Tetrahedron Letters,Vol.29,No.18,pp 2197-2200,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

PREPARATION OF CHIRAL C_5-BUILDING BLOCKS FOR TERPENE SYNTHESIS BY BAKERS' YEAST REDUCTION OF SULFUR-FUNCTIONALIZED PRENYL DERIVATIVES

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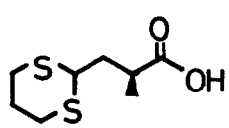
Summary: *Enantioselective hydrogenation of several α,β-unsaturated aldehydes and allylic alcohols of sulfur-functionalized prenyl derivatives with bakers' yeast gave bifunctional chiral (S)- and (R)-C_5-building blocks for terpene synthesis with high enantiomeric excess.*

Microorganism- or purified enzyme-mediated reactions of synthetic substrates provide a useful method for preparing chiral building blocks in natural product synthesis.[1] Of the microorganisms so far used, *Saccharomyces cerevisiae* (bakers' yeast) has been widely employed for the asymmetric reduction of carbonyl compounds to prepare the corresponding chiral secondary alcohols.[2] Although bakers' yeast is effectively used in reduction of variety of carbonyl compounds, it can also enantioselectively reduce carbon-carbon double bond in limited kinds of α,β-unsaturated carbonyl compounds,[3~7] allylic alcohols,[8] and nitroalkenes.[9] Recently, we have demonstrated that introduction of sulfur functional group to ketone is an effective way both for the stereocontrol in the asymmetric reduction with bakers' yeast and for further manipulation of the reduction product into natural products.[10] Herein we wish to report enantioselective preparation of useful bifunctional chiral C_5-building blocks for optically active terpenes,[3,4,7] *i.e.*, (S)-3-(1,3-dithian-2-yl)-2-methylpropanoic acid (1), (S)-2-methyl-4-phenylsulfonylbutanoic acid (2), (S)-3-methyl-4-phenylthio-1-butanol (3), and (R)-2-methyl-4-phenylthiobutanoic acid (4) by asymmetric hydrogenation of sulfur-functionalized prenyl derivatives, (E)-3-(1,3-dithian-2-yl)-2-methylpropenal(5), (E)-2-methyl-4-phenylsulfonyl-2-butenal (9), (E)-3-methyl-4-phenylthio-2-buten-1-ol (11), and 2-methylene-4-phenylthio-1-butanol (15) with bakers' yeast, respectively.

α,β-Unsaturated aldehyde 5, prepared from 2-formyl-1,3-dithiane[11] and α-formylethylidenetriphenylphosphorane[12] in 72% yield, was incubated with bakers'



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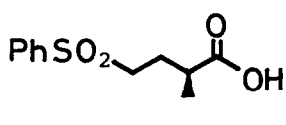

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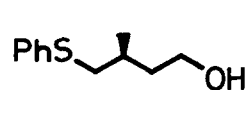

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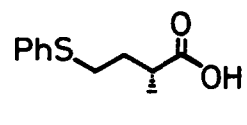

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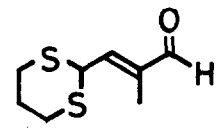
yeast (2.6 mmol of 5, 12 g of bakers' yeast (Oriental Yeast Co.) and 12 g of saccharose in 120 ml of water). Within 3 d, aldehyde 5 was completely consumed to give allylic alcohol 6. However, 5 was incubated for a long time[13] of 19 d by adding 6 g of saccharose every day and 6 g of bakers' yeast in 50 ml of water every three days with bubbling air to give optically pure (S)-propanoic acid derivative 1 in 48% yield, $[\alpha]_D^{23}$ +4.26°(c 0.41, CH_3OH), which was produced by hydrogenation of the carbon-carbon double bond and oxidation of aldehyde to carboxylic acid. The absolute configuration and optical purity of 3 were determined as follows: Acid 1 was treated with diazomethane to give the corresponding methyl ester, $[\alpha]_D^{23}$ +21.43°(c 0.78, CH_3OH). The dithiane was hydrolyzed to aldehyde,[14] followed by reduction with sodium borohydride and subsequent lactonization gave (S)-α-methyl-γ-butyrolactone (7), $[\alpha]_D^{23}$ -22.1° (c 0.20, C_2H_5OH), lit.[3] $[\alpha]_D^{20}$ -22.9°(c 2, C_2H_5OH), which was shown to be optically pure by ^1H NMR analysis in the presence of $Eu(hfc)_3$. In the literatures on the bakers' yeast-mediated reduction of α,β-unsaturated aldehydes or allylic alcohols, oxidation of alcohol or aldehyde in the substrates into carboxylic acid has not been reported so far. The observation that incubation of (E)-3-(1,3-dithian-2-yl)-2-methylpropenoic acid (8) instead of aldehyde 5 gave no reduction product suggests that oxidation into carboxylic acid proceeds after hydrogenation of the carbon-carbon double bond of 5.

Next, phenylsulfonylbutenal 9, prepared by selenium dioxide oxidation of phenyl prenyl sulfone[15] in 34% yield, was subjected to the bakers' yeast reduction as described above for 17 d to give hydrogenated acid 2, $[\alpha]_D^{23}$ -3.55°(c 0.17, CH_3OH) in 35% yield, of which optical purity was determined to be 86% ee by ^1H NMR of the corresponding methyl ester, $[\alpha]_D^{23}$ +11.0°(c 0.42, CH_3OH), in the presence of $Eu(hfc)_3$. The absolute configuration was confirmed by transformation of 2 into (S)-2-methylbutanoic acid (10), $[\alpha]_D^{23}$ +14.6°(c 0.10, heptane), lit.[16] $[\alpha]_D^{25}$ +15.92°(c 3.3, heptane) with Raney nickel.

Allylic alcohol with γ-methyl group 11, prepared from (E)-4-chloro-3-methyl-2-buten-1-ol[17] and benzenethiol in the presence of triethylamine in 73% yield, was incubated with bakers' yeast for 21 d to give the desired reduction product 3, $[\alpha]_D^{23}$ +9.24°(c 0.82, CH_3OH), in 22% yield along with the double bond-migrated product 12 (12%). In contrast with the above result, formation of 4-phenylthio-3-methylbutanoic acid was not observed. Comparison of the specific rotation value of 3 with that of authentic sample of (S)-3[18] with 88%ee, $[\alpha]_D^{23}$ +11.89°(c 1.0, CH_3OH), shows that the yeast reduction product 3 is (S)-alcohol with 68%ee. Instead of phenylthiobutenol 11, 4-phenylsulfinyl- and 4-phenylsulfonyl-3-methyl-2-buten-1-ol (13 and 14) were also examined in the bakers' yeast reduction, however, resulting in only the double bond migration of the starting materials. Thus the kinds of sulfur functional groups and the position of methyl group in the substrates greatly affect the present yeast reduction.[7]

For comparison with the reduction of trisubstituted double bond as described above, allylic alcohol with methylene double bond 15 was prepared by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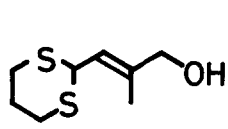
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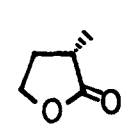
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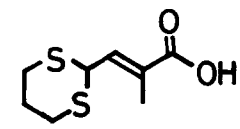
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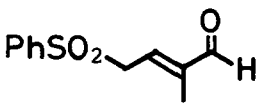
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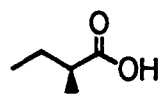
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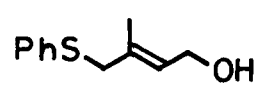
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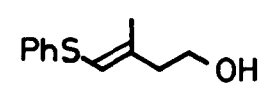
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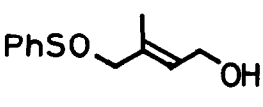
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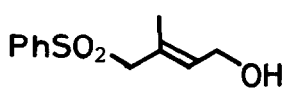
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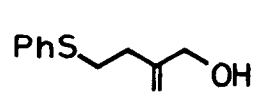
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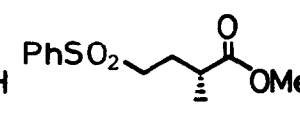
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the reaction of (2-((trimethylsilyloxy)methyl)-2-propenyl)trimethylsilane with[19] chloromethyl phenyl sulfide in the presence of titanium tetrachloride[20] in 44% yield and incubated with bakers' yeast for 21 d to give the desired acid **4**, $[\alpha]_D^{23}$ -12.65° (c 0.32, CH_3OH), in 39% yield. On treatment with CH_2N_2 and oxidation with m-chloroperbenzoic acid, **4** gave methyl 2-methyl-4-phenylsulfonylbutanoate (**16**), $[\alpha]_D^{23}$ -14.4° (c 0.32, CH_3OH). Comparison of the specific rotation value of **16** with that of the methyl ester of (S)-**2** and ^1H NMR analysis in the presence of Eu(hfc)$_3$ show the (R)-configuration of **4** with over 96%ee. Thus, changing the feature of the double bond from trisubstituted one to methylene one resulted in reversal of the hydrogen delivery by the yeast.

As mentioned above, the position of methyl group and the feature of the carbon-carbon double bond in the substrates affect the course of hydrogen delivery. Based on the present results and the data in the literatures reported so far, the following trends in the yeast reduction of di- or trisubstituted carbon-carbon double bond have been observed: In the case of α,β-unsaturated aldehydes with α-methyl group such as **5** and **9**, hydrogen attacks at the prochiral sp^2 carbon from *re*-face.[3,4,7] In the reduction of α,β-unsaturated aldehydes with β-methyl group[7] and allylic alcohols with γ-methyl group,[8] if one considers the hydroxymethyl group in **11** as the ligand of the first order of priority in the present case, hydrogen comes from *si*-face. On the other hand, the substrate with methylene group **15** and α-methylene ketones[6] are reduced from *si*-face.

In conclusion, the bakers' yeast-mediated reduction of carbon-carbon double bond of sulfur-functionalized prenyl derivatives can provide both enan-

tiomers of bifunctional chiral C_5-building blocks for terpene synthesis by changing the structure of the substrates.

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13. Incubation of 5 for 10 d gave an inseparable mixture of 6, the corresponding saturated alcohol, 3-(1,3-dithian-2-yl)-2-methyl-1-propanol and unidentified products along with 1 (16%). Although the incubation time of 19 d was long, it was preferable for easy isolation of 1. Similarly, long time incubation of 9 and 15 was necessary for isolation of pure reduction products.
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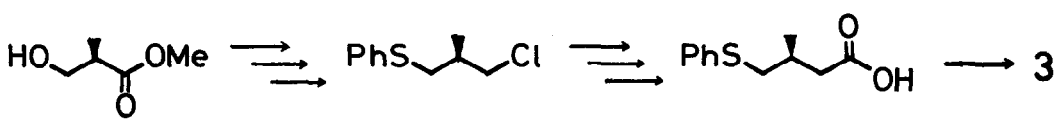
18. (S)-Alcohol 3 was prepared from methyl (R)-3-hydroxy-2-methylpropanoate (88%ee) as follows: Tosylation of the hydroxy ester, substitution with



benzenethiol in the presence of triethylamine, reduction of the ester with $LiAlH_4$ and chlorination of the resulting alcohol with $SOCl_2$ gave 2-methyl-3-phenylthio-1-chloropropane in 67% overall yield. The chloride was converted into the corresponding Grignard Reagent followed by reaction with CO_2 and reduction with $LiAlH_4$ gave 3 in 10% yield.
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(Received in Japan 17 December 1987)