Stereoselective Synthesis of Enantiomerically Pure β-Fluoroalkyl γ-Butyrolactones by Sulfoxide-Directed Lactonization

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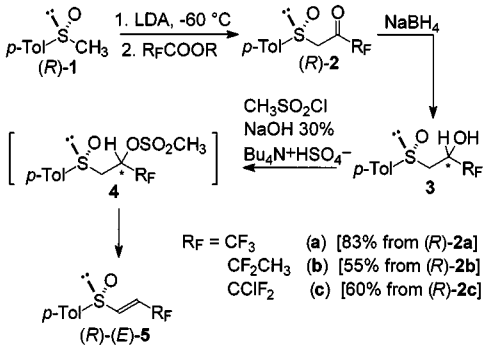
Enantiomerically pure α,α-dichloro β-fluoroalkyl γ-*p*-tolylthio γ-butyrolactones *trans*-**6a–c** have been obtained with excellent stereocontrol (> 98:2) and enantiomeric purity (> 98:2) by sulfoxide-directed lactonization (Marino's annulation reaction) of β-fluoroalkyl vinyl sulfoxides (*R*)-(*E*)-**5a–c** with dichloroketene. Highly chemoselective dechlorination and desulfurization reactions performed on *trans*-**6c** efficiently provided the β-chlorodifluoromethyl γ-butyrolactone (*S*)-**8c**, the absolute stereochemistry of which was determined by X-ray diffraction analysis of its γ-*p*-tolylthio precursor (2*R*,3*S*)-**7c**.

Chiral γ-butyrolactone frameworks are widespread in nature, and are associated with a plethora of biological activities. For example, several insect species use functionalized γ-butyrolactones as sex attractant pheromones, whereas some other γ-butyrolactones are industrially used as flavouring components. On the other hand, it is well known that both enantiomeric purity and absolute configuration are key factors in determining the physiological activities of these molecules.

In conjunction with a program aimed at the synthesis of new chemical agents for selective use against insect species, we became interested in the development of an efficient strategy for the synthesis of chiral, non-racemic β-fluoroalkyl γ-butyrolactones. An overview of relevant literature revealed that only a few examples of β-fluoroalkyl γ-butyrolactones have been reported to date.[1] In the light of our experience gained in the field of chiral sulfoxide chemistry,[2] we envisaged the enantioselective sulfoxide-directed lactonization, first reported by Marino in 1984,[3] as a viable strategy for achieving our target. To the best of our knowledge, fluorinated vinyl sulfoxides have not previously been reacted with ketenes. Considering the dramatic change of reactivity often brought about by the introduction of fluorine,[4] the outcome of these reactions was certainly not predictable, and therefore worthy of investigation.

Results and Discussion

β-Ketosulfoxides (*R*)-**2a−c** (Scheme 1) were obtained by fluoroacylation of lithiated (*R*)-methyl *p*-tolylsulfoxide **1** with the appropriate fluoroacetic acid ester in THF at −60°C.[5] Starting from these readily available materials, the corresponding β-fluoroalkyl vinyl sulfoxides (*R*)-**5a−c** were prepared in one-pot processes, in moderate to good yields (55−83%), according to the following procedure[6]: (1) Reduction of (*R*)-**2a−c** with $NaBH_4$ to give a diastereomeric mixture of β-hydroxy sulfoxides **3a−c**, which was used without purification; (2) dehydration under phase-transfer conditions (30−90 min., CH_2Cl_2, NaOH 30%, Bu_4NHSO_4) via the corresponding transient mesylates **4a−c**. In all cases, the vinyl sulfoxides (*R*)-**5a−c** were obtained almost exclusively in the (*E*) form, with the sulfinyl and the fluoroalkyl groups in a *trans* arrangement, as indicated by *J* values of ca. 15 Hz for the vinylic protons. This point is of great importance for obtaining high stereocontrol in the subsequent annulation step, since the sulfoxide-directed lactonization is known to be a stereoconservative process, reflecting the stereochemistry of the starting vinyl sulfoxides.



Scheme 1

The key lactonization step (Scheme 2) was performed by adding an excess of dichloroketene (ca. 5 equiv.), generated from trichloroacetyl chloride and zinc/copper couple in refluxing diethyl ether, to the vinyl sulfoxides (*R*)-(*E*)-**5a−c** and allowing reaction to proceed for 10 min. at 0°C. In all cases, irrespective of the nature of the fluoroalkyl residue,

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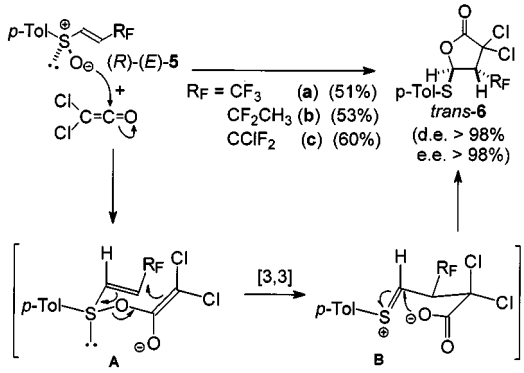
the reactions occurred with excellent stereocontrol, only the corresponding β-fluoroalkyl γ-*p*-tolylthio γ-butyrolactones *trans*-**6a−c** being formed, in fair yields and in enantiomerically pure form (vide infra).

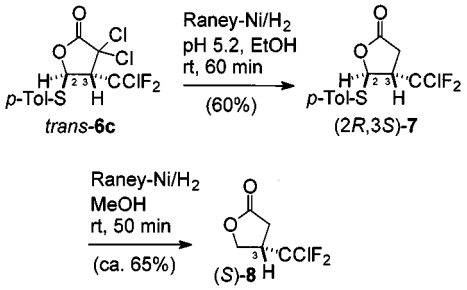


Scheme 2

This excellent stereocontrol can be explained in terms of the mechanism proposed by Marino.[3] The process, belonging to the family of vinylogous Pummerer reactions,[7] should be triggered by acylation of the sulfinyl oxygen by dichloroketene, thereby producing the chiral vinyl oxysulfonium enolate **A** (Scheme 2). This intermediate is believed to undergo a [3,3]-sigmatropic rearrangement, proceeding from a single, thermodynamically preferred conformation with both the sterically demanding fluoroalkyl and *p*-tolylthio groups in pseudoequatorial positions. This gives rise to the zwitterionic species **B** with absolute enantiocontrol. Stereoselective ring-closure of **B** by intramolecular nucleophilic attack of the carboxylate residue on the stabilized carbocation at C-2, attached to the sulfenyl group, represents the final step of the reaction. The overall process can be viewed as a highly enantioselective tandem Michael addition of the enolate of dichloroacetic acid to the vinyl sulfoxide, followed by a Pummerer reaction involving the sulfinyl and the carboxylate groups.

To test the viability of this synthetic route for preparing sulfur-free β-fluoroalkyl γ-butyrolactones of biological interest, we next addressed dechlorination and desulfurization of the chlorodifluoro derivative *trans*-(2*R*,3*S*)-**6c**, chosen as a reference compound (Scheme 3). Dechlorination at C-4 of *trans*-(2*R*,3*S*)-**6c** was achieved in a highly chemoselective manner (60% isolated yield) by treatment with Raney Ni/H_2 at pH 5.2 in the presence of aqueous NaH_2PO_2 (60 min., room temp.),[8] without concomitant desulfurization at C-2, and without further dechlorination of the chlorodifluoromethyl group at C-3. The enantiomeric purity of the resulting γ-*p*-tolylthio γ-butyrolactone (2*R*,3*S*)-**7c** was determined to be > 98% by NMR analysis in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$.

Desulfurization of (2*R*,3*S*)-**7c** was smoothly achieved by further treatment with Raney Ni/H_2 for 50 min. (methanol, room temp.), which produced the rather volatile β-chlorodifluoromethyl γ-butyrolactone (*S*)-**8c**. This was isolated (ca. 65% yield) by filtering off the Raney Ni and then carefully evaporating the solvent, and was characterized without further purification.



Scheme 3

Structural Assignments: γ-*p*-Tolylthio γ-butyrolactone (2*R*,3*S*)-**7c** was crystallized from *n*-hexane, which allowed us to obtain single crystals suitable for X-ray diffraction analysis. The ORTEP[9] representation of the molecular structure is shown in Figure 1. Bond distances and angles are not significantly different from those in the related 4-methylthio-2-phthalimido-γ-butyrolactones.[10,11] The carbonyl moieties of O1, O2, C3 and C4 of the γ-butyrolactone ring are planar within ±0.002 Å, while C2 and C5 reside above (0.239 Å) and below (−0.150 Å) this plane, respectively. At the C2−C5 bond of the lactone ring, the chlorodifluoromethyl group is *trans* to the *p*-tolylthio group. The conformation about the C2−C1 bond is staggered, with the C1−Cl1 bond situated over the lactone ring. The dihedral angle between the mean plane of the benzene ring and that of the carbonyl moiety of the γ-butyrolactone ring is 16.3(3)°. There are no unusually short contacts between the molecules.

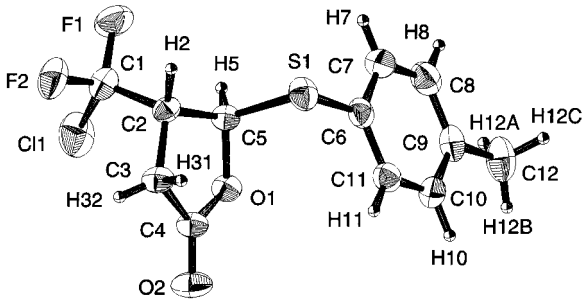


Figure 1. ORTEP view of (2*R*,3*S*)-**7c** showing the atomic labelling scheme

With the absolute stereochemistry of compound **7c** established, the stereochemistry of the precursor compound **6c** could be unequivocally assigned as *trans*-(2*R*,3*S*), while the *trans* relationship between 2-H and 3-H in compounds **6a**,**b** followed from the close similarity of the magnitudes of the coupling constants exhibited by these protons compared to those of compound **6c** (^3J = 9.5 and 9.6 *vs.* 8.7 Hz).

Concluding Remarks

A convenient access to biologically interesting, selectively fluorinated, enantiomerically pure, chiral lactones is provided by a highly stereoselective approach to enantiomerically pure β-fluoroalkyl γ-butyrolactones by sulfoxide-di-

rected lactonization of β-fluoroalkyl vinyl sulfoxides with dichloroketene. Features of this protocol are excellent enantiocontrol, high chemoselectivity, mild conditions, and reasonable overall yields.

Experimental Section

General: Samples for ^{1}H-, ^{19}F- and ^{13}C-NMR were prepared as dilute solutions in $CDCl_3$ and spectra were recorded on Bruker ARX 400 and AC 250L spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as an internal standard (δ_H and δ_C = 0.00) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as an external standard (δ_F = −162.90) for the ^{19}F nucleus. Peak multiplicities are abbreviated as: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m. In the ^{13}C-NMR signal assignments, capital letters refer to the patterns resulting from directly bonded (C,H) couplings and lower-case letters to those from (C,F) couplings. − $[\alpha]_D^{20}$ values were measured on Jasco-Dip or W. Kernchen Propol polarimeters. − IR spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrophotometer. − Mass spectra were recorded on a Hitachi-Perkin-Elmer ZAB 2F instrument. − Anhydrous THF was distilled from sodium and benzophenone. In all other cases, commercially available reagent-grade solvents were employed without purification. Reactions performed in dry solvents were carried out under nitrogen atmosphere. − Melting points were obtained on a capillary apparatus and are uncorrected. − Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230−400 ASTM mesh) was employed for column chromatography. − Combustion microanalyses were performed by Redox SNC, Cologno M. (Milano). Compounds **2a**,**c**,[5] **2b**,[12] **3a**,[6] and **5a**[6] were prepared according to the literature.

Synthesis of β-Hydroxy Sulfoxides 3b,c: To a stirred solution of the β-ketosulfoxide **2b**,**c** (2.5 mmol) in ethanol (6.5 mL), $NaBH_4$ (3.3 mmol) was added at 0°C. After 30 min. stirring at the same temperature, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (15 mL). After extraction with ethyl acetate (3 × 15 mL) and drying of the combined extracts over sodium sulfate, the solvent was removed under reduced pressure. The residue was flash chromatographed on a silica gel column using a *n*-hexane/ethyl acetate mixture (50:50) as eluent, affording β-hydroxy sulfoxides **3b** (92%) and **3c** (95%), respectively, as mixtures of diastereoisomers.

3,3-Difluoro-1-(*p*-tolylsulfinyl)butan-2-ol (**3b**): Major diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 7.56 and 7.38 (m, 4 H, ArH), 4.41 (dddd, *J* = 15.4, 8.6, 5.1 and 3.0 Hz, 1 H, C*H*OH), 3.15 (br s, 1 H, OH), 3.07 (dd, *J* = 13.6 and 3.0 Hz, 1 H, C*H*HS), 3.00 (dd, *J* = 13.6 and 8.6 Hz, 1 H, CH*H*S), 2.43 (br s, 3 H, $ArCH_3$), 1.68 (t, *J* = 19.3 Hz, 3 H, CF_2CH_3). − ^{19}F NMR ($CDCl_3$): δ = −101.00 (ddq, *J* = 247.8, 19.3 and 5.1 Hz, 1 F, C*F*FCH$_3$), −108.36 (ddq, *J* = 247.8, 19.3 and 15.4 Hz, 1 F, CF*F*CH$_3$). − Minor diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 7.54 and 7.38 (m, 4 H, ArH), 4.21 (dddd, *J* = 15.3, 10.4, 5.3 and 2.0 Hz, 1 H, C*H*OH), 3.20 (dd, *J* = 13.6 and 10.4 Hz, 1 H, C*H*HS), 3.15 (br s, 1 H, OH), 2.84 (dd, *J* = 13.6 and 2.0 Hz, 1 H, CH*H*S), 2.43 (br s, 3 H, $ArCH_3$), 1.63 (t, *J* = 19.3 Hz, 3 H, CF_2CH_3). − ^{19}F NMR ($CDCl_3$): δ = −101.46 (ddq, *J* = 247.8, 19.3 and 5.3 Hz, 1 F, C*F*FMe), −107.38 (ddq, *J* = 247.8, 19.3 and 15.3 Hz, 1 F, CF*F*Me). − MS (EI); *m/z*: 248 [M^+]. − $C_{11}H_{14}F_2O_2S$: calcd. C 53.21, H 5.68; found C 53.05, H 5.80.

1-Chloro-1,1-difluoro-3-(*p*-tolylsulfinyl)propan-2-ol (**3c**): Major diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 7.57 and 7.38 (m, 4 H, ArH), 4.63 (ddt, *J* = 6.8, 5.5 and 7.1 Hz, 1 H, C*H*OH), 3.40 (br s, 1 H, OH), 3.14 (dd, *J* = 13.3 and 6.8 Hz, 1 H, C*H*HS), 3.10 (dd, *J* = 13.3 and 5.5 Hz, 1 H, CH*H*S), 2.43 (br s, 3 H, $ArCH_3$). − ^{19}F NMR ($CDCl_3$): δ = −65.22 and −67.11 (dd, *J* = 167.4 and 7.1 Hz, 2 F, CF_2). − Minor diastereoisomer: ^{1}H NMR ($CDCl_3$): δ = 7.55 and 7.38 (m, 4 H, ArH), 4.56 (ddt, *J* = 10.5, 2.3 and 7.1 Hz, 1 H, C*H*OH), 3.40 (br s, 1 H, OH), 3.12 (dd, *J* = 13.3 and 10.5 Hz, 1 H, C*H*HS), 2.99 (dd, *J* = 13.3 and 2.3 Hz, 1 H, CH*H*S), 2.43 (br s, 3 H, $ArCH_3$). − ^{19}F NMR ($CDCl_3$): δ = −65.08 and −66.52 (dd, *J* = 167.4 and 7.1 Hz, 2 F, CF_2). − MS (EI); *m/z*: 268 [M^+]. − $C_{10}H_{11}ClF_2O_2S$: calcd. C 44.70, H 4.13; found C 44.86, H 4.01.

Synthesis of Vinyl Sulfoxides 5b,c: To a solution of the β-hydroxy sulfoxide **3b**,**c** (0.65 mmol) in dichloromethane (5 mL), the phase-transfer catalyst (Bu_4NHSO_4) and 30% aqueous NaOH (5 mL) were added at room temperature. The mixture was cooled to 0°C, and then methanesulfonyl chloride (75 μL) was slowly added under vigorous stirring. After 30 min. at 0°C followed by 1 h at room temperature, the reaction mixture was extracted with ethyl acetate (2 × 10 mL). After drying of the combined extracts over sodium sulfate, the solvent was evaporated under reduced pressure and the residue was flash chromatographed on a silica gel column using a 40:60 *n*-hexane/ethyl acetate mixture as eluent, affording vinyl sulfoxides (*E*)-**5b** (65%) and (*E*)-**5c** (72%), respectively.

(*E*)-3,3-Difluoro-1-(*p*-tolylsulfinyl)but-1-ene (**5b**): $[\alpha]_D^{20}$ = +436 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 7.51 and 7.34 (m, 4 H, ArH), 6.77 (dt, *J* = 15.1 and 1.9 Hz, 1 H, CHSO), 6.61 (dt, *J* = 15.1 and 10.7 Hz, 1 H, $CHCF_2$), 2.42 (br s, 3 H, $ArCH_3$), 1.75 (t, *J* = 18.0 Hz, 3 H, CF_2CH_3). − ^{13}C NMR ($CDCl_3$): δ = 142.56 (S), 139.86 (S), 130.42 (D), 125.04 (D) (ArC); 139.74 (Dt, J_{CF} = 7.4 Hz), 130.11 (Dt, J_{CF} = 28.7 Hz) (CH=CH); 119.57 (St, J_{CF} = 238.0 Hz, CF_2); 24.29 (Qt, J_{CF} = 28.5 Hz, CF_2CH_3); 21.47 (Q, $ArCH_3$). − ^{19}F NMR ($CDCl_3$): δ = −90.70 and −91.10 (dddq, *J* = 256.0, 10.7, 1.9 and 18.0 Hz, 2 F, CF_2). − MS (EI); *m/z*: 230 [M^+]. − $C_{11}H_{12}F_2OS$: calcd. C 57.38, H 5.25; found C 57.43, H 5.12.

(*E*)-3-Chloro-3,3-difluoro-1-(*p*-tolylsulfinyl)prop-1-ene (**5c**): ^{1}H NMR ($CDCl_3$): δ = 7.52 and 7.36 (m, 4 H, ArH), 6.95 (dt, *J* = 14.8 and 1.5 Hz, 1 H, CHSO), 6.75 (dt, *J* = 14.8 and 8.9 Hz, 1 H, $CHClF_2$), 2.43 (br s, 3 H, $ArCH_3$). − ^{19}F NMR ($CDCl_3$): δ = −52.20 and −52.50 (m, 2 F, CF_2). − MS (EI); *m/z*: 250 [M^+]. − $C_{10}H_9ClF_2OS$: calcd. C 47.91, H 3.62; found C 48.04, H 3.51.

Synthesis of β-Fluoroalkyl γ-Butyrolactones 6a−c. *General Procedure:* A suspension of zinc dust (605 mg, 9.25 mmol) and anhydrous CuCl (1663 mg, 16.8 mmol) in anhydrous THF (11 mL) was refluxed for 1 h. After cooling to 0°C, a solution of the vinyl sulfoxide **5a−c** (0.84 mmol) in anhydrous THF (17 mL) was slowly added under nitrogen. Trichloroacetyl chloride (4.2 mmol) was then added over a period of 30 min. with stirring. After a further 15 min. at 0°C, the mixture was filtered through a Celite pad into a saturated aqueous $NaHCO_3$ solution (20 mL), kept at 0°C. The resulting suspension was stirred for 5 min., and then extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed with a saturated aqueous solution of ammonium chloride, dried over sodium sulfate, and concentrated to dryness under reduced pressure. The residue was flash chromatographed on a silica gel column using a 96:4 *n*-hexane/ethyl acetate mixture as eluent, giving γ-butyrolactones **6a** (51%), **6b** (53%), and **6c** (60%), respectively.

(2*R*,3*S*)-4,4-Dichloro-3,4-dihydro-2-(*p*-tolylthio)-3-trifluoromethyl-5(2*H*)-furanone (**6a**): ^{1}H NMR ($CDCl_3$): δ = 7.48 and 7.23 (m, 4

H, ArH), 5.74 (d, J = 9.5 Hz, 1 H, 2-H), 3.40 (dq, J = 9.5 and 6.6 Hz, 1 H, 3-H), 2.38 (br s, 3 H, $ArCH_3$). − ^{19}F NMR ($CDCl_3$): δ = −63.72 (d, J = 6.6 Hz, 3 F, CF_3). − MS (EI); *m/z*: 344 [M^+]. − $C_{12}H_9Cl_2F_3O_2S$: calcd. C 41.76, H 2.63; found C 41.62, H 2.71.

(2*R*,3*S*)-4,4-Dichloro-3,4-dihydro-2-(*p*-tolylthio)-3-(1,1-difluoroethyl)-5(2*H*)-furanone (**6b**): $[\alpha]_D^{20}$ = +86.7 (*c* = 1.0, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 7.46 and 7.21 (m, 4 H, ArH), 5.79 (d, J = 9.6 Hz, 1 H, 2-H), 3.15 (ddd, J = 9.6, 13.0 and 9.0 Hz, 1 H, 3-H), 2.37 (br s, 3 H, $ArCH_3$), 1.98 (t, J = 19.5 Hz, 3 H, CF_2CH_3). − ^{13}C NMR ($CDCl_3$): δ = 164.94 (S, C-5); 140.59 (S), 135.04 (D), 130.42 (D), 124.71 (S) (ArC); 120.07 (Sdd, J_{CF} = 247.8 and 242.3 Hz, CF_2); 84.20 (D br d, J_{CF} = 6.0 Hz, C-2), 75.91 (D br d, J_{CF} = 7.0 Hz, C-4), 60.66 (Ddd, J_{CF} = 28.0 and 25.0 Hz, C-3), 23.47 (Qt, J_{CF} = 25.9 Hz, CF_2CH_3), 21.26 (Q, $ArCH_3$). − ^{19}F NMR ($CDCl_3$): δ = −84.44 (ddd, J = 255.5, 19.5 and 9.0 Hz, 1 F, C*F*FMe), −92.62 (ddd, J = 255.5, 19.5 and 13.0 Hz, 1 F, CF*F*Me). − MS (EI); *m/z*: 340 [M^+]. − $C_{13}H_{12}Cl_2F_2O_2S$: calcd. C 45.76, H 3.54; found C 45.88, H 3.45.

(2*R*,3*S*)-3-Chlorodifluoromethyl-4,4-dichloro-3,4-dihydro-2-(*p*-tolylthio)-5(2*H*)-furanone (**6c**): ^1H NMR ($CDCl_3$): δ = 7.48 and 7.23 (m, 4 H, ArH), 5.80 (d, J = 8.7 Hz, 1 H, 2-H), 3.58 (ddd, J = 9.2, 8.7 and 7.5 Hz, 1 H, 3-H), 2.38 (br s, 3 H, $ArCH_3$). − ^{19}F NMR ($CDCl_3$): δ = −49.72 (dd, J = 175.0 and 7.5 Hz, 1 F, C*F*FCl), −50.97 (dd, J = 175.0 and 9.2 Hz, 1 F, CF*F*Cl). − MS (EI); *m/z*: 360 [M^+]. − $C_{12}H_9Cl_3F_2O_2S$: calcd. C 39.86, H 2.51; found C 39.72, H 2.63.

Dechlorination of γ-Butyrolactone (2*R*,3*S*)-6c: To a solution of γ-butyrolactone **6c** (0.80 mmol) in ethanol (8 mL), a buffer solution (AcOH/AcONa, pH 5.2, 3.0 mL) and Raney Ni (4 equiv.) were added. Immediately thereafter, 5 mL of aqueous $NaPH_2O_2 \cdot H_2O$ (8.0 mmol) solution was added. The reaction mixture was hydrogenated at atmospheric pressure for 1 h, then filtered through a Celite pad, which was rinsed with dichloromethane. After washing with saturated aqueous NaCl solution, the organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was flash chromatographed on a silica gel column using a 90:10 *n*-hexane/ethyl acetate mixture as eluent, affording (2*R*,3*S*)-3-chlorodifluoromethyl-3,4-dihydro-2-(*p*-tolylthio)-5(2*H*)-furanone (**7c**) (60%): $[\alpha]_D^{20}$ = +106 (*c* = 0.9, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 7.47 and 7.21 (m, 4 H, ArH), 5.79 (d, J = 3.4 Hz, 1 H, 2-H), 3.33 (ddt, J = 10.2, 4.2 and 10.3 Hz, 1 H, 3-H), 2.62 (br dd, J = 18.5 and 4.2 Hz, 1 H, 4a-H), 2.43 (dd, J = 18.5 and 10.2 Hz, 1 H, 4b-H), 2.38 (br s, 3 H, $ArCH_3$). − ^{13}C NMR ($CDCl_3$): δ = 172.35 (S, C-5); 140.39 (S), 135.11 (D), 130.50 (D), 125.30 (S) (ArC); 128.43 (St, J_{CF} = 294.5 Hz, $CClF_2$); 84.79 (Dt, J_{CF} = 3.0 Hz, C-2); 51.89 (Dt, J_{CF} = 26.0 Hz, C-3); 29.74 (T br d, J_{CF} = 4.0 Hz, C-4); 21.27 (Q, $ArCH_3$). − ^{19}F NMR ($CDCl_3$): δ = −59.44 and −59.65 (br dd, J = 167.5 and 10.3 Hz, 2 F, CF_2). − MS (EI); *m/z*: 292 [M^+]. − $C_{12}H_{11}ClF_2O_2S$: calcd. C 49.24, H 3.79; found C 49.28, H 3.70.

X-ray Crystal Structure Determination of (2*R*,3*S*)-7c: Crystals of (2*R*,3*S*)-**7c**, suitable for X-ray diffraction analysis, were obtained by crystallization from *n*-hexane. Crystal data: $C_{11}H_9ClF_2O_2S$, M_r = 278.69; orthorhombic; a = 9.996(2), b = 21.123(2), c = 6.4285(7) Å, V = 1357.4(3) Å^3, space group $P2_12_12_1$, Z = 4, Dx = 1.364 Mg.m^{-3}, μ = 4.069 mm^{-1}, F(000) = 568. Colorless prismatic crystal, dimensions 0.4 × 0.3 × 0.3 mm.

Data Collection: Rigaku AFC-5R diffractometer, ω−2θ scan technique, graphite-monochromated Cu-K_α radiation (λ = 1.54184 Å); 1334 reflections measured (8° < 2θ < 135°, +*h*, +*k*, +*l*), 1334 unique. Three standard reflections measured every 100 reflections showed no significant decay. Data were corrected for Lorentz and polarization effects. An empirical absorption correction[13] was also applied.

Structure Analysis and Refinement: The crystal structure was solved by direct methods using the program SIR-92[14], and refined by full-matrix least-squares on F^2 values using SHELXL-97[15]. Non-hydrogen atoms were refined with anisotropic temperature factors. Hydrogen atoms were included at calculated positions and refined in the riding mode, except for H2 and H5, which were located on a difference map and refined with isotropic temperature factors. The final values of the residual R and w$R2$ [for 1230 reflections with $I > 2\sigma(I)$] were 0.057 and 0.143, respectively, with S = 1.08. In the final refinement $(\Delta/\sigma)_{max}$ became 0.000. The maximum and minimum peaks on the final difference map were 0.28 and −0.52 Å^{-3}. The refined value of the Flack χ parameter[16], 0.10(4), clearly indicates the absolute configuration as being (2*R*,3*S*).

Desulfurization of γ-Butyrolactone (2*R*,3*S*)-7c: A suspension of γ-butyrolactone **7c** (0.17 mmol) and Raney Ni (70 mg) in methanol was hydrogenated at atmospheric pressure for 50 min. at room temperature. After filtration through a Celite pad and extraction with dichloromethane (3 × 10 mL), the organic layer was dried over sodium sulfate and the solvent was carefully evaporated under a nitrogen stream with no heating. The residue contained (*S*)-4-chlorodifluoromethyl-4,5-dihydro-2(3*H*)-furanone (**8c**) (65%), which was characterized without further purification: $[\alpha]_D^{20}$ = +19.4 (*c* = 0.73, $CHCl_3$). − ^1H NMR ($CDCl_3$): δ = 4.48 (dd, J = 10.2 and 8.2 Hz, 1 H, 5a-H), 4.42 (dd, J = 10.2 and 5.5 Hz, 1 H, 5b-H), 3.01 (dddddd, J = 11.0, 9.8, 9.5, 8.2, 6.5 and 5.5 Hz, 1 H, 4-H), 2.80 (dd, J = 18.4 and 9.5 Hz, 1 H, 3a-H), 2.75 (dd, J = 18.4 and 6.5 Hz, 1 H, 3b-H). − ^{13}C NMR ($CDCl_3$): δ = 173.80 (S, C-2), 128.78 (St, J_{CF} = 292.5 Hz, CF_2), 66.70 (Tt, J_{CF} = 3.3 Hz, C-5), 45.71 (Dt, J_{CF} = 25.8 Hz, C-4), 29.13 (Tt, J_{CF} = 2.4 Hz, C-3). − ^{19}F NMR ($CDCl_3$): δ = −59.01 (dd, J = 167.2 and 9.8 Hz, 1 F, C*F*FCl), −60.16 (dd, J = 167.2 and 11.0 Hz, 1 F, CF*F*Cl). − MS (EI); *m/z*: 170 [M^+].

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