NMR δ 7.27-7.75 (m, 6 H), 8.26 (d, J = 7.7 Hz, 4 H, $H_{3,3'',5,5''}$), 9.92 (s, 4 H, C*H*O); ^{13}C NMR δ 128.7, 129.0, 131.0, 132.2, 133.4, 133.5, 134.7, 146.0, 190.1. Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 77.06; H, 4.24.

2,2'',6,6''-Tetrakis(hydroxymethyl)-1,1':3',1''-terphenyl (19). To a solution of tetraldehyde 18 (7.08 g, 20.7 mmol) in 400 mL of THF/MeOH (3:1) was added at rt 1.56 g (41.2 mmol) of $NaBH_4$, and the mixture was stirred at rt for 16 h. The reaction was quenched with concentrated HCl until slightly acidic. The solvent was removed (Rotavap) and the crude product was extracted (soxhlet) with MeOH/$CHCl_3$ (2:3) for 3 d to yield 7.10 g (98%) of **19**, mp 192 °C: ^1H NMR (DMSO) δ 4.20 (d, J = 5.5 Hz, 8 H, C*H*$_2$), 5.11 (t, J = 5.5 Hz, 4 H, O*H*), 6.89 (t, J = 1.5 Hz, 1 H, $H_{2'}$), 7.15 (dd, J = 7.5, 1.5 Hz, 2 H, $H_{4',6'}$), 7.35-7.53 (m, 7 H); ^{13}C NMR δ 60.9, 125.0, 127.2, 127.8, 128.4, 129.5, 137.4, 138.0, 139.6. Anal. Calcd for $C_{22}H_{22}O_4 \cdot B_2O_3$: C, 62.90; H, 5.28. Found: C, 63.04; H, 5.42.

Coupling of Tetrol 19 with *m*-Xylylene Dichloride. *m*-Tetraoxacyclophane 20. To a solution of tetrol 19 (300 mg, 0.86 mmol) in dry DMF (30 mL) was added 282 mg (1.61 mmol) of 1,3-bis(chloromethyl)benzene, and the resulting mixture was added dropwise over 8-10 h to a stirred suspension of NaH (210 mg 80% in oil, 7.0 mmol) in dry DMF (30 mL) under Ar at 65-70 °C. After addition was complete, the cooled mixture was cautiously quenched with water to destroy the excess NaH. The mixture was evaporated to dryness, the residue was taken up in CH_2Cl_2 and filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel using 1:1 ethyl acetate/hexanes as eluent to give 200 mg (42%) of **20**, mp 267-269 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR, see Table I; ^{13}C NMR δ 67.7, 72.7, 126.2, 127.8, 127.9, 128.2, 128.3, 128.9, 129.1, 130.0, 136.1, 136.9, 137.8, 138.3; MS (FAB) 553 (MH^+ - 2 H). Anal. Calcd for $C_{38}H_{34}O_4$: C, 82.28; H, 6.18. Found: C, 82.25; H, 6.06.

***p*-Tetraoxacyclophane 21.** The procedure was the same as for the meta isomer, except that 1,4-bis(chloromethyl)benzene was used; yield 167 mg (35%), mp 247-249 °C: ^1H NMR, see Table I; ^{13}C NMR δ 66.8, 72.4, 127.2, 127.4, 127.6, 127.8, 129.3, 129.5, 129.7, 136.2, 137.1, 137.6, 138.9; MS (FAB) 553 (MH^+ - 2 H). Anal. Calcd for $C_{38}H_{34}O_4$: C, 82.28; H, 6.18. Found: C, 81.93; H, 6.15.

***o*-Tetraoxacyclophane 22.** The procedure was the same as for the meta isomer, except that 1,2-bis(chloromethyl)benzene was used; yield 95 mg (20%), mp 215-217 °C: ^1H NMR δ 4.30, 4.33 (AB q, J = 10.7 Hz, 8 H, C*H*$_2$), 4.40, 4.44 (AB q, J = 10.7 Hz, 8 H, C*H*$_2$), 7.17-7.30 (m, 10 H), 7.19 (t, J = 1.6 Hz, 1 H, $H_{2'}$), 7.40-7.57 (m, 7 H); ^{13}C NMR δ 70.4, 71.1, 127.6, 128.1, 128.2, 128.5, 129.8, 130.1, 132.5, 136.0, 136.8, 138.6, 141.9; MS (FAB) 555 (MH^+); HRMS calcd for $C_{38}H_{34}O_4$ (M^+), 554.2457, found 554.2469. Anal. Calcd for $C_{38}H_{34}O_4$: C, 82.28; H, 6.18. Found: C, 82.33; H, 6.13.

Bis(*n*-pentyl)tetraoxacyclophane 23. To a solution of tetrol 19 (250 mg, 0.71 mmol) in dry DMF (30 mL) was added 588 mg (1.43 mmol) of 1,5-pentanediol ditosylate,[10] and the resulting solution was added dropwise over 8-10 h under Ar to a stirred suspension of NaH (180 mg 80% in oil, 7.0 mmol) in dry DMF (30 mL) at 65-70 °C. After addition was complete, the cooled mixture was quenched with water to destroy the excess NaH and evaporated to dryness. The residue was taken up in CH_2Cl_2 and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel using 1:1 ethyl acetate/hexane as eluent to afford 52 mg (15%) of **23**, mp 157-159 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR δ 1.20-1.40 (m, 4 H, central C*H*$_2$), 1.41-1.57 (m, 8 H, methylenes adjacent to central CH_2), 3.38-3.57 (m, 8 H, C*H*$_2$ adjacent to O), 4.23, 4.36 (AB q, J = 11.8 Hz, 8 H, benzylic C*H*$_2$), 7.11 (dd, J = 7.5, 1.6 Hz, $H_{4',6'}$), 7.19 (t, J = 1.6 Hz, 1 H, $H_{2'}$), 7.36-7.50 (m, 7 H); ^{13}C NMR δ 22.1, 27.9, 69.6, 70.0, 127.7, 127.8, 128.0, 128.6, 129.8, 136.6, 138.4, 140.2; MS (FAB) 487 (MH^+); HRMS calcd for $C_{32}H_{39}O_4$ (MH^+) 487.2849, found 487.2844. Anal. Calcd for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87. Found: C, 79.08; H, 7.73.

Hexaoxacyclophane 24. The procedure was the same as for **23** except that diethylene glycol ditosylate (591 mg, 1.43 mmol) was used; yield 56 mg (16%), mp 146-148 °C (recrystallized from hexanes/CH_2Cl_2): ^1H NMR δ 3.44-3.73 (m, 16 H, C*H*$_2$ adjacent to O), 4.27, 4.66 (AB q, J = 12.8 Hz, 8 H, benzylic), 7.05 (t, J = 1.6 Hz, 1 H, $H_{2'}$), 7.12 (dd, J = 7.6, 1.6 Hz, 2 H, $H_{4',6'}$), 7.35-7.49 (m, 7 H); ^{13}C NMR δ 69.9, 71.5, 72.3, 126.5, 127.6, 128.2, 130.2, 136.7, 138.3, 139.4 (one overlapped); MS (FAB) 491 (MH^+); HRMS calcd for $C_{30}H_{35}O_6$ (MH^+) 491.2434, found 491.2439. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C. 73.65; H, 6.83.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of 19 (8 pages). Ordering information is given on any current masthead page.

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Asymmetric Synthesis of Oxygen- and Nitrogen-Substituted Difluoromethylene Products

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1,1-Difluoroalkyl sulfinylmethyl ketones **3** are synthesized in enantiomerically pure form through acylation of (+)-(*R*)-methyl *p*-tolyl sulfoxide (**1**) with α,α-difluorocarboxylates **2**. These ketones have been reduced with complete diastereoselection to give the corresponding alcohols. Removal of the auxiliary sulfinyl group and further elaborations afforded enantiomerically pure 2-(benzyloxy)-3,3-difluoro alcohols, esters, oximes, hydroxylamines, and nitriles.

The selective introduction of a fluorine atom or a perfluorinated residue into a chiral organic compound imparts specific and often useful properties with respect to those of the parent, unfluorinated product.[1]

For these reasons, various chemical and enzymatic approaches have been recently reported for the asymmetric synthesis of monofluoro[2] or trifluoromethyl[3] substituted compounds, while very few methods are available for the

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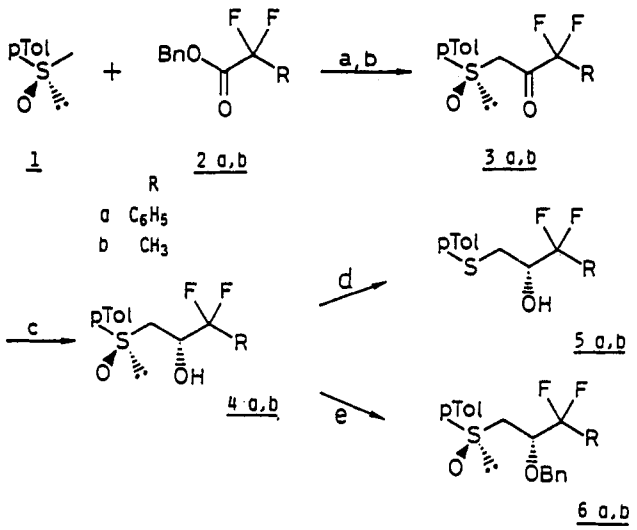
Scheme I[a]



[a] Reagents and conditions: (a) LDA, THF, −78 °C; (b) molecular sieves (4 Å), CH_2Cl_2, rt; (c) DIBAL-H, THF, −78 °C; (d) $(CF_3CO)_2O$, NaI, acetone, −40 °C; (e) NaH, BnBr, DMF, 0 °C.

asymmetric synthesis of chiral products containing the difluoromethylene group.[4]

The difluoromethylene residue has been effectively employed for the isosteric and isopolar replacement of methylene units and oxygen atoms.[5] Successful examples of this kind of replacement are, for instance, the obtainment of transition-state analogue enzyme inhibitors[6] and mechanism-based enzyme inhibitors.[7] Nevertheless, the only general method for the synthesis of geminal difluoro-substituted products which employs a "chiron approach"[8] is the Reformatsky reaction of ethyl bromo- or iododifluoroacetate on chiral aldehydes and imines.[9]

We have decided to study a new "chiron approach" for the asymmetric synthesis of polyfunctional compounds containing the difluoromethylene residue. Here we report how α,α-difluoro-α'-sulfinyl alcohols 4 can be obtained in enantiomerically and diastereoisomerically pure form through stereoselective reduction of corresponding ketones **3**. The removal of the auxiliary sulfinyl residue from these intermediates with concomitant introduction of oxygen functionalities produced optically pure 2-(benzyloxy)-3,3-difluoro alcohols **8** and esters **9**. Some other reaction sequences have been settled which allow the overall substitution of a nitrogen residue for the sulfinyl one so that 2-(benzyloxy)-3,3-difluoro oximes, hydroxylamines, and nitriles **11–15** have also been prepared.

Results and Discussion

The lithium derivative of (+)-(*R*)-methyl 4-methylphenyl sulfoxide (**1**) was acylated by treatment with α,α-difluoro esters **2a,b** in THF solution at −78 °C (Scheme I). The difluoroalkanones **3a,b** were isolated in high yields as a mixture of keto and hydrated (*gem*-diol) forms ($\delta_{CH_2S} \simeq$ 4.1 and 3.1 ppm, respectively). This is an intermediate situation with respect to that observed for analogue α-monofluoroalkyl[10,11] and perfluoroalkyl ketones[12] which were isolated in the keto or hydrated forms, respectively, after the same workup.

Borohydride agents in methanol solution reduced in quantitative yields the mixture of the two forms of carbonyl compounds **3a,b**. A stereochemical behavior similar to that shown in the borohydride reduction of perfluoroalkyl sulfinylmethyl ketones was observed.[13] The difluoroalkanols **4a,b** were formed with low diastereoselection and the two isomers having the $(2R,R_S)$ and $(2S,R_S)$ absolute configuration were produced for both substrates **3a,b**.

Differently, diisobutylaluminum hydride (DIBAL-H) reduced exclusively the keto form of **3a,b** producing only the alcohols **4a,b** having the $(2S,R_S)$ configuration. This stereochemical course was already observed in the DIBAL-H reduction of α-monofluoroalkyl sulfinylmethyl ketones[11] and several other substrates.[14] It is due to the entrance of the hydride from the *Re* face of the β-keto sulfoxide moiety. This face is in fact the less hindered one in the most probable ground-state conformation of β-keto sulfoxides.[15]

In order to have high chemical yields in the diastereoselective reduction of **3a,b** it was necessary to transform its hydrated form into the keto one. A complete dehydration of the substrates could be performed by simple treatment with molecular sieves (4 Å), and an overall yield from (*R*)-**1** to $(2S,R_S)$-**4** of ≃80% could be obtained.

The deoxygenation of the sulfoxide residue of diastereoisomerically pure alcohols **4a,b**, obtained through the reduction with DIBAL-H, afforded the corresponding (*S*)-difluorosulfenylalkanols **5a,b**. Benzylation of the hydroxyl group of the same substrates $(2S,R_S)$-**4a,b** under standard conditions gave the $(2S,R_S)$ derivatives **6a,b**. They were the key intermediates for the synthesis of sulfur-free and enantiomerically pure difluoro compounds

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8–15 (Scheme II) all of which were obtained by removing the sulfinyl residue with the Pummerer rearrangement.[16]

Treatment of (2*S*,R_S)-2-(benzyloxy)-3,3-difluorosulfinylalkanes **6a,b** with trifluoroacetic anhydride and 2,4,6-trimethylpyridine in acetonitrile solution afforded the geminal (trifluoroacetyl)oxy tolylthio intermediates **7a,b** in quantitative yields (TLC analyses). These intermediates underwent in situ hydrolyses (mercury(II) chloride in water solution) to give (*R*)-2-(benzyloxy)-3,3-difluoro aldehydes **7'a,b**. α-Alkoxy aldehydes are known to have a marked proclivity for becoming hydrated,[17,18] and so crude **7'a,b** were used in successive reactions without any purification.

Reduction (sodium borohydride/acetonitrile/2-propanol) afforded the (*R*)-(benzyloxy) difluoro alcohols **8a,b** in good overall yields. Oxidation with sodium chlorite (*tert*-butyl alcohol/2-methyl-1-butene solution)[19] and successive esterification gave the (*R*)-methyl 2-(benzyloxy)-3,3-difluoro carboxylates **9a,b**.

Treatment of the same aldehydes **7'a,b** with *N,N*-dimethylhydrazine, hydroxylamine, or its *O*-benzyl derivative in ethanol solution and in the presence of molecular sieves afforded (*R*)-difluoro *N,N*-dimethylhydrazones **10a,b**, oximes **11a,b**, and *O*-benzyloximes **12a,b** (overall yields >72%).

Both hydrazones and oximes are useful compounds for alkylation,[20] condensation,[21] and oxidoreduction reactions.[22]

An example of these transformations is the synthesis of (*R*)-2-(benzyloxy)-3,3-difluoro nitriles **13a,b** through dehydration of oximes **11a,b** with trifluoromethanesulfonic anhydride/triethylamine.[23] Another example is the high-yield preparation of hydroxylamines **14a,b** and their *O*-benzyl analogues **15a,b** through reduction of corresponding oximes **11a,b** and **12a,b**, respectively, by using sodium cyanoborohydride at pH 3≃4.[24]

All the compounds in this work showed ^1H and ^{19}F NMR properties in accordance with the proposed structure. The two geminal hydrogens at C-1 of compounds **4–6**, **8**, and **14–15** were always present as the AB part of an ABX system and only occasionally (**6b**, **14b**) was a long range coupling constant with the fluorine atoms observed. The two geminal fluorines were always anisochronous, the unique exception being the keto form of the α,α-difluoro α'-sulfinyl ketone **3b**.

The absolute configuration at the carbon stereocenter of all derivatives **6–15** follows from the assignment of the stereochemistry of the sulfenyl alcohols **5a,b**. The (*S*) configuration was attributed to these secondary alcohols by comparing the chemical shift differences between external diastereotopic protons in couples of their (*S*)- and (*R*)-2-phenylpropionic esters.[25]

In conclusion, a new approach is reported for the total synthesis of enantiomerically pure, polyfunctional compounds containing the difluoromethylene residue. α,α-Difluoro carboxylic esters are the source of the fluorinated part of final molecules, and an optically pure sulfinyl residue is the source of chirality. Difluorocarboxylic esters are easily available starting compounds,[26] and both enantiomeric forms of difluoro-sulfinyl ketones **3** are available[10] (they are obtained starting from (–)- or (+)-menthol). The enantiomers of all compounds here described are therefore available by using the reported reaction sequence.

The manifold reactivity of the sulfoxide group has been exploited in order to obtain various sulfur-free and difluorinated compounds containing oxygen functionalities. The overall replacement of the sulfoxide group of **6** with nitrogen functionalities has also been achieved. (+)-(*R*)-Methyl sulfoxide **1** has been used as a chiral, nitrogen-substituted d^1 synthon,[27] and very limited and quite different approaches for a similar employment have been reported until now.[28]

Experimental Section

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker CPX-300 or a Bruker AC 250L spectrometer in $CDCl_3$. C_6F_6 was used as internal standard (δ_F –162.90) for ^{19}F.

Mps are uncorrected and were obtained on a capillary apparatus. TLC was run on silica gel 60 F_{254} Merck; flash column chromatographies were performed with silica gel 60 (60–200 μm, Merck). Reactions with lithium derivatives and with DIBAL-H were carried out under Ar free from oxygen and water. THF was freshly distilled from $LiAlH_4$, and diisopropylamine was distilled from CaH_2 and stored over molecular sieves (4 Å). A 2.6 mol dm^{-3} solution of butyllithium in hexanes (Aldrich) was employed. DMF was stored over molecular sieves (4 Å and 13 Å). In other cases commercially available reagent-grade solvents were employed without purification. Benzyl 2,2-difluoro-2-phenylacetate (**2a**) and benzyl 2,2-difluoropropionate (**2b**) were prepared by treatment with DAST of the corresponding α-keto esters.[26] A detailed procedure is described for phenyl-substituted compounds **3a–15a**. The same experimental procedure was used for methyl compounds **3b–15b**.

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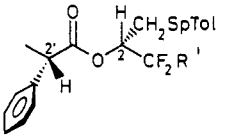
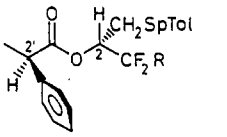


(2S, 2'S)-16 a,b



(2S, 2'R)-16 a,b

The hydrogens of the sulfenylated carbons of the esters **16a,b**, obtained from (*R*)-2-phenylpropionic acid were at lower fields than the corresponding hydrogens of the esters prepared from the (*S*)-2-phenylpropionic acid. This is due to the shielding effect that the phenyl ring of the esterifying acid exerts on the facing protons of the secondary alcohols according to the preferred conformations reported in the formulas. The validity of this conformational model was supported by the high esterification shift of the carbinol proton (H-2). The (*S*) absolute configuration of the alcoholic stereocenter is thus established. Furthermore, the nonequivalence of the methylene protons α the sulfoxide group was smaller in (2*R*,R_S)-**4a,b** than in (2*S*,R_S)-**4a,b** and the proton α to the hydroxyl was more deshielded in the former isomer. The same trend was already observed in several other substrates (refs 11, 14b,c).

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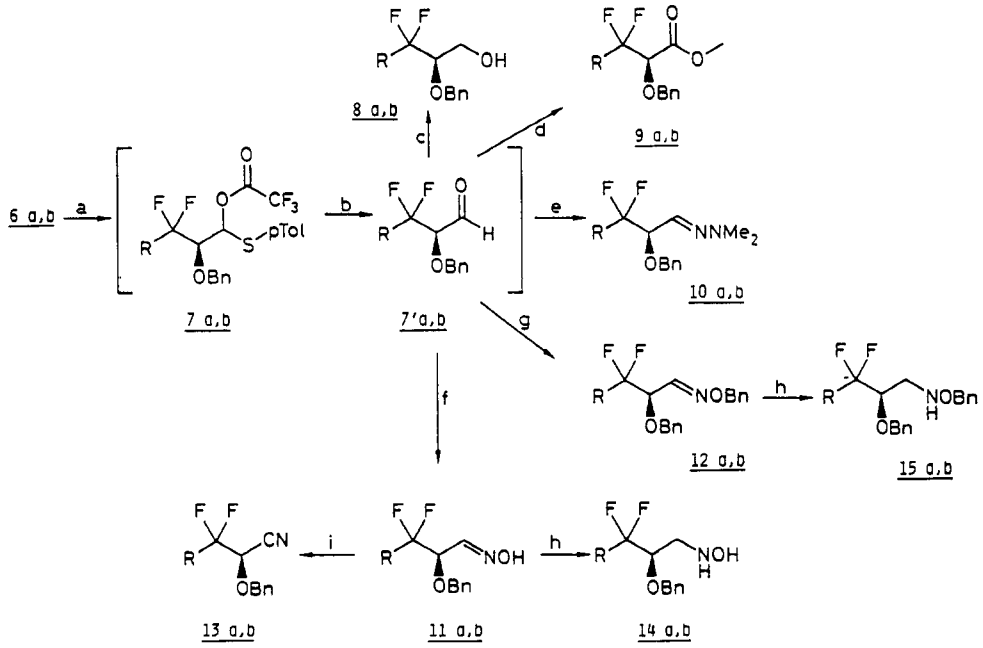
Scheme II[a]



[a] Reagents and conditions: (a) $(CF_3CO)_2O$, 2,4,6-trimethylpyridine, acetonitrile, rt; (b) $HgCl_2$, water, 0 °C; (c) sodium borohydride, acetonitrile, 2-propanol, 0 °C; (d) $NaClO_2$, KH_2PO_4, *tert*-butyl alcohol, 2-methyl-2-butene, rt; then CH_2N_2, Et_2O, rt; (e) *N,N*-dimethylhydrazine, AcOH, ethanol, molecular sieves (4 Å); (f) NH_2OH, AcOH, ethanol, molecular sieves (4 Å); (g) *O*-benzylhydroxylamine, AcOH, ethanol, molecular sieves (4 Å); (h) $NaBH_3CN$, methanol, HCl (pH 3); (i) Tf_2O triethylamine, CH_2Cl_2, −78 °C.

(*R*)-3,3-Difluoro-3-phenyl-1-[(4-methylphenyl)sulfinyl]-propan-2-one (3a). A solution of (+)-(*R*)-1 (4.77 g, 31 mmol) in THF (50 mL) was added dropwise to a stirred solution of lithium diisopropylamide (34 mmol) in the same solvent (50 mL) at −78 °C. After 3 min, a solution of benzyl 2,2-difluoro-2-phenylacetate (**2a**) (8.14 g, 31 mmol) in THF (15 mL) was added to the stirred solution at −78 °C. After 5 min, the reaction was quenched by adding saturated aqueous NH_4Cl (150 mL). The aqueous layer was extracted with ethyl acetate (3 × 200 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was flash-chromatographed (*n*-hexane/ethyl acetate (65:35)) to give the propanone **3a** (9.05 g, 92% yield) as a mixture of the keto and hydrated forms: ^1H NMR δ 2.40 (s, 3 H, CH_3), 3.14 and 3.24 (AB system, H-1 of hydrated form), 4.01 and 4.25 (d each, 1 H each, H-1 of keto form); ^{19}F NMR δ −107.3 and −108.0 (keto form), −111.3 and −113.3 (hydrated form).

(*R*)-3,3-Difluoro-1-[(4-methylphenyl)sulfinyl]butan-2-one (3b). The compound was isolated (7.44 g, 94% yield) as a mixture of the keto and hydrated forms: ^1H NMR δ 1.67 (t, 3 H, H-4), 2.43 (s, 3 H, CH_3-Ar) 3.06 and 3.12 (AB system, H-1 of hydrated form), 4.01 and 4.23 (AB system, H-1 of keto form); ^{19}F NMR δ −100.7 (q, $J_{H,F}$ = 18.8 Hz, keto form), −107.6 and −110.0 (ABX_3 system, $J_{H,F}$ = 18.8 Hz, hydrated form).

3,3-Difluoro-3-phenyl-1(*R*)-[(4-methylphenyl)sulfinyl]-propan-2-ol (4a). Method A. $NaBH_4$. A solution of $NaBH_4$ (250 mg, 6.7 mmol) in methanol/aqueous NH_3 (32%) (9:1, 13 mL) was added dropwise into a solution of the ketone **3a** (mixture of the keto and hydrated forms, 2.13 g, 6.7 mmol) in the same solvent (7 mL) under magnetic stirring at 0 °C. After 10 min at the same temperature diluted HCl was added until pH 2 was reached. Methanol was removed under reduced pressure, the residue was extracted with ethyl acetate (3 × 100 mL) and collected organic phases were dried (Na_2SO_4). Propanol **4a** was isolated (1.93 g, 93% yield) as an 8:2 mixture of the (2*R*,*R*$_S$) and (2*S*,*R*$_S$) diastereoisomers after flash chromatography (*n*-hexane/ethyl acetate (55:45)). (2*R*,*R*$_S$)-**4a**: ^1H NMR δ 2.42 (s, 3 H, CH_3), 3.01 and 3.12 (AB system, 2 H, H-1), 4.67 (m, 1 H, H-2). Anal. Calcd for $C_{16}H_{16}F_2O_2S$: C, 61.92; H, 5.20. Found: C, 61.72; H, 5.44. (2*S*,*R*$_S$)-**4a**: $[\alpha]^{20}_D$ +257° (*c* 1.10; $CHCl_3$); mp 164–166 °C (CH_2Cl_2/diisopropyl ether); ^1H NMR δ 2.47 (s, 3 H, CH_3), 2.89 (dd, 1 H, ^2J = 13 Hz, ^3J = 2.0 Hz, H-1), 3.09 (dd, 1 H, ^3J = 10.5 Hz, H-1), 4.53 (m, 1 H, H-2); ^{19}F NMR δ −105.6 (dd, 1 F, $^2J_{F,F}$ = 250 Hz, $^3J_{F,H}$ = 5.0 Hz), −112.9 (dd, 1 F, $^3J_{F,H}$ = 13 Hz). Anal. Calcd for $C_{16}H_{16}F_2O_2S$: C, 61.92; H, 5.20. Found: C, 61.77; H, 5.49.

Method B. DIBAL-H. A solution of the difluoro ketone **3a** was left in CH_2Cl_2 solution over molecular sieves (4 Å) at room temperature for 2 h. Sieves were removed by filtration, and the solvent was evaporated under reduced pressure. The hygroscopic ketone (6.0 mmol) was dissolved in anhydrous THF (5 mL), the solution was cooled at −78 °C, and DIBAL-H (1.0 N solution in hexane, 9.0 mL, 9.0 mmol) was added dropwise with stirring. After 10 min the reaction was quenched by addition of aqueous NH_4Cl and the pH was adjusted at ca. 3 with diluted HCl. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), the collected organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The exclusive formation of the diastereoisomeric alcohols **4a** having the (2*S*,*R*$_S$) configuration was shown by ^1H NMR of crude reaction mixtures. After flash chromatography 1.66 g (89% yield) of pure (2*S*,*R*$_S$)-**4a** was isolated.

3,3-Difluoro-1-[(4-methylphenyl)sulfinyl]butan-2-ol (4b). When method A was employed starting from **3b**, the difluoro alcohols **3b** were isolated (1.56 g, 94% yield) as a 3:1 mixture of the (2*R*,*R*$_S$) and (2*S*,*R*$_S$) diastereoisomers after flash chromatography (*n*-hexane/ethyl acetate (1:1)). (2*R*,*R*$_S$)-**4b**: ^1H NMR δ 1.68 (t, 3 H, $J_{H,F}$ = 19 Hz, H-4), 2.44 (s, 3 H, CH_3Ar), 2.9–3.1 (m, 2 H, H-1), 4.38 (m, 1 H, H-2). Anal. Calcd for $C_{11}H_{14}F_2O_2S$: C, 53.16; H, 5.68. Found: C, 53.28; H, 5.53. (2*S*,*R*$_S$)-**4b**: $[\alpha]^{20}_D$ +266° (*c* 1.05, $CHCl_3$); mp 135–136 °C (CH_2Cl_2/diisopropyl ether); ^1H NMR δ 1.66 (t, 3 H, $J_{H,F}$ = 19 Hz, H-4), 2.44 (s, 3 H, CH_3Ar), 2.92 (dd, 1 H, ^2J = 11 Hz, ^3J = 2 Hz, H-1), 3.11 (dd, 1 H, ^3J = 10.5 Hz, H-1), 4.22 (m, 1 H, H-2); ^{19}F NMR δ −101.1 (ddq, $J_{F,F}$ = 247 Hz, $J_{F,H-4}$ = 18 Hz, $J_{F,H-2}$ = 5 Hz), −107.4 (ddq, 1 F, $J_{F,H-2}$ = 17 Hz). Anal. Calcd for $C_{11}H_{14}F_2O_2S$: C, 53.16; H, 5.68. Found: C, 53.33, H, 5.57. When method B was employed for the reduction of **3b**, the (2*S*,*R*$_S$) alcohol **4b** was obtained with complete diastereoselection (1.28 g, 86% yield).

(*S*)-3,3-Difluoro-3-phenyl-1-[(4-methylphenyl)thio]-propan-2-ol (5a). A solution of trifluoroacetic anhydride (2.12 mL, 15.0 mmol) in acetone (5 mL) was added dropwise into a stirred suspension of the (2*S*,*R*$_S$)-difluoro alcohol **4a** (931 mg, 3.0 mmol) and sodium iodide (1.34 g, 9.0 mmol) in the same solvent (20 mL) at −40 °C under an argon atmosphere. The reaction mixture was stirred for 20 min at the same temperature, and an excess of saturated aqueous Na_2SO_3 and Na_2CO_3 were added. Acetone was removed under reduced pressure, the aqueous layer was extracted with diethyl ether (3 × 20 mL), and combined

organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was flash chromatographed (*n*-hexane/ethyl acetate (85:15)) to give the sulfenyl alcohol **5a** (830 mg, 94% yield): $[\alpha]^{20}_D$ +88.4° (*c* 1.1; $CHCl_3$); ^1H NMR δ 2.31 (s, 3 H, CH_3Ar), 2.84 (dd, 1 H, ^2J = 13 Hz, ^3J = 10 Hz, H-1), 3.28 (dd, 1 H, ^3J = 4 Hz, H-1), 4.00 (m, 1 H, H-2); ^{19}F NMR δ −106.1 (dd, 1 F, $^2J_{F,F}$ = 250 Hz, $^3J_{F,H}$ = 8.0 Hz), −112.4 (dd, 1 F, $^3J_{F,H}$ = 12.5 Hz). Anal. Calcd for $C_{16}H_{16}F_2OS$: C, 65.28; H, 5.48. Found: C, 65.31; H, 5.67.

(*S*)-3,3-Difluoro-1-[(4-methylphenyl)thio]-2-butanol (5b): eluting system for flash chromatography *n*-pentane/diethyl ether (95:5); isolated yield 662 mg, 95%; $[\alpha]^{20}_D$ +73° (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.65 (t, 3 H, $^3J_{H,F}$ = 19 Hz, H-4), 2.33 (s, 3 H, CH_3Ar), 2.87 (dd, 1 H, ^2J = 13 Hz, ^3J = 10.5 Hz, H-1), 3.29 (dd, 1 H, ^3J = 2.6 Hz, H-1), 3.69 (m, 1 H, H-2); ^{19}F NMR δ −100.6 (ddq, 1 F, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H-4}$ = 19 Hz, $^3J_{F,H-2}$ = 6.0 Hz), −107.1 (ddq, 1 F, $^3J_{F,H-2}$ = 13 Hz). Anal. Calcd for $C_{11}H_{14}F_2OS$: C, 56.87; H, 6.07. Found: C, 56.73; H, 6.12.

(2*S*)-2-(Benzyloxy)-3,3-difluoro-3-phenyl-1(*R*)-[(4-methylphenyl)sulfinyl]propane (6a). A solution of (2*S*,R_S)-difluoropropanol **4a** (4.34 g, 14 mmol) in DMF (15 mL) was added dropwise into a suspension of oil-free sodium hydride (1.52 g, 35 mmol) and benzyl bromide (14.8 g, 86.5 mmol) in the same solvent (15 mL) with magnetic stirring under argon at 0 °C. The reaction mixture was stirred 10 min at 20 °C and then quenched at −40 °C by adding 0.1 N HCl until pH 4 was reached. Organic products were extracted with ethyl acetate (3 × 150 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. Crude residue was purified through flash chromatography (*n*-hexane/ethyl acetate (75:25)) to give 5.21 g (93% yield) of pure **6a**: $[\alpha]^{20}_D$ +184° (*c* 0.85, $CHCl_3$); ^1H NMR δ 2.41 (s, 3 H, CH_3), 2.87 (dd, 1 H, $^2J_{H,H}$ = 13 Hz, $^3J_{H,H}$ = 11 Hz, H-1), 3.06 (dd, 1 H, $^3J_{H,H}$ = 2.5 Hz, H-1), 4.45 (m, 1 H, H-2), 4.39 and 4.71 (d each, 1 H each, ^2J = 10 Hz, CH_2Ph), 7.2–7.6 (m, 14 H, CH Ar); ^{19}F NMR δ −102.4 (dd, 1 F, $^3J_{H,F}$ = 6.5 Hz), −110.6 (dd, 1 F, $^3J_{F,H}$ = 12.5 Hz). Anal. Calcd for $C_{23}H_{22}F_2O_2S$: C, 61.92; H, 5.20. Found: C, 61.72; H, 5.34.

(2*S*)-2-(Benzyloxy)-3,3-difluoro-1(*R*)-[(4-methylphenyl)-sulfinyl]butane (6b): eluting system for flash chromatography *n*-hexane/ethyl acetate (75:25); isolated yield 4.50 g, 95%; $[\alpha]^{20}_D$ +158° (*c*, 1.1, $CHCl_3$); ^1H NMR δ 1.62 (t, 3 H, $J_{H,F}$ = 18.8 Hz, H-4), 2.42 (s, 3 H, CH_3Ar), 2.86 (dd, 1 H, $J_{H,H}$ = 13 Hz, $^3J_{H,H}$ = 10 Hz, H-1), 3.01 (ddd, 1 H, $^3J_{H,H}$ = 2 Hz, $^4J_{H,F}$ = 1.5 Hz, H-1), 4.25 (m, 1 H, H-2), 4.89 (br s, 2 H, CH_2Ph), 7.2–7.6 (m, 9 H, CH Ar); ^{19}F NMR δ −96.8 (ddq, 1 F), −100.7 (ddq, 1 F). Anal. Calcd for $C_{18}H_{20}F_2O_2S$: C, 63.89; H, 5.96. Found: C, 63.66, H, 6.06.

Pummerer Rearrangement of the α-(Benzyloxy)-β,β-difluoro Sulfoxides 6 to Corresponding Aldehydes 7′. A solution of trifluoroacetic anhydride (0.82 mL, 6.0 mmol) in acetonitrile (4.9 mL) was added dropwise to a stirred solution of α-(benzyloxy)-β,β-difluoro sulfoxides **6a,b** (3.0 mmol) and 2,4,6-trimethylpyridine (0.8 mL, 6.0 mmol) in the same solvent (8.0 mL) at 0 °C and under Ar. After 30 min at room temperature the starting compounds had disappeared (TLC analyses) and higher R_f compounds (the α-[(trifluoroacetyl)oxy]-β-alkoxy-γ,γ-difluoro thio derivatives **7a,b** were formed (TLC analyses). A solution of $HgCl_2$ (1.14 g, 4.2 mmol) in water (30 mL) was added, and the resulting mixture was stirred at 0 °C for 2 h. The white precipitate was removed by filtration and washed with ethyl acetate. The collected liquid phases were evaporated under reduced pressure to give a residue containing the crude, hygroscopic[18] α-alkoxy-β,β-difluoro aldehydes **7′a,b** which were used in successive reactions without further purification.

(*R*)-2-(Benzyloxy)-3,3-difluoro-3-phenylpropan-1-ol (8a). Sodium borohydride (22.8 mg, 6.0 mmol) was added at 0 °C in one portion to a stirred solution of crude (*R*)-2-(benzyloxy)-3,3-difluoro-3-phenylpropanal **7′a** (obtained as described above starting from 600 mg (1.5 mmol) of difluoro sulfoxide **6a**) in acetonitrile–2-propanol (1:1, 4.5 mL). The mixture was stirred at room temperature for 2.0 h, 1.0 N HCl was added until pH 1 was reached, and volatiles were evaporated under reduced pressure. The residue was extracted with diethyl ether (3 × 100 mL), and combined organic phases were dried (Na_2SO_4) and then evaporated under reduced pressure. Flash chromatography of the residue (*n*-hexane/ethyl acetate (7:3)) gave 313 mg (75% yield) of pure (*R*)-**8a**: $[\alpha]^{20}_D$ +41.4° (*c* 0.8, $CHCl_3$); ^1H NMR δ 3.60 and 3.74 (m each, 1 H each, H-1), 3.94 (m, 1 H, H-2), 4.53 and 4.74 (d each, 1 H each, CH_2Ph), 7.2–7.6 (m, 10 H, CH Ar); ^{19}F NMR δ −103.4 (dd, 1 F, $^3J_{F,H}$ = 9 Hz), −108.0 (dd, 1 F, $^3J_{F,H}$ = 11 Hz). Anal. Calcd for $C_{16}H_{16}F_2O_2$: C, 69.05; H, 5.80. Found: C, 69.10; H, 5.68.

(*R*)-2-(Benzyloxy)-3,3-difluoro-1-butanol (8b): eluting system for flash chromatography *n*-hexane/diethyl ether (1:1); isolated yield 230 mg, 71%; $[\alpha]^{20}_D$ +32° (*c* 0.8, $CHCl_3$); ^1H NMR δ 1.64 (t, 3 H, H-4), 3.6–3.9 (m, 3 H, H-1 and H-2), 4.66 and 4.87 (d each, 1 H each, CH_2Ph), 7.4 (m, 5 H, CH Ar); ^{19}F NMR δ −93.9 (ddq, 1 F), −99.5 (ddq, 1 F). Anal. Calcd for $C_{11}H_{14}F_2O_2$: C, 61.10; H, 6.53. Found: C, 61.28; H, 6.71.

(*R*)-Methyl 2-(Benzyloxy)-3,3-difluoro-3-phenylpropionate (9a). A solution of sodium chlorite (0.58 g, 6.39 mmol) and potassium dihydrogen phosphate (0.80 g, 5.85 mmol) in water (2.0 mL) was added dropwise at room temperature to a stirred solution of crude difluoro aldehyde **7′a** (prepared from 444 mg, 1.11 mmol of 3,3-difluoro sulfoxide **6a**) in *tert*-butyl alcohol (5.0 mL) and 2-methylbut-1-ene (1.0 mL). The mixture was stirred for 30 min, volatile materials were removed under reduced pressure, and the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in diethyl ether (10.0 mL), and an ethereal solution of diazomethane was added dropwise at 0 °C until the light-yellow color remained. A drop of AcOH was added, and the solvent was removed under reduced pressure. Flash chromatography of the residue (*n*-hexane/diethyl ether (8:2)) afforded 224 mg (66% yield) of pure (*R*)-**9a**: $[\alpha]^{20}_D$ −34° (*c* 1.0, $CHCl_3$); ^1H NMR δ 3.72 (s, 3 H, CH_3), 4.31 (dd, 1 H, $^3J_{H,F}$ = 14 and 6.5 Hz, H-2), 4.44 and 4.68 (d each, 2 H, CH_2Ph), 7.0–7.5 (m, 10 H, CH Ar); ^{19}F NMR δ −101.7 (dd, 1 F, $^3J_{F,H}$ = 6.5 Hz), −108.6 (dd, 1 F, $^3J_{F,H}$ = 14 Hz). Anal. Calcd for $C_{17}H_{16}F_2O_3$: C, 66.66; H, 5.26. Found: C, 66.32; H, 5.08.

(*R*)-Methyl 2-(benzyloxy)-3,3-difluorobutanoate (9b): eluting system for flash chromatography *n*-hexane/diethyl ether (85:15); isolated yield 165 mg, 61%; $[\alpha]^{20}_D$ −44.8° (*c* 1.1, $CHCl_3$); ^1H NMR δ 1.70 (t, 3 H, $J_{H,F}$ = 19 Hz, H-4), 3.78 (s, 3 H, CH_3O), 4.13 (dd, 1 H, $J_{H,F}$ = 9.5 and 8.0 Hz, H-2), 4.57 and 4.74 (d each, 1 H each, CH_2Ph), 7.4 (m, 5 H, CH Ar); ^{19}F NMR δ −95.7 (ddq, 1 F), −100.2 (ddq, 1 F).

(*R*)-2-(Benzyloxy)-3,3-difluoro-3-phenylpropanal *N*,*N*-Dimethylhydrazone (10a). A solution of *N*,*N*-dimethylhydrazine (0.19 g, 3.25 mmol) and acetic acid (0.20 mL, 3.25 mmol), in absolute ethanol (3.0 mL) was added dropwise into a solution of the crude 2-(benzyloxy)-3,3-difluoro aldehyde **7′a** (from 641 mg, 1.6 mmol of **6a**) in the same solvent (5.0 mL). The mixture was left overnight over molecular sieves (4 Å); the precipitate was removed by filtration and washed with ethanol. Combined organic phases were evaporated under reduced pressure, and flash chromatography of the residue (*n*-hexane/diethyl ether/triethylamine (80:20:3)) afforded 387 mg (76% yield) of the pure hydrazone **10a**: $[\alpha]^{20}_D$ −57° (*c* 0.80, $CHCl_3$); ^1H NMR δ 2.85 (s, 6 H, 2xCH_3), 4.28 (ddd, 1 H, $J_{H,H}$ = 7.5, 6.5, and 13.5 Hz, H-2), 4.40 and 4.60 (d each, 1 H each, CH_2Ph), 6.36 (d, 1 H, J = 6.5 Hz, H-1), 7.0–7.5 (m, 10 H, CH Ar); ^{19}F NMR δ −101.1 (dd, 1 F, $J_{F,F}$ = 250 Hz, $J_{F,H}$ = 6.0 Hz), −112.4 (dd, 1 F, $J_{F,H}$ = 14 Hz). Anal. Calcd for $C_{18}H_{20}F_2N_2O$: C, 67.91; H, 6.33; N, 8.80. Found: C, 67.68; H, 6.28; N, 8.65.

(*R*)-2-(Benzyloxy)-3,3-difluorobutanal *N*,*N*-dimethylhydrazone (10b): eluting system for flash chromatography *n*-hexane/diethyl ether/triethylamine (85:15:5); isolated yield 311 mg, 76%; $[\alpha]^{20}_D$ −101° (*c* 0.80, $CHCl_3$); ^1H NMR δ 1.65 (t, 3 H, $J_{H,F}$ = 17 Hz, H-4), 2.86 (s, 6 H, 2xCH_3), 4.04 (ddd, 1 H, $J_{H,H}$ = 7 Hz, $J_{H,F}$ = 8.5 and 13.5 Hz, H-2), 4.53 and 4.67 (d each, 1 H each, CH_2Ph), 6.36 (d, 1 H, H-1), 7.3 (m, 5 H, CH Ar); ^{19}F NMR δ −99.4 (ddq, 1 F, $J_{F,H-2}$ = 8.0 Hz, $J_{F,H-4}$ = 18 Hz, $J_{F,F}$ = 250 Hz), 103.7 (ddq, 1 F). Anal. Calcd for $C_{13}H_{18}F_2N_2O$: C, 60.91; H, 7.00; N, 10.93. Found: C, 60.82; H, 6.93; N, 10.78.

(*R*,*E*)-2-(Benzyloxy)-3,3-difluoro-3-phenylpropanal Oxime (11a). A procedure similar to that described above for hydrazone **10a** was used, and hydroxylamine was employed: eluting system for flash chromatography *n*-hexane/diethyl ether (8:2); isolated yield 293 mg, 72%; $[\alpha]^{20}_D$ −25.1 ° (*c* 1.0, $CHCl_3$); ^1H NMR δ 4.26 (ddd, 1 H, $J_{H,H}$ = 7.5 Hz, $J_{H,F}$ = 6.5 and 14.0 Hz, H-2), 4.40 and 4.63 (d each, 1 H each, CH_2Ph), 7.0–7.6 (m, 10 H, CH Ar); ^{19}F NMR δ −102.0 (dd, 1 F, $J_{F,H}$ = 6.0 Hz, $J_{F,F}$ = 244 Hz), −111.4 (dd, 1 F, $J_{F,H}$ = 15 Hz). Anal. Calcd for $C_{16}H_{15}F_2NO_2$: C, 65.97; H,

5.19; N, 4.81. Found: C, 66.22; H, 5.33; N, 5.03.

(*R,E*)-2-(Benzyloxy)-3,3-difluorobutanal oxime (11b): eluting system for flash chromatography *n*-hexane/ethyl acetate (80:20); isolated yield 247 mg, 77%; $[\alpha]^{20}_D$ −57° (*c* 0.53, $CHCl_3$); ^1H NMR δ 1.65 (t, 3 H, $J_{H,F}$ = 18 Hz, H-4), 4.06 (dt, 1 H, *J* = 12.5 and 7.5 Hz, H-2), 4.50 and 4.70 (d each, 1 H each, CH_2Ph), 7.2–7.4 (m, 5 H, CH Ar); ^{19}F NMR δ −98.7 (ddq, 1 F, $J_{F,F}$ = 252 Hz), −103.1 (ddq, 1 F). Anal. Calcd for $C_{11}H_{13}F_2NO_2$: C, 57.63; H, 5.71; N, 6.11. Found: C, 57.89; H, 5.99; N, 6.39.

(*R*)-2-(Benzyloxy)-3,3-difluoro-3-phenylpropanal *O*-Benzyloxime (12a). A procedure similar to that described above for hydrazone **10a** was used by employing *O*-benzylhydroxylamine: eluting system for flash chromatography *n*-hexane/diisopropyl ether (97:3); isolated yield 452 mg, 79%; $[\alpha]^{20}_D$ −37° (*c* 0.57, $CHCl_3$); ^1H NMR δ 4.23 (ddd, 1 H, H-2), 4.31 and 4.55 (d each, 1 H each, CH_2Ph), 5.14 (s, 2 H, CH_2O), 6.9–7.5 (m, 16 H, CH Ar and H-1); ^{19}F NMR δ −112.0 (dd, 1 F), −101.7 (dd, 1 F). Anal. Calcd for $C_{23}H_{21}F_2NO_2$: C, 72.42; H, 5.55; N, 3.67. Found: C, 72.13; H, 5.66; N, 3.64.

(*R,E*)-2-(Benzyloxy)-3,3-difluorobutanal *O*-benzyloxime (12b): eluting system for flash chromatography *n*-hexane/diisopropyl ether (98:2); isolated yield 359 mg, 75%; $[\alpha]^{20}_D$ −69° (*c* 1.05, $CHCl_3$); ^1H NMR δ 1.61 (t, 3 H, H-4), 4.00 (dt, 1 H, *J* = 12 and 8 Hz, H-2), 4.41 and 4.62 (d each, 1 H each, CH_2Ph), 5.15 (s, 2 H, CH_2O), 7.2–7.4 (m, 11 H, CH Ar and H-1); ^{19}F NMR δ −99.1 (ddq, 1 F, $J_{F,F}$ = 245 Hz, $J_{F,H-2}$ = 7.5 Hz, $J_{F,H-4}$ = 19 Hz), −103.2 (ddq, 1 F). Anal. Calcd for $C_{18}H_{19}F_2NO_2$: C, 67.70; H, 6.00; N, 4.39. Found: C, 67.81; H, 6.09; N, 4.10.

(*R*)-2-(Benzyloxy)-3,3-difluoro-3-phenylpropionitrile (13a). A solution of trifluoromethanesulfonic anhydride (2.08 mL, 12.4 mmol) in dichloromethane (6.0 mL, freshly distilled from phosphoric anhydride) was added dropwise at −78 °C to a stirred solution of (*R*)-**11a** (3.61 g, 12.4 mmol) and triethylamine (4.28 mL, 37.20 mmol) in the same solvent (12.0 mL). After 2 h at room temperature the mixture was washed with water and brine; the organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was flash chromatographed to afford the nitrile (*R*)-**13a** in pure form (2.07 g, 61% yield): eluting system for flash chromatography *n*-hexane/diethyl ether (8:2); $[\alpha]^{20}_D$ −93° (*c* 1.00, $CHCl_3$); ^1H NMR δ 4.50 (dd, 1 H, $J_{H,F}$ = 6.5 and 10.5 Hz, H-2), 4.59 and 4.85 (d each, 1 H each, CH_2Ph), 7.1–7.6 (m, 10 H, CH Ar); ^{19}F NMR δ −102.9 (dd, 1 F, $J_{F,F}$ = 255 Hz, $J_{F,H}$ = 6.5 Hz), −106.6 (dd, 1 F, $J_{F,H}$ = 10.0 Hz); ^{13}C NMR δ 70.61 (t, $J_{C,F}$ = 36 Hz, C-2), 72.98 (s, CH_2Ph), 113.61 (C-1), 117.70 (t, $J_{C,F}$ = 251 Hz, C-3). Anal. Calcd for $C_{16}H_{13}F_2NO$: C, 70.32; H, 4.80; N, 5.13. Found: C, 70.05; H, 4.83; N, 5.32.

(*R*)-2-(Benzyloxy)-3,3-difluorobutyronitrile (13b): eluting system for flash chromatography *n*-hexane/diethyl ether (8:2); isolated yield 1.52 g, 58%; $[\alpha]^{20}_D$ −141° (*c* 2.07, $CHCl_3$); ^1H NMR δ 1.78 (t, 3 H, $J_{H,F}$ = 21 Hz, H-4), 4.28 (t, 1 H, $J_{H,F}$ = 5 Hz, H-2), 4.65 and 4.94 (d each, 1 H each, CH_2Ph), 7.4 (m, 5 H, CH Ar); ^{19}F NMR δ −99.28 (dq, 1 F), −99.32 (dq, 1 F); ^{13}C NMR δ 19.39 (t, $J_{C,F}$ = 25 Hz, C-4), 69.86 (t, $J_{C,F}$ = 31 Hz, C-2), 73.08 (CH_2Ph), 119.69 (t, $J_{C,F}$ = 246 Hz, C-3), 114.0 (C-1).

(*R*)-*N*-1-[2-(Benzyloxy)-3,3-difluoro-3-phenylpropyl]-hydroxylamine (14a). An aqueous solution of HCl (1:1 v/v) was added dropwise to a stirred solution of oxime **11a** (583 mg, 2.0 mmol), sodium cyanoborohydride (503 mg, 8.0 mmol), and methyl orange (0.1% solution, 1 drop) in methanol (6.0 mL). The rate of addition was controlled so that the color of the reaction mixture remained reddish-orange (pH 3–4) for 1 h, and then the reaction was quenched with HCl (2.0 mL). Methanol was removed under reduced pressure, the residue was treated with saturated K_2CO_3, and the aqueous phase was extracted with ethyl acetate (3 × 150 mL). Combined organic phases were dried (K_2CO_3) and evaporated under reduced pressure. Flash-chromatography of the residue (*n*-hexane/ethyl acetate (6:4)) gave pure hydroxylamine (*R*)-**14a** (469 mg, 80% yield): $[\alpha]^{20}_D$ +71° (*c* 0.81, $CHCl_3$); ^1H NMR δ 2.81 (dd, 1 H, $^2J_{H,H}$ = 12 Hz, $^3J_{H,H}$ = 9.5 Hz, H-1), 3.20 (dd, 1 H, $^3J_{H,H}$ = 3 Hz, H-1), 4.27 (m, 1 H, H-2), 4.52 and 4.61 (AB system, 2 H, CH_2Ph), 7.2–7.6 (m, 10 H, CH Ar); ^{19}F NMR δ −103.8 (dd, 1 F, $J_{F,F}$ = 255 Hz, $J_{F,H}$ = 8 Hz), −108.8 (dd, 1 F, $J_{F,H}$ = 10 Hz). Anal. Calcd for $C_{16}H_{17}F_2NO_2$: C, 65.51; H, 5.84; N, 4.77. Found: C, 65.22; H, 5.99; N, 4.84.

(*R*)-*N*-1-[2-(Benzyloxy)-3,3-difluorobutyl]hydroxylamine (14b): eluting system for flash chromatography *n*-hexane/ethyl ether (4:6); isolated yield 379 mg, 82%; $[\alpha]^{20}_D$ +88° (*c* 1.03, $CHCl_3$); ^1H NMR δ 1.61 (t, 3 H, $J_{H,F}$ = 22 Hz, H-4), 2.88 (dd, 1 H, $^2J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 8.5 Hz, H-1), 3.19 (ddd, 1 H, $^3J_{H,H}$ = 3.0 Hz, $^4J_{H,F}$ = 1.5 Hz, H-1), 4.03 (m, 1 H, H-2), 4.66 and 4.85 (d each, 1 H each, CH_2Ph), 7.4 (m, 5 H, CH Ar); ^{19}F NMR δ −95.5 (dq, 1 F, $J_{F,F}$ = 256 Hz, $J_{F,H}$ = 10 Hz), −100.5 (dq, 1 F, $J_{F,H}$ = 8 Hz). Anal. Calcd for $C_{11}H_{15}F_2NO_2$: C, 57.13; H, 6.54; N, 6.06. Found: C, 56.86; H, 6.28; N, 5.86.

(*R*)-*N*-1-[2-(Benzyloxy)-3,3-difluoro-3-phenylpropyl]-*O*-benzylhydroxylamine (15a). *O*-Benzyloxime **12a** was reduced following the procedure described above for the oxime (*R*)-**11a**: eluting system for flash chromatography *n*-hexane/diethyl ether (95:5); isolated yield 613 mg, 80%; $[\alpha]^{20}_D$ +81° (*c* 1.01, $CHCl_3$); ^1H NMR δ 2.75 (dd, 1 H, $^2J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 9.5 Hz, H-1), 3.23 (dd, 1 H, $^3J_{H,H}$ = 2.5 Hz, H-1), 4.22 (m, 1 H, H-2), 4.47 and 4.53 (AB system, 2 H, OCH_2Ph), 4.63 and 4.64 (AB system, 2 H, $NOCH_2Ph$), 7.1–7.6 (m, 15 H, CH Ar); ^{19}F NMR δ −104.1 (dd, 1 F, $^2J_{F,F}$ = 253 Hz, $^3J_{F,H}$ = 9.5 Hz), −108.8 (dd, 1 F, $^3J_{F,H}$ = 11 Hz). Anal. Calcd for $C_{23}H_{23}F_2NO_2$: C, 72.04; H, 6.05; N, 3.65. Found: C, 72.35; H, 6.05; N, 3.79.

(*R*)-*N*-1-[2-(Benzyloxy)-3,3-difluorobutyl]-*O*-benzylhydroxylamine (15b): eluting system for flash chromatography *n*-hexane/diethyl ether (85:15); isolated yield 501 mg, 78%; $[\alpha]^{20}_D$ +99° (*c* 1.02, $CHCl_3$); ^1H NMR δ 1.59 (t, 3 H, $J_{H,F}$ = 17.5 Hz, H-4), 2.81 (dd, 1 H, $^2J_{H,H}$ = 12 Hz, $^3J_{H,H}$ = 9 Hz, H-1), 3.23 (ddd, 1 H, H-1), 3.99 (m, 1 H, H-2), 4.67 and 4.68 (AB system, 2 H, $NOCH_2Ph$), 4.60 and 4.79 (d each, 1 H each, CH_2Ph), 7.2–7.5 (m, 10 H, CH Ar); ^{19}F NMR δ −95.6 (dq, 1 F, $J_{F,F}$ = 256 Hz, $J_{F,H}$ = 11 Hz), −100.3 (dq, 1 F, $J_{F,H}$ = 6 Hz). Anal. Calcd for $C_{18}H_{21}F_2NO_2$: C, 67.27; H, 6.59; N, 4.36. Found: C, 67.42; H, 6.54; N, 4.24.

Esters 16 from (+)-(*S*)-2-Phenylpropionic Acid or Its (−)-(*R*) Enantiomer and (*S*)-3,3-Difluoro-1-[(4-methylphenyl)thio]-2-alkanols 5. The esterification was performed as already described in refs 13 and 25. (2*S*,2′*S*)-**16a**: ^1H NMR δ 1.38 (d, 3 H, CH_3CH), 2.31 (s, 3 H, CH_3Ar), 2.92 (dd, 1 H, H-1), 3.21 (dd, 1 H, H-1), 3.64 (q, 1 H, $CHCH_3$), 5.42 (m, 1 H, H-2), 6.9–7.4 (m, 14 H, CH Ar). (2*S*,2′*R*)-**16a**: ^1H NMR δ 1.42 (d, 3 H, CH_3CH), 2.33 (s, 3 H, CH_3Ar), 2.94 (dd, 1 H, H-1), 3.21 (dd, 1 H, H-1), 3.50 (q, 1 H, $CHCH_3$), 5.49 (m, 1 H, H-2), 6.9–7.4 (m, 14 H, CH Ar).

(2*S*,2′*S*)-**16b**: ^1H NMR δ 1.45 (t, 3 H, H-4), 1.55 (d, 3 H, CH_3CH), 2.31 (s, 3 H, CH_3Ar), 2.91 (dd, 1 H, H-1), 3.20 (dd, 1 H, H-1), 3.79 (9, 1 H, $CHCH_3$), 5.14 (m, 1 H, H-2), 7.0–7.4 (m, 9 H, CH Ar). (2*S*,2′*R*)-**16b**: ^1H NMR δ 1.18 (t, 3 H, H-4), 1.51 (d, 3 H, CH_3CH), 2.34 (s, 3 H, CH_3Ar), 3.02 (dd, 1 H, H-1), 3.21 (dd, 1 H, H-1), 3.60 (q, 1 H, $CHCH_3$), 5.15 (m, 1 H, H-2), 7.0–7.4 (m, 9 H, CH Ar).

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