CHEMISTRY LETTERS, pp. 41-44, 1987.

Enantioselective Syntheses of (+)- and (-)-Frontalin#

Masaki OHWA and Ernest L. ELIEL*
Department of Chemistry, University of North Carolina,
Chapel Hill, NC 27514, U.S.A.

(+)- and (-)-Frontalin have been obtained from a chiral 1,3-oxathiane precursor in a short (3-step) synthesis in moderate (70%) enantiomeric excess (e.e.). A longer (6-step) modification gives the two enantiomers in 96% e.e. Overall yields range from 28 to 43%.

Frontalin, the aggregation pheromone of females of the southern pine bark beetle, Dendroctonus frontalis and of males of the western pine bark beetle, Dendroctonus brevicomis[1)] was first synthesized in its two enantiomeric forms by Mori.[2)] The natural pheromone is predominantly the (1*S*)-(-) isomer, as evidenced by the fact that only this enantiomer has pheromone activity.[3,4)]

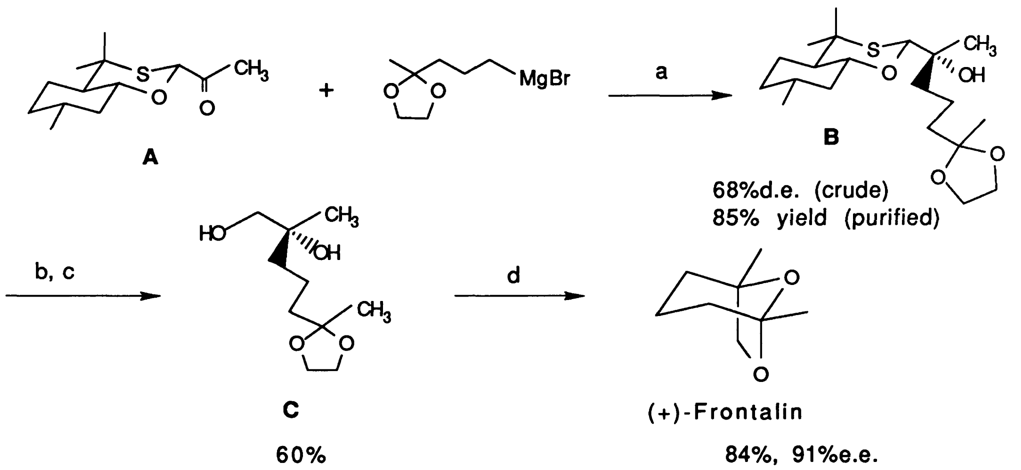
A number of enantioselective syntheses of both (+)- and (-)-frontalin[5)] as well as syntheses from naturally occurring chiral precursors[6)] have been reported. Some of these syntheses are quite convenient and produce product of over 90% enantiomeric purity. We report here enantioselective syntheses based on our previously reported[7)] oxathiane route.

Scheme 1 shows a synthesis of (+)-frontalin. Addition of the Grignard reagent[8)] prepared, at 0 °C, from the ethylene ketal of 5-bromo-2-pentanone[9)] to the previously described[10)] acetyloxathiane A proceeds in good yield to give carbinol B; however, in contrast to previous experience,[7)] the diastereomeric excess of B was only 68%.[11)] We had previously found[12)] that, when the Grignard reagent complexes with an alkoxyl group in the side chain of the oxathianyl ketone substrate, the stereoselectivity of the oxathiane based synthesis is depressed (as a result of competitive interference with chelation to the oxathianyl oxygen). It now appears that self-complexation of the Grignard component in the reaction also leads to lowered stereoselectivity.

In the further course of the synthesis - purification of B by chromatography, N-chlorosuccinimide/$AgNO_3$ cleavage[13)] and borohydride reduction to C, as previously described,[7)] followed by intramolecular ketalization to (+)-frontalin - an augmentation of the enantiomeric purity occurred, presumably in the chromatographic step. However, in the natural [(-)-frontalin] series (Scheme 2), no such augmentation occurred and the final product was obtained in only 70% e.e.[14)] It is of interest that, though the enantiomeric purity of the product might be

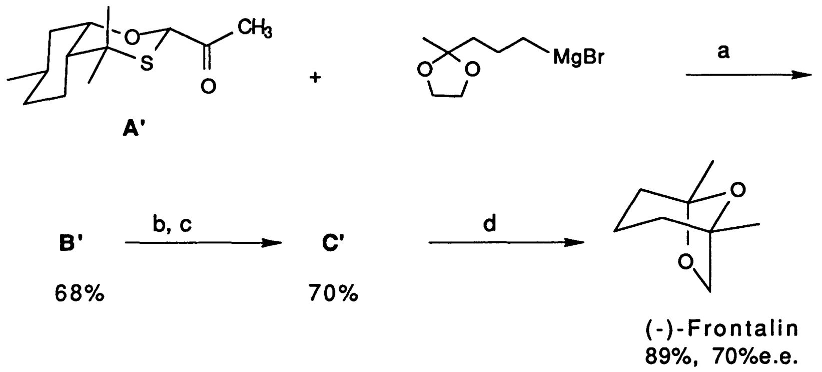
---

#Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.



(a) THF, -78 °C (b) NCS, $AgNO_3$ (c) $NaBH_4$ (d) see Scheme 3

Scheme 1.

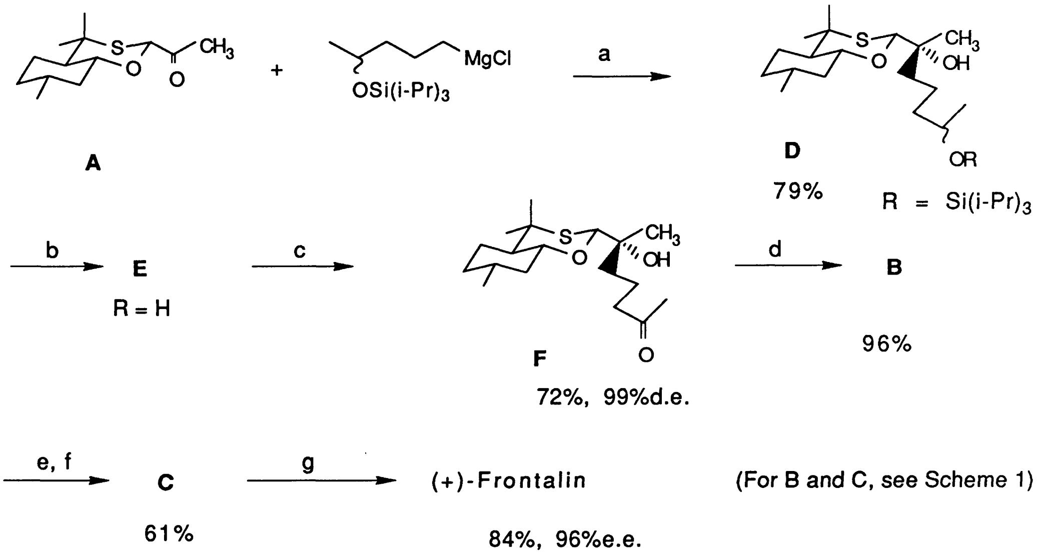


B' is a diastereomer of B (Scheme 1) and C' is the enantiomer of C.
The reagents are the same as in Schemes1 and 3.

Scheme 2.

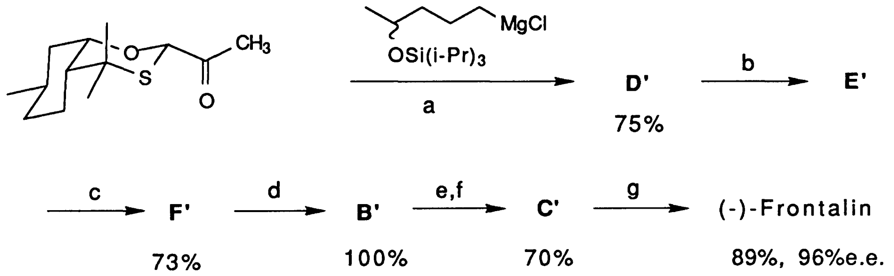
considered unsatisfactory, it does, in fact, almost exactly correspond to the composition (85:15) of the natural pheromone isolated from the Dendroctonus frontalis female![4)]

In previous studies[12)] we had noted that, though an alkoxy group in the side chain depresses the stereoselectivity of the Grignard addition, the same is not true for a triisopropylsililoxy (TIPS) group. Apparently the greater steric demand of the TIPS group prevents chelation with it and thus the desired chelation with the oxathiane oxygen is not interfered with. We felt that the same might be true for a TIPS group in the Grignard reagent. As shown in Scheme 3, this expectation was fulfilled;[15)] however, the synthesis now requires a slight detour in that the (commercially available) 5-chloro-2-pentanone needs to be reduced and sililated prior to reaction and that the product of the Grignard addition must be deprotected, oxidized and ketalized before the synthesis continues according to



(a) THF, -78 °C; (b) 5% HF, CH$_3$CN; (c) PCC, CH$_2$Cl$_2$; (d) HOCH$_2$CH$_2$OH, PPTS, Bz; (e) NCS, AgNO$_3$; (f) NaBH$_4$; (g) p-TsOH.H$_2$O, CH$_2$Cl$_2$, chromatography

Scheme 3.



D', E', F' are diastereomers of the corresponding intermediates (D-F) in Scheme 3. For structures of A' and B', see Schemes 1 and 2.
The reagents are the same as in Scheme 3.

Scheme 4.

Scheme 1. This increases the number of steps from three to six, but, in return, (+)-frontalin is obtained in 96%. e.e.

The synthesis of (-)-frontalin (Scheme 4) proceeded analogously, though in somewhat better overall yield; the e.e. of the product was again 96%.14)

The oxathiane precursor of acetyloxathiane A' may be obtained as a by-product in the synthesis of A;16) a more rational synthesis of this material will be reported elsewhere.17) Preparation of A' by lithiation of the oxathiane precursor, treatment with acetaldehyde and Swern oxidation18) was analogous to the preparation of A.10)

To obtain the TIPS-protected 5-chloro-2-pentanol, the corresponding ketone was reduced with BH$_3$-THF and subsequently protected with (iPr)$_3$SiCl in methylene chloride with imidazole and 4-dimethylaminopyridine as catalysts.

We thank the National Science Foundation, USA for support under grant CHE-8508279.

References

1) G.W. Kinzer, A.F. Fentiman, Jr., T.F. Page, Jr., R.L. Foltz, J.P. Vite, and G.B. Pitman, Nature, 221, 477 (1969).
2) K. Mori, Tetrahedron, 31, 1381 (1975).
3) D.L. Wood, L.E. Browne, B. Ewing, K. Lindahl, W.D. Bedard, P.E. Tilden, K. Mori, G.B. Pitman, and P.R. Hughes, Science, 192, 896 (1976).
4) It was later found - T.E. Stewart, E.L. Plummer, L.L. McCandless, J.R. West, and R.M. Silverstein, J.Chem.Ecol., 3, 27 (1977) - that, whereas the pheromone of *Dendroctonus brevicomis* is (within limits of detection) pure (-)-frontalin, the pheromone of *Dendroctonus frontalis* is 85% (-)- and 15% (+)-isomer.
5) Y. Sakito and T. Mukaiyama, Chem.Lett., 1979, 1027; C. Meister and H.-D Scharf, Liebigs Ann.Chem. 1983, 913; C. Fuganti, P. Grasselli, and S. Servi, J.Chem.Soc., Perkin Trans.1, 1983, 241; A.W.M. Lee, J.Chem.Soc.,Chem.Commun., 1984, 578; J.S. Yadav, B.V. Joshi, and A.B. Sahasrabidje, Synthetic Commun., 15, 797 (1985); T. Hosokawa, Y. Makabe, T. Shinohara, and S.-I. Murahashi, Chem.Lett., 1985, 1529
6) H. Ohrui and S. Emoto, Agric.Biol.Chem., 40, 2267 (1976); J. Jarsosoz, D.R. Hicks, and B. Fraser-Reid, J.Org.Chem., 47, 935 (1982); F. Cooke, G. Roy and P. Magnus, Organometallics, 1, 893 (1982); R. Naef and D. Seebach, Liebigs Ann. Chem., 1983, 1930; R. Barner and J. Hübscher, Helv.Chim.Acta, 66, (1983).
7) cf. E.L. Eliel, Phosphorus and Sulfur, 24, 73 (1985).
8) Using magnesium activated with anthracene: H. Bonnemann, B. Bogdanovic, R. Brinkman, D.-W. Hew, and B. Spliethoff, Angew.Chem.,Int.Ed.Engl., 22, 728 (1983); see also W. Oppolzer and P. Schneider, Tetrahedron Lett., 25, 3305 (1985).
9) Prepared analogously as the corresponding chlorine compound: G.W. Cannon, R.C. Ellis, and J.R. Leal, Org.Syn.Coll.Vol.IV, p. 597, followed by standard ketalization.
10) S.V. Frye and E.L. Eliel, J.Org.Chem., 50, 3402 (1985).
11) The diastereomers of B gave coincident proton and ^{13}C NMR spectra and it was necessary to hydrolyze the ketal to the corresponding ketone for nmr analysis of diastereomer composition. In the case of B', analysis of diastereomer composition was unsuccessful under all conditions tried.
12) S.V. Frye and E.L. Eliel, Tetrahedron Lett., 27, 3223 (1986). See also Scheme 13 in Ref. 7.
13) E.J. Corey and B.W. Erickson, J.Org.Chem., 36, 3553 (1971).
14) Analysis was by proton nmr in presence of the Eu(hfc)$_3$ shift reagent.
15) As in the previous case investigated,[12] the dimethyl-*t*-butylsilyloxy group was ineffective in preventing chelation, d.e. 68%, essentially the same as with the Grignard reagent derived from the ketal-protected halide.
16) J.E. Lynch and E.L. Eliel, J.Am.Chem.Soc., 106, 2943 (1984).
17) T. Kogure and E.L. Eliel, to be published.
18) K. Omura, A.K. Sharma, and D. Swern, J.Org.Chem., 41, 957 (1976).

(Received September 1, 1986)