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Intramolecular Trapping of Difluoroalkyl Radicals by Tethered Olefins in the Asymmetric Synthesis of 2,4-Disubstituted-3,3-difluorotetrahydrofurans[1]

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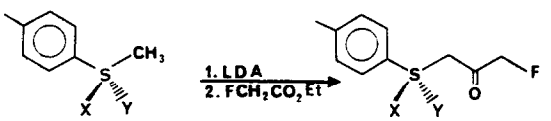
Abstract: *Optically pure propenyl ethers of 3-sulphenyl-, 3-sulphinyl-, and 3-sulphonyl-1-chloro-1,1-difluoropropan-2-ols were submitted to radical cyclization affording, with moderate to high diastereoselectivity, 3,3-difluorotetrahydrofurans containing in 2 and 4 positions various substituents. Detailed NMR analysis allowed to measure trans/cis ratios and to establish the structure of the products.*

Incorporation of fluorine into organic molecules leads to profound changes in chemical and physical properties, yielding new products which may found practical application in many fields[2]. The ability of fluorine to modify the reactivity of biologically active molecules is of particular interest, and an impressive number of bioactive compounds, synthesized and tested today, are based on fluorinated molecules[3].

As part of a program to develop an asymmetric approach to fluorosubstituted complex organic molecules, we have envisaged an unified synthetic strategy based upon the stereocontrolled assembly of the molecules around a C-3 building block already possessing the fluorine atom and a chiral auxiliary[4]. Both (*R*)- and (*S*)-1-fluoro-3-[(4-methylphenyl)sulphinyl] propan-2-one (2) have been prepared[5] by acylating with ethyl fluoroacetate (*R*)- and (*S*)-methyl 4-methylphenyl sulphoxides 1, obtained starting from (+)- or (-)-menthol as primary chiral auxiliaries borrowed from the pool of chirality (Scheme 1).



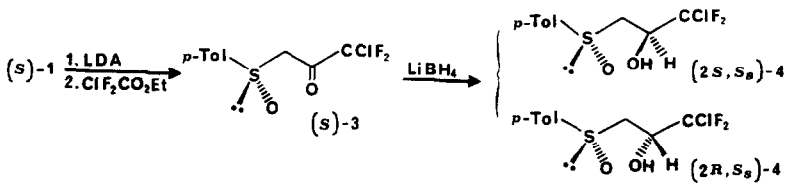
(*R*)-1 X = O, Y = : (*R*)-2
(*S*)-1 X = :, Y = O (*S*)-2

Scheme 1

Their easy preparation, and the possibility of chain elongation on both side and of chirality transfer from sulphur to the central atom, make synthons (*R*)- and (*S*)-**2** ideal substrates for modeling experiments in the asymmetric synthesis of fluoroorganic compounds. A large number of small molecules containing fluorine and different oxygen functionalities have been indeed obtained[6], starting from **2**, by manipulating the chiral auxiliary, and a few fluoroanalogs of molecules of biological and pharmacological interest, like muscarines[7] and acyclic nucleoside analogs[8], have been synthetized from them, and tested for biological activity.

In view of the high versatility of monofluorinated chirons **2**, we thought that parent C-3 chirons, containing groups capable to generate radical intermediates, should be extremely useful synthetic blocks for the preparation of specifically fluorinated molecules by using well established radical chemistry[9].

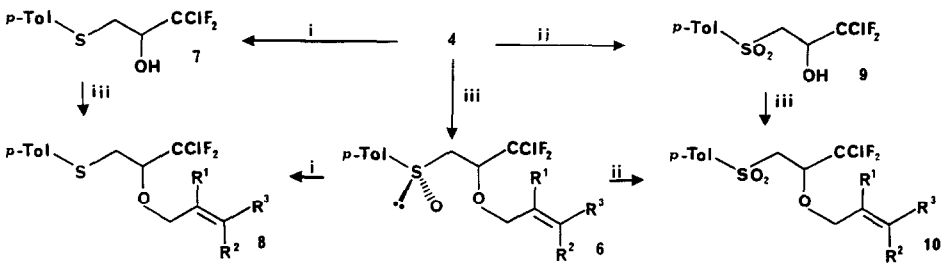
Previous papers from our laboratory[5b,10] on the subject of "EPC synthesis[11] directed towards fluoroorganic compounds" reported on the preparation of some differently substituted enantiomerically pure compounds which could meet those requirements. Acylation of the lithium derivative of (*S*)-**1** with ethyl chlorodifluoroacetate gave the intermediate (*S*)-1-chloro-1,1-difluoro-3-[(4-methylphenyl)sulphinyl]propan-2-one **3** as a mixture of the keto and hydrate forms. Reduction of (*S*)-**3** gave the secondary alcohols 1-chloro-1,1-difluoro-3-[(4-methylphenyl)sulphinyl]propan-2-ols **4** having the ($2S,S_S$) and ($2R,S_S$) configuration, which were isolated in high yields and in optically pure form by flash chromatography (Scheme 2).

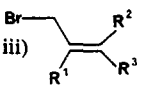


i) LDA, THF, -70°C; ii) ClF_2CO_2Et; iii) $LiBH_4$, MeOH/aq. NH_3, -40°C.

Scheme 2

The propenyl ethers **6** were obtained by reacting secondary alcohols **4** with some differently substituted allyl bromides **5** in phase-transfer conditions. Furthermore, the corresponding sulphenyl derivatives, **8**, or sulphonyl derivatives, **10**, have been obtained, respectively, by selective reduction or oxidation of the sulphinyl sulphur of secondary alcohols **4** to the sulphenyl and sulphonyl alcohols **7** and **9** followed by the etherification, or alternatively by performing the reduction or oxidation on preformed ethers **6**, as outlined on Scheme 3.

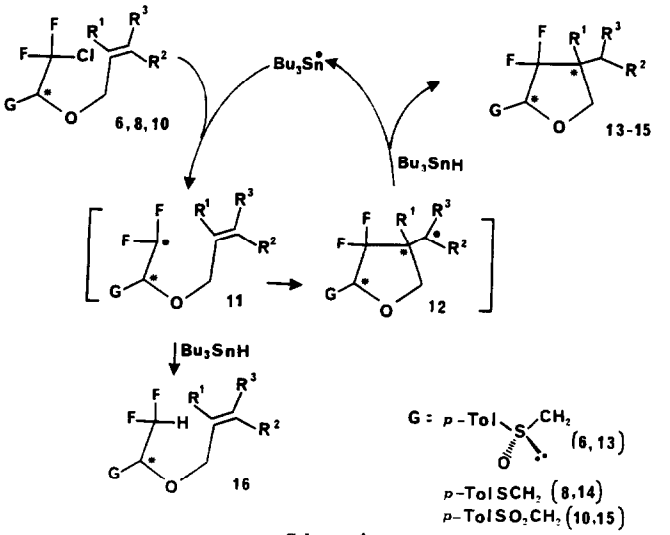


i) $(CF_3CO)_2O$, NaI; ii) aq. $KMnO_4$, acetic acid, CH_2Cl_2, phase transfer catalyst; iii)  (**5**), CH_2Cl_2, aq. NaOH, phase transfer catalyst.

Scheme 3

The propenyl ethers ($2R,S_S$)-**6a**, ($2S,S_S$)-**6a**, (*R*)-**8a**, ($2S,S_S$)-**6c**, ($2S,S_S$)-**6d**, and ($2R,S_S$)-**6f** (see Table 1) were already described[10]. The remaining ethers have been obtained in moderate to excellent yields (see Experimental).

Compounds **6**, **8**, and **10** could be suitable substrates for the asymmetric synthesis of fluorinated heterocycles by using radical chemistry. One of the most used methods to generate alkyl radicals from halogenated organic compounds is the tributyltin hydride method, consisting in heating at temperatures up to *ca.* 80 °C organic compounds containing halogens (or some other functional groups linked with bonds which can be easily broken homolytically) and tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) as radical initiator. Homolytic dissociation of AIBN and hydrogen abstraction from tributyltin hydride generates a tributyltin radical, thus starting a chain reaction. When applied to substrates possessing, besides a suitable radical precursor, a tethered olefin, a chain reaction, as outlined on Scheme 4, may take place. Tributyltin radical abstracts the halogen from the substrate, forming an alkyl radical (**11**), which reacts intramolecularly on the olefinic bond giving a cyclic alkyl radical (**12**). Trapping of **12** by tributyltin hydride gives the final reduced products **13-15** and a new tributyltin radical, which enters a new cycle.



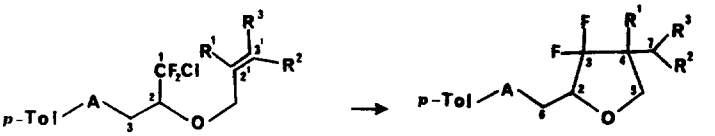
Scheme 4

For the reaction to have practical interest, yields in cyclic products **13-15** must be high, and that is possible when the chain reactions have much higher rates than competitive reactions like the reduction (by tributyltin hydride) of the olefinic double bond, or of the acyclic radicals **11**, which would give compounds **16**. For that reason alkyl bromides and iodides are usually preferred, because they react at much higher rates than chlorides, for which halogen abstraction and the alternative reduction of the olefinic double bond may be competitive. However, when operating on substrates having a chlorodifluoroalkyl group (such as those considered in the present paper), one may expect a clean selectivity in the first step of the cycle. It is known that C-Cl bonds, when activated by electron-withdrawing substituents close to the halogen being abstracted, become reactive toward the "nucleophilic" tributyltin radical (on the contrary, C-F bonds are quite inert).

Indeed, when the tributyltin hydride method was applied on substrates **6**, **8**, and **10**, difluoroalkyl radicals **11** were easily generated. The reactions following the generation of radicals **11** depended mainly on the substituents present on the olefinic double bond tethered through the oxygen of the secondary alcohol. The results obtained in a number of experiments are reported on Table 1.

Among the cyclic products which could arise, only tetrahydrofurans formed in all of the tested cases, thus showing that the "*5-exo*" pathway is by far preferred over the "*6-endo*" one, in line with what is observed in hex-5-enyl radical rearrangement[9] and according with Baldwin rules[12]. Along with the high regioselection, a moderate to fair diastereoselection is observed in the formation of the carbon-carbon bond. The *trans* arrangement of the G group (see Scheme 4) and of the methyl or substituted-methyl group, present respectively in 2 and 4 positions of obtained tetrahydrofurans, prevails in all of the cases studied. Neither the different oxidation state of the sulphur atom (entries 1, 3, 4, 5-7, and 9,10) nor the (*R*) or (*S*) configuration of C-2 of reagent (entries 1,2 and 11,12) seem to play a remarkable role on diastereoselection.

Table 1. Overall yields and *trans/cis* ratios of radical cyclizations.



Substrates → Products

Entry	A	Compound	R^1	R^2	R^3	Compound	Overall Yield (%)	*trans/cis*[a]
1[b]	SO	(2*R*,S_S)-**6a**	H	H	H	(2*S*)-**13a**	87	9:1
2[b]	SO	(2*S*,S_S)-**6a**	H	H	H	(2*R*)-**13a**	70	9:1
3[b]	S	(*R*)-**8a**	H	H	H	(2*S*)-**14a**	55	9:1
4[c]	SO_2	(*R*)-**10a**	H	H	H	(2*S*)-**15a**	51	9:1
5	SO	(2*R*,S_S)-**6b**	H	H	C_6H_5	(2*S*)-**13b**	80	4:1
6	S	(*R*)-**8b**	H	H	C_6H_5	(2*S*)-**14b**	59	4:1
7	SO_2	(*R*)-**10b**	H	H	C_6H_5	(2*S*)-**15b**	66	4:1
8[b]	SO	(2*S*,S_S)-**6c**	H	H	$CO_2C_2H_5$	(2*R*)-**13c**	92	4:1
9[b]	SO	(2*S*,S_S)-**6d**	H	CH_3	CH_3	(2*R*)-**13d**	85	2:1
10	S	(*S*)-**8d**	H	CH_3	CH_3	(2*R*)-**14d**	67	3:1
11	SO	(2*S*,S_S)-**6e**	H	H	Cl	(2*R*)-**13e**	84(17)[d]	3:1
12	SO	(2*R*,S_S)-**6e**	H	H	Cl	(2*S*)-**13e**	62(25)[e]	3:1
13	SO	(2*R*,S_S)-**6f**	Cl	H	H	(2*S*)-**13e**	25(3)[f]	1:1

[a]Measured from ^{19}F NMR spectra; [b]Ref. 10; [c]Ref. 13; [d]yield of (2*R*)-**13a** (3:1 *trans/cis* mixture); [e]yield of (2*S*)-**13a** (3:1 *trans/cis* mixture); [f]yield of (2*S*)-**13a** (1:1 *trans/cis* mixture).

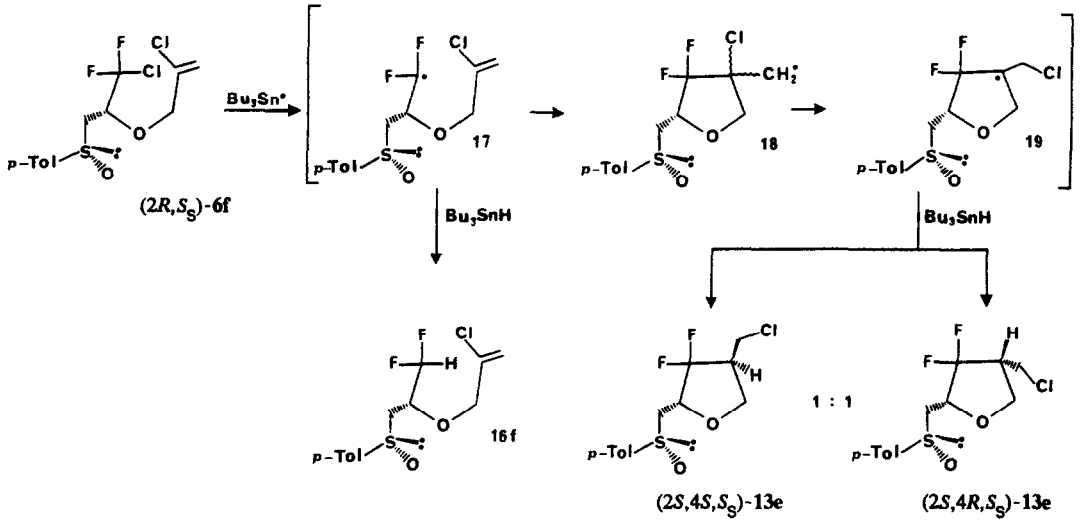
The yields in final products are satisfactory (see Table 1), thus showing that the tributyltin radical is much more reactive towards the C-Cl bond than towards the C-S bond[14], present in all of our substrates, and that the hydrogen atom transfer from tributyltin hydride to the initially formed radical **11**, which would give **16**, does not compete with cyclization.

The radical cyclization outlined in Scheme 4, ending by a reductive step, results in a neat loss of functionalities (Cl and C=C bond) in proceeding from starting materials **6**, **8**, and **10** to the reaction products **13-15**. However one of the requirements for the formed tetrahydrofurans to be employed as chirons in asymmetric synthesis of more complex molecules lies in the possibility of direct functionalization of the initially formed cyclic radical **12**. The best answer to this problem was elaborated by Curran with atom transfer cyclization of iodides[15]. However, as preliminary experiments of I for Cl substitution (in order to obtain iodine-substituted substrates as required in atom transfer cyclizations), made on substrate (2*R*,S_S)-**6a**, resulted unsuccessful, a different approach was explored.

Substrates with tethered olefins already possessing a functional group (ethoxycarbonyl, entry 8, and chloro, entries 11,12,and 13) were prepared and submitted to radical cyclization under standard conditions (see Experimental Section). Upon reaction of (2*S*,S_S)-**6e** (entry 11), 4-chloromethyl-3,3-difluoro-2-[(4-methylphenylsulphinyl)methyl]tetrahydrofuran (2*R*)-**13e** was obtained in 67% yield as a 3 to 1 mixture of the *trans* and *cis* diastereoisomers. A 3 to 1 mixture (17%) of *trans*-(2*R*)-**13a** and *cis*-(2*R*)-**13a** was also obtained. Similar results were observed upon reaction of (2*R*,S_S)-**6e** (entry 12). Compounds **13a** derived from **13e** through reductive dehalogenation, promoted by tributyltin hydride.

On the contrary, the cyclization of (2*R*,S_S)-**6f** (entry 13) followed an unexpected way. The reaction was very slow:

heating at 75°C for 48 hours and a large excess of tributyltin hydride was necessary in order to use up all of the starting compound. The reaction products resulted to be a 1 to 1 mixture of (4*R*) and (4*S*) epimers of 4-chloromethyl-derivative (2*S*)-**13e** (22% yield) along with minor amounts (*ca.* 3%) of a 1 to 1 mixture of dehalogenated tetrahydrofurans (2*S*)-**13a** and of the allyl ether of (2*S*,S_S)-1,1-difluoro-3-[(4-methylphenyl)sulphinyl]propan-2-ol (**16f**, see Scheme 4). Such results may be rationalized as follows. The chlorine on the tethered olefin reduces the reactivity of the double bond towards attack of the electrophilic difluoroalkyl radical. Moreover, in the reaction intermediates **18** (see Scheme 5) steric interactions and electronic repulsion respectively between chlorine and tolylsulphinylmethyl and between chlorine and fluorine substituents on adjacent carbon atoms are at work, so that a slow or reversible addition would result in an accumulation of difluoroalkyl radicals **17** which could be reduced in part to **16f**. On the other hand the primary cyclic radicals **18** as soon as formed would rapidly isomerize to the much more stable tertiary radical **19**, which upon tributyltin hydride reduction would give (2*S*,4*S*,S_S)- and (2*S*,4*R*,S_S)-**13e** as a 1:1 mixture.



Scheme 5

NMR Analysis of the Products.

The evidence for the proposed structure of the title compounds **13**, **14**, and **15**, obtained by the corresponding ethers **6**, **8**, and **10**, was provided by the following spectral findings: the absence of any olefinic resonances in the ^{1}H NMR spectra of compounds **13**, **14**, and **15**, with the concomitant introduction of signals attributable to the protons of the -C(4)H-C(7)HR_2 groupings; the presence of vicinal ^{1}H-^{19}F coupling constants, ranging between 8.0 and 21.4 Hz, between the C-4 proton and the C-3 fluorine atoms which defines the linkage between the C-3 and the C-4 carbons of the tetrahydrofuran system. The remaining ^{1}H and ^{19}F NMR data together with those obtained from the ^{13}C NMR spectra are summarized in Tables 2 and 3 and are typical for tetrahydrofurans with substituents at positions 2, 3, and 4.

The absolute configuration at C-2 in the tetrahydrofuran rings derived from that of the precursor alcohols **4**, while the assignment of the configuration at the newly-formed stereocentre C-4 followed from NOE difference experiments. In fact, the NOE enhancements observed between the C-2 and the C-4 protons (2.5-3.5%) and those observed between the C-2 and the C-7 protons (0.5-1.5%) require that the substituents at C-2 and C-4 are *cis*- and *trans*-disposed, respectively.

EXPERIMENTAL

IR spectra were obtained on a Perkin Elmer 683 infrared spectrophotometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AC 250L spectrometer. Chemical shifts are in p.p.m. (δ); tetramethylsilane was used as internal standard

Table 2. Selected ^{1}H and ^{19}F NMR chemical shifts (δ) and coupling constants (J/Hz) for compounds 13a-e, 14a,b,d, and 15a,b in $CDCl_3$

	13a		13a		14a		15a		13b		14b		15b		13c		13d		14d		13e		13e	
	2S,4S	2S,4R	2R,4R	2R,4S	2S,4S	2S,4R	2S,4S	2S,4R	2S,4S	2S,4R	2S,4S	2S,4R	2S,4S	2S,4R	2R,4R	2R,4S	2R,4R	1R,4S	2R,4R	2R,4S	2R,4R	2R,4S	2S,4S	2S,4R
H-2	3.96	4.10	4.32	4.46	3.91	4.15	4.30	4.45	4.05	ca.4.1	3.98	ca.4.1	4.39	4.48	4.31	4.40	4.28	4.45	3.90	4.03	4.34	4.40	4.03	4.07
H-4	2.54	2.60	2.54	2.60	2.53	2.60	2.43	2.50	2.75	ca.2.8	2.79	ca.2.9	2.65	ca.2.7	2.94	3.00	2.12	1.30	2.13	2.28	2.95	ca.3.0	2.93	2.95
H-5a	4.19	3.64	3.56	4.22	3.43	4.08	4.14	3.58	4.02	3.79	4.01	3.78	3.97	3.74	3.65	4.35	3.63	4.24	3.50	4.12	3.84	4.28	4.33	3.97
H-5B	3.43	4.08	4.27	3.72	4.15	3.63	3.44	4.10	3.57	3.94	3.57	3.94	3.58	3.95	4.44	3.84	4.21	3.82	4.12	3.74	4.41	4.03	3.71	4.13
H-6a	3.18	3.19	3.02	3.01	3.15	3.14	3.39	ca.3.4	3.17	3.23	3.16	3.18	3.41	ca.3.4	3.02	3.01	3.03	2.99	3.14	3.14	3.01	3.02	3.18	3.16
H-6b	3.02	3.02	2.83	2.85	3.02	3.03	3.34	ca.3.3	3.04	3.05	3.02	3.06	3.34	ca.3.3	2.84	2.83	2.80	1.83	3.00	3.02	2.85	2.82	3.04	3.02
H-7a	1.07	1.10	1.12	1.12	1.07	1.09	1.07	1.07	3.03	ca.3.0	3.05	ca.3.0	3.04	ca.3.0	2.71	2.72	1.90	1.91	1.89	1.86	3.75	3.76	3.73	3.75
H-7b									2.51	ca.2.5	2.60	ca.2.5	2.59	ca.2.6	2.42	2.45					3.53	3.52	3.49	3.51
P-3a	-110.10	-113.04	-109.04	-115.40	-110.16	c	-108.81	-114.87	-108.47	-111.74	-110.73	-110.21	-107.20	-113.50	-107.83	-113.59	-103.69	-113.75	-106.79	-110.53	-105.53	-109.84	-106.00	-107.98
P-3b	-114.98	-124.27	-116.76	-125.01	-114.94	c	-116.37	-124.78	-112.66	-122.60	-111.42	-124.22	-114.00	-123.00	-114.49	-122.17	-112.61	-126.00	-110.23	-126.70	-116.55	-122.75	-115.04	-122.16
J(2,6a)	8.5	8.5	2.6	2.6	4.8	4.8	3.1	3.3	8.4	8.7	4.9	ca.5	3.0	c	2.3	2.3	2.5	2.3	4.7	4.8	2.6	2.6	8.4	8.5
J(2,6b)	4.3	4.3	10.5	10.5	8.0	8.0	8.7	8.5	4.5	c	7.9	8.0	8.6	c	10.5	10.5	10.5	10.4	7.7	8.2	10.5	10.5	4.0	4.0
J(2,P-3a)	11.0	8.5[a]	13.1	7.5[a]	11.0	c	12.9	7.5[a]	11.0	7.9[a]	11.5[a]	8.5[a]	12.5	7.1[a]	13.0	7.5[a]	10.9	5.5	8.8	7.0	14.0	8.0[a]	12.6[a]	8.4[a]
J(2,P-3b)	13.2	16.5[b]	12.2	17.5[b]	14.0	c	11.5	17.5[b]	13.5	16.0	13.5	16.0	12.3	17.2	12.0	17.0[b]	15.2	18.7	16.0	18.0	11.5	17.0[b]	12.2[b]	16.0[b]
J(4,5a)	7.8	7.8	9.3	8.2	9.6	8.0	8.0	8.3	7.8	7.8	7.5	7.7	7.1	7.9	9.2	8.1	11.0	10.8	11.0	ca.10	9.0	7.1	8.0	5.9
J(4,5B)	9.1	7.9	7.9	8.2	7.9	8.1	9.0	8.0	9.4	7.9	9.5	7.6	9.0	8.0	8.0	7.3	8.0	9.5	ca.8.5	9.8	7.7	6.2	9.1	8.0
J(4,P-3a)	19.0	13.0[a]	20.2	12.2[a]	18.5	c	20.2	12.1[a]	18.3	12.4[a]	16.5[a]	12.5[a]	19.3	11.8[a]	19.6	12.5[a]	20.0	10.8	18.0	11.0	20.0	13.0[a]	19.2[a]	13.5[a]
J(4,P-3b)	11.0	16.0[b]	9.5	17.0[b]	12.5	c	9.7	16.5[b]	11.5	16.0	13.5	16.0	10.0	17.2	10.0	16.0[b]	13.4	21.4	16.0	20.0	8.0	13.0[b]	9.0[b]	13.0[b]
J(4,7a)	7.0	7.5	7.1	7.0	7.0	7.2	7.0	7.0	c	c	c	c	c	c	5.2	c	10.2	9.5	c	c			5.9	6.0
J(4,7b)									c	c	c	c	c	c	9.8	c							9.2	10.0
J(5a,5B)	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.5	9.3	9.5	9.2	9.5	9.4	9.5	9.5	9.3	9.0	9.0	9.0	9.6	9.6	9.6	9.6
J(6a,6b)	13.3	13.3	13.3	13.3	13.9	13.9	14.6	c	13.5	13.5	13.9	13.9	14.8	c	13.4	13.4	13.3	13.3	13.7	13.7	13.4	13.4	13.5	13.5
J(P-3a,P-3b)	232.0	230.5	232.5	230.5	232.5	c	232.0	230.5	234.8	231.2	234.0	232.5	232.5	231.0	234.5	232.0	235.2	231.5	235.5	232.8	238.0	236.5	237.5	236.5

[a,b]Assignments within each column may be interchanged. [c]Not assigned.

Table 3. Selected ^{13}C NMR chemical shifts (δ)[a] for compounds 13a-e, 14a,b,d, and 15a,b in $CDCl_3$

	13a		13a		14a		15a	13b	14b	15b	13c		13d		14d		13e		13e	
Carbon	2S,4S	2S,4R	2R,4R	2R,4S	2S,4S	2S,4R	2S,4S	2S,4S	2S,4S	2S,4S	2R,4R	2R,4S	2R,4R	2R,4S	2R,4R	2R,4S	2R,4R	2R,4S	2S,4S	2S,4R
2	75.38	74.97	75.35	75.05	80.07	79.16	75.92	76.06	80.66	76.66	75.83	75.30	77.32	75.28	81.62	79.80	76.36	76.10	71.27	76.69
3	127.94	126.91	128.68	b	128.60	b	128.48	b	b	b	b	b	b	b	128.89	127.28	b	b	b	b
4	39.23	38.94	40.69	40.50	40.81	40.54	39.98	46.05	47.65	47.70	42.32	42.22	53.02	51.21	52.99	51.81	48.23	48.13	41.68	48.04
5	71.66	71.47	72.79	72.55	72.11	72.00	72.84	70.30	70.67	71.35	71.34	71.13	70.55	70.79	70.13	70.30	70.25	69.79	70.30	69.85
6	55.83	55.24	57.79	57.44	33.32	33.26	55.98	55.70	33.91	55.92	57.69	57.16	58.34	57.25	34.40	32.84	57.20	56.76	55.87	55.30
7	8.43	8.43	9.97	9.42	9.29	9.35	9.85	30.35	31.30	31.61	30.96	31.05	25.45	26.24	25.41	26.02	39.11	39.38	38.98	39.33

[a]The observed ^{13}C-^{19}F coupling constants range between 259 and 254 (^{1}J), 36 and 19 (^{2}J) and 13 and ca. 0 (^{3}J), respectively. [b]Not assigned.

(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. NOE difference spectra were obtained by subtracting alternatively right-off resonance-free induction decays (FIDs) from right-on resonance-induced FIDs. Mass spectra were registered on an Hitachi-Perkin-Elmer RMU 6D or a VG MM ZAB 2F instrument. Exact mass 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. $[\alpha]_D$ Values were obtained on a Jasco DIP-181 or a Perkin-Elmer 241 polarimeter. Melting points are uncorrected and were obtained on a capillary apparatus; TLC were run on silica gel Merck $60F_{254}$ plates. Reactions with lithium derivatives were carried out under a nitrogen atmosphere. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride and diisopropylamine was distilled from calcium hydride and stored on 4A molecular sieves. A 1.6 *M* solution of butyllithium in hexanes (Aldrich) was employed. Ethyl chlorodifluoroacetate was purchased from Fluorochem. In other cases, commercially available reagent grade solvents and reagents were employed without purification.

The preparation of the diastereoisomeric sulphinyl alcohols (2*R*,S_S)-**4** and (2*S*,S_S)-**4**, and of the sulphonyl alcohol (*R*)-**7**, as well as that of the propenyl ethers (2*R*,S_S)-**6a**, (2*S*,S_S)-**6a**, (*R*)-**8a**, (2*S*,S_S)-**6c**, (2*S*,S_S)-**6d** (whose cyclization was already described[10]), and (2*R*,S_S)-**6f**, were reported in ref. 5b. The synthesis of the sulphonyl alcohol (*R*)-**9** and the cyclization of the ether (*R*)-**10a** were reported in ref. 13.

General Procedure of Synthesis of Allyl Ether of (2R,S_S)-1-Chloro-1,1-difluoro-3-[(4-methylphenyl)sulphinyl]propan-2-ol, (2R,S_S)-6a, and of Cinnamyl Ethers of the same Alcohol, (2R,S_S)-6b, and of Sulphenyl- and Sulphonyl- Analogs, (R)-8b and (R)-10b.

This is exemplified by the synthesis of (2*R*,S_S)-**6a**. A solution of alcohol (2*R*,S_S)-**4** (2.0 g, 7.4 mmol), 3-bromopropene **5a** (3.22 ml, 37.3 mmol) and ethyltrioctylammonium bromide (170 mg, 0.37 mmol) in dichloromethane (100 mL), and 14.8 mL of a 5 *M* aqueous solution of sodium hydroxide (74 mmol) were vigorously stirred at room temperature, following the reaction progress by TLC (eluting mixture 9/1 hexane/ethyl acetate). When no more starting compound was present (*ca.* 1 h), the biphasic system was treated with 200 mL of dichloromethane and 300 mL of a saturated aqueous solution of ammonium chloride. The two layers were separated, the aqueous layer was extracted with dichloromethane (2 x 200 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 2.22 g (97% yield) of (2*R*,S_S)-**6a** as a pure product. M.p 30-31°C (ethyl acetate); $[\alpha]_D^{25}$ -86.98 (*c* 1.1, $CHCl_3$); found C, 50.8; H, 4.8. $C_{13}H_{15}ClF_2O_2S$ requires C, 50.6; H, 4.9%; IR (film) 1720, 1580, 1480, 1100, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.54 and 7.35 (4 H, m, *p*-TolH), 5.65 (1 H, dddd, *J* = 17.0, 10.5, 5.8, and 5.6 Hz, H-2'), 5.19 (1 H, br d, *J* = 17.0 Hz, H-3'a), 5.15 (1 H, br d, *J* = 10.5 Hz, H-3'b), 4.17 (1 H, br dd, *J* = 11.7 and 5.8 Hz, H-1'a), 4.11 (1 H, m, H-2), 3.88 (1 H, br dd, *J* = 11.7 and 5.6 Hz, H-1'b), 3.28 (1 H, dd, *J* = 13.8 and 3.5 Hz, H-3a), 3.16 (1 H, dd, *J* = 13.8 and 7.2 Hz, H-3b), and 2.43 (3 H, br s, Me); ms: found M^+ 308.0417; $C_{13}H_{15}ClF_2O_2S$ requires M^+ 308.0445.

Similarly, by reacting (2*R*,S_S)-**4** (280 mg, 1.05 mmol) with 3-bromo-1-phenylpropene **5b** (1.03 g, 5.23 mmol), 325 mg (81% yield) of (2*R*,S_S)-**6b** were obtained. M.p. 92-4°C (ethyl acetate/hexane); $[\alpha]_D^{25}$ -30.3° (*c* 0.9, $CHCl_3$); found C, 59.5; H, 5.0. $C_{19}H_{19}ClF_2O_2S$ requires C, 59.3; H, 5.0%; IR (nujol) 1100, 1005, 960, 790, and 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.53 and 7.32 (4 H, m, *p*TolH), 7.4-7.2 (5 H, m, ArH), 6.43 (1 H, dt, *J* = 15.9 and 1.3 Hz, H-3'), 5.93 (1 H, dt, *J* = 15.9 and 6.3 Hz, H-2'), 4.36 (1 H, br ddd, *J* = 11.9, 6.3, and 1.3 Hz, H-1'a), 4.22 (1 H, dddd, *J* = 7.9, 7.8, 5.3, and 3.0 Hz, H-2), 4.04 (1 H, br ddd, *J* = 11.9, 6.3, and 1.3 Hz, H-1'b), 3.34 (1 H, dd, *J* = 14.0 and 3.0 Hz, H-3a), 3.19 (1 H, br dd, *J* = 14.0 and 7.8 Hz, H-3b), and 2.36 (3 H, br s, Me); ^{19}F NMR ($CDCl_3$) δ: -62.0 (1 F, br dd, *J* = 168 and 7.9 Hz, F-1a) and -62.5 (1 F, br dd, *J* = 168 and 5.3 Hz, F-1b).

By reacting (*R*)-**7** (95 mg, 0.37 mmol) with **5b** (146 mg, 0.74 mmol), (*R*)-**8b** was obtained (69 mg, 50% yield) as an oil. $[\alpha]_D^{25}$ +100.0° (*c* 1.1, $CHCl_3$); IR (film) 1240, 1090, 1010, and 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.4-7.2 (5 H, m, ArH), 7.31 and 7.07 (4 H, m, *p*TolH), 6.52 (1 H, dt, *J* = 15.9 and 1.3 Hz, H-3'), 6.23 (1 H, dt, *J* = 15.9 and 6.4 Hz, H-2'), 4.49 (1 H, br ddd, *J* = 12.0, 6.4, and 1.3 Hz, H-1'a), 4.34 (1 H, br ddd, *J* = 12.0, 6.4, and 1.3 Hz, H-1'b), 3.87 (1 H, dddd, *J* = 9.7, 7.7, 5.9, and 2.4 Hz, H-2), 3.28 (1 H, br dd, *J* = 14.3 and 2.4 Hz, H-3a), 3.06 (1 H, dd, *J* = 14.3 and 9.7 Hz, H-3b), and 2.30 (3 H, br s, Me); ^{19}F NMR ($CDCl_3$) δ: -62.3 (1 F, br dd, *J* = 168 and 7.7 Hz, F-1a) and -62.7 (1 F, br dd, *J* = 168 and 5.9 Hz, F-1b); $[\alpha]_D^{25}$; ms: found M^+ 368.0789; $C_{19}H_{19}ClF_2OS$ requires M^+ 368.0808.

By reacting (*R*)-**9** (189 mg, 0.66 mmol) with **5b** (654 mg, 3.31 mmol), 195 mg (74% yield) of (*R*)-**10b** were obtained. M.p. 84-6°C (ethyl acetate/hexane); $[\alpha]_D^{25}$ +0.9° (*c* 0.7, $CHCl_3$); found C, 56.8; H, 4.9. $C_{19}H_{19}ClF_2O_3S$ requires C, 56.9; H, 4.8%; IR (nujol) 1130, 1105, 1010, and 955 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.80 and 7.31 (4 H, m, *p*TolH), 7.4-7.2 (5 H, m, ArH), 6.48 (1 H, dt, *J* = 15.9 and 1.3 Hz, H-3'), 6.05 (1 H, dt, *J* = 15.9 and 6.3 Hz, H-2'), 4.47 (1 H, br ddd, *J* = 11.8, 6.3, and 1.3 Hz, H-1'a), 4.46 (1 H, dddd, *J* = 8.7, 7.6, 5.5, and 2.2 Hz, H-2), 4.30 (1 H, br ddd, *J* = 11.8, 6.3, and 1.3 Hz, H-1'b), 3.56 (1 H, dd, *J* = 14.7 and 8.7 Hz, H-3a), 3.46 (1 H, dd, *J* = 14.7 and 2.2 Hz, H-3b), and 2.37 (3 H, m, Me); ^{19}F NMR ($CDCl_3$) δ: -62.7 (1 F, br dd, *J* = 167 and 7.6 Hz, F-1a) and -63.1 (1 F, br dd, *J* = 167 and 5.5 Hz, F-1b); ms: found M^+ 400.0732; $C_{19}H_{19}ClF_2O_3S$ requires M^+ 400.0706.

*Synthesis of 1-Chloropropen-3-yl Ether (2S,S_S)-***6e**.

To a solution of sodium iodide (4.18 g, 22 mmol) in acetone (10 ml) 1,3-dichloropropene **5e** (3.11 g, 22 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The sodium chloride formed was filtered off and the solvent evaporated. The crude 1-chloro-3-iodopropene was reacted with the alcohol (2*S*,S_S)-**4** (750 mg, 2.80 mmol) following the general phase transfer procedure [5.6 ml of 5 *M* aqueous NaOH (28 mmol), 64 mg (0.14 mmol) of ethyltrioctylammonium bromide and 10 ml of dichloromethane], and 696 mg (64% yield) of (2*S*,S_S)-**6e** were obtained. M.p. 35-7°C (ethyl acetate); $[\alpha]_D^{25}$ -163.8° (*c* 1.9, $CHCl_3$); found C, 45.2; H, 4.4. $C_{13}H_{15}ClF_2O_2S$ requires C, 45.5; H, 4.1%; IR (film) 1620, 1480, 1190, 1100, 1030, and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.55 and 7.36 (4 H, m, pTolH), 6.40 and 6.28 (1 H; dt, *J* = 13.3 and 1.3 Hz, H-3' *trans*, and dt, *J* = 7.3 and 1.6 Hz, H-3' *cis*), 6.13 and 6.10 (1 H; dt, *J* = 13.3 and 6.5 Hz, H-2' *trans*, and dt, *J* = 7.3 and 6.1 Hz, H-2' *cis*), 4.68, 4.64, and 4.45, 4.37 (2 H; br ddd, *J* = 12.7, 6.1, and 1.6 Hz, H_2-1' *cis*, and br ddd, *J* = 12.1, 6.5, and 1.3 Hz, H_2-1' *trans*), 4.38 and 4.35 (1 H; m, H-2 *cis* and *trans*), 3.05 (1 H; br dd, *J* = 13.0 and 2.5 Hz, H-3a *cis* and *trans*), 2.93 and 2.91 (1 H; dd, *J* = 13.0 and 4.8 Hz, H-3b *trans*, and *J* = 13.0 and 4.9 Hz, H-3b *cis*) and 2.42 (3 H, br s, Me); ms: found M^+ 308.0478; $C_{13}H_{15}ClF_2O_2S$ requires M^+ 308.0445.

*Attempted Substitution of Chlorine by Iodine in Sulphinyl Ether (2R,S_S)-***6a**.

A solution of (2*R*,S_S)-**6a** (100 mg, 0.32 mmol) and sodium iodide (99 mg, 0.39 mmol) in acetone (2 ml) was stirred at 50°C for 24 h. The solvent was evaporated and the residue was treated with dichloromethane (5 ml). The slurry was washed with water (2x5 ml) and brine (5 ml) and dried with anhydrous sodium sulphate. The residue obtained after solvent evaporation showed the same physical and spectroscopic data of the starting sulphinyl ether (95% recovery).

*Reduction of Sulphinyl Ether (2S,S_S)-***6d** *to the Corresponding Sulphenyl Derivative (S)-***8d**.

Trifluoroacetic anhydride (0.29 ml, 2.08 mmol) was added under nitrogen to a cooled (-40°C) solution of sulphinyl compound (2*S*,S_S)-**6d** (140 mg, 0.45 mmol) and of sodium iodide (187 mg, 1.24 mmol) in acetone (5 ml). Stirring was continued at -40 °C for 15 min, then saturated aqueous sodium sulphite (20 mL) was added. The resultant yellow mixture was treated with saturated sodium hydrogen carbonate solution until evolution of carbon dioxide had ceased. Acetone was evaporated *in vacuo* and the residual aqueous phase was extracted with Et_2O (3x30 ml). The collected organic extracts were dried with sodium sulphate and evaporated. The residue was flash chromatographed with hexane, giving 109 mg (82% yield) of pure sulphenyl derivative (*S*)-**8d**. $[\alpha]_D^{20}$ -2.65 (*c* 1.04, $CHCl_3$); found C, 56.0; H, 5.8. $C_{15}H_{19}ClF_2OS$ requires C, 56.1; H, 6.0%; IR (film) 1430, 1090, 1030, and 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.30 and 7.13 (4 H, m, *p*-TolH), 5.36 (1 H, br dd, *J* = 7.4 and 7.0 Hz, H-2'), 4.30 (1 H, br dd, *J* = 11.1 and 7.0 Hz, H-1'a), 4.20 (1 H, br dd, *J* = 11.1 and 7.4 Hz, H-1'b), 3.79 (1 H, dddd, *J* = 9.7, 7.9, 6.0, and 2.4 Hz, H-2), 3.26 (1 H, br dd, *J* = 14.2 and 2.4 Hz, H-3a), 3.03 (1 H, dd, *J* = 14.2 and 9.7 Hz, H-3b), 2.33 (3 H, br s, ArMe), 1.73 and 1.63 (6 H, br s, 2xMe-3'); ^{19}F NMR ($CDCl_3$) δ: -62.1 (1 F, br dd, *J* = 167.5 and 7.9 Hz, F-1a) and -62.7 (1 F, br dd, *J* = 167.5 and 6.0 Hz, F-1b).

*Oxidation of Sulphinyl Ether (2R,S_S)-***6a** *to the Corresponding Sulphonyl Derivative (R)-***10a**.

A solution of potassium permanganate (37 mg, 0.23 mmol) and of ethyltrioctylammonium bromide (6.5 mg, 0.014 mmol) in water (2 ml) was dropped at room temperature into a solution of (2*R*,S_S)-**6a** (44 mg, 0.14 mmol) in 2.0 ml of dichloromethane/acetic acid (95/5, v/v). A vigorous magnetic stirring was maintained for 4 h, then water (20 ml), a saturated aqueous solution of sodium thiosulphate (5.0 ml), and diluted hydrochloric acid (1.0 ml) were added in the order. The aqueous phase was extracted with dichloromethane (3 x 20 ml), and the combined organic phases were dried over anhydrous sodium

sulphate and evaporated under reduced pressure to give a residue which, upon flash chromatography (7:3 hexane/ethyl acetate), afforded 20 mg (48% yield) of (*R*)-**10a**. IR and NMR data for this compound are identical to those already reported[13].

General Procedure of Radical Cyclization of [1-Chloro-1,1-difluoro-3-(p-tolylsulphinyl)-2-yl] [1-phenylpropen-3-yl] Ether (2*R*,S_S)-**6b**, *of the Corresponding Sulphenyl- and Sulphonyl- Analogs (R)*-**8b** *and (R)*-**10b**, *and of [1-Chloro-1,1-difluoro-3-(p-tolylsulphenyl)-2-yl] [3-methyl-2-buten-1-yl] Ether (S)*-**8d**.

This is exemplified by the cyclization of (2*R*,S_S)-**6b**. To a stirred solution of (2*R*,S_S)-**6b** (325 mg, 0.85 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 4.4 mg, 0.025 mmol) in oxygen-free benzene (2 ml) at 75 °C in a nitrogen atmosphere, a solution of tributyltin hydride (0.23 ml, 0.85 mmol) in the same solvent (10 ml) was added very slowly (*ca.* 3 h). The reaction mixture was further stirred (*ca.* 3 h) at 75 °C. As a TLC control revealed the presence of substantial amounts of starting compound, the reaction mixture was kept at 75°C for further 24 h, by adding, after each 6 h period, the same amounts of neat tributyltin hydride and AIBN of the starting conditions. After solvent evaporation, the residue was vigorously stirred for 1 h with a saturated aqueous solution of sodium fluoride. The slurry was extracted with ethyl acetate, and the organic layer was filtered, dried and the solvent was evaporated. Flash chromatography of the residue on a silica gel column using 8/2 hexane/ethyl acetate as eluant afforded a low polarity fraction (2 mg, R_F 0.71) which, from NMR control, resulted to be a mixture of compounds containing the tri-*n*-butyltin group, 2 mg of reagent, and a fraction (238 mg, R_F 0.10) which, upon NMR analysis, resulted to be a mixture of (2*S*,4*S*,S_S)-**13b** (*trans* isomer) and (2*S*,4*R*,S_S)-**13b** (*cis* isomer). IR (film) 1030 cm^{-1} (SO); ms: found M^+ 350.1153; $C_{19}H_{20}F_2SO_2$ requires M^+ 350.1147.

Similarly, from (*R*)-**8b** after radical reaction (36 h) a flash chromatography (hexane) afforded a fraction which, upon NMR analysis, resulted to be a mixture of (2*R*,4*R*)-**14b** and (2*R*,4*S*)-**14b**. Found C, 67.9; H, 5.7. $C_{19}H_{20}F_2OS$ requires C, 68.2; H, 6.0%; IR (film) 1080 cm^{-1} (ArS); ms: found M^+ 334.1213; $C_{19}H_{20}F_2SO$ requires M^+ 334.1198. From (*R*)-**10b** after reaction (36 h) and flash chromatography (8/2 hexane/ethyl acetate as eluant) a mixture of (2*R*,4*R*)-**15b** and (2*R*,4*S*)-**15b** was obtained. IR (film) 1305 and 1130 cm^{-1} (SO_2); ms: found M^+ 366.1076; $C_{19}H_{20}F_2SO_3$ requires M^+ 366.1096. From (*S*)-**8d** after reaction (12 h) and flash chromatography (hexane) a mixture of (2*R*,4*R*)-**15d** and (2*R*,4*S*)-**15d** was obtained. IR (film) 1090 cm^{-1} (ArS); ms: 288 (M^+).

Yields and *trans/cis* ratios are reported in Table 1. Selected ^1H and ^{19}F NMR chemical shifts and coupling constants for compounds **13a-d**, **14a,b,d**, and **15a,b** are in Table 2; selected ^{13}C NMR chemical shifts for the same compounds are in Table 3.

Radical Cyclization of 1-Chloropropen-3-yl Ethers (2S,S_S)-**6e** *and (2R,S_S)*-**6e**, *and of 2-Chloropropen-3-yl Ether (2R,S_S)*-**6f**.

This is exemplified by the cyclization of (2*S*,S_S)-**6e**. To a stirred solution of (2*S*,S_S)-**6e** (114 mg, 0.33 mmol) and AIBN (1.63 mg, 0.01 mmol) in oxygen-free benzene (2 ml) at 75°C in a nitrogen atmosphere, a solution of tributyltin hydride (0.095 ml, 0.33 mmol) in the same solvent (10 ml) was added. After 42 h (tributyltin hydride and AIBN were added as described in General Procedure), the reaction was stopped (no more starting compound was present). After usual work-up and flash cromatography (7/3 hexane/ethyl acetate as eluant), the following compounds were found upon detailed NMR analysis: (2*R*,4*S*,S_S)-**13e** (53.3 mg, 52% yield), (2*R*,4*R*,S_S)-**13e** (17.4 mg, 17%), (2*R*,4*S*,S_S)-**13a** (12 mg, 13%), and (2*R*,4*R*,S_S)-**16a** (3.6 mg, 4%).

Similarly from (2*R*,S_S)-**6e** (95.5 mg, 0.28 mmol), after reaction (24 h) and flash cromatography (7/3 hexane/ethyl acetate), the following compounds were found upon NMR analysis: (2*S*,4*S*,S_S)-**13e** (24 mg, 28%), (2*S*,4*R*,S_S)-**13e** (7.8 mg, 9%), (2*S*,4*S*,S_S)-**13a** (14.5 mg, 19%), and (2*S*,4*S*,S_S)-**13a** (4.6 mg, 6%).

Finally, from (2*R*,S_S)-**6f** (215 mg, 0.63 mmol) after reaction (48 h) and flash cromatography (7/3 hexane/ethyl acetate) the following compounds were found upon NMR analysis: (2*S*,4*S*,S_S)-**13e** and (2*S*,4*R*,S_S)-**13e** (21.3 mg each, 11% each), (2*S*,4*S*,S_S)-**13a** and (2*S*,4*R*,S_S)-**13a** (2.5 mg each, 1.5% each), and (2*S*,S_s)-**16f** (3%).

Yields and *trans/cis* ratios are reported in Table 1. Selected ^1H and ^{19}F NMR chemical shifts and coupling constants for compounds (2*R*,4*S*,S_S)-**13e**, (2*R*,4*R*,S_S)-**13e**, (2*S*,4*R*,S_S)-**13e**, and (2*S*,4*S*,S_S)-**13e** are reported in Table 2; selected ^{13}C NMR chemical shifts for the same compounds are in Table 3.

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