

Asymmetric Syntheses of (-)-Malyngolide and (-)-Frontalin
by Utilizing Bakers' Yeast Reduction of S-Ethyl 2-Cyclopentanonecarboxylthioate

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Bakers' yeast reduction of S-ethyl 2-cyclopentanonecarboxylthioate affords optically pure S-ethyl (1R,2S)-2-hydroxycyclopentanecarboxylthioate which is stereoselectively converted into (-)-malyngolide and (-)-frontalin.

The asymmetric reduction of β -keto esters with bakers' yeast has provided optically active β -hydroxy esters which have been efficiently employed as chiral building blocks for natural product synthesis.¹⁾ Although the stereochemical course of the bakers' yeast reduction is generally explained by the Prelog's rule,²⁾ several enzymes in the microorganism can operate together in some cases to alter the course of hydrogen delivery and / or to reduce the enantioselectivity.³⁾ For example, ethyl 3-oxobutanoate is reduced to give (S)-3-hydroxybutanoate with >90%ee,⁴⁾ while ethyl 3-oxopentanoate give (R)-3-hydroxypentanoate with 40%ee.⁵⁾ For application of the reduction in organic synthesis, several methods have been developed to prepare enantiomerically pure compounds: immobilization of the yeast,⁶⁾ addition of enzyme inhibitor,⁷⁾ culture conditions,⁸⁾ and chemical modification of substrates.^{3,9)} Recently, introduction of sulfenyl group into β -keto esters¹⁰⁾ or use of dithioesters instead of usual esters¹¹⁾ has been found to control both stereochemical course and degree of enantioselectivity to give optically pure (S)-hydroxy esters. In this communication, we wish to report the enantio- and diastereoselective reduction of S-ethyl 2-cyclopentanonecarboxylthioate (1) leading into S-ethyl (1R,2S)-2-hydroxycyclopentanecarboxylthioate (*cis*-2) and a new strategy of conversion of β -hydroxy esters into chiral tertiary alcohol derivatives as shown in the asymmetric syntheses of (-)-malyngolide (6) and (-)-frontalin (10).

β -Keto thiol ester 1a (3.44 g, 20 mmol), prepared from di-S-ethyl hexanebis-(dithioate) by the Dieckmann condensation,¹²⁾ was incubated with 100 g of pressed

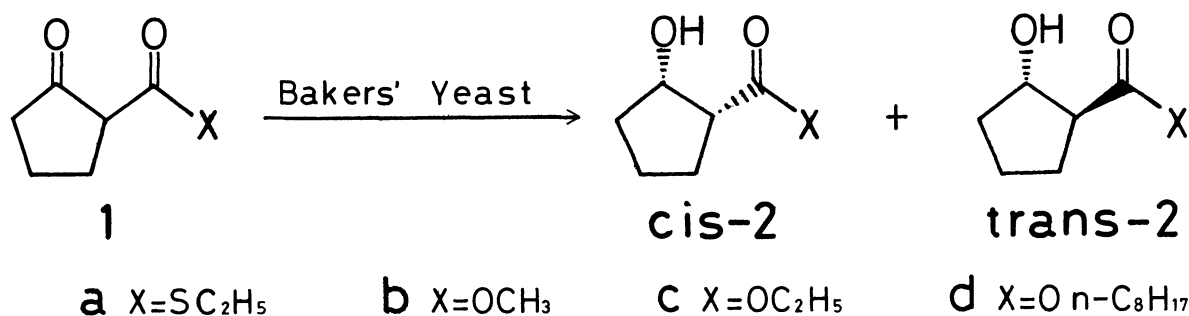


Table 1. Bakers' Yeast Reduction of Cyclopentanonecarboxylate 1 to 2

X of 1	Time	Yield of 2/% (<i>cis</i> : <i>trans</i>) ^{a)}	<i>cis</i> -2 %ee ^{b)}	$[\alpha]_D^{23c)}/^\circ$
O CH ₃	1 d	35 (93 : 7)	94	+15.8 (c 1.06)
O C ₂ H ₅	2 d	50 (97 : 3)	89	+14.4 (c 1.37) ^{d)} +21.1 (c 0.36) ^{e)}
O n-C ₈ H ₁₇	6 d	62 (100 : 0)	>96	+81.7 (c 2.13)
S C ₂ H ₅	3.5 h	88 (100 : 0)	>96	+29.3 (c 1.05)

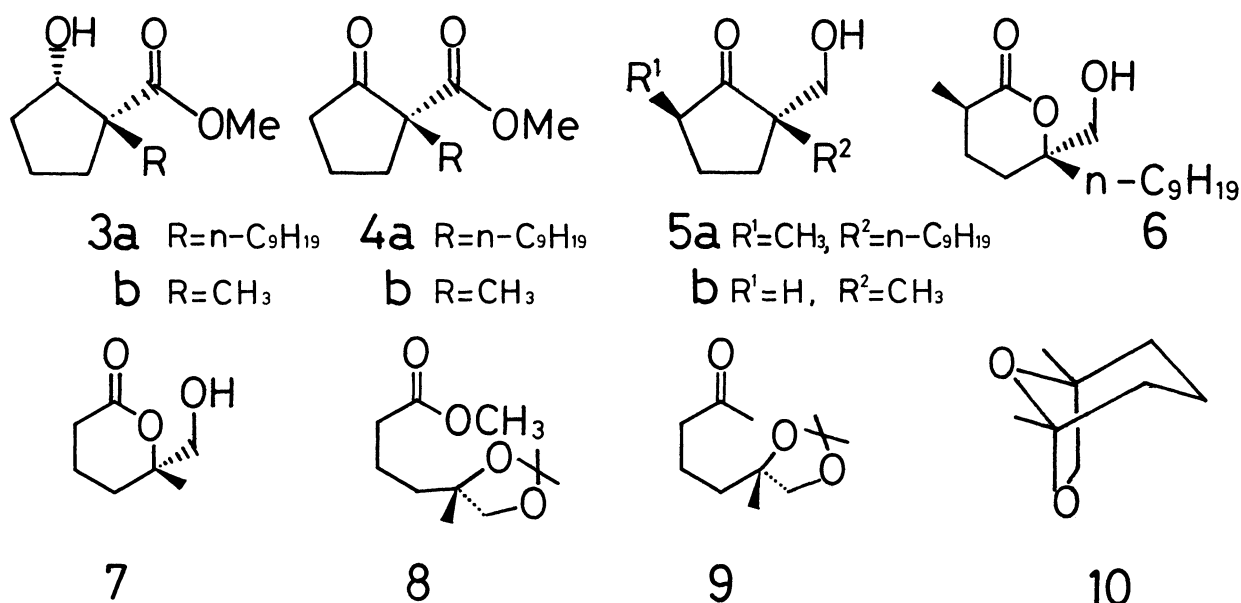
a) Determined by separation of each diastereomer by silica-gel TLC (hexane : AcOEt = 5 : 1). b) Determined by ¹H NMR of the corresponding MTPA ester. c) Measured in CHCl₃, unless otherwise noted. d) Lit.¹³⁾ $[\alpha]_D +14.66^\circ$ (c 2.08, CHCl₃). e) Measured in MeOH, lit.¹⁴⁾ $[\alpha]_D^{20} +23.5^\circ$ (c 0.83, MeOH).

bakers' yeast (Oriental Yeast Co.) and 120 g of saccharose in 1 l of tap water for 3.5 h. After filtration through a celite pad and extraction with ethyl acetate, bulb-to-bulb distillation gave *cis*-β-hydroxy ester 2a in 88% yield, bp 90 °C (3 mmHg). Diastereomerical purity of *cis*-2a was confirmed by comparison of its TLC and GLPC with those of authentic samples of racemic *cis*- and *trans*-2a, prepared by the reduction of 1a with sodium borohydride. The 2S-configuration of 2a was supported by its positive sign of rotation same as that of *cis*-2c and further confirmed by transformation of 2a into 6 and 10.

Table 1 illustrates the remarkable improvement on reactivity, enantio- and diastereoselectivity in the bakers' yeast reduction by introduction of sulfur atom instead of oxygen atom into ester. Thiol ester 1a was much superior to methyl and ethyl esters (1b and 1c) with respect to enantio- and diastereoselectivity.^{13,14)} Although octyl ester 1d gave optically pure 2d, completion of the reduction required a longer time of 6 d.

Optically active β-hydroxy esters, obtained by the bakers' yeast mediated reduction, have been applied to synthesis of various kinds of natural products possessing chiral secondary hydroxyl group or tertiary carbon derived through a carbon-carbon bond formation from the secondary alcohol derivatives.¹⁾ Here we wish to describe creation of a quaternary center *via anti*-α-alkylation of the dianion of chiral β-hydroxy esters¹⁵⁾ and conversion into natural products possessing chiral tertiary alcohol moiety through oxidation to β-keto ester and the subsequent Baeyer-Villiger oxidation.

(2R,5S)-(-)-Malyngolide (6), isolated from the marine blue-green alga, *Lyngbya majuscula*, was the major antibiotic against *Mycobacterium smegmatis* and *Micrococcus pyogenes*.^{16,17)} Hydroxy ester 2a seems to have proper carbon skeleton with potent hydroxymethyl group at C₅ of 6, requiring only two carbon-carbon bond formations at C₂ and C₅. First, thiol ester 2a was converted into more stable methyl ester 2b in methanol in the presence of a catalytic amount of sodium methoxide in 94% yield. Ester 2b was treated with 2 equiv. lithium diisopropylamide (LDA) and nonyl iodide to furnish the *anti*-alkylated ester 3a, $[\alpha]_D^{23} +20.0^\circ$ (c 1.11, CHCl₃),



and its diastereomer in 82% and 2% yields, respectively, which were easily separated by silica-gel column chromatography.¹⁵⁾ Oxidation of 3a with chromic acid gave β -keto ester 4a, $[\alpha]_D^{23} +20.9^\circ$ (c 1.13, CHCl₃), in 90% yield, which was converted into 6 according to the Matsuo's procedure.¹⁸⁾ Thus, α -methylation of 4a and sequential treatment with LDA and lithium aluminum hydride furnished 5a, $[\alpha]_D^{23} -10.8^\circ$ (c 1.02, CHCl₃), in 53% yield. The Baeyer-Villiger oxidation of 5a gave the desired lactone (1R,5S)-6 in 66% yield; $[\alpha]_D^{23} -13.1^\circ$ (c 0.58, CHCl₃), lit.¹⁶⁾ $[\alpha]_D -13^\circ$ (c 2, CHCl₃).

(1S,5R)-(-)-Frontalin (10), the aggregation pheromone of the southern pine bark beetle, *Dendroctonus frontalis* and of the western pine bark beetle, *Dendroctonus brevicornis*,¹⁹⁾ was first synthesized and determined to be the (1S,5R)-isomer by Mori.²⁰⁾ The chiral quaternary center at C₁ was constructed in the same manner as the above synthesis of 6. α -Methylation of 2b gave a separable mixture of 3b, $[\alpha]_D^{23} +27.7^\circ$ (c 1.09, CHCl₃), and its isomer in 70% and 3% yields, respectively. Ester 3b upon treatment with chromic acid gave 4b, $[\alpha]_D^{23} -10.6^\circ$ (c 1.15, CHCl₃), in 80% yield, followed by reduction (66%) and the Baeyer-Villiger oxidation of 5b (82%) to afford lactone 7, $[\alpha]_D^{23} -20.0^\circ$ (c 1.06, CHCl₃). Attempt to produce 10 by two step reactions with methyllithium²¹⁾ and aq hydrochloric acid failed due to formation of an inseparable mixture including 10. Therefore 7 was transformed into ester 8, $[\alpha]_D^{23} -1.65^\circ$ (c 5.44, CHCl₃), in 90% yield by treatment with 2,2-dimethoxypropane under the influence of p-toluenesulfonic acid. Conversion of 8 into the corresponding lithium salt with lithium hydroxide, followed by treatment with methyllithium²²⁾ gave methyl ketone 9, $[\alpha]_D^{23} -0.90^\circ$ (c 9.54, CHCl₃), in 86% yield. After intramolecular ketalization of 9 in refluxing ether in the presence of p-toluenesulfonic acid for 3 h, bulb-to-bulb distillation gave 10 in 69% yield, bp 90 °C (100 mmHg), $[\alpha]_D^{23} -51.7^\circ$ (c 2.2, ether), lit.^{20a)} -52.0° (c 1.06, ether).

Thus, bakers' yeast-mediated reduction of β -keto thiol ester provides optically pure β -hydroxy thiol ester, which is efficiently utilized for the syntheses of natural products possessing chiral quaternary center.

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