Tetrahedron Letters,Vol.23,No.52,pp 5489-5492,1982 0040-4039/82/525489-04$03.00/0
Printed in Great Britain

BIFUNCTIONAL CHIRAL SYNTHONS VIA MICROBIOLOGICAL METHODS. 2. OPTICALLY-ACTIVE α-HYDROXY ALDEHYDES.[1]

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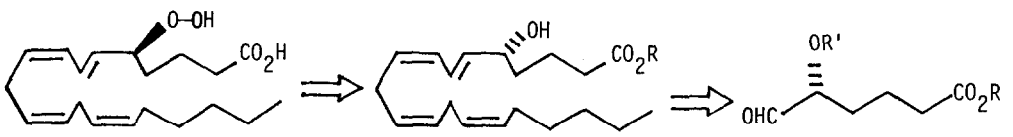
Summary: A versatile chemical-microbiological approach has been developed for the preparation of chiral α-hydroxy aldehydes via stereoselective reduction of the corresponding α-keto thioacetals or via optical resolution of the racemic α-acetoxy esters.

As part of our continued interest in the preparation of intermediates of the arachidonic acid cascade[2], we have been concerned with the development of a synthetic procedure to make 5(S)-HPETE[3], 1 available for chemical and enzymatic mechanistic studies. This hydroperoxide, 1, is a key precursor[4] in the biosynthesis of the Leukotrienes[5] (A, B, C, D, E) from arachidonic acid. Although small quantities of 1 may be obtained from biochemical incubations[3], tedious separations of the complex incubation mixtures are required. We envisaged that 1 may be derived from 5(R)-HETE[6], 2, which in turn may be prepared from the aldehydic ester, 3, using conventional chemical methodology. Herein, we report methods for the syntheses of chiral α-hydroxy aldehydic esters using microbial enzymes.



1 2 3

Although stereoselective reductions by fermenting yeasts are well known, there are a few examples of similar reductions of aliphatic ketones with adjacent functional groups[7]. These reactions have been confined to the reduction of α-hydroxyketones, to ketoacids, and to haloketones. Hence, we decided to examine the microbial reduction of 6. The thioacetal in 6 not only serves as a latent aldehydic functionality, but its electron-withdrawing property should enhance the rate of microbial reduction of the adjacent carbonyl. Further, 6 may be readily prepared as follows: Reaction of the sodium salt of mono-methylglutarate (4) with two equivalents of 2-lithio-1,3-dithiane[8] in THF at -78°C for two hours, and then at 25°C for four hours, gave 5 in 78% yield. Refluxing of 5 with 2,2-dimethoxypropane in methanol (pTSOH) for three hours afforded 6 in 98% yield.

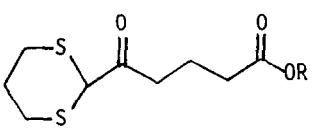
Most of the microbes[9] examined did transform 6 into 7, but the optical purity and yield of 7 were only moderate. It is evident that different microorganisms or even different strains of the same species markedly differ in their product stereoselectivity[10] (Table 1). However, the most promising organism appeared to be Kloeckera corticis ATCC 20109, which not only converted 6 into (-)7, $[\alpha]_D^{25}$ -21.3° (c = 3.2, $CHCl_3$) in 40% yield, but also this yeast was found to have a relaxed substrate specificity capable of reducing a variety of α-ketothioacetals into chiral alcohols[11] in excellent optical yields.

Table 1. Stereoselective reduction of the α-keto thioacetal, 6.

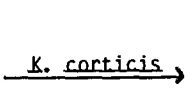
Microorganism[a]	Yield %	$[\alpha]_D^{25}$ ($CHCl_3$)
Saccharomyces cerevisiae strain 2235	12.2	+5.4
Saccharomyces cerevisiae strain 567	16.8	-21.1
Saccharomyces cerevisiae strain 24-R_1	25.8	-10.8
Schizosaccharomyces octosporus	49.0	-19.9
Zygosaccharomyces priorianus	18.8	+3.4
Hansenula subpelliculosa	66.6	-19.2
Kloeckera corticis ATCC 20109	40.0	-21.3

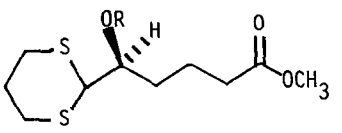
[a]Each of the microorganisms was incubated[9] with 1 g/L of 6 for 72 hrs.

To define the absolute configuration of the hydroxyl function, (-)7 was treated with benzoyl chloride in pyridine (25°C, 1 h) to furnish 8, $[\alpha]_D^{25}$ +3.41° (c = 2.2, $CHCl_3$) in 86% yield. Cleavage of the thioacetal[12] (CH_3I; $CaCO_3$; CH_3CN:H_2O, 4:1) gave the known aldehyde (62%), 9, $[\alpha]_D^{25}$ -34.2° (c = 3.7, $CHCl_3$), [lit.[13] $[\alpha]_D^{25}$ -33.3° (c = 2.5, $CHCl_3$)], an useful synthon for Leukotriene B syntheses[13,14]. This correlation thereby establishes that the newly generated hydroxyl group in (-)7 bears the S configuration. PMR analyses of the corresponding (-)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester[15] revealed that the optical purity of (-)7 was greater than 98% enantiomeric excess (e.e.).

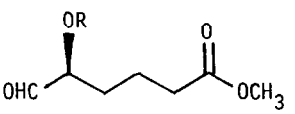


5 R = H
6 R = CH_3



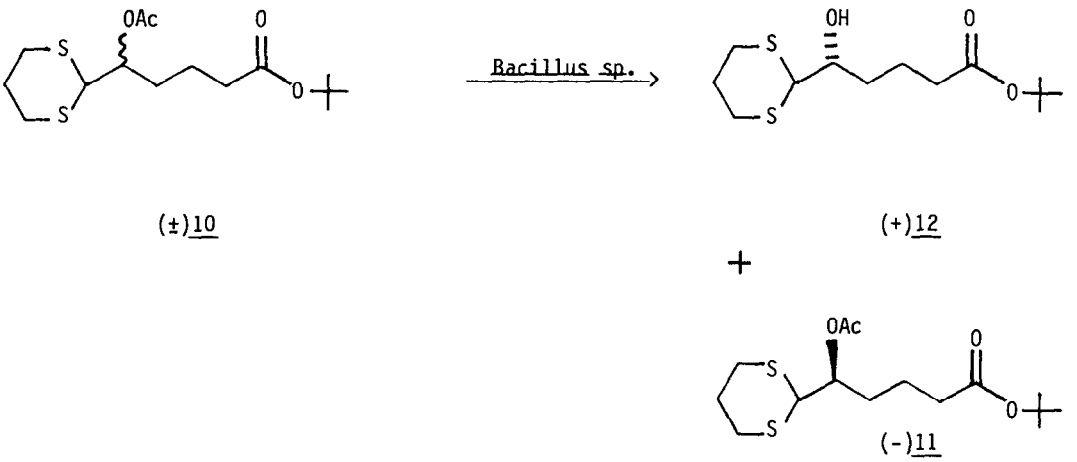


(-)7 R = H
8 R = $-\overset{O}{\overset{\|}{C}}-\phi$



9 R = $-\overset{O}{\overset{\|}{C}}-\phi$

Since we were unsuccessful in finding a suitable microbe to catalyze the reduction of 6 into (+)7 with a high degree of stereoselectivity, we turned our attention to the use of bacterial acylases for the synthesis of (+)7 using kinetic resolution methods[16]. Because bacteria have a general proclivity to cleave carbomethoxy esters, we used the t-butyl ester, (±)10 as the substrate for our incubation studies. Using a selection technique[17] previously described, we have found a soil isolate designated as Bacillus sp. 1d-5 that cleaved the acetoxy ester grouping of (±)10 to give (+)12, $[\alpha]_D^{25}$ +19.9° (c = 4.1, $CHCl_3$) in 32% yield, accompanied by 46% of (-)11, $[\alpha]_D^{25}$ -21.4° (c = 1.9, $CHCl_3$). Because (-)11 was transformed into (-)8, it follows that this microbial esterase preferentially hydrolyzed the R-acetoxy ester to furnish R(+)12. After converting (-)11 and (+)12 to their respective MTPA esters, PMR analyses showed the optical purities were 94% ee and >98% ee respectively, indicating that this microbial esterase possesses an E value[16] of >100.



(±)10 (+)12 (-)11

This combined chemo-microbiological approach provides a convenient method for the preparation of α-hydroxyaldehydes in quantities suitable for use as starter units in organic syntheses. The scope of these microbial reactions as well as the utilization of these chiral synthons for natural products syntheses are currently under investigation.

Acknowledgments. This study was supported in part by grant HL25772 from the National Institutes of Health.

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(Received in USA 26 August 1982)