Synthesis of Enantiomerically Pure Fluoro- and *gem*-Chlorofluorocyclohexane Derivatives

Alberto Arnone, Pierfrancesco Bravo,* Massimo Frigerio, and Fiorenza Viani

Centro di Studio per le Sostanze Organiche Naturali del Consiglio Nazionale delle Ricerche; Dipartimento di Chimica, Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy

Giancarlo Cavicchio and Marcello Crucianelli

Dipartimento di Chimica, Ingegneria Chimica e Materiali, Università di L'Aquila, via Vetoio, I-67010 L'Aquila, Italy

Received April 27, 1994®

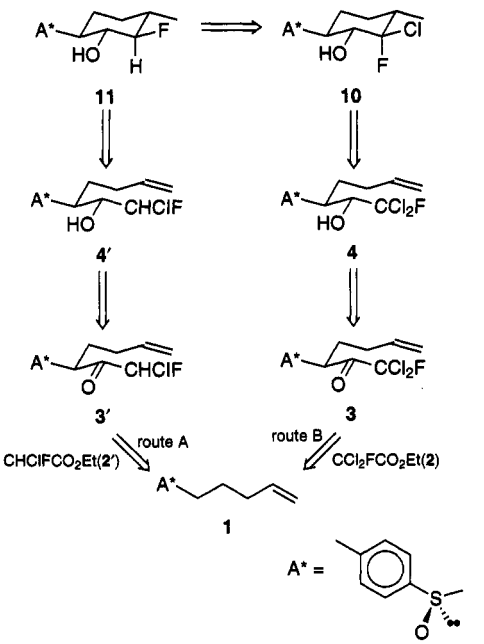
gem-Chlorofluorocyclohexanols **10** are prepared in good yields by radical-promoted cyclization from the corresponding ω-dichlorofluoroheptenols **4**. Fluorocyclohexanols **11** are obtained either from **10** or in a single step from open-chain alcohols **4**. The stereochemical outcome of both the radical cyclization and the reductive dechlorination is discussed. Elimination of the chiral auxiliary sulfinyl group and appropriate elaborations afford enantiomerically pure derivatives **12**–**17**. Relative and absolute configurations as well as preferred conformations in solution for all final compounds are provided.

Introduction

As a part of a continuing program directed toward the asymmetric syntheses of selectively fluorinated organic molecules by the chiron route,[1] we became interested in the construction of selectively fluorinated carbo- and heterocyclic molecules.[2] As reported in previous papers,[3] the connection through ionic and radical reactions of ethyl fluoroacetate, a two-carbon fluorinated fragment, and arylsulfinylpent-5-ene, a five-carbon fragment holding the radical acceptor along with the chiral auxiliary group A* for asymmetric induction, provided an appropriate route to the carbon skeleton of optically pure polysubstituted difluorocyclohexane derivatives.

Two strategies are conceivable for the construction of monofluorocyclohexane derivatives from commercially available ethyl chlorofluoro-substituted acetates as sources of the fluorinated fragment. Racemic ethyl chlorofluoroacetate (**2'**), upon condensation with alkenyl sulfoxide **1** and hydride-promoted reduction of the obtained β-keto sulfoxide **3'**, would give rise to open-chain intermediates **4'** which, upon radical cyclization, would straightforwardly lead to the desired monofluorocyclohexane derivatives **11** as shown in Scheme 1. On the other hand, ethyl dichlorofluoroacetate (**2**) and alkenyl sulfoxide **1** would provide open-chain intermediate **4**. Radical-promoted cyclization to *gem*-chlorofluorocyclohexane derivatives **10** and reductive dechlorination would provide the monofluorocyclohexane derivatives **11**.

Scheme 1



The route A would provide a mixture of eight diastereoisomer intermediates **4'** because of the newly introduced stereogenic carbons and the use of racemic ethyl chlorofluoroacetate, and moreover, the chirality at C-1 would be lost during the radical-mediated ring forming reaction. Therefore, the route B, which makes use of sulfenyl pentene **1**, bearing the chiral auxiliary group A*, and of ethyl dichlorofluoroacetate (**2**) as fluorinated starting material, has been explored.

Results and Discussion

Substrate Synthesis. The required open-chain intermediates **4** were obtained by condensing the lithium

* Author to whom correspondence should be addressed. Phone: (39) 2-23993033. Fax: (39) 2-23993080.

® Abstract published in *Advance ACS Abstracts,* September 1, 1994.

(1) (a) Bravo, P.; Resnati, G. *Tetrahedron Lett.* **1985**, *26*, 5601–5604; (b) *Tetrahedron Lett.* **1987**, *28*, 4865–4866; (c) *J. Chem. Soc., Chem. Commun.* **1988**, 218–219; (d) *Tetrahedron: Asymmetry* **1990**, *1*, 661–692. (e) Bravo, P.; Piovosi, E.; Resnati, G. *Synthesis* **1986**, 579–582; (f) *J. Chem. Res., Synop.* **1989**, 134–135; *J. Chem. Res., Miniprint* 1115–1147; (g) *J. Chem. Soc., Perkin Trans. 1* **1989**, 1201–1208. (h) Bravo, P.; Piovosi, E.; Resnati, G.; De Munari, S. *Gazz. Chim. Ital.* **1988**, *118*, 115–122. (i) Bravo, P.; Frigerio, M.; Resnati, G. *Synthesis* **1988**, 955–960. (j) Bravo, P.; Resnati, G.; Viani, F.; Arnone, A. *J. Chem. Soc., Perkin Trans. 1* **1989**, 839–840.

(2) (a) Cavicchio, G.; Marchetti, V.; Arnone, A.; Bravo, P.; Viani, F. *Tetrahedron* **1991**, *47*, 9439–9448. (b) Arnone, A.; Bravo, P.; Viani, F.; Cavicchio, G. *Tetrahedron: Asymmetry* **1991**, *2*, 399–402. (c) Arnone, A.; Bravo, P.; Cavicchio, G.; Frigerio, M.; Viani, F. *Tetrahedron* **1992**, *48*, 8523–8540. (d) *Tetrahedron* **1993**, *49*, 6873–6884. (e) Arnone, A.; Bravo, P.; Viani, F.; Cavicchio, G.; Crucianelli, M.; Marchetti, V. *Tetrahedron* **1993**, *49*, 4253–4266.

(3) (a) Arnone, A.; Bravo, P.; Cavicchio, G.; Frigerio, M.; Viani, F. *Tetrahedron: Asymmetry* **1992**, *3*, 9–12 (preliminary results on the subject are reported). (b) Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1994**, *59*, 3459–3466.

0022-3263/94/1959-6448$04.50/0

derivative of (R_S)-5-[(4-methylphenyl)sulfinyl]pent-1-ene (**1**) and ethyl dichlorofluoroacetate (**2**) (Scheme 1). 1,1-Dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl]hept-6-en-2-one (**3**) was obtained in 80% yield as a mixture of the (3*R*,R_S)- and (3*S*,R_S)-diastereoisomers both as mixtures of their keto and hydrate forms. Because of the difficulties connected with separation of labile ketones **3** from the mixture, the crude product was submitted to hydride-promoted reduction with DIBALH in THF or with sodium borohydride in methanol/aqueous ammonia. All four (2*S*,3*R*,R_S)-, (2*R*,3*R*,R_S)-, (2*S*,3*S*,R_S)-, and (2*R*,3*S*,R_S)-1,1-dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl]hept-6-en-2-ols **4** were separated in optically pure form by column chromatography of the mixtures of the corresponding secondary alcohols **4** obtained in different ratios. In order to determine absolute configuration at C-2 for substrates **4**, single diastereoisomers **4** were reduced at sulfur with sodium iodide and trifluoroacetic anhydride in acetone and the corresponding thio derivatives **5**, obtained in nearly quantitative yields, were esterified alternatively with (*R*)-(−)- and (*S*)-(+)-phenylpropionic acid **6**.[4]

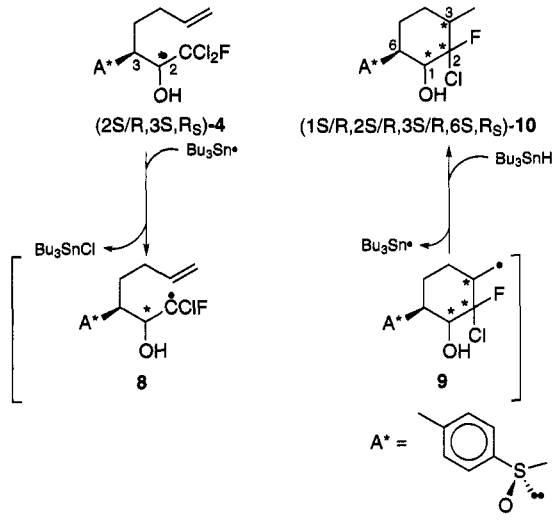
Chlorofluorocyclohexane Derivatives. Single diastereoisomeric ω-dichlorofluoro olefins (2*S*,3*S*,R_S)- and (2*R*,3*S*,R_S)-**4** were treated with an excess of tributyltin hydride in benzene solution in the presence of AIBN as radical-chain initiator. The energy required for bond breaking on AIBN was supplied by heating the benzene solution at 74 °C or alternatively by irradiating the solution kept at 35 °C with a mercury discharge lamp. In both cases a radical-chain reaction takes place as follows (Scheme 2). Hydrogen abstraction from tributyltin hydride by dissociated AIBN generates a tributyltin radical, which upon abstraction of a chlorine atom from the dichlorofluoroalkyl group generates a chlorofluoroalkyl radical **8**. The electrophilic radical **8** is trapped intramolecularly by the terminal vinyl group in a fast *exo-trig* cyclization process giving the cyclohexylmethyl radical **9**, which upon hydrogen abstraction from a second tributyltin hydride molecule led to final molecules **10** and to a new tributyltin radical, which propagates the chain reaction. Global yields and diastereoisomeric ratios of the obtained product mixtures are reported in the Experimental Section.

Some useful observations on the results can be drawn as follows. In line with what has been already observed for cyclization of similar hept-6-enyl radicals,[2b] only cyclohexane derivatives are formed through the *exo-trig* pathway. The reaction carried out at refluxing benzene temperature (AIBN) and at room temperature (*hν*) gave mixtures of the same products in similar ratios and comparable yields (see Experimental Section). The reactivity of the chlorine of the terminal dichlorofluoroalkyl group of **4** must be large enough compared with that of the chlorofluoromethylene inserted in the cyclic product **10**; in fact, when a large excess of tributyltin hydride is avoided and the reaction is quenched as soon as open-chain starting compound **4** is consumed, the *gem*-chlorofluorocyclohexanes **10** are the only reaction products. Moreover, the capture of the radical by the olefin is fast enough to avoid reductive quenching by the tributyltin hydride.

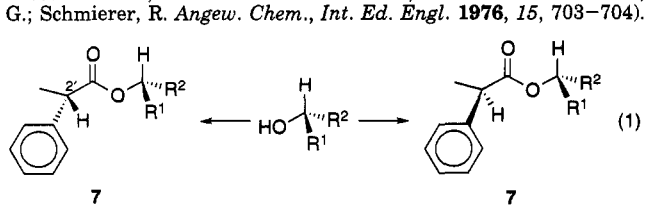
During the cyclization two new asymmetric centers are formed. The product mixture ratios show that asymmetric induction depends primarily on the relative stereochemistry at C-2 and C-3 in the open-chain derivatives **4**, and the results can be explained by assuming an early transition state so that the more favorable conformations are assumed by the radical intermediate **8** when folding in the intramolecular process to give **10**.[5] For (2*S*,3*S*,R_S)-**8**, a chairlike conformation as depicted in Scheme 3 will be the most favorable one because the bulkier substituent A* lies in an equatorial position. Therefore, in order to avoid 1,3-diaxial interactions the axially disposed hydroxyl group forces the terminal vinyl group to assume a pseudoequatorial position. On the other hand, the chlorofluoroalkyl radical can approach the vinyl group in both orientations because, although the difference of the van der Waals radii of the atoms is noticeable (r_F = 1.35 Å, r_{Cl} = 1.80 Å), no significant steric interactions arise in both arrangements. This also accounts for the formation of (2*S*,3*S*)-**10** and (2*R*,3*S*)-**10** in a relative ratio of 1.0:1.4.

In the open-chain intermediates **8** arising from (2*R*,-3*S*,R_S)-**4** the two substituents, having a *threo* relative arrangement, in the preferred conformation are both equatorially disposed. The terminal vinyl group lacking 1,3-diaxial interaction with the hydroxyl may therefore assume either a pseudoequatorial or a pseudoaxial orientation (Scheme 4). Therefore, a quite equimolecular mixture of diastereoisomers is formed. The two most

Scheme 2. Radical Cyclization of Alcohols



(4) The assignment was based on the upfield shift (Δδ ≃ 0.05−0.35 ppm) observed for the protons of the pentenyl chain of compounds (2*R*,3*S*,2′*S*)- and (2*R*,3*R*,2′*S*)-**7** and (2*S*,3*R*,2′*R*)- and (2*S*,3*S*,2′*R*)-**7** with respect to the corresponding protons of the C-2′ epimers as a consequence of the shielding effect exerted by the phenyl group of the esterifying acid in the preferred conformations shown in eq 1. (Bravo, P.; Ganazzoli, F.; Resnati, G.; De Munari, S.; Albinati, A. *J. Chem. Res., Synop.* **1988**, 216−217; *J. Chem. Res., Miniprint* **1988**, 1701−1739. Helchen, G. *Tetrahedron Lett.* **1974**, 1527−1530. Helmchen, G.; Schmierer, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 703−704).

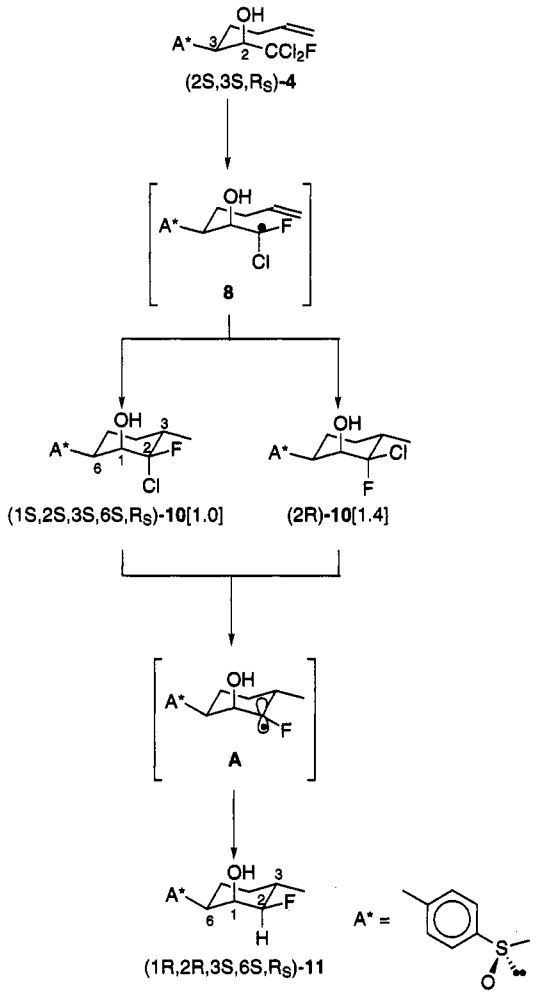


(1)

(2S,3R/S)-**5** R^1 = CH(S-*p*-Tol)$CH_2CH_2CH{=}CH_2$
R^2 = CCl_2F
(2R,3R/S)-**5** R^1 = CCl_2F
R^2 = CH(S-*p*-Tol)$CH_2CH_2CH{=}CH_2$

(5) Zipse, H.; He, J.; Houk, K. N.; Giese, B. *J. Am. Chem. Soc.* **1991**, *113*, 4324−4325.

Scheme 3[a]



[a] Reaction conditions: Bu_3SnH, C_6H_6, $h\nu$ (350 nm), 35 °C, or Δ (74 °C).

abundant diastereoisomers were (3,*S*)-epimers, having the methyl group equatorially disposed.

Fluorocyclohexane Derivatives. Reductive dechlorination by tributyltin hydride[6] of compounds **10** to monofluoro derivatives **11** partially occurred when the cyclization reactions were run photochemically.

Starting from chlorofluorocyclohexanol (1*S*,2*S*,3*S*)-**10** having the chlorine atom axially disposed, through exhaustive treatment with tributyltin hydride at 74 °C in benzene monofluorocyclohexane derivative (1*R*,2*R*,3*S*)-**11** was obtained with a clean retention of configuration (Scheme 3). The same dechlorination reaction applied on derivatives **10** having chlorine equatorially disposed led, with inversion of configuration, to monofluoro derivatives (1*R*,2*R*,3*S*)- and (1*S*,2*R*,3*S*)-**11** from, respectively, (1*S*,2*R*,3*S*)- and (1*R*,2*R*,3*S*)-**10** (Schemes 3 and 4).

Though some stereochemical studies have been made on the reduction with tributyltin hydride of *gem*-dihalocyclopropane[7] and cyclobutane[8] derivatives, there is no evidence for the same reaction performed on *gem*-dihalocyclohexanes. In general, steric factors play a key role in determining the stereochemical course of the tin hydride reaction.[9] Moreover, in secondary six-membered radicals axial substituents in a β position with respect to the radical center lead to an increase in *anti* (axial) attack.[10] The high diastereoselectivity of the process herewith described can be rationalized taking into account the attack of the good radical trap Bu_3SnH[11] on the planar[12] radicals **A**–**C** from the less hindered side of the preferred conformation (axial attack) because of the high tendency for an axial C–H bond in cyclohexanes[13] to be formed.

From the above results the production of monofluorocyclohexanols from open-chain alcohols **4** in a single step would be a more profitable procedure. Only one diastereoisomer, (1*R*,2*R*,3*S*)-**11**, having the methyl and fluorine substituents in a *trans*-diequatorial arrangement, was isolated when (2*S*,3*S*,*R*S)-**4** was reacted with an excess of Bu_3SnH for longer reaction times (Experimental Section), while a 1.3:1.0 ratio mixture of monofluorohexanols (1*S*,2*R*,3*S*)- and (1*S*,2*R*,3*R*)-**11** was obtained starting from (2*R*,3*S*,*R*S)-**4** as shown in Schemes 3 and 4.

Sulfur-Free Cyclohexane Derivatives. A brief survey of the potential use of the manifold reactivity of the sulfinyl chiral auxiliary group for introducing functionalities on the ring completed this study (Scheme 5). Typical reactions of alkyl aryl sulfoxides, like the reductive desulfenylation and the thermal elimination of sulfinic acid to introduce in the ring a double bond, were chosen. (1*S*,2*R*,3*S*)-2-Fluoro-3-methylcyclohexan-1-ol benzoate (**14**) was obtained in rather good yields through deoxygenation at sulfur (with trifluoroacetic anhydride and sodium iodide) of the corresponding sulfinyl derivative **11** followed by benzoylation and reductive desulfurization with hydrogen in ethanol in the presence of Raney-nickel.

On the other hand, the benzyl derivative (1*R*,2*R*,3*S*)-**15** was heated at reflux in ethanediol to give the corresponding cyclohexene derivative (3*S*,4*R*,5*S*)-**16**. Osmium tetraoxide was chosen to perform on **16** the dihydroxylation leading to (1*R*,2*R*,3*S*,4*R*,5*S*)-3-(benzyloxy)-4-fluoro-5-methylcyclohexane-1,2-diol **17** as unique reaction product.

Structural Assignments. The structure elucidation of the *gem*-chlorofluorocyclohexanols **10**, their precursors **4**, and their derivatives **11**–**17** was performed using ^1H, ^{13}C, and ^{19}F NMR spectroscopy. The absolute configuration at the alcohol centers of compounds **10** followed from that established for the starting alcohols **4** by comparing the chemical shifts of the protons of the pentenyl chain of the esters 7 obtained by reacting the corresponding

(6) Kmvila, H. G. Reduction of Organic Compounds by Organotin Hydrides. *Synthesis* **1970**, *10*, 499–509.

(7) (a) Seyferth, D.; Yamazaki, H.; Alleston, D. L. *J. Org. Chem.* **1963**, *28*, 703–706. (b) Gawronska, K.; Gawronski, J.; Walborsky, H. M. *J. Org. Chem.* **1991**, *56*, 2193–2197.

(8) (a) Aimetti, J. A.; Hamanaka, E. S.; Johnson, D. A.; Kellogg, M. S. *Tetrahedron Lett.* **1979**, *48*, 4631–4634. (b) John, D. I.; Thomas, E. J.; Tyrrell, N. D. *J. Chem. Soc., Chem. Commun.* **1979**, 345–347.

(9) (a) Harton, D.; Priebe, W.; Sznaidman, M. L. *J. Org. Chem.* **1993**, *58*, 1821–1826. (b) Giese, B.; Gröninger, K. S. *Tetrahedron Lett.* **1984**, 2743–2746.

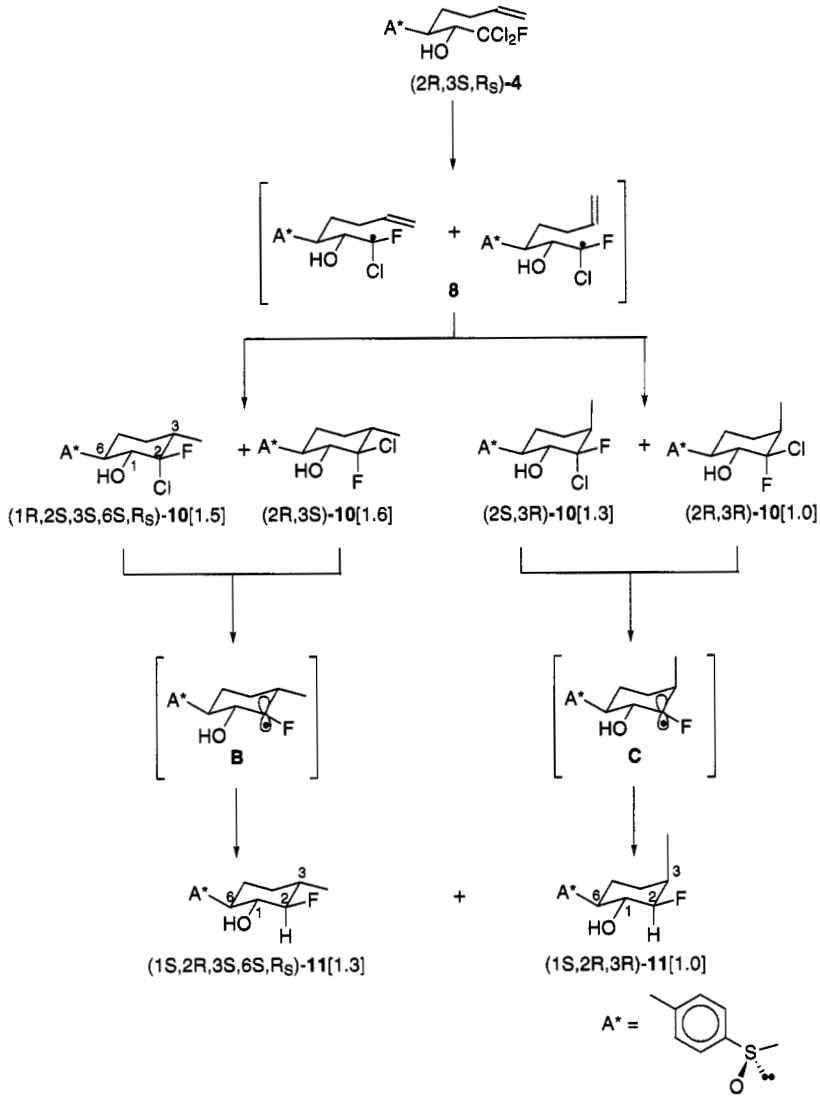
(10) (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969–1146. (b) Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, K. N.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067–4079. (c) Koch, A.; Lamberth, C.; Wetterich, F.; Giese, B. *J. Org. Chem.* **1993**, *58*, 1083–1089.

(11) Jensen, F. R.; Gale, L. H.; Rodgers, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 5793–5799.

(12) (a) Gretter, R. J.; Alliers, R. J. *J. Org. Chem.* **1964**, *29*, 728–731. (b) Fessender, R. W.; Schuler, R. H. *J. Chem. Phys.* **1965**, *43*, 2704–2708. (c) Krusic, P. J.; Bingham, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 230–232. For conformational studies on pyransoyl radicals see: (d) Korth, H. G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* 1986, 1453–1459. (e) Korth, H. G.; Sustmann, R.; Gröninger, K. S.; Witzel, T.; Giese, B. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1461–1464.

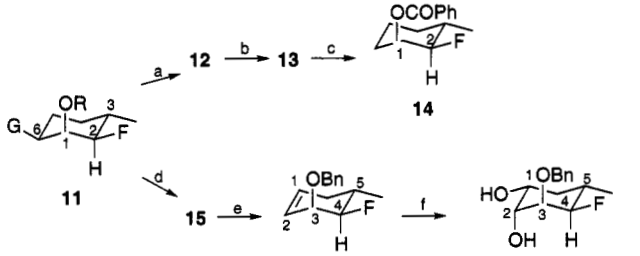
(13) For a comparison with tertiary nitro compounds reduction see: Baumberger, F.; Vasella, A. *Helv. Chim. Acta* **1983**, *66*, 2210–2222.

Scheme 4[a]



[a] Reaction conditions: Bu_3SnH, C_6H_6, *hν* (350 nm), 35 °C, or Δ (74 °C).

Scheme 5. Functional Group Elaborations[a]



	R	G
(1R,2R,3S,6S,RS)-**11**	H	*p*-TolSO
(1R,2R,3S,6S)-**12**	H	*p*-TolS
(1R,2R,3S,6S)-**13**	PhCO	*p*-TolS
(1R,2R,3S,6S,RS)-**15**	Bn	*p*-TolSO

[a] Key: (a) NaI, $(CF_3CO)_2O$, acetone, −40 °C; (b) $PhCO_2H$, 4-(dimethylamino)pyridine, DCC, CH_2Cl_2, rt; (c) Raney-Ni, EtOH, H_2, 80 °C; (d) NaH, benzyl bromide, DMF, 0 °C; (e) ethanediol, 155 °C, 8 h; (f) OsO_4, THF/H_2O, 0 °C, 4 h.

thio alcohols **5** with (*R*)- and (*S*)-2-phenylpropionic acid **6**.[4] The absolute stereochemistry at C-6 and at the C-2 and C-3 chiral centers formed during the radical-mediated cyclization was determined by coupling constant analysis and NOE experiments (Figure 1). The two diastereoisomers (1*S*,2*R*,3*S*)- and (1*S*,2*S*,3*S*)-**10** obtained from (2*S*,3*S*,*R*S)-**4** presented coupling constants between H-3β and H-4α, H-4α and H-5β, and H-5β and H-6α ranging from 12.5 to 13.3 Hz and couplings of 2.2 to 2.3 Hz between H-1α and H-6α. Vicinal couplings of this magnitude can be associated with *trans*-diaxial and *gauche* relationships, respectively, thus suggesting that the two compounds preferentially adopt chair conformations.

The NOEs observed for both the compounds between H-4α and H-6α (2.5 and 2%), H-3β and H-5β (1.5 and 2%), and OH-1 and both H-3β (3.5 and 2%) and H-5β (1.5 and 1.5%) and the couplings of 30.5 and 7.2 Hz exhibited by H-3β and F-2, which are consistent with axial−axial and axial−equatorial interactions,[14] not only supported the above evidence but also indicated that the two compounds are epimeric at C-2.

Also, the two fluoro derivatives obtained from (1*S*,2*R*,-3*S*)**10**, *i.e.*, (1*R*,2*S*,3*S*)-**11** (detected in traces in the crude

(14) (a) Jonás, J.; Allerhand, A.; Gutowsky, H. S. *J. Chem. Phys.* **1965**, *42*, 3396−3399. (b) Phillis, L.; Wray, V. *J. Chem. Soc. B* **1971**, 1618−1624.

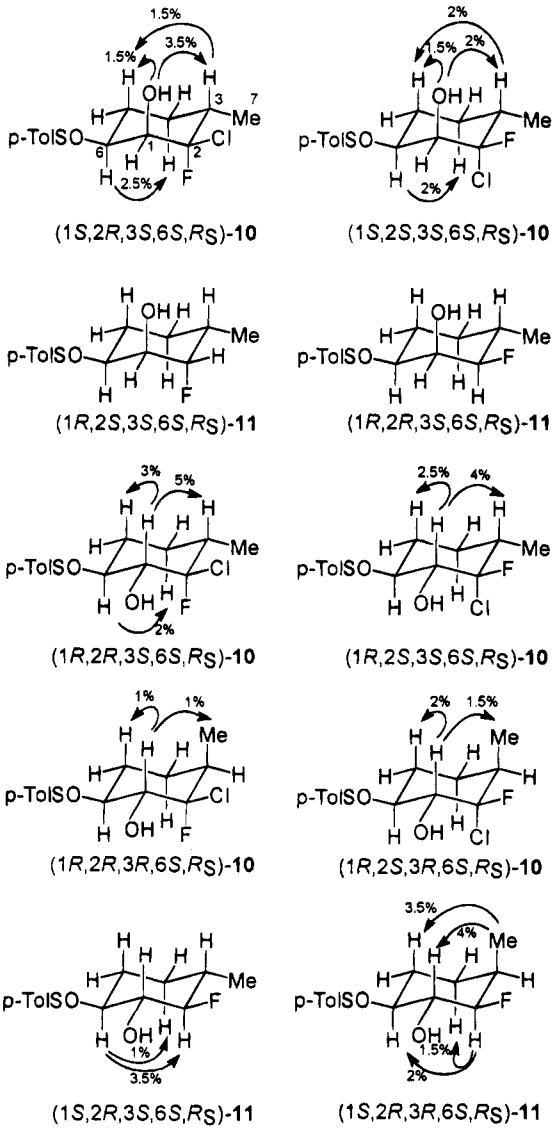


Figure 1. Selected NOE enhancements and preferred conformations for compounds **10** and **11**.

reaction mixture) and (1*R*,2*R*,3*S*)-**11** (the main component), are epimeric at C-2. In fact, the two compounds preferentially assume a chair conformation in which F-2 is, respectively, α-axially and β-equatorially disposed as shown by couplings of 38.5 and 8.5 Hz with H-3β.[15]

The ^{1}H NMR spectrum of (1*R*,2*R*,3*S*)-**10**, one of the four diastereoisomers obtained from (2*R*,3*S*,*R*S)-**4**, exhibited coupling constants between H-1β and H-6α, H-3β and H-4α, H-4α and H-5β, and H-5β and H-6α ranging from 10.8 to 12.8 Hz indicating that the cyclohexane ring preferentially adopts a chair conformation in which the C-1, C-3, and C-6 substituents are all equatorially disposed. The NOEs observed between H-4α and H-6α (2%) and between H-1β and both H-3β (5 and 4%) and H-5β (3 and 2.5%) in this isomer as well as in (1*R*,2*S*,3*S*)-**10** agreed with the above evidence and, moreover, suggested that the two compounds are epimeric at C-2. This supposition was substantiated by the fact that in the first compound F-2 presented couplings of 21.6 and 28.0 Hz with H-1β and H-3β indicating *trans*-diaxial relationships whereas in the second one F-2 exhibited a coupling of 7.6 Hz with H-1β typical of a *gauche* interaction.

(15) Williamson, K. L.; Li-Hsu, Y.-F.; Hall, F. H.; Swager, S.; Coulter, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 6717–6722.

In the remaining isomers, (1*R*,2*R*,3*R*)- and (1*R*,2*S*,3*R*)-**10**, the NOEs observed between H-1β and both H-5β (1 and 2%) and H_3-7β (1 and 1.5%) established as (*R*) the chirality at C-3. These findings, together with the values of 10.5 and 10.0 Hz observed between H-1β and H-6α and of 22.5 and 7.1 Hz observed between H-1β and F-2, indicated that in each isomer the cyclohexane ring preferentially assumes a chair conformation in which the axially-disposed H-1β gives rise to axial–axial and axial–equatorial interactions with F-2. As a consequence, the two compounds are epimeric at the C-2 center.

Finally, the value of the vicinal coupling constants and the NOEs observed between H_3-7β and both H-1β (4%) and H-5β (3.5%) and between H-2α and both H-4α (1.5%) and H-6α (2%) in (1*S*,2*R*,3*R*)-**11**, obtained from (1*R*,2*R*,3*R*)-**10**, and those observed between H-6α and both H-2α (3.5%) and H-4α (1%) in (1*S*,2*R*,3*S*)-**11**, obtained from (1*R*,2*R*,3*S*)-**10**, indicated that in each isomer the cyclohexane ring preferentially adopts a chair conformation in which F-2 is β-equatorially disposed because it presented couplings of 11.6 and 11.0 Hz with the β-axially disposed H-1. It follows that the two dechlorinated compounds are epimeric at the C-3 center.

Conclusions. In summary, we have shown that the approach to enantiomerically pure selectively fluorinated and polyhydroxylated cyclohexane derivatives through the building up of the ring from two fragments, one bearing the fluorine atom and two reactive chlorine atoms and the second one the sulfinyl chiral auxiliary group and an unsaturation, is feasible. The two fragments can be joined together through a C–C forming ionic reaction to give a fluorinated sulfinyl intermediate which can be cyclized through a C–C forming radical-mediated reaction and contemporary reductively dehalogenated to final monofluorocyclohexanes in high de. Moreover, the presence of the sulfinyl group in cyclic products allows us to introduce new functional groups in a stereocontrolled way.

Experimental Section

General Methods. Mass spectra were registered on a Hitachi-Perkin-Elmer ZAB 2F instrument. All other spectral and physical characterizations of new compounds, chromatographic separations, and solvent purifications, as well as the synthesis of (*R*S)-5-[(4-methylphenyl)sulfinyl]pent-1-ene (**1**), have been made as already described.[3b]

(3*R*,*R*S)- and (3*S*,*R*S)-1,1-Dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl]hept-6-en-2-one (3). Ethyl dichlorofluoroacetate (**2**, 1.87 g, 11.50 mmol) in THF (2 mL) was added dropwise at −65 °C to a solution of the lithium derivative [generated with LDA (12.50 mmol) in THF (20 mL)] of (*R*S)-5-[(4-methylphenyl)sulfinyl]pent-1-ene (**1**, 2.00 g, 9.61 mmol) stirred under argon. After 5 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 (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue [a mixture of (3*R*,*R*S)- and (3*S*,*R*S)-**3**, both in the keto and hydrate forms, as shown by ^{1}H and ^{19}F NMR analyses, in about 80% yield] was reduced to give a mixture of the corresponding more stable alcohols.

(2*S*,3*R*,*R*S)-, (2*R*,3*R*,*R*S)-, (2*S*,3*S*,*R*S)-, and (2*R*,3*S*,*R*S)-1,1-Dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl]hept-6-en-2-ols (4). Method A. A suspension of sodium borohydride (0.40 g, 10.30 mmol) in a 9:1 mixture of methanol/30% aqueous ammonia (5 mL) was dropped into a solution of the mixture (3*R*,*R*S)/(3*S*,*R*S)-**3** (3.2 g, 9.6 mmol) 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 (3 × 50 mL). The combined organic phases were dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give a mixture of the four diastereoisomeric alcohols **4**. The residue was flash chromatographed (8:2 cyclohexane/ethyl acetate) to give (2*S*,3*R*,*R*$_S$)-**4** (0.62 g, 19.0% yield) and (2*R*,3*S*,*R*$_S$)-**4** (0.36 g, 11.0% yield) as pure compounds and (2*R*,3*R*,*R*$_S$)- and (2*S*,3*S*,*R*$_S$)-**4** as a mixture which upon flash chromatography (85:15 toluene/ethyl acetate) gave (2*R*,3*R*,*R*$_S$)-**4** (0.36 g, 11.0% yield) and (2*S*,3*S*,*R*$_S$)-**4** (0.62 g, 19.0% yield) as pure compounds. (2*S*,3*R*,*R*$_S$)-**4**: R_f (8:2 cyclohexane/ethyl acetate) 0.30; R_f (85:15 toluene/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +113° (*c* 1.0, $CHCl_3$); mp 84–85 °C (isopropyl ether); ^{1}H NMR ($CDCl_3$) δ 7.62 and 7.36 (4 H, m), 5.62 (1 H, m), 5.51 (1 H, d, J = 5.4 Hz), 4.98 and 4.97 (2 H, m), 4.49 (1 H, ddd, J = 7.1, 6.0 and 5.4 Hz), 3.23 (1 H, dt, J = 7.1 and 5.5 Hz), 2.44 (3 H, br s) and 2.18, 2.10, 1.89, and 1.66 (4 H, m). Found: C, 49.6; H, 5.1. $C_{14}H_{17}Cl_2FO_2S$ requires: C, 49.6; H, 5.05. (2*R*,3*R*,*R*$_S$)-**4**: R_f (8:2 cyclohexane/ethyl acetate) 0.35; R_f (85:15 toluene/ethyl acetate) 0.30; $[\alpha]^{20}_D$ +156° (*c* 0.9, $CHCl_3$); yellowish liquid; ^{1}H NMR ($CDCl_3$) δ 7.48 and 7.38 (4 H, m), 5.74 (1 H, m), 5.11 and 5.09 (2 H, m), 4.50 (1 H, d, J = 3.5 Hz), 4.45 (1 H, ddd, J = 15.5, 3.5, and 1.1 Hz), 3.07 (1 H, ddd, J = 9.7, 3.3, and 1.1 Hz), 2.44 (3 H, br s) and 2.37, 2.37, 2.34, and 2.23 (4 H, m). Found: C, 49.55; H, 5.0. $C_{14}H_{17}Cl_2FO_2S$ requires: C, 49.6; H, 5.05. (2*S*,3*S*,*R*$_S$)-**4**: R_f (8:2 cyclohexane/ethyl acetate) 0.30; R_f (85:15 toluene/ethyl acetate) 0.30; $[\alpha]^{20}_D$ +58° (*c* 1.0, $CHCl_3$); yellowish liquid; ^{1}H NMR ($CDCl_3$) δ 7.52 and 7.35 (4 H, m), 5.60 (1 H, m), 4.96 and 4.93 (2 H, m), 4.75 (1 H, ddd, J = 13.1, 5.3 and 1.7 Hz), 3.63 (1 H, d, J = 5.3 Hz), 3.34 (1 H, ddd, J = 7.9, 3.3 and 1.7 Hz), 2.44 (3 H, br s) and 2.08, 2.05, 2.03 and 1.73 (4 H, m). Found: C, 49.55; H, 5.1. $C_{14}H_{17}Cl_2FO_2S$ requires: C, 49.6; H, 5.05. (2*R*,3*S*,*R*$_S$)-**4**: R_f (8:2 cyclohexane/ethyl acetate) 0.25; R_f (85:15 toluene/ethyl acetate) 0.25; $[\alpha]^{20}_D$ +97° (*c* 1.0, $CHCl_3$); mp 114–115 °C (isopropyl ether); ^{1}H NMR ($CDCl_3$) δ 7.47 and 7.36 (4 H, m), 5.96 (1 H, br s), 5.45 (1 H, m), 4.91 and 4.87 (2 H, m), 4.37 (1 H, dd, J = 10.5 and 4.0 Hz), 3.08 (1 H, ddd, J = 7.6, 4.9 and 4.0 Hz), 2.44 (3 H, br s) and 2.10, 1.88, 1.83 and 1.68 (4 H, m). Found: C, 49.6; H, 5.1. $C_{14}H_{17}Cl_2FO_2S$ requires: C, 49.6; H, 5.05.

Method B. A solution of DIBALH (2.5 M in hexane, 18.7 mL) was added dropwise to a solution of (3*R*)/(3*S*,*R*$_S$)-**3** mixture (3.2 g, 9.6 mmol) in THF (50 mL) at −60 °C under Ar atmosphere. After 10 min, the reaction was quenched by adding a saturated aqueous solution of ammonium chloride, diluted with an about 3M hydrochloric acid solution up to pH 3 and extracted with ethyl acetate (20 mL × 3). The crude was purified by flash chromatography (75:25 cyclohexane/ethyl acetate) to give (2*R*,3*R*,*R*$_S$)-, (2*S*,3*S*,*R*$_S$)-, and (2*R*,3*S*,*R*$_S$)-**4** in 42% global yield and in HPLC (7:3 hexane/ethyl acetate) ratio of, respectively, 6.7;4.7:1.0.

(2*S*,3*R*)-, (2*R*,3*R*)-, (2*S*,3*S*)-, and (2*R*,3*S*)-1,1-Dichloro-1-fluoro-3-[(4-methylphenyl)thio]hept-6-en-2-ols (5). Trifluoroacetic anhydride (0.72 mL, 4.55 mmol) was added to a mixture of (2*S*,3*R*,*R*$_S$)-**4** (220 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 solution of sodium hydrogen carbonate. Acetone was removed under reduced pressure, and the aqueous layer was extracted with ethyl ether (3 × 20 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 liquid compound in 95% yield. An analytical sample was obtained through flash chromatography (9:1 hexane/ethyl ether): $[\alpha]^{20}_D$ +22.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37 and 7.13 (4 H, m), 5.76 (1 H, m), 5.06 and 5.02 (2 H, m), 3.92 (1 H, ddd, J = 7.1, 7.1, and 4.1 Hz), 3.88 (1 H, d, J = 7.1 Hz), 3.52 (1 H, ddd, J = 9.4, 5.0, and 4.1 Hz), 2.38, 2.33, 1.87, and 1.71 (4 H, m) and 2.33 (3 H, br s). Found: C, 52.1; H, 5.2. $C_{14}H_{17}Cl_2FOS$ requires: C, 52.0; H, 5.3. From (2*R*,3*R*,*R*$_S$)**4**: (2*R*,3*R*)-**5** (95% yield); $[\alpha]^{20}_D$ +46.3° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34 and 7.13 (4 H, m), 5.80 (1 H, m), 5.11 and 5.05 (2 H, m), 4.16 (1 H, ddd, J = 15.2, 4.7, and 1.9 Hz), 3.65 (1 H, ddd, J = 11.0, 2.8, and 1.9 Hz), 3.01 (1 H, d J = 4.7 Hz), 2.45, 2.30, 2.08, and 1.66 (4 H, m) and 2.34 (3 H, br s). Found: C, 52.05; H, 5.2. $C_{14}H_{17}Cl_2FOS$ requires: C, 52.0; H, 5.3. From (2*S*,3*S*,*R*$_S$)-**4**: (2*S*,3*S*)-**5** (95% yield); $[\alpha]^{20}_D$-45.2° (*c* 0.8, $CHCl_3$); the ^{1}H NMR spectrum ($CDCl_3$) is identical to that of (2*R*,3*R*)-**5**. Found: C, 52.0; H, 5.3. $C_{14}H_{17}Cl_2FOS$ requires: C, 52.0; H, 5.3. From (2*R*,3*S*,*R*$_S$)-**4**: (2*R*,3*S*)-**5** (95% yield); $[\alpha]^{20}_D$ −17.0° (*c* 0.7, $CHCl_3$); the ^{1}H NMR spectrum ($CDCl_3$) is identical to that of (2*S*,3*R*)-**5**. Found: C, 52.1; H, 5.25. $C_{14}H_{17}Cl_2FOS$ requires: C, 52.0; H, 5.3.

Phenylpropionic Esters 7 of Alcohols (2*S*,3*R*)-, (2*R*,3*R*)-, and (2*R*,3*S*)-5. 4-(Dimethylamino)pyridine (1.2 mg, 0.01 mmol) was added to a dichloromethane solution (1 mL) containing the thio alcohol (2*S*,3*R*)-**5** (34 mg, 0.10 mmol), (−)-(*R*)-2-phenylpropionic acid (**6**, 27 mg, 0.11 mmol), and dicyclohexylcarbodiimide (22 mg, 0.11 mmol). After 30 min at room temperature the dicyclohexyl urea was removed by filtration and washed with hexane. The collected organic phases were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromtographed (95:5 hexane/ethyl ether) to give (*R*)-2-phenylpropanoate (**7**) of the alcohol (2*S*,3*R*)-**5**: ^{1}H NMR ($CDCl_3$) δ 7.4–7.0 (9 H, m), 5.59 (1 H, m), 5.53 (1 H, dd, J = 11.0 and 4.5 Hz), 4.93 and 4.91 (2 H, m), 3.83 (1 H, q, J = 7.2 Hz), 3.44 (1 H, ddd, J = 8.2, 5.7, and 4.5 Hz),2.32 (3 H, br s), 2.18 (2 H, m), 1.60 and 1.54 (2 H, m) and 1.57 (3 H, d, J = 7.2 Hz). When the same alcohol was reacted with (+)-(*S*)-**6**, the corresponding (*S*)-2-phenylpropanoate (**7**) was obtained: ^{1}H NMR ($CDCl_3$) δ 7.4–7.1 (9 H, m), 5.68 (1 H, m), 5.51 (1 H, dd, J = 9.3 and 5.5 Hz), 4.98 and 4.97 (2 H, m), 3.68 (1 H, q, J = 7.2 Hz), 3.50 (1 H, ddd, J = 8.6, 5.5, and 5.2 Hz), 2.34 (3 H, br s), 2.29 (2 H, m), 1.82 and 1.64 (2 H, m) and 1.56 (3 H, d, J = 7.2 Hz). From (−)-(*R*)-**6** and (2*R*,3*R*)-**5**, the obtained ester (**7**) showed: ^{1}H NMR ($CDCl_3$) δ 7.5–7.1 (9 H, m), 5.78 (1 H, m), 5.51 (1 H, dd, J = 17.0 and 1.7 Hz), 5.12 and 5.06 (2 H, m), 3.88 (1 H, q, J = 7.2 Hz), 3.60 (1 H, ddd, J = 10.8, 2.4, and 1.7 Hz), 2.43 and 2.27 (2 H, m), 2.33 (3 H, br s), 2.03 and 1.45 (2 H, m) and 1.63 (3 H, d, J = 7.2 Hz). When (2*R*,3*R*)-**5** was esterified with (+)-(*S*)-**6**, the ester (**7**) showed: ^{1}H NMR ($CDCl_3$) δ 7.5–7.1 (9 H, m), 5.69 (1 H, m), 5.51 (1 H, dd, J = 17.3 and 1.7 Hz), 5.04 and 5.01 (2 H, m), 3.87 (1 H, q, J = 7.2 Hz), 3.54 (1 H, ddd, J = 10.9, 2.5 and 1.7 Hz), 2.33 (3 H, br s), 2.30 and 2.16 (2 H, m), 1.88 and 1.08 (2 H, m), 1.60 (3 H, d, J = 7.2 Hz). When (2*S*,3*S*)-**5** was reacted with (−)-(*R*)-**6**, the ester (**7**) showed a ^{1}H NMR spectrum ($CDCl_3$) identical to that of the (+)-(*S*)-**6** ester (**7**) of (2*R*,3*R*)-**5**, and when (2*S*,3*S*)-**5** was reacted with (+)-(*S*)-**6**, the ester (**7**) showed a ^{1}H NMR spectrum ($CDCl_3$) identical to that of the (−)-(*R*)-PPA ester (**7**) of (2*R*,3*R*)-**5**. From (2*R*,3*S*)-**5** and (−)-(*R*)-**6**, the ester **7** showed the ^{1}H NMR spectrum ($CDCl_3$) identical to that of the (+)-(*S*)-**6** ester of (2*S*,3*R*)-**5**, and the ester **7** obtained from the same alcohol and (+)-(*S*)-**6** showed the ^{1}H NMR spectrum ($CDCl_3$) identical to that of the (−)-(*R*)-**6** ester **7** of (2*S*,3*R*)-**5**.

Radical Cyclization of Alcohols 4. General Procedure of thermal Reaction. To a stirred solution of alcohol (1.0 mmol) and AIBN (0.1 mmol) in oxygen-free benzene (6.0 mL) at 74 °C in argon atmosphere was slowly added (ca. 1 h) a solution of tributyltin hydride (1.0 mL) in the same solvent (3.0 mL). The reaction mixture was further stirred at the same temperature for a period of time depending on the substrates. Benzene was removed under reduced pressure, acetonitrile (5.0 mL) was added, and the mixture was washed with hexane (3 × 5.0 mL).[17] Acetonitrile was removed under reduced pressure, and the residue was flash chromatographed.

Specifically, cyclization of (2*S*,3*S*,*R*$_S$)-**4** afforded, after 5 h, a 1.0:1.4 (^{19}F NMR and HPLC ratio) mixture of (1*S*,2*S*,-3*S*,6*S*,*R*$_S$)-2-chloro-2-fluoro-3-methyl-6-[(4-methylphenyl)sulfinyl]cyclohexan-1-ol (**10**) (26.5% yield) and (1*S*,2*R*,3*S*,6*S*,*R*$_S$)-**10** (33.1% yield) along with about 20% of unreacted starting material **4**. Fractional crystallization from isopropyl ether afforded the pure compounds (1*S*,2*S*,3*S*,6*S*,*R*$_S$)-**10**: R_f (8:2 chloroform/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +112.7° (*c* 0.7, $CHCl_3$); m.p. 210–211 °C (ethyl acetate); t_R (SiO_2, 60 μm, 5:5 hexane/ethyl acetate, 1.0 mL/min) 11.70 min. Found: C, 55.3; H, 6.0. $C_{14}H_{18}ClFO_2S$ requires: C, 55.2; H, 5.95. (1*S*,2*R*,3*S*,6*S*,*R*$_S$)-**10**: R_f (8:2 chloroform/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +97.3° (*c* 0.7,

$CHCl_3$); m.p. 168–170 °C (isopropyl ether); t_R (SiO_2, 60 μm, 5:5 hexane/ethyl acetate, 1.0 mL/min) 10.50 min. Found: C, 55.0; H, 6.0. $C_{14}H_{18}ClFO_2S$ requires: C, 55.2; H, 5.95. The same radical reaction gave, after 24 h, an about 1:1 (2*S*)/(2*R*)-**10** mixture in a 40% global yield. No dechlorination products were detected by TLC, but much more higher R_f decomposition products were visible. All starting alcohol had completely disappeared. Cyclization of (2*R*,3*S*,R_S)-**4** gave in 2 h a 1.0:1.6:1.3:1.5 mixture (HPLC ratio) of, respectively, (1*R*,2*R*,3*R*,6*S*,R_S)-**10** (11.1% yield), (1*R*,2*R*,3*S*,6*S*,R_S)-**10** (17.8% yield), (1*R*,2*S*,3*R*,6*S*,R_S)-**10** (14.4% yield), and (1*R*,2*S*,3*S*,6*S*,R_S)-**10** (16.7% yield) together with about 20% of unreacted starting compound **4**. The mixture of the four diastereoisomeric alcohols was submitted to fractional crystallizations in order to obtain pure cyclohexanols. After several crystallizations from isopropyl ether, only (1*R*,2*R*,3*S*,6*S*,R_S)-**10** was obtained as a pure solid: R_f (1:1 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +244.3° (*c* 0.2, $CHCl_3$); m.p. 216–217 °C (isopropyl ether); t_R (SiO_2, 60 μm, 55:45 hexane/ethyl acetate, 1.0 mL/min) 10.47 min. Found: C, 55.2; H, 5.95. $C_{14}H_{18}ClFO_2S$ requires: C, 55.2; H, 5.95, *m/z* 304 (required 304). (1*R*,2*R*,3*R*,6*S*,R_S)-**10**: R_f (1:1 cyclohexane/ethyl acetate) 0.35; t_R (SiO_2, 60-μm, 55:45 hexane/ethyl acetate, 1.0 mL/min) 10.02 min. (1*R*,2*S*,3*R*,6*S*,R_S)-**10**: R_f (1:1 cyclohexane/ethyl acetate) 0.35; t_R (SiO_2, 60 μm, 55:45 hexane/ethyl acetate, 1.0 mL/min) 11.62 min. (1*R*,2*S*,3*S*,6*S*,R_S)-**10**: R_f (1:1 cyclohexane/ethyl acetate) 0.35; t_R (SiO_2, 60 μm, 55:45 hexane/ethyl acetate, 1.0 mL/min) 12.23 min.

General Procedure of Photolytic Reaction. A solution of alcohol **4** (1.0 mmol) and tributyltin hydride (1.2 mL) in degassed 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. Workup was already described for the thermal procedure.

Specifically, (2*S*,3*S*,R_S)-**4** gave, after 16 h, a 1.0:1.4:1.6 mixture of, respectively, (1*S*,2*S*,3*S*,6*S*,R_S)-**10**. (1*S*,2*R*,3*S*,6*S*,R_S)-**10**, and (1*R*,2*R*,3*S*,6*S*,R_S)-2-fluoro-3-methyl-6-[(4-methylphenyl)sulfinyl]cyclohexan-1-ol (**11**) in about 60% global yield. The last compound was easily obtained as pure by flash chromatography (1:1 hexane/ethyl acetate). (1*R*,2*R*,3*S*,6*S*,R_S)-**11**: R_f (1:1 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +120° (*c* 0.4, $CHCl_3$); mp 190–192 °C (isopropyl ether); t_R (SiO_2, 60 μm, 4:6 hexane/ethyl acetate), 1.0 mL/min) 14.36 min. Found: C, 62.0; H, 7.05. $C_{14}H_{19}FO_2S$ requires C, 62.2; H, 7.1, *m/z* 270 (required 270). (2*R*,3*S*,R_S)-**4** gave, after 10 h, the same ratio (HPLC) of the four diastereoisomeric cyclohexanols **10** in 56% global yield, in addition to a 1.2:1.0 mixture (HPLC) of (1*S*,2*R*,3*S*,6*S*,R_S)-**11** (11% yield) and (1*S*,2*R*,3*R*,6*S*,R_S)-**11** (9.1% yield). The last two compounds were separated by flash chromatography (1:1 cyclohexane/ethyl acetate). (1*S*,2*R*,3*S*,6*S*,R_S)-**11**: R_f (1:1 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +233.5° (*c* 0.1, $CHCl_3$); mp 162–164 °C (3:1:1 pentane/isopropyl ether/ethyl acetate); t_R (SiO_2, 60 μm, 55:45 hexane/ethyl acetate, 1.0 mL/min) 12.17 min. Found: C, 62.45; H, 7.0. $C_{14}H_{19}FO_2S$ requires: C, 62.2; H, 7.1, *m/z* 270 (required 270). (1*S*,2*R*,3*R*,6*S*,R_S)-**11**: R_f (1:1 cyclohexane/ethyl acetate) 0.40; $[\alpha]^{20}_D$ +216.5° (*c* 0.7, $CHCl_3$); mp 158–160 °C (isopropyl ether); t_R (SiO_2, 60 m, 50:50 hexane/ethyl acetate, 1.0 mL/min) 15.21 min. Found: C, 62.2; H, 7.05. $C_{14}H_{19}FO_2S$ requires: C, 62.2; H, 7.1, *m/z* 270 (required 270).

(1*S*,2*R*,3*S*,6*S*,R_S)-, (1*S*,2*R*,3*R*,6*S*,R_S)-, and (1*R*,2*R*,3*S*,6*S*,R_S)-11. A solution of tributyltin hydride (0.38 mL, 1.39 mmol) in degassed benzene (10 mL) was added slowly (1 h) under argon atmosphere to a stirred solution of (2*R*,3*S*,R_S)-**4** (0.40 g, 1.16 mmol) and AIBN (6.57 mg, 0.04 mmol) in the same solvent (20 mL) preheated to 74 °C (oil bath). The reaction mixture was further stirred at the same temperature, and after 6.5 h, the starting alcohol **4** had completely disappeared. The HPLC analysis (SiO_2, 60 μm, 55:45 hexane/ethyl acetate, 1.0 mL/min) of the crude revealed the presence, as only reaction products, of the two dechlorinated cyclohexanol diastereoisomers (1*S*,2*R*,3*S*,6*S*,R_S)-**11**, t_R 12.17 min, and (1*S*,2*R*,3*R*,6*S*,R_S)-**11**, t_R 15.21 min, in, respectively, a 1.3:1.0 ratio. The benzene was removed in vacuo, acetonitrile (10 mL) was added, and the mixture was washed with hexane (3 × 5 mL). After removal of acetonitrile under reduced pressure, the residue (0.20 g) was flash chromatographed (1:1 cyclohexane/ethyl acetate) to give (3*S*)-**11** (R_f 0.35) and (3*R*)-**11** (R_f 0.40) as pure compounds in 60% global yield. The analytical and physical data of the isolated compounds were identical to those already described. The same reaction, run under photolytic conditions, needed 16 h in order to give the same results. No differences in diastereoisomeric ratio were noticed. The photolytic procedure on (2*S*,3*S*,R_S)-**4** gave in 20 h only one diastereoisomer, (1*R*,2*R*,3*S*,6*S*,R_S)-**11** in 50% yield. The analytical and physical data of the compound were identical to those already described.

Reductive Dechlorination of Chlorofluorocyclohexanols 10. General Procedure. To a stirred solution of **10** (1.0 mmol) in oxygen-free benzene (10 mL) preheated to 74 °C was slowly (1 h) added under argon atmosphere a solution of tributyltin hydride (2.0 mmol) in the same solvent (5 mL). The reaction mixture was stirred at the same temperature for an additional period of time depending on the substrate. The reaction progress was monitored by HPLC (SiO_2, 60 μm, 1:1 hexane/ethyl acetate, 1.0 mL/min), and after the starting compounds **10** had been completely used up, benzene was removed under reduced pressure, acetonitrile was added (10 mL), the mixture was washed with hexane (3 × 5 mL), acetonitrile was evaporated off, and the residues were flash chromatographed in order to obtain the pure compounds.

Specifically, (1*R*,2*R*,3*S*,6*S*,R_S)-**10** gave, after 5 h, exclusively (1*S*,2*R*,3*S*,6*S*,R_S)-**11** (t_R 12.20 min, 70% yield); (1*S*,2*S*,3*S*,6*S*,R_S)-**10** gave, after 3 h, exclusively (1*R*,2*R*,3*S*,6*S*,R_S)-**11** (t_R 20.33 min, 80% yield); (1*S*,2*R*,3*S*,6*S*,R_S)-**10** gave, after 5 h, (1*R*,2*R*,3*S*,6*S*,R_S)-**11** (t_R 14.36 min, 40% yield) and only traces of (1*R*,2*S*,3*S*,6*S*,R_S)-**11** (t_R 14.36 min). The analytical and physical data of (1*R*,2*R*,3*S*,6*S*,R_S)-**11** were identical to those of the already isolated compound. The (1*R*,2*S*,3*S*,6*S*,R_S)-**11** diastereoisomer was characterized only by ^1H and ^{19}F NMR because it was not isolated as the pure compound.

(1*R*,2*R*,3*S*,6*S*)-2-Fluoro-3-methyl-6-[(4-methylphenyl)thio]cyclohexan-1-ol (12). To a solution of (1*R*,2*R*,3*S*,6*S*,R_S)-**11** (100 mg, 0.37 mmol) and sodium iodide (166 mg, 1.11 mmol) in acetone (7 mL) at −40 °C under nitrogen atmosphere was added dropwise a solution of trifluoroacetic anhydride (0.26 mL, 1.84 mmol) in the same solvent (2 mL). The reaction mixture was stirred at the same temperature for 10 min, and then a saturated aqueous solution of sodium sulfite (5 mL) was added, the temperature was raised to room temperature, the solvent was evaporated in vacuo, the reaction mixture was extracted with ethyl acetate (3 × 5 mL), and the combined organic extracts were washed with water (3 × 5 mL), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was flash chromatographed (4:1 hexane/ethyl acetate) to give (1*R*,2*R*,3*S*,6*S*)-**12** as a pure compound (83 mg, 88% yield): R_f (4:1 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ −36.6° (*c* 1.0, $CHCl_3$); mp 84–85 °C (9:1 hexane/ethyl ether); ^1H NMR ($CDCl_3$) δ 7.35 and 7.13 (4 H, m), 4.04 (1 H, br ddd, *J* = 9.5, 2.7, and 1.5 Hz), 3.96 (1 H, ddd, *J* = 47.0, 10.8, and 2.7 Hz), 3.04 (1 H, dddd, *J* = 10.5, 6.1, 2.0, and 1.5 Hz), 2.48 (1 H, br s), 2.34 (3 H, br s), 2.14 (1 H, m), 1.9–1.6 (3 H, m), 1.04 (1 H, m) and 1.01 (3 H, d, *J* = 6.5 Hz); ^{19}F NMR ($CDCl_3$) δ −188.38 (1 F, br d, *J* = 47.0 Hz). Found: C, 66.1; H, 7.45. $C_{14}H_{19}FOS$ requires: C, 66.1; H, 7.5.

(1*R*,2*R*,3*S*,6*S*)-2-Fluoro-3-methyl-6-[(4-methylphenyl)thio]cyclohexan-1-ol Benzoate (13). 4-(Dimethylamino)-pyridine (2.4 mg, 0.02 mmol) was added to a dichloromethane solution (5 mL) of the thio alcohol (1*R*,2*R*,3*S*,6*S*)-**12** (50 mg, 0.20 mmol), and benzoic acid (26 mg, 0.22 mmol) and DCC (45 mg, 0.22 mmol) were added at 0 °C. After 48 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 under vacuo, and the residue was flash chromatographed (4:1 hexane/ethyl ether) to give (1*R*,2*R*,3*S*,6*S*)-**13** as a pure yellowish liquid (52 mg, 72% yield). (1*R*,2*R*,3*S*,6*S*)-**13**: R_f (4:1 hexane/ethyl ether) 0.35; $[\alpha]^{20}_D$ −87.8° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.2–7.0 (9 H, m), 5.80 (1 H, br ddd, *J* = 8.0, 2.8, and 2.2 Hz), 4.11 (1 H, ddd, *J* = 46.0, 10.7, and 2.8 Hz), 3.09 (1 H, m), 2.32 (3 H, br s), 2.16 (1 H, m), 2.0–1.1 (4 H, m) and 1.03 (3 H, d, *J*

= 6.4 Hz). Found: C, 70.3; H, 6.4. $C_{21}H_{23}FO_2S$ requires: C, 70.4; H, 6.5.

(1S,2R,3S)-2-Fluoro-3-methylcyclohexan-1-ol Benzoate (14). To a solution of (1*R*,2*R*,3*S*,6*S*)-**13** (50 mg, 0.14 mmol) in absolute ethanol (15 mL) was added Raney-Ni (150 mg). The slurry was heated to 80 °C and stirred under hydrogen atmosphere for 5 min. Then, Raney-Ni was filtered off and washed twice with ethanol. Solvent was removed under reduced pressure, and the residue was flash chromatographed (9:1 hexane/ethyl ether) to give (1*S*,2*R*,3*S*)-**14** as a pure yellowish liquid (30 mg, 91% yield). (1*S*,2*R*,3*S*)-**14**: R_f ((9:1 hexane/ethyl ether) 0.35; $[\alpha]^{20}_D$ +58.1° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.2–7.4 (5 H, m), 5.53 (1 H, m), 4.24 (1 H, ddd, J = 46.8, 9.8 and 3.0 Hz), 2.25 (1 H, m), 2.2–1.4 (5 H, m), 1.11 (1 H, m) and 1.09 (3 H, J = 6.5 Hz): ^{19}F NMR ($CDCl_3$) δ −189.50 (1 F, br d, J = 46.8 Hz). Found: C, 71.05; H, 7.1. $C_{14}H_{17}FO_2$ requires: C, 71.15; H, 7.3.

(1*R*,2*R*,3*S*,6*S*,*R*$_S$)-2-(Benzyloxy)-1-fluoro-6-methyl-3-[(4-methylphenyl)sulfinyl]cyclohexane (15). To a suspension of sodium hydride (50.0, 1.04 mmol) in DMF (5 mL) at 0 °C was added dropwise a solution of (1*R*,2*R*,3*S*,6*S*,*R*$_S$)-**11** (140 mg, 0.52 mmol) and benzyl bromide (0.62 mL, 5.20 mmol) in DMF (5 mL). Stirring was continued at the same temperature for 1 h, and then the suspension was poured into a water/ice bath, extracted with ethyl ether (3 × 10 mL), and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was flash chromatographed to give (1*R*,2*R*,3*S*,6*S*,*R*$_S$)-**15** in 85% yield: R_f (7:3 chloroform/ethyl acetate) 0.35; $[\alpha]^{20}_D$ −32.5° (*c* 0.6, $CHCl_3$); mp (isopropyl ether) 114–115 °C; ^1H NMR ($CDCl_3$) δ 7.5–7.2 (9 H, m), 4.88 (1 H, dd, J = 12.0 and 0.7 Hz), 4.41 (1 H, d, J = 12.0 Hz), 3.91 (1 H, ddd, J = 46.7, 10.9, and 2.2 Hz), 3.61 (1 H, br ddd, J = 8.1, 2.3, and 2.2 Hz), 2.57 (1 H, m), 2.41 (3 H, br s), 2.4–1.9 (4 H, m), 1.04 (1 H, m) and 1.02 (3 H, d, J = 6.5 Hz); ^{19}F NMR ($CDCl_3$) δ −185.37 (1 F, br d, J = 46.7 Hz). Found: C, 70.0; H, 7.0. $C_{21}H_{25}FO_2S$ requires: C, 70.0; H, 7.0.

(3S,4*R*,5*S*)-3-(Benzyloxy)-4-fluoro-5-methylcyclohex-1-1-ene (16). A solution of (1*R*,2*R*,3*S*,6*S*,*R*$_S$)-**15** (66.0 mg, 0.19 mmol) in ethanediol (0.5 mL) was heated at 155 °C under argon atmosphere and stirred for 8 h. Then, the solution was poured into water (1 mL) and extracted with ethyl ether (3 × 2 mL). The crude was flash chromatographed (9:1 hexane/ethyl ether) in order to give (3*S*,4*R*,5*S*)-**16** as a pure compound in 60% yield: R_f (9:1 hexane/ethyl ether) 0.35; $[\alpha]^{20}_D$ +173.1° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.4–7.2 (5 H, m), 5.82 (1 H, br dddd, J = 9.9, 4.0, 2.5, and 1.6 Hz), 5.72 (1 H, ddddd, J = 9.9, 4.8, 4.5, 2.2, and 1.1 Hz), 4.83 (1 H, br d, J = 12.0 Hz) 4.61 (1 H, d, J = 12.0 Hz), 4.39 (1 H, ddd, J = 48.1, 10.5, and 3.6 Hz), 4.07 (1 H, m), 2.41 (1 H, m), 2.36 and 1.76 (2 H, m) and 1.08 (3 H, dd, J = 6.4 and 0.8 Hz); ^{19}F NMR ($CDCl_3$) δ −196.44 (1 F, br d, J = 48.1 Hz). Found: C, 76.3; H, 7.7. $C_{14}H_{17}FO$ requires: C, 76.3; H, 7.8.

(1*R*,2*R*,3*S*,4*R*,5*S*)-3-(Benzyloxy)-4-fluoro-5-methylcyclohexane-1,2-diol (17). Osmium tetraoxide (4% wt in water) (20.4 mg, 0.08 mmol) was added at 0 °C to a stirred solution of cyclohexane **16** (150 mg, 0.67 mmol) in THF (4 mL) and water (0.12 mL) under nitrogen atmosphere. The reaction mixture, kept in the dark, was stirred at the same temperature for 10 min, and then trimethylamine-N-oxide (74.7 mg, 0.67 mmol) was added. Stirring was continued for 4 h, and then a saturated aqueous solution of sodium sulfite (1 mL) and citric acid (10 mg) was added. Stirring was continued for 10 min, and then the solution was extracted with ethyl acetate (2 × 5 mL), the organic layers were combined and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromatographed (1:1 hexane/ethyl acetate) to give (1*R*,2*R*,3*S*,4*R*,5*S*)-**17** in 70% yield: R_f (6:4 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ −16.24° (*c* 0.5, $CHCl_3$); mp (pentane) 63–65 °C; ^1H NMR ($CDCl_3$) δ 7.4–7.2 (5 H, m), 4.79 (1 H, br d, J = 11.7 Hz), 4.59 (1 H, d, J = 11.7 Hz), 4.50 (1 H, ddd, J = 47.1, 9.7, and 2.6 Hz), 4.08 (1 H, br dddd, J = 10.0, 4.5, 4.5, and 3.0 Hz), 4.02 (1 H, m), 3.98 (1 H, ddd, J = 10.0, 4.8, and 2.6 Hz), 2.30 (1 H, br d, J = 3.0 Hz), 2.24 (1 H, ddddq, J = 10.9, 9.7, 8.3, 4.4, and 6.7 Hz), 1.80 (1 H, br d, J = 4.5 Hz), 1.76 (1 H, ddddd, J = 13.2, 5.7, 4.5, 4.4, and 1.3 Hz), 1.48 (1 H, dddd, J = 13.2, 10.9, 10.0, and 1.0 Hz) and 1.07 (3 H, dd, J = 6.7 and 0.6 Hz); ^{19}F NMR ($CDCl_3$) δ −202.90 (1 F, br d, J = 47.1 Hz). Found: C, 66.1; H, 7.5. $C_{14}H_{19}FO_3$ requires: C, 66.1; H, 7.5.

Acknowledgment. We thank Consiglio Nazionale delle Ricerche, Progetto Chimica Fine, for financial support.

Supplementary Material Available: Selected ^1H and ^{19}F NMR chemical shifts (δ), coupling constants (Hz), and ^{13}C NMR data for compounds **10** and **11**, all in $CDCl_3$ (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.