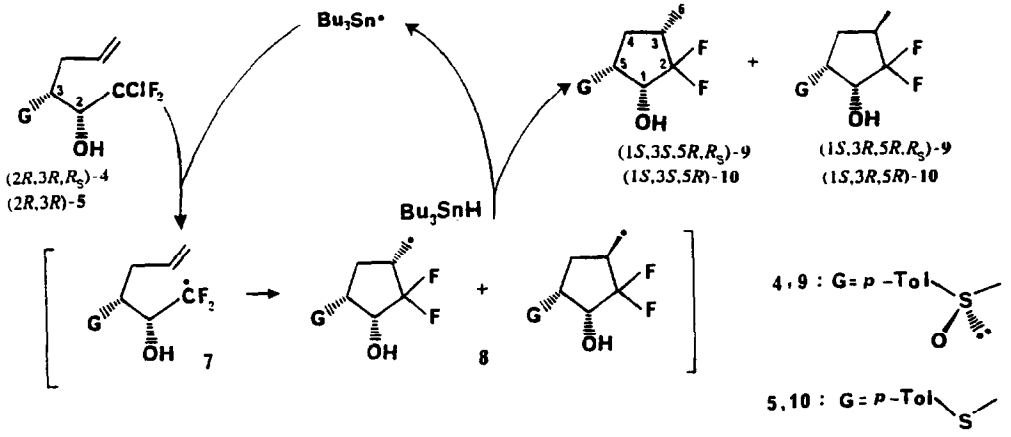


Scheme 2

The required (2*S*,3*R*)-; (2*R*,3*S*)-, (2*R*,3*R*)-, and (2*S*,3*S*)-**5** alcohols were prepared in nearly quantitative yields by deoxygenating with sodium iodide and trifluoroacetic anhydride the sulfur atom of the corresponding sulfinyl derivatives **4**. A couple of PPA esters **6** for all diastereoisomeric alcohols **5** was obtained from the free acids and alcohols by condensation promoted by dicyclohexylcarbodiimide in dichloromethane in the presence of 4-dimethylaminopyridine.

Only the couple of the (2*S*,3*R*,*R*$_S$)- and (2*R*,3*R*,*R*$_S$)-**4** derivatives, having at the two contiguous carbons to be placed inside the cyclic products a different steric relationship which therefore will govern the asymmetric induction of the process, has been submitted to the radical promoted cyclization.

The tributyltin hydride method, the most used one for homolytically abstracting halogens from haloalkyl derivatives, was chosen for generating the difluoroalkyl radical intermediates[14]. The radical chain reaction, outlined on Scheme 3, should take place when azobisisobutyronitrile (AIBN) is used as initiator in a benzene solution of tributyltin hydride. Homolytic dissociation of AIBN followed by hydrogen abstraction from tributyltin hydride generates a tributyltin radical which, through chlorine abstraction from **4**, generates the difluoroalkyl radical intermediate **7** which is trapped intramolecularly by the double bond to



Scheme 3

give the cyclic primary alkyl radicals **8**. Hydrogen abstraction from a second mole of tributyltin hydride gives the final products **9** and a new tin radical which starts a new cycle. The energy required for bond breaking on AIBN initiator was supplied as usual by heating the benzene solution at reflux or much better by irradiating the solution with a mercury discharge lamp with significant emission at 350 nm and keeping the solution cold.

Some observations are pertinent. Because of the high difference in bond energies between C-F and C-Cl bonds, chlorine atoms are abstracted selectively by the mild nucleophilic tributyltin radical. Although experimental values for polar parameters to describe polar effects at radicals are lacking[15], radical intermediates must have electrophilic character because of the two fluorine atoms and probably must be quite pyramidal.

In line with what has been already observed for cyclization of a large number of hex-5-enyl radicals and of some similar substrates having an oxygen substitution for a methylene, the "5-*exo*" pathway was preferred over the "6-*endo*" one[14]. Only cyclopentane derivatives were formed in this case as outlined in Scheme 2, as it was for similar oxygen substituted substrates[7], the two small fluorine atoms having no steric influence on the course of the reaction.

Lower global yields and lower stereodifferentiation were observed when the reaction was started and kept on going by heating at reflux. Thermal elimination of arylsulfenic acid from starting material should be responsible for lower yields. When using photochemical activation the reaction was run at lower temperature, nevertheless it required shorter reaction time to come to the end. Higher global yields of a mixture more rich in the prevailing stereoisomer were thus obtained.

Yields and chemico-physical data for obtained compounds are reported on Table 1.

The moderate diastereoselection in favour of (1*S*,3*S*,5*R*,R_S)-**9** and of (1*R*,3*S*,5*R*,R_S)-**9** epimers, having the methyl and the sulfinyl group in a 1,3-*cis* relationship (respectively of 4.2 to 1 and 5.6 to 1)

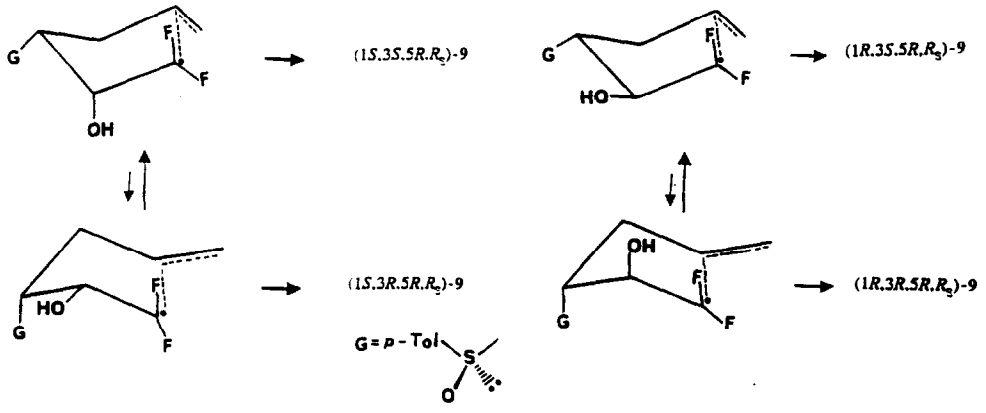
Table 1.- Yields and chemico-physical data for compounds **9**, **12**, **15** and **16**

Substrate	Yield (%)	$[\alpha]_D^{25}$ (*c*, $CHCl_3$)	M.p.(°C) (*i*-Pr_2O)	R_F (eluents[b], ratio)	R_T (min.)[a]
(1*R*,3*R*,5*R*,R_S)-**9**	11.1	+7.0 (0.4)	120-122	0.35 (A, 45:55)	8.07 (B, 1:1)
(1*R*,3*S*,5*R*,R_S)-**9**	61.9	+146.0 (0.5)	128-130	0.40 (A, 45:55)	12.52 (B, 1:1)
(1*R*,3*R*,5*S*,R_S)-**9**	16.5	+150.0 (0.1)	154-156	0.35 (B, 70:30)	10.33 (B, 2:3)
(1*R*,3*S*,5*S*,R_S)-**9**	69.1	+183.8 (0.5)	160-162	0.30 (B, 70:30)	11.93 (B, 2:3)
(1*R*,3*S*)-**12**	85	-27.6	oil	0.35 (C, 80:20)	
(3*R*,5*S*)-**15**	80	+22.1 (0.3)	oil	0.36 (D, 90:10)	
(1*S*,2*S*,3*R*,5*S*)-**16**	90	+34.8 (0.6)	oil	0.35 (C, 95:5)	

a) flow rate: 1.0 ml/min; b) A, cyclohexane/ethyl acetate; B, hexane/ethyl acetate; C, hexane/diethyl ether; D, pentane/diethyl ether.

may be tentatively explained as follows[16].

Since the addition of alkyl radicals proceeds via an unsymmetrical transition state, in which the incoming radical must approach the olefin along a direction having an angle of about 105°[17] with the C-C bond, the chair like arrangements will be the most favourable ones for an early transition state when no large steric effects would arise from 1,3-diaxial interactions. That is the case for intermediates arising from both the epimers submitted to the reaction as shown below:



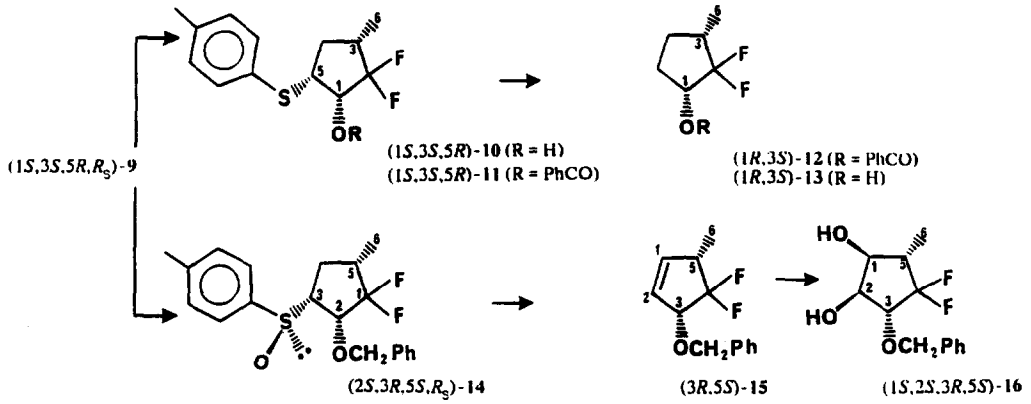
Therefore between the two atom arrangements considered for each stereoisomer, the lower in energy and consequently the most populated one should be the one having the larger sulfinyl substituent in a pseudo-equatorial position.

The arylthio derivative (2*S*,3*R*)-**5** was also subjected to cyclization under thermal conditions. The corresponding cyclic thio derivatives **10** were obtained in 69% overall yield but as a mixture in nearly equimolar ratio of (1*R*,3*R*,5*R*)- and (1*R*,3*S*,5*R*)-**10**, whose structures were determined by comparison of their ^{1}H and ^{19}F NMR spectra with those of analogous compounds obtained by deoxygenating at sulfur the corresponding sulfinyl derivatives **9** (see Experimental).

Finally we completed this study with a brief survey of the potential use of the reactivity of the sulfinyl group for producing differently functionalized and sulfur free fluorinated cyclopentane derivatives. For this purpose among the typical reactions of sulfoxides we chose the following: a) reductive elimination to generate a methylene group, and b) thermal elimination to introduce a double bond in the ring, which could be quite useful for introducing new functional groups.

The results, useful as synthetic transformations, are reported on Scheme 4.

The chiral auxiliary was removed from (1*S*,3*S*,5*R*,R_S)-**9** by deoxygenating the sulfur with trifluoroacetic anhydride and sodium iodide, thus obtaining the alcohol (1*S*,3*S*,5*R*)-**10**, by protecting the hydroxyl group through benzoylation and by submitting (1*S*,3*S*,5*R*)-**11** to reductive desulfurization in the presence of Raney-nickel. (1*R*,3*S*)-2,2-Difluoro-3-methylcyclopentan-1-ol benzoate **12** was obtained in 70% overall yield from (1*S*,3*S*,5*R*,R_S)-**9**. Alkaline hydrolysis afforded the deprotected alcohol (1*R*,3*S*)-**13** as a volatile compound.



Scheme 4

On the other hand (3*R*,5*S*)-3-benzyloxy-4,4-difluoro-5-methylcyclopent-1-ene **15** was obtained in 51% overall yield as the sole product when an ethylene glycol solution of benzylderivative (2*S*,3*R*,5*S*,R_S)-**14** was heated at reflux for five hours. From the many functional group elaborations of the allylic portion of a cyclic product known for their high diastereoselectivity, the dihydroxylation with trimethylamine-N-oxide in the presence of catalytic amounts of osmium tetroxide was chosen and performed on (3*R*,5*S*)-**15**. The (1*S*,2*S*,3*R*,5*S*)-3-benzyloxy-4,4-difluoro-5-methylcyclopentan-1,2-diol **16** was obtained in 90% yield.

In summary we have demonstrated that the approach to enantiomerically pure selectively fluorinated and polyfunctionalized carbocycles through the building up of the rings from small fragments, one of which contains the fluorine atom and a second the chiral sulfinyl auxiliary group, through condensation and radical promoted cyclization, is feasible. The approach shows good potential for use in the synthesis of fluoro analogs of biologically interesting molecules, and provides a new route from quite simple starting materials.

Structural assignments

The structure elucidation of the title compounds was based on the ^1H, ^{13}C and ^{19}F NMR data reported in Tables 2 and 3 and in Experimental, and on ^1H-{^1H} and ^1H-{^{19}F} NOE difference experiments.

The four diastereoisomeric cyclopentanols **9** presented signals which we readily assigned on the basis of chemical-shift criteria and coupling constant analysis to a -C(1)HOH-CH(SO-*p*Tol)-CH $_2$C(3)HMe moiety. The two remaining fluorine atoms, which are geminally coupled[18] ($^2J_{F,F}$ = 223.5-237.5 Hz), showed in the ^1H NMR spectra coupling constants ranging between 2.8 and 25.3 Hz[19] with H-1 and H-3 and in the ^{13}C NMR spectra ranging between 20.5 and 36.5 Hz[20] with C-1 and C-3 indicating vicinal and geminal interactions, respectively. These data imply the presence in each compound of a $>C(2)F_2$ group whose carbon is linked to C-1 and C-3 to form a five-membered ring. The absolute configuration at C-1

derived from that previously assigned in the precursor alcohols **4** while the chirality at C-5 and at the newly-formed C-3 stereocentre followed from NOE results.

In compound (1*R*,3*S*,5*R*,R_S)-**9** the NOEs observed between H-1, assumed as α in Figure 1, and H_3-6 (1.5%) and H-3 and H-5 (1.5%) permitted the assignment of the chirality at C-3 and C-5 as *S* and *R* whereas the NOE observed between H-1α and H-3 (2%) in the C-3 epimer (1*R*,3*R*,5*R*,R_S)-**9**, deriving from the alcohol (2*S*,3*R*,R_S)-**4** too, requires that these protons are *cis* disposed.

Table 2. Selected ^1H and ^{19}F NMR Chemical Shifts (δ) and Coupling Constants (*J*/Hz) for Compounds 9 in $CDCl_3$.

	1*R*,3*S*,5*R*	1*R*,3*R*,5*R*	1*S*,3*S*,5*R*	1*S*,3*R*,5*R*	*J*	1*R*,3*S*,5*R*	1*R*,3*R*,5*R*	1*S*,3*S*,5*R*	1*S*,3*R*,5*R*
H-1	4.50	4.56	4.46	4.43	1,5	5.1	7.2	5.0	4.6
H-3	2.37	2.35	2.33	2.80	3,4α	10.7	8.9		10.9
H-4α	1.40	2.20	1.85	2.25				16.0[a]	
H-4β	1.88	1.81	1.85	1.28	3,4β	7.8	11.5		7.6
H-5	3.12	3.02	3.10	3.21	3,6	6.8	6.6	7.2	7.0
H_3-6	1.09	1.07	1.19	1.16	4α,4β	13.4	13.6	b	13.8
OH-1	3.06	2.05	4.75	5.03	4α,5	9.8	4.4		8.0
F-2α	-119.39	-118.48	-127.09	-124.98				19.3[c]	
F-2β	-118.17	-133.79	-100.71	-122.45	4β,5	8.9	11.0		10.2
	7.57	7.53	7.61	7.62	Fα,Fβ	234.0	223.5	237.5	234.0
p-Tol	7.35	7.35	7.36	7.36	Fα,1	12.4	6.5	2.8	b
	2.43	2.42	2.43	2.43	Fα,3	18.0	6.5	6.5	8.8
					Fα,6	1.0	≈0	2.0	≈0
					Fβ,1	5.1	15.8	6.4	3.8
					Fβ,3	12.7	23.6	22.4	25.3
					Fβ,6	≈0	0.8	≈0	0.8

[a] $J_{3,4\alpha} + J_{3,4\beta}$; [b] not assigned; [c] $J_{4\alpha,5} + J_{4\beta,5}$.

The NOEs observed between H-1, assumed as β in Figure 1, and H-3 (1%) and H-3 and H-5 (1%) in compound (1*S*,3*S*,5*R*,R_S)-**9**, deriving from the alcohol (2*R*,3*R*,R_S)-**4**, indicated that these protons are on the same β-face of the ring thus allowing the assignment of the chirality at C-3 and C-5 as *S* and *R*, respectively. In the last diastereoisomer (1*S*,3*R*,5*R*,R_S)-**9**, the NOEs observed for H-5β (2%) and H_3-6 (1%) upon the irradiation of the fluorine atom at δ_F -122.45 ppm and the NOE observed between the fluorine atom at δ_F -124.98 ppm and H-3 (2%) suggest that H-5β and H_3-6 are *cis* disposed and that the chirality at C-3 is *R*.

The NMR spectra of the sulfenyl cyclopentanols (1*R*,3*S*,5*R*)-, (1*R*,3*R*,5*R*)- and (1*S*,3*S*,5*R*)-**10** and

of the derivatives **11-16** obtained from (1*S*,3*S*,5*R*,R_S)-**9** were in accord with the proposed structures.

For compound **16** ^1H-{^{19}F} NOE experiments permitted to distinguish, as in (1*S*,3*R*,5*R*,R_S)-**9**, between the geminal fluorine atoms and to assign as *S* the absolute configuration of the newly-formed C-1 and C-2 chiral centres. In fact, the NOEs observed for H-1 (1%), H-2 (2%) and H_3-6α (1%), but not for H-5β, upon irradiation of the fluorine atom at δ_F -123.24 ppm indicated that these atoms are on the same α-face of the molecule. As expected, H-3β and H-5β underwent NOE enhancements (3 and 5%) upon irradiation of the *cis* disposed fluorine atom at δ_F -103.77 ppm, the *trans* disposed 6α-methyl protons presenting a weaker NOE (≤ 0.2%).

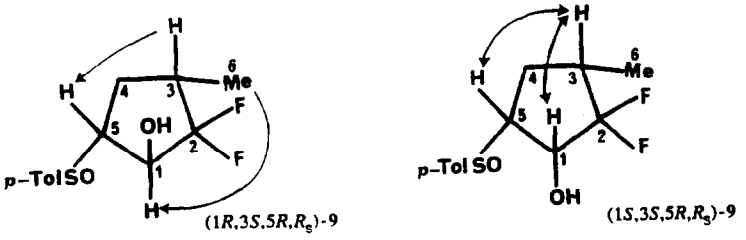


Figure 1

Table 3. Selected C NMR Data for Compounds **9** and **10** in CDCl

	9			**10**		
	1*R*,3*S*,5*R*	1*R*,3*R*,5*R*	1*S*,3*S*,5*R*	1*S*,3*R*,5*R*	1*R*,3*S*,5*R*	1*R*,3*R*,5*R*
C-1	72.58	70.65	73.71	72.74	78.88	78.85
	(33, 23.5)[a]	(27, 20.5)	(36.5, 22.5)	(35, 23)	(31, 21)	(26.5, 20.5)
C-3	37.27	36.07	38.58	35.23	37.63	35.84
	(23, 23)	(22, 22)	(23.5, 22.5)	(23.5, 22.5)	(23, 23)	(22, 22)
C-4	27.96	28.81	30.08	27.66	34.51	34.11
	(6.5, 1.5)	(7, ≈0)	(3.5, 3.5)	(b, b)	(7.5, ≈0)	(6.5, ≈0)
C-5	66.71	63.51	64.17	63.77	48.78	48.34
	(3, 3)	(7, ≈1)	(2.5, ≈0)	(3.5, ≈0)	(5, 2)	(7.2, ≈0)
C-6	11.32	10.84	14.75	10.81	11.81	11.80
	(5.5, 1.5)	(6.5, ≈0)	(7, 4.5)	(9, ≈0)	(7, ≈1)	(8, b)

[a]Values in parentheses refer to $J_{(C,F)}$/Hz. [b]Not assigned.

An inspection of the ^{19}F NMR data of the cyclopentane derivatives **9-16** reveals that the difference of the chemical-shift values of the two geminal fluorine atoms is larger in those compounds having the two substituents vicinal to the fluorine atoms *cis*-disposed ($\Delta\delta_F$ = 15-29 ppm) with respect to the compounds having the two substituents *trans*-disposed ($\Delta\delta_F$ = 1-3 ppm). This can be attributed to the fact that in the former compounds the shielding γ-effects[20] due to *gauche*-like interactions are greater than those due to *trans*-like ones. Moreover, it can be evidenced that the methyl protons exhibited sizeable four-bond coupling constants only with the fluorine atom *cis* disposed ($^4J_{H,F}$ = 0.8-2.5 Hz).

Experimental

^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker CXP 300, or a Bruker AC 250L spectrometer; chemical shifts are in p.p.m. (δ); tetramethylsilane was used as internal standard (δ_H and δ_C 0.00) for ^1H and ^{13}C nuclei, while C_6F_6 was used as internal standard (δ_F -162.90) for ^{19}F nuclei. $[\alpha]_D$ Values were obtained on a Jasco DIP-181 polarimeter. Melting points are uncorrected and were obtained on a capillary apparatus; TLC were run on silica gel Merck $60F_{254}$ plates; column chromatographies were performed with silica gel 60 (60-200 μm, Merck). Run times were determined on a Waters 600E HPLC instrument, using Lichrosorb Si60 (5 μm) (Merck) prepacked columns and ethyl acetate/hexane as HPLC-grade solvents (Merck). Ethyl ether and tetrahydrofuran (THF) were freshly distilled from lithium aluminum hydride and diisopropylamine was distilled from calcium hydride and stored on 4Å molecular sieves; dimethylformamide was stored over molecular sieves (4Å and 13Å); benzene was distilled over calcium chloride and stored over molecular sieves (4Å); in other cases, commercially available reagent-grade solvents were employed without purification.

Synthesis of (R)-4-[(4-Methylphenyl)sulfinyl]but-1-ene (**1**).

4-Bromo-1-butene (66 g, 48.80 mmol) in anhydrous ether (150 ml) was added dropwise to a stirred suspension, in the same solvent (70 ml), of Mg (11.8 g, 48.80 mmol) activated by adding a crystal of iodine. The reaction mixture was stirred for two additional hours, the ether was removed under reduced pressure and anhydrous benzene (800 ml) was added. The benzene solution of the Grignard reagent was cooled to 5-10 °C and a solution of (-)-(1*R*,2*S*,5*R*)-menthyl (*S*)-*p*-toluene sulfinate (71.8 g, 24.40 mmol) in benzene (300 ml) was added dropwise at the same temperature. The mixture was stirred at room temperature for additional 30 min, a saturated aqueous solution of ammonium chloride (300 ml) was added while cooling with an ice-water bath and the pH of the mixture was adjusted to 3 by adding 10 *N* hydrochloric acid. The mixture was extracted with ether (3x400 ml); the combined organic layers were washed with a diluted solution of sodium hydrogen carbonate (2x100 ml), with water (100 ml) and dried over anhydrous sodium sulfate. Solvent removal under reduced pressure gave a residue which, upon flash chromatography on silica gel (eluent: 6:4 hexane/ethyl acetate) gave 46.5 g (98.2% yield) of pure (R)-4-[(4-methylphenyl)sulfinyl]but-1-ene as a yellowish oil. $[\alpha]_D^{20}$+ 20.3° (*c* 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$), δ: 7.6-7.2 (4 H, m, ArH), 5.76 (1 H, m, H-2), 5.06 and 5.03 (2 H, m, H_2-1), 2.85 (2 H, m, H_2-4), 2.43 (3 H, s, CH_3) and 2.6-2.1 (2 H, m, H_2-3).

Synthesis of (3R,R_S)- and (3S,R_S)-1-Chloro-1,1-difluoro-3-[(4-methylphenyl)sulfinyl]hex-5-en-2-one (**3**).

A solution of 4-[(4-methylphenyl)sulfinyl]but-1-ene (**1**) (2.00 g, 10.3 mmol) in dry THF (10 ml) was added dropwise to a stirred solution of lithium diisopropylamide (12.5 mmol) in the same solvent (10 ml). After 3 min, a solution of methyl chlorodifluoroacetate (**2**) (1.77 g, 12.3 mmol) in THF (2 ml) was added dropwise at -65°C and stirring was continued for 5 min. The reaction mixture was then quenched at -65°C by adding a saturated aqueous solution of ammonium chloride (100 ml). The pH was adjusted to *ca.* 3 with 2*N* hydrochloric acid, the layers were separated and the aqueous phase was extracted with ethyl acetate (3x50 ml). The combined organic layers were washed with a saturated aqueous solution of sodium

chloride and dried over anhydrous sodium sulfate. The oily residue, obtained after evaporation of the solvent under reduced pressure, resulted from NMR analysis to be a 3:2 mixture of (3*R*,R_S)- and (3*S*,R_S)-3, both in their keto forms (90% overall yield).

^{1}H NMR ($CDCl_3$), δ: 7.6-7.2 (4 H, m, ArH), 5.65 (1 H, m, H-5), 5.25-5.05 (2 H, m, H_2-6), 4.39 and 4.20 (1 H, dd, *J* = 10.1, 4.0 and 9.6, 4.1 Hz, respectively, H-3), 3.0-2.4 (2 H, m, H_2-4), 2.43 (3 H, br s, ArMe); ^{19}F NMR ($CDCl_3$), δ: -69.6, -70.1 and -69.5, -69.7 (2 F, d, *J* = 162 Hz, F_2-1).

Reduction of the Ketones 3 *to the Corresponding Alcohols (2S,3R,R_S)-, (2R,3R,R_S)-, (2S,3S,R_S)-, and (2R,3S,R_S)-1-Chloro-1,1-difluoro-3-[(4-methylphenyl)sulfinyl]hex-5-en-1-ol* 4.

A cooled suspension (-20°C) of sodium borohydride (0.40 g, 10.57 mmol) in 5 ml of a 9:1 (*v/v*) mixture of MeOH and aqueous NH_3 (30%) was dropped into the mixture of ketones 3 (3.14 g, 10,24 mmol), obtained from the previous reaction, dissolved in the same solvent mixture (20 ml) under nitrogen at -20°C. After stirring for 10 min, a solution of hydrochloric acid was added until pH ≈ 4 was reached. Methanol was evaporated under reduced pressure and the residue was extracted with ethyl acetate (3x50 ml). The combined organic layers were dried over anhydrous sodium sulfate. Evaporation under reduced pressure gave a mixture of the four diastereoisomeric alcohols 4. Flash chromatography of the crude mixture when using as eluent 7:3 chloroform/ethyl acetate gave (2*S*,3*R*,R_S)-4 (0.98 g, 30.8% from 1) in pure form, a mixture of (2*R*,3*R*,R_S)-4 and (2*S*,3*S*,R_S)-4, and (2*R*,3*S*,R_S)-4 (0.28 g, 8.8% from 1) as a pure compound. Flash chromatography of the mixture of (2*R*,3*R*,R_S)-4 and (2*S*,3*S*,R_S)-4 on silica gel using 7:3 cyclohexane/ethyl acetate allowed to obtain the two compounds in optically pure form (respectively, 0.42 g, 13.3% yield from 1, and 0.55 g, 17.2% yield from 1).

(2*S*,3*R*,R_S)-4: R_f (7:3 chloroform/ethyl acetate) 0.35; $[\alpha]_D^{20}$+75.8° (*c* 1.0, $CHCl_3$); m.p. 113-114°C (1:1 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$), δ: 7.62 and 7.36 (4 H, m, ArH), 5.71 (1 H, m, H-5), 5.40 (1 H, d, *J* = 5.0 Hz, OH-2), 5.18 and 5.12 (2 H, m, H_2-6), 4.52 (1 H, m, H-2), 3.19 (1 H, dt, *J* = 7.5 and 5.5 Hz, H-3), 2.55 and 2.25 (2 H, m, H_2-4) and 2.44 (3 H, br s, Me); ^{19}F NMR ($CDCl_3$), δ: -59.9 (1 F, dd, *J* = 168.5 and 5.5 Hz, F-1a) and -62.9 (1 F, dd, *J* = 168.5 and 9.5 Hz, F-1b). R_t (SiO_2-60μ; 7:3 ethyl acetate/hexane; 1.0 ml/min) 8.29 min; R_t (7:3 chloroform/ethyl acetate) 5.03 min. Found: C, 50.5; H, 4.80. $C_{13}H_{15}ClF_2O_2S$ requires C, 50.6, H, 4.86.

(2*R*,3*S*,R_S)-4: R_f (7:3 chloroform/ethyl acetate) 0.20; $[\alpha]_D^{20}$+168.2° (*c* 1.0, $CHCl_3$); m.p. 103-104°C (1:1 ethyl ether/pentane); ^{1}H NMR ($CDCl_3$), δ: 7.46 and 7.36 (4 H, m, ArH), 5.72 (1 H, d, *J* = 6.5 Hz, OH-2), 5.55 (1 H, m, H-5), 5.11 and 5.10 (2 H, m, H_2-6), 4.39 (1 H, m, H-2), 2.95 (1 H, ddd, *J* = 9.8, 4.8 and 4.0 Hz, H-3), 2.58 and 2.21 (2 H, m, H_2-4) and 2.43 (3 H, br s, Me); ^{19}F NMR ($CDCl_3$), δ: -62.1 (1 F, dd, *J* = 166 and 8.5 Hz, F-1a) and -63.2 (1 F, dd, *J* = 166 and 10 Hz, F-1b). R_t (SiO_2-60μ; 7:3 ethyl acetate/hexane; 1.0 ml/min) 13.57 min; R_t (7:3 chloroform/ethyl acetate) 7.01 min. Found: C, 50.7; H, 4.83. $C_{13}H_{15}ClF_2O_2S$ requires C, 50.6; H, 4.86.

(2*R*,3*R*,R_S)-4: R_f (7:3 chloroform/ethyl acetate) 0.30; R_f (7:3 hexane/ethyl acetate) 0.35; $[\alpha]_D^{20}$ +183.6° (*c* 1.0, $CHCl_3$); m.p. 85-87°C (1:1 ethyl ether/pentane); ^{1}H NMR ($CDCl_3$), δ: 7.53 and 7.38 (4 H, m, ArH), 5.85 (1 H, m, H-5), 5.20 and 5.18 (2 H, m, H_2-6), 4.88 (1 H, d, *J* = 4.1 Hz, OH-2), 4.53 (1 H, m, H-2), 2.91 (1 H, ddd, *J* = 9.5, 3.6 and 1.4 Hz, H-3), 2.86 and 2.79 (2 H, m, H_2-4) and 2.45 (3 H, br s, Me); ^{19}F NMR ($CDCl_3$), δ: -63.8 (1 F, dd, *J* = 164 and 10 Hz, F-1a) and -64.3 (1 F, dd, *J* = 164 and 10.5 Hz, F-1b). R_t (SiO_2-60μ; 7:3 ethyl acetate/hexane; 1.0 ml/min) 8.29 min; R_t (7:3 chloroform/ethyl

acetate) 5.69 min. Found: C, 51.0; H, 4.86. $C_{13}H_{15}ClF_2O_2S$ requires C, 50.6; H, 4.86.

(2*S*,3*S*,R_S)-**4**: R_f (7:3 chloroform/ethyl acetate) 0.30; R_f (7:3 hexane/ethyl acetate) 0.30; $[\alpha]_D^{20}$+51.0° (*c* 0.5, $CHCl_3$); oil; ^{1}H NMR ($CDCl_3$), δ: 7.53 and 7.36 (4 H, m, ArH), 5.69 (1 H, m, H-5), 5.04 and 5.02 (2 H, m, H_2-6), 4.71 (1 H, m, H-2), 3.23 (1 H, ddd, *J* = 7.9, 4.3 and 1.7 Hz, H-3), 3.07 (1 H, d, *J* = 5.6 Hz, OH-2), 2.71 and 2.40 (2 H, m, H_2-4) and 2.42 (3 H, br s, Me); ^{19}F NMR ($CDCl_3$), δ: -63.8 (1 F, dd, *J* = 164 and 9.5 Hz, F-1a) and -64.4 (1 F, dd, *J* = 164 and 10.5 Hz, F-1b). R_t (SiO_2-60μ; 7:3 ethyl acetate/hexane; 1.0 ml/min) 9.11 min; R_t (7:3 chloroform/ethyl acetate) 5.03 min. Found: C, 52.3; H, 4.85. $C_{13}H_{15}ClF_2O_2S$ requires C, 50.6; H, 4.86.

The same ketones mixture (0.43 g, 1.39 mmol) was reduced in THF (5 ml) by DIBAH (2.63 ml of 1*M* hexane solution, 2.63 mmol) at -60°C under argon, affording alcohols **4** in 78.1% global yield. After flash chromatography, performed as above described, the alcohols were isolated in pure form: (2*S*,3*R*,R_S)-**4**, 3.0 mg (0.7% from **3**), (2*R*,3*S*,R_S)-**4**, 16.6 mg (3.9% from **3**), (2*R*,3*R*,R_S)-**4**, 189.3 mg (44.1% from **3**) and (2*S*,3*S*,R_S)-**4**, 126.2 mg (29.4% from **3**).

General Procedure of Reduction of Sulfinyl Alcohols **4** *to the Corresponding Thio Alcohols* **5**.

This is exemplified by the synthesis of (2*S*,3*R*)-**5**. Trifluoroacetic anhydride (0.72 ml, 4.55 mmol) was added to a mixture of (2*S*,3*R*,R_S)-**4** (200 mg, 0.65 mmol) and sodium iodide (300 mg, 1.95 mmol) in acetone (10 ml) with stirring at -40°C under argon. After 10 min at the same temperature the reaction was quenched with an excess of a saturated aqueous solution of sodium sulfite and of a saturated aqueous solution of sodium hydrogen carbonate. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl ether (3x20 ml). The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed to give (2*S*,3*R*)-**5** as a pure compound in 97% yield.

An analytical sample was obtained through flash chromatography (9:1 hexane/ethyl ether); $[\alpha]_D^{20}$+2.3° (*c* 1.2, $CHCl_3$); $[\alpha]_{365}^{20}$ +11.6° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 7.38 and 7.14 (4 H, m, ArH), 5.88 (1 H, m, H-5), 5.19 and 5.16 (2 H, m, H_2-6), 3.95 (1 H, m, H-2), 3.45 (1 H, d, *J* = 7.2 Hz, OH-2), 3.42 (1 H, ddd, *J* = 7.5, 6.8 and 4.3 Hz, H-3), 2.51 and 2.39 (2 H, m, H_2-4) and 2.34 (3 H, br s, Me).

Similarly, from (2*R*,3*R*,R_S)-**4** after reaction a flash chromatography (9:1 hexane/ethyl ether) afforded (2*R*,3*R*)-**5** in 95% yield; R_f (9:1 hexane/ethyl ether) 0.35; $[\alpha]_D^{20}$+11.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 7.33 and 7.13 (4 H, m, ArH), 6.00 (1 H, m, H-5), 5.19 and 5.15 (2 H, m, H_2-6), 4.09 (1 H, m, H-2), 3.53 (1 H, ddd, *J* = 9.5, 4.0 and 2.8 Hz, H-3), 2.95 (1 H, d, *J* = 5.5 Hz, OH-2), 2.68 and 2.42 (2 H, m, H_2-4) and 2.34 (3 H, br s, Me).

From (2*S*,3*S*,R_S)-**4** after reaction a flash chromatography (9:1 hexane/ethyl ether) afforded (2*S*,3*S*)-**5** in 97% yield; R_f (9:1 hexane/ethyl ether) 0.35; $[\alpha]_D^{20}$-10.7° (*c* 1.0, $CHCl_3$); the ^{1}H NMR spectrum is identical with that of its enantiomer (2*R*,3*R*)-**5**.

From (2*R*,3*S*,R_S)-**4** after reaction a flash chromatography (9:1 hexane/ethyl ether) afforded (2*R*,3*S*)-**5** in 93% yield; R_f (9:1 hexane/ethyl ether) 0.35; $[\alpha]_D^{20}$-3.07° (*c* 0.8, $CHCl_3$); the ^{1}H NMR spectrum is identical with that of its enantiomer (2*S*,3*R*)-**5**.

General Procedure for the Synthesis of Phenylpropionic Esters (**6**) *of (2S,3R)*-**5**, *(2R,3R)*-**5**, *(2S,3S)*-**5**, *and (2R,3S)*-**5**.

4-(Dimethylamino)pyridine (1.2 mg, 0.01 mmol) was added to a dichloromethane solution (1 ml)

containing the sulfenyl alcohol **5** (30 mg, 0.10 mmol), the (+)-(*S*)-2-phenylpropionic acid (27 mg, 0.11 mmol) and dicyclohexylcarbodiimide (22 mg, 0,11 mmol). After 30 min at room temperature the dicyclohexylurea was removed by filtration and washed with hexane. The combined organic phases were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromatographed (95:5 hexane/ethyl ether) to give (*S*)-2-phenylpropionate **6**.

From (2*S*,3*R*)-**5** and (+)-(*S*)-PPA: ^{1}H NMR ($CDCl_3$), δ: 7.4-7.1 (9 H, m, ArH), 5.80 (1 H, m, H-5), 5.49 (1 H, m, H-2), 5.13 and 5.10 (2 H, m, H_2-6), 3.71 (1 H, q, *J* = 7.1 Hz, H-2'), 3.41 (1 H, dt, *J* = 5.2 and 6.8 Hz, H-3), 2.39 and 2.36 (2 H, m, H_2-4), 2.35 (3 H, br s, ArMe) and 1.55 (3 H, d, *J* = 7.1 Hz, H_3-3').

From (2*S*,3*R*)-**5** and (-)-(*R*)-PPA: ^{1}H NMR ($CDCl_3$), δ: 7.4-7.0 (9 H, m, ArH), 5.67 (1 H, m, H-5), 5.50 (1 H, m, H-2), 5.05 and 4.96 (2 H, m, H_2-6), 3.83 (1 H, q, *J* = 7.1 Hz, H-2'), 3.33 (1 H, dt, *J* = 4.2 and 7.0 Hz, H-3), 2.33 (3 H, br s, ArMe), 2.21 and 2.15 (2 H, m, H_2-4), and 1.57 (3 H, d, *J* = 7.1 Hz, H_3-3').

From (2*R*,3*R*)-**5** and (+)-(*S*)-PPA: ^{1}H NMR ($CDCl_3$), δ: 7.4-7.1 (9 H, m, ArH), 5.82 (1 H, m, H-5), 5.46 (1 H, m, H-2), 5.04 and 4.98 (2 H, m, H_2-6), 3.86 (1 H, q, *J* = 7.1 Hz, H-2'), 3.42 (1 H, br ddd, *J* = 10.5, 3.5 and 2.1 Hz, H-3), 2.50 and 1.80 (2 H, m, H_2-4), 2.34 (3 H, br s, ArMe) and 1.59 (3 H, d, *J* = 7.1 Hz, H_3-3').

From (2*R*,3*R*)-**5** and (-)-(*R*)-PPA: ^{1}H NMR ($CDCl_3$), δ: 7.4-7.1 (9 H, m, ArH), 5.95 (1 H, m, H-5), 5.46 (1 H, m, H-2), 5.13 and 5.12 (2 H, m, H_2-6), 3.87 (1 H, q, *J* = 7.1 Hz, H-2'), 3.46 (1 H, br ddd, *J* = 10.3, 3.4 and 2.1 Hz, H-3), 2.64 and 2.17 (2 H, m, H_2-4), 2.34 (3 H, br s, ArMe) and 1.61 (3 H, d, *J* = 7.1 Hz, H_3-3').

From (2*S*,3*S*)-**5** and (+)-(*S*)-PPA: ^{1}H NMR ($CDCl_3$), δ: 7.4-7.0 (9 H, m, ArH), 5.95 (1 H, m, H-5), 5.45 (1 H, m, H-2), 5.13 and 5.12 (2 H, m, H_2-6), 3.86 (1 H, q, *J* = 7.2 Hz, H-2'), 3.46 (1 H, br ddd, *J* = 10.3, 3.5 and 2.1 Hz, H-3), 2.64 and 2.17 (2 H, m, H_2-4), 2.33 (3 H, br s, ArMe) and 1.61 (3 H, d, *J* = 7.2 Hz, H_3-3').

From (2*S*,3*S*)-**5** and (-)-(*R*)-PPA: ^{1}H NMR ($CDCl_3$), δ: 7.4-7.0 (9 H, m, ArH), 5.79 (1 H, m, H-5), 5.44 (1 H, m, H-2), 5.02 and 4.96 (2 H, m, H_2-6), 3.84 (1 H, q, *J* = 7.1 Hz, H-2'), 3.38 (1 H, br ddd, *J* = 10.3, 3.3 and 2.1 Hz, H-3), 2.49 and 1.81 (2 H, m, H_2-4), 2.32 (3 H, br s, ArMe) and 1.57 (3 H, d, *J* = 7.1 Hz, H_3-3').

From (2*R*,3*S*)-**5** and (+)-(*S*)-PPA: ^{1}H NMR ($CDCl_3$), δ: 7.4-7.0 (9 H, m, ArH), 5.67 (1 H, m, H-5), 5.49 (1 H, m, H-2), 5.05 and 4.96 (2 H, m, H_2-6), 3.82 (1 H, q, *J* = 7.2 Hz, H-2'), 3.32 (1 H, dt, *J* = 4.2 and 7.0 Hz, H-3), 2.33 (3 H, br s, ArMe), 2.20 and 2.16 (2 H, m, H_2-4) and 1.57 (3 H, d, *J* = 7.2 Hz, H_3-3').

From (2*R*,3*S*)-**5** and (-)-(*S*)-PPA: ^{1}H NMR ($CDCl_3$), δ: 7.4-7.0 (9 H, m, ArH), 5.81 (1 H, m, H-5), 5.50 (1 H, m, H-2), 5.13 and 5.10 (2 H, m, H_2-6), 3.69 (1 H, q, *J* = 7.1 Hz, H-2'), 3.41 (1 H, dt, *J* = 5.2 and 6.8 Hz, H-3), 2.39 and 2.37 (2 H, m, H_2-4), 2.34 (3 H, br s, ArMe) and 1.55 (3 H, d, *J* = 7.1 Hz, H_3-3').

General Procedure for Radical Cyclization of Alcohols **4**.

A) Thermal Reaction.

To a stirred solution of alcohol **4** (1.0 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 0.05 mmol) in

oxygen-free benzene (15 ml) at 60°C in an argon atmosphere, a solution of tributyltin hydride (1.0 mmol) in the same solvent (30 ml) was added slowly (*ca.* 1 h). The reaction mixture was further stirred for a period depending on the substrate at the same temperature.

The benzene was removed under reduced pressure, and the residue was dissolved in acetonitrile (10 ml) and the solution was washed with hexane in order to remove all alkyltin derivatives. Acetonitrile was removed under reduced pressure and the residue was flash chromatographed.

From (2*S*,3*R*,R_S)-**4** after a reaction time of 5 h flash chromatography (7:3 cyclohexane/ethyl acetate) afforded (1*R*,3*R*,5*R*,R_S)- and (1*R*,3*S*,5*R*,R_S)-3,3-difluoro-4-methyl-2-[(4-methylphenyl)sulfinyl]cyclopentan-1-ol (**9**) as optically pure compounds in a 1:2 ratio (global yield 11%).

From (2*R*,3*R*,R_S)-**4** after a reaction time of 6 h flash chromatography (7:3 cyclohexane/ethyl acetate) afforded (1*S*,3*R*,5*R*,R_S)- and (1*S*,3*S*,5*R*,R_S)-3,3-difluoro-4-methyl-2-[(4-methylphenyl)sulfinyl]cyclopentan-1-ol (**9**) as optically pure compounds in a 1:4 ratio (global yield 72%).

B) Photolytic Reaction.

A solution of alcohol **4** (1 mmol) and tributyltin hydride (1.2 mmol) in oxygen-free benzene (6 ml) in a Pyrex tube was irradiated with a 350 nm lamp in a Rayonet apparatus for different periods of time depending on the substrate. During the irradiation, the temperature was kept at 35°C. After evaporation of the benzene, acetonitrile (5 ml) was added and the solution was washed with hexane (3x5 ml). Acetonitrile was removed under reduced pressure and the residue was flash chromatographed.

From (2*S*,3*R*,R_S)-**4** after a reaction time of 105 min a 1:5.6 mixture (HPLC ratio) of (1*R*,3*R*,5*R*,R_S)- and (1*R*,3*S*,5*R*,R_S)-3,3-difluoro-4-methyl-2-[(4-methylphenyl)sulfinyl]cyclopentan-1-ol (**9**) was obtained. Upon flash chromatography (7:3 cyclohexane/ethyl acetate) the single diastereoisomers were obtained as optically pure compounds.

(1*R*,3*R*,5*R*,R_S)-**9**: 11.1% yield; R_f (45:55 cyclohexane/ethyl acetate) 0.35; $[\alpha]_D^{20}$+7.04° (*c* 0.4, $CHCl_3$); m.p. 120-122°C (isopropyl ether). R_T (SiO_2-60μm; 1:1 hexane/ethyl acetate; 1.0 ml/min) 8.07 min. Found: C, 55.1; H, 6.10. $C_{13}H_{16}F_2O_2S$ requires C, 56.9; H, 5.88.

(1*R*,3*S*,5*R*,R_S)-**9**: 62% yield; R_f (45:55 cyclohexane/ethyl acetate) 0.40; $[\alpha]_D^{20}$+146.0° (*c* 0.6, $CHCl_3$); m.p. 128-130°C (isopropyl ether). R_T (SiO_2-60μm; 1:1 hexane/ethyl acetate; 1.0 ml/min) 12.52 min. Found: C, 59.0; H, 6.01. $C_{13}H_{16}F_2O_2S$ requires C, 56.9; H, 5.88.

Similarly from (2*R*,3*R*,R_S)-**4** a 1:4.2 mixture (HPLC ratio) of (1*S*,3*R*,5*R*,R_S)-**9** and (1*S*,3*S*,5*R*,R_S)-**9** was obtained after a reaction time of 4 h. Flash chromatography (7:3 cyclohexane/ethyl acetate) allowed to obtain the single pure diastereoisomers.

(1*S*,3*R*,5*R*,R_S)-**9**: 16.6% yield; R_F (7:3 hexane/ethyl acetate) 0.35; $[\alpha]_D^{20}$+150.0° (*c* 0.1, $CHCl_3$); m.p. 154-156°C (isopropyl ether). R_T (SiO_2-60μm; 2:3 hexane/ethyl acetate; 1.0 ml/min) 10.33 min. Found: C, 56.5; H, 6.02. $C_{13}H_{16}F_2O_2S$ requires C, 56.9; H, 5.88.

(1*S*,3*S*,5*R*,R_S)-**9**: 69.9% yield; R_F (7:3 hexane/ethyl acetate) 0.30; $[\alpha]_D^{20}$+184.0° (*c* 0.5, $CHCl_3$); m.p. 160-162°C (isopropyl ether). R_T (SiO_2-60μm; 2:3 hexane/ethyl acetate; 1.0 ml/min) 11.93 min. Found: C, 56.8; H, 5.82. $C_{13}H_{16}F_2O_2S$ requires C, 56.9; H, 5.88.

Selected ^1H and ^{19}F NMR data for compounds **9** are collected in Table 2; selected ^{13}C NMR data are in Table 3.

*Synthesis of (1R,3R,5R)- and (1R,3S,5R)-***10** *by Radical Cyclization of the Corresponding Alcohols* **5**.

To a stirred solution of sulfenyl alcohol (2*S*,3*R*)-**5** (1.0 mmol) and AIBN (0.05 mmol) in oxygen-free benzene (15 ml) at 75°C in an argon atmosphere, a solution of tributyltin hydride (1.0 mmol) in the same solvent (30 ml) was slowly added (ca. 1 h). The reaction mixture was further stirred for 1 h at the same temperature. After the usual work-up procedure, a residue, containing a 45:55 mixture of (1*R*,3*R*,5*R*)-**10** and (1*R*,3*S*,5*R*)-**10** in 69% global yield was obtained. The diastereoisomers ratio was determined on LiChrocart 250-4 Superspher 100 RP-18 column using 7:3 water/acetonitrile as eluent. After flash chromatography in 75:25 hexane/isopropyl ether, (1*R*,3*S*,5*R*)-**10** was obtained in pure form as a solid. R_F (7:3 hexane/ethyl ether) 0.30; $[\alpha]_D^{20}$+16.2° (*c* 1.1, $CHCl_3$); m.p. 51-53°C (ethyl ether); ^{1}H NMR ($CDCl_3$), δ: 7.36 and 7.12 (4 H, m, ArH), 3.91 (1 H, m, H-1), 3.27 (1 H, m, H-5), 2.34 (1 H, m, H-3), 2.33 (3 H, br s, ArMe), 2.31 and 1.28 (2 H, m, H_2-4), 2.30 (1 H, br signal, OH-1) and 1.05 (3 H, dd, *J* = 6.6 and 1.3 Hz, H_3-6); ^{19}F NMR ($CDCl_3$), δ: -114.43 and -116.62 (2 F, m, F_2-2).

For (1*R*,3*R*,5*R*)-**10** only NMR data could be obtained. ^{1}H NMR ($CDCl_3$), δ: 7.36 and 7.12 (4 H, m, ArH), 4.01 (1 H, m, H-1), 3.31 (1 H, m, H-5), 2.33 (3 H, br s, ArMe), 2.31 (1 H, m, H-3), 2.30 (1 H, br signal, OH-1), 1.93 and 1.87 (2 H, m, H_2-4) and 1.06 (3 H, dd, *J* = 7.0 and 1.3 Hz, H_3-6); ^{19}F NMR ($CDCl_3$), δ: -113.23 and -130.79 (2 F, m, F_2-2).

Synthesis of (1S,3S,5R)-2,2-Difluoro-3-methyl-5-[(4-methylphenyl)sulfenyl]cyclopentan-1-ol (**10**) *by Deoxygenation of (1S,3S,5R,*R_S*)-***9**.

To a solution of (1*S*,3*S*,5*R*,R_S)-**9** (110 mg, 0.40 mmol) and NaI (179 mg, 1.20 mmol) in acetone (10 ml) at -40°C under nitrogen atmosphere, a solution of trifluoroacetic anhydride (0.28 ml, 2.01 mmol) in the same solvent (1 ml) was added dropwise. The reaction mixture was stirred at the same temperature for 10 min, then a saturated aqueous solution of sodium sulfite (5 ml) was added, and, when temperature raised to the room value, acetone was evaporated *in vacuo*. The aqueous phase was extracted with ethyl acetate (3x10 ml), the combined organic phases were washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was flash chromatographed (9:1 hexane/ethyl ether) to give (1*S*,3*S*,5*R*)-**10** as a light yellow liquid (98 mg, 95% yield). R_f (9:1 hexane/ethyl ether) 0.40; $[\alpha]_D^{20}$+63.0° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 7.33 and 7.12 (4 H, m, ArH), 4.03 (1 H, m, H-1), 3.64 (1 H, m, H-5), 2.95 (1 H, dt, *J* = 5.3 and 1.0 Hz, OH-1), 2.47 and 1.55 (2 H, m, H_2-4), 2.33 (3 H, br s, ArMe), 2.26 (1 H, m, H-3) and 1.13 (3 H, dd, *J* = 7.0 and 1.7 Hz, H_3-6); ^{19}F NMR ($CDCl_3$), δ: -103.60 (1 F, br ddd, *J* = 235, 19 and 6.5 Hz, F-2β) and -127.00 (1 F, br ddd, *J* = 235, 11 and 6 Hz, F-2α). Found: C, 60.7; H, 6.29. $C_{13}H_{16}F_2OS$ requires C, 60.4; H, 6.24.

Synthesis of (1S,3S,5R)-2,2-Difluoro-3-methyl-5-[(4-methylphenyl)sulfenyl]cyclopentan-1-ol Benzoate (**11**).

4-(Dimethylamino)pyridine (4.7 mg, 0.03 mmol) was added to a dichloromethane solution (10 ml) of the sulfenyl alcohol (1*S*,3*S*,5*R*)-**10** (100 mg, 0.39 mmol), benzoic acid (51.9 mg, 0.43 mmol) and dicyclohexylcarbodiimide (87.8 mg, 0.43 mmol) at 0°C were added. After 20 h at room temperature, the dicyclohexylurea was removed by filtration and washed with hexane. The organic layers were dried over anhydrous sodium sulfate, the solvent was removed *in vacuo* and the residue was flash chromatographed (9:1 hexane/ethyl ether) to give (1*S*,3*S*,5*R*)-**11** as a yellowish oil (126 mg, 90% yield).

R_f (9:1 hexane/ethyl ether) 0.35; $[\alpha]_D^{20}$+148.0° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 8.2-7.0 (9 H, m, ArH), 5.54 (1 H, m, H-1), 3.73 (1 H, m, H-5), 2.54 and 1.80 (2 H, m, H_2-4), 2.40 (1 H, m, H-3), 2.29 (3 H, br s, ArMe) and 1.17 (3 H, dd, *J* = 6.9 and 1.9 Hz, H_3-6); ^{19}F NMR ($CDCl_3$), δ: -99.05 (1 F, br ddd, *J* = 239, 21 and 7 Hz, F-2β) and -122.10 (1 F, br d, *J* = 239 Hz, F-2α). Found: C, 66.7; H, 5.59. $C_{20}H_{20}F_2O_2S$ requires C, 66.3; H, 5.56.

Synthesis of (1R,3S)-2,2-Difluoro-3-methylcyclopentan-1-ol Benzoate (**12**).

To a solution of (1*S*,3*S*,5*R*)-**11** (120 mg, 0.32 mmol) in absolute ethanol (10 ml) Raney-Ni (360 mg) was added. The slurry was heated to 80°C and stirred under hydrogen atmosphere for 40 min. Then Raney-Ni was filtered off and washed twice with ethanol. Solvent was removed under reduced pressure and flash chromatography (95:5 hexane/ethyl ether) afforded (1*R*,3*S*)-**12** as a pure oil (70 mg, 85% yield).

R_f (95:5 hexane/ethyl ether) 0.40; $[\alpha]_D^{20}$-27.6° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 8.07, 7.59 and 7.46 (5 H, m, ArH), 5.39 (1 H, m, H-1), 2.33 and 1.88 (2 H, m, H_2-5), 2.29 (1 H, m, H-3), 2.05 and 1.62 (2 H, m, H_2-4) and 1.15 (3 H, dd, *J* = 7.0 and 1.5 Hz, H_3-6); ^{19}F NMR ($CDCl_3$), δ: -109.13 (1 F, ddd, *J* = 232, 13.5 and 8.5 Hz, F-2β) and -128.33 (1 F, br ddd, *J* = 232, 15.5 and 9.5 Hz, F-2α). Found: C, 67.2; H, 6.10. $C_{13}H_{14}F_2O_2$ requires C, 65.0; H, 5.87.

*Deprotection of (1R,3S)-***12** *to (1R,3S)-2,2-Difluoro-3-methylcyclopentan-1-ol* (**13**).

To a solution of (1*R*,3*S*)-**12** (55 mg, 0.23 mmol) in methanol (0.5 ml) an 1% aqueous solution of potassium hydroxide (0.3 ml) was added, and stirring was continued for 2 h. Methanol was carefully removed, the aqueous phase was extracted with ethyl ether (3x1 ml), the combined organic phases were dried over anhydrous sodium sulfate and the solvent was carefully removed. Flash chromatography (6:4 pentane/ethyl ether) gave 80% yield of (1*R*,3*S*)-**13** as a volatile liquid. $[\alpha]_D^{20}$+3.6°, $[\alpha]_{365}^{20}$ +12.0° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 4.14 (1 H, m, H-1), 3.58 (1 H, br signal, OH-1), 2.24 (1 H, m, H-3), 2.04 and 1.69 (2 H, m, H_2-5), 1.94 and 1.53 (2 H, m, H_2-4) and 1.10 (3 H, dd, *J* = 7.0 and 1.5 Hz, H_3-6); ^{19}F NMR (CD_3OD), δ: -110.75 (1 F, ddd, *J* = 227, 12.5 and 7.5 Hz, F-2β) and -129.62 (1 F, br ddd, *J* = 227, 18 and 13 Hz, F-2α).

Synthesis of (2S,3R,5S,R_S*)-2-Benzyloxy-1,1-difluoro-5-methyl-3-[(4-methylphenyl)sulfinyl] cyclopentane* (**14**).

To a suspension of sodium hydride (50.0 mg, 1.04 mmol) in dimethylformamide (5.0 ml) at 0°C a solution of (1*S*,3*S*,5*R*,R_S)-**9** (160 mg, 0.52 mmol) and benzyl bromide (0.62 ml, 5.20 mmol) in the same solvent (3.0 ml) was added dropwise. Stirring was continued at the same temperature for 1 h, then the suspension was poured into a water/ice bath, extracted with ethyl ether (3x10 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was flash chromatographed to give (2*S*,3*R*,5*S*,R_S)-**13** (133 mg, 70% yield).

$[\alpha]_D^{20}$+118.78° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 7.7-7.2 (9 H, m, ArH), 4.94 (1 H, d, *J* = 10.9 Hz, OCHa), 4.84 (1 H, d, *J* = 10.9 Hz, OCHb), 4.33 (1 H, m, H-2), 3.29 (1 H, m, H-3), 2.42 (3 H, br s, ArMe), 2.21 (1 H, m, H-5), 1.54 and 1.47 (2 H, m, H_2-4) and 1.12 (3 H, dd, *J* = 7.1 and 2.2 Hz, H_3-6); ^{19}F NMR ($CDCl_3$), δ: -95.11 (1 F, br dd, *J* = 240 and 23 Hz, F-1β) and -123.44 (1 F, br d, *J* = 240 Hz, F-1α). Found: C, 66.0; H, 6.07. $C_{20}H_{22}F_2O_2S$ requires C, 65.9; H, 6.08.

Synthesis of (3R,5S)-3-Benzyloxy-4,4-difluoro-5-methylcyclopent-1-ene (**15**).

A solution of (2*S*,3*R*,5*S*,R_S)-**14** (69.2 mg, 0.19 mmol) in 1,2-ethandiol (0.5 ml) was heated at 190°C under argon atmosphere and magnetically stirred for 12 h. The solution was poured into water (1.0 ml) and extracted with ethyl ether (3x2 ml). After solvent evaporation the residue was flash chromatographed (9:1 pentane/ethyl ether) to give (3*R*,5*S*)-**15** as pure compound (21.7 mg, 51% yield).

R_f (95:5 pentane/ethyl ether) 0.35; $[\alpha]_D^{20}$+18.4° (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 7.5-7.2 (5 H, m, ArH), 5.89 and 5.76 (2 H, m, H-1 and -2), 4.86 (1 H, d, *J* = 11.6 Hz, OCHa), 4.60 (1 H, d, *J* = 11.6 Hz, OCHb), 4.45 (1 H, br d, *J* = 12.5 Hz, H-3), 2.89 (1 H, m, H-5) and 1.16 (3 H, dd, *J* = 7.2 and 2.5 Hz, H_3-6); ^{19}F NMR ($CDCl_3$), δ: -101.18 (1 F, br ddd, *J* = 235.5, 18.0 and 12.5 Hz, F-4β) and -125.48 (1 F, m, F-4α).

Synthesis of (1S,2S,3R,5S)-3-Benzyloxy-4,4-difluoro-5-methylcyclopentan-1,2-diol (**16**).

A 4% (w/w) aqueous solution of osmium tetroxide (0.08 mmol, 20.4 mg) was added at 0°C to a stirred solution of cyclopentene derivative **15** (150 mg, 0.67 mmol) in THF (4.0 ml) and water (0.12 ml) under nitrogen atmosphere. The reaction mixture was stirred at the same temperature in the dark for 10 min, then trimethylamine-N-oxide (74.7 mg, 0.67 mmol) was added. Stirring was continued for 1.5 h, then a saturated aqueous solution of sodium sulfite (1.0 ml) and citric acid (10 mg) were added. After further stirring for 10 min, the solution was extracted with ethyl acetate (5x2.0 ml), the combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the residue (4:1 hexane/ethyl ether) gave (1*S*,2*S*,3*R*,5*S*)-**16** (156 mg, 90% yield) as pure compound.

R_f (7:3 hexane/ethyl acetate) 0.35; $[\alpha]_D^{20}$+34.8°, $[\alpha]_{365}^{20}$ +119.5° (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 7.5-7.2 (5 H, m, ArH), 4.87 (1 H, dd, *J* = 11.5 and 1.0 Hz, OCHa), 4.63 (1 H, d, *J* = 11.5 Hz, OCHb), 4.04 (1 H, m, H-2), 4.00 (1 H, m, H-3), 3.77 (1 H, m, H-1), 2.60 (1 H, d, *J* = 4.1 Hz, OH-2), 2.51 (1 H, d, *J* = 4.5 Hz, OH-1), 2.34 (1 H, dddq, *J* = 18.5, 11.7, 7.0 and 7.2 Hz, H-5) and 1.16 (3 H, dd, *J* = 7.2 and 1.5 Hz, H_3-6); ^{19}F NMR ($CDCl_3$), δ: -103.77 (1 F, m, *J* = 236 Hz, F-4β) and -123.24 (1 F, m, *J* = 236 Hz, F-4α).

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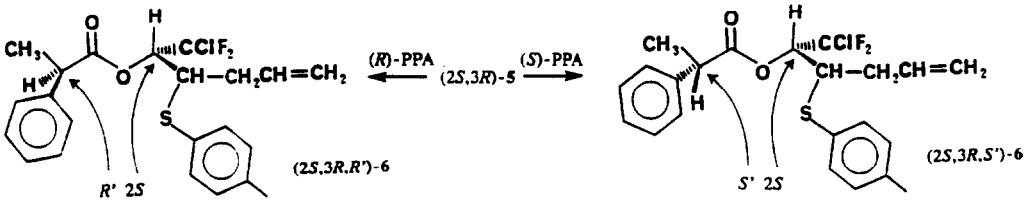

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