Stereoselective Synthesis of Trifluoro- and Monofluoro-Analogues of Frontalin and Evaluation of Their Biological Activity†

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The stereoselective synthesis of both enantiomers of trifluoro frontalin (−)-(1*S*,5*R*)- and (+)-(1*R*,5*S*)-**8**, as well as of diastereomeric monofluoro frontalines (−)-(1*R*,2*R*,5*R*)-**18** and (−)-(1*R*,2*S*,5*R*)-**20**, analogues of the bioactive component of the aggregation pheromone of the *Scolytidae* insect family, has been accomplished starting from (−)-(1*R*)- and (+)-(1*S*)-menthyl (*S*)-toluene-4-sulfinate as a source of chirality and methyl trifluoroacetate or fluoroacetate, respectively, as sources of fluorine. The C-1 stereocenters were installed via stereoselective epoxidation of *β*-sulfinyl ketones **2** and **13** with diazomethane. The bicyclic core was obtained by totally stereocontrolled and chemoselective tandem Wacker oxidation/intramolecular ketalization of the intermediate unsatured sulfinyl diols **5**, **15**, and **19**. Axially fluorinated (−)-**20** elicited a strong electroantennographic response in laboratory tests on females of *Dendroctonus micans*, whereas equatorially fluorinated (−)-**18** and the trifluoroanalogue (−)-**8** showed modest responses. Field trials using (−)-**20** were not indicative owing to the locally scarce population of *D. micans*, but it showed some attractiveness for other *Coleoptera* families.

Introduction

In the search for new strategies in insect control three different synthetic tools are emerging: the inhibitors of insect pheromone biosynthesis,[1] the inhibitors of the pheromone-catabolizing enzyme,[2] and the attractants having pheromone-mimicking activity.[3] On the other hand, fluorine-containing compounds are well-known to play an important role in a number of fields, including bio- and agrochemistry.[4] For example, replacement of hydrogen atoms by fluorine in pheromones has been shown to produce a variety of effects on the insect response, some of them a priori unpredictable. Thus, the activity of the parent nonfluorinated compounds can be lost,[5] mimicked,[6] or increased.[7] This might be ascribed

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to the fact that fluorine substitution causes only a small steric difference but large perturbation in electronic distribution that can be reflected on the interaction between the fluorinated pheromone and the active sites of its complementary receptors.[8] Moreover, fluorosubstitution increases volatility[9] and thermal and oxidative stability and lipophilicity,[10] with respect to the parent compounds.[11] This might be of potential interest in field trials. Alternatively, fluorinated pheromones can be used as tracers for metabolic pathways.[12]

It should be stressed that, due to the importance of the stereochemistry of chiral pheromones in the expression of bioactivity,[13] fluorinated-pheromones should be prepared in a stereodefined manner in order to have a possible practical usefulness. For example, frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane),[14a] that is the bioactive component of the aggregation pheromone of the Southern Pine Beetle (SPB) *Dendroctonus frontalis* (Zimmermann) (Coleoptera Scolytidae), is produced as an 85:15 (−)-(1*S*,5*R*)/(+)-(1*R*,5*S*) mixture of enantiomers. SPB is the most destructive insect pest of pine in the southern United States.[14b,c] The species is not present in Europe where, instead of it, *Dendroctonus micans* (Kugelann) is quite spread. In Italy, *D. micans* occurs on Alps, mainly on the eastern Alps where it is a constant threat to *Picea Abies* forests.[14d,e] Very recently, a combination of pheromones produced by SPB has been successfully used in a novel strategy to halt the progression of SPB infestations in pine forests.[14f] Laboratory and field bioassays showed that the (−)-enantiomer of frontalin is much more active than the (+)-enantiomer.[15] Many papers devoted to the synthesis of natural frontalin recently appeared,[16] but to our knowledge, no synthesis of the corresponding fluoroanalogues has ever been published.[17] In this paper we describe the stereocontrolled synthesis of several enantiopure frontalin analogues where one or three hydrogens are replaced by fluorine atoms. These novel molecules are (1) both diastereo- and enantiopure epimers of (−)-1,5-dimethyl-2-fluoro-6,8-dioxabicyclo[3.2.1]octane, where the introduction of fluorine creates an additional and synthetically challenging endocyclic stereocenter, and (2) both enantiomers of 5-methyl-1-trifluoromethyl-6,8-dioxabicyclo[3.2.1]octane, where the F for H substitution is exocyclic.[18] To evaluate the activity and the potential of the three stereochemically pure fluoroanalogues of natural frontalin for the control of *D. micans* population in forest, electroantennographic and field tests have been also performed.

Results and Discussion

Synthesis of Trifluorofrontalin. As a part of our goal of developing practical routes to selectively fluorinated and enantiomerically pure compounds, we have been studying the reactions between enantiopure γ-fluoro-β-ketosulfoxides and diazomethane as a general approach to epoxides bearing a quaternary fluoroalkyl-substituted carbon stereocenter.[19] Thus, we envisaged such a strategy as a viable route to install the quaternary CF_3-substituted center of trifluorofrontalin.

Condensation of ω-pentenylmagnesium bromide with (−)-(1*R*)-menthyl (*S*)-toluene-4-sulfinate following the Andersen-modified procedure[20] gave the enantiopure sulfoxide (R_S)-**1** (Scheme 1). Subsequent acylation of its lithium derivative with ethyl trifluoroacetate afforded the α-butenyl-γ,γ,γ-trifluoro-β-keto sulfoxide **2** as a 1:1 mixture of *C*-epimers (Scheme 1). Diastereocontrolled methylene insertion reaction from diazomethane across the carbonyl group of (3*R*/*S*,R_S)-**2** at − 40 °C provided a diastereomeric mixture of oxiranes **3** (69% d.e. at C-2) from which the major (2*S*)-configured ones were isolated by flash chromatography (FC) in 76% overall yield.[21] This unresolved 4.1:1.0 (1′*S*)/(1′*R*) epimeric mixture was submitted to electrophilic ring opening reaction with aque-

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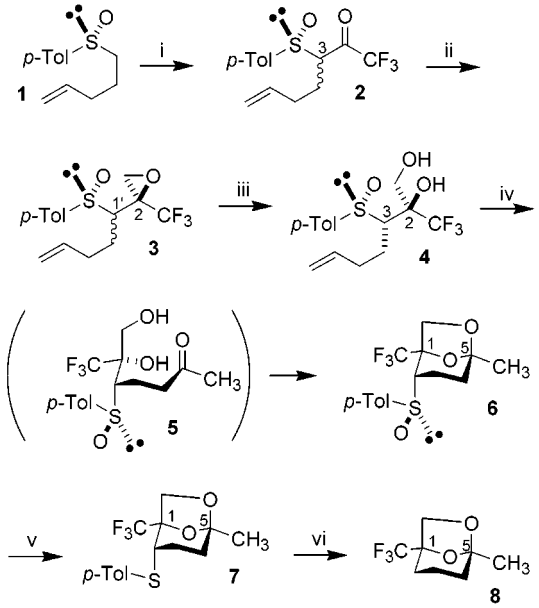
Scheme 1[a]



[a] Key: (i) LDA, THF, CF_3COOEt (87%); (ii) CH_2N_2, MeOH, −40 °C (69% d.e., 90% overall yield); (iii) $HClO_4$, THF/H_2O, 40 °C, 7 d (78%); (iv) $CuCl_2/PdCl_2$, DME (72%); (v) NaI, TFAA, acetone (92%); (vi) Raney-Ni, $(HOCH_2)_2$ (90%).

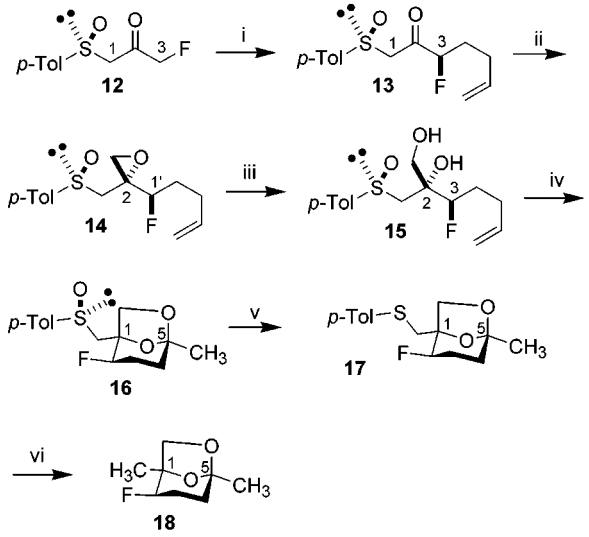
ous perchloric acid. The diol (2*S*,3*S*,R_S)-**4** was isolated, as a pure compound, in good chemical yield (78%) after 7 days at 40 °C. The less abundant epoxide (1′*R*,2*S*,R_S)-**3** was recovered unchanged and could be processed under more severe conditions (2 weeks at reflux) to give (2*S*,3*R*,R_S)-**4**.[22]

Next, we addressed the construction of the bicyclic core of trifluoro frontalin. A Wacker oxidative process[23] of the terminal C=C bond of (2*S*,3*S*,R_S)-**4** (Scheme 1), followed by intramolecular ketalization of the reactive intermediate methyl ketone **5**, proved to be extremely effective in producing the bicyclic framework in a totally stereocontrolled manner, affording the intermediate (1*S*,2*S*,5*R*,R_S)-**6** in 72% yield. It is worth noting that the Wacker oxidation proceeded with excellent chemoselectivity, as witnessed by the fact that sulfinyl to sulfonyl group oxidation was never observed.

Subsequent deoxygenation of **6** to the sulfide **7**,[24] followed by hydrogenolytic removal[25] of the *p*-tolylthio group led to the enantio- and diastereopure trifluoroanalogue of (−)-frontalin (1*S*,5*R*)-**8**. Analogously, the enantiomer (+)-trifluorofrontalin **8** was obtained from the enantiomeric (+)−(1*S*)-menthyl (*R*)-toluene-4-sulfinate repeating the same synthetic sequence (see Experimental Section).[26]

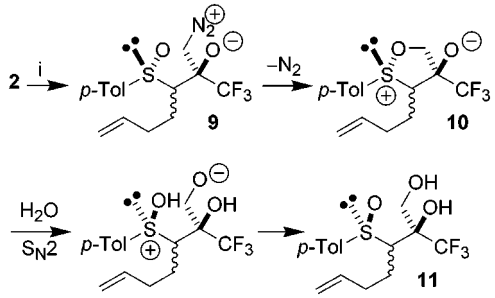
Synthesis of Monofluorofrontalin.[27] α,γ-Dilithium derivative of (*S*)-γ-fluoro-β-ketosulfoxide **12**[28] (Scheme 2) was treated with 3-butenyl bromide in the presence of HMPA to afford **13** in nearly equimolar mixture with its C-3 epimer **19**, from which it was separated by FC. Treatment of **13** with diazomethane produced the oxirane **14** with good diastereocontrol (6.5:1.0) and excellent

Scheme 2[a]



[a] Key: (i) (a) LDA, *n*-C_4H_7Br, HMPA, THF, −60 °C; (b) FC (85% overall **13** + **19**); (ii) CH_2N_2, MeOH, 0 °C (79%); (iii) $HClO_4$, THF/H_2O, 40 °C (75%); (iv) $PdCl_2/CuCl_2$, O_2, diglyme, rt (80%); (v) NaI, TFAA, acetone, −20 °C (95%); (vi) Raney-Ni, $(CH_2OH)_2$, 110 °C (88%).

(21) When the methylene insertion was run at room temperature, three diastereomeric diols **11** were formed as byproducts (40% overall yield), while oxiranes **3** were formed with the same stereoselectivity observed at −40 °C (55% overall). Surprisingly, X-ray diffraction[17] of the most abundant diol, in combination with polarimetric analyses, which showed a negative $[\alpha]_D$ value for all of the three diols **11**, allowed us to assess that inversion of configuration at sulfur had occurred in all cases. A hypothesis accounting for such an event involves intramolecular N_2 displacement performed by the sulfinyl oxygen of the intermediate **9** to give the cyclic intermediate **10**. A water molecule (from the methanolic medium) may act as a nucleophile attacking in S_N2-manner the sulfur atom, which leads to inversion of configuration at the sulfur stereocentre, providing the diol (2*S*,3*R*,S_S)-**11** as the final product.



X-ray diffraction of (2*S*,3*R*,S_S)-**11** allowed us to assign the stereochemistry of the CF_3-substituted compounds described herein (see ref 17). A similar side-reaction was observed for the reaction of monofluoro derivative **13** with diazomethane, although to a lower extent (see Experimental Section).

(22) Despite the severe reaction conditions, an experiment performed with the Lanthanide shift reagent Eu(tfc)$_3$ evidenced that no epimerization at the sulfur stereocentre occurred.

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(26) The methylene insertion reaction carried out in multigram scale under the optimized conditions produced synthetically useful amounts of coproducts such as the diols **11** and minor diastereomeric epoxides such as (1′*R*,2*S*,R_S)-**3**. Thus, we developed experimental conditions for utilizing single diastereomers or mixtures of epimers of these compounds for preparing the corresponding enantiomers of trifluorofrontalin **8**. For example, trifluorofrontalin (−)-(1*S*,5*R*)-**8** was also obtained from the diastereopure diol (2*S*,3*R*,S_S)-**11**. Analogously, the less abundant mixture (13.9%) of oxiranes (1′*R*/*S*,2*R*,R_S)-**3** obtained from (3*R*/*S*,R_S)-**2** and diazomethane at −40 °C afforded trifluorofrontalin (+)−(1*R*,5*S*)-**8**.

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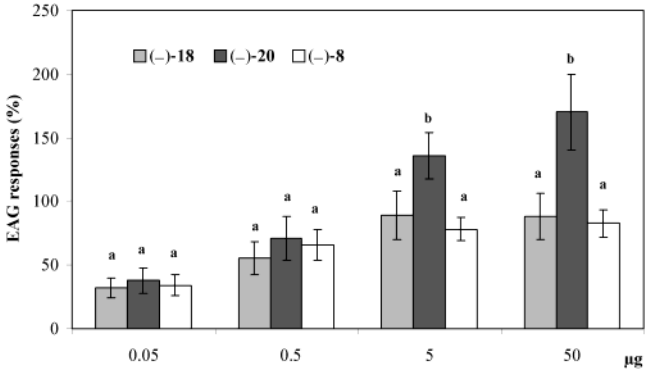
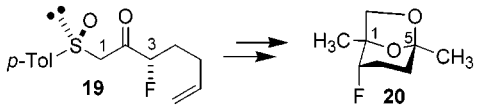


Figure 1. Normalized EAG responses of *D. micans* females to different doses of (−)-**8**, (−)-**18**, and (−)-**20**. Vertical lines indicate standard deviation. Within a dose, bars with the same letter are not significantly different for $P = 0.01$ (Duncan's test).

overall yield (79%). Oxirane ring opening was achieved in THF/H_2O with catalysis of $HClO_4$ at 40 °C (5 days), which afforded the diol **15** in 85% yield.

Treatment of **15** (Scheme 2) with $PdCl_2/CuCl_2/O_2$ at room temperature gave rise to the tandem Wacker oxidation/intramolecular ketalization of the intermediate methyl ketone, providing with the usual total stereocontrol and chemoselectivity the bicyclic sulfoxide **16**, featuring the structural framework of monofluorofrontalin. Deoxygenation of **16** to **17** (95%) and subsequent reductive desulfenylation with Raney-Ni (88%) delivered the target molecule (1*R*,2*R*,5*R*)-**18**, having the fluorine atom in equatorial position.

The axially fluorosubstituted diastereomer (1*R*,2*S*,5*R*)-**20** was prepared according to an identical sequence of reactions from the diastereomer **19** (see Experimental Section). It is worth noting that formation of the corresponding intermediate oxirane by action of diazomethane on **19** occurred with higher diastereocontrol (12:1) than that achieved with the epimer **13**.



X-ray diffraction of (1*R*,2*R*,5*R*,S_S)-**16** allowed us to assign the stereochemistry to all of the monofluorinated products.[27]

Electroantennographic Test (EAG). The three enantiomerically pure analogues of natural (−)-frontalin, namely (−)-**8**, (−)-**18**, and (−)-**20**, were tested in laboratory on females of *D. micans*, to evaluate their capacity to generate a response by the insects. Adult beetles were collected from infested pine logs and submitted to electroantennographic test (EAG).[29] EAG responses to different doses of the fluorinated frontalins are portrayed in Figure 1. It clearly appears that the axially monofluorinated molecule (−)-**20** elicited strong, dose-dependent EAG responses, significantly higher ($P = 0.01$) than equatorially monofluorinated (−)-**18** and trifluoro-frontalin (−)-**8** at doses of 5 and 50 μg.

(29) (a) De Cristofaro, A.; Rotundo, G.; Germinara, G. S. *IOBC/WPRS Bulletin* **2000**, *23*, 189−194. (b) Den Otter, C. J.; De Cristofaro, A.; Voskamp, K. E.; Rotundo, G. *J. Appl. Ent.* **1996**, *120*, 413−421. (c) Rotundo, G.; Giacometti, R.; Rotundo, A. *Boll. Lab. Ent. Zool. agr. Filippo Silvestri (Portici)* **1984**, *41*, 211−224.

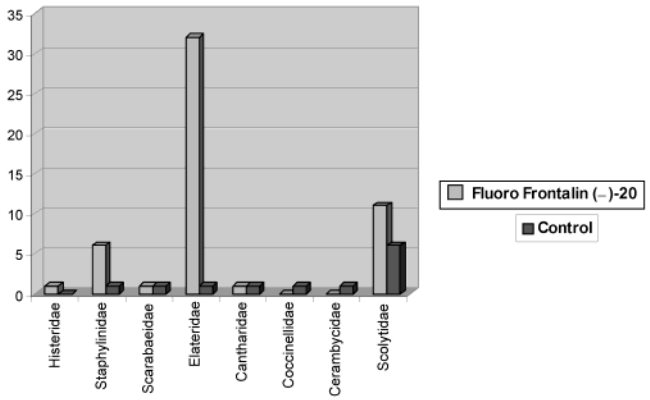


Figure 2. Number of *Coleoptera* beetles caught in traps baited with fluoro-frontalin (−)-**20**.

Field Trials. The active fluoro-frontalin (−)-**20** was submitted also to field trials, to evaluate its attractiveness for *D. micans* population monitoring in forest. Field trials were carried out in a *P. abies* forest near Trento (Italy) where occurrence of *D. micans* was recorded in the last years. Six trapping points, ca. 10 m apart, were set up located at the vertexes of a hexagonal shape. Three groups of traps were baited with 50 μL of (−)-**20**, the other three as controls. Disappointingly, trapping tests yielded no records of *D. micans*. Field surveys, carried out during the same period, showed that *D. micans* was very rare in the area, therefore the absence of the bark beetle in the traps can be regarded as not indicative of the attractiveness of (−)-**20** in field. For this reason, further studies will be necessary to understand the response of wild population of the European *Dendroctonus* species to these compounds. However, the samples collected from the traps made up a collection of other *Coleoptera* belonging to the following eight families (Figure 2): *Histeridae*, *Staphylinidae*, *Scarabaeidae*, *Elateridae*, *Cantharidae*, *Coccinellidae*, *Cerambycidae*, and *Scolytidae*. Scolytids were represented by four species: *Dryocoetes autographus* (Ratzeburg), *Polygraphus grandiclava* (Thomson), *Pityogenes calchographus* (Linnaeus), and *Ips typographus* (Linnaeus). The first two species are linked to died spruces or logs felled on the ground, while the other two are common on living or weakened trees. The number of *P. calchographus* in traps baited with (−)-**20** was higher than in the control traps, while *D. autographus* was absent in the latter ones. Of some interest are the higher captures of specimens belonging to *Histeridae*, *Staphylinidae*, and mostly to *Elateridae*.

In conclusion, three diastereo- and enantiopure monofluoro- and trifluoroanalogues of (−)-frontalin and (+)-trifluoro-frontalin were obtained following the chiral building block approach, choosing (−)- or (+)-toluene menthyl sulfinate as a source of chirality. The overall processes are remarkably stereoselective and allow for the enantiopure targets to be obtained in good chemical yields. Laboratory tests on females of *Dendroctonus micans* showed that the axially fluorinated frontalin-analogue (−)-**20** has very interesting activity, generating a strong electroantennographic stimulus. Field trials were not indicative of the attractiveness of (−)-**20** on *D. micans*, but evidenced some attractive properties for other *Coleoptera*, in particular those belonging to *Elateridae* family.

Experimental Section

General Details. THF was freshly distilled from Na; diisopropylamine was freshly distilled from CaH_2. In all other cases, commercially available reagent-grade solvents were employed without purification. All reactions where an organic solvent was employed were performed under nitrogen atmosphere, after flame-drying of the glass apparatus. Melting points (mp) are uncorrected and were obtained on a capillary apparatus. TLC were run on silica gel 60 F_{254} Merck. Flash chromatographies (FC) were performed with silica gel 60 (60−200 μm, Merck). ^{1}H-, ^{13}C-, and ^{19}F NMR spectra were run at 250, 400, or 500 MHz. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and $\delta_C = 0.00$), while C_6F_6 was used as external standard (δ_F −162.90) for ^{19}F. Gas-chromatographic (GC) analyses were performed on a DB-5 Fused Silica Capillaries column [5% phenyl, 95% methyl silicone; 30 m × 0.25 mm; ∅ = 0.25 μm; carrier gas, He; 12 mL/min; temperature gradient operating: 40 °C(1′)→200 °C(1′); 10 °C/min→285(24′)]. Combustion microanalyses were performed by Redox SNC, Cologno Monzese (Milano).

Synthesis of (3*R*/*S*,*R*$_S$)- and (3*S*/*R*,*S*$_S$)-3-[(4-Methylphenyl)sulfinyl]-1,1,1-trifluoro-hept-6-en-2-ones (2). A solution of (*R*)-**1** (7.21 mmol, 1.50 g) in THF (5 mL) was added dropwise to a solution of LDA (8.65 mmol) in THF (15 mL) at 60 °C. The resulting yellow solution was cooled at −70 °C, and neat ethyl trifluoroacetate (8.65 mmol, 1.23 g) was added dropwise by syringe. After 10 min, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution and the organic layers were extracted with AcOEt. The combined extracts were dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue thus obtained [1:1 mixture of (3*R*/*S*,*R*$_S$)-**2**, $R_f = 0.35$ (*n*-hexane/EtOAc, 3:2)] was used for the next step without further purification.

Enantiomeric (3*S*/*R*,*S*$_S$)-**2** were analogously obtained from (*S*)-**1**.

Reaction of β-Oxo Sulfoxides 2 with Diazomethane. General Procedure. To a solution of crude (3*R*/*S*,*R*$_S$)-**2** (theoretical 7.21 mmol) in methanol (60 mL) cooled at −40 °C was added portion-wise an ethereal solution of diazomethane until persistence of the yellow color (ca. 30 min). Then the excess of CH_2N_2 was destroyed by addition of neat acetic acid at the same temperature until the yellow color of the solution disappeared. The solvent was removed in vacuo, and the residue was purified by FC with *n*-hexane/AcOEt, 6:4, affording the following products: (1′*R*/*S*,2*S*,*R*$_S$)-**3** (ratio 4:1), 1.51 g (76.1%), oil; (1′*S*/*R*,2*R*,*R*$_S$)-**3** (ratio 1.4:1.0), 0.28 g (13.9%), oil; (2*R*,3*S*,*S*$_S$)-**11**, 0.04 g (2.1%), solid; (2*S*/*R*,3*R*,*S*$_S$)-**11** (ratio 1.2:1.0), 0.12 g (5.8%), solid.[31]

2-Trifluoromethyl-2-[1′-(4-methylphenyl)sulfinyl]pent-3′-enyloxirane. (1′*S*,2*S*,*R*$_S$)-**3**: $R_f = 0.35$; ^{1}H NMR ($CDCl_3$) δ 1.5−2.4 (m, 4 H), 2.43 (br. s, 3 H), 2.86 (dq, J = 4.7 and 2.0 Hz, 1 H), 2.90 (dd, J = 7.1 and 5.2 Hz, 1 H), 3.09 (d, J = 4.7 Hz, 1 H), 4.85 and 4.93 (m, 2 H), 5.55 (m, 1 H), 7.33 and 7.51 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −75.64 (br s).

(1′*R*,2*S*,*R*$_S$)-**3**: $R_f = 0.35$; ^{1}H NMR ($CDCl_3$) δ 1.5−2.4 (m, 4 H), 2.43 (br s, 3 H), 3.11 (d, J = 4.6 Hz, 1 H), 3.25 (dd, J = 9.1 and 4.9 Hz, 1 H), 3.53 (dq, J = 4.6 and 1.9 Hz, 1 H), 5.00 and 5.01 (m, 2 H), 5.65 (m, 1 H), 7.33 and 7.51 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −77.68 (br s). Anal. Calcd for $C_{15}H_{17}F_3O_2S$: C, 56.59; H, 5.39; F, 17.92. Found: C, 56.56; H, 5.40; F, 17.95.

(1′*S*,2*R*,*R*$_S$)-**3**: $R_f = 0.40$; ^{1}H NMR ($CDCl_3$) δ 1.3−2.3 (m, 4 H), 2.41 (br s, 3 H), 3.02 (br dd, J = 7.4 and 1.8 Hz, 1 H), 3.50 (m, 2 H), 4.51 and 4.86 (m, 2 H), 5.33 (m, 1 H), 7.32 and 7.51 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −76.74 (br s).

(1′*R*,2*R*,*R*$_S$)-**3**: $R_f = 0.40$; ^{1}H NMR ($CDCl_3$) δ 1.3−2.3 (m, 4 H), 2.44 (br s, 3 H), 2.96 (dd, J = 9.7 and 3.0 Hz, 1 H), 3.28 (d, 1 H, J = 4.7 Hz, 1 H), 3.44 (dq, J = 4.7 and 1.9 Hz, 1 H), 4.77 and 4.80 (m, 2 H), 5.43 (m, 1 H), 7.47 and 7.36 (m, 4 H). ^{19}F NMR ($CDCl_3$) δ −77.10 (br s). Anal. Calcd for $C_{15}H_{17}F_3O_2S$: C, 56.59; H, 5.34; F, 17.92. Found: C, 56.33; H, 5.37; F, 17.90.

2-Trifluoromethyl-3-[(4-methylphenyl)sulfinyl]-hept-6-en-1,2-diol. (2*R*,3*S*,*S*$_S$)-**11**: $R_f = 0.25$; $[\alpha]^{20}_D$ −78.58 (c 0.6, $CHCl_3$); mp (diisopropyl-ether) 85−86 °C; ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.09 and 1.22 (m, 2 H), 1.73 and 1.80 (m, 2 H), 2.47 (br s, 3 H), 3.21 (m, 1 H), 3.73 and 3.80 (d, J = 12.6 Hz, 2H), 4.69 and 4.81 (m, 2 H), 5.31 (m, 1 H), 7.37 and 7.72 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −74.16 (br s); IR (KBr) ν (cm^{-1}) 3498, 3217, 2949, 1639, 1494. MS (DIS EI, 70 eV) *m*/*z* (%) 337 [$(M + H)^+$] (65), 319 (7), 287 (23). Anal. Calcd for $C_{15}H_{19}F_3O_3S$: C, 53.56; H, 5.70; F, 16.96. Found: C, 53.60; H, 5.72; F 16.94.

(2*S*,3*R*,*S*$_S$)-**11**: $R_f = 0.20$; $[\alpha]^{20}_D$ −48.62 (c 0.5, $CHCl_3$); mp (diisopropyl-ether) 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 1.55, 1.73, 1.88, and 1.96 (m, 4 H), 2.45 (br s, 3 H), 2.93 (dd, J = 5.0 and 4.1 Hz, 1 H), 3.40 (br signal, 2 H), 4.07 and 4.26 (d, J = 12.9 Hz, 2 H), 4.67 and 4.77 (m, 2 H), 5.19 (m, 1 H), 7.35 and 7.43 (m, 4 H). ^{19}F NMR ($CDCl_3$) δ −78.18 (br s).

(2*R*,3*R*,*S*$_S$)-**11**: $R_f = 0.20$; $[\alpha]^{20}_D$ −100.81 (c 0.5, $CHCl_3$); mp (diisopropyl-ether) 105−106 °C; ^{1}H NMR ($CDCl_3$ + D_2O) δ 1.15, 1.49, 1.53 and 2.05 (m, 4 H), 2.43 (br s, 3 H), 2.90 (dd, J = 5.4 and 2.2 Hz, 1 H), 3.74 and 4.02 (d, J = 12.4 Hz, 2 H), 4.60 and 4.78 (m, 2 H), 5.28 (m, 1 H), 7.37 and 7.51 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −77.61 (br s). Anal. Calcd for $C_{15}H_{19}F_3O_3S$: C, 53.56; H, 5.70; F 16.96. Found: C, 53.53; H, 5.69; F, 16.97.

When the reaction was carried out at r.t., the rate of the methylene insertion reaction changed from 30 to 5 min. The overall yields in oxiranes **3** decreased to 55.4%. The global amount of diols **11** increased to 40.5% (^{19}F NMR analyses of the crude mixture). The diastereomeric ratios did not change substantially.

Electrophilic Oxirane Opening Reaction. Perchloric acid (425 μL, 5.0 mmol, 70% solution in water) was added to a solution of oxiranes (1′*S*/*R*,2*S*,*R*$_S$)-**3** (4:1 ratio, 318 mg, 1.0 mmol) in a 1:1 mixture of H_2O/THF (2 mL) stirred at 40 °C for 7 days. The reaction mixture was poured into an ice/water bath (2 mL) and extracted with ethyl ether (3 × 2 mL). The combined organics were washed three times with water and, after standard workup, the residue was purified by FC (*n*-hexane/AcOEt, 1:1) affording (2*S*,3*S*,*R*$_S$)-**4** (204 mg, 78%) and 20% of unreacted (1′*R*,2*S*,*R*$_S$)-**3**.

(2*S*,3*S*,*R*$_S$)-**4**: solid; $R_f = 0.30$; $[\alpha]^{20}_D$ +104.18 (c 0.5, $CHCl_3$); mp 108−109 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H, ^{19}F NMR and MS spectra matched those of the enantiomer **11** (see above). Anal. Calcd for $C_{15}H_{19}F_3O_3S$: C, 53.56; H, 5.70; F, 16.96. Found: C, 53.60; H, 5.70; F, 16.98.

Wacker Oxidation. $CuCl_2$ (134 mg, 1.0 mmol) and $PdCl_2$ (54 mg, 0.18 mmol, 59% in weight) were added to 1,2-dimethoxyethane DME (1 mL), and the mixture was stirred for 1 h at room temperature while an air stream was bubbled into the slurry. A solution of sulfinyl diol (2*S*,3*S*,*R*$_S$)-**4** (336 mg, 1.0 mmol) in DME (1.2 mL) was added slowly to the mixture under stirring. The stirring was continued overnight, then the reaction mixture was diluted with water and extracted with diethyl ether. The aqueous layer was acidified with HCl 0.5 N (1.0 mL) to pH 2, left to stand 2 h and extracted with diethyl ether. Standard workup and FC purification allowed the isolation of the diastereomerically pure **6** (240 mg, 72%).

5-Methyl-1-trifluoromethyl-2-[(methylphenyl)sulfinyl]-6,8-dioxabicyclo[3.2.1]octane. (1*S*,2*S*,5*R*,*R*$_S$)-**6**: $R_f = 0.35$ (C_6H_6/CH_3COCH_3, 9:1); $[\alpha]^{20}_D$ +191.13 (c 1.0, $CHCl_3$); mp 158−159 °C (diisopropyl ether); ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 3 H),1.69 (br ddd, J = 13.2, 6.0, and 1.3 Hz, 1 H), 1.95 (dddd, J = 14.7, 11.7, 6.1, and 6.0 Hz, 1 H), 2.19 (ddd, J = 13.2, 11.7, and 5.9 Hz, 1 H), 2.37 (br dd, J = 14.7, and 5.9 Hz, 1 H), 2.41 (br s, 3 H), 2.87 (br d, J = 6.1 Hz, 1 H), 3.98 (dq, J = 7.9 and 1.3 Hz, 1 H), 4.08 (d, J = 7.9 Hz, 1 H), 7.33 and 7.48 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −74.11 (br s); ^{13}C NMR ($CDCl_3$) δ 15.2, 21.2, 23.6, 33.2, 62.0, 70.0 ($J_{C,F}$ = 3 Hz), 82.7 ($J_{C,F}$ = 31 Hz); 112.6, 123.63 ($J_{C,F}$ = 283 Hz), 123.64, 130.0, 141.2, 141.4; IR (KBr) (cm^{-1}) ν 3434, 2938, 1492. MS (DIS EI, 70 eV) *m*/*z* (%) 335 [$(M + H)^+$] (35), 318 [$(M + H - OH)^{\bullet+}$] (3), 195 (100). Anal. Calcd for $C_{15}H_{17}F_3O_3S$: C, 53.88; H, 5.13; F, 17.06. Found: C, 53.90; H, 5.12; F, 17.08.

(30) Van Der Pers, J. N. C. *Ent. Exp. Appl.* **1981**, *30*, 181−192.

(31) Analytical samples of diastereo- and enantiomerically pure diols **11** were obtained by benzoylation, chromatographic separation, and finally alkaline saponification.

(2*S*,3*S*,*R*$_S$)-2-Hydroxy-2-trifluoromethyl-3-[(4-methylphenyl-)sulfinyl]6-oxo-eptan-1-ol (**5**) could also be isolated (70 mg, 20%): oil; R_f = 0.20 (C_6H_6/CH_3COCH_3, 9:1); $[\alpha]^{20}_D$ +48.63 (c 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.63, 1.81, 1.97, and 2.25 (m, 4 H), 1.80 (s, 3H), 2.45 (br s, 3 H), 2.98 (m, 1 H), 3.70 (br signal, 2 H), 3.84 and 4.09 (d, J = 12.5 Hz, 2 H), 7.36 and 7.51 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −77.28 (br s); ^{13}C NMR ($CDCl_3$) (selected signal) δ 207.67. MS (DIS EI, 70 eV) *m*/*z* (%) 353 [(M + H)$^+$] (100), 335 [(M + H − H_2O)$^+$] (10), 213 (7). After 1 h at room temperature this intermediate spontaneously cyclized to the bicyclic structure **6**.

Deoxygenation Reaction. A solution of trifluoroacetic anhydride (3.0 mmol) in acetone (2 mL) was added dropwise to a mixture of sulfinyl frontalin **6** (1.0 mmol, 334 mg) and NaI (2.0 mmol, 300 mg) in acetone (10 mL) stirred at −40 °C under nitrogen. After 10 min, a saturated solution of sodium sulfite and $NaHCO_3$ was added. The mixture was extracted with diethyl ether and the extract dried with anhydrous sodium sulfate. After filtration, the solvent was removed in vacuo. FC purification allowed the isolation of pure **7** (293 mg, 92%).

5-Methyl-1-trifluoromethyl-2-[(methylphenyl)sulfenyl]-6,8-dioxabicyclo[3.2.1]octane. (1*S*,2*S*,5*R*)-**7**: R_f = 0.35 (*n*-hexane/EtOAc, 9:1); $[\alpha]^{20}_D$ +92.80 (c 0.4, $CHCl_3$); mp 106−108 °C (diisopropyl ether); ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3H), 1.62, 1.87, 2.15 and 2.21 (m, 4 H), 2.33 (br s, 3H), 3.34 (br dd, J = 3.2 and 1.8 Hz, 1 H), 4.03 (dq, J = 7.9 and 1.3 Hz, 1 H), 4.12 (d, J = 7.9 Hz, 1 H), 7.13 and 7.35 (m, 4 H); ^{19}F NMR ($CDCl_3$) δ −74.54 (br s). IR (KBr) ν (cm^{-1}) 3434, 2958, 2926, 1493; MS (DIS EI, 70 eV) *m*/*z* (%) 318 [M$^{\bullet+}$] (100), 258 (3). Anal. Calcd for $C_{15}H_{17}F_3O_2S$: C, 56.59; H, 5.39; F, 17.92. Found: C, 56.60; H, 5.40; F, 17.90. A pure sample of the compound was utilized for checking the enantiopurity by chiral HPLC (Chiralcel OD column): e.e. >98%, t_r = 8.25 min (*n*-hexane/diisopropyl ether 4:1, 0.5 mL/min).

Reaction of (1*R*,2*R*,5*S*,*S*$_S$)-**6** afforded (1*R*,2*R*,5*S*)-**7** (92%): R_f = 0.30 (*n*-hexane/EtOAc, 9:1); $[\alpha]^{20}_D$ −91.33 (c 0.4, $CHCl_3$); the other physical and spectral properties matched those of the enantiomer. A pure sample of the compound was employed for the checking of the enantiopurity by chiral HPLC (Chiralcel OD): e.e. >98%, t_r = 7.80 min (*n*-hexane/diisopropyl ether 4:1, 0.5 mL/min).

Reductive Desulfenylation Reaction. Synthesis of Trifluoro-frontalin 8. Raney-Nickel (ca. 0.9 g) was added to a solution of (1*S*,2*S*,5*R*)-**7** (318 mg, 1.0 mmol) in 1,2-dihydroxyethane (3 mL), and the black slurry was stirred under hydrogen atmosphere at 90 °C for 1 h. When the substrate was completely consumed (TLC monitoring in *n*-hexane/diethyl ether 9:1), the black powder was filtered off and the filtrate was submitted to distillation under atmospheric pressure, affording (1*S*,5*R*)-**8** (176 mg, 90%) as a clear oil.

5-Methyl-1-trifluoromethyl-6,8-dioxabicyclo[3.2.1]-octane. (1*S*,5*R*)-**8**: $[\alpha]^{20}_D$ −42.50 (*c* = 2.0, $CDCl_3$); $[\alpha]^{20}_D$ −35.0 (c 2.0, Et_2O); bp 90 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 3H), 1.6−2.0 (m, 6 H), 3.92 (br dd, J = 7.2 and 1.4 Hz, 1 H) and 4.02 (br d, J = 7.2 Hz, 1 H); ^{19}F NMR ($CDCl_3$) δ −80.85 (br s); ^{13}C NMR ($CDCl_3$) δ 16.6, 24.0, 26.1, 34.4, 68.6, 81.4 ($J_{C,F}$ = 31.5 Hz), 110.7, 123.9 ($J_{C,F}$ = 280.5 Hz); MS (GC EI); *m*/*z* (%) 196 [M$^{\bullet+}$] (30), 168 (13), 166 (12), 147 (9). GC/MS, t_r, *m*/*z* (%) 5.12 min, 196 (95) [M$^{+\bullet}$, (1*S*,5*R*)-**8**].

Reaction of (1*R*,2*R*,5*S*)-**7** afforded (1*R*,5*S*)-**8** (87%): $[\alpha]^{20}_D$ +40.26 (*c* = 1.4, $CDCl_3$); $[\alpha]^{20}_D$ +34.12 (c 1.4, Et_2O); the other physical and spectral properties matched those of the enantiomer.

Synthesis of (3*R*,*S*$_S$)- and (3*S*,*S*$_S$)-13. A solution of enantiopure (*S*)-**12** (2.0 g, 9.35 mmol) in THF (20 mL) was added dropwise to a cooled (- 60 °C) solution of LDA (20.56 mmol) in THF (20 mL). A neat mixture of 1-bromo-4-butene (0.85 mL, 8.5 mmol) and HMPA (2 mL) was added dropwise to the yellow solution kept under stirring at −70 °C, and after 5 min the reaction was quenched by adding a NH_4Cl saturated solution. The pH was adjusted to 3 by adding diluted aqueous HCl, the organics were extracted with diethyl ether (3 × 50 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness in vacuo. After FC purification (*n*-hexane/ethyl acetate = 7:3) of the residue, the following compounds were isolated: starting (*S*)-**12** (182 mg, 0.85 mmol) and a ca. 1:1 mixture of ketones **13/19** (1.94 g, 85% global yields). After repeated FC purifications in diethyl ether/cyclohexane = 1:1, the two diastereopure ketones were obtained.

(3*R*,*S*$_S$)-1-[(4-Methylphenyl)sulfinyl]-3-fluoro-hept-6-en-2-one 13: R_f = 0.35 (diethyl ether/cyclohexane = 7:3); $[\alpha]^{20}_D$ −174.37 (c 0.62, $CHCl_3$); mp 42−43 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.85, 1.95, 2.18 and 2.22 (m, 4H), 2.43 (br s, 3H), 4.03 (dd, J = 14.6 and 3.3 Hz, 1H), 4.08 (dd, J = 14.6 and 3.2 Hz, 1H), 4.73 (ddd, J = 50.0, 7.4 and 5.4 Hz, 1H), 5.03 and 5.06 (m, 2H), 5.75 (m, 1H), 7.35 and 7.57 (m, 4H). ^{19}F NMR ($CDCl_3$) δ −192.8 (br ddd, J = 50.0, 26.4, and 23.2 Hz); IR (KBr) ν (cm^{-1}) 3423, 1726, 1494; MS (DIS EI, 70 eV) *m*/*z* (%) 269 [(M + H)$^+$] (58), 268 [M$^{+\bullet}$] (38), 252 (36), 214 (58). Anal. Calcd for $C_{14}H_{17}FO_2S$: C, 62.66; H, 6.39; F, 7.09. Found: C, 62.62; H, 6.40; F, 7.10.

(3*S*,*S*$_S$)-**19**: R_f = 0.33 (diethyl ether/cyclohexane = 7:3); $[\alpha]^{20}_D$ −204.77 (c 0.63, $CHCl_3$); mp 51−52 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.75, 1.88, 2.13, and 2.18 (m, 4H), 2.42 (br s, 3H), 3.95 (dd, J = 14.6 and 2.9 Hz, 1H), 4.18 (dd, J = 14.6 and 3.3 Hz, 1H), 4.71 (ddd, J = 49.5, 8.4 and 4.2 Hz, 1H), 5.01 and 5.03 (m, 2H), 5.72 (m, 1H), 7.35 and 7.57 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −193.12 (br ddd, J = 49.5, 31.0 and 21.0 Hz); IR (KBr) ν (cm^{-1}) 3430, 2953, 2918, 2894, 1724, 1644; MS (DIS EI, 70 eV) *m*/*z* (%) 269 [(M + H)$^+$] (3), 268 [M$^{+\bullet}$] (5), 246 (6), 214 (20). Anal. Calcd for $C_{14}H_{17}FO_2S$: C, 62,66; H, 6.39; F, 7.09. Found: C, 62.68; H, 6.36; F, 7.10.

Reaction of β-Oxo Sulfoxides 13 with Diazomethane. The general procedure used for preparing trifluoro-derivatives **3** at 0 °C was used (see above). Starting from (3*R*,*S*$_S$)-**13**, the following main compounds were isolated: oxiranes (1′*R*,2*R*/*S*,*S*$_S$)-**14** [(2*R*)/(2*S*) = 6.5:1.0] (750 mg, 79% overall yields); an unresolvable mixture of diols (2*R*/*S*,3*R*,*R*/*S*$_S$)-**15** (140 mg, 14% overall yields). After repeated FC in cyclohexane/ethyl acetate 6:4, the most abundant oxirane [(1′*R*,2*R*,*S*$_S$)-**14**] was isolated in diastereopure form. The minor one (1′*R*,2*S*,*S*$_S$)-**14** was characterized only through NMR.

Starting from (3*S*,*S*$_S$)-**19**, the following main compounds were isolated: oxiranes (1′*S*,2*R*/*S*,*S*$_S$)-**14** [(2*R*)/(2*S*) = 12:1] (760 mg, 80% overall yields) and an unresolvable mixture of diols (2*R*/*S*,3*S*,*R*/*S*$_S$)-**15** (120 mg, 12% overall yields). After repeated FC with the same eluent, the most abundant oxirane [(1′*S*,2*R*,*S*$_S$)-**14**] was isolated in diastereopure form. The minor one [(1′*S*,2*S*,*S*$_S$)-**2**] was charachterized only through ^{19}F NMR.

2-{[(4-Methylphenyl)sulfinyl]methyl}-2-(1′-fluoro)pent-3′-enyloxirane. (1′*R*,2*R*,*S*$_S$)-**14**: $[\alpha]^{20}_D$ −197.51 (c 0.92, $CHCl_3$); yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.70, 1.80, 2.15, and 2.25 (m, 4H), 2.43 (br s, 3H), 2.91 (d, J = 4.0 Hz, 1H), 3.03 and 3.29 (d, J = 14.5 Hz, 2H), 3.33 (dd, J = 4.8 and 4.0 Hz, 1H), 4.35 (ddd, J = 48.0, 9.8, and 3.7 Hz, 1H), 5.03 and 5.05 (m, 2H), 5.73 (m, 1H), 7.33 and 7.55 (m, 4H). ^{19}F NMR ($CDCl_3$) δ −191.45 (dddd, J = 48.0, 34.6, 15.2, and 4.8 Hz). IR (Neat) ν (cm^{-1}) 2924, 1642, 1495; MS (DIS EI, 70 eV) *m*/*z* (%) 283 [(M + H)$^+$] (4), 282 [M$^{+\bullet}$] (5), 265 (22). Anal. Calcd for $C_{15}H_{19}FO_2S$: C, 63.80; H, 6.78; F, 6.73. Found: C, 63.85; H, 6.80; F, 6.71.

(1′*R*,2*S*,*S*$_S$)-**14**: ^{1}H NMR ($CDCl_3$) δ 1.70, 1.80, 2.15, and 2.25 (m, 4H), 2.43 (br s, 3H), 2.84 (br d, J = 4.2 Hz, 1H), 2.85 and 3.53 (br d, J = 13.8 Hz, 2H), 3.10 (dd, J = 4.2 and 1.9 Hz, 1H), 4.38 (ddd, J = 48.0, 10.0, and 3.0 Hz, 3H), 5.01 and 5.05 (m, 2H), 5.88 (m, 1H), 7.34 and 7.57 (m, 4H). ^{19}F NMR ($CDCl_3$) δ −191.88 (br ddd, J = 48.0, 38.0, and 15.0 Hz).

(1′*S*,2*R*,*S*$_S$)-**14**: $[\alpha]^{20}_D$ −191.44 (c 0.56, $CHCl_3$); mp 57−58 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.5−2.4 (m, 4H), 2.43 (br s, 3H), 2.75 and 3.37 (br d, J = 13.8 Hz, 2H), 2.92 (br d, J = 4.5 Hz, 1H), 3.07 (dd, J = 4.5 and 2.2 Hz, 1H), 4.86 (ddd, J = 48.2, 9.8, and 2.9 Hz, 1H), 5.07 and 5.09 (m, 2H), 5.80 (m, 2H), 7.35 and 7.55 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −192.88 (br ddd, J = 48.2, 37.8 and 15.0 Hz); IR (KBr) ν (cm^{-1}) 2921, 1643, 1494; MS (DIS EI, 70 eV) *m*/*z* (%) 283 [(M + H)$^+$] (2), 282 [M$^{+\bullet}$] (5), 265 (8). Anal. Calcd for $C_{15}H_{19}FO_2S$: C, 63,80; H, 6.78; F, 6.73. Found: C, 63.78; H, 6.77; F, 6.75.

(1′*S*,2*S*,*S*$_S$)-**14**: ^{19}F NMR ($CDCl_3$) δ −190.45 (dddd, J = 48.5, 35.0, 15.0, and 5.0 Hz).

Electrophilic Oxirane Opening Reaction. The general procedure used for preparing trifluoro-derivatives **4** was applied on oxiranes **14**. The reactions lasted 5 days at 40 °C. FC purification with *n*-hexane/ethyl acetate, 3:7 allowed the isolation of the pure compounds **15**.

Starting from (1′*R*,2*R*,S_S)-**14** (700 mg, 2.48 mmol), the diol (2*R*,3*R*,S_S)-**15** (560 mg, 75% yield) was isolated. Some of the starting compound **14** (130 mg, 20%) was recovered unreacted.

2-{[(4-Methylphenyl)sulfinyl]methyl}-3-fluoro-hept-6-en-1,2-diol (2*R*,3*R*,S_S)-**15**: $[\alpha]^{20}_D$ −164.80 (c 0.53, $CHCl_3$); mp 79−80 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.70, 1.85, 2.18, and 2.31 (m, 4H), 2.42 (br s, 3H), 2.91 (dd, J = 13.8 and 1.0 Hz, 1H), 3.16 (dd, J = 13.8 and 1.2 Hz, 1H), 3.36 (br signal, 2H), 3.67 (dd, J = 13.0 and 1.2 Hz, 1H), 3.74 (dd, J = 13.0 and 1.5 Hz, 1H), 4.66 (ddd, J = 48.5, 9.5, and 3.2 Hz, 1H), 5.02 and 5.07 (m, 2H), 5.79 (m, 1H), 7.36 and 7.56 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −194.20 (br ddd, J = 48.5, 38.8, and 18.0 Hz); IR (KBr) ν (cm^{-1}) 3415, 2927, 1641, 1494; MS (DIS EI, 70 eV) *m*/*z* (%) 301 [(M + H)$^+$] (75), 283 (18), 269 (14). Anal. Calcd for $C_{15}H_{21}FO_3S$: C, 59.98; H, 7.05; F, 6.32. Found: C, 60.01; H, 7.06; F, 6.30.

Starting from (1′*S*,2*R*,S_S)-**14** (702 mg), the diol (2*S*,3*S*,S_S)-**15** (575 mg, 77% yield) was isolated. Some of the starting compound **14** (100 mg, 15%) was recovered unreacted.

(2*R*,3*S*,S_S)-**15**: $[\alpha]^{20}_D$ −152.43 (c 0.57, $CHCl_3$); mp 57−60 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.75, 1.85, 2.17, and 2.30 (m, 4H), 2.42 (br s, 3H), 2.91 (br d, J = 14.0 Hz, 1H), 3.14 (dd, J = 14.0 and 1.2 Hz, 1H), 3.70 (br d, J = 12.5 Hz, 1H), 3.74 (br signal, 2H), 3.88 (br d, J = 12.5 Hz, 1H), 4.43 (ddd, J = 48.0, 9.2, and 3.5 Hz, 1H), 5.01 and 5.06 (m, 2H), 5.79 (m, 1H), 7.36 and 7.57 (m, 4H). ^{19}F NMR ($CDCl_3$) δ −196.20 (br ddd, J = 48.0, 36.0, and 21.0 Hz); IR (KBr) ν (cm^{-1}) 3396, 2926, 1639, 1495; MS (DIS EI, 70 eV) *m*/*z* (%) 301 [(M + H)$^+$] (20), 283 (19), 269 (16), 213 (5). Anal. Calcd for $C_{15}H_{21}FO_3S$: C, 59.98; H, 7.05; F, 6.32. Found: C, 60.00; H, 7.02; F, 6.31.

Wacker Oxidation. $CuCl_2$ (333 mg, 2.49 mmol) and $PdCl_2$ (249 mg, 1.41 mmol, 59% in weight) were added to 1,2-dimethoxyethane (DME 2 mL), and the mixture was stirred for 1 h at room temperature while an air stream was bubbled into the slurry. A solution of sulfinyl diol **15** (500 mg, 1.67 mmol) in DME (2 mL) was added slowly to the vigorously stirred mixture. The stirring was continued overnight, then the reaction mixture was diluted with water and extracted with ether (3 × 2 mL). The aqueous layer was acidified with dilute HCl (0.5 N, 1.0 mL) to pH 2, left 2 h at room temperature, and extracted with diethyl ether (3 × 5 mL). The combined organics were washed with water, dried (Na_2SO_4), and concentrated in vacuo. FC purification allowed the isolation of the corresponding diastereomerically pure compound **16**.

Starting from (2*R*,3*R*,S_S)-**15**, (1*R*,2*R*,5*R*,S_S)-**16** was obtained (400 mg, 1.34 mmol) in 80% yield (FC with chloroform/ethyl acetate, 7:3).

(1*R*,2*R*,5*R*,S_S)-**16**: $[\alpha]^{20}_D$ −163.33 (c 0.32, $CHCl_3$); mp 104−106 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 3H), 1.7−2.2 (m, 4H), 2.42 (br s, 3 H), 3.02 (dd, J = 14.4 and 1.0 Hz, 1H), 3.26 (dd, J = 14.4 and 2.1 Hz, 1H), 4.10 (br d, J = 8.1 Hz, 1H), 4.21 (dd, J = 8.1 and 1.8 Hz, 1H), 4.65 (dddd, J = 49.5, 9.7, 6.6, and 1.5 Hz, 1H), 7.34 and 7.57 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −187.64 (br dd, J = 49.5 and 16.0 Hz); ^{13}C NMR ($CDCl_3$) δ 21.3, 23.1 ($J_{C,F}$ = 4 Hz), 24.0 ($J_{C,F}$ = 20 Hz), 35.6 ($J_{C,F}$ = 7.5 Hz), 61.5, 68.3 ($J_{C,F}$ = 2 Hz), 80.5 ($J_{C,F}$ = 22.5 Hz), 89.6 ($J_{C,F}$ = 184 Hz), 108.8, 124.0, 130.1, 141.5, 141.9; IR (KBr) ν (cm^{-1}) 3436, 2962, 1635, 1494; MS (DIS EI, 70 eV) *m*/*z* (%) 299 [(M + H)$^+$] (1), 298 [M$^{+\bullet}$] (1), 236 (2), 159 (5). Anal. Calcd for $C_{15}H_{19}FO_3S$: C, 60.38; H, 6.42; F, 16.10. Found: C, 60.41; H, 6.40; F, 16.07.

Starting from (2*R*,3*S*,S_S)-**15**, (1*R*,2*S*,5*R*,S_S)-**16** was obtained (450 mg, 1.51 mmol) in 90% yield (FC with chloroform/ethyl acetate, 7:3): $[\alpha]^{20}_D$ −168.56 (c 0.50, $CHCl_3$); mp 98−9 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 3H), 1.68, 1.91, 1.98, and 2.16 (m, 4H), 2.42 (br s, 3 H), 3.13 (br d, J = 14.4 Hz, 1H), 3.26 (br dd, J = 14.4 Hz, 1H), 3.94 (d, J = 8.4 Hz, 1H), 4.29 (dd, J = 8.4 and 7.0 Hz, 1H), 4.48 (ddd, J = 48.8, 3.3, and 1.7 Hz, 1H), 7.34 and 7.56 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −192.35 (dddd, J = 48.8, 45.8, 18.0, and 7.2 Hz). ^{13}C NMR ($CDCl_3$) δ 21.4, 23.4 ($J_{C,F}$ = 22 Hz); 24.0, 30.9, 59.6, 68.9 ($J_{C,F}$ = 3 Hz), 81.4 ($J_{C,F}$ = 18 Hz), 87.2 ($J_{C,F}$ = 181 Hz), 108.7, 123.9, 130.1, 141.1, 141.8; IR (KBr) ν (cm^{-1}) 3440, 2933, 1493; MS (DIS EI, 70 eV) *m*/*z* (%) 299 [(M + H)$^+$] (1), 298 [M$^{+\bullet}$] (1), 236 (18). Anal. Calcd for $C_{15}H_{19}FO_3S$ (298): C, 60.38; H, 6.42; F, 16.10. Found: C, 60.35; H, 6.44; F, 16.09.

Deoxygenation Reaction. The general procedure used for preparing trifluoro-derivatives **7** was applied on **16** (400 mg, 1.34 mmol). FC purification (diisopropyl ether/*n*-hexane 1:1) allowed the isolation of pure **17** (358 mg, 1.27 mmol) (95%).

2-{[(4-Methylphenyl)sulfenyl]methyl}-5-methyl-6,8-dioxabicyclo[3.2.1]octane. (1*R*,2*R*,5*R*)-**17**: $[\alpha]^{20}_D$ −14.75 (c 0.66, $CHCl_3$); mp 35−37 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 3H), 1.7−2.2 (m, 4H), 2.31 (br s, 3 H), 3.23 (dd, J = 13.7 and 1.8 Hz, 1H), 3.34 (dd, J = 13.7 and 1.2 Hz, 1H), 3.72 (br d, J = 7.9 Hz, 1H), 4.17 (dd, J = 7.9 and 1.8 Hz, 1H), 4.80 (dddd, J = 49.6, 9.6, 6.8 and 1.3 Hz, 1H), 7.10 and 7.33 (m, 4H). ^{19}F NMR ($CDCl_3$) δ −187.63 (br dd, J = 49.6 and 17.0 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 23.2 ($J_{C,F}$ = 3.5 Hz), 24.1 ($J_{C,F}$ = 19.5 Hz), 35.5 ($J_{C,F}$ = 7.5 Hz), 37.3, 69.0, 82.0 ($J_{C,F}$ = 22.5 Hz), 88.0 ($J_{C,F}$ = 183 Hz), 108.0, 129.6, 130.2, 132.8, 136.3; IR (KBr) ν (cm^{-1}) 2935, 1494, 1440, 1390; MS (DIS EI, 70 eV) *m*/*z* (%) 282 [M$^{+\bullet}$] (55), 207 (6), 193 (5). Anal. Calcd for $C_{15}H_{19}FO_2S$ (282): C, 63.81; H, 6.79; F, 6.73. Found: C, 63.80; H, 6.82; F, 6.70.

Starting from (1*R*,2*S*,5*R*,S_S)-**16**, the compound (1*R*,2*S*,5*R*)-**17** was obtained (350 mg, 1.23 mmol) in 92% yield.

(1*R*,2*S*,5*R*)-**17**: $[\alpha]^{20}_D$ −24.10 (c 0.50, $CHCl_3$); mp 54−55 °C (diisopropyl ether/*n*-hexane 1:1); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3H), 1.61, 1.87, 1.89 and 2.04 (m, 4H), 2.32 (br s, 3 H), 3.13 (br d, J = 13.4 Hz, 1H), 3.47 (dd, J = 8.4 and 7.0 Hz, 1H), 3.48 (dd, J = 13.4 and 1.0 Hz, 1H), 3.70 (d, J = 8.4 Hz, 1H), 4.69 (ddd, J = 48.4, 3.0 and 2.4 Hz, 1H), 7.11 and 7.31 (m, 4H); ^{19}F NMR ($CDCl_3$) δ −193.16 (dddd, J = 48.4, 35.8, 27.2 and 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.0, 23.5 ($J_{C,F}$ = 22.5 Hz), 24.1, 31.1, 36.6 ($J_{C,F}$ = 3.5 Hz), 70.4 ($J_{C,F}$ = 4 Hz), 83.4 ($J_{C,F}$ = 18 Hz), 85.1 ($J_{C,F}$ = 181.5 Hz), 108.6, 129.8, 130.7, 131.6, 137.0; IR (KBr) ν (cm^{-1}) 2940, 2891, 1494, 1447; MS (DIS EI, 70 eV) *m*/*z* (%) 282 [M$^{+\bullet}$] (23), 211 (4), 207 (5). Anal. Calcd for $C_{15}H_{19}FO_2S$: C, 63.81; H, 6.79; F, 6.73. Found: C, 63.83; H, 6.78; F, 6.75.

Reductive Desulfenylation Reaction. The general procedure used for preparing trifluoro-frontalines **8** was applied on (1*R*,2*R*,5*R*)-**17** (358 mg, 1.27 mmol). After distillation (oven temperature 115 °C), fluorofrontalin (1*R*,2*R*,5*R*)-**18** (176 mg, 1.1 mmol) was isolated in 88% yield as a clear oil.

1,5-Dimethyl-2-fluoro-6,8-dioxabicyclo[3.2.1]octane (1*R*,2*R*,5*R*)-**18**: $[\alpha]^{20}_D$ −31.85 (c 2.7, $CDCl_3$); bp ca. 105 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 and 1.45 (s, 6H), 1.6−2.2 (m, 4H), 3.46 (dd, J = 7.5 and 1.1 Hz, 1H), 4.17 (dd, J = 7.5 and 1.5 Hz, 1H), 4.43 (dddd, J = 49.2, 9.2, 7.0, and 1.5 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −186.83 (br dd, J = 49.2 and 16.5 Hz); ^{13}C NMR ($CDCl_3$) δ 19.0, 23.5 ($J_{C,F}$ = 3.5 Hz), 24.4 ($J_{C,F}$ = 20 Hz), 35.9 ($J_{C,F}$ = 7.5 Hz), 70.7 ($J_{C,F}$ = 2 Hz), 80.3 ($J_{C,F}$ = 22.5 Hz), 90.8 ($J_{C,F}$ = 182.5 Hz), 107.4 ($J_{C,F}$ = 2 Hz); IR (film) ν (cm^{-1}) 2940, 2889, 1719, 1458; MS (GC EI) *m*/*z* (%) 160 [M$^{+\bullet}$] (28), 130 (25), 118 (70), 114 (45); GC/MS, t_r, *m*/*z* (%) 7.16 min, 160 (99) [M$^{+\bullet}$, (1*R*,2*R*,5*R*)-**18**].

From (1*R*,2*S*,5*R*)-**17** (350 mg, 1.23 mmol), keeping the oven temperature at 115 °C, (1*R*,2*S*,5*R*)-**20** (180 mg, 1.13 mmol) was isolated in 90% yield as a clear oil.

(1*R*,2*S*,5*R*)-**20**: $[\alpha]^{20}_D$ −39.48 (c 1.5, $CDCl_3$); bp ca. 105 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (d, J = 0.7, 3H), 1.48 (s, 3H), 1.5−2.2 (m, 4H), 3.50 (dd, J = 7.7 and 7.0 Hz, 1H), 3.78 (br d, J = 7.0 Hz, 1H), 4.30 (ddd, J = 48.2, 3.0, and 1.8 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −191.30 (dddd, J = 48.2, 40.8, 20.5 and 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 18.3 ($J_{C,F}$ = 4 Hz), 23.9 ($J_{C,F}$ = 22.5 Hz), 24.3, 30.9, 72.0 ($J_{C,F}$ = 4 Hz), 80.3 ($J_{C,F}$ = 18.5 Hz), 88.3 ($J_{C,F}$ = 181.5 Hz), 108.4; IR ($CDCl_3$ solution) ν (cm^{-1}) 2940, 2887, 1645, 1603; MS (DIS EI, 70 eV) *m*/*z* (%) 160 [M$^{+\bullet}$] (5), 130 (5), 118 (18), 98 (19); GC/MS, t_r, *m*/*z* (%): 7.18 min, 160 (95) [M$^{+\bullet}$, (1*R*,2*S*,5*R*)-**20**].

Electroantennographic Tests (EAG). *D. micans* infested pine logs were collected on Faverghera Mount (1550 m above sea level), province of Belluno (Veneto, Italy), and kept in a climatic chamber at 18 ± 2 °C, 65 ± 5 r.h., and light regime L16:D8. Adult beetles were collected daily and used after 48 h for the tests. The EAG technique was similar to that used in previous studies.[29] Antennae were excised from females. The base of the antenna was inserted in the indifferent electrode and the recording electrode (ø 5−8 μm) put in contact with the terminal antennal club segment. Compounds (−)-**8**, (−)-**18**, and (−)-**20** were tested using 10 μL of hexane solutions (from 0.05 to 50 μg/μl) absorbed on a piece of filter paper (2.0 cm^2) and inserted into a Pasteur pipet which served as an odor cartridge. The antenna was continuously flushed with an active carbon-filtered and humidified air flow at room temperature (23 °C). The air flowing at 0.5 m/s through a stainless steel tube (i.d. 8 mm). During 0.1 s, 2.5 cm^3 of vapor from an odor cartridge was added. Intervals between stimuli were 1 min. A reference stimulus (100 ng of *cis*-3-hexen-1-ol) was applied to correct for changes in EAG response one minute before each series of stimulations with the same dose of chemicals. EAG responses recorded from 5 different antennae were normalized according to Van Der Pers[30] and dose-response curve calculated.

Field Trials. Field trials were carried out in a *P. abies* forest in Val di Fiemme (province of Trento, Trentino Alto Adige, Italy) where *D. micans* attacks were observed in the last years on small groups of mature trees. In this area, at the end of June 2001, six trapping points, ca. 10 m apart, were set up located at vertexes of an hexagonal shape. At each point a group of three Theyson traps were hung to stakes hammered in the ground. Three groups of traps were baited with 50 μL (−)-**20** of frontalin fluoroanalogues, the other three as control. Trap control and dispenser change were assessed in 17/7/01, 31/7/01, 14/8/01, 28/8/01, and 11/9/01. All beetles caught in the traps were collected and examined.

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