CHEMISTRY LETTERS, pp. 1739-1742, 1988.

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

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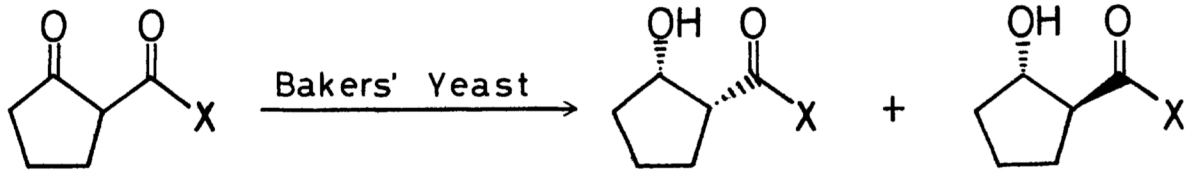
Bakers' yeast reduction of S-ethyl 2-cyclopentanonecarboxylthioate affords optically pure S-ethyl (1R,2S)-2-hydroxycyclopentanecarboxylthioate which is stereoselectively converted into (-)-malyngolide and (-)-frontalin.

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 esters[10] or use of dithioesters instead of usual esters[11] 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



1 **cis-2** **trans-2**

a X=SC_2H_5 **b** X=OCH_3 **c** X=OC_2H_5 **d** X=O n-C_8H_{17}

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

X of 1	Time	Yield of 2/% (*cis* : *trans*)[a]	*cis*-2 %ee[b]	*cis*-2 $[\alpha]_D^{23}$[c]/ °
O CH_3	1 d	35 (93 : 7)	94	+15.8 (c 1.06)
O C_2H_5	2 d	50 (97 : 3)	89	+14.4 (c 1.37)[d]
				+21.1 (c 0.36)[e]
O n-C_8H_{17}	6 d	62 (100 : 0)	>96	+81.7 (c 2.13)
S C_2H_5	3.5 h	88 (100 : 0)	>96	+29.3 (c 1.05)

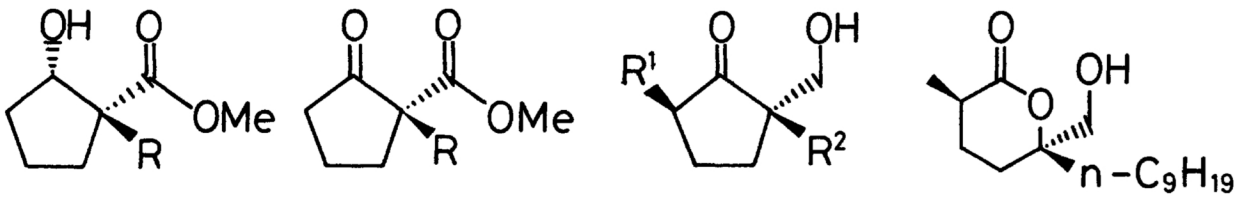
a) Determined by separation of each diastereomer by silica-gel TLC (hexane : AcOEt = 5 : 1). b) Determined by ^1H NMR of the corresponding MTPA ester. c) Measured in $CHCl_3$ unless otherwise noted. d) Lit.[13] $[\alpha]_D$ +14.66° (c 2.08, $CHCl_3$). e) Measured in MeOH, lit.[14] $[\alpha]_D^{20}$ +23.5° (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**.

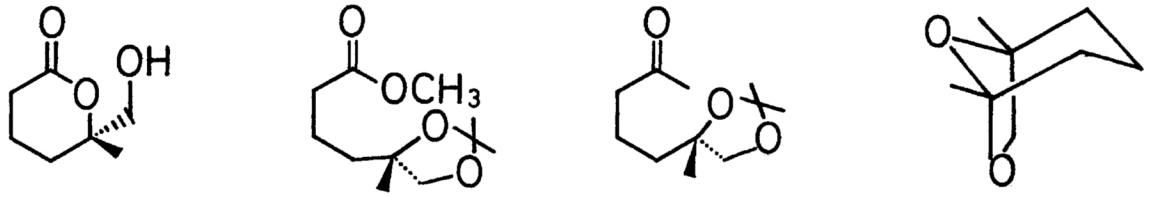
Table 1 illustrates the remarkable improvement on reactivity, enantio- and diastereoselectivity in the bakers' yeast reduction by introduction of sulfur atom instead of oxygen atom into ester. Thiol ester **1a** was much superior to methyl and ethyl esters (**1b** and **1c**) with respect to enantio- 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 esters[15] 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 C_5 of **6**, requiring only two carbon-carbon bond formations at C_2 and C_5. 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° (c 1.11, $CHCl_3$),



3a R=n-C9H19 b R=CH3 4a R=n-C9H19 b R=CH3 5a R1=CH3, R2=n-C9H19 b R1=H, R2=CH3 6



7 8 9 10

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° (c 1.13, $CHCl_3$), 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° (c 1.02, $CHCl_3$), in 53% yield. The Baeyer-Villiger oxidation of **5a** gave the desired lactone (1R,5S)-**6** in 66% yield; $[\alpha]_D^{23}$ -13.1° (c 0.58, $CHCl_3$), lit.[16] $[\alpha]_D$ -13° (c 2, $CHCl_3$).

(1S,5R)-(-)-Frontalin (**10**), the aggregation pheromone of the southern pine bark beetle, *Dendroctonus frontalis* and of the western pine bark beetle, *Dendroctonus brevicomis*,[19] was first synthesized and determined to be the (1S,5R)-isomer by Mori.[20] The chiral quaternary center at C_1 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° (c 1.09, $CHCl_3$), and its isomer in 70% and 3% yields, respectively. Ester **3b** upon treatment with chromic acid gave **4b**, $[\alpha]_D^{23}$ -10.6° (c 1.15, $CHCl_3$), in 80% yield, followed by reduction (66%) and the Baeyer-Villiger oxidation of **5b** (82%) to afford lactone **7**, $[\alpha]_D^{23}$ -20.0° (c 1.06, $CHCl_3$). Attempt to produce **10** by two step reactions with methyllithium[21] 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° (c 5.44, $CHCl_3$), 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 methyllithium[22] gave methyl ketone **9**, $[\alpha]_D^{23}$ -0.90° (c 9.54, $CHCl_3$), 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° (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.

References

1) T. Fujisawa, T. Sato, and T. Itoh, Yuki Gosei Kagaku Kyokai Shi, 44, 519 (1986).
2) V. Prelog, Pure Appl. Chem., 9, 119 (1964).
3) W.-R. Shieh, A. S. Gopalon, and C. J. Sih, J. Am. Chem. Soc., 107, 2993 (1985).
4) T. Sugai, M. Fujita, and K. Mori, Nippon Kagaku Kaishi, 1983, 1315.
5) G. Fráter, Helv. Chim. Acta, 62, 2829 (1979).
6) K. Nakamura, M. Higaki, K. Ushio, S. Oka, and A. Ohno, Tetrahedron Lett., 26, 4213 (1985).
7) K. Nakamura, K. Inoue, K. Ushio, S. Oka, and A. Ohno, Chem. Lett., 1987, 679.
8) A. Manzocchi, R. Casati, A. Fiecchi, and E. Santaniello, J. Chem. Soc., Perkin Trans. 1, 1987, 2753 and references cited therein.
9) M. Hirama, M. Shimizu, and M. Iwashita, J. Chem. Soc., Chem. Commun., 1983, 599; D. W. Brooks, R. P. Kellogg, and C. S. Cooper, J. Org. Chem., 52, 192 (1987) and references cited therein.
10) T. Fujisawa, T. Itoh, and T. Sato, Tetrahedron Lett., 25, 5083 (1984); K. Nakamura, K. Ushio, S. Oka, A. Ohno, and S. Yasui, ibid., 25, 3979 (1984); K. W. Hoffmann, W. Ladner, and W. Helbig, Justus Liebigs Ann. Chem., 1984, 1170; R. W. Hoffmann and W. Ladner, Chem. Ber., 116, 1631 (1983).
11) T. Itoh, Y. Yonekawa, T. Sato, and T. Fujisawa, Tetrahedron Lett., 27, 5405 (1986); T. Itoh, T. Sato, and T. Fujisawa, Nippon Kagaku Kaishi, 1987, 1414.
12) H.-J. Liu and H. K. Lai, Tetrahedron Lett., 1979, 1193.
13) During our investigation Seebach *et al.* reported that the bakers' yeast reduction of **1c** without nutrients gave optically pure **2c**: D. Seebach, S. Roggo, T. Maetzke H. Braunshweiger, J. Cercus, and M. Krieger, Helv. Chim. Acta, 70, 1605 (1987).
14) Reduction of **1c** with various yeasts and mould strains was reported: D. Buisson and R. Azerad, Tetrahedron Lett., 27, 2631 (1986).
15) G. Fráter, U. Müller, and W. Günther, Tetrahedron, 40, 1269 (1984).
16) J. H. Cardllina II, R. E. Moore, E. V. Arnold, and J. Clardy, J. Org. Chem., 44, 4039 (1979).
17) For recent asymmetric synthesis of (-)-malyngolide see: B. Giese and R. Rupaner, Justus Liebigs Ann. Chem., 1987, 231.
18) K. Matsuo and K. Tanaka, Chem. Pharm. Bull., 29, 3070 (1981).
19) G. W. Kinzor, A. F. Fentiman. Jr., T. F. Page, Jr., R. L. Foltz, J. P. Vite, and G. B. Pitman, Nature, 221, 477 (1969).
20) a) K. Mori, Tetrahedron, 31, 1381 (1975); b) D. L. Wood, L. E. Browne, B. Ewing, K. Lindahl, W. D. Bedard, P. E. Tidlen, K. Mori, G. B. Pitman, and P. R. Hughes, Science, 192, 896 (1976); c) M. Ohwa and E. L. Eliel, Chem. Lett., 1987, 41 and references cited therein.
21) J. E. Hernández, A. Cisneros, and S. Fernández, Synth. Commun., 13, 191 (1983).
22) G. M. Rubottom and C. Kim, J. Org. Chem., 48, 1550 (1983).

(Received August 1, 1988)