Synthesis of Enantiomerically Pure *gem*-Difluorocyclohexane Derivatives by Intramolecular Trapping of α,α-Difluoroalkyl Radicals[1]

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

Centro di Studio per le Sostanze Organiche Naturali del Consiglio Nazionale delle Ricerche and 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 Assergi 6, I-67100 L'Aquila, Italy

Received October 19, 1993•

gem-Difluorocyclohexanols **7** and **16** bearing, respectively, the arylsulfinyl and the arylthio substituent are obtained by radical-promoted cyclization from the corresponding ω-chlorodifluoroheptenols **6** and **9** in good yields. Intermediates **6** are made available by condensing the lithium derivative of chiral arylsulfinyl pentene **4** on ethyl chlorodifluoroacetate and by reducing the carbonyl with hydride-releasing agents. Elimination of the chiral auxiliary sulfinyl group and appropriate elaborations afford enantiomerically pure α-hydroxy-, α-hydroxy-Δ3,4-, α,β,γ-trihydroxy-, and α-hydroxy-β,γ-epoxy-*gem*-difluorocyclohexane derivatives **19**, **21**, **22**, and **23**. Absolute and relative configurations as well as preferred conformations in solution are given. The degree of asymmetric induction during the radical-promoted cyclization is correlated with the relative configuration of substituted carbons in open-chain compounds.

Introduction

In the last 10 years our attention was focused on developing synthetic strategies which exploit the stereocontrolling properties of sulfoxides and also utilize the array of latent functional groups that they possess.[2] In connection with that subject we have investigated primarily the production of optically pure, fluorinated synthons in which the sulfinyl group constitutes the chiral auxiliary.[3] We have also utilized some of those fluorinated chirons in the synthesis of selectively fluorinated molecules of biological and potentially pharmacological interest.[4]

In the present and in a following paper[5] we discuss the synthetic methodology which makes use of some "fluorinated sulfinyl chirons" and of well-established radical chemistry in the synthesis of some chiral and optically pure *gem*-difluoro and monofluoro, mono- and polyhydroxylated cyclohexane derivatives.[6,7]

The carbon backbone of the cyclic molecules is obtained via carbon–carbon-forming reactions by linking together the two fragments **3** and **4** as shown in Scheme 1. Ethyl chlorodifluoroacetate (**3**) is an easily available fluorinated material;[8] it furnishes the cyclohexane ring with a two-carbon fragment, the geminally positioned fluorine atoms, and an oxygen function. It possesses the ionic acceptor center (a) and a potential radical donor site (·) necessary for the C–C-forming reactions.[9] Sulfiny pentene **4**, obtained from menthyl *p*-tolyl sulfinate (**1**) and pentenylmagnesium bromide (**2**), furnishes the cyclohexane ring with a four-carbon fragment and holds a potential ionic donor site (d) and an acceptor radical site (o) for the C–C-forming reactions and the chiral auxiliary (CA) sulfinyl group for asymmetric induction. Acylation of the α-lithium derivative of **4** by ethyl chlorodifluoroacetate (**3**) furnishes the open-chain carbon backbone **5**, which, after reduction to the corresponding alcohol **6**, by radical-

* To whom correspondence should be addressed.

• Abstract published in *Advance ACS Abstracts*, May 1, 1994.

(1) Reported in preliminary form: Arnone, A.; Bravo, P.; Viani, F.; Cavicchio, G. *Tetrahedron: Asymmetry* **1991**, *2*, 399–402.

(2) Bravo, P.; Resnati, G. In *Perspectives in the Organic Chemistry of Sulphur*; Zwanenburg, B., Klunder, A. J. H., Eds.; Elsevier: Amsterdam, 1987; pp 89–103 and references cited therein. For some general references on the use of sulfoxides in synthesis see: Posner, G. H. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, J., Eds.; John Wiley: New York, 1988; p 833. Kagan, H. B. *Efficient Asymmetric Synthesis of Chiral Sulphoxides and Some Synthetic Applications*; *Heteroatom Chemistry*; Block, E., Ed.; Verlag: New York, 1990.

(3) (a) Bravo, P.; Resnati, G. *Tetrahedron Lett.* **1985**, *26*, 5601–5604; (b) **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* **1989**, 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.

(4) Bravo, P.; Piovosi, E.; Resnati, G.; Fronza, G. *J. Org. Chem.* **1989**, *54*, 5171–5176 (fluorohexoses). Bravo, P.; Resnati, G.; Angeli, P.; Frigerio, M.; Viani, F.; Arnone, A.; Marucci, G.; Cantalamessa, F. *J. Med. Chem.* **1992**, *35*, 3102–3110 (fluoromuscarines). Bravo, P.; Resnati, G.; Viani, F. *Tetrahedron* **1993**, *49*, 713–722; *Gazz. Chim. Ital.* **1992**, *122*, 493–497. Bravo, P.; Resnati, G.; Viani, F.; De Montis, A.; Corrias, S.; La Colla, P. *Il Farmaco* **1993**, *48*, 1113–1120. Bravo, P.; Frigerio, M.; Soloshonok, V.; Viani, F. *Tetrahedron Lett.* **1993**, *48*, 7771–7772 (fluoronucleoside analogs). For general information on the subject see: *Biomedical Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y., Eds.; Kodansha Ltd.: Tokyo and Elsevier Biomedical: Amsterdam, 1982. Welch, J. T.; Eswarakrishnan, S. In *Fluorine in Bioorganic Chemistry*; John Wiley and Sons: New York, 1991; *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; American Chemical Society: Washington, DC, 1991; *Fluorine Containing Molecules, Structure, Reactivity, Synthesis and Applications*; Liebman, J. F., Greenburg, A., Dolbier, W. R., Jr., Eds.; VCH Publishers, Inc.: New York, 1988; *Fluorine-18 Labeling of Radiopharmaceuticals*; Kilb, M. R., Ed.; National Academy Press: Washington, DC, 1990.

(5) Arnone, A.; Bravo, P.; Frigerio, M.; Viani, F.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.*, submitted.

(6) For the synthesis of optically active *gem*-difluorocyclopentane and -tetrahydrofuran derivatives by intramolecular trapping of α,α-difluoroalkyl radicals see: (a) Arnone, A.; Bravo, P.; Cavicchio, G.; Frigerio, M.; Viani, F. *Tetrahedron* **1992**, *48*, 8523–8540. (b) Cavicchio, G.; Marchetti, V.; Arnone, A.; Bravo, P.; Viani, F. *Tetrahedron* **1991**, *47*, 9439–9448.

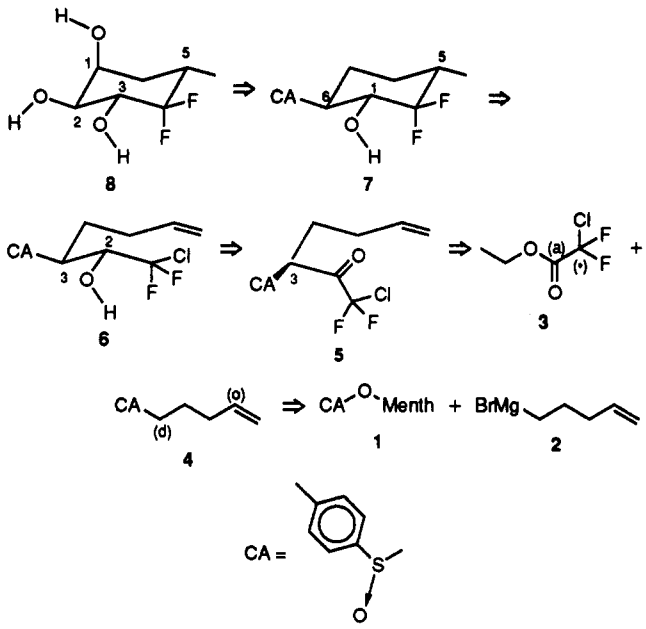
(7) For the synthesis of racemic *gem*-difluorocyclohexane and -tetrahydropyran derivatives by intramolecular trapping of β,β-difluoroalkyl radicals see: Morikawa, T.; Kodama, Y.; Uchida, J.; Takano, M.; Washio, Y.; Taguchi, T. *Tetrahedron* **1992**, *48*, 8915–8926.

(8) Available from Fluorochem Ltd., Derbyshire, U.K.

(9) Curran, D. P. *Synlett* **1991**, 63–72.

0022-3263/94/1959-3459$04.50/0

Scheme 1



mediated cyclization gives rise to the cyclic intermediates **7**. Functional group elaborations on the sulfinyl compounds **7** gave optically pure, sulfur-free compounds like **8**.

In an effort to gain some insight on the factors governing the stereochemical control for six-membered rings formation we have isolated and submitted to radical cyclization all four diastereoisomeric secondary alcohols **6**.

Results and Discussion

Synthesis of Substrates. Chlorodifluorosulfinylhept-6-en-2-one (**5**) was obtained in ca. 70% yield as a mixture of the two (3*R*,*R*S)- and (3*S*,*R*S)-**5** diastereoisomers, both in their keto and hydrate form, from the lithium derivative of sulfoxide **4** and ethyl chlorodifluoroacetate (**3**). The crude mixture was reduced with diisobutylaluminium hydride (DIBALH) in tetrahydrofuran (THF) and with sodium borohydride in methanol/aqueous ammonia in order to obtain all four diastereoisomeric secondary alcohols **6** in reasonable amounts. As is already known for the reduction of similar α-substituted β-keto sulfoxides,[3g,i] DIBALH gives preferentially, from (*R*S)-sulfoxides, (2*R*)-alcohols **6**, while sodium borohydride in protic and basic medium allows epimerization at the α-carbon during the reduction affording predominantly (2*S*)-alcohols **6** (see Experimental Section).

Single diastereoisomers were isolated in optically pure form, reduced at sulfur by the Oae procedure[10] to the corresponding thio derivatives **9**, which were esterified with (*R*)-(−)- and (*S*)-(+)-phenylpropionic acids in order to establish the absolute configuration at C-2 by ^{1}H NMR analyses.[11]

Cyclization Results. ω-Chloro-ω,ω-difluoro sulfinyl olefins **6** were treated with an excess of tributyltin hydride in a degassed benzene solution in the presence of azobisisobutyronitrile (AIBN) as radical chain initiator. Dissociation of AIBN (by heating the solution at reflux or by irradiating with a mercury discharge lamp), followed by hydrogen abstraction from tributyltin hydride, generates a tributyltin radical. Chlorine abstraction from the terminal chlorodifluoromethyl group on **6** or **9** generates the difluoroalkyl radical **12** or **14**. The reactive electrophilic radicals are trapped by the terminal vinyl group in a fast "*exo-trig*" cyclization process giving the cyclohexyl primary radical **13**, **13′**, or **15**, which abstracts hydrogen from the stannane to give the final products **7** and a new tributyltin radical and, hence, propagate the chain reaction.

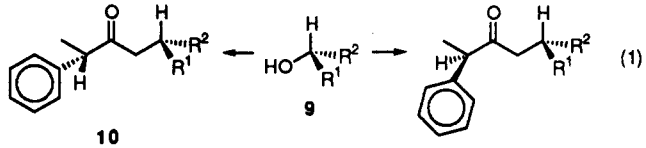
Difluorocyclohexanols **7** were obtained in optically pure form by flash chromatographic separation, and their relative stereochemistry was established by careful ^{1}H and ^{19}F NMR analysis.

Structures of obtained products are reported in Schemes 2 and 3, and yields and diastereoisomeric ratios (HPLC or ^{19}F NMR) are in Table 1.

Some features of the radical cyclization process could be stressed:[12] (a) the rate of the difluoroalkyl radical trapping by the vinyl group should be fast because no reduction products from radicals **12** or **14** were detectable by NMR analyses of the crude reaction products. Moreover, the yields of the six-membered cyclic products **7** are comparable with the yields of the five-membered cyclic products obtained from the corresponding difluoroalkyl hexenyl radicals.[6a] (b) Heptenyl radicals possess a moderately bulky substituent (arylsulfinyl group) in the 3-position, and hence, the preferred transition states for cyclization should have the bulk substituent quasiequatorially disposed.[13] Therefore, when the two substituents arylsulfinyl and hydroxy are in a *threo* relative arrangement [as in radical intermediates from (2*S*,3*R*,*R*S)-**6** and (2*R*,3*S*,*R*S)-**6**], they should be both equatorially disposed in the most favorable transition states. In this case the two transition states having the methyl axially or equatorially disposed should be nearly equally populated and therefore give rise to a nearly equimolar mixture of compounds (Scheme 2 and entries 1 and 2 of Table 1). However, the most favorable conformation for transition states having the two substituents in an *erythro* relative arrangement [(2*R*,3*R*,*R*S)-**6**, (2*S*,3*S*,*R*S)-**6**, as well as (2*R*,3*R*)-

(10) Drabowicz, J.; Oae, S. *Synthesis* **1977**, 404–405.

(11) The assignment was based on the upfield shift ($\Delta\delta$ = 0.04–0.34 ppm) observed for the protons of the pentenyl chain of compounds (2*R*,3*S*,2′*S*)- and (2*R*,3*R*,2′*S*)-**10** and (2*S*,3*R*,2′*R*)- and (2*S*,3*S*,2′*R*)-**11** 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. Helmchen, G. *Tetrahedron Lett.* **1974**, 1527–1530. Helmchen, G.; Schmierer, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 703–704).



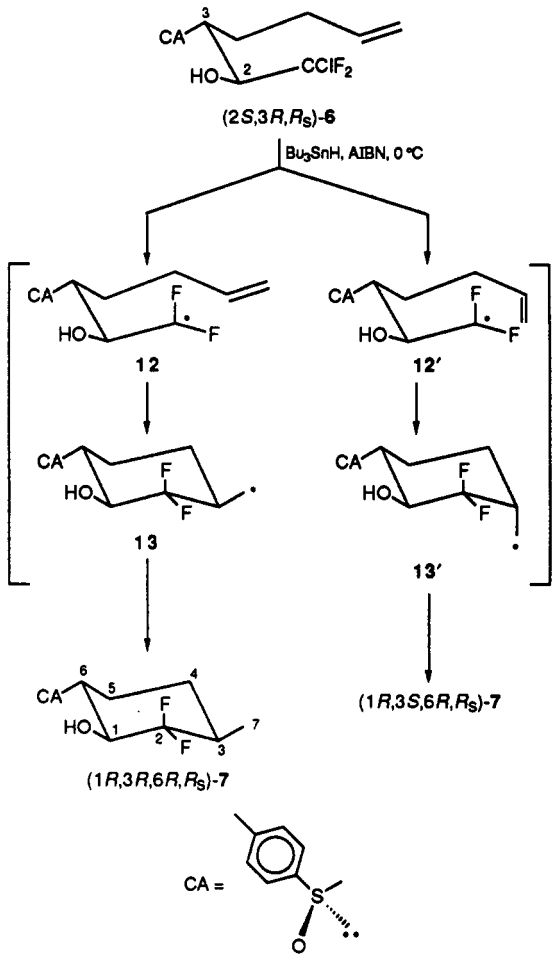
(2*S*,3/*R*S)-**9**: R^1 = CH(*p*-TolS)$CH_2CH_2CH{=}CH_2$; R^2 = $CCIF_2$

(2*R*,3/*R*S)-**9**: R^1 = $CCIF_2$; R^2 = CH(*p*-TolS)$CH_2CH_2CH{=}CH_2$

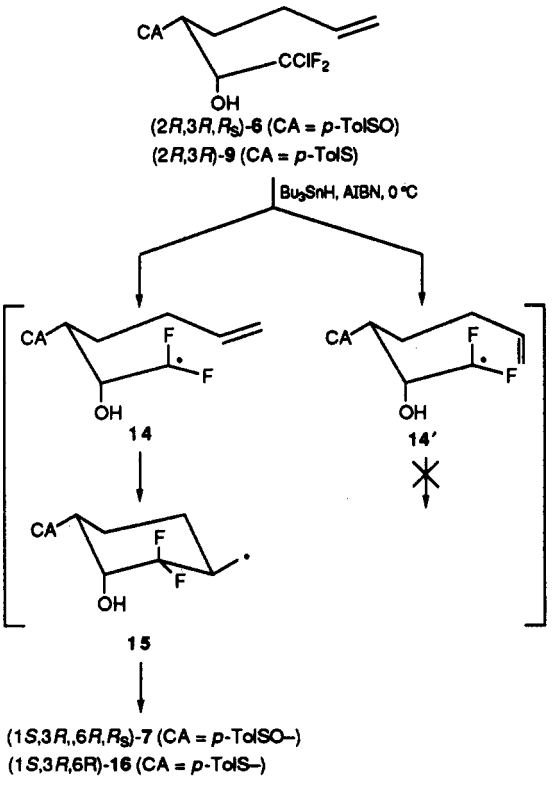
(12) For lead references see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: New York, 1986. For further references: (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969–980. (c) Curran, D. P. *Synthesis* **1988**, 417–439; (d) *Ibid.* **1988**, 489–513. (e) Ramajah, M. *Tetrahedron* **1987**, *43*, 3541–3676. (f) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759–1769.

(13) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073–3100. (b) Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* **1972**, *94*, 9205–9210.

Scheme 2



Scheme 3

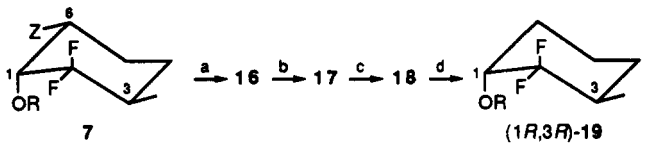


9] should be that in which the incoming methyl group is pseudoequatorially disposed, in order to avoid 1,3-diaxial interactions with the hydroxy group. Actually, in these cases a single cyclization product was obtained (Scheme 3 and entries 3–5 of Table 1). Therefore, the asymmetric induction in the cyclization process may be mainly attributable to the relative arrangement of the arylsulfinyl and hydroxy substituents in the intermediate radicals (**12** or **14**). The presence of the external chiral sulfur atom seems to have little influence as it can be seen by comparing data of entries 3 and 5 of Table 1.

Table 1. Cyclization of 1,1-Difluoro-6-heptenyl Radical

entry	substrate	products	ratio	global yield (%)
1	(2*S*,3*R*,*R*S)-**6**	(1*R*,3*R*,6*R*,*R*S)-**7** + (1*R*,3*S*,6*R*,*R*S)-**7**	64:36	84
2	(2*R*,3*S*,*R*S)-**6**	(1*S*,3*S*,6*S*,*R*S)-**7** + (1*S*,3*R*,6*S*,*R*S)-**7**	62:38	79
3	(2*R*,3*R*,*R*S)-**6**	(1*S*,3*R*,6*R*,*R*S)-**7**		50
4	(2*S*,3*S*,*R*S)-**6**	(1*R*,3*S*,6*S*,*R*S)-**7**		76
5	(2*R*,3*R*)-**9**	(1*S*,3*R*,6*R*)-**16**		60

Scheme 4[a]



	Z	R
(1*S*,3*R*,6*R*,*R*S)-**7**	*p*-TolSO	H
(1*S*,3*R*,6*R*)-**16**	*p*-TolS	H
(1*S*,3*R*,6*R*)-**17**	*p*-TolS	PhCO
(1*R*,3*R*)-**18**	H	PhCO

[a] Key: (a) NaI, $(CF_3CO)_2O$, acetone, −40 °C; (b) PhCOOH, DMAP, DCC, CH_2Cl_2, rt; (c) Raney-Ni, ethanol, 80 °C; (d) aqueous KOH, rt.

Sulfur-Free Difluorocyclohexane Derivatives. Some polyfuntionalized and sulfur-free difluorocyclohexane derivatives were chosen as targets for the new synthetic route: α-difluorocyclohexanol, α-hydroxydifluorocyclohexene, α,β,γ-trihydroxydifluorocyclohexane, α-hydroxy-β,γ-epoxydifluorocyclohexane, and α-hydroxy-β-oxodifluorocyclohexane. The compound (1*S*,3*R*,6*R*,*R*S)-**7** was used as the starting material for the synthesis of the α-difluorohydroxy derivative **19**, obtained in four steps (65% overall yield) as shown in Scheme 4. Deoxygenation at sulfur gave the corresponding arylthio derivative (1*S*,3*R*,6*R*)-**16** in 96% yield. The secondary alcohol was protected, and benzoyl derivative **17** (79% yield) was reductively desulfurized with W-2 Raney-Ni to give (1*R*,3*R*)-**18** in 87% yield. The target compound (1*R*,3*R*)-2,2-difluoro-3-methylcyclohexanol (**19**) was obtained in 99% yield upon base-catalyzed hydrolysis.

On the other hand, treatment of (1*R*,3*S*,6*S*,*R*S)-**7** (Scheme 5) with benzyl bromide gave benzyl derivative (1*R*,3*S*,6*S*,*R*S)-**20**, which was heated at 155 °C in 1,2-ethandiol under Ar atmosphere to give, upon sulfenic acid elimination, (3*S*,5*S*)-3-(benzyloxy)-4,4-difluoro-5-methylcyclohex-1-ene (**21**) in 51% yield. Moreover, oxidation of the double bond of (3*S*,5*S*)-**21** with osmium tetraoxide and trimethylamine N-oxide gave, in 93% yield and with high diastereoselection, the corresponding *cis*-diol (1*R*,2*R*,3*S*,5*S*)-**22** arising through the attack of oxygens opposite to the benzyloxy group. On the contrary, the benzyloxy epoxide **23** was obtained as a 2:1 mixture of diastereoisomers [(1*S*,2*S*,4*S*,6*S*)- and (1*R*,2*S*,4*S*,6*R*)-**23**] by *m*-CPBA oxidation of olefin (3*S*,5*S*)-**21**.

Finally, when the benzyloxy derivative (1*S*,3*R*,6*R*,*R*S)-**20** was submitted to the Pummerer rearrangement condi-

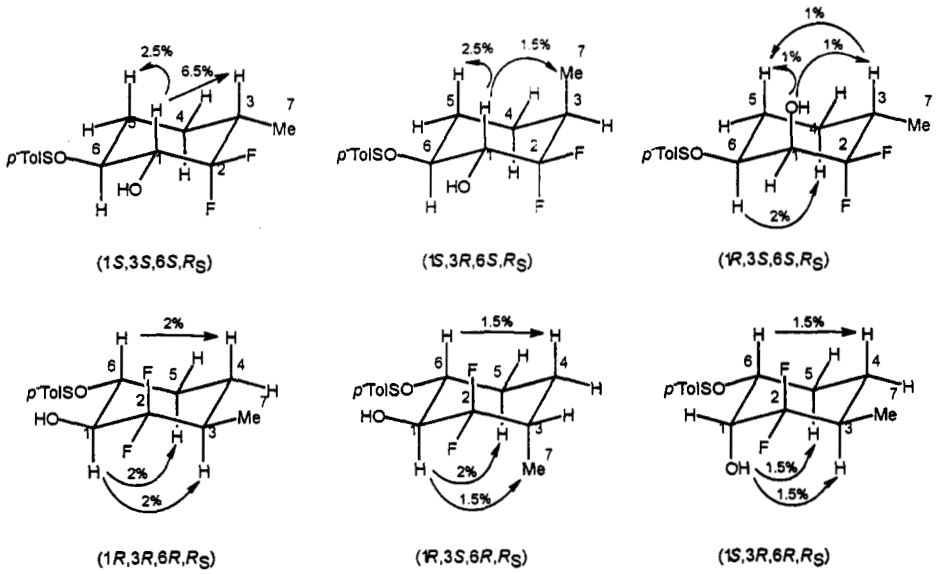
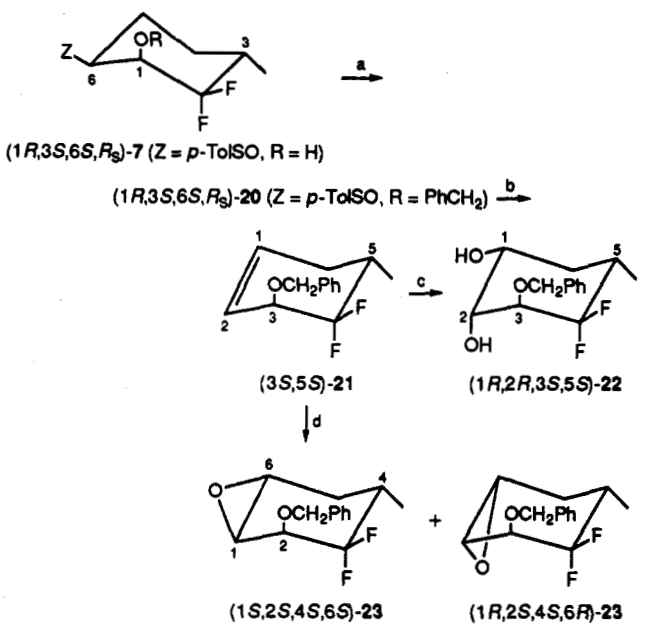


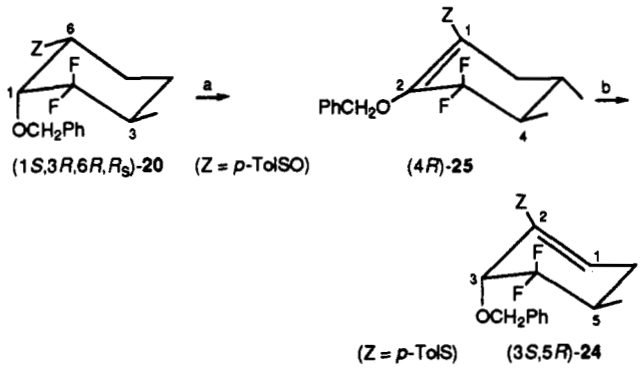
Figure 1. Selected NOE enhancements and preferred conformations for compounds **7**.

Scheme 5[a]



[a] Key: (a) NaH, $PhCH_2Br$, DMF, 0 °C; (b) 1,2-ethandiol, 155 °C; (c) OsO_4, THF/H_2O, 0 °C; (d) *m*-CPBA, CH_2Cl_2, rt.

Scheme 6[a]



[a] Key: (a) $(CF_3CO)_2O$, 2,4,6-trimethylpyridine, CH_3CN, 0 °C; (b) SiO_2, rt.

tions[14] in an attempt to introduce a carbonyl function α to the hydroxy group (Scheme 6), a mixture of the two arylthio olefins **24** and **25** formed. Probably, arylthio trifluoroacetoxy intermediate [(*p*-TolS)(CF_3COO)C<] easily loses trifluoroacetic acid to give the olefins **24** and **25**. During column chromatographic separation only **24** is collected; evidently, **25** isomerized to the more stable **24** under silica gel catalysis.

Structural Assignments. Structure and relative stereochemistry for sulfinyl (**7**, **20**) and thio (**9**, **16**, **17**, **24**, **25**) compounds, as well as for final sulfur-free compounds **18**, **19**, and **21–23**, were assigned on the basis of elemental analyses and ^1H, ^{13}C, and ^{19}F NMR spectral data. The absolute configuration at C-1 for all sulfinyl- and thio-substituted compounds should be the same as that found upon derivatization for the corresponding open-chain secondary alcohols **9**.[11] The configuration at C-3 and C-6 stereocenters relative to that found for C-1 followed from the results of NOE experiments, some of which are reported in Figure 1, and from conformational analyses through ^1H coupling constants.

In the case of the C-3 epimers **7** deriving from (2*R*,3*S*,R_S)-**6** the magnitude of the vicinal coupling constants observed between H-1 (assumed as β) and H-6α, H-4α and H-5β, and H-5β and H-6α (^3J = 10.2–13.0 Hz) indicated that these protons are axially disposed, thus suggesting that the two compounds preferentially adopt the chair conformations shown in Figure 1. The NOEs observed in compound (1*S*,3*S*,6*S*,R_S)-**7** between H-1β and both H-3β (6.5%) and H-5β (2.5%) and in compound (1*S*,3*R*,6*S*,R_S)-**7** between H-1β and both H-5β (2.5%) and H_3-7β (1.5%) confirmed the above results, permitting the assignment of the absolute configuration to the products. Analogous arguments allowed us to assign the absolute configuration to the C-3 epimers (1*R*,3*R*,6*R*,R_S)- and (1*R*,3*S*,6*R*,R_S)-**7** obtained from (2*S*,3*R*,R_S)-**6**. Regarding the compound (1*R*,3*S*,6*S*,R_S)-**7** deriving from (2*S*,3*S*,R_S)-**6** the values of the vicinal coupling constants between H-3β and H-4α, H-α and H-5β, and H-5β and H-6α (^3J = 12.7–

(14) Pummerer rearrangement is an useful oxidation procedure for primary carbons bearing a sulfinyl substituent: Russell, G. A.; Mikol, G. J. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1968; Vol. 1, p 157. Durst, T. *Adv. Org. Chem.* **1969**, 6, 285–388. Application on secondary carbons: Arnone, A.; Bravo, P.; Frigerio, M.; Resnati, G.; Viani, F. *J. Chem. Res., Synop.* **1989**, 278–279; *J. Chem. Res., Miniprint* **1989**, 2201–2231.

13.3 Hz) and H-1α and H-6α (^3J = 2.3 Hz) indicated *trans*-diaxial and gauche relationships, respectively. These findings, combined with the NOEs observed between H-4α and H-6α (2%), H-3β and H-5β (1%), and OH-1 and both H-3β (1%) and H-5β (1%) imply that the cyclohexane ring preferentially assumes the chair conformation shown in Figure 1 in which the C-3 and C-6 substituents are equatorially disposed. Similar reasonings allowed us to assign the absolute configuration to the remaining derivative (1*S*,3*R*,6*R*,R_S)-7 obtained from (2*R*,3*R*,R_S)-6.

Conclusions. Enantiomerically pure *gem*-difluoro-substituted and polyfunctionalized cyclohexane derivatives have been prepared by assembling two fragments, ethyl chlorodifluoroacetate, containing the fluorine atoms, and pent-6-en-1-yl p-tolyl sulfoxide, holding the chiral auxiliary group. The carbon skeleton is made via a base-catalyzed condensation followed by a radical-promoted cyclization. The diastereoselection during the radical cyclization ranges from high to moderate and depends on the relative configuration of the two contiguous substituted carbons of the open-chain substrate. Chiral auxiliary manipulation opens the way to many polyfunctionalized derivatives, which could be difficult to prepare alternatively by the use of fluorinating reagents.

Experimental Section

General Methods. $[\alpha]_D$ values were obtained on a JASCO DIP-181 polarimeter. Benzene was distilled from calcium chloride and stored over molecular sieves (4 Å). Elution values (t_R) were determined on a Waters 600E HPLC using LiChrosorb Si60 (5 μm, Merck) prepacked columns and ethyl acetate and hexane as HPLC-grade solvents (Merck). All other spectral and physical characterizations of new compounds as well as chromatographic separations and solvent purifications have been made as already described.[15]

(R_S)-5-[(4-Methylphenyl)sulfinyl]pent-1-ene (4). Reaction of (−)-(1*R*,2*S*,5*R*)-menthyl (*S*)-*p*-toluenesulfinate (1, 72 g, 24.5 mmol) with the Grignard reagent prepared from 5-bromo-1-pentene (63 g, 42.0 mmol) and magnesium (12.5 g, 42.0 mmol) gave, upon flash chromatography on silica gel (eluent: 6:4 hexane/ethyl acetate), 43.0 g (85% yield) of pure (+)-(*R*)-5-[(4-methylphenyl)sulfinyl]pent-1-ene (4) as a yellowish oil: R_f (6:4 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +20.13° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50 and 7.32 (4 H, m), 5.72 (1 H, m), 5.01 and 5.00 (2 H, m), 2.77 (2 H, t, *J* 7.7 Hz), 2.41 (3 H, br s), 2.17 (2 H, m), 1.83 and 1.73 (2 H, m). Anal. Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 69.01; H, 7.72.

(3*R*,R_S)- and (3*S*,R_S)-1-Chloro-1,1-difluoro-3-[(4-methylphenyl)sulfinyl]hept-6-en-2-one (5). Ethyl chlorodifluoroacetate (3, 1.70 g, 11.5 mmol) in THF (2 mL) was added dropwise at −65 °C to a solution of the lithium derivative [generated with LDA (12.5 mmol) in THF (20 mL)] of 5-[(4-methylphenyl)-sulfinyl]pent-1-ene (4, 2.00 g, 9.61 mmol) stirred under argon. After 5 min at the same temperature, an excess of an 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 extracts 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)-5, both in the keto and hydrate forms (ca. 70% yield)] was reduced to give a mixture of the corresponding more stable secondary alcohols.

(2*S*,3*R*,R_S)-6, (2*R*,3*R*,R_S)-6, (2*S*,3*S*,R_S)-6, and (2*R*,3*S*,R_S)-1-Chloro-1,1-difluoro-3-[(4-methylphenyl)sulfinyl]hept-6-en-2-ols (6). (a) Method A. A suspension of sodium borohydride (0.40 g, 10.3 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)-5 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 collected 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 (7). The residue was flash chromatographed (8:2 chloroform/ethyl acetate) to give (2*S*,3*R*,R_S)-6 (0.77 g, 25.6% yield) and (2*R*,3*S*,R_S)-6 (0.44 g, 14.6% yield) as pure compounds and (2*R*,3*R*,R_S)- and (2*S*,3*S*,R_S)-6 as a mixture which upon flash chromatography (6:4 cyclohexane/ethyl acetate) gave (2*R*,3*R*,R_S)-6 (0.44 g, 14.6% yield) and (2*S*,3*S*,R_S)-6 (0.76 g, 25.2% yield) as pure compounds. (2*S*,3*R*,R_S)-6: R_f (8:2 chloroform/ethyl acetate) 0.35, R_f (6:4 cyclohexane/ethyl acetate) 0.30; $[\alpha]^{20}_D$ + 89° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.61 and 7.36 (4 H, m), 5.61 (1 H, m), 5.33 (1 H, d, *J* = 4.7 Hz), 4.98 and 4.97 (2 H, m), 4.50 (1 H, dddd, *J* = 9.3, 7.7, 5.2, and 4.7 Hz), 3.13 (1 H, ddd, *J* = 7.7, 6.0, and 5.0 Hz), 2.44 (3 H, br s), 2.21, 2.11, 1.84, and 1.68 (4 H, m); ^{19}F NMR ($CDCl_3$) δ −59.49 (1 F, br dd, *J* = 169.0 and 5.2 Hz) and −63.24 (1 F, br dd, *J* = 169.0 and 9.3 Hz). Anal. Calcd for $C_{14}H_{17}ClF_2O_2S$: C, 52.09; H, 5.31. Found: C, 51.88; H, 5.25. (2*R*,3*R*,R_S)-6: R_f (8:2 chloroform/ethyl acetate) 0.30, R_f (6:4 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ + 149° (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.48 and 7.38 (4 H, m), 5.72 (1 H, m), 5.10 and 5.09 (2 H, m), 4.57 (1 H, d, *J* = 3.5 Hz), 4.46 (1 H, dddd, *J* = 11.2, 10.2, 3.5, and 1.3 Hz), 2.86 (1 H, ddd, *J* = 8.5, 4.5 and 1.3 Hz), 2.45 (3 H, br s), 2.35 and 2.22 (4 H, m); ^{19}F NMR ($CDCl_3$) δ −64.03 (1 F, br dd, *J* = 164.5 and 11.2 Hz) and −64.55 (1 F, br dd, *J* = 164.5 and 10.2 Hz). Anal. Calcd for $C_{14}H_{17}ClF_2O_2S$: C, 52.09; H, 5.31. Found: C, 51.92; H, 5.25. (2*S*,3*S*,R_S)-6: R_f (8:2 chloroform/ethyl acetate) 0.30, R_f (6:4 cyclohexane/ethyl acetate) 0.30; $[\alpha]^{20}_D$ +75° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.51 and 7.35 (4 H, m), 5.56 (1 H, m), 4.97 and 4.92 (2 H, m), 4.75 (1 H, dddd, *J* = 10.8, 9.2, 4.9, and 1.4 Hz), 3.15 (1 H, ddd, *J* = 7.6, 3.5, and 1.4 Hz), 3.10 (1 H, d, *J* = 4.9 Hz), 2.43 (3 H, br s), 2.02, 2.00, 1.96, and 1.75 (4 H, m); ^{19}F NMR ($CDCl_3$) δ −64.00 (1 F, br dd, *J* = 164.0 and 9.2 Hz) and −64.78 (1 F, br dd, *J* = 164.0 and 10.8 Hz). Anal. Calcd for $C_{14}H_{17}ClF_2O_2S$: C, 52.09; H, 5.31. Found: C, 51.94; H, 5.26. (2*R*,3*S*,R_S)-6: R_f (8:2 chloroform/ethyl acetate) 0.25, R_f (6:4 cyclohexane/ethyl acetate) 0.25; mp 101–103 °C (isopropyl ether); $[\alpha]^{20}_D$ +110° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.47 and 7.36 (4 H, m), 5.98 (1 H, d, *J* = 6.0 Hz), 5.44 (1 H, m), 4.92 and 4.87 (2 H, m), 4.32 (1 H, dddd, *J* = 9.4, 7.7, 6.0, and 5.1 Hz), 2.96 (1 H, ddd, *J* = 7.0, 5.2, and 5.1 Hz), 2.44 (3 H, br s), 2.08, 1.84, 1.80, and 1.66 (4 H, m); ^{19}F NMR ($CDCl_3$) δ −61.34 (1 F, br dd, *J* = 166.5 and 7.7 Hz) and −63.25 (1 F, br dd, *J* = 166.5 and 9.4 Hz). Anal. Calcd for $C_{14}H_{17}ClF_2O_2S$: C, 52.09; H, 5.31. Found: C, 51.90; H, 5.28.

(b) 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)-5 mixture (12.47 g, 38.9 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 and diluted (~3 M) hydrochloric acid up to pH 3 and extracted with ethyl acetate (3 × 20 mL). 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)-6 in 42% global yield and according to HPLC (7:3 hexane/ethyl acetate) a ratio of, respectively, 6.7:4.7:1.0.

(2*S*,3*R*)-9, (2*R*,3*R*)-9, (2*S*,3*S*)-9, and (2*R*,3*S*)-1-Chloro-1,1-difluoro-3-[(4-methylphenyl)thio]hept-6-en-2-ols (9). Trifluoroacetic anhydride (0.72 ml, 4.55 mmol) was added to a mixture of (2*S*,3*R*,R_S)-6 (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 (3 × 20 mL). The combined organic phases were dried over anhydrous sodium sulfate, and the solvent was removed to give (2*S*,3*R*)-9 as a pure compound in 92% yield. An analytical sample was obtained through flash chromatography (85:15 hexane/ethyl ether): $[\alpha]^{20}_D$ +23.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35 and 7.12 (4 H, m), 5.76 (1 H, m), 5.05 and 5.03 (2 H, m), 3.83 (1 H, ddd, *J* = 8.7, 6.8, and 5.5 Hz), 3.66 (1 H, br signal), 3.34 (1

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H, ddd, J = 10.0, 5.5, and 4.5 Hz), 2.42, 2.33, 1.83 and 1.65 (4 H, m), and 2.33 (3 H, br s). Anal. Calcd for $C_{14}H_{17}ClF_2OS$: C, 54.81; H, 5.59. Found: C, 54.70; H, 5.61. When (2*R*,3*R*,*R*$_S$)-**6** was similarly reacted, the thio alcohol (2*R*,3*R*)-**9** was obtained in 96% yield through flash chromatography (85:15 hexane/ethyl ether): $[\alpha]^{20}_D$ +21.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32 and 7.12 (4 H, m), 5.79 (1 H, m), 5.09 and 5.03 (2 H, m), 4.09 (1 H, ddd, J = 11.5, 9.5, and 2.5 Hz), 3.47 (1 H, ddd, J = 10.7, 3.0, and 2.5 Hz), 2.91 (1 H, br signal), 2.45, 2.28, 2.02 and 1.70 (4 H, m), and 2.33 (3 H, br s). Anal. Calcd for $C_{14}H_{17}ClF_2OS$: C, 54.81; H, 5.59. Found: C, 54.96; H, 5.57. When (2*S*,3*S*,*R*$_S$)-**6** was reacted, the thio alcohol (2*S*,3*S*)-**9** was obtained in 98% yield through flash chromatography (80:20 hexane/ethyl ether): $[\alpha]^{20}_D$ −22.4° (*c* 1.0, $CHCl_3$); the ^1H NMR spectrum is identical to that of (2*R*,3*R*)-**9**. Anal. Calcd for $C_{14}H_{17}ClF_2OS$: C, 54.81; H, 5.59. Found: C, 54.78; H, 5.57. (2*R*,3*S*,*R*$_S$)-**6** gave the thio alcohol (2*R*,3*S*)-**9** in 95% yield through flash chromatography (80:20 hexane/ethyl ether): $[\alpha]^{20}_D$ −22.7° (*c* 1.0, $CHCl_3$); the ^1H NMR spectrum is identical to that of (2*S*,3*R*)-**9**. Anal. Calcd for $C_{14}H_{17}ClF_2OS$: C, 54.81; H, 5.59. Found: C, 54.60; H, 5.58.

Phenylpropionic Esters 10 and 11 of Heptenols (2*S*,3*R*)-9, (2*R*,3*R*)-9, (2*S*,3*S*)-9, and (2*R*,3*S*)-9. 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*)-**9** (30 mg, 0.10 mmol), the (+)-(*S*)-phenylpropionic acid [(+)-(*S*)-PPA, 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 collected 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-phenylpropanoate **10** of the alcohol (2*S*,3*R*)-**9**: ^1H NMR ($CDCl_3$) δ 7.5–7.0 (9 H, m), 5.67 (1 H, m), 5.44 (1 H, ddd, J = 9.8, 6.3 and 6.0 Hz), 4.98 and 4.97 (2 H, m), 3.64 (1 H, q, J = 7.2 Hz), 3.33 (1 H, ddd, J = 9.2, 6.3 and 4.9 Hz), 2.34 (3 H, br s), 2.32 and 2.27 (2 H, m), 1.77 and 1.60 (2 H, m), and 1.53 (3 H, d, J = 7.2 Hz). Similarly, by using (−)-(*R*)-PPA and (2*S*,3*R*)-**9**, the corresponding (*R*)-2-phenylpropanoate **11** was obtained through flash chromatography (95:5 hexane/ethyl ether): ^1H NMR ($CDCl_3$) δ 7.5–7.0 (9 H, m), 5.56 (1 H, m), 5.45 (1 H, ddd, J = 9.9, 7.3, and 5.0 Hz), 4.92 and 4.90 (2 H, m), 3.80 (1 H, q, J = 7.2 Hz), 3.25 (1 H, ddd, J = 8.9, 5.4, and 5.2 Hz), 2.32 (3 H, br s), 2.21 and 2.13 (2 H, m), 1.56 and 1.48 (2 H, m), and 1.54 (3 H, d, J = 7.2 Hz). When (2*R*,3*R*)-**9** was esterified with (+)-(*S*)-PPA, the obtained ester **10** showed the following spectrum: ^1H NMR ($CDCl_3$) δ 7.5–7.0 (9 H, m), 5.68 (1 H, m), 5.46 (1 H, ddd, J = 11.0, 10.5, and 2.0 Hz), 5.04 and 5.02 (2 H, m), 3.85 (1 H, q, J = 7.2 Hz), 3.35 (1 H, br ddd, J = 10.9, 2.9, and 2.0 Hz), 2.32 (3 H, br s), 2.28 and 2.17 (2 H, m), 1.80 and 1.16 (2 H, m), and 1.59 (3 H, d, J = 7.2 Hz). Similarly, the ester **11** obtained from (−)-(*R*)-PPA and the alcohol (2*R*,3*R*)-**9** showed the following spectrum: ^1H NMR ($CDCl_3$) δ 7.5–7.0 (9 H, m), 5.77 (1 H, m), 5.46 (1 H, ddd, J = 10.7, 10.5, and 2.0 Hz), 5.11 and 5.06 (2 H, m), 3.86 (1 H, q, J = 7.2 Hz), 3.41 (1 H, br ddd, J = 10.7, 3.0, and 2.0 Hz), 2.41 and 2.28 (2 H, m), 2.33 (3 H, br s), 1.95 and 1.50 (2 H, m), and 1.60 (3 H, d, J = 7.2 Hz). When (2*S*,3*S*)-**9** was esterified with (+)-(*S*)-PPA the obtained ester **10** showed the same ^1H NMR spectrum of the (−)-(*R*)-PPA ester of (2*R*,3*R*)-**9**, and similarly, the ester **11** obtained from the same (2*S*,3*S*)-**9** and (−)-(*R*)-PPA showed the same ^1H NMR spectrum of the (+)-(*S*)-PPA ester of (2*R*,3*R*)-**9**. Finally, the esters obtained by reacting (2*R*,3*S*)-**9** with (+)-(*S*)-PPA and with (−)-(*R*)-PPA showed the same ^1H NMR spectra of, respectively, the (−)-(*R*)-PPA and (+)-(*S*)-PPA esters of (2*S*,3*R*)-**9**.

Radical Cyclization of Alcohols 6 and 9. General Procedure. (a) Thermal Reaction. To a stirred solution of alcohol (1 mmol) and 2,2′-azobisisobutyronitrile (AIBN, 0.05 mmol) in oxygen-free benzene (15 mL) at 70 °C in an argon atmosphere was slowly added (ca. 1 h) a solution of tributyltin hydride (1.0 mmol) in the same solvent (30 mL). The reaction mixture was further stirred for different periods of time, depending of the substrate, at the same temperature. The benzene was removed under reduced pressure, acetonitrile (10 mL) was added, and the mixture was washed with hexane (3 × 5 mL). Acetonitrile was removed under reduced pressure, and the residue was flash chromatographed.

Specifically, (2*S*,3*R*,*R*$_S$)-**6** gave in 4 h, after flash chromatography (75:25 chloroform/ethyl acetate), (1*R*,3*R*,6*R*,*R*$_S$)-2,2-difluoro-3-methyl-6-[(4-methylphenyl)sulfinyl]cyclohexanol (**7**, 53.6% yield) and (1*R*,3*S*,6*R*,*R*$_S$)-**7** (30.4% yield) as pure compounds. (1*R*,3*R*,6*R*,*R*$_S$)-**7**: R_f (75:25 chloroform/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +80.7° (*c* 0.4, $CHCl_3$); mp 153–155 °C (1:1 hexane/isopropyl ether). Anal. Calcd for $C_{14}H_{18}F_2O_2S$: C, 58.32; H, 6.29. Found: C, 58.54; H, 6.27. (1*R*,3*S*,6*R*,*R*$_S$)-**7**: R_f (75:25 chloroform/ethyl acetate) 0.30; $[\alpha]^{20}_D$ +98.9° (*c* 0.7, $CHCl_3$); mp 166–168 °C (isopropyl ether). Anal. Calcd for $C_{14}H_{18}F_2O_2S$: C, 58.32; H, 6.29. Found: C, 58.46; H, 6.27. (2*R*,3*R*,*R*$_S$)-**6** gave in 6 h, after flash chromatography (7:3 cyclohexane/ethyl acetate) of the reaction mixture, (1*S*,3*R*,6*R*,*R*$_S$)-**7** (50% yield): R_f (7:3 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +245.1° (*c* 1.0, $CHCl_3$); mp 185–187 °C (1:1 hexane/isopropyl ether). Anal. Calcd for $C_{14}H_{18}F_2O_2S$: C, 58.32; H, 6.29. Found: C, 58.48; H, 6.28. (2*S*,3*S*,*R*$_S$)-**6** gave in 7 h after flash chromatography (7:3 chloroform/ethyl acetate), (1*R*,3*S*,6*S*,*R*$_S$)-**7** (52% yield): R_f (7:3 chloroform/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +133.7° (*c* 1.0, $CHCl_3$); mp 204–205 °C (1:1 hexane/isopropyl ether). Anal. Calcd for $C_{14}H_{18}F_2O_2S$: C, 58.32; H, 6.29. Found: C, 58.42; H, 6.27. (2*R*,3*S*,*R*$_S$)-**6** gave, after 5 h reaction and flash chromatography (7:3 chloroform/ethyl acetate), a 62:38 mixture of (1*S*,3*S*,6*S*,*R*$_S$)-**7** and (1*S*,3*R*,6*S*,*R*$_S$)-**7** (global yield: 78.5%). The mixture of the two diastereoisomers was treated with (−)-(*R*)-PPA in order to obtain the two diastereoisomeric esters. Flash chromatography of the crude (7:3 cyclohexane/ethyl acetate) gave the (−)-(*R*)-PPA esters of (1*S*,3*S*,6*S*,*R*$_S$)-**7** [R_f (7:3 cyclohexane/ethyl acetate) 0.35]. The two separated diastereoisomeric esters (1 mmol) were dissolved in methanol (3 mL) and treated with a 1% aqueous solution of potassium hydroxide at room temperature. After 2 h, methanol was removed under reduced pressure, and the organic products were extracted with ethyl ether (3 × 3 mL). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The two residues were flash chromatographed (7:3 chloroform/ethyl acetate) to give (1*S*,3*S*,6*S*,*R*$_S$)-**7** (49% yield): R_f (7:3 chloroform/ethyl acetate) 0.35, R_f (7:3 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +217.3° (*c* 1.1, $CHCl_3$); mp 176–177 °C (isopropyl ether). Anal. Calcd for $C_{14}H_{18}F_2O_2S$: C, 58.32; H, 6.29. Found: C, 58.13; H, 6.27. (1*S*,3*R*,6*S*,*R*$_S$)-**7** (30% yield): R_f (7:3 chloroform/ethyl acetate) 0.35, R_f (7:3 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +190.5° (*c* 0.7, $CHCl_3$); mp 173–174 °C (isopropyl ether). Anal. Cald for $C_{14}H_{18}F_2O_2S$: C, 58.32; H, 6.29. Found: C, 58.13; H, 6.30. When (2*R*,3*R*)-**9** was reacted under the same conditions, (1*S*,3*R*,6*R*)-2,2-difluoro-3-methyl-6-[(4-methylphenyl)thio]cyclohexanol (**16**, 60% yield) was obtained as single compound: R_f (9:1 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +45.3° (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}F_2OS$: C, 61.74; H, 6.66. Found: C, 61.60; H, 6.68.

(b) Photolytic Reaction. A solution of alcohol (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. 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 (3 × 5 mL). Acetonitrile was removed under reduced pressure, and the residue was flash chromatographed. From (2*S*,3*S*,*R*$_S$)-**6**, after 2 h reaction (1*R*,3*S*,6*S*,*R*$_S$)-**7** was isolated in 76% yield.

(1*S*,3*R*,6*R*)-2,2-Difluoro-3-methyl-6-[(4-methylphenyl)thio]cyclohexanol (16). To a solution of (1*S*,3*R*,6*R*,*R*$_S$)-**7** (150 mg, 0.52 mmol) and NaI (234 mg, 1.56 mmol) in acetone (10 mL) at −40 °C under nitrogen atmosphere was added dropwise a solution of trifluoroacetic anhydride (0.36 mL, 2.6 mmol) in acetone (4 mL). The reaction mixture was stirred at −40 °C for 20 min, and then a saturated aqueous solution of sodium sulfite (10 mL) was added, acetone was evaporated off, the aqueous solution was extracted with ethyl acetate (3 × 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed in vacuum. The residue was flash chromatographed (9:1 cyclohexane/ethyl acetate) to give the pure compound (1*S*,3*R*,6*R*)-**16** as a yellowish liquid in 96% yield: R_f (9:1 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +45.4° (*c* 1.3, $CHCl_3$).

(1*S*,3*R*,6*R*)-2,2-Difluoro-3-methyl-6-[(4-methylphenyl)thio]cyclohexyl Benzoate (17). 4-(Dimethylamino)pyridine (3.0 mg, 0.03 mmol) was added to a dichloromethane solution (3 mL)

containing the thio alcohol (1*S*,3*R*,6*R*)-**16** (70.0 mg, 0.26 mmol), benzoic acid (35.0 mg, 0.28 mmol), and dicyclohexylcarbodiimide (58.3 mg, 0.28 mmol) at 0 °C. After 1 h at room temperature, dicyclohexylurea was removed by filtration and washed with hexane. The organic phases were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromatographed (95:5 cyclohexane/ethyl acetate) to give the desired product (1*S*,3*R*,6*R*)-**17** (76.3 mg, 79% yield): R_f (95:5 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +117.9° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.1–7.1 (9 H, m), 5.59 (1 H, m), 3.35 (1 H, m), 2.32 (3 H, br s), 2.23 (1 H, m), 2.1–1.7 (3 H, m), 1.42 (1 H, m), and 1.05 (3 H, d, *J* = 6.7 Hz); ^{19}F NMR ($CDCl_3$) δ −110.17 (1 F, br d, *J* = 251.5 Hz), and −122.98 (1 F, br dd, *J* = 251.5 and 29.5 Hz). Anal. Calcd for $C_{21}H_{22}F_2O_2S$: C, 67.00; H, 5.89. Found: C, 66.25; H, 6.35.

(1*R*,3*R*)-2,2-Difluoro-3-methylcyclohexyl Benzoate (18). To a solution of (1*S*,3*R*,6*R*)-**17** (60 mg, 0.15 mmol) in ethanol (15 mL) was added Raney-Ni (180.0 mg). The suspension was heated to 80 °C and stirred for 10 min. After that, the Raney-Ni was filtered and washed twice with ethanol. The solvent was removed under reduced pressure, and the residue was flash chromatographed (90:10 cyclohexane/ethyl acetate) to give (1*R*,3*R*)-**18** (34 mg, 87% yield): R_f (90:10 cyclohexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ −23.0° (*c* 1.7, $CHCl_3$); mp 54–57 °C (isopropyl ether); ^1H NMR ($CDCl_3$) δ 8.05, 7.59, and 7.46 (5 H, m), 5.39 (1 H, m), 2.30 (1 H, m), 2.15–1.25 (6 H, m), and 1.10 (3 H, d, *J* = 6.8 Hz); ^{19}F NMR ($CDCl_3$) δ −112.40 (1 F, br d, *J* = 249.0 Hz) and −122.55 (1 F, br d, *J* = 249.0 Hz). Anal. Calcd for $C_{14}H_{16}F_2O_2$: C, 66.13; H, 6.34. Found: C, 66.25; H, 6.35.

(1*R*,3*R*)-2,2-Difluoro-3-methylcyclohexanol (19). To a solution of (1*R*,3*R*)-**18** (17.0 mg, 0.07 mmol) in methanol (0.5 mL) was added a 1% aqueous solution of potassium hydroxide (0.4 mL) at room temperature. After 1 h methanol was evaporated under reduced pressure and the organic products were extracted with ethyl ether (3 × 1 mL). The combined organic layers were dried over anhydrous sodium sulfate, the solvent was evaporated, and the crude was flash chromatographed (7:3 petroleum ether/ethyl ether) to give (1*R*,3*R*)-**19** (10.0 mg, 99% yield): R_f (7:3 petroleum ether/ethyl ether) 0.35; $[\alpha]^{20}_D$ −3.9° (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.95 (1 H, m), 2.21 (1 H, m), 2.1–1.1 (7 H, m), and 1.03 (3 H, d, *J* = 6.8 Hz); ^{19}F NMR ($CDCl_3$) δ −113.54 (1 F, br d, *J* = 247.0 Hz) and −123.60 (1 F, br d, *J* = 247.0 Hz). Anal. Calcd for $C_7H_{12}F_2O$: C, 55.99; H, 8.05. Found: C, 56.12; H, 8.02.

(1*R*,3*S*,6*S*,R_S)-1-(Benzyloxy)-2,2-difluoro-3-methyl-6-[(4-methylphenyl)sulfinyl]cyclohexane (20). To a suspension of sodium hydride (50.0 mg, 1.04 mmol) in dimethylformamide (DMF, 5 mL) at 0 °C was added dropwise a solution of (1*R*,3*S*,6*S*,R_S)-**7** (150 mg, 0.52 mmol) and benzyl bromide (0.62 mL, 5.20 mmol) in DMF (3 mL). Stirring was continued at 0 °C 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*,3*S*,6*S*,R_S)-**20** (160.0 mg, 81% yield): R_f (6:4 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ −13.6° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.5–7.2 (9 H, m), 4.82 (1 H, dd, *J* = 11.6 and 1.9 Hz), 4.41 (1 H, d, *J* = 11.6 Hz), 3.42 (1 H, ddd, *J* = 6.2, 3.5, and 2.7 Hz), 2.85 (1 H, ddddd, *J* = 12.8, 4.5, 4.5, 2.7, and 1.8 Hz), 2.42 (3 H, br s), 2.31 (1 H, m), 2.14 and 2.10 (2 H, m), 1.87 and 1.30 (2 H, m), and 1.02 (3 H, d, *J* = 6.7 Hz); ^{19}F NMR ($CDCl_3$) δ −108.25 (1 F, br d, *J* = 252.5 Hz) and −119.65 (1 F, br dd, *J* = 252.5 and 29.5 Hz). Anal. Calcd for $C_{21}H_{24}F_2O_2S$: C, 66.64; H, 6.39. Found: C, 66.41; H, 6.38.

(3*S*,5*S*)-3-(Benzyloxy)-4,4-difluoro-5-methylcyclohex-1-ene (21). A solution of (1*R*,3*S*,6*S*,R_S)-**20** (70.0 mg, 0.19 mmol) in 1,2-ethandiol (0.5 mL) was heated at 155 °C under Ar atmosphere and magnetically 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 (95:5 hexane/ethyl ether) to give (3*S*,5*S*)-**21** as pure compound (20.0 mg, 51% yield): R_f (95:5 hexane/ethyl ether) 0.30; $[\alpha]^{20}_D$ +154.4° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.5–7.2 (5 H, m), 5.87 and 5.69 (2 H, m), 4.85 (1 H, br d, *J* = 11.9 Hz), 4.67 (1 H, d, *J* = 11.9 Hz), 3.90 (1 H, br ddd, *J* = 8.4, 5.5, and 4.5 Hz), 2.42 (1 H, m), 2.35 and 2.00 (2 H, m), and 1.11 (3 H, d, *J* = 6.7 Hz); ^{19}F NMR ($CDCl_3$) δ −116.95 (1 F, br d, *J* = 246.0 Hz) and −121.33 (1 F, br ddd, *J* = 246.0, 29.7, and 8.2 Hz). Anal. Calcd for $C_{14}H_{16}F_2O$: C, 70.57; H, 6.77. Found: C, 70.65; H, 6.75.

(1*R*,2*R*,3*S*,5*S*)-3-(Benzyloxy)-4,4-difluoro-5-methylcyclohexane-1,2-diol (22). Osmium tetraoxide (4% wt in water, 20.4 mg, 0.08 mmol) was added at 0 °C to a stirred solution of cyclohexene derivative **21** (160 mg, 0.67 mmol) in THF (4 mL) and water (0.12 mL) under Ar atmosphere. The reaction mixture was stirred at 0 °C for 10 min and kept in the dark, 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) were added. Stirring was continued for 10 min, and then the solution was extracted with ethyl acetate (5 × 2 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*,5*S*)-**22** (170 mg, 93% yield) as a pure compound: R_f (7:3 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ −21.18° (*c* 1.1, $CHCl_3$); mp 75–76 °C (isopropyl ether); ^1H NMR ($CDCl_3$) δ 7.5–7.2 (5 H, m), 4.86 (1 H, br d, *J* = 11.5 Hz), 4.62 (1 H, d, *J* = 11.5 Hz), 4.06 (1 H, br dddd, *J* = 9.0, 6.1, 4.8, and 3.2 Hz), 3.93 (1 H, m), 3.82 (1 H, ddd, *J* = 8.0, 6.8, and 5.4 Hz), 2.32 (1 H, m), 2.32 (1 H, ddd, *J* = 5.2, 2.0, and 1.7 Hz), 2.24 (1 H, br d, *J* = 6.1 Hz), 1.77 and 1.69 (2 H, m), and 1.14 (3 H, d, *J* = 7.0 Hz); ^{19}F NMR ($CDCl_3$) δ −112.51 (1 F, br d, *J* = 256.0 Hz) and −116.06 (1 F, br d, *J* = 256.0 Hz). Anal. Calcd for $C_{14}H_{18}F_2O_3$: C, 61.76; H, 6.66. Found: C, 61.73; H, 6.68.

(1*S*,2*S*,4*S*,6*S*)- and (1*R*,2*S*,4*S*,6*R*)-2-(Benzyloxy)-3,3-difluoro-4-methyl-7-oxabicyclo[4.1.0]heptane (23). To a solution of (3*S*,5*S*)-**21** (200 mg, 0.84 mmol) in dichloromethane (5 mL) at room temperature was added *m*-CPBA (205 mg, 1.01 mmol). After 2 days at room temperature, the reaction mixture was washed with an aqueous solution of $Na_2S_2O_5$ and $NaHCO_3$. The organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum. Flash chromatography (49:1 cyclohexane/ethyl ether) gave (1*S*,2*S*,4*S*,6*S*)-**23** (60 mg, 28% yield) and (1*R*,2*S*,4*S*,6*R*)-**23** (60 mg, 28% yield). (1*S*,2*S*,4*S*,6*S*)-**23**: R_f (98:2 cyclohexane/ethyl ether) 0.35; $[\alpha]^{20}_D$ +50.9° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.5–7.2 (5 H, m), 4.87 (1 H, d, *J* = 12.2 Hz), 4.77 (1 H, d, *J* = 12.2 Hz), 3.85 (1 H, ddd, *J* = 10.5, 5.2, and 4.8 Hz), 3.26 (1 H, ddd, *J* = 3.6, 2.3, and 1.9 Hz), 3.24 (1 H, ddddd, *J* = 4.8, 4.2, 3.6, 1.3, and 1.1 Hz), 2.30 (1 H, ddddd, *J* = 23.2, 11.8, 8.7, 7.0, and 5.3 Hz), 2.26 (1 H, br d, *J* = 14.9 Hz), 1.80 (1 H, ddd, *J* = 14.9, 11.8, and 1.9 Hz) and 1.02 (3 H, d, *J* = 7.0 Hz); ^{19}F NMR ($CDCl_3$) δ −119.48 (1 F, br ddddd, *J* = 250.5, 8.7, 5.2, 4.2, and 3.0 Hz) and −119.75 (1 F, br ddd, *J* = 250.5, 23.2, and 10.5 Hz). Anal. Calcd for $C_{14}H_{16}F_2O_2$: C, 66.13; H, 6.34. Found: C, 66.07; H, 6.32. (1*R*,2*S*,4*S*,6*R*)-**23**: R_f (98:2 cyclohexane/ethyl ether) 0.35; $[\alpha]^{20}_D$ +17.3° (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.5–7.2 (5 H, m), 4.91 (1 H, d, *J* = 11.8 Hz), 4.71 (1 H, d, *J* = 11.8 Hz), 3.98 (1 H, ddd, *J* = 9.0, 8.0, and 1.6 Hz), 3.23 (1 H, ddddd, *J* = 3.9, 3.6, 2.6, 1.6, and 1.0 Hz), 3.21 (1 H, dddd, *J* = 4.2, 3.6, 1.0, and 0.5 Hz), 2.28 (1 H, ddddq, *J* = 18.4, 10.4, 8.2, 7.2, and 6.8 Hz), 2.18 (1 H, dddd, *J* = 15.2, 7.2, 4.2, and 2.0 Hz), 1.87 (1 H, dddd, *J* = 15.2, 8.2, 1.0, and 1.0 Hz) and 1.03 (3 H, d, *J* = 6.8 Hz); ^{19}F NMR ($CDCl_3$) δ −113.49 (1 F, br ddddd, *J* = 250.0, 10.4, 9.0, 3.9, and 2.0 Hz) and −114.23 (1 F, dddd, *J* = 250.0, 18.4, 8.0, and 2.6 Hz). Anal. Calcd for $C_{14}H_{16}F_2O_2$: C, 66.13; H, 6.34. Found: C, 66.10; H, 6.33. ^{13}C NMR ($CDCl_3$) selected resonances, δ: 74.62, 72.85, 54.56, and 51.00 [^1J(C,H) = 183 and 179.5 Hz], 30.18, 28.86 and 13.16.

(3*S*,5*R*)-3-(Benzyloxy)-4,4-difluoro-2-[(4-methylphenyl)-thio]cyclohexene (24) and (4*R*)-2-(Benzyloxy)-3,3-difluoro-1-[(4-methylphenyl)thio]cyclohexene (25). As already described for (1*R*,3*S*,6*S*,R_S)-**20**. (1*S*,3*R*,6*R*,R_S)-1-(benzyloxy)-2,2-difluoro-3-methyl-6-[(4-methylphenyl)sulfinyl]cyclohexane (**20**) was synthesized in 48% yield: R_f (75:25 hexane/ethyl acetate) 0.35; $[\alpha]^{20}_D$ +136.0° (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.7–7.2 (9 H, m), 4.92 (1 H, br d, *J* = 10.7 Hz), 4.85 (1 H, d, *J* = 10.7 Hz), 4.42 (1 H, m), 2.89 (1 H, m), 2.42 (3 H, br s), 2.4–1.1 (5 H, m), and 1.02 (3 H, d, *J* = 6.7 Hz); ^{19}F NMR ($CDCl_3$) δ −110.59 (1 F, br d, *J* = 251.5 Hz) and −120.99 (1 F, br dd, *J* = 251.5 and 29.5 Hz). Anal. Calcd for $C_{21}H_{24}F_2O_2S$: C, 66.64; H, 6.39. Found: C, 66.40; H, 6.41. To a solution of (1*S*,3*R*,6*R*,R_S)-**20** (300 mg, 0.78 mmol) and 2,4,6-trimethylpyridine (230 μL, 1.72 mg) in acetonitrile (3 mL) cooled at −20 °C under Ar atmosphere was added a solution of trifluoroacetic anhydride (313 μL, 1.56 mmol) in

acetonitrile (1 mL) dropwise. Stirring was continued for 0.5 h at room temperature, and then the solution was again cooled to −20 °C, potassium carbonate was added up to pH 7, and a solution of mercuric chloride (638 mg, 2.35 mmol) in acetonitrile (3 mL) was added dropwise. After 12 h at room temperature, the reaction was monitored by TLC, but any improvement was not detected. The reaction mixture was filtered on Celite, and the yellow liquid was diluted with water and extracted with ethyl ether (3 × 5 mL). The combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated under vacuum. Flash chromatography (98:2 hexane/ethyl ether) of the residue gave (3*S*,5*R*)-3-(benzyloxy)-4,4-difluoro-2-[(4-methylphenyl)thio]cyclohexene (**24**) [R_f (98:2 hexane/ethyl ether) 0.35; ^{1}H NMR ($CDCl_3$) δ 7.5–7.0 (9 H, m), 6.11 (1 H, ddd, J = 5.0, 2.7 and 1.3 Hz), 4.77 (1 H, br d, J = 10.8 Hz), 4.56 (1 H, d, J = 10.8 Hz), 3.82 (1 H, br ddd, J = 7.0, 5.0, and 1.3 Hz), 2.43 (1 H, m), 2.36 and 2.12 (2 H, m), 2.33 (3 H, br s), and 1.11 (3 H, d, J = 6.7 Hz); ^{19}F NMR ($CDCl_3$) δ −115.77 (1 F, br d, J = 246.5 Hz) and −123.20 (1 F, br ddd, J = 246.5, 32.5, and 7.0 Hz). Anal. Calcd for $C_{21}H_{22}F_2OS$: C, 69.97; H, 6.15. Found: C, 70.11; H, 6.14] and (4*R*)-2-(benzyloxy)-3,3-difluoro-1-[(4-methylphenyl)thio]cyclohexene (**25**) [R_f 0.32; ^{1}H NMR ($CDCl_3$) δ 7.6–7.1 (9 H, m), 5.09 (1 H, d, J = 11.0 Hz), 5.05 (1 H, d, J = 11.0 Hz), 2.35 (3 H, br s), 2.15 (1 H, m), 2.05 (2 H, m), 1.65 and 1.55 (2 H, m) and 1.09 (3 H, dd, J = 6.8 and 1.0 Hz); ^{19}F NMR ($CDCl_3$) δ −105.99 (1 F, br d, J = 263.0 Hz), and −107.34 (1 F, br d, J = 263.0 Hz)] in a 2:1 relative ratio and in 71% global yield.

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

Supplementary Material Available: Selected ^{1}H and ^{19}F NMR chemical shifts (δ) for compounds **7** and **16** and selected coupling constants (Hz) and ^{13}C NMR data for compounds **7**, 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.