Tetrahedron: Asymmetry Vol. 3, No. 11, pp. 1385-1386, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00

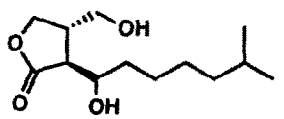
Asymmetric Reduction of 3-Hydroxymethylbutenolide Derivatives by Bakers' Yeast: A New Approach to the Synthesis of Factor-I

Kunihiko Takabe,* Masaya Tanaka, Masahisa Sugimoto, Takashi Yamada, and Hidemi Yoda
Department of Applied Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432, Japan

(*Received* 22 *September* 1992)

Abstract: Bakers' yeast reduction of 3-benzyloxymethylbutenolide gave (S)-3-benzyloxymethylbutanolide, and its transformation to Factor-I, the autoregulator of *Streptomyces viridocchromogenes*, was examined.

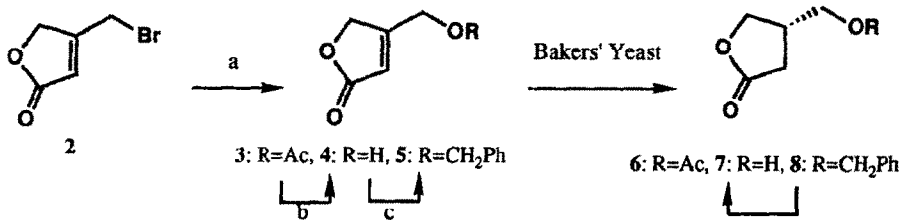
Since the discovery of A-factor from *S. griseus* in 1976,[1] 2,3-disubstituted butanolides such as factor-I(**1**)[2] and virginiae butanolides A-E[3], have been isolated as the autoregulators for the production of antibiotics in *Streptomyces*. All of these molecules have a common structural feature, a chiral 3-hydroxymethylbutanolide skeleton, and the asymmetric synthesis of the autoregulators such as A-factor and virginiae butanolides have been, thus far, reported by several groups.[4] On the other hand, bakers' yeast (*Saccharomyces cerevisae*) has been well known[5] to reduce carbonyl compounds to chiral alcohols. However, there have been relatively few reports[6] concerning the asymmetric reduction of carbon-carbon double bonds with bakers' yeast.



1 : Factor -I

With these considerations in mind, this paper describes an efficient synthesis of chiral 3-hydroxymethylbutanolide and its derivatives, which are versatile chiral building blocks[4] for the synthesis of the autoregulators, utilizing bakers' yeast reduction of the corresponding butenolides.

The butenolides, **3**, **4** and **5**, was easily prepared from 3-bromomethylbutenolide (**2**)[7] according to the following scheme. The bakers' yeast reduction of 3-acetoxymethylbutenolide(**3**) in the presence of saccharose

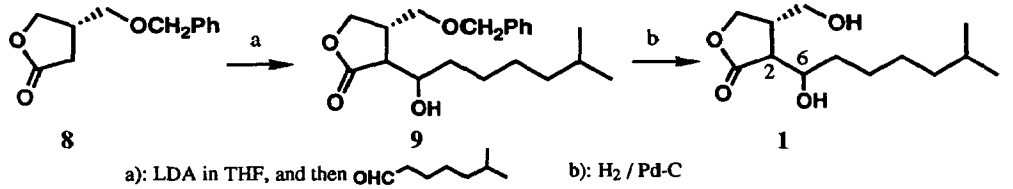


a): KOAc, 18-crown-6 /CH_3CN, 60°C, 3 hrs (80% yield), b): CH_3COCl /EtOH, 50°C, 4 hrs (72% yield).
c): $PhCH_2OC(=NH)CCl_3$[8] /CH_2Cl_2-cyclohexane /CF_3CO_2H (60% yield).

gave optically active (+)-3-acetoxymethylbutanolide (**6**), $[\alpha]_D^{23}$+34.5 (c4.11,$CHCl_3$), in 60 % yield. The absolute configuration of **6** was defined to be (S) by comparison with the specific rotation of its antipode, (R)-**6**: $[\alpha]_D^{24}$-25.3 (c0.96,$CHCl_3$)[4b], $[\alpha]_D^{23}$-33.1 ($CHCl_3$)[4e]. Since the conversion of the chiral acetate **6** into the chiral alcohol **7** by chemical hydrolysis was found to be difficult without racemization ,[4b] the reduction of 3-hydroxymethylbutenolide(**4**) by bakers' yeast was also examined. However, the yield and the optical purity of (S)-3-hydroxymethylbutanolide (**7**) obtained here were very low.[9]

In order to prepare the synthetically useful chiral 3-hydroxymethylbutanolide derivatives, the bakers' yeast reduction of 3-benzyloxymethylbutenolide (**5**) was examined. The treatment of **5** with bakers' yeast in the presence of saccharose gave (+)-3-benzyloxymethylbutanolide (**8**) [95% e.e.[10], $[\alpha]_D^{23}$ +32.5 (c0.93,$CHCl_3$)] in 34% yield. To determine the absolute configuration of **8**, the benzyl group of **8** was deprotected by hydrogenolysis in ethanol using Pd-C to afford (S)-(+)-7($[\alpha]_D^{23}$+41.2 (c0.86,$CHCl_3$) in 89% yield. On the basis of this result, the absolute configuration of **8** was determined to be (S).

To illustrate the use of (S)-**8** as a chiral building block, the following approach to the synthesis of factor-I was examined. The treatment of (S)-**8** with LDA in THF at -78°C, followed by the addition of 6-methylheptanal solution of THF at -78°C gave the alkylated butanolide (**9**) in 66% yield, which was then subjected on hydrogenolysis (Pd-C) to afford Factor-I (**1**): $[\alpha]_D^{19.5}$+13.9 (c1.21,$CHCl_3$), in 92% yield.



Further study including the stereochemistry at C-2 and C-6 positions of synthetic **1** is now in progress.

Acknowledgements: The authors are grateful to Professor T. Katagiri for his encouragements. We also thank Mr. A. Miyazaki and T. Ishioka for their preliminary experiments.

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9. (S)-**7**: 7% yield, $[\alpha]_D^{23}$+22.2 (c0.75,$CHCl_3$) [Lit.[6c,d] $[\alpha]_D^{21.5}$+44.8 (c1.552,$CHCl_3$)].
10. The e.e. of **8** was determined by HPLC anaysis (YMC A-012, sil) of the diastereomeric amides which could be obtained by the reaction of chiral (**8**) with (S)-(-)-1-(α-naphthyl)ethylamine.