

Baker's Yeast Reduction of 3-Phenylthiomethyl-2-butenolide and Its Derivatives: Synthesis of Versatile Chiral C₅-Building Blocks for Terpenoid Synthesis

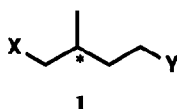
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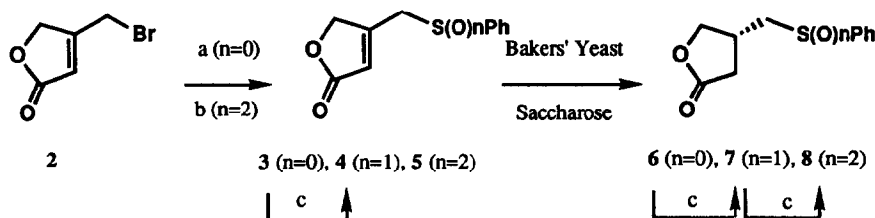
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Abstract: Bakers' yeast reduction of 3-phenylthiomethyl-2-butenolide gave (R)-3-phenylthiomethylbutanolide (99% e.e.), a versatile chiral C₅-building block for terpenoid synthesis.

Utilization of enzymatic reactions¹ on synthetic substrates is one of the effective methods in asymmetric induction to organic molecules, and common bakers' yeast (*Saccharomyces cerevisiae*) is a particularly easy microorganism to use for this purpose.² On the other hand, the chiral C₅-isoprenoid building blocks of general formula **1** is the useful intermediates for the synthesis of various natural products and has been prepared by several chemoenzymatic approaches.³ In a recent continuation of our work⁴ on the synthesis of chiral lactones as pivotal synthons, this paper describes that the sulfur-containing chiral C₅-building blocks with high optical purity can be easily prepared by bakers' yeast reduction of 3-phenylthiomethyl-2-butenolide derivatives, **3**, **4** and **5**.

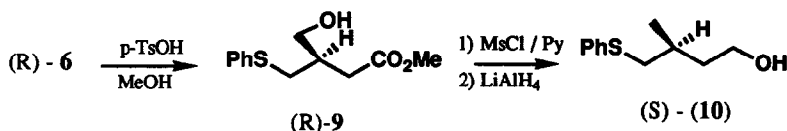


The butenolides **3**, **4** and **5**⁵ were prepared from 3-bromomethyl-2-butenolide (**2**)⁶ according to the following scheme. Bakers' yeast reduction of 3-phenylthiomethyl-2-butenolide (**3**) was performed at 35°C for



a) PhSH-pyridine / CH₂Cl₂ (77% yield), b) PhSO₂Na / DMF (88% yield), c) m-CPBA

five days in the presence of saccharose to afford (+)-2-phenylthiomethylbutanolide (**6**) in 41% yield [**6**: [α]_D²³ +15.8 (c0.985, CHCl₃)]. The enantiomeric excess of **6** was determined to be 99% e.e. by HPLC analysis (Chiralcel OD, hexane:2-propanol=7:3). To determine the absolute configuration of (+)-**6**, the chiral **6** was converted to the known (S)-3-methyl-4-phenylthio-1-butanol (**10**),⁷ a versatile bifunctional chiral building



block, $[\alpha]_{\text{D}}^{23} +13.7$ (c0.85, CH₃OH), Lit.^{3b} $[\alpha]_{\text{D}}^{23} +11.89$ (c1.0, CH₃OH) for (S)-**10** with 88% e.e.. On the basis of this result, the absolute configuration of **6** obtained by bakers' yeast reduction was defined to be (R). The sulfide **6** with 99% e.e. was then treated with 1 eq. of m-CPBA to afford (3R)-phenylsulfinylmethylbutanolide (**7**), [74% yield, $[\alpha]_{\text{D}}^{19} +4.53$ (0.67, CHCl₃)], which was finally converted into (R)-3-phenylsulfonylmethylbutanolide (**8**), $[\alpha]_{\text{D}}^{20} +6.21$ (c0.85, CHCl₃), in 97% yield.

Furthermore, bakers' yeast reduction of 3-phenylsulfinylmethyl- and 3-phenylsulfonylmethyl-2-butenolide (**4** and **5**) were also examined instead of **3**. Bakers' yeast reduction of **4** in the presence of saccharose at 35°C for seven days gave the corresponding chiral sulfoxide **7**, [49% yield, $[\alpha]_{\text{D}}^{23} +10.3$ (c1.15, CHCl₃)]. The absolute configuration and the optical purity at C-3 position of (+)-**7** were determined to be (R)⁸ and 97% e.e.⁹ by its conversion to the sulfone, (R)-(**8**), by m-CPBA oxidation, [(R)-**8**: 82% yield, $[\alpha]_{\text{D}}^{22} +6.08$ (c1.04, CHCl₃)]. In case of the reduction of **5** by bakers' yeast (35°C, 7 days), however, the yield and the e.e. of R-(+)-**8** obtained were very low. [14% yield, 77% e.e.,⁹ $[\alpha]_{\text{D}}^{21} +4.70$ (c0.84, CHCl₃)].

In conclusion, bakers' yeast reduction of the double bonds of sulfur-functionalised butenolides could provide the trifunctional chiral C5-building blocks useful for terpenoid synthesis. Further study on the synthesis of chiral terpenoids using these building blocks is now in progress.

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References and Notes:

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- Fujisawa *et al.*^{3b} reported that bakers' yeast reduction (21 days) of (E)-3-methyl-4-phenylthio-2-buten-1-ol gave (S)-**10** with 68% e.e. in 22% yield.
- The absolute configuration and the optical purity of sulfinyl group of (+)-**7** could not be established. However, the small specific rotation value of the chiral **7** obtained here indicates that the bakers' yeast could not satisfactorily discriminate the chirality of sulfinyl group of the butenolide **4**.
- The e.e. was determined on the basis of the value of the specific rotation.