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Synthesis of (−)-(1*S*,5*R*)- and (+)-(1*R*,5*S*)-trifluoroanalogues of frontalin

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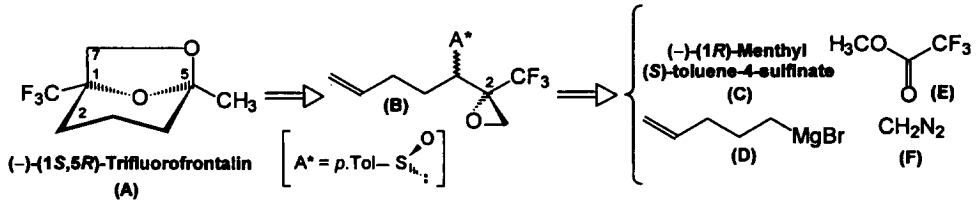
Abstract

The synthesis of enantiomerically pure (−)-(1*S*,5*R*)-1-trifluoromethyl frontalin **7** starting from (−)-(1*R*)-menthyl (*S*)-toluene-4-sulfinate, 5-pentenylmagnesium bromide and methyl trifluoroacetate is described. The synthetic procedures to obtain the enantiomer (+)-(1*R*,5*S*)-**7** are also mentioned. Absolute stereochemistry was unambiguously assigned by X-ray analysis of intermediates **3** and **5**. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: sulfoxides; epoxides; diastereoselection; trifluorofrontalin.

(−)-(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]

Many enantioselective syntheses of frontalin have been reported[2] but, to our knowledge, no syntheses of corresponding fluoro-analogues have ever been published. We wish to present here the preparation, in both enantiomerically pure forms, of the first trifluoro-analogue of frontalin, 5-methyl-1-trifluoromethyl-6,8-dioxabicyclo[3,2,1]octane.



The molecular skeleton was assembled following the chiral building block approach. As shown in the retrosynthetic scheme above, the C-1 stereocentre of the targeted trifluorofrontalin **A**, which corresponds to the quaternary stereocentre (C-2) of the epoxide **B**, sets the absolute stereochemistry

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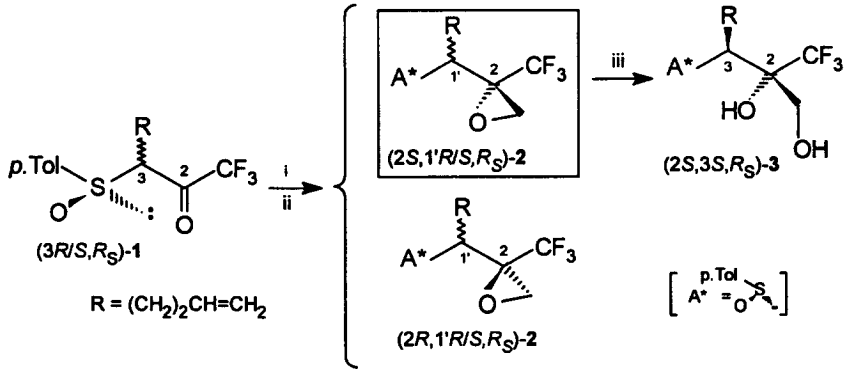
of the synthesis. So, an efficient synthetic method is dependent on the possibility of obtaining, with high diastereoselectivity,[2f] intermediate **B**.

For the synthesis of the (−)-trifluorofrontalin enantiomer (**A**), (−)-(1*R*)-menthyl (*S*)-toluene-4-sulfinate **C** was the source of chirality and the commercially available trifluoroacetic acid methyl ester **E** was the source of fluorine. The Grignard reagent, 5-pentenylmagnesium bromide (**D**) furnished the hydrocarbon part of the ring together with the methyl group at C-5, whilst diazomethane (**F**) allowed insertion of the methylene at C-7 of the bicyclic ring. The detailed synthetic steps to give the intermediate **B**, described in previous full papers for similar substrates,[3a] consist of the preparation of chiral (R_S)-[(4-methylphenyl)sulfinyl]pent-4-enyl sulfoxide and acylation of the corresponding α-lithio derivative with methyl trifluoroacetate.

Chiral oxirane **2** was prepared through a diastereoselective methylene insertion from diazomethane[3] onto the carbonyl group of (3*R*/*S*,R_S)-**1** performed in methanol at 0°C. The reaction led to a diastereomeric mixture of the four possible epoxides, from which the (2*S*)-configured ones were isolated, after flash chromatographic purification, in yields higher than 80% [(2*S*):(2*R*)-**2** ~6:1] (Scheme 1).



Scheme 1. Key: (i) CH_2N_2, CH_3OH, 0°C; (ii) flash chromatography; (iii) $HClO_4$, THF/H_2O, rt

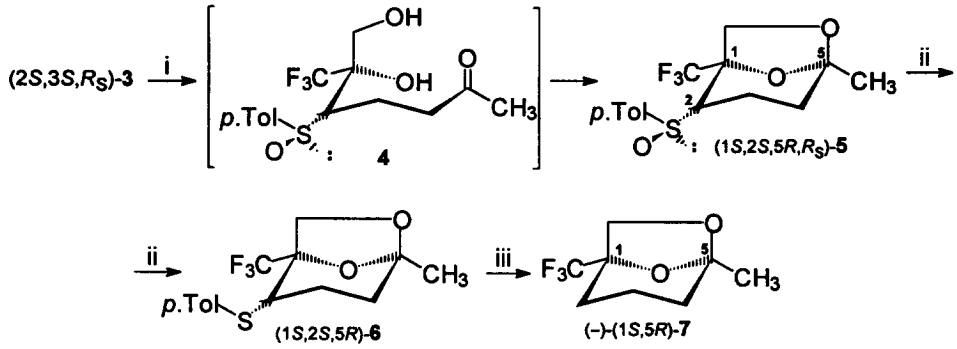
The unresolved 4:1 (1′*S*):(1′*R*) mixture of (2*S*)-**2** was submitted to an electrophilic ring opening reaction with catalytic perchloric acid in aqueous THF at room temperature to give only the diol (2*S*,3*S*,R_S)-**3** in 70% yield. The less abundant epoxide (1′*R*,2*S*)-**2** was recovered unreacted; the electrophilic ring opening of this diastereomer required more vigorous reaction conditions.

A Wacker oxidative process was performed on the terminal olefin ($PdCl_2/CuCl_2$ in diglyme, previously saturated by oxygen) of (2*S*,3*S*,R_S)-**3**, followed by a spontaneous ketalization of the intermediate ketone **4**, affording the bicyclic structure of 2-*p*-tolylthio frontalin **5** (72%). The subsequent sulfoxide deoxygenation reaction using the $NaI/(CF_3CO)_2O$/acetone system[4] at −20°C (92%), followed by hydrogenolytic removal of the *p*-tolylthio group of **6** performed by Raney-Ni in ethylene glycol at 90°C, led to the enantio- and diastereomerically pure (−)-(1*S*,5*R*)-**7**, 1-trifluoro analogue of frontalin.[5]

The enantiomeric (+)-trifluorofrontalin was obtained following two different strategies.

Firstly, the less abundant mixture of oxiranes (2*R*,1′*R*/*S*,R_S)-**2** (obtained in a a nearly 1:1 ratio) was used as a substrate. In this case, the electrophilic opening reaction ($HClO_4/THF/H_2O$/rt) was less stereoselective: both the diastereomers reacted giving rise to an epimeric mixture of the diols (2*R*,3*R*/*S*,R_S)-**3**. However, the synthetic procedure was performed on the mixture: the hydrogenolytic removal of the sulfenyl moiety of **6** gave pure (+)-(1*R*,5*S*)-**7** because the C-2 stereocentre disappeared (Scheme 2).

Secondly, (+)-(1*S*)-menthyl (*R*)-toluene-4-sulfinate was employed as the chiral source of the process to synthesize the enantiomeric key intermediates, (2*R*,1′*S*/*R*,S_S)-**2**. Again, the (2*R*) stereochemistry at the



Scheme 2. Key: (i) $PdCl_2/CuCl_2$, O_2, diglyme, rt; (ii) NaI, $(CF_3CO)_2O$, CH_3COCH_3, –20°C; (iii) Raney-Ni, $HOCH_2CH_2OH$, 90°C

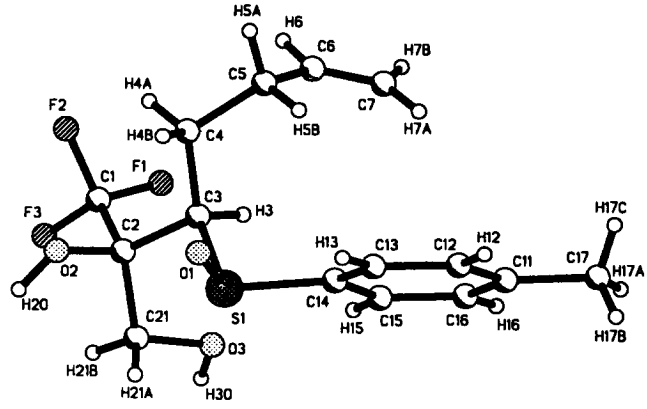


Figure 1. Perspective view of (2*S*,3*R*,S_S)-**3**

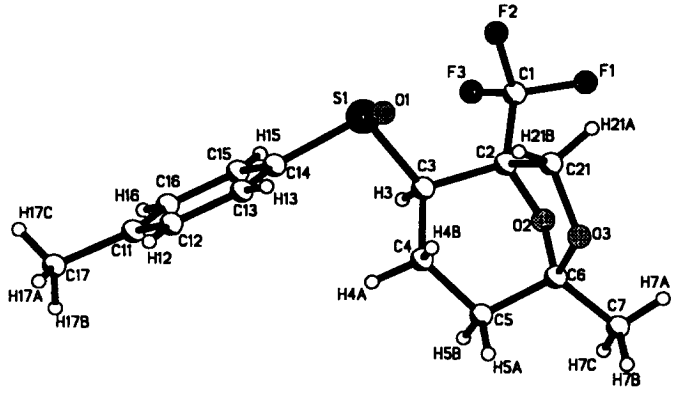


Figure 2. Perspective view of (1*S*,2*R*,5*R*,S_S)-**5**

C-2 quaternary stereocentre of the oxiranes **2** drove the subsequent enantioselection of the synthesis to the final trifluorofrontalin (+)-(1*R*,5*S*)-**7**.

The enantio- and diastereomerically pure diol (2*S*,3*R*,S_S)-**3**, as well as the 2-*p*-tolylsulfinyl-substituted frontalin (1*S*,2*R*,5*R*,S_S)-**5** gave suitable crystals for X-ray analysis.[6] In Figs. 1 and 2 the respective views are shown.[7] For both compounds, bond distances and angles fall within the expected range.

Acknowledgements

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5. Raney-nickel (1.5 g) was added to a solution of (1*S*,2*S*,5*R*)-**6** (500 mg, 1.72 mmol) in 1,2-dihydroxyethane (4 ml) and the black slurry was stirred under a 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: 250 mg of trifluorofrontalin **7** (87% yield) were isolated: $[\alpha]_D^{20}$ –42.5 (c 2.0, $CDCl_3$); –35.0 (c 2.0, Et_2O); b.p.=86°C; ^1H NMR ($CDCl_3$), δ: 1.50 (3H, s, 5-Me), 1.6–2.0 (6H, m, H_2-2, -3 and -4), 3.92 (1H, brdd, *J*=7.2 and 1.6Hz, H-7a) and 4.02 (1H, brd, *J*=7.2Hz, H-7b). ^{13}C NMR ($CDCl_3$), δ: 16.59 (T, C-3), 24.00 (Q, 5-Me), 26.14 and 34.38 (T, C-4 and -2), 68.55 (T, C-7), 81.36 (Sq, $^2J_{C,F}$=31.5Hz, C-1), 110.67 (S, C-5), and 123.87 (Sq, $^1J_{C,F}$=280.5Hz, 1-CF_3). ^{19}F NMR ($CDCl_3$), δ: –80.85 (3F, brs, 1-CF_3).
6. Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
7. Full X-ray diffraction data will be published in due course.