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

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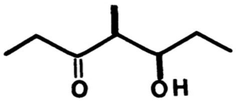
Optically active (3S,4R)-3,4-dihydroxy-4-methyl-6-phenyl-hex-5-ene and (2S,3RS)-2,3-dihydroxy-3-methyl-5-phenyl-pent-4-ene, previously obtained from fermenting baker's yeast reduction of the corresponding ketones, are transformed either into optically active α-ethyl and α-methyl ketones, or into α-methyl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

A recent report[2)] on the synthesis of the (4R,5S) form 1 of the pheromone sitophilure[3)] and of its enantiomer from yeast generated methyl (3R) 3-hydroxy pentanoate through the key intermediacy of (2S,3R)-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 (3S,4R)-3,4-dihydroxy-4-methyl-6-phenyl-hex-5-ene 3 and (2S,3RS)-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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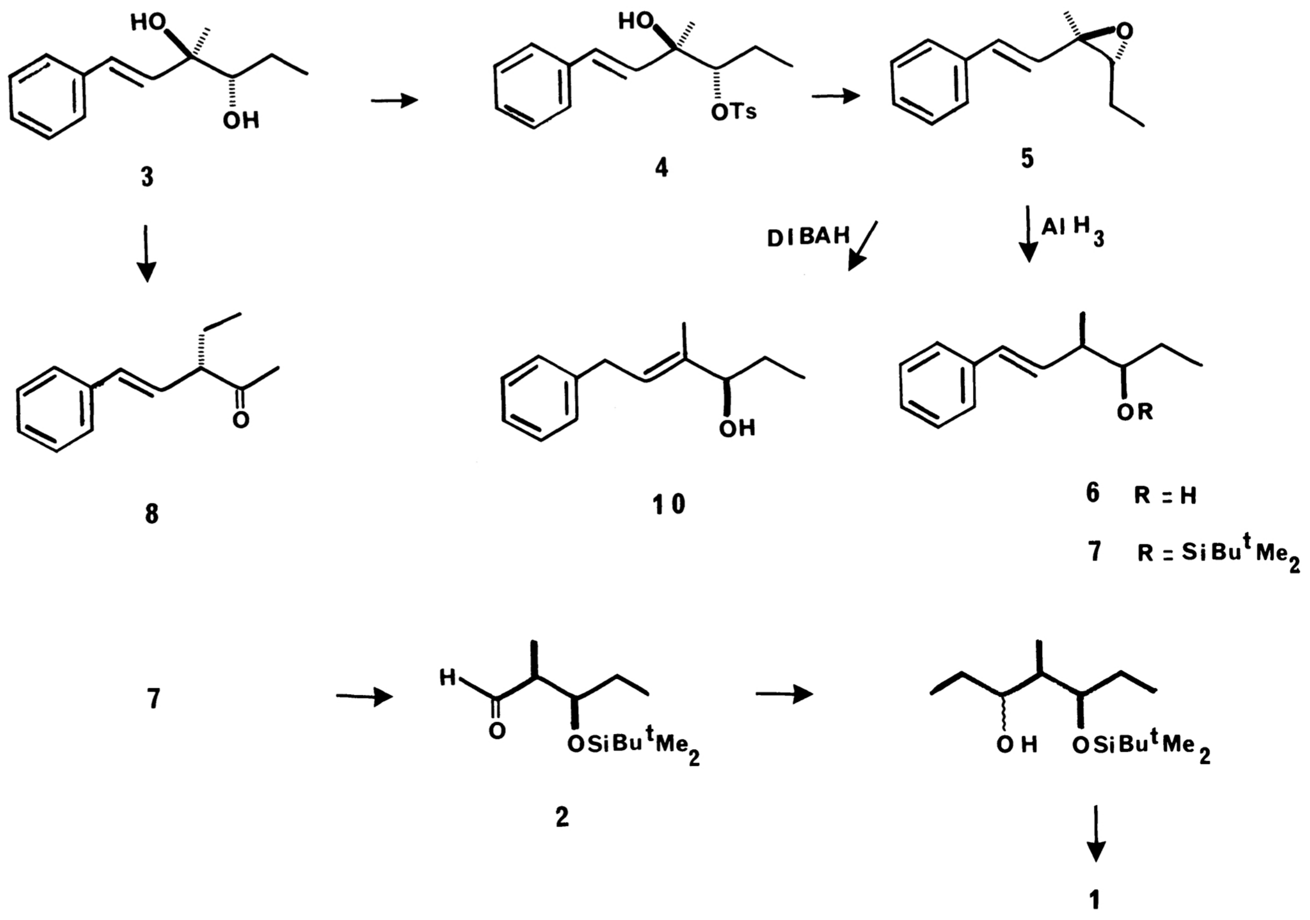
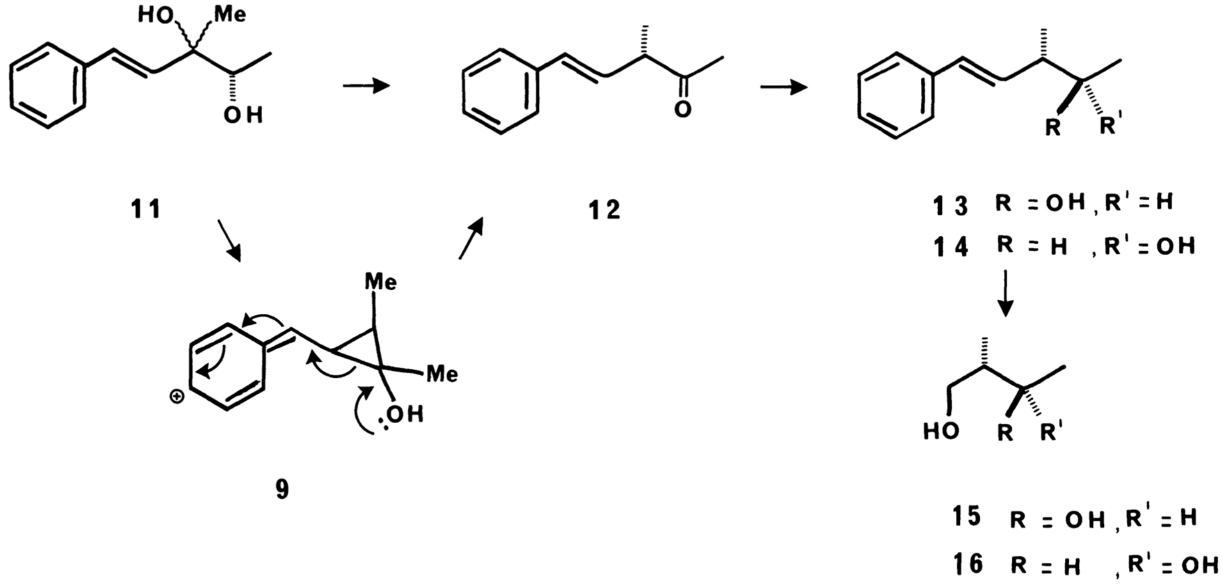
We aimed to convert 3 into 2 through the tosylate 4, the epoxide 5 and the product of 1,2-opening 6, according to earlier experience.[5)] Ozonolysis of the O-protected product 7 would subsequently produce the required 2. Rather unexpectedly, the diol 3 when treated with 1 mol equiv. of TsCl in pyridine 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 (2*S*,3*RS*) 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 (3S) enantiomer, and proceeding through 9 as a possible intermediate, in a not unprecedented fashion.[7] Indeed, product 12 on DIBAH reduction afforded (2R,3S) 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_2Cl_2/MeOH, $NaBH_4$ and aqueous NaOH to give (3R,2S) 15, $[\alpha]_D^{20}$ -3.7° (c 3.5, EtOH)[8] and (2S,3S) 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 (2R,3R) 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 (2R,3R) 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 (2R,3R) 2-methyl-3-benzyloxy butanal, conceivably accessible from 13 via benzylation and ozonolysis, from (2S)-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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