Synthesis of (−)-Frontalin from α-D-Isosaccharino-1,4-lactone

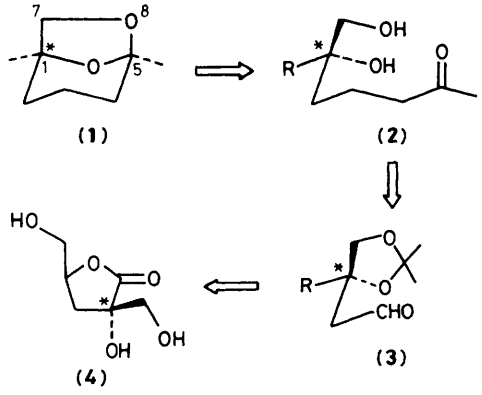
Minh-Chau Trinh, Jean-Claude Florent, and Claude Monneret*

Département de Pharmacognosie associé au CNRS, UA n° 484, Université Paris V, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France

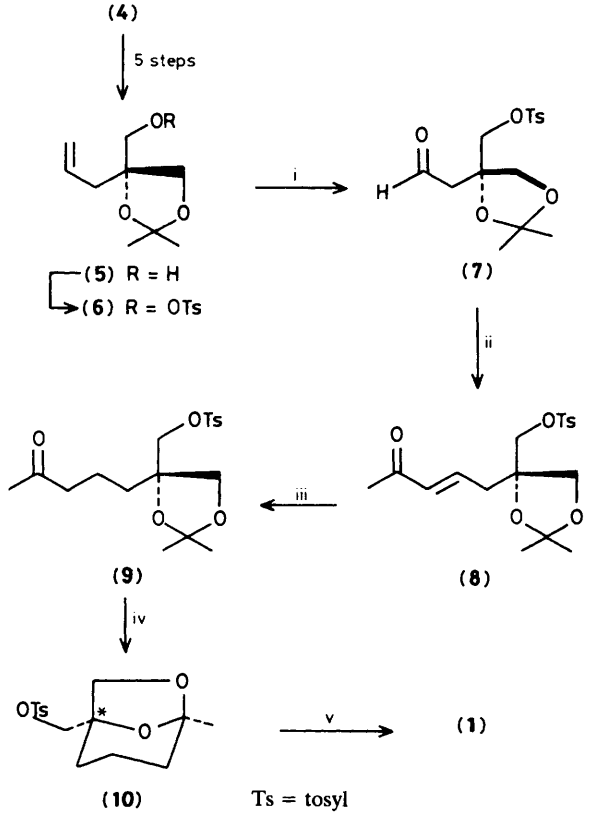
A chiral pool synthesis of (−)-frontalin has been achieved in a ten step sequence and 17% overall yield from α-D-isosaccharino-lactone.

(−)-Frontalin is known to be the aggregation pheromone of southern pine beetle *Dendroctonus frontalis*.[1] The biologically active form of this 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane is the 1(*S*),5(*R*) enantiomer. Since its antipode has been reported to be inactive,[2] enantioselective syntheses of frontalin are of great interest. The reported synthetic methods giving optically active products have relied on the incorporation of chiral building blocks,[3] asymmetric syntheses (*e.g.*, self reproduction of chirality,[4] or Sharpless asymmetric epoxidation of allylic alcohol[5]), baker's yeast mediated transformation,[6] use of a chiral auxiliary,[7] and optical resolution.[8] Although frontalin contains two asymmetric centres, only the (1*S*) needs to be considered for its synthesis. This one of the type R, R′, R″, (OR‴) occurs only rarely in the usually available chiral building blocks (carbohydrate, aminoacids, and terpenes). For example, suitable chiral starting materials previously used in synthesis of frontalin have been prepared by alkylation with MeLi or MeMgI of ketoses[3a–c] obtained in a multi-step synthesis or from very expensive (*S*)-(+)-citramalic acid.[3d] In contrast, deoxyaldonic acids which are readily obtained from reducing sugars under the influence of aqueous bases[9] represent some available 'chirons' having such an asymmetric centre. Thus within the frame-work of our studies concerning the synthesis of biological compounds from these aldonic acids or from their corresponding lactones,[10] we report herein the preparation of natural frontalin (**1**) from α-D-isosaccharino-1,4-lactone (**4**). The retrosynthetic analysis illustrated in Scheme 1 suggests that the dioxabicyclo-[3.2.1]octane compound (**1**) can be viewed as formed by internal acetalization of the dihydroxyketone (**2**) obtained by chain elongation of aldehyde (**3**), resulting itself from the lactone (**4**).

This lactone is usually prepared by alkaline treatment of lactose following the process reported by Whistler *et al.*[9] Further transformation of (**4**) into the target δ,ε-dihydroxylated ketone (**9**) was carried out as follows. Firstly α-D-isosaccharinolactone (**4**) was converted into the key intermediate, the unsaturated alcohol (**5**)[11] in an overall yield of 30—35%. Subsequently, alcohol (**5**) was transformed into the tosylate (**6**)† in 95% yield, $[\alpha]_D^{20} = -5°$ (*c* 3, $CHCl_3$), and (**6**) into the aldehyde (**7**) by oxidation[12] of the terminal double bond (catalyt. OsO_4 and 6 equiv. $NaIO_4$) in 70% yield, m.p. 65 °C, $[\alpha]_D^{20} = +11°$ (*c* 3, $CHCl_3$). The condensation of 1-triphenylphosphoranylidenepropan-2-one with (**7**) afforded only the *trans* unsaturated ketone (**8**), m.p. 68 °C, $[\alpha]_D^{20} = -8.5°$ (*c* 1.3, chloroform) in 80% yield. The reduction of the double bond of (**8**) by hydrogenation over 10% palladium-on-charcoal afforded a mixture of the expected compound (**9**), m.p. 61 °C, $[\alpha]_D^{20} = +1.5°$ (*c* 1, $CHCl_3$) with the dioxabicyclo derivative (**10**), m.p. 112 °C, $[\alpha]_D^{20} = -20°$ (*c* 1, $CHCl_3$) in a 2:1 ratio. However when this hydrogenation was performed in the presence of triethylamine to remove any traces of acid



Scheme 1. R = Me or precursor.



Scheme 2. *Reagents:* i, OsO_4 (5 mol%), $NaIO_4$ (6 mol. equiv.), H_2O–Et_2O, room temp.; ii, Ph_3P=CHCOMe, MeCN, reflux; iii, Pd–C, MeOH or Pd–C, MeOH + Et_3N; iv, Amberlyst-15, $CHCl_3$, room temp.; v, $LiEt_3BH$ (10 equiv.), tetrahydrofuran (THF), reflux.

† The structural assignments for all new compounds were supported by satisfactory spectroscopic data (270 MHz ^1H n.m.r., i.r., and mass) and elemental analyses.

present in the catalyst,[13] exclusive formation of the acyclic derivative (**9**) was observed in 95% yield.

This intermediate was easily converted into the dioxabicyclo derivative (**10**) in 95% yield by treatment with Amberlyst-15 ion-exchange resin. Finally, reduction of the neopentyl tosylate with lithium triethylborohydride or 'superhydride' in tetrahydrofuran (THF) at reflux gave, after distillation, the desired (−)-frontalin (**1**), $[\alpha]_D^{20} = -52°$ (*c* 1, diethyl ether) in 95% yield, lit.,[8] $[\alpha]_D^{20} = -52°$ (*c* 1.63, diethyl ether).

Received, 27th October 1986; Com. 1532

References

1 G. W. Kinzer, A. F. Fentiman, Jr., T. F. Page, Jr., R. L. Foltz, J. P. Vité, and G. B. Pitman, *Nature*, 1969, **221**, 477.

2 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*, 1976, **192**, 896.

3 (a) H. Orhui and S. Emoto, *Agr. Biol. Chem.*, 1976, **40**, 2267; (b) D. R. Hicks and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1976, 869; (c) S. Jarosz, D. R. Hicks, and B. Fraser-Reid, *J. Org. Chem.*, 1982, **47**, 935; (d) R. Barner and J. Hubscher, *Helv. Chim. Acta*, 1983, **66**, 880.

4 R. Naef and D. Seebach, *Liebigs Ann. Chem.*, 1983, 1930.

5 C. Meister and H. D. Scharf, *Liebigs Ann. Chem.*, 1983, 913; A. W. M. Lee, *J. Chem. Soc., Chem. Commun.*, 1984, 578; B. D. Johnston and A. C. Oehlschlager, *Can. J. Chem.*, 1984, **62**, 2148; J. S. Yadav, B. V. Joshi, and A. B. Sahasrabudhe, *Synth. Commun.*, 1985, **15**, 797; T. Hosokawa, Y. Makabe, T. Shinohara, and S. I. Murahashi, *Chem. Lett.*, 1985, 1529.

6 C. Fuganti, P. Grasselli, and S. Servi, *J. Chem. Soc., Perkin Trans. 1*, 1983, 241.

7 Y. Sakito and T. Mukaiyama, *Chem. Lett.*, 1979, 1027; T. Mukaiyama, *Tetrahedron*, 1981, **37**, 4111.

8 K. Mori, *Tetrahedron*, 1975, **31**, 1381.

9 R. L. Whistler and J. N. BeMiller, 'Methods in Carbohydrate Chemistry,' Academic Press, New York, 1963, vol 2, p. 477 and references cited therein. See also as general review: Rodd's Chemistry of Carbon Compounds, vol. I, Part. F, Elsevier Publishing Company, 1967, p. 251.

10 F. Bennani, J. C. Florent, M. Koch, and C. Monneret, *Tetrahedron*, 1984, **40**, 4669.

11 J. C. Florent, J. Ughetto-Monfrin, and C. Monneret, *J. Org. Chem.*, 1987, in the press.

12 R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478.

13 P. N. Rylander, 'Catalytic hydrogenation in Organic synthesis,' Academic Press, New York, 1979, p. 235.