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Asymmetric Synthesis of *gem*-Chlorofluorocyclopentane Derivatives by Intramolecular Trapping of Dihaloalkyl Radicals

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Abstract: *Radical promoted cyclization of enantiomerically pure substituted 1,1-dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl]hex-5-en-2-ols (6) afforded the title compounds 12 in good overall yields. The regio and stereochemical outcome of the cyclizations are explained by considering the respective transition states. The structure and configuration of the products were elucidated with the aid of ^{1}H, ^{13}C and ^{19}F NMR spectra and ^{1}H- $\{^{1}H\}$ and ^{1}H-$\{^{19}F\}$ NOE difference experiments.*

INTRODUCTION

In recent years ring formation by radical cyclization has become an important tool in organic synthesis.[1] The cyclization of hex-5-enyl radicals, obtained by homolytic cleavage of the corresponding alkenyl halides, to give the cyclopentylmethyl radicals is one of the best known radical rearrangements. Application of this strategy to 1-chloro and to 1,1,1-trichloro derivatives to give the corresponding cyclopentanes and *gem*-dichlorocyclopentanes in good yields has been already reported.[2]

In our continuing interest in the development of strategies for the synthesis of optically pure selectively fluorinated molecules,[3] the radical cyclization method to form carbon-carbon bonds has proved valuable, as shown by the recently reported synthesis of *gem*-difluoro-cyclopentane,[4] -tetrahydrofuran[5] and -cyclohexane[6] derivatives.

In this paper we describe the application of this strategy to the asymmetric synthesis of *gem*-chlorofluorocyclopentane derivatives.

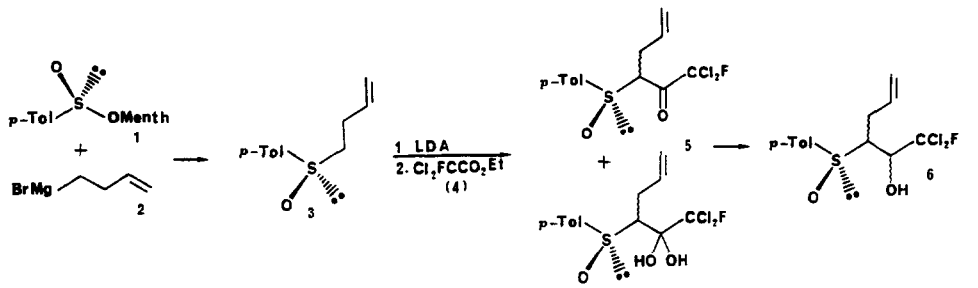
RESULTS AND DISCUSSION

Synthesis of ω-Hexenyl Dichlorofluoro Starting Materials 6.

Sulfoxides are useful chiral starting materials for the synthesis of a large variety of natural products

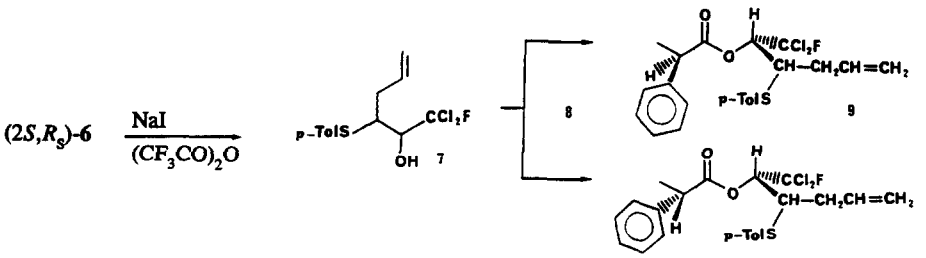
and biologically active compounds.[7] This is due to their manifold reactivity and easy availability in both enantiomerically pure form from (+)- and (-)-menthol through the Mikolajczyk improved procedure of the Andersen synthesis.[8] For this reason we have used chiral sulfoxides for the preparation of the key open chain intermediates (scheme 1).

Acylation by ethyl dichlorofluoroacetate (**4**) of the lithium derivative of 4-[(4-methylphenyl)sulfinyl]but-1-ene (**3**) [obtained from (-)-(1*R*,2*S*,5*R*)-menthyl 4-methylphenyl-(*S*)-sulfinate (**1**) and but-1-ene-4-yl magnesium bromide (**2**)][9] afforded a mixture of the two diastereoisomeric ketones ($3R,R_S$)- and ($3S,R_S$)-**5** in the keto and hydrate forms. The hydride-promoted reduction[10] of **5** gave, in 80% global yield from **3**, the key open-chain alcohols ($2S,3R,R_S$)-, ($2R,3R,R_S$)-, ($2S,3S,R_S$)- and ($2R,3S,R_S$)-**6** in a 3.5:1.5:2.0:1.0 relative ratio (table 1). The single compounds were obtained in enantiomerically pure form by flash chromatography.



Scheme 1

In order to establish the absolute configuration at C-2, all the four diastereoisomeric sulfinyl secondary alcohols **6** were deoxygenated at the sulfur atom by the action of sodium iodide and trifluoroacetic anhydride in acetone at -40°C[11] (scheme 2). The corresponding thio alcohols **7** were obtained in nearly quantitative yields and were reacted separately with (R)- and (S)-2-phenylpropionic acids (PPA, **8**) and dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine to give the corresponding esters (**9**). The absolute configuration of the hydroxy-bearing carbon of all the four diastereoisomeric alcohols **6** was established from ^{1}H NMR spectra by measuring the chemical shift differences which derive from the shielding effect exerted by the phenyl ring of the esterifying acid on the protons of the allyl group of the secondary alcohols.[12]



Scheme 2

Radical Promoted Cyclization.

Tributyltin hydride was the reagent of choice to bring about the radical promoted cyclization of open

chain compounds **6**. Azobisisobutyronitrile (AIBN) under irradiation (350 nm) in cold benzene was used as initiator, in order to minimize sulfenic acid elimination from starting alcohols **6** to give stable 1,1-dichloro-1-fluorohexa-3,5-dien-2-ol which was the main product using thermal dissociation of AIBN.

Table 1. Yields and Physical Data for Compounds **6** and **12**

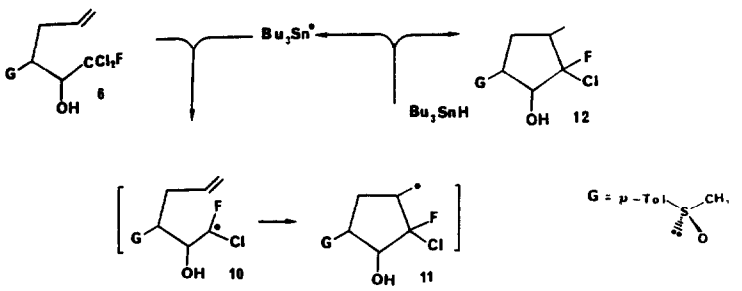
Compound	Yield (%)	M.p./°C (*i*-Pr_2O)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	R_F (eluant)[a]	R_T/min (eluant)[a]
(2*S*,3*R*,R_S)-**6**	35	130-132	+97.3 (1.0)	0.35 (9:1 A)	4.39 (3:2 A)
(2*R*,3*R*,R_S)-**6**	15	73-74	+183.9	0.30 (9:1 A) 0.35 (4:1 B)	5.65 (3:2 A)
(2*S*,3*S*,R_S)-**6**	20	76-78	+179.0	0.30 (9:1 A) 0.30 (4:1 B)	4.90 (3:2 A)
(2*R*,3*S*,R_S)-**6**	10	123-125	+145.4 (1.0)	0.20 (9:1 A)	
(1*S*,2*R*,3*S*,5*R*,R_S)-**12**	33	150-152	+147.3 (0.5)	0.25 (9:2 B)	12.37 (1:1 C)
(1*R*,2*S*,3*R*,5*R*,R_S)-**12**	12	195-197	+2.2 (1.1)	0.35 (3:2 B)	11.52 (3:2 C)
(1*R*,2*S*,3*S*,5*R*,R_S)-**12**	54	149-151	+189.0 (0.9)	0.30 (3:2 B)	17.50 (3:2 C)
(1*R*,2*R*,3*S*,5*R*,R_S)-**12**	19	200-202	+115.1 (0.8)	0.20 (3:2 B)	20.30 (3:2 C)

[a]A, chloroform/ethyl acetate; B, cyclohexane/ethyl acetate; C, hexane/ethyl acetate.

When tributyltin radical was generated in appropriate conditions, the chain reaction reported on scheme 3 operated quite efficiently. Because of the high difference in bond energies between C-F and C-Cl bonds, chlorine atom was selectively abstracted from the $-CCl_2F$ group by the mild nucleophilic tributyltin radical[13] to give the stabilized chlorofluoroalkyl radical **10**[14] which reacted quite fast intramolecularly on the double bond[15] to give the cyclopentylmethyl radical **11**.

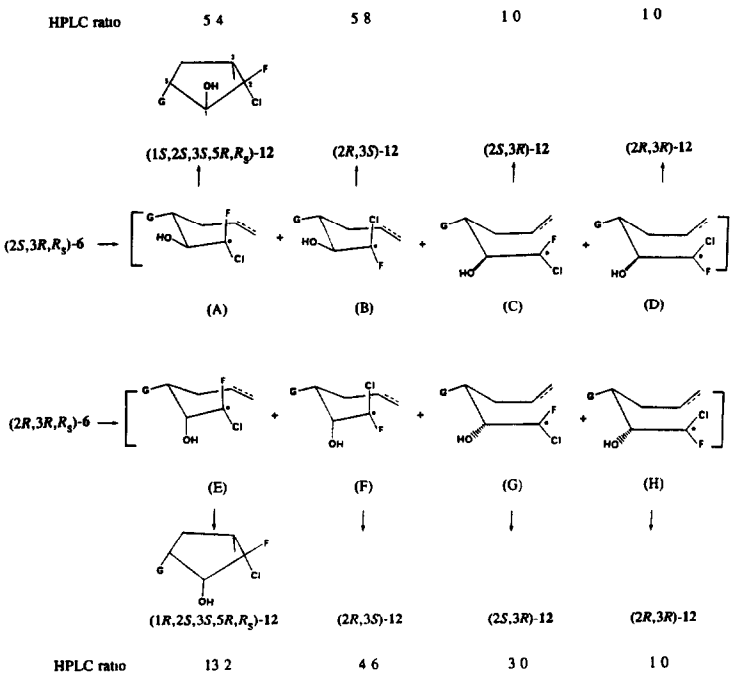
Hydrogen abstraction from a second mole of tributyltin hydride gave final products **12** and formed a new tin radical which propagated the homolytic chain process.

Some observations on the regio and stereochemical control during the cyclization may now be focused. Only methylcyclopentane derivatives have been isolated from the reaction and therefore only cyclopentylmethyl radicals **11** were formed during the cyclization. This followed from predictive Baldwin rules[16]: *exo*-trig cyclizations are more favored than the corresponding *endo*-trig ones, despite a less stable primary radical is generated.[17] Moreover, the diastereoisomeric ratios reported in Scheme 4 for compounds **12** may be explained by considering the respective transition states (A)-(H) and the Beckwith rules [18,19] which require, *inter alia*, that the 1,5-*exo* ring closure of a 3-monosubstituted system affords mainly a *cis*-disubstituted product. Although the starting alcohols **6** possess additional substituents, this



Scheme 3

rule is respected in all the examined cases, since the most abundant products **12** presented a 1,3-*cis* relationship between the sulfoxide and the newly-formed methyl group. These findings suggest that the reactions proceed preferentially *via* the chair-like transition states (A), (B), (E) and (F), having the sulfoxide and the incipient methyl groups pseudoequatorially disposed in order to avoid severe 1,3-diaxial interactions. Accordingly, the less abundant cyclopentanols **12** may arise *via* the more crowded boat-like conformations (C), (D), (G) and (H)[20] which still show the sulfoxide group pseudoequatorially disposed but in a *trans* relationship in respect with the incipient methyl group.



Scheme 4

The influence of the configuration of the hydroxy-bearing carbon C-1 may give provide a reason for the observed ratio for the four pairs of C-2 epimers **12**, *i.e.* 1:1 for the products deriving from (2*S*,3*R*,R_S)-**6** and 3:1 for those deriving from (2*R*,3*R*,R_S)-**6** Specifically, in all the transition states (A)-

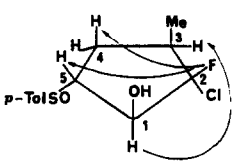
(D), the pseudoequatorially disposed hydroxylic group is in a *gauche* relationship to fluorine and chlorine atoms. It can thus interact always in a similar way with the halogen atoms, and therefore a 1:1 ratio for the corresponding epimers (2*S*,3*S*)-/(2*R*,3*S*)-**12** and (2*S*,3*R*)-/(2*R*,3*R*)-**12** is observed. On the other hand, the 3:1 observed ratio for both the remaining couples of epimers **12** implies that the transition states (E) and (G) have a greater weight than (F) and (H). This may be attributed to the preference of the chlorine, compared to the fluorine atom, to give intramolecular hydrogen bonds with the pseudoaxially disposed hydroxylic group;[21-23] in fact, in (E) and (G) the latter group can better interact with the chlorine atom than with the *anti* disposed fluorine atom. However stereoelectronic effects due to the presence of the fluorine cannot be excluded.

In order to transform *gem*-chlorofluorocyclopentanol derivatives **12** into the corresponding fluoro-derivatives, (1*R*,2*S*,3*S*,5*R*,R_S)-**12** was submitted to reductive dechlorination. Under the same reaction conditions (Bu_3SnH, cat. AIBN, benzene, reflux) previously used on similar *gem*-chlorofluorocyclohexane derivatives,[24] no reduction was observed. After a very long reaction time (two weeks) a complex mixture of not separable and not analyzable (by NMR) products was obtained, along with a large quantity (about 50%) of unreacted starting material.

Assignment of Structure and Configuration.

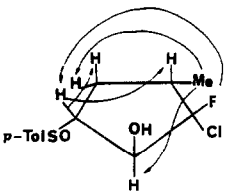
The structure and relative configurations of the title compounds **12** were elucidated with the aid of ^1H, ^{13}C and ^{19}F NMR spectra (Tables 2 and 3), ^1H-{^1H} and ^1H-{^{19}F} NOE difference experiments (Table 4), chemical-shift considerations and comparison with the corresponding *gem*-difluoro derivatives.[4]

The absolute configuration at C-1 followed from that established for the precursor alcohols (2*S*,3*R*,R_S)- and (2*R*,3*R*,R_S)-**6** since no change in configuration has ever been observed during analogous cyclizations. Thus, the four diastereoisomers **12** obtained from each alcohol **6** possess the same chirality at C-1 and C-5 and differ from each other in relation to chirality at the newly-formed C-2 and C-3 centres.



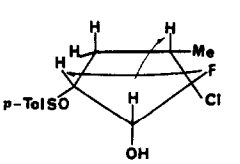
(1*S*,2*S*,3*R*,5*R*,R_S)-**12**

A



(1*S*,2*S*,3*S*,5*R*,R_S)-**12**

B



(1*R*,2*S*,3*S*,5*R*,R_S)-**12**

C

Figure 1

In compound (1*S*,2*S*,3*R*,5*R*,R_S)-**12** the fact that F-2 resonates at higher field than in the other three diastereoisomers (δ_F = -140.08 *vs* -126.12, -121.58 and -116.86) indicates that it experiences a greater shielding γ-effect.[4,25] As a consequence, F-2 is *syn* disposed with respect to the C-1 and C-3 substituents and the chirality at C-2 and C-3 is *S* and *R*, being determined as *S* that of C-1. The NOE observed for H-3 (6%), but not for H_3-6, upon irradiation of H-1, assumed as α in the figure 1A, and those observed for H-4 at δ 1.95 (1.5%) and H-5 (2%) upon irradiation of F-2β permitted us to distinguish between the C-4 geminal protons and to assign as *R* the chirality of the C-5 carbon of the above cyclopentanol, and hence of the C-3 carbon of the starting alcohol.

Also in the (1*S*,2*S*,3*S*,5*R*,R_S)-**12** isomer a NOE was observed between H-5ß and F-2 (1%)(figure 1B); moreover, irradiation of H_3-6 enhanced H-1α (2.5%) and H-4 at 1.31 (3.5%) but not H-4 at 1.81 (<0.5%), while irradiation of H-5ß enhanced H-3 (1.5%) and H-4 at δ 1.81 (4.5%) but not H-4 at 1.31 (≤0.5%). These findings indicate that the chirality at C-2 and C-3 is *S*.

Table 2. Selected ^{1}H and ^{19}F NMR Chemical Shifts (δ) and Coupling Constants (*J*/Hz) for Compounds **12** in $CDCl_3$

	(1*R*,2*S*,3*S*)	(1*R*,2*R*,3*S*)	(1*R*,2*S*,3*R*)	(1*R*,2*R*,3*R*)	(1*S*,2*S*,3*S*)	(1*S*,2*R*,3*S*)	(1*S*,2*S*,3*R*)	(1*S*,2*R*,3*R*)
H-1	4.54	4.66	4.46	4.63	4.70	4.61	4.56	4.70
H-3	2.46	2.36	2.82	3.04	2.63	2.48	2.35	2.50
H-4α	1.74	1.53	2.24	2.02	1.31	1.40	2.23	2.16
H-4ß	1.85	1.75	1.40	1.26	1.81	1.81	1.95	1.83
H-5	3.26	3.39	3.32	3.04	3.22	3.25	3.08	2.91
H_3-6	1.23	1.20	1.12	1.12	1.13	1.15	1.16	1.16
OH-1	5.31	5.01	5.24	5.18	4.21	3.95	2.28	2.29
F-2	-102.45	-137.17	-129.16	-127.66	-121.58	-126.12	-140.08	-116.86
J								
H-1,H-5	5.2	7.4	4.3	4.5	3.9	3.0	7.5	7.5
H-1,OH	3.8	4.9	4.2	4.5	4.5	4.2	6.2	6.6
H-1,F	6.5	15.0	4.0	≤0.5	5.5	13.6	19.4	9.6
H-3,H-4α	8.2	10.2	10.7	10.0	9.3	11.0	*ca.* 8.6	8.3
H-3,H-4ß	8.3	8.1	8.0	9.5	7.5	7.5	*ca.* 11.2	11.6
H-3,H_3-6	7.1	7.0	7.0	6.7	6.7	6.8	6.6	6.7
H-3,F	24.0	19.6	30.3	11.0	13.5	25.9	28.0	9.4
H-4α,H-4ß	13.4	13.7	13.7	14.1	13.5	13.4	*ca.* 13.5	14.2
H-4α,H-5	10.5	8.5	7.7	6.5	8.2	8.8	*ca.* 4.0	3.9
H-4α,F	≤0.5	1.5	0.6	1.0	≤0.5	1.5	≤0.5	1.1
H-4ß,H-5	8.7	8.8	10.7	11.2	9.9	9.4	*ca.* 11.4	11.4
H-4ß,F	≤0.5	0.6	≤0.5	≤0.5	1.3	≤0.5	≤0.5	0.8
H-5,F	3.3	1.3	4.5	2.0	1.8	1.2	1.5	≤0.5
H_3-6,F	≤0.5	1.3	0.7	a	≤0.5	≤0.5	1.1	a

[a]Not assigned

In compound (1*S*,2*R*,3*S*,5*R*,R_S)-**12** irradiation of H-5ß enhanced H-3 (2%) and H-4 at δ 1.81 (6%) but not H_3-6 and H-4 at δ 1.40 (<0.5%) and a NOE was observed between F-2 and H-4 at 1.40 (1%). Thus the absolute configuration at C-2 and C-3 is *R* and *S*.

In the case of the fourth isomer (1*S*,2*R*,3*R*,5*R*,R_S)-**12** the NOE observed between H-1α and H-3 (4%), but not with H_3-6, established as *R* the chirality at C-3 while the greater NOE observed between F-2 and H-1α with respect to the corresponding NOE observed in the C-2 epimer (6 *vs* 1.5%) allowed the assignment of the *R* configuration to the C-2 carbon.

The assignment of the *R* absolute configuration at C-1 and C-5 for the remaining cyclopentanols **12**

was based on the fact that the starting (2*R*,3*R*,R_S)-**6** alcohol possesses *R* configuration at C-2 and C-3. The chirality at C-2 of the alcohol followed from the above described evidence while that at C-3 could be assigned by considering that the corresponding thio alcohol (2*R*,3*R*)-**7** and the thio alcohol (2*S*,3*R*)-**7** obtained from (2*S*,3*R*,R_S)-**6** are diastereoisomers having different NMR spectra.

Table 3. Selected ^{13}C NMR Data for Compounds **12** in $CDCl_3$

	(1*R*,2*S*,3*S*)	(1*R*,2*R*,3*S*)	(1*R*,2*S*,3*R*)	(1*R*,2*R*,3*R*)	(1*S*,2*S*,3*S*)	(1*S*,2*R*,3*S*)	(1*S*,2*S*.3*R*)	(1*S*,2*R*,3*R*)
C-1	78.23	80.45	77.20	77.53	76.90	76.23	75.75	73.38
	(31)[a]	(19)	(31.5)	(19.5)	(18.5)	(33.5)	(18.5)	(24)
C-2	121.14	b	119.41	b	119.10	119.90	b	b
	(246.5)	b	(247)	b	(261)	(249.5)	b	b
C-3	42.54	42.95	41.96	39.13	40.60	43.23	41.98	39.92
	(23)	(21)	(20.5)	(20.5)	(21)	(22)	(20)	(20.5)
C-4	30.50	30.27	29.17	27.68	28.51	29.47	30.41	29.06
	(≤0.5)	(≤0.5)	(≤0.5)	(7.5)	(5)	(≤0.5)	(≤0.5)	(6)
C-5	62.72	61.79	63.83	63.24	66.62	67.98	63.62	62.99
	(≤0.5)	(≤0.5)	(≤0.5)	(≤0.5)	(≤0.5)	(≤0.5)	(2)	(5.5)
C-6	17.81	12.96	11.18	13.11	14.30	11.14	11.15	13.03
	(4.5)	(5.5)	(7.5)	(≤0.5)	(≤0.5)	(4.5)	(5)	(≤0.5)

[a]Values in parentheses refer to *J*(C,F)/Hz; [b]not assigned.

In the (1*R*,2*S*,3*S*,5*R*,R_S)-**12** isomer the NOE observed between H-1, assumed as ß in figure 1C, and H-3 (2%) but not with H_3-6 and that observed between H-5ß and F-2 (3%) permitted to assign as *S* the chirality at C-2 and C-3 while in compound (1*R*,2*S*,3*R*,5*R*,R_S)-**12** the NOE observed between H-5ß and F-2 (4.5%) and the fact that a smaller NOE was observed between F-2ß and H-3 with respect to that observed for the corresponding atoms in the C-3 epimer (0.5 *vs* 4%) indicate as *S* and *R* the chirality at C-

Table 4. Selected Connectivities Established by ^1H-{^{19}F} NOE Difference Experiments in $CDCl_3$

	Protons affected (%)							
	(1*R*,2*S*,3*S*)	(1*R*,2*R*,3*S*)	(1*R*,2*S*,3*R*)	(1*R*,2*R*,3*R*)	(1*S*,2*S*,3*S*)	(1*S*,2*R*,3*S*)	(1*S*,2*S*,3*R*)	(1*S*,2*R*,3*R*)
H-1	5.5	1.5	5	2.5	2.5	7.5	1.5	6
H-3	4	1.5	<0.5	7	6 5	<0.5	<0.5	2
H-4α		1 5				1		
H-4ß			1				1.5	
H-5	3		4 5		1		2	
H_3-6	<0.5	1	1	0.5	0.5	0 5	1	<0.5

2 and C-3.

For the remaining couple of cyclopentanols **12**, both having the *R* configuration at C-2, the assignment of the *S* chirality at C-3 was based on the higher field experienced by the fluorine atom in compound (1*R*,2*R*,3*S*,5*R*,R_S)-**12** than in the C-3 epimer (-137.17 *vs* -127.66). As expected, a greater NOE was observed for the latter compound, (1*R*,2*R*,3*R*,5*R*,R_S)-**12**, between the *syn*-disposed F-2α and H-3α atoms with respect to that exhibited by the corresponding *anti*-disposed atoms in the former epimer (7 *vs* 1.5%).

In conclusion, although the diastereoselectivity of the process is moderate, it must be emphasized that the radical methodology discussed here offers very mild reaction conditions, under which the reactive chlorine atom and the three chiral centres at the non-radical carbon and at sulfur survive unaltered, so that highly functionalized *gem*-chlorofluoro-substituted cyclopentanol derivatives can be obtained.

EXPERIMENTAL

General Details

^{1}H, ^{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 ^{1}H 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 $60F_{254}$ Merck plates; column chromatographies were performed with silica gel 60 (60-200 μm, Merck). Run times (R_T) were determined on a Waters 600E HPLC instrument using LiChrosorb Si60 (5 μm, Merck) prepacked columns and hexane and ethyl acetate HPLC-grade solvents (Merck). Tetrahydrofuran (THF) was freshly distilled from lithium aluminium hydride; diisopropylamine was distilled from calcium hydride and stored over molecular sieves (4Ä); benzene was distilled over calcium chloride and stored over molecular sieves (4Ä); in all other cases, commercially available reagent-grade solvents were employed without purification.

(R)-4-[(4-Methylphenyl)sulfinyl]but-1-ene (3)

4-Bromo-1-butene (66.0 g, 48.8 mmol) in anhydrous ethyl ether (150 ml) was added dropwise to a stirred suspension of Mg (11.8 g, 48.8 mmol), activated by adding a crystal of iodine, in the same solvent (70 ml). The solution was stirred for two additional hours, ethyl ether was removed under reduced pressure and benzene (800 ml) was added. The benzene solution of the Grignard reagent (**2**) was cooled to 5-10 °C and a solution of (-)-(1*R*,2*S*,5*R*)-menthyl (*S*)-*p*-toluene-sulfinate (**1**) (71.8 g, 24.4 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 ethyl ether (3x400 ml); the combined organic layers were washed with a diluted solution of $NaHCO_3$ (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 (3:2 hexane/ethyl acetate), gave (+)-(*R*)-4-[(4-methylphenyl)sulfinyl]but-1-ene (**3**) (46.5 g, 24.0 mmol; 98.2% yield) as a yellowish oil: $[\alpha]_D^{20}$ + 20.33° (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 7.6-7.2 (4 H, m, ArH), 5.75 (1 H, m, C<u>H</u>=CH_2), 5.06 and 5.03 (2 H, m, CH=C<u>H</u>$_2$), 2.85 and 2.40 (4 H, m, C<u>H</u>$_2$-C<u>H</u>$_2$) and 2.43 (3 H, br s, Me)

(3R,R_S)- and (3S,R_S)-1,1-Dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl]hex-5-en-2-one (5)

Ethyl dichlorofluoroacetate (**4**) (2.10 g, 12.0 mmol) in THF (2 ml) was added dropwise at -65°C under argon to a solution of the lithium derivative [generated by LDA (12.5 mmol) in THF (20 ml)] of (R_S)-4-[(4-methylphenyl)sulfinyl] butene (**3**) (2.00 g, 10.3 mmol). After five min at the same temperature, an excess of a saturated aqueous solution of ammonium chloride was added, the layers were separated and the aqueous phase was extracted with ethyl acetate (3x50 ml). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure and the residue [a mixture of (3R,R_S)- and (3S,R_S)-**5**, both in keto and hydrate forms (c.a. 80% yield)] was reduced without purification to give a mixture of the corresponding more stable secondary alcohols.

(2S,3R,R_S)-, (2R,3R,R_S)-, (2S,3S,R_S)- and (2R,3S,R_S)-1,1-Dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl] hex-5-en-2-ols (6)

A suspension of $NaBH_4$ (0.40 g, 10.3 mmol) in a 9:1 mixture of methanol/30% aq. NH_3 (5 ml) was dropped into a solution of (3R,R_S)/(3S,R_S)-**5** mixture (10.0 mmol) dissolved in the same solvent (20 ml) at -20°C. After 10 min at the same temperature, a solution of hydrochloric acid was added to pH 4, methanol was evaporated under reduced pressure and the organic products were extracted with ethyl acetate (3x50 ml). The collected organic phases were dried on anhydrous sodium sulfate and the solvent was removed under reduced pressure to give a 3.5:1.5:1.9:1.0 mixture (HPLC ratio, 6:4 $CHCl_3$/AcOEt) of the four diastereoisomeric alcohols **6**. The residue was flash chromatographed (9:1 $CHCl_3$/AcOEt) in order to obtain (2S,3R,R_S)-**6** (1.18 g, 35.2% yield from **3**) and (2R,3S,R_S)-**6** (0.34 g, 10.0% yield from **3**) in optically pure form and the (2R,3R,R_S)-/(2S,3S,R_S)-**6** mixture. Flash chromatography (4:1 cyclohexane/ethyl acetate) gave (2R,3R,R_S)-**6** (0.51 g, 15.2% yield from **3**) and (2S,3S,R_S)-**6** (0.66 g, 19.6% yield from **3**) as pure compounds.

(2S,3R,R_S)-**6**: R_f 0.35 (9:1 $CHCl_3$/AcOEt); $[\alpha]_D^{20}$ + 97.3° (*c* 1.0, $CHCl_3$); m.p. 130-132°C (isopropyl ether); ^{1}H NMR ($CDCl_3$), δ: 7.63 and 7.36 (4 H, m, ArH), 5.72 (1 H, m, H-5), 5.46 (1 H, d, J = 6.0 Hz, OH-2), 5.18 and 5.11 (2 H, m, H_2-6), 4.54 (1 H, ddd, J = 6.7, 6.5 and 6.0 Hz, H-2), 3.28 (1 H, dt, J = 6.7 and 5.5 Hz, H-3), 2.58 and 2.23 (2 H, m, H_2-3) and 2.44 (3 H, br s, Me). R_T 4.39 min (3:2 $CHCl_3$/AcOEt, 1.0 ml/min). Found: C, 48.2; H, 4.60; $C_{13}H_{15}Cl_2FO_2S$ requires: C, 48.0; H, 4.61%.

(2R,3S,R_S)-**6**: R_f 0.20 (9:1 $CHCl_3$/AcOEt); $[\alpha]_D^{20}$ + 145.4° (*c* 1.0, $CHCl_3$); m.p. 123-125°C (isopropyl ether); ^{1}H NMR ($CDCl_3$), δ: 7.48 and 7.35 (4 H, m, ArH), 6.30 (1 H, d, J = 6.6 Hz, OH-2), 5.55 (1 H, m, H-5), 5.14 and 5.12 (2 H, m, H_2-6), 4.47 (1 H, ddd, J = 10.9, 6.6 and 2.9 Hz, H-2), 3.07 (1 H, ddd, J = 9.7, 4.3 and 2.9 Hz, H-3), 2.60 and 2.32 (2 H, m, H_2-4) and 2.42 (3 H, br s, Me). R_T 7.37 min (3:2 $CHCl_3$/AcOEt).

(2R,3R,R_S)-**6**: R_f 0.30 (9:1 $CHCl_3$/AcOEt), 0.35 (4:1 cyclohexane/AcOEt); $[\alpha]_D^{20}$ + 183.9° (*c* 1.0, $CHCl_3$); m.p. 73-74°C (isopropyl ether); ^{1}H NMR ($CDCl_3$), δ: 7.49 and 7.38 (4 H, m, ArH), 5.94 (1 H, m, H-5), 5.27 and 5.23 (2 H, m, H_2-6), 4.45 (1 H, ddd, J = 15.0, 3.5 and 1.4 Hz, H-2), 3.07 (1 H, ddd, J = 10.2, 3.6 and 1.4 Hz, H-3), 2.96 and 2.84 (2 H, m, H_2-4) and 2.44 (3 H, br s, Me). R_T 5.65 min (3:2 $CHCl_3$/AcOEt).

(2S,3S,R_S)-**6**: R_f 0.30 (9:1 $CHCl_3$/AcOEt), 0.30 (4:1 cyclohexane/AcOEt); $[\alpha]_D^{20}$ +179.0° (*c* 1.0, $CHCl_3$); m.p. 76-78°C (isopropyl ether); ^{1}H NMR ($CDCl_3$), δ: 7.48 and 7.33 (4 H, m, ArH), 5.84 (1 H, m, H-5), 5.17 and 5.15 (2 H, m, H_2-6), 4.80 (1 H, br signal, OH-2), 4.51 (1 H, dd, J = 14.7 and 1.3 Hz, H-2), 3.09 (1 H, ddd, J = 9.6, 3.8 and 1.3 Hz, H-3), 2.91 and 2.77 (2 H, m, H_2-4) and 2.42 (3 H, br s, Me). R_T 4.90 min (3:2 $CHCl_3$/AcOEt).

(2S,3R)-, (2R,3R)-, (2S,3S)-, and (2R,3S)-1,1-Dichloro-1-fluoro-3-[(4-methylphenyl)thio]hex-5-en-2-ols **7**. *General procedure*

Trifluoroacetic anhydride (0.72 ml, 4.55 mmol) was added to a mixture of alcohol **6** (0.65 mmol) and sodium iodide (300 mg, 1.95 mmol) in acetone (10 ml) stirred at -40°C under argon. After 10 min. at the same temperature the reaction was quenched with an excess of a saturated aqueous sodium sulfite and sodium hydrogen carbonate solutions. 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 a residue which, upon flash chromatography (9:1 hexane/Et_2O) gave, like yellowish oils: (2*S*,3*R*)-**7**: R_f 0.35; $[\alpha]_D^{20}$ +2.24° (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 7.38 and 7.12 (4 H, m, ArH), 5.87 (1 H, m, H-5), 5.17 and 5.15 (2 H, m, H_2-6), 4.03 (1 H, ddd, *J* = 10.3, 8.0 and 3.5 Hz, H-2), 3.69 (1 H, d, *J* = 8.0 Hz, OH-2), 3.60 (1 H, dt, *J* = 3.5 and 7.1 Hz, H-3), 2.50 and 2.45 (2 H, m, H_2-4) and 2.33 (3 H, br s, Me). Found: C, 49.8; H, 4.81; $C_{13}H_{15}Cl_2FOS$ requires: C, 50.5; H, 4.85%.

(2*R*,3*R*)-**7**: R_f 0.35; $[\alpha]_D^{20}$ +39.4° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$), δ: 7.35 and 7.13 (4 H, m, ArH), 6.03 (1 H, m, H-5), 5.19 and 5.14 (2 H, m, H_2-6), 4.17 (1 H, ddd, *J* = 14.8, 5.4 and 2.2 Hz, H-2), 3.70 (1 H, ddd, *J* = 9.8, 3.7 and 2.2 Hz, H-3), 3.06 (1 H, d, *J* = 5.4 Hz, OH-2), 2.75 and 2.42 (2 H, m, H_2-4) and 2.34 (3 H, br s, Me).

(2*S*,3*S*)-**7**: R_f 0.35; $[\alpha]_D^{20}$ -42.8° (*c* 0.5, $CHCl_3$); its ^1H NMR ($CDCl_3$) is identical to that of the enantiomer (2*R*,3*R*)-**7**.

(2*R*,3*S*)-**7**: R_f 0.35; $[\alpha]_D^{20}$ -2.1° (*c* 1.1, $CHCl_3$); its ^1H NMR ($CDCl_3$) is identical to that of the enantiomer (2*S*,3*R*)-**7**.

Phenylpropionic Esters (9) of (2S,3R)-, (2R,3R)-, (2S,3S)-, and (2R,3S)-7. General Procedure.

4-(Dimethylamino)pyridine (1.2 mg, 0.01 mmol) was added to a dichloromethane solution (1 ml) of thio alcohol **7** (0.10 mmol), (+)-(*S*)-2-phenylpropionic acid (15.3 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 *n*-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/AcOEt) to give the propionic ester **9**. Similarly, starting from (-)-(*R*)-**8**, the corresponding diastereoisomeric ester was obtained.

From (2*S*,3*R*)-**7**: (+)-(*S*)-**9**, ^1H NMR ($CDCl_3$), δ: 7.45-7.05 (9 H, m, ArH), 5.80 (1 H, m, H-5), 5.55 (1 H, dd, *J* = 10.3 and 4.3 Hz, H-2), 5.13 and 5.12 (2 H, m, H_2-6), 3.75 (1 H, q, *J* = 7.2 Hz, H-2'), 3.57 (1 H, dt, *J* = 4.3 and 6.8 Hz, H-3), 2.40 (2 H, m, H_2-4), 2.35 (3 H, br s, ArMe) and 1.58 (3 H, br s, H_3-3'); (-)-(*R*)-**9**, ^1H NMR ($CDCl_3$), δ: 7.45-7.05 (9 H, m, ArH), 5.69 (1 H, m, H-5), 5.57 (1 H, dd, *J* = 11.9 and 3.5 Hz, H-2), 5.07 and 5.02 (2 H, m, H_2-6), 3.86 (1 H, q, *J* = 7.2 Hz, H-2'), 3.52 (1 H, ddd, *J* = 7.6, 6.3 and 3.5 Hz, H-3), 2.32 (3 H, br s, ArMe), 2.26 and 2.18 (2 H, m, H_2-4) and 1.60 (3 H, d, *J* = 7.2 Hz, H-3').

From (2*R*,3*R*)-**7**: (+)-(*S*)-**9**, ^1H NMR ($CDCl_3$), δ: 7.45-7.05 (9 H, m, ArH), 5.83 (1 H, m, H-5), 5.52 (1 H, dd, *J* = 16.9 and 1.6 Hz, H-2), 5.04 and 4.98 (2 H, m, H_2-6), 3.87 (1 H, q, *J* = 7.2 Hz, H-2'), 3.59 (1 H, ddd, *J* = 10.7, 3.2 and 1.6 Hz, H-3), 2.57 and 1.75 (2 H, m, H_2-4), 2.33 (3 H, br s, ArMe) and 1.60 (3 H, br s, H_3-3'); (-)-(*R*)-**9**, ^1H NMR ($CDCl_3$), δ: 7.45-7.05 (9 H, m, ArH), 5.96 (1 H, m, H-5), 5.52 (1 H, dd, *J* = 16.5 and 1.8 Hz, H-2), 5.13 (2 H, m, H_2-6), 3.89 (1 H, q, *J* = 7.2 Hz, H-2'), 3.65 (1 H, ddd, *J* = 10.3, 3.2 and 1.8 Hz, H-3), 2.72 and 2.13 (2 H, m, H_2-4), 2.34 (3 H, br s,

ArMe) and 1.64 (3 H, d, J = 7.2 Hz, H_3-3').

The couples of esters obtained by reacting with the two enantiomers of phenylpropionic acid the thio alcohols (2*S*,3*S*)-**7** and (2*R*,3*S*)-**7** showed ^{1}H NMR spectra identical to those of the corresponding esters of the enantiomeric thio alcohols (2*R*,3*R*)-**7** and (2*S*,3*R*)-**7**.

General Procedure of Radical Cyclization of Alcohols **6** *by the Photolytic Method.*

A solution of alcohol **6** (1.0 mmol) and tributyltin hydride (1.2 mmol) in deoxygenated 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 substrates. During the irradiation, the temperature was kept at 35°C. After evaporation of the benzene, acetonitrile (5 ml) was added and washed with hexane (3x5ml). Acetonitrile was removed under reduced pressure and the residue was flash chromatographed.

From (2S,3R,R_S)-**6** a 1.0 : 1.0 : 5.4 : 5.8 (HPLC ratio, 1:1 hexane/AcOEt, 1.0 ml/min) mixture of (1*S*,2*S*,3*R*,5*R*,R_S)-/(1*S*,2*R*,3*R*,5*R*,R_S)-/(1*S*,2*S*,3*R*,5*R*,R_S)-/(1*S*,2*R*,3*S*,5*R*,R_S)-**12** in 105 min was obtained (global yield: 75%). By flash chromatography (3:2 cyclohexane/ethyl acetate), the (1*S*,2*S*,3*R*,5*R*,R_S)-/(1*S*,2*R*,3*R*,5*R*,R_S)-**12** mixture (R_f 0.35) was separated from the (1*S*,2*S*,3*R*,5*R*,R_S)-/(1*S*,2*R*,3*S*,5*R*,R_S)-**12** mixture (R_f 0.25). By successive fractional crystallizations (isopropyl ether) (1*S*,2*R*,3*S*,5*R*,R_S)-**12** (33% yield) was obtained in optically pure form: R_f 0.25 (3:2 cyclohexane/AcOEt); $[\alpha]_D^{20}$ +147.3° (*c* 0.5, $CHCl_3$); m.p. 150-152 °C (isopropyl ether); R_T 12.37 min. (1:1 hexane/AcOEt, 1.0 ml/min). Found C, 53.8; H, 5.54; $C_{13}H_{16}ClFO_2S$ requires: C, 53.7; H, 5.50%.

From (2*R*,3*R*,R_S)-**6** a 3.0:1.0:13.2:4.6 (HPLC ratio, 3:2 hexane/AcOEt) mixture of (1*R*,2*S*,3*R*,5*R*,R_S)-/(1*R*,2*R*,3*R*,5*R*,R_S)-/(1*R*,2*S*,3*S*,5*R*,R_S)-/(1*R*,2*R*,3*S*,5*R*,R_S)-**12** in 60 min was obtained (90% overall yield). Flash chromatographic separation (3:2 cyclohexane/ethyl acetate) gave (1*R*,2*S*,3*R*,5*R*,R_S)-/(1*R*,2*R*,3*S*,5*R*,R_S)-**12** mixture (R_f 0.35) and (1*R*,2*S*,3*S*,5*R*,R_S)-**12** (R_f 0.30) and (1*R*,2*R*,3*S*,5*R*,R_S)-**12** (R_f 0.20) both in optically pure form. By fractional crystallization (isopropyl ether) of the obtained diastereoisomeric mixture (1*R*,2*S*,3*R*,5*R*,R_S)-**12** was obtained as pure compound. (1*R*,2*S*,3*R*,5*R*,R_S)-**12** (12.4% yield): $[\alpha]_D^{20}$ +2.2° (*c* 1.1, $CHCl_3$); m.p. 195-197°C (isopropyl ether). R_T 11.52 min (3:2 hexane/ethyl acetate, 1.0 ml/min). Found C, 53.6; H, 5.12; $C_{13}H_{16}ClFO_2S$ requires: C, 53.7; H, 5.50%.

(1*R*,2*S*,3*S*,5*R*,R_S)-**12** (54.4% yield): $[\alpha]_D^{20}$ +189° (*c* 0.9, $CHCl_3$); m.p. 149-151 °C (isopropyl ether); R_T 17.50 min. Found C, 53.3; H, 5.30; $C_{13}H_{16}ClFO_2S$ requires: C, 53.7; H, 5.50%.

(1*R*,2*R*,3*S*,5*R*,R_S)-**12** (19.0% yield): $[\alpha]_D^{20}$ +115.1° (*c* 0.8, $CHCl_3$); m.p. 200-202 °C (isopropyl ether); R_T 20.30 min. Found C, 53.7; H, 5.50; $C_{13}H_{16}ClFO_2S$ requires: C, 53.7; H, 5.50%.

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