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Asymmetric Synthesis of 3-Chloro-3-fluoro- and 3-Fluoro-2,4-disubstituted Tetrahydrofurans by the "Fluorinated Sulfoxide Chiron" Route

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Abstract: *An efficient procedure for the preparation of the title compounds in moderate to high enantiomeric purity has been realized starting from olefins tethered on the fluorinated sulfinyl chiron 6, prepared from methyl 4-methylphenyl sulfoxide and ethyl dichlorofluoroacetate. Radical-promoted cyclization of intermediates 9 according to the tributyltin hydride method afforded 3-chloro-3-fluorotetrahydrofuran derivatives 12, from which the corresponding 3-fluorotetrahydrofurans 15 were obtained by reductive dechlorination. Structural assignments have been done on the basis of ^{1}H, ^{13}C and ^{19}F NMR data and NOE difference experiments.*

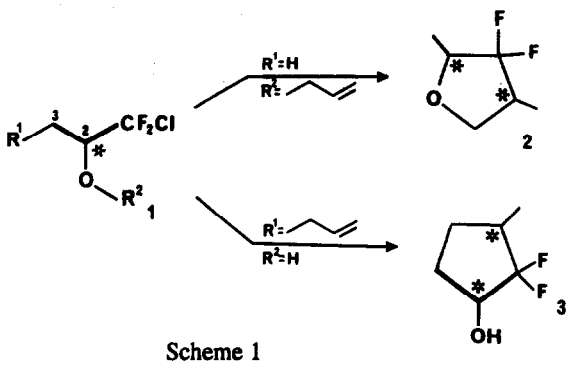
INTRODUCTION

The tetrahydrofuran ring system is common to many naturally occurring and medicinally important[1] compounds. Fluorine substitution for hydrogen or hydroxyl may lead to profound changes in chemical and physical properties or in conformational preferences of the single compounds and therefore in their biological activity.[2]

Among the large number of synthetic methods available in the literature for preparing tetrahydrofurans, free-radical cyclizations have become an important one for constructing a ring skeleton bearing halogens as substituents.[3,4]

In recent years a number of reports have originated from our laboratories concerning the construction of enantiomerically pure selectively fluorinated organic molecules *via* "chiral fluorinated sulfoxides".[5] The three-carbon chirons 1 (scheme 1), containing olefins tethered on oxygen or on C-3 and

groups capable to generate terminal fluoroalkyl radicals, have been shown to be extremely useful building blocks for the preparation of fluorinated heterocycles[4a,c] **2** and carbocycles[6] **3** by using well established radical chemistry.

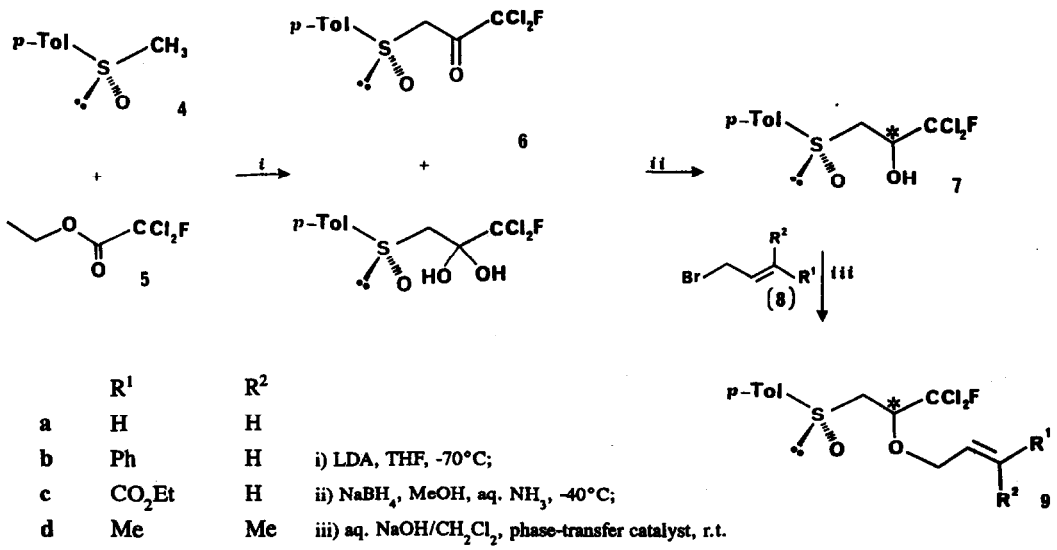


Scheme 1

Herein we describe the asymmetric synthesis of some 3-chloro-3-fluoro- and 3-fluoro-2,5-disubstituted tetrahydrofurans that should find general applicability.

RESULTS AND DISCUSSION

Optically pure substrates **9**, having the group for radical generation, the double bond for its intramolecular trapping and chiral centres for asymmetric induction, to be used in the synthesis of title compounds, were prepared following the route already described for the synthesis of some of the corresponding chlorodifluoro-derivatives[4a,c,7] (Scheme 2).



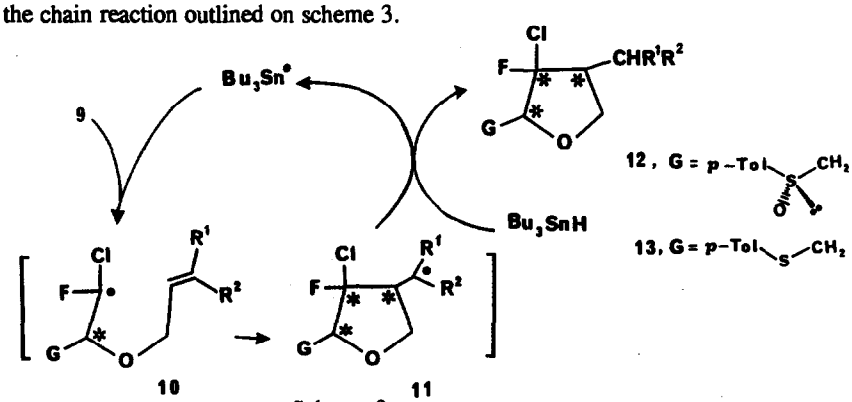
	R^1	R^2
a	H	H
b	Ph	H
c	CO_2Et	H
d	Me	Me

i) LDA, THF, -70°C;
ii) $NaBH_4$, MeOH, aq. NH_3, -40°C;
iii) aq. $NaOH/CH_2Cl_2$, phase-transfer catalyst, r.t.

Scheme 2

Alkylation of the lithium derivative of (*S*)-(-) methyl (4-methylphenyl) sulfoxide (**4**) with ethyl dichlorofluoroacetate (**5**) gave the 1,1-dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl]propan-2-one (**6**) as a mixture of the keto and hydrate forms. Reduction with sodium borohydride in methanol/aqueous ammonia solution gave, in a 2:3 ratio, the corresponding alcohols (2*R*,S_S)- and (2*S*,S_S)-**7**, which were obtained in optically pure form by flash chromatography. Secondary alcohols **7** were reacted with substituted allyl bromides **8** in phase-transfer conditions, and the corresponding propenyl ethers **9a-d** were obtained in high yields (see Experimental).

The tributyltin hydride method, one of the most popular routes for homolytically abstracting halogens from halocarbons, was adopted, and AIBN was used as initiator in benzene at 75°C. Homolytic dissociation of AIBN, followed by hydrogen abstraction on tributyltin hydride, generates the tributyltin radical which starts the chain reaction outlined on scheme 3.



Scheme 3

Chlorine abstraction from the CCl_2F group of **9** by the nucleophilic tributyiltin radical is quite a favored process and generates a chlorofluoroalkyl radical (**10**). The intramolecular capture of **10** by the double bond in an "*exo*" way to give the substituted tetrahydrofuranylmethyl radical **11** completely predominates over the corresponding "*endo*" one, which would form a six-membered ring, owing to stereoelectronic effects.[8] Hydride abstraction from another molecule of tributyltin hydride generates the tetrahydrofuran derivatives **12** and a new tributyltin radical, which enters a new cycle.

Reaction conditions, yields and diastereoisomeric ratios of title compounds are reported in Table 1.

A careful inspection of the data reported on Table 1 allows to draw some observations on the diastereoselectivity of the cyclization. As predicted by the Beckwith model for monosubstituted ω-hexenyl radicals, the preferred stereochemistry between C-2 and C-4 is always *trans*, ranging from 90:10 for entries 1 and 2 to a lower 64:36 for entry 5. For the stereochemical arrangement at C-3 relative to C-2 and C-4 there is a moderate preference for 2,3-*trans* isomers in all cases except for entry 2.[9]

Sulfinyl tetrahydrofurans **12** were reduced to the corresponding thio derivatives **13** by treatment with trifluoroacetic anhydride and sodium iodide in acetone.[10]

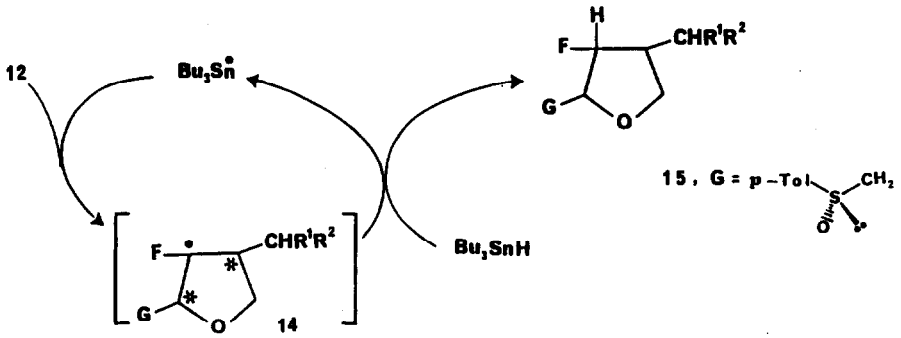
Compounds **12** still contain a chlorine atom which can be homolytically abstracted by tributyltin radical to give radicals **14** (scheme 4). Fortunately **14** is generated at a much lower rate than **10**.[11] Therefore nearly in all of the tested cases appropriate reaction conditions could be chosen for the selective generation of chlorofluorotetrahydrofurans **12**.

Thus the synthesis of 3-fluorotetrahydrofurans **15** has been achieved either in a two-step process, by reducing chlorofluorotetrahydrofurans **12**, or by reacting propenyl ethers **9** with excess tributyltin hydride for a longer reaction time without isolating intermediates **12**.

Table 1. Reaction Conditions, Global Yields and Diastereoisomeric Ratios for Compounds **12a-d** and **15a,c,d**

Entry	Substrate[a]	h[b] (n/n)[c]	Yields **12**	Yields **15**	Diastereoisomeric Ratios
1	(2*R*)-**9a**	12 (2)	72		62 (2*R*,3*S*,4*S*) : 28 (2*R*,3*R*,4*S*) : 7 (2*R*,3*S*,4*R*) : 3 (2*R*,3*R*,4*R*)
2	(2*S*)-**9a**	8 (2)	77		6 (2*S*,3*R*,4*S*) : 58 (2*S*,3*S*,4*R*) : 32 (2*S*,3*R*,4*R*) : 4 (2*S*,3*S*,4*S*)
3	(2*R*)-**9b**	8 (1)	70		40 (2*R*,3*S*,4*S*) : 38 (2*R*,3*R*,4*S*) : 12 (2*R*,3*S*,4*R*) : 10 (2*R*,3*R*,4*R*)
4[d]	(2*R*)-**9c**	8 (2)	74	24	51 (2*R*,3*S*,4*S*) : 33 (2*R*,3*R*,4*S*) : 10 (2*R*,3*S*,4*R*) : 6 (2*R*,3*R*,4*R*)
5	(2*R*)-**9d**	1 (1)	93		40 (2*R*,3*S*,4*S*) : 24 (2*R*,3*R*,4*S*) : 24 (2*R*,3*S*,4*R*) : 12 (2*R*,3*R*,4*R*)
6	**12a** (2*R*,3*R*,4*S*)	12 (2)		61	57 (2*S*,3*R*,4*S*) : 43 (2*S*,3*S*,4*S*)
7	**12d**[e]	6 (1)		58	47 (2*S*,3*R*,4*S*) : 21 (2*S*,3*S*,4*S*) : 18 (2*S*,3*R*,4*R*) : 14 (2*S*,3*S*,4*R*)
8	(2*R*)-**9c**	12 (4)		68	44 (2*S*,3*R*,4*S*) : 43 (2*S*,3*S*,4*S*) : 10 (2*S*,3*R*,4*R*) : 3 (2*S*,3*S*,4*R*)
9	(2*R*)-**9d**	12 (2)		35	47 (2*S*,3*R*,4*S*) : 21 (2*S*,3*S*,4*S*) : 18 (2*S*,3*R*,4*R*) : 14 (2*S*,3*S*,4*R*)

[a]The configuration of the sulfur (always *S*) is omitted; [b]Reaction time (hours); [c]Equivalents of tributyltin hydride per mole of substrate; [d]Diastereoisomeric ratios refer to the derivatives **12c**; [e]Mixture of diastereoisomers (see entry 5).



Scheme 4

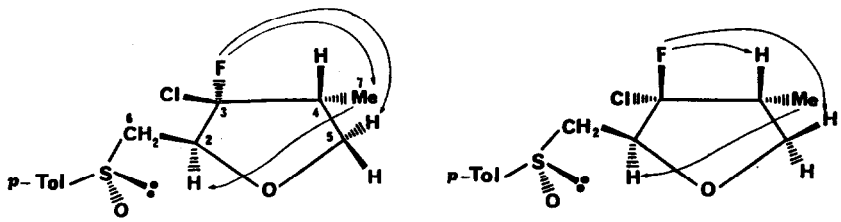
In conclusion we have developed a convenient synthesis for fluoro-substituted tetrahydrofurans, since further elaborations on the sulfinyl-bearing methylene, in order to obtain sulfur-free compounds, can be made as previously done in similar cases.[12]

Structural Assignments

The structure elucidation of the title compounds was determined on the basis of elemental analyses or HRMS measurements, and of the ^{1}H, ^{13}C and ^{19}F NMR data reported in Tables 2 and 3 and in Experimental.

The absolute configuration at C-2 followed from that established for the precursor alcohols $(2R,S_S)$- and $(2S,S_S)$-**7**, while that at the newly formed C-3 and C-4 centres followed from $\{^{1}H\}$- and $\{^{19}F\}$-^{1}H NOE difference experiments (see Table 4) and chemical shift considerations.

For example, in compounds $(2S,3S,4R,S_S)$- and $(2S,3R,4R,S_S)$-**12a** the NOEs observed for H-2, assumed as α in fig. 1 (1 and 5%, respectively), but not for H_2-6, upon irradiation of H_3-7, indicated that the chirality at C-4 is *R*. In compound $(2S,3R,4R,S_S)$-**12a** the NOEs observed for H-4 (4%) and H-5 at 4.36 ppm (1%), but not for H_3-7α and H-5 at 3.62 ppm, upon irradiation of F-3 at -109.56 ppm permitted us to assign as *R* the chirality at C-3 and to distinguish between the geminal C-5 protons. Accordingly, in compound $(2S,3S,4R,R_S)$-**12a** irradiation of F-3 at -115.99 ppm caused enhancements of H_3-7α and H-5 at 3.62 ppm (1%) whereas no sizeable NOEs ($\leq$0.2%) were observed for H-4β and H-5 at 4.22 ppm.



$(2S,3S,4R,S_S)$-**12a** $(2S,3R,4R,S_S)$-**12a**

Figure 1

It must be noted that the above-described assignment of the 5-methylene protons is in agreement with the behaviour observed in related five-membered rings[13] in which the geminal proton *syn* to a vicinal methyl group resonates at higher field with respect to the *anti* one.

The assignment of the chirality at C-3 for the two remaining minor isomers (2*S*,3*S*,4*S*,S_S)- and (2*S*,3*R*,4*S*,S_S)-**12a** was based on the observed chemical shift values of the fluorine atoms. In fact, in compound (2*S*,3*R*,4*S*,S_S)-**12a** F-3, which is *syn*-disposed with respect to the C-2 and C-4 substituents, resonates at higher field ($\Delta\delta$ = 16.6 ppm) relative to the *anti* one because it experiences a greater shielding γ-effect[14].

The close similarity of the chemical-shift values exhibited by the fluorine atoms in compounds **12c** and **12d** relative to the reference compounds **12a** and **12b** ($\delta \approx$ 108, 113, 118 and 134 *vs* 108, 114, 119 and 135 ppm) allowed us to assign the absolute configuration to **12c** and **12d**. A similar trend holds for compounds **15c** relative to the reference compounds **15d**.

EXPERIMENTAL

General Details

IR spectra were taken on a Perkin-Elmer 683 spectrophotometer. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AC 250L spectrometer. Chemical shifts are in ppm downfield from tetramethylsilane as internal standard (δ_H and δ_C 0.00) for ^1H and ^{13}C nuclei, while C_6F_6 was used as internal standard (δ_F -162.90) for ^{19}F nuclei. *J*-Values are given in Hz. NOE difference spectra were obtained by subtracting, alternatively, right-off resonance-free induction decays (FIDs) from right-on resonance-induced FIDs. HRMS measurements were performed by peak matching technique at 10.000 resolving power (10% valley definition), using a VG ZAB 2F instrument operating in electron impact conditions (70 eV, 200 A). Samples were introduced under direct electron impact (DEI) conditions with a source temperature of 200°C.

M.p.s were obtained on a capillary apparatus and are uncorrected; flash chromatographies were performed on Merck silica gel and preparative TLC separations were performed on Merck 60 F_{254} PSC precoated plates. All reactions were monitored by TLC performed on Merck silica gel 60 F_{254} TLC and HPTLC precoated glass plates.

Tetrahydrofuran was refluxed over $LiAlH_4$, while benzene was refluxed over CaH_2 for several hours and distilled onto activated 4Ä molecular sieves. In other cases commercially available reagent-grade solvents and reagents were employed without purification.

The synthesis of the propenyl ether (2*S*,S_S)-**9a** was already described.[7]

Table 2. Selected ^1H NMR Chemical Shifts (δ) and ^1H-^1H and ^1H-^{19}F Coupling Constants (J/Hz) for Compounds **12a** and **15a**

	12a				**15a**	
	(2*S*,3*S*,4*R*)	(2*S*,3*R*,4*R*)	(2*R*,3*S*,4*S*)	(2*R*,3*R*,4*S*)	(2*S*,3*S*,4*S*)	(2*S*,3*R*,4*S*)
2	4.62(α)	4.36(α)	4.04(ß)	4.14(ß)	4.18(ß)	4.08(ß)
3					5.06(α)	4.82(ß)
4	2.63(ß)	2.74(ß)	2.68(α)	2.62(α)	2.50(α)	2.55(α)
5α	3.62	3.62	4.26	4.18	4.11	4.17
5ß	4.22	4.36	3.45	3.50	3.50	3.37
6a	3.18	3.12	3.21	3.23	3.08	3.23
6b	2.80	2.88	3.14	3.13	2.91	3.07
7	1.18	1.20	1.14	1.15	1.09	1.04
J(2,3)					1.3	3.2
J(2,6a)	2.4	2.1	8.2	9.1	5.6	6.7
J(2,6b)	10.8	10.6	4.1	4.3	5.9	7.0
J(2,F)	19.1	19.7	18.2	19.8	29.0	26.9
J(3,4)					4.8	1.4
J(3,F)					55.2	53.9
J(4,5α)	9.8	6.0	7.2	7.8	7.4	6.7
J(4,5ß)	7.6	7.2	9.0	10.1	11.2	4.4
J(4,7)	7.0	7.1	7.2	6.9	6.9	7.4
J(4,F)	17.4	24.1	24.0	20.0	31.3	26.2
J(5α,5ß)	8.9	8.9	9.0	8.8	8.3	8.6
J(5α,F)	1.0	0.7	≤0.5	≤0.5	≤0.5	≤0.5
J(5ß,F)	0	≤0.5	1.0	1.2	≤0.5	0.7
J(6a,6b)	13.0	13.3	13.5	13.1	13.4	13.1
J(6a,F)	0.8	0	1.3	0	≤0.5	1.7
J(6b,F)	≤0.5	1.0	0.7	1.0	≤0.5	0.7
J(7,F)	1.8	0	0	1.7	1.7	1.0

Table 3. ^{19}F NMR Chemical Shifts (δ) and Vicinal ^{1}H-^{19}F Coupling Constants for Compounds **12a-d** and **15a,c,d** in $CDCl_3$

Compound	δ_F	Hz	Compound	δ_F	Hz
(2*S*,3*S*,4*R*)-**12a**	-115.99	19.1, 17.4	(2*R*,3*R*,4*R*)-**12c**	-118.38	13.6, 8.2
(2*S*,3*R*,4*R*)-**12a**	-109.56	24.1, 19.7	(2*R*,3*S*,4*S*)-**12d**	-107.03	23.7, 11.2
(2*S*,3*S*,4*S*)-**12a**	-120.56	13.7, 8.2	(2*R*,3*R*,4*S*)-**12d**	-113.58	19.5, 19.0
(2*S*,3*R*,4*S*)-**12a**	-136.16	25.0, 22.6	(2*R*,3*S*,4*R*)-**12d**	-134.71	25.1, 20.6
(2*R*,3*S*,4*S*)-**12a**	-109.59	24.0, 18.2	(2*R*,3*R*,4*R*)-**12d**	-119.83	12.6, 6.5
(2*R*,3*R*,4*S*)-**12a**	-115.29	20.0, 19.8	(2*S*,3*S*,4*S*)-**15a**	-191.82	31.3, 29.0
(2*R*,3*S*,4*R*)-**12a**	-135.66	24.3, 21.5	(2*S*,3*R*,4*S*)-**15a**	-187.15	26.9, 26.2
(2*R*,3*R*,4*R*)-**12a**	-118.26	14.5, 8.5	(2*S*,3*S*,4*S*)-**15c**	-190.74	30.0, 29.0
(2*R*,3*S*,4*S*)-**12b**	-108.20	23.8, 17.5	(2*S*,3*R*,4*S*)-**15c**	-187.36	28.0, 26.0
(2*R*,3*R*,4*S*)-**12b**	-113.36	20.5, 18.5	(2*S*,3*S*,4*R*)-**15c**	-179.75	26.0, 23.0
(2*R*,3*S*,4*R*)-**12b**	-133.58	24.5, 21.3	(2*S*,3*R*,4*R*)-**15c**	-209.19	32.0, 27.0
(2*R*,3*R*,4*R*)-**12b**	-118.35	12.5, 8.5	(2*S*,3*S*,4*S*)-**15d**	-191.29	32.5, 30.0
(2*R*,3*S*,4*S*)-**12c**	-108.37	24.3, 17.6	(2*S*,3*R*,4*S*)-**15d**	-185.64	33.5, 25.5
(2*R*,3*R*,4*S*)-**12c**	-113.22	20.0, 19.5	(2*S*,3*S*,4*R*)-**15d**	-183.68	27.0, 20.0
(2*R*,3*S*,4*R*)-**12c**	-132.70	24.3, 21.5	(2*S*,3*R*,4*R*)-**15d**	-211.51	33.5, 28.0

Reaction of (2R,S_S)-1,1-Dichloro-1-fluoro-3-[(4-methylphenyl)sulfinyl]propan-2-ol, (2R,S_S)-7, with Allyl Bromide (8a), Cinnamyl Bromide (8b), Ethyl 4-Bromo-2-butenoate (8c) and 4-Bromo-2-methylbut-2-ene (8d). General Procedure of Synthesis of Unsaturated Ethers 9a-d

This is exemplified by the synthesis of (2*R*,S_S)-**9a**. A solution of alcohol (2*R*,S_S)-**7** (0.82 g, 2.87 mmol), allyl bromide (**8a**, 1.74 g, 14.4 mmol) and ethyltrioctylammonium bromide (66 mg, 0.14 mmol) in dichloromethane (10 ml), and 5 ml of a 5 *M* aqueous solution of sodium hydroxide (25 mmol) were vigorously stirred for 2 h at room temperature. The biphasic system was treated with 10 ml of dichloromethane and 30 ml of a saturated aqueous solution of ammonium chloride. The two layers were separated, the aqueous layer was extracted with dichloromethane (2x20 ml) and the combined organic layers were dried with sodium sulphate. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (9:1 hexane/ethyl acetate), giving 0.74 g (80% yield) of (2*R*,S_S)-**9a** as an oil. $[\alpha]_D^{20}$ -70.7° (*c* 0.4, $CHCl_3$); HRMS calcd for $C_{13}H_{15}Cl_2FO_2S$ 324.0147; found 324.0125. ^1H NMR ($CDCl_3$) δ: 7.56 and 7.36 (4 H, m, *p*-TolH), 5.67 (1 H, br dddd, J = 17.2, 10.3, 5.8 and 5.7 Hz, H-2'), 5.20 and 5.15 (2 H, m, H_2-3'), 4.23 (1 H, dddt, J = 12.0, 5.8, 1.3 and 1.3 Hz, H-1'a), 4.18 (1 H, ddd, J = 7.3, 5.9 and 3.1 Hz, H-2), 3.92 (1 H, br ddt, J = 12.0, 5.7 and 2.9 Hz, H-1'b), 3.41 (1 H, ddd, J = 14.0, 3.1 and 0.7 Hz, H-3a), 3.22 (1 H, dd, J = 14.0 and 7.3 Hz, H-3b) and 2.43 (3 H, br s, ArMe).

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

	Proton affected (%)							
Compound	2	4	5α	5ß	6a	6b	7a	7b
(2*S*,3*S*,4*R*)-**12a**	9	≤0.2	1	0	0.5	0	1	
(2*S*,3*R*,4*R*)-**12a**	1	4	0	1	1.5	4	0	
(2*R*,3*S*,4*S*)-**12a**	0.5	6	0.5	0	2	2	≤0.2	
(2*R*,3*R*,4*S*)-**12a**	9	0.5	0	1	0	≤0.2	1	
(2*R*,3*S*,4*S*)-**12b**	0.5	5	0.5	0	3.5	3.5	0	0
(2*R*,3*R*,4*S*)-**12b**	9	≤0.2	0	3	≤0.2	≤0.2	4	3
(2*R*,3*S*,4*R*)-**12b**	≤0.2	≤0.2	1.5	0	4	4	3	3
(2*R*,3*R*,4*R*)-**12b**	6	3	0	0	≤0.2	≤0.2	≤0.2	≤0.2
(2*S*,3*S*,4*S*)-**15a**	6.5	0	0	1	0	0	1	
(2*S*,3*R*,4*S*)-**15a**	0	4.5	1	0	1.5	2	0	
(2*S*,3*S*,4*S*)-**15d**	6	0	0	1	≤0.2	≤0.2	3.5	
(2*S*,3*S*,4*R*)-**15d**	2.5	3	0	0	0	0	0	
(2*S*,3*R*,4*S*)-**15d**	0	11	0	0	2	3	0	
(2*S*,3*R*,4*R*)-**15d**	≤0.2	≤0.2	1.5	0	3	3	3	

Similarly, by reacting (2*R*,S_S)-**7** (0.96 g, 3.35 mmol) with 3-bromo-1-phenylpropene (**8b**), 0.94 g (98% yield) of (2*R*,S_S)-**9b** were obtained. $[\alpha]_D^{20}$ -34.7° (*c* 0.3, $CHCl_3$) (Found: C, 56.8; H, 4.81. $C_{19}H_{19}Cl_2FO_2S$ requires C, 56.9; H, 4.77%). ^1H NMR ($CDCl_3$) δ: 7.6-7.2 (9 H, m, ArH), 6.45 (1 H, dt, *J* = 15.9 and 1.4 Hz, H-3'), 5.96 (1 H, dt, *J* = 15.9 and 6.3 Hz, H-2'), 4.42 (1 H, dddd, *J* = 11.9, 6.3, 1.4 and 1.2 Hz, H-1'a), 4.29 (1 H, ddd, *J* = 7.5, 6.0 and 2.8 Hz, H-2), 3.98 (1 H, br ddd, *J* = 11.9, 6.3 and 1.4 Hz, H-1'b), 3.47 (1 H, ddd, *J* = 14.0, 2.8 and 0.7 Hz, H-3a), 3.24 (1 H, dd, *J* = 14.0 and 7.5 Hz, H-3b) and 2.36 (3 H, br s, ArMe); ^{19}F NMR ($CDCl_3$), δ: -61.80 (1 F, br d, *J* = 6.0 Hz, F-1).

By reacting (2*R*,S_S)-**7** (0.50 g, 1.75 mmol) with ethyl 4-bromo-2-butenoate (**8c**, 1.70 g, 8.76 mmol), (2*R*,S_S)-**9c** was obtained (0.63 g, 90% yield) as a solid. M.p. (ethyl acetate) 61-62°C; $[\alpha]_D^{20}$ -39.3° (*c* 0.27, $CHCl_3$); HRMS calcd for $C_{16}H_{19}Cl_2FO_4S$ 396.0359; found 396.0355. ^1H NMR ($CDCl_3$) δ: 7.50 and 7.34 (4 H, m, *p*-TolH), 6.59 (1 H, dt, *J* = 15.7 and 4.2 Hz, H-2'), 5.76 (1 H, dt, *J* = 15.7 and 2.1 Hz, H-3'), 4.38 (1 H, dddd, *J* = 15.2, 4.2, 2.1 and 1.0 Hz, H-1'a), 4.30 (1 H, ddd, *J* = 7.7, 5.7 and 2.3 Hz, H-2), 4.19 (2 H, q, *J* = 7.1 Hz, CO_2CH_2), 4.00 (1 H, ddd, *J* = 15.2, 4.2 and 2.1 Hz, H-1'b), 3.54 (1 H, ddd, *J* = 14.3, 2.3 and 0.8 Hz, H-3a), 3.17 (1 H, dd, *J* = 14.3 and 7.7 Hz, H-3b), 2.40 (3 H, br s, ArMe) and 1.30 (3 H, t, *J* = 7.1 Hz, Me); ^{19}F NMR ($CDCl_3$) δ: -62.15 (1 F, br d, *J* = 5.7 Hz, F-1).

By reacting (2*R*,S_S)-**7** (0.30 g, 1.05 mmol) with 4-bromo-2-methylbut-2-ene (**8d**, 0.14 g, 9.45 mmol), (2*R*,S_S)-**9d** was obtained (0.26 g, 69% yield) as an oil. $[\alpha]_D^{20}$ -56.4° (*c* 0.34, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.56 and 7.37 (4 H, m, *p*-TolH), 5.03 (1 H, br dd, *J* = 7.4 and 7.0 Hz, H-2'), 4.26 (1 H, br dd, *J* = 11.0 and 7.4 Hz, H-2'), 4.17 (1 H, ddd, *J* = 7.4, 5.8 and 3.0 Hz, H-2), 3.89 (1 H, br dd, *J* =

11.0 and 7.0 Hz, H-1'b), 3.42 (1 H, ddd, J = 13.9, 3.0 and 0.8 Hz, H-3a), 3.20 (1 H, dd, J = 13.9 and 7.4 Hz, H-3b), 2.44 (3 H, br s, ArMe), 1.72 and 1.63 (6 H, br s, 2xMe-3'); ^{19}F NMR ($CDCl_3$) δ: -61.73 (1 F, br d, J = 5.8 Hz, F-1).

General Procedure of Radical Cyclization of the Unsaturated Ethers 9a-d

This is exemplified by the cyclization of (2*R*,S_S)-**9a**. To a stirred solution of (2*R*,S_S)-**9a** (0.67 g, 2.07 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 20 mg, 0.124 mmol) in oxygen-free benzene (15 ml) in a nitrogen atmosphere, a solution of tributyltin hydride (0.57 ml, 2.07 mmol) in the same solvent (5 ml) was added dropwise. The reaction mixture was stirred at 75°C for 6 h. As a TLC control revealed the presence of substantial amounts of starting compound, the same amounts of tributyltin hydride and AIBN of the starting conditions were added and the reaction mixture was kept at 75°C for further 6 h. After solvent evaporation the residue was treated with acetonitrile (5 ml) and the solution was extracted with hexane (3x5 ml). After separation of the layers, the combined hexane phases were re-extracted with acetonitrile (5 ml). The combined acetonitrile phases were evaporated and the residue was flash chromatographed (7:3 hexane/ethyl acetate), giving 0.43 g (72% global yield) of a mixture of the four tetrahydrofuran derivatives. A careful chromatographic separation performed on preparative TLC plates (7:3 hexane/ethyl acetate) afforded two fractions which resulted homogeneous on analytical HPTLC plates (R_F 0.24 and 0.22, 7:3 hexane/ethyl acetate) and were submitted to NMR analysis. The fraction with R_F 0.24 resulted to be a 9:1 mixture of two stereoisomers: (2*R*,3*S*,4*S*,S_S)-3-chloro-3-fluoro-4-methyl-2-[(4-methylphenylsulfinyl)methyl]tetrahydrofuran (2*R*,3*S*,4*S*,S_S)-**12a**, 45% yield (NMR data are on Tables 2, 3 and 4), and the C-4 epimer (2*R*,3*S*,4*R*,S_S)-**12a**, 5% yield (C, 53.6; H, 5.64. $C_{13}H_{16}ClFO_2S$ requires C, 53.7; H, 5.55%). ^{1}H NMR ($CDCl_3$) δ: 7.59 and 7.33 (4 H, m, *p*-TolH), 4.15 (1 H, m, H-2ß), 4.15 and 3.62 (2 H, m, H_2-5), 3.21 and 3.12 (2 H, m, H_2-6), 2.70 (1 H, m, H-4), 2.42 (3 H, br s, ArMe) and 1.14 (3 H, dd, J = 6.8 and 1.7 Hz, H_3-7). The fraction with R_F 0.22 resulted also a 9:1 mixture of the other two diastereoisomers: (2*R*,3*R*,4*S*,S_S)-**12a**, 20% yield (NMR data are in Tables 2, 3 and 4), and (2*R*,3*R*,4*R*,S_S)-**12a**, 2.2% yield; ^{1}H NMR ($CDCl_3$) δ: 7.60 and 7.35 (4 H, m, *p*-TolH), 4.3-4.1 (2 H, m, H-2ß and H-5ß), 3.58 (1 H, m, H-5α), 3.25 and 3.14 (2 H, m, H_2-6), 2.70 (1 H, m, H-4), 2.42 (3 H, br s, ArMe) and 1.16 (3 H, d, J = 7.0 Hz, H_3-7).

Similarly, starting from the epimeric allyl ether (2*S*,S_S)-**9a** (0.46 g, 1.5 mmol), 0.34 g (77% global yield) of the corresponding tetrahydrofuran derivatives were obtained as a HPTLC-homogeneous substance. NMR analysis revealed the presence of the following stereoisomers: (2*S*,3*S*,4*R*,S_S)-**12a**, 45% yield, ^{13}C NMR ($CDCl_3$) δ: 141.93 (s), 140.94 (s), 130.18 (d), 120.03 (d) and 21.45 (q)(*p*-TolC); 117.82 (d, $^1J_{C,F}$ = 256 Hz, C-3); 79.64 (dd, $^2J_{CF}$ = 32 Hz, C-2); 72.47 (t, C-5); 61.86 (dt, $^3J_{C,F}$ = 4 Hz, C-6); 46.94 (dd, $^2J_{C,F}$ = 20.5 Hz, C-4) and 9.07 (dq, $^3J_{C,F}$ = 7.5 Hz, C-7); (2*S*,3*R*,4*R*,S_S)-**12a**, 25% yield, ^{13}C NMR ($CDCl_3$) δ: 141.93 (s), 140.94 (s), 130.18 (d), 120.03 (d) and 21.45 (q)(*p*-TolC); 118.00 (d, $^1J_{C,F}$ = 252 Hz, C-3); 79.80 (dd, $^2J_{C,F}$ = 22.5 Hz, C-2); 73.51 (t, C-5); 57.15 (dt, $^3J_{C,F}$ = 4 Hz, C-6); 44.51 (dd, $^2J_{C,F}$ = 23.5 Hz, C-4) and 15.69 (dq, $^3J_{C,F}$ = 4.5 Hz, C-7), (2*S*,3*R*,4*S*,S_S)-**12a**, 4% yield, and (2*S*,3*S*,4*S*,S_S)-**12a**, 3% yield.

Starting from the cinnamyl ether (2*R*,S_S)-**9b** (0.90 g, 3.16 mmol), 0.78 g (70% global yield) of tetrahydrofuran derivatives were collected, and NMR analysis revealed the presence of the following stereoisomeric tetrahydrofuran derivatives: (2*R*,3*S*,4*S*,S_S)-**12b**, 28% yield, ^{1}H NMR ($CDCl_3$) δ: 7.7-7.1

(9 H, m, ArH), 4.15 (1 H, ddd, J = 17.5, 7.0 and 5.2 Hz, H-2ß), 4.01 (1 H, dd, J = 9.3 and 7.0 Hz, H-5α), 3.54 (1 H, dd, J = 9.3 and 7.0 Hz, H-5ß), 3.22 (1 H, dd, J = 13.1 and 7.0 Hz, H-6a), 3.21 (1 H, dd, J = 13.6 and 4.7 Hz, H-7a), 3.18 (1 H, dd, J = 13.1 and 5.2 Hz, H-6b), 2.91 (1 H, ddddd, J = 23.8, 11.5, 7.0, 7.0 and 4.7 Hz, H-4), 2.49 (1 H, dd, J = 13.6 and 11.5 Hz, H-7b) and 2.43 (3 H, br s, ArMe); (2*R*,3*R*,4*S*,S_S)-**12b**, 27%, (2*R*,3*S*,4*R*,S_S)-**12b**, 8.5%, and (2*R*,3*R*,4*R*,S_S)-**12b**, 7.5% yield. For the last three stereoisomers it was not possible to assign the respective ^{1}H NMR chemical shifts, which resulted to be ($CDCl_3$) at δ: 7.7-7.1 (9 H, m, ArH), 4.3-3.6 (3 H, m, H-2ß and H_2-5), 3.4-2.6 (5 H, m, H-4, H_2-6 and H_2-7) and 2.43 (3 H, br s, ArMe).

Starting from the ether (2*R*,S_S)-**9c**, 0.20 g (0.5 mmol) of tetrahydrofuran derivatives were collected, and a flash chromatography (6:4 hexane/ethyl acetate) of the residue resulting from usual work-up afforded two fractions, homogeneous to HPTLC control, with R_F 0.42 (74% yield) and 0.17 (24% yield). NMR analysis of the fraction with R_F 0.42 revealed the presence of the following compounds: (2*R*,3*S*,4*S*,S_S)-**12c**, 38%, (2*R*,3*R*,4*S*,S_S)-**12c**, 24.5%, (2*R*,3*S*,4*R*,S_S)-**12c**, 7.5%, and (2*R*,3*R*,4*R*,S_S)-**12c**, 4.5%. For the four isomers: HRMS calcd for $C_{16}H_{20}ClFO_4S$ 362.0749; found 362.0719; ^{1}H NMR chemical shifts ($CDCl_3$) are at δ: 7.7-7.3 (4 H, m, *p*-TolH), 4.5-3.4 (5 H, m, H-2ß, H_2-5 and CO_2CH_2), 3.3-2.3 (5 H, m, H-4, H_2-6 and H_2-7), 2.44 (3 H, br s, ArMe) and 1.5-1.2 (3 H, m, Me). NMR analysis of the fraction with R_F 0.17 revealed the presence of the corresponding stereoisomers **15c** deriving from reductive dechlorination of compounds **12c**. The synthesis and characterization of dechlorinated tetrahydrofuran derivatives are reported below.

Finally, starting from the ether (2*R*,S_S)-**9d** (0.26 g, 0.73 mmol), 0.21 g (93% yield) of tetrahydrofuran derivatives were collected, and NMR analysis revealed the presence of the following stereoisomers: (2*R*,3*S*,4*S*,S_S)-**12d**, 37.5%, (2*R*,3*R*,4*S*,S_S)-**12d**, 22%, (2*R*,3*S*,4*R*,S_S)-**12d**, 22%, and (2*R*,3*R*,4*R*,S_S)-**12d**, 11.5%. For the four isomers HRMS calcd for $C_{15}H_{20}ClFO_2S$ 318.0851; found 318.0872; ^{1}H NMR chemical shifts ($CDCl_3$) are at δ: 7.7-7.3 (4 H, m, *p*-TolH), 4.3-3.4 (3 H, m, H-2ß and H_2-5), 3.4-3.0 (2 H, m, H_2-6), 2.42 (3 H, br s, ArMe) and 2.5-0.9 (8 H, m, H-4 and $CHMe_2$).

Reaction conditions (reaction time and moles of tributyltin hydride per mole of starting compound), global yields and diastereoisomers ratios are collected in Table 1. Selected ^{1}H NMR chemical shifts and ^{1}H-^{1}H and ^{1}H-^{19}F coupling constants of some **12a** stereoisomers are in Table 2, ^{19}F NMR chemical shifts and vicinal ^{1}H-^{19}F coupling constants for compounds **12a-d** are in Table 3, and data obtained from $\{^{19}F\}$-^{1}H NOE difference experiments for some compounds **12a,b** are collected in Table 4.

Reduction of Sulfinyl Tetrahydrofuran Derivatives 12a to the Corresponding Thio Derivatives 13a. General Procedure

Trifluoroacetic anhydride (1.04 mmol) was added under nitrogen to a cooled (-40°C) solution of sulfinyl compound (0.22 mmol) and of sodium iodide (0.62 mmol) in acetone (3 ml). Stirring was continued at -40°C for 15 min, then saturated aqueous sodium sulfite (10 ml) was added. The resulting mixture was treated with saturated aqueous sodium hydrogen carbonate until evolution of carbon dioxide had ceased. Acetone was evaporated under reduced pressure and the residual aqueous phase was extracted with ethyl ether (3x15 ml). The collected organic extracts were dried with sodium sulfate and evaporated. The residue was flash chromatographed with hexane, giving the thio derivative in 90-95% yields.

By this procedure the following compounds were obtained: (2*R*,3*S*,4*S*)-**13a**, ^{1}H NMR ($CDCl_3$) δ:

7.33 and 7.12 (4 H, m, *p*-TolH), 4.15 (1 H, dd, *J* = 8.8 and 7.1 Hz, H-5α), 4.00 (1 H, ddd, *J* = 17.5, 8.9 and 3.2 Hz, H-2ß), 3.47 (1 H, dd, *J* = 8.8 and 6.6 Hz, H-5ß), 3.31 (1 H, dd, *J* = 13.7 and 3.2 Hz, H-6a), 3.05 (1 H, ddd, *J* = 13.7, 8.9 and 1.3 Hz, H-6b), 2.71 (1 H, m, H-4α), 2.32 (3 H, br s, ArMe) and 1.15 (3 H, d, *J* = 6.9 Hz, H_3-7); (2*R*,3*R*,4*S*)-**13a**, ^{1}H NMR ($CDCl_3$) δ: 7.33 and 7.12 (4 H, m, *p*-TolH), 4.22 (1 H, ddd, *J* = 20.7, 8.0 and 4.0 Hz, H-2ß), 4.12 (1 H, dd, *J* = 8.5 and 7.8 Hz, H-5α), 3.51 (1 H, ddd, *J* = 10.0, 8.5 and 1.1 Hz, H-5α), 3.29 (1 H, dd, *J* = 13.5 and 4.0 Hz, H-6a), 3.02 (1 H, dd, *J* = 13.5 and 8.0 Hz, H-6b), 2.64 (1 H, m, H-4α), 2.32 (3 H, br s, ArMe) and 1.15 (3 H, dd, *J* = 6.9 and 1.6 Hz, H_3-7); (2*S*,3*R*,4*R*)-**13a**, ^{1}H NMR ($CDCl_3$) δ: 7.33 and 7.12 (4 H, m, *p*-TolH), 4.25 (1 H, dd, *J* = 8.7 and 8.1 Hz, H-5ß), 4.00 (1 H, ddd, *J* = 17.4, 8.9 and 3.1 Hz, H-2α), 3.47 (1 H, dd, *J* = 8.7 and 7.0 Hz, H-5α), 3.31 (1 H, dd, *J* = 13.7 and 3.1 Hz, H-6a), 3.05 (1 H, ddd, *J* = 13.7, 8.9 and 1.3 Hz, H-6b), 2.71 (1 H, m, H-4ß), 2.32 (3 H, br s, ArMe) and 1.15 (3 H, d, *J* = 7.0 Hz, , H_3-7); and (2*S*,3*S*,4*R*)-**13a**, ^{1}H NMR ($CDCl_3$) δ: 7.33 and 7.12 (4 H, m, *p*-TolH), 4.22 (1 H, ddd, *J* = 20.7, 7.9 and 4.1 Hz, H-2α), 4.12 (1 H, dd, *J* = 8.5 and 7.7 Hz, H-5ß), 3.51 (1 H, ddd, *J* = 10.0, 8.5 and 1.1 Hz, H-5α), 3.29 (1 H, dd, *J* = 13.5 and 4.1 Hz, H-6a), 3.02 (1 H, dd, *J* = 13.5 and 7.9 Hz, H-6b), 2.67 (1 H, m, H-4ß), 2.32 (3 H, br s, ArMe) and 1.15 (3 H, dd, *J* = 6.8 and 1.6 Hz, H_3-7).

Reductive Dechlorination of Chlorofluorosulfinyl Tetrahydrofurans 12a,d. General Procedure

A stirred solution of **12a,d** (1 mmol), AIBN (0.05 mmol) and tributyltin hydride (0.57 ml, 2.07 mmol) was kept at 75°C for the time reported in Table 1. The work-up and chromatographic separation were the same as those adopted for the cyclization (see above). From the 9:1 mixture of tetrahydrofuran derivatives (2*R*,3*R*,4*S*,S_S)- and (2*R*,3*R*,4*R*,S_S)-**12a** eluting at R_F 0.22 (see above) (44.6 mg, 0.15 mmol), 24 mg (61% global yield) of dechlorinated tetrahydrofuran derivatives were obtained, and an NMR analysis revealed the presence of the following compounds: (2*S*,3*R*,4*S*,S_S)-**15a**, 35% yield, and (2*S*,3*S*,4*S*,S_S)-**15a**, 26% (NMR data are in Tables 2,3,4).

Similarly, from the mixture of diastereoisomers **12d** (see above)(0.20 g, 0.63 mmol), 0.10 g (58% global yield) of dechlorinated tetrahydrofuran derivatives was obtained, and the following compounds were revealed by NMR analysis: (2*S*,3*R*,4*S*,S_S)-**15d**, 27.5% yield, ^{1}H NMR ($CDCl_3$) δ: 7.57 and 7.35 (4 H, m, *p*-TolH), 4.93 (1 H, ddd, *J* = 54.9, 3.9 and 2.2 Hz, H-3ß), 4.15 (1 H, dd, *J* = 8.9 and 8.3 Hz, H-5α), 3.87 (1 H, m, H-2ß), 3.35 (1 H, dd, *J* = 9.0 and 8.0 Hz, H-5ß), 3.24 (1 H, ddd, *J* = 13.2, 6.8 and 1.7 Hz, H-6a), 3.10 (1 H, dd, *J* = 13.2 and 6.7 Hz, H-6b), 2.43 (3 H, br s, ArMe), 2.15 (1 H, m, H-4α), 1.30 (1 H, m, H-7), 1.04 and 0.90 (6 H, d, *J* = 6.6 Hz, 2xMe-7); (2*S*,3*S*,4*S*,S_S)-**15d**, 12.5%, ^{1}H NMR ($CDCl_3$) δ: 7.57 and 7.35 (4 H, m, *p*-TolH), 5.16 (1 H, br dd, *J* = 55.0 and 4.3 Hz, H-3α), 4.23 (1 H, m, H-2ß), 4.16 and 3.61 (2 H, m, H_2-5), 3.06 (1 H, dd, *J* = 13.3 and 5.8 Hz, H-6a), 2.91 (1 H, dd, *J* = 13.3 and 6.0 Hz, H-6b), 2.43 (3 H, br s, ArMe), 2.03 (1 H, m, H-4α), 1.87 (1 H, m, H-7), 1.07 and 0.92 (6 H, d, *J* = 6.3 Hz, 2xMe-7); (2*S*,3*R*,4*R*,S_S)-**15d**, 10.5%, ^{1}H NMR ($CDCl_3$) δ: 7.57 and 7.35 (4 H, m, *p*-TolH), 5.08 (1 H, ddd, *J* = 53.6, 3.5 and 2.5 Hz, H-3ß), 4.12 (1 H, m, H-2ß), 4.02 (1 H, dd, *J* = 8.5 and 8.0 Hz, H-5ß), 3.71 (1 H, dd, *J* = 10.5 and 8.0 Hz, H-5α), 3.22 (1 H, ddd, *J* = 13.2, 6.5 and 1.7 Hz, H-6a), 3.10 (1 H, dd, *J* = 13.2 and 6.7 Hz, H-6b), 2.43 (3 H, br s, ArMe), 2.00 (1 H, m, H-4ß), 1.87 (1 H, m, H-7), 1.06 and 0.88 (6 H, d, *J* = 6.2 Hz, 2xMe-7); and (2*S*,3*S*,4*R*,S_S)-**15d**, 7.5%, ^{1}H NMR ($CDCl_3$) δ: 7.57 and 7.35 (4 H, m, *p*-TolH), 4.89 (1 H, dt, *J* = 55.5 and 4.8 Hz, H-3α), 4.12 and 3.80 (2 H, m, H_2-5), 4.01 (1 H, m, H-2ß), 3.21 (1 H, dd, *J* = 13.3 and 7.2 Hz, H-6a), 2.99 (1

H, dd, J = 13.3 and 5.0 Hz, H-6b), 2.43 (3 H, br s, ArMe), 2.12 (1 H, m, H-4ß), 1.30 (1 H, m, H-7), 1.04 and 0.92 (6 H, d, J = 6.5 Hz, 2xMe-7).

Cyclization of Unsaturated Ethers (2R,S_S)-9c,d and in Situ Dechlorination of the Tetrahydrofuran Derivatives

The cyclizations were performed following the previously described protocol, but adopting the reaction conditions reported in Table 1. From (2R,S_S)-**9c** (0.55 g, 1.40 mmol), after usual work-up and chromatographic separation, 0.48 g (68% global yield) of chlorine-free tetrahydrofuran derivatives was obtained, and an NMR analysis of the mixture revealed the following stereoisomers: (2S,3R,4S,S_S)-**15c**, 30% yield, (2S,3S,4S,S_S)-**15c**, 29.5%, (2S,3R,4R,S_S)-**15c**, 7%, and (2S,3S,4R,S_S)-**15c**, 1.5%. Only ^{1}H NMR chemical shifts of the mixture could be measured ($CDCl_3$) at δ: 7.6-7.3 (4 H, m, *p*-TolH), 5.4-4.8 (1 H, m, H-3), 4.3-3.4 (5 H, m, H-2ß, H_2-5 and CO_2CH_2), 3.3-2.3 (5 H, m, H-4, H_2-6 and H_2-7), 2.43 (3 H, br s, ArMe) and 1.4-1.2 (3 H, m, Me).

Similarly, from (2R,S_S)-**9d** (210 mg, 0.59 mmol), 67 mg (35% global yield) of dechlorinated tetrahydrofuran derivatives **15d** were obtained, the relative amounts of the four stereoisomers being, within the experimental error, the same reported above.

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