Synthesis of 2-Fluoro Analogues of Frontalin

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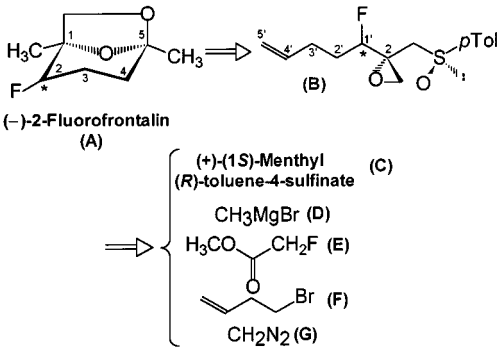
The synthesis of enantiomerically and diastereomerically pure (–)-(1*R*,2*R*,5*R*)- and (–)-(1*R*,2*S*,5*R*)-2-fluoro frontalin **(7)** starting from (+)-(1*S*)-menthyl-(*R*)-toluene-4-sulfinate, methylmagnesium bromide, methyl fluoroacetate, 4-pentenyl bromide and diazomethane is described. The absolute stereochemistry was unambiguously determined by X-ray analysis of (+)-(1*S*,2*R*,5*S*,R_S)-**5**, an intermediate in the synthesis of the enantiomeric (+)-(1*S*,2*R*,5*S*)-2-fluoro frontalin **(7)**.

Introduction

(–)-(1*S*,5*R*)-Frontalin, (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]-octane) is the bioactive component of the aggregation pheromone of pine beetles of the *Dendroctonus* family.[1] The first synthesis of the enantio- and diastereopure fluoro-analogues of frontalin was recently published.[2] In that case, each hydrogen atom of the methyl group at C-1 of the (–)-frontalin skeleton was replaced by a fluorine. We now report the preparation of the first corresponding enantio- and diastereopure 2-fluoro analogues, in which one of the two hydrogen atoms of the methylenic carbon at C-2 of the six-membered ring of the bicycle structure of frontalin is selectively replaced by one atom of fluorine, following the synthetic chiral building block approach (Scheme 1).[3]



Scheme 1. Retrosynthetic scheme

As shown in the retrosynthetic scheme, the key intermediate of the global process is the chiral, diastereo- and enantiopure α-fluorosubstituted oxirane **B** whose framework was assembled following a pattern already employed for the synthesis of different selectively fluorinated biologically relevant compounds,[4] and whose stereochemistry is strictly dependent on that of the chiral auxiliary.[5] As the C-1 stereocenter of the final frontalin **A** corresponds to the C-2 stereocenter of **B**, the choice of the appropriate source of chirality, (+)-(1*S*)-menthyl-(*R*)-toluene-4-sulfinate (**C**) or the corresponding (–)-enantiomer, drives the synthesis towards (–)-(1*R*,5*R*)- or (+)-(1*S*,5*S*)-2-fluorofrontalin **A**, respectively.

Methyl magnesium bromide **D** furnished the methylene group α to the sulfoxide of **B** and fluoroacetic acid methyl ester **E** was the source of the "CHF" grouping on the six-membered ring of frontalin **A**. The 4-pentenyl bromide **F** furnished the C-2′–C-5′ carbons of the intermediate **B** (C-3, C-4 and the quaternary C-5 of **A**). Diazomethane **G** gave the methylene of the epoxide ring of **B**. The fluorine atom at C-2 of **A** can be equatorial (2*R*) or axial (2*S*) depending on the C-1′ stereocenter of **B**.

Results and Discussion

A nucleophilic substitution performed on (+)-(1*S*)-menthyl-(*R*)-toluene-4-sulfinate by methylmagnesium bromide gave (S_S)-methyl-(4-methylphenyl)sulfoxide whose lithium anion, acylated by methylfluoroacetate, gave (S_S)-3-fluoro-1-[(4-methylphenyl)sulfinyl]propan-2-one (**1**). The α,γ-bis-anion was alkylated by reaction with 4-butenyl bromide to afford (3*R*/*S*,S_S)-3-fluoro-1-[(4-methylphenyl)sulfinyl]hept-6-en-2-one (**2**) in acceptable yield (66%) and as a nearly 1:1 diastereomeric mixture. The two ketones were separated by repeated flash chromatography in cyclohexane/ethyl acetate (7:3) and were processed separately in order to isolate and identify all the new obtained intermediates as pure compounds. From now to the end of the discussion, the syn-

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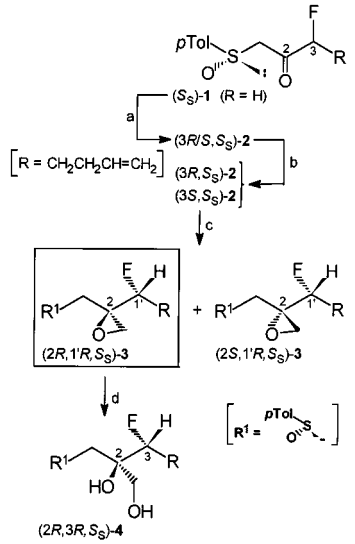
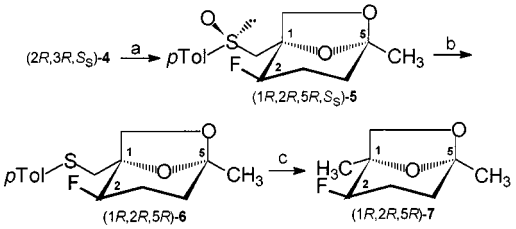
thetic process will be described mainly for the ketone (3*R*,S_S)-**2** (R_f = 0.35). The diastereomeric compounds obtained from the (3*S*,S_S)-epimer **2** (R_f = 0.30) will be mentioned only in the case of significant differences in chemical behavior.

The chiral oxiranes (2*R*,1′*R*,S_S)- and (2*S*,1′*R*,S_S)-**3** were prepared through a methylene insertion reaction[6] from diazomethane onto the carbonyl group of (3*R*,S_S)-**2** (Scheme 2). This reaction led to a 6.5:1 diastereomeric mixture of (2*R*,1′*R*,S_S)- and (2*S*,1′*R*,S_S)-**3**, respectively, in a combined yield of 95%. The same reaction, performed on the (3*S*,S_S) epimer **2**, was even more diastereoselective, leading to a 12:1 mixture of (2*R*,1′*S*,S_S)- and (2*S*,1′*S*,S_S)-**3**, respectively. In both cases the main diastereomers were easily obtained in pure form by flash chromatography.



Scheme 2. Synthesis of diol (2*R*,3*R*,S_S)-**4** from ketone (S_S)-**1**; reagents: (a) LDA, C_4H_7Br, HMPA, THF, –60 °C; (b) flash chromatography; (c) CH_2N_2, CH_3OH, 0 °C; (d) $HClO_4$, THF/H_2O, 40 °C

The acidic electrophilic opening reaction of the oxirane ring of pure (2*R*,1′*R*,S_S)-**3** gave, in 5 days at 40 °C and in good yield (85%), the diol (2*R*,3*R*,S_S)-**4**. A Wacker oxidative process of the terminal olefin of **4**, followed by spontaneous ketalization of the reactive intermediate ketone, afforded the bicyclic structure of frontalin. Subsequent sulfoxide reduction,[7] followed by hydrogenolytic removal of the *p*-tolylthio group, led to the enantio- and diastereomerically pure 2-fluoro analogue of fontalin, (–)-(1*R*,2*R*,5*R*)-**7** (fluorine equatorially disposed), in 74% yield from (2*R*,3*R*,S_S)-**4** (Scheme 3).



Scheme 3. Synthesis of 2-fluorofrontalin (1*R*,2*R*,5*R*)-**7** from diol (2*R*,3*R*,S_S)-**4**; reagents: (a) $PdCl_2/CuCl_2$, O_2, diglyme, room temp.; (b) NaI, $(CF_3CO)_2O$, CH_3COCH_3, –20 °C; (c) Raney-Ni, $(CH_2OH)_2$, 110 °C

Moreover, starting from (3*S*,S_S)-**2**, the epimer (–)-(1*R*,2*S*,5*R*)-**7**, with the fluorine atom in an axial position (Figure 1), was easily obtained and isolated in comparable overall yield (76%).

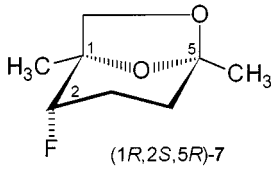


Figure 1. 2-Fluorofrontalin (–)-(1*R*,2*S*,5*R*)-**7**

Both the C-2 epimers of enantiomeric (+)-fluorofrontalin, (1*S*,2*S*,5*S*)- and (1*S*,2*R*,5*S*)-**7**, were obtained following an identical synthetic procedure starting from (−)-(1*R*)-menthyl-(*S*)-toluene-4-sulfinate as the chiral source of the synthesis.[8] The assignment of the stereochemistry was based on an X-ray analysis of (1*S*,2*R*,5*S*,R_S)-**5**, one of the intermediates in the synthesis of (+)-(1*S*,2*R*,5*S*)-**7** frontalin.[9] Figure 2 shows the corresponding perspective view.[10]

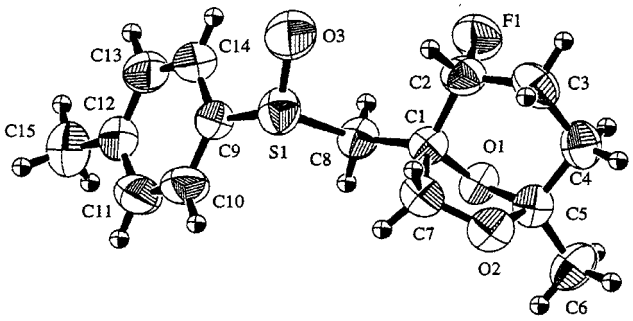


Figure 2. Perspective view of (1*S*,2*R*,5*S*,R_S)-**5**

Having determined the configuration at the C-1 and C-2 stereocenters of (1*S*,2*R*,5*S*,R_S)-**5**, the stereochemistries of the precursors easily followed. As a consequence, the stereochemistries of all the intermediates leading to (–)-frontalins were deduced from the enantiomeric relationships existing between the two different series of compounds.

Conclusion

Two diastereo- and enantiopure fluoro analogues of (−)-frontalin, the natural pheromone, and of (+)-frontalin, its enantiomer, were obtained following the synthetic chiral building block approach. The choice of the appropriate source of chirality, (+)-menthyl toluene-4-sulfinate or the corresponding (−)-enantiomer, neatly drove the process towards (−)- or (+)-2-fluorofrontalin, respectively.

Experimental Section

Preparation of 2-Fluorofrontalin (7) from 1-Sulfenylmethyl-2-Fluorofrontalin (6): Raney-Nickel (840 mg) was added to a solution of (1*R*,2*R*,5*R*)-**6** (280 mg, 1.00 mmol) in 1,2-dihydroxyethane (3 mL) and the black slurry was stirred under a hydrogen atmosphere at 110 °C for 24 h. When the substrate was completely used up (TLC

monitoring in *n*-hexane/ethyl acetate, 9:1), the white solution was transferred into a flask, the residual black powder was washed twice with 1,2-dihydroxyethane (2 × 1 mL) which was combined with the white solution. After distillation (oven temperature = 115 °C) fluorofrontalin (1*R*,2*R*,5*R*)-**7** (140 mg, 88% yield) was isolated. – $[\alpha]_D^{20}$ = –31.85 (*c* = 2.0, $CDCl_3$). – b.p. = 110 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.41 and 1.44 (s, 2 × 3 H, 1- and 5-CH_3), 1.63–2.14 (m, 4 H, 3- and 4-H_2), 3.46 (br. d, *J* = 7.22 Hz, 1 H, 7a-H) and 4.17 (br. dd, *J* = 7.22 and 1.23 Hz, 1 H, 7b-H), 4.43 (br. ddd, *J* = 49.21, 9.62 and 6.65 Hz, 1 H, 2-H). – ^{19}F NMR ($CDCl_3$): δ = –186.83 (br. dd, *J* = 49.21, 17.42 and 16.25 Hz, 1 F, 1-F). – IR (film): $\tilde{\nu}$ = 2889 cm^{-1}, 2940, 1719, 1458, 1380, 1357, 1259, 1202, 1132, 1036, 934, 874, 850, 829, 732. – DIS-EI-MS (70 eV): *m/z* (%) = 160 [$M^{+\bullet}$] (28), 130 [$C_6H_7O_2F^{+\bullet}$] (25), 118 [$C_6H_{11}OF^{+\bullet}$] (70), 114 [$C_6H_7OF^{+\bullet}$] (45), 98 [$C_6H_{10}O^{+\bullet}$] (95), 95 [$C_6H_7O^+$] (45), 89 [$C_5H_8F^+$] (72), 85 [$C_5H_8F^+$] (45), 72 [$C_5H_{12}^{+\bullet}$] (100), 71 [$C_5H_{11}^+$] (70), 69 [$C_5H_9^+$] (71), 59 [$C_3H_4F^+$] (35), 57 [$C_4H_9^+$] (20), 55 [$C_4H_7^+$] (33), 43 [$C_2H_3O^+$] (85), 41 [$C_3H_5^+$] (55). – GC-MS; t_1, *m/z* (%): 7.16 min., 160 (99) [M^+, (1*R*,2*R*,5*R*)-**7**]. – $C_8H_{13}FO_2$ (160.19): calcd. C 59.97, H 8.18; found C 59.95, H 8.21.

From (1*R*,2*S*,5*R*)-**6**, keeping the oven temperature at 125 °C, (1*R*,2*S*,5*R*)-**7** (145 mg, 90% yield) was isolated. – $[\alpha]_D^{20}$ = –39.48 (*c* = 2.0, $CDCl_3$). – b.p. = 120 °C. – ^{1}H NMR ($CDCl_3$): δ = 1.42 and 1.48 (s, 2 × 3 H, 1- and 5-CH_3), 1.55–2.50 (m, 4 H, 3- and 4-H_2), 3.48 (br. dd, *J* = 7.51 and 7.22 Hz, 1 H, 7a-H), 3.78 (br. d, *J* = 7.51 Hz, 1 H, 7b-H), 4.30 (br. ddd, *J* = 49.00, 3.75 and 3.25 Hz, 1 H, 2-H). – ^{19}F NMR ($CDCl_3$): δ = –191.3 (br. dddd, *J* = 49.00, 44.04, 20.01 and 8.23 Hz, 1 F, 1-F). – IR ($CDCl_3$): $\tilde{\nu}$ = 3689 cm^{-1}, 3156, 2940, 2887, 2255, 1817, 1794, 1712, 1645, 1603, 1561, 1469, 1447, 1390, 1382, 1358, 1271, 1257, 1209, 1173, 1111, 1038, 991, 934, 885, 849, 817. – DIS-EI-MS (70 eV): *m/z* (%) = 160 [$M^{+\bullet}$] (5), 130 [$C_6H_7O_2F^{+\bullet}$] (5), 118 [$C_6H_{11}OF^{+\bullet}$] (18), 98 [$C_6H_{10}O^{+\bullet}$] (19), 89 [$C_5H_8F^+$] (20), 72 [$C_5H_{12}^{+\bullet}$] (22), 71 [$C_5H_{11}^+$] (20), 59 [$C_3H_4F^+$] (10), 57 [$C_4H_9^+$] (5), 43 [$C_2H_3O^+$] (100). – GC-MS; t_1, *m/z* (%): 7.18 min, 160 (95) [M^+, (1*R*,2*S*,5*R*)-**7**]. – $C_8H_{13}FO_2$ (160.19): calcd. C 59.97, H 8.18; found C 60.00, H 8.20.

Acknowledgments

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[9] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-141139 Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44–1223/336–033; E-mail: deposit@ccdc.cam.ac.uk].
[10] Full X-ray diffraction data will be published in due course.

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