Synthesis of One Enantiomer, the Other Enantiomer, and a Mixture of Both Enantiomers of Frontalin† from a Derivative of Methyl-α-D-glucopyranoside

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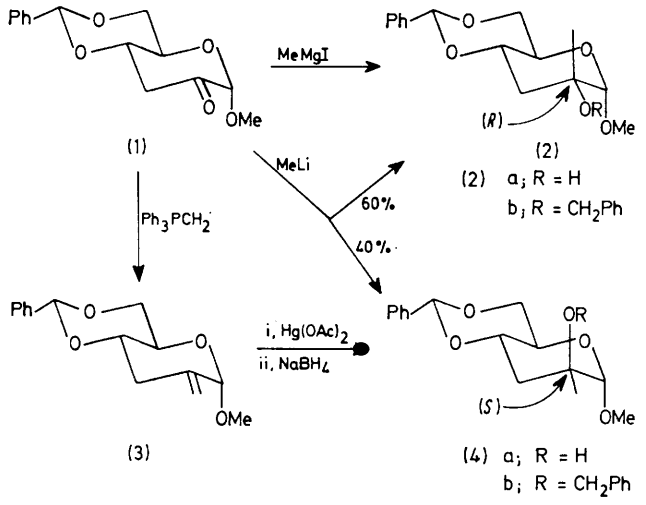
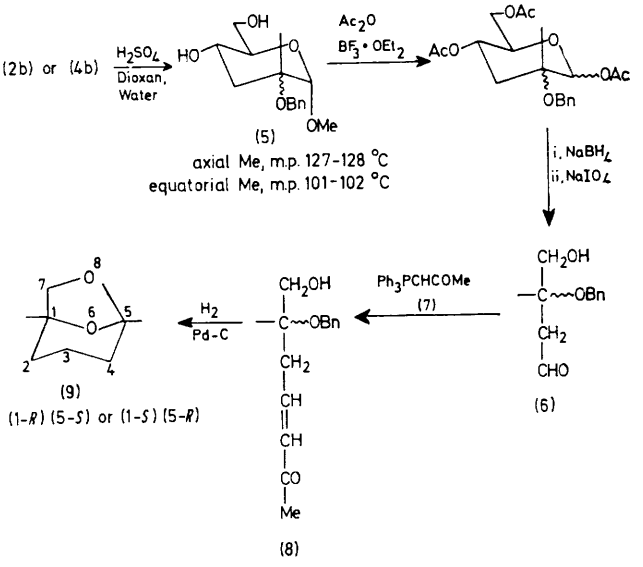
Summary The ketone (**1**), derivable from methyl-α-D-glucopyranoside in four steps, may be converted into one enantiomer, the other enantiomer, or a mixture of both enantiomers of frontalin in 13% overall yield.

THE enantioselectivity of chemoreceptors in nature requires that synthetic biologically active compounds be available in optically pure forms, a requirement that is traditionally met by resolving synthetic racemic mixtures. However, many compounds, and in particular the majority of insect pheromones, are not amenable to this approach since they are volatile oils and usually lack appropriate functionality.[1] The use of optically pure progenitors[2] circumvents this problem, and sugars, the most abundant natural source of optical purity, are often well suited for this purpose.[3]



SCHEME 1

The ideal synthetic route should have the capability of yielding one enantiomer, the other enantiomer, or a mixture of both enantiomers as desired, in order to (a) avoid the wastage associated with resolution of racemic mixtures, (b) facilitate identification of the naturally occurring form, and (c) permit evaluation of the phenomenon of enantioselectivity. We report herein a synthesis‡ of (+)- and (−)-frontalin (**9**), in which this goal has been achieved in seven steps (13% overall yield) from ketone (**1**)[4] readily prepared from methyl-α-D-glucopyranoside in four steps involving benzylidination,[5] oxiran formation,[6] $LiAlH_4$ reduction, and oxidation.[7] Although frontalin (**9**) contains two asymmetric centres, only one needs to be considered in a synthetic route. Thus the strategy adopted required the creation of a suitably functionalised fragment bearing the tertiary hydroxy group in known chiral form. The aldehyde (**6**) is such a fragment, and its synthesis in (*R*) and (*S*) forms was therefore undertaken.



SCHEME 2

Owing to the anomeric effect which ensures axial orientation of polar groups at the anomeric centre of pyranosides,[8] the approach of reagents to the trigonal centre in (**1**) should occur predominantly from 'above'. Accordingly alkylation of (**1**) with methyl-lithium [tetrahydrofuran (THF), −78 °C] afforded compounds (**2a**) and (**4a**) in the ratio 3:2 in 77% yield. These were separated by chromatography on silica and their structures were assigned on the basis of ^1H and ^{13}C n.m.r. analyses.§

When MeMgI (Et_2O, −65 °C) was the alkylating agent, the ratio (**2a**):(**4a**) increased to 9:1 (^1H n.m.r. estimate) and pure (**2a**) crystallised out in 73% yield (Scheme 1). On the other hand, pure (**4a**) was obtained as the exclusive

† Frontalin is a pheromone of several species of beetles (*e.g.*, western pine, southern pine, and spruce) belonging to the genus *Dendoctonus* (G. W. Kinzer, A. F. Fentiman, Jr., T. F. Page, Jr., R. L. Faltz, J. P. Vite, and G. B. Pitman, *Nature*, 1969, **221**, 447).

‡ While this work was in progress, Mori reported the synthesis of (+) and (−) forms of frontalin (K. Mori, *Tetrahedron*, 1975, **31**, 1381), using as starting materials the enantiomers of 2-hydroxy-2-methylpentane-1,5-dioic acid 5 → 2 lactone, obtained by quinine resolution of the racemate and identified by *X*-ray analysis.

§ The ^1H n.m.r. acetyl resonances for the acetates derived from (**2a**) and (**4a**) occurred at δ 2·01 and 2·08 respectively in agreement with the criteria for assigning the orientation of an epimeric pair of acetates (R. U. Lemieux and J. D. Stevens, *Canad. J. Chem.*, 1965, **43**, 2059; F. W. Lichtenthaler and P. Emig, *Tetrahedron Letters*, 1967, 577). ^{13}C n.m.r spectra provide independent support. Thus the tertiary methyl group in (**2a**) is downfield from that in (**4a**) (23·1 and 20·93 p.p.m., respectively) in accordance with the shielding (γ-effect) of the axial group,at C-1 (J. B. Stothers, 'Carbon-13 NMR Spectroscopy', Academic Press, New York, 1972, Ch. 5).

product, upon oxymercuration–demercuration[9] of the olefin (**3**), the latter being prepared in 95% yield from (**1**) (Ph_3PCH_2, dimethoxyethane, 23 °C).

After protection of the hydroxy groups by benzylation (NaH, dimethylformamide, $PhCH_2Cl$, 85%) to (**2b**) and (**4b**), the chiral aldehydes (**6**) [(*R*) or (*S*)] were excised as indicated in Scheme 2. The three steps from the crystalline diols (**5**) (axial or equatorial) to (**6**) were carried out without purification, the yield of (**6**) after chromatography being 55%.

Reaction of (**6**) with 1 equiv. of the preformed ylide (**7**) derived from chloroacetone[10] (THF, reflux, 12 h) gave the oily enone (**8**) in 73% yield after chromatography. Treatment of (**8**) with hydrogen (EtOH, 1 atm, 23 °C, 10% Pd–C) caused saturation of the double bond and cleavage of the benzyl ether, the resulting keto-diol cyclising spontaneously. The process, which could be followed by t.l.c., required 24–36 h.

The conversion of (**1**) into (**9**) can be accomplished in 13% overall yield, and 1 g of optically pure frontalin may be obtained from 21 g of methyl-α-D-glucopyranoside.

The (*R*) alcohol (**2a**) afforded the dextrorotatory (+)-frontalin, $[\alpha]_D = +51{\cdot}3°$ (*c*, 1·05 in $CHCl_3$), while the (*S*) alcohol (**4a**) gave the laevorotatory (−)-frontalin, $[\alpha]_D = 50{\cdot}7°$ (*c*, 1·0 in $CHCl_3$), in good agreement with Mori's values‡ [(+), 53·4°, and (−), −52.0°].

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