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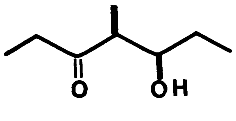
Chiral α-Methyl-homoallylic Alcohols from Yeast-Generated Precursors. Synthesis of (4*R*,5*S*) Sitophilure

Giovanni FRONZA, Claudio FUGANTI, Hans-Erik HÖGBERG,[1)]
Giuseppe PEDROCCHI-FANTONI, and Stefano SERVI
CNR Centro per lo Studio delle Sostanze Organiche Naturali. Dipartimento di Chimica
Politecnico di Milano, Piazza L. da Vinci 32, 20133 Milano, Italy

Optically active (3*S*,4*R*)-3,4-dihydroxy-4-methyl-6-phenyl-hex-5-ene and (2*S*,3*RS*)-2,3-dihydroxy-3-methyl-5-phenyl-pent-4-ene, previously obtained from fermenting baker's yeast reduction of the corresponding ketones, are transformed either into optically active α-ethyl and α-methyl ketones, or into α-methyl homoallylic alcohols from which enantiomerically pure (4*S*, 5*R*) sitophilure, (2*S*,3*R*)-2-methyl-1,3-butandiol and its (2*S*, 3*S*)-diastereoisomer have been prepared.

A recent report[2)] on the synthesis of the (4*R*,5*S*) form **1** of the pheromone sitophilure[3)] and of its enantiomer from yeast generated methyl (3*R*) 3-hydroxy pentanoate through the key intermediacy of (2*S*,3*R*)-2-methyl-3-^{t}butyl-dimethyl-silyloxy-pentanal **2** induces us to present a short preparation of 1 realized in a study designed to obtain synthetically useful chiral α-methyl homoallylic alcohols from (3*S*,4*R*)-3,4-dihydroxy-4-methyl-6-phenyl-hex-5-ene **3** and (2*S*,3*RS*)-2,3-dihydroxy-3-methyl-5-phenyl-pent-4-ene **11**, obtained from baker's yeast treatment of the corresponding ketones.[4)]



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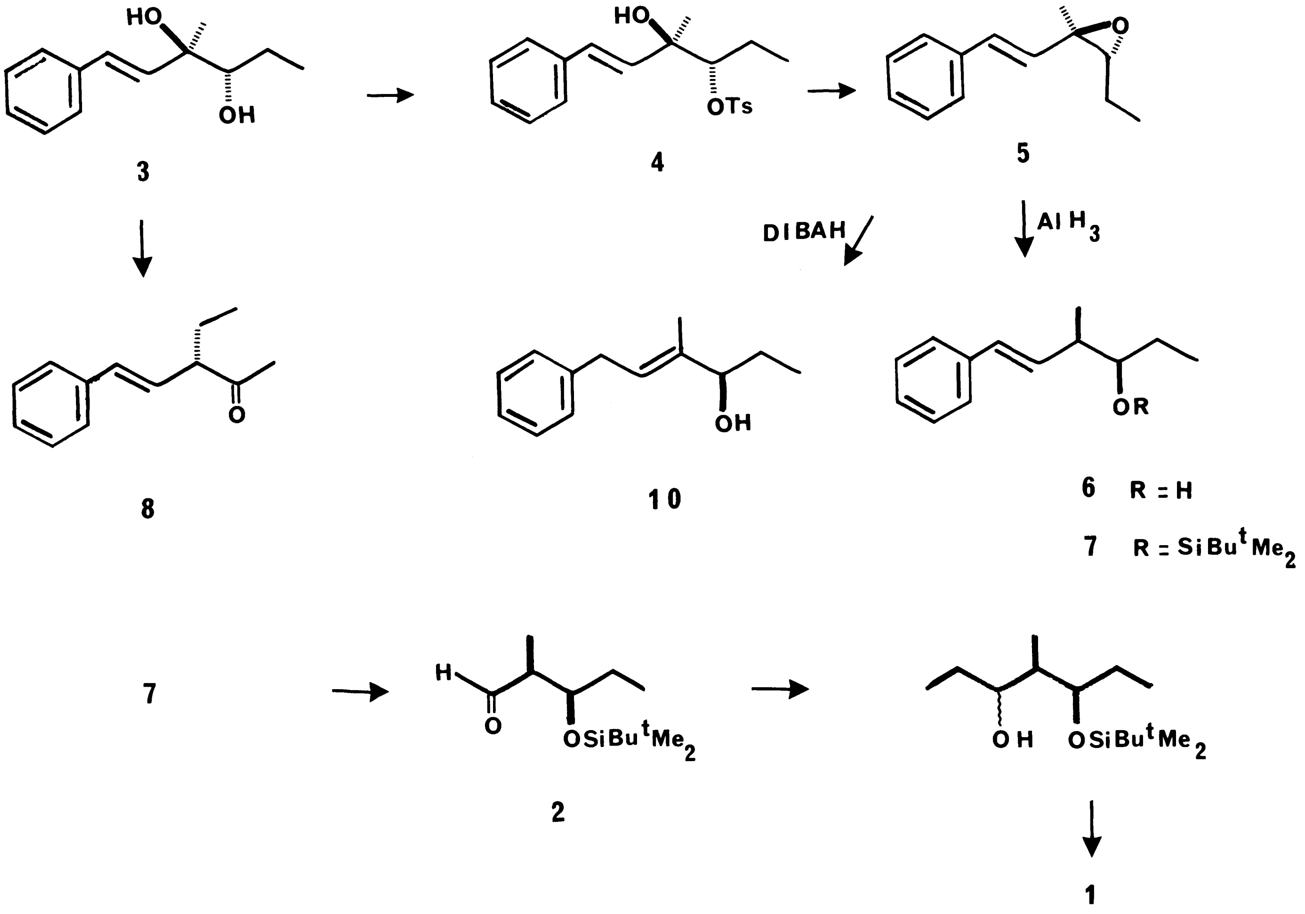
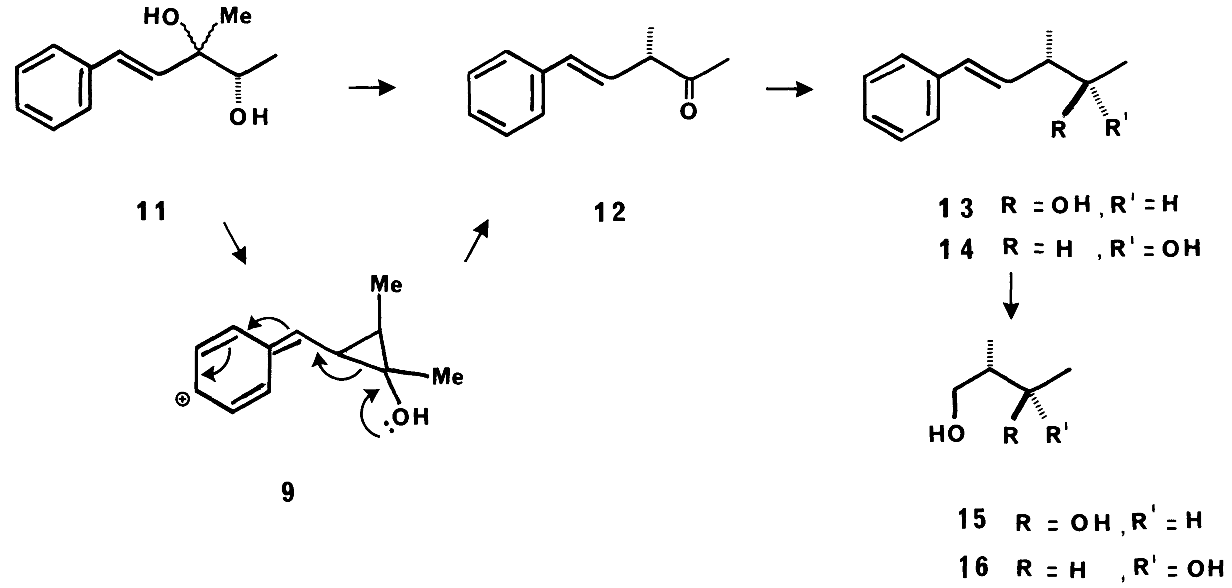
We aimed to convert **3** into **2** through the tosylate **4**, the epoxide **5** and the product of 1,2-opening **6**, according to earlier experience.[5)] Ozonolysis of the *O*-protected product **7** would subsequently produce the required **2**. Rather unexpectedly, the diol 3 when treated with 1 mol equiv. of TsCl in pyridine at 0 °C, did not give the anticipated tosylate 4 but instead the ethyl ketone 8 (vide infra). However, this difficulty was circumvented by trapping the unstable tosylate as the required epoxide 5 which was isolated in 70% yield when the diol 3 was reacted with excess solid TsCl in 1,2-dimethoxyethane in the presence of powdered KOH.$^{6)}$ Treatment of 5 with DIBAH in THF at -50 °C afforded the product of 1,4-opening 10, in 90% yield, whereas with AlH_3 in Et_2O at -30 °C gave rise to the required carbinol 6, which was converted into the protected compound 7, $[\alpha]_D^{20}$ -14.6° (c 1, $CHCl_3$), in ca. 40% overall yield. Product 7 on ozonolysis in CH_2Cl_2 at -78 °C and Ph_3P treatment afforded benzaldehyde and compound 2. This mixture was immediately reacted with ethereal $BrMgCH_2CH_3$. The adduct was separated by chromatography from 1-phenylpropan-1-ol, and after Swern oxidation followed by deprotection, it afforded as reported,$^{2)}$ compound (1), $[\alpha]_D^{20}$ +26.2° (c 1, Et_2O) (96% by GLC) (lit.$^{2)}$ +26.7°) in 45% from 7.



Scheme 1.

The (2S,3RS) diol 11 behaved similarly to compound 3 when reacted with TsCl/pyridine, furnishing 3-methyl-5-phenylpent-4-en-2-one, 12 $[\alpha]_D^{20}$ +76.3° (c 1, CHCl$_3$), containing an excess of the (3*S*) enantiomer, and proceeding through **9** as a possible intermediate, in a not unprecedented fashion.7) Indeed, product **12** on DIBAH reduction afforded (2*R*,3*S*) **13**, $[\alpha]_D^{20}$ -29.3° (c 1, CHCl$_3$) and **14**,$[\alpha]_D^{20}$ -16.5° (c 1, CHCl$_3$), in 2:1 ratio, separated by fractional crystallization of the 3,5-dinitrobenzoates, in 70% overall yield.



Scheme 2.

These materials, in separate runs, were benzoylated and treated sequentially with O$_3$ in CH$_2$Cl$_2$/MeOH, NaBH$_4$ and aqueous NaOH to give (3*R*,2*S*) **15**, $[\alpha]_D^{20}$ -3.7° (c 3.5, EtOH)8) and (2*S*,3*S*) **16**,$[\alpha]_D^{20}$ +2.5° (c 3.5, EtOH)8) of *ca*. 0.6 ee, as confirmed by Mosher's analysis 9) of the intermediate 3-benzoate yielding **15**. These results, seen together, indicate that the conversion of the tosylate in the α-methyl ketone **12** is accompanied by inversion of configuration at C-2, being the loss of optical purity possibly due to the poor configurational stability of the intermediate ketone **12** to the basic conditions. Subsequently, the diol **11** was converted 7) into a mixture of diastereoisomeric epoxides, yielding on hydride opening, as above, product **13**, $[\alpha]_D^{20}$ -49° and the (2*R*,3*R*) diastereoisomer,$[\alpha]_D^{20}$ +30.2° (c 1, CHCl$_3$). These materials were similarly converted into optically pure **15**, $[\alpha]_D^{20}$ -6.4° (lit.8) -6.3°) and into the (2*R*,3*R*) diastereoisomer, $[\alpha]_D^{20}$ -4.2° (c 3.5, EtOH) (enantiomer of **16**), respectively, in *ca*. 35% overall yield from **11**. Recently,10) a ten steps preparation of (2*R*,3*R*) 2-methyl-3-benzyloxy butanal, conceivably accessible from **13** *via* benzylation and ozonolysis, from (2*S*)-3-hydroxy-2-methyl propionic acid has been reported.

The preparation from the diols **3** and **11** of the chiral α-methyl homoallylic alcohols **6**, **13** and the enantiomer of **14** in optically pure form, from which synthetically useful α-methyl-β-alkoxy C_5 and C_4 aldehydes can be obtained, is a further illustration of the significance to the synthesis of natural products of the microbial transformations of non conventional substrates leading to small highly functionalized educts.

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