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BAKER'S YEAST HYDROGENATION OF CARBONYL ACTIVATED DOUBLE BONDS. ENANTIOSELECTIVE SYNTHESIS OF THE (S)-FORM OF THE DIHYDROTERPENEDIOL SECRETED BY *DANAUS CHRYSIPPUS* AND OF A PHEROMONE OF *CALLOSOBRUCHUS CHINENSIS* L.

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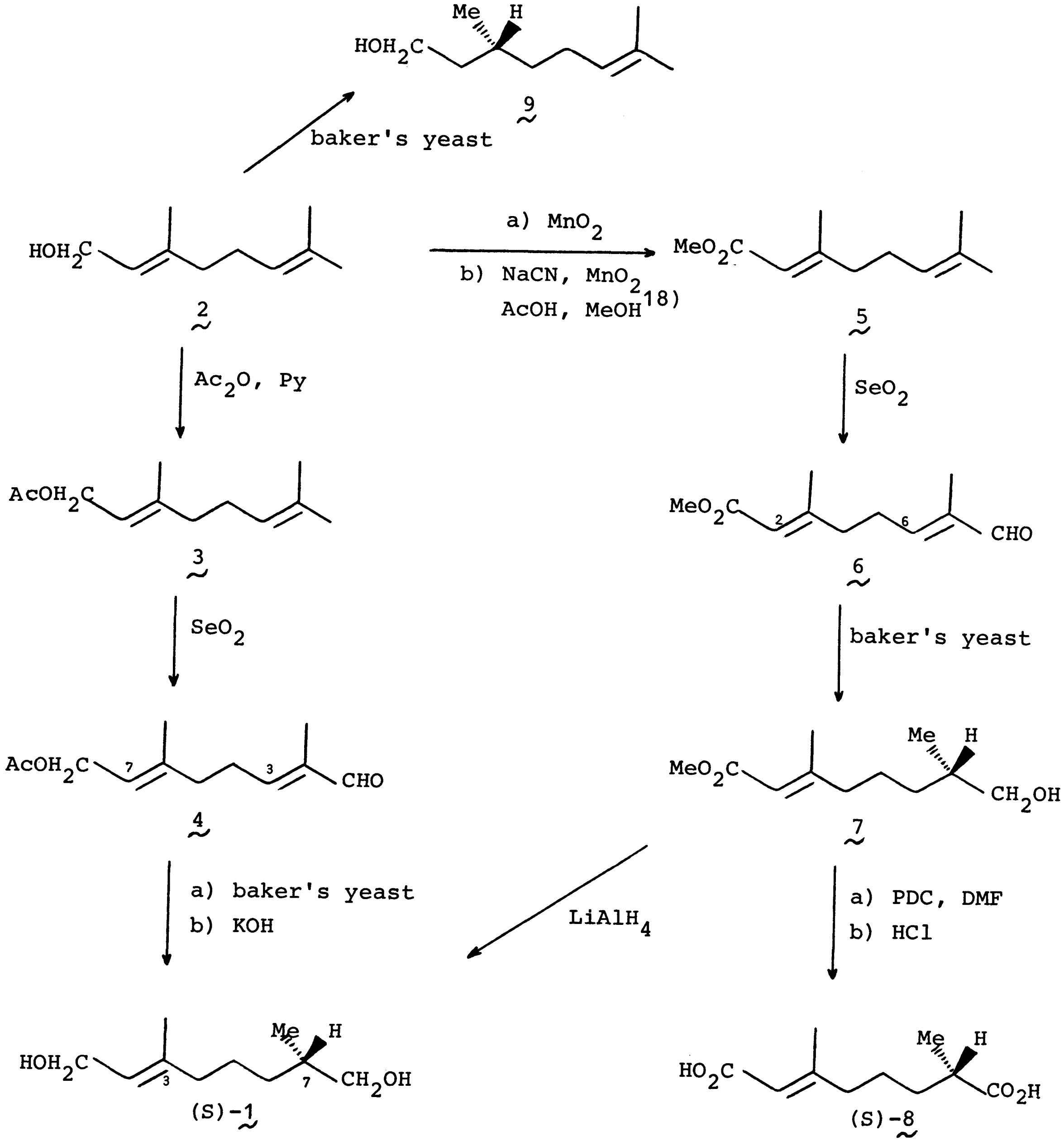
The (S)-forms of (E)-3,7-dimethyl-2-octene-1,8-diol (secreted by male danaid butterflies) and of (E)-3,7-dimethyl-2-octene-1,8-dioic acid (a pheromone of the azuki bean weevil) were synthesized *via* stereoselective hydrogenation by baker's yeast of the carbonyl activated double bond of achiral precursors.

(E)-3,7-Dimethyl-2-octene-1,8-diol (dihydroterpenediol, **1**) was isolated by Meinwald *et al*. as one of the major components of the hairpencil secretion of male danaid butterflies (*Danaus chrysippus*, commonly called "the African Monarch");1) its absolute configuration, however, remained unknown. To our knowledge, no report has so far been published on the preparation of **1** in one enantiomerically pure form,2) although a number of syntheses have been performed giving racemic **1**.1,3)

In this paper we report two independent syntheses of (S)-**1**, both based on the stereoselective reduction by baker's yeast of a carbonyl activated double bond.

Previous findings that α-methyl-α,β-unsaturated aldehydes (alcohols or acetals) are reduced by *Saccharomyces cerevisiae* to give the corresponding α-methyl saturated alcohols4) prompted us to utilize such a biological hydrogenation in order to obtain enantiomerically pure (S)-**1**5) from 8-acetoxy-2,6-dimethylocta-2(E),6(E)-dienal (**4**). This compound was in turn prepared from geraniol (**2**), an achiral and readily available material, through the acetylation (Ac_2O in dry Py) and subsequent oxidation of the resulting **3** with SeO_2 in EtOH6) (36% overall yield from **2**).7,8) The protection of the allylic hydroxyl group in **4** was retained to avoid the hydrogenation of the adjacent double bond, which occurs in the yeast catalysed conversion of geraniol (**2**) into (R)-(+)-citronellol (**9**).9)

Reduction of **4** by baker's yeast (3 g educt, 1 kg yeast, 3 l H_2O, 3 d at r.t.), followed by ether extraction, afforded a crude product, which was then treated with alcoholic KOH (5%) for 4 h at 40 °C. After flash chromatography (silica gel-$AgNO_3$ 5%; hexane:EtOAc 1:2 as eluent) (S)-**1**10) was isolated in 20% yield:11) $[\alpha]_D^{25}$ -9.1° (c 4.6, $CHCl_3$); e.e.$>$ 97% as estimated by a comparison of its rotatory power with that of (S)-**1** prepared from **7** as described below (see Scheme 1).



Scheme 1.

Methyl-(S)-8-hydroxy-3,7-dimethyl-2(E)-octenoate (7) was obtained by baker's yeast hydrogenation of 6[12] (fermentation conditions as mentioned above; ether extraction; flash chromatography silica gel-$AgNO_3$ 10%, hexane:EtOAc 1:1 as eluent; 35% yield):[11] $[\alpha]_D^{21}$ -10.1° (c 2.4, $CHCl_3$); IR (liquid film): 3420, 1715, 1650 cm^{-1}; ^1H-NMR ($CDCl_3$, δ, TMS): 0.9 (2H, d, J=6 Hz, 7-CH_3), 1.0-2.2 (7H, m, CH_2 and CH), 2.18 (3H, d, J=1 Hz, 3-CH_3), 2.28 (1H, s, OH), 3.44 (2H, d, J=6 Hz, $C\underline{H}_2OH$), 3.65 (3H, s, OCH_3), 5.65 (1H, q, J=1 Hz, =CH); ^{13}C-NMR ($CDCl_3$, δ, TMS): 16.4 (7-CH_3), 18.6 (3-CH_3), 24.8 (C-5), 32.7 (C-6), 35.6 (C-7), 41.0 (C-4), 50.6 (OCH_3), 68.0 (C-8), 115.1 (C-2), 159.9 (C-3), 167.0 (C-1).

The conversion (PDC oxidation in DMF[13]) followed by HCl-hydrolysis of the monomethyl ester) of 7 into the diacid (S)-8 (65% yield, $[\alpha]_D^{21}$ +11.2° (c 0.66, $CHCl_3$)),[14] whose absolute configuration and optical activity were interrelated by Mori et al.[15] through unambiguous asymmetric synthesis and accurate estimation of the e.e. of the product, clearly defines the (S)-configuration and the enantiomeric excess (> 97%) of 7.

$LiAlH_4$ reduction of 7 gave (S)-1 (82% yield; $[\alpha]_D^{25}$ -8.9° (c 1.55, $CHCl_3$)).[16]

The diacid 8 is also known as callosobruchusic acid in that it is a component of the copulation release pheromone (erectin) of the azuki bean weevil (Callosobruchus chinensis L.).[17] The absolute configuration of the naturally occurring 8 is still unknown. Although both enantiomers of 8 were found to be biologically active, the potency of the (S)-form appeared higher than that of its antipode and significantly closer to that of the natural pheromone.[15]

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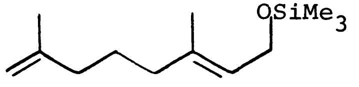
References

1) J. Meinwald, W.R. Thompson, T. Eisner, and D.F. Owen, Tetrahedron Lett., 1971, 3485.

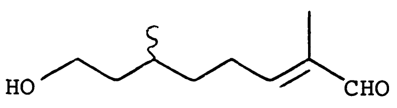
2) The only attempt to obtain optically active 1 by asymmetric hydroboration of:



with isopinocamphenylborane (from B_2H_6 and (-)-α-pinene) afforded a product having $[\alpha]_D^{20}$ +2.2° , which appears to be the (R)-isomer (e.e. ca. 23% from the data of the present paper): M. Julia and J.N. Verpeaux, Tetrahedron, 39, 3289 (1983).

3) a) J.P. Morizur, G. Bidan, and J. Kossanyi, Tetrahedron Lett., 1975, 4167; b) G. Bidan, J. Kossanyi, V. Meyer, and J.P. Morizur, Tetrahedron, 33, 2193 (1977); c) T. Fujisawa, T. Sato, T. Kawara, and A. Noda, Tetrahedron Lett., 23, 3193 (1982).

4) a) C. Fuganti, D. Ghiringhelli, and P. Grasselli, J. Chem. Soc., Chem. Commun., 1975, 846; b) M.G.W. Leuenberger, W. Boguth, R. Barner, M. Schmid, and R. Zell, Helv. Chim. Acta, 62, 455 (1979); c) C. Fuganti and P. Grasselli, J. Chem. Soc., Chem. Commun., 1979, 995; d) P. Gramatica, B.M. Ranzi, and P. Manitto, Bioorg. Chem., 10, 22 (1981); e) P. Gramatica, P. Manitto, and L. Poli, results to be published concerning the microbial conversion of:



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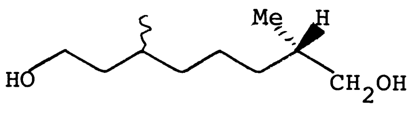

5) It must be pointed out that, in all cases examined from a stereochemical point of view,[4b,c,e] the hydrogenation of α-methyl-α,β-unsaturated aldehydes by baker's yeast was shown to give the (S)-configuration at C-α of the resulting alcohols.

6) This reaction is known to be stereoselective: U.T. Bhalerao and H. Rapoport, J. Am. Chem. Soc., 93, 4835 (1971).

7) All compounds reported gave satisfactory spectroscopic and analytical data.

8) **4**: IR (liquid film): 1730, 1680, 1640 cm^{-1}; ^1H-NMR ($CDCl_3$, δ, TMS): 1.8 (6H, s, $2CH_3$-C=), 2.1 (3H, s, CH_3CO), 2.0-2.8 (4H, m, CH_2), 4.6 (2H, d, J=6 Hz, CH_2-OAc), 5.4 (1H, t, J=6 Hz, 7-H), 6.45 (1H, t, J=6 Hz, 3-H), 9.4 (1H, s, (E)-CHO); ^{13}C-NMR ($CDCl_3$, δ, TMS): 9.1 (2-CH_3), 16.3 (6-CH_3), 20.8 ($\underline{C}H_3CO$), 27.0 (C-4), 37.7 (C-5), 60.9 (C-8), 119.7 (C-7), 139.6 (C-2), 140.0 (C-6), 152.8 (C-3), 170.4 ($CH_3\underline{C}O$), 194.4 (C-1).

9) P. Gramatica, P. Manitto, B.M. Ranzi, A. Delbianco, and M. Francavilla, Experientia, 38, 775 (1982).

10) (S)-**1**: IR and ^1H-NMR spectra were identical with those reported in Refs.1, 3b,c for racemic **1**. ^{13}C-NMR ($CDCl_3$, δ, TMS): 16.1 (3-CH_3), 16.5 (7-CH_3), 24.9 (C-5), 32.6 (C-6), 35.5 (C-7), 39.6 (C-4), 60.8 (C-1), 67.9 (C-8), 123.5 (C-2), 138.9 (C-3). Its physiological activities remain to be clarified.

11) The rather low yields are likely due to an extensive degradation of the starting material.

12) Methyl geraniate was converted into **6** by SeO_2 oxidation according to Ref.6 (32% yield): IR (liquid film): 1715, 1680, 1640 cm^{-1}; ^1H-NMR ($CDCl_3$, δ, TMS): 1.8 (3H, d, J=1 Hz, 7-CH_3), 2.2 (3H, d, J=1 Hz, 3-CH_3), 2.0-2.8 (4H, m, $2CH_2$), 3.75 (3H, s, OCH_3), 5.8 (1H, q, J=1 Hz, 2-H), 6.45 (1H, tq, J=6 and 1 Hz, 6-H), 9.4 (1H, s, (E)-CHO). ^{13}C-NMR ($CDCl_3$, δ, TMS): 9.23 (7-CH_3), 18.6 (3-CH_3), 26.7 (C-5), 39.0 (C-4), 50.7 (OCH_3), 116.1 (C-2), 139.9 (C-7), 151.7 (C-6), 157.4 (C-3), 166.5 (C-1), 194.4 (C-8).

13) E.J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399.

14) Lit,[15] $[\alpha]_D^{21}$ +11.4° (c 0.10, $CHCl_3$), calcd. assuming 100% e.e. Analytical and spectroscopic data of (S)-**8** were identical with those reported by Mori.[15]

15) K. Mori, T. Ito, K. Tanaka, H. Honda, and I. Yamamoto, Tetrahedron, 39, 2303 (1983).

16) It may be pointed out that rotations observed for the (S)-form of **1**, **7** (levo) and **8** (dextro) are in agreement with the empirical rules relating the sign of rotation at the sodium D line to the absolute configuration in the homologous series Me-$(CH_2)_n$-CHMe-CH_2OH and Me-$(CH_2)_n$-CHMe-CO_2H where $n \geqslant 1$; cf.: W. Kline and J. Buckingham, "Atlas of Stereochemistry," 2nd ed, Chapman and Hall, London (1978), Vol.1 pp. 64-65; P.A. Levene and A. Rothen, J. Org. Chem., 1, 76 (1936).

17) K. Tanaka, K. Ohsawa, H. Honda, and I. Yamamoto, J. Pesticide Sci., 6, 75 (1981).

18) E.J. Corey, N.W. Gilman, and B.E. Ganem, J. Am. Chem. Soc., 90, 5616 (1968).

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