Tetrahedron Letters,Vol.26,No.49,pp 6089-6092,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain 

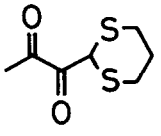
# DIASTEREO- AND ENANTIOSELECTIVE REDUCTION OF α,β-DIKETODITHIANE WITH THE BAKER'S YEAST

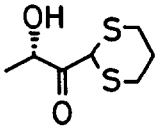
Tamotsu FUJISAWA,* Eiji KOJIMA, Toshiyuki ITOH, and Toshio SATO
Chemistry Department of Resources, Mie University, Tsu, Mie 514, Japan

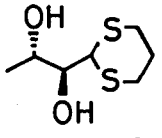
Summary: *The Baker's yeast reduction of 1-(1,3-dithian-2-yl)-1,2-propanedione gave highly enantio- and diastereoselectively (S)-(+)-1-(1,3-dithian-2-yl)-2-hydroxy-1-propanone or (1S,2S)-(+)-1-(1,3-dithian-2-yl)-1,2-propanediol, depending on the reaction time. The hydroxy ketone was reduced with diisobutylaluminum hydride to give (1R,2S)-1-(1,3-dithian-2-yl)-1,2-propanediol with high diastereoselectivity. The former (1S,2S)-diol was converted into L-digitoxose.*

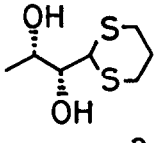
The Baker's yeast reduction of ketones has provided a useful method for the synthesis of highly optically active alcohols which have been employed as chiral building blocks for natural product synthesis.[1,2] Almost all the yeast reduction reported so far has been applied on mono-ketones except for only a few examples.[3] Recently many efforts have been devoted to the diastereoselective synthesis of 1,2-diol or 1,2,3-triol derivatives for macrolide or sugar synthesis.[4] If 1,2-diketone derivatives are enantio- and diastereoselectively reduced to the corresponding 1,2-diols, it will provide a novel and convenient way for them. We describe here that the Baker's yeast reduction of 1-(1,3-dithian-2-yl)-1,2-propanedione (1) furnished (S)-1-(1,3-dithan-2-yl)-2-hydroxy-1-propanone (2) or (1S,2S)-1-(1,3-dithian-2-yl)-1,2-propanediol (3) with high enantio- and diastereoselectivity, depending on the reaction time. Since the dithiane group is easily hydrolyzed to an aldehyde which can diastereoselctively react with organometallics, the present method provides a convenient path for the synthesis of the optically active compounds.

A typical procedure for the Baker's yeast reduction of 1-(1,3-dithian-2-yl)-1,2-propanedione (1)[5] is described as follows: A suspension of 12 g of D-glucose and 10 g of the Baker's yeast (Oriental Yeast Co.) in 80 ml of water, was stirred for 1 h at room temperature, and then 10 ml of an ethanol solution


1


2


anti-3


syn-3

of 1 (2.0 mmol) was added to the yeast suspension. After 48 h, celite and ethyl acetate were added, and the mixture was stirred for 6 h, and then filtered through a celite pad. The filtrate was extracted with ethyl acetate. The extracts were evaporated in vacuo to give the crude product of *anti*-(+)-(1S,2S)-1-(1,3-dithian-2-yl)-1,2-propanediol (3) accompanied with 5% *syn*-isomer 3. The two diastereomers were easily separated by TLC on silica-gel to give diastereomerically pure *anti*-3 in 82% yield, mp 92 °C, $[\alpha]_D^{23}$ +10.5° (c 1.01, $CHCl_3$).[8] The optical purity of *anti*-3 was 97% ee determined by the comparison of the specific rotation with the authentic sample (*vide infra*). Recrystallization from n-hexane gave optically pure *anti*-3, mp 93 °C, $[\alpha]_D^{23}$ +10.8° (c 1.00, $CHCl_3$).

The glc analysis of the reaction mixture of the above Baker's yeast reduction gave an interesting feature as shown in Figure. The reduction of two carbonyl groups in 1 proceeded stepwise. The β-keto group was reduced much faster than the α-keto group. After 2 h the starting material, α,β-diketodithiane 1 was completely reduced to β-hydroxy-α-ketodithiane 2 and then the α-keto group in 2 began to be reduced to produce α,β-dihydroxydithiane 3. After 48 h 2 was completely reduced to furnish 3. The large difference between the reduction rates of two carbonyl groups seems to be due to the different bulkiness around them. After 2 h β-hydroxy-α-ketodithiane 2 was isolated in 60% yield, mp 85 °C, $[\alpha]_D^{23}$ +91.9° (c 1.06, $CHCl_3$), 93% ee. Recrystallization from n-hexane gave optically pure 2, mp 90 °C, $[\alpha]_D^{23}$ +98.6° (c 1.03, $CHCl_3$).

As mentioned above, *anti*-3 was easily obtained by the Baker's yeast reduction. Next, the diastereoselective reduction of optically pure 2 with several metal hydrides was examined to obtain *syn*-3 as shown in Table. The reduction of 2 with sodium borohydride preferred the formation of the *anti*-3. Disobutylaluminum hydride (DIBAL) or Zinc borohydride at low temperature predominantly produced *syn*-3.[9] Purification by TLC on silica-gel gave optically pure *syn*-3, mp 72 °C, $[\alpha]_D^{23}$ +4.34° (c 1.00, $CHCl_3$).

The optical purity of 2, *anti*-3 and *syn*-3 was determined by the comparison of the specific rotation with authentic samples which were prepared from (S)-methyl lactate as follows. Protection of the hydroxy group of the lactate with dihydropyran, treatment with 2-lithio-1,3-dithiane, and deprotection gave the optically pure 2, mp 90 °C, $[\alpha]_D^{23}$ +98.4° (c 1.02, $CHCl_3$). Reduction of 2 with sodium borohydride in methanol gave 3. Purification by TLC and recrystallization provided optically pure *anti*-3, mp 93 °C, $[\alpha]_D^{23}$ +10.8° (c 1.00, $CHCl_3$) and *syn*-3, mp 72 °C, $[\alpha]_D^{23}$ +4.35° (c 1.01, $CHCl_3$).

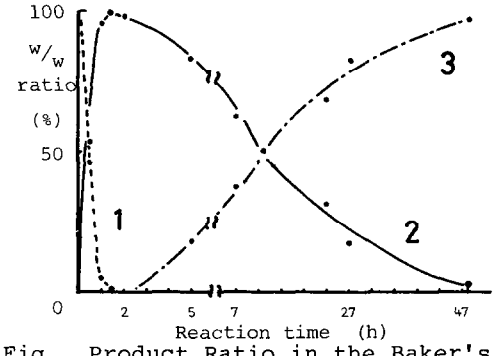



Fig. Product Ratio in the Baker's Yeast Reduction of 1

The utility of the present Baker's

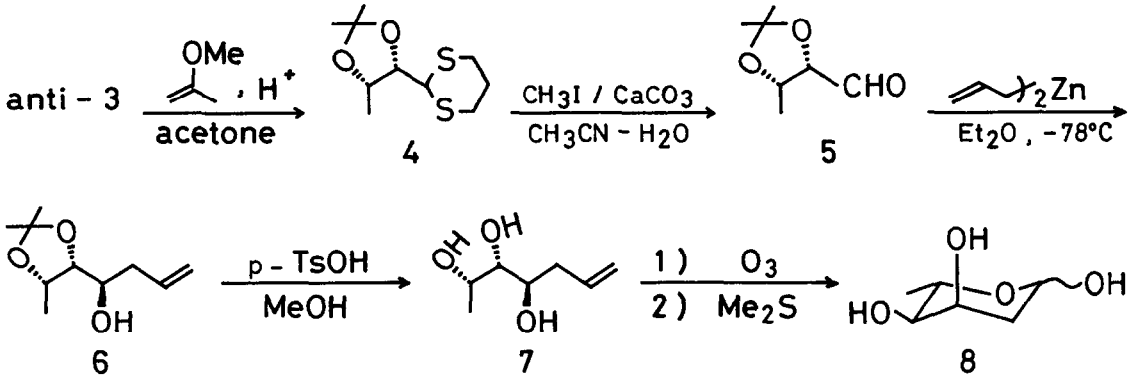
Table Diastereoselective Reduction of 2 to 3 with Various Metal Hydride Reagents

| Metal Hydride | Temp. (°C) | Solvent | Yield[a] (%) | *syn*-3 / *anti*-3 [b,c] |
|---|---|---|---|---|
| $Zn(BH_4)_2$ | 0 | $Et_2O$ | 93 | 40 / 54 |
| | -50 | | 75 | 70 / 30 |
| | -90 | | 58 | 86 / 14 |
| $NaBH_4$ | 0 | MeOH | 74 | 36 / 64 |
| | -90 | | 88 | 36 / 64 |
| $LiAlH_4$ | -90 | $Et_2O$ | 83 | 69 / 31 |
| $LiAlH_2(OCH_2CH_2OCH_3)_2$ | -90 | Toluene | 91 | 51 / 49 |
| DIBAL | -90 | $Et_2O$ | 74 | 89 / 11 |

a) An Isolated yield. b) The structures of two diastereomers were determined by the comparison of $^1H$ NMR data with the racemic *syn*-1,2-diol in the literature.[8] c) The ratio of two diastereomers was determined by the capillary glc (PEG 50m).

yeast reduction is demonstrated in the following synthesis of 2,6-dideoxy-L-ribohexose (L-digitoxose 8),[10,11] a rare sugar in nature. The optically pure *anti*-3 was protected with 2-methoxypropene to give the isopropylidene derivative 4 in 97% yield, $bp_{0.4}$ 120 °C, $[\alpha]_D^{23}$ -18.6° (c 1.04, $CHCl_3$). Deprotection of the dithiane group of 4 gave the optically pure glyceraldehyde derivative 5, in 58% yield, $bp_{100}$ 80 °C, $[\alpha]_D^{23}$ -14.5° (c 1.02, $CHCl_3$), which has been known as a useful key intermediate for several natural product synthesis.[12] According to the procedure reported by Fuganti et al.,[11] the aldehyde 5 was converted to the protected triol 6 (*anti* : *syn* = 92 : 8)[13] in 59% yield by the *anti*-selective addition of diallylzinc in ether. Hydrolysis to the corresponding triol 7 followed by ozonolysis and treatment with dimethyl sulfide gave 8 in 65% yield, $[\alpha]_D^{23}$ -45.6° (c 0.16, $H_2O$), lit.[11] $[\alpha]_D^{23}$ -47.8° (c 0.8, $H_2O$), the sugar component of digitalis which is an effective heart medicine.

In conclusion, the Baker's yeast reduction of α,β-diketodithiane provided an efficient method for the synthesis of optically active 1,2-dihydroxydithiane which is a useful synthon especially for the sugar synthesis.




The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture in Japan, and the Naito Foundation.

References and Notes


1. B. Seuring and D. Seebach, *Helv. Chim. Acta*, 60, 1175 (1977); D. Seebach and M. F. Züger, *ibid.*, 65, 495 (1982); K. Mori, *Tetrahedron*, 37, 1341 (1981); K. Mori and K. Tanida, *ibid.*, 37, 3221 (1981); T. Kitahara, K. Koseki, and K. Mori, *Agric. Biol. Chem.*, 47, 389 (1983); K. Mori and T. Sugai, *Synthesis*, 1982, 752; G. Fráter, *Helv. Chim. Acta*, 62, 2829 (1979); R. W. Hoffmann, W. Ladner, K. Steinbach, W. Massa, R. Schmidt, and G. Snatzke, *Chem. Ber.*, 114, 2786 (1981); M. Hirama and M. Uei, *J. Am. Chem. Soc.*, 104, 4251 (1982); R. F. Newton, J. Paton, D. P. Reynolds, and S. Young, *J. Chem. Soc., Chem. Commun.*, 1979, 908.
2. Introduction of sulfenyl group to the neighbouring position of the carbonyl group has been known to improve the chemical yield and enantioselectivity in the Baker's yeast reduction, for example; R. L. Crumbie, B. S. Deol, J. E. Nemorin, and D. D. Ridley, *Aust. J. Chem.*, 31, 1965 (1978); S. Iriuchijima and N. Kojima, *Agric. Biol. Chem.*, 42, 451 (1978); R. W. Hoffmann, W. Helbig, and W. Ladner, *Tetrahedron Lett.*, 23, 3479 (1982); Y. Takaishi, Y.-L. Yang, D. Ditullio, and C. J. Sih, *ibid.*, 23, 5489 (1982); D. Ghiringhelli, *ibid.*, 24, 287 (1983); K. Nakamura, K. Ushio, S. Oka, and A. Ohno, *ibid.*, 25, 3879 (1984); T. Fujisawa, T. Itoh, and T. Sato, *ibid.*, 25, 5083 (1984); T. Fujisawa, T. Itoh, M. Nakai, and T. Sato, *ibid.*, 26, 771 (1985).
3. H. G. W. Leuenberger, W. Boguth, E. Widmer, and R. Zell, *Helv. Chim. Acta*, 59, 1832 (1976); J. K. Lieser, *Synth. Commun.*, 13, 765 (1983); D. W. Brooks, P. G. Grothaus, and W. L. Irwin, *J. Org. Chem.*, 47, 2821 (1982).
4. J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, 98, 4925 (1976); H. Gerlach and H. Wetter, *Helv. Chim. Acta*, 57, 2306 (1974); H. Gerlach, K. Oertle, A. Thalmann, and S. Servi, *ibid.*, 58, 2036 (1975); S. Hanessian and G. Rancourt, *Can. J. Chem.*, 55, 1111 (1977); M. Yamaguchi and T. Mukaiyama, *Chem. Lett.*, 1981, 1005; K. Suzuki, Y. Yumi, and T. Mukaiyama, *ibid.*, 1981, 1529; S. Masamune and W. Choy, *Aldrichimica Acta*, 15, 47 (1982).
5. The α,β-diketodithiane 1 was easily prepared from ethyl pyruvate. Protection of the ketone moiety of the pyruvate as diethylketal[6] and treatment with 2-lithio-1,3-dithiane in THF at -90 °C for 2 h gave 1-(1,3-dithian-2-yl)-2,2-diethoxy-1-propanone in 80% yield, followed by hydrolysis with conc. HCl in acetone to give 1 in 91% yield.[7]
6. C. L. Stevens and A. E. Sherr, *J. Org. Chem.*, 17, 1228 (1952).
7. I. Kawamoto, S. Muramatsu, and Y. Yura, *Tetrahedron Lett.*, 1974, 4223.
8. The δ value of the methine protons at α position of the dithianes, *anti*-3 and *syn*-3, is clearly different in $^1$H NMR, *anti*-3; NMR ($CDCl_3$) δ 1.25 (3H, d, J = 6Hz, $CH_3CH$), 2.05 (2H, m, $SCH_2CH_2CH_2S$), 2.3 ~ 3.25 (6H, m, OH, OH, $SCH_2CH_2CH_2S$), 3.7 ~ 4.3 (3H, m, $CH_3CH(OH)CH(OH)CH$). *Syn*-3; NMR ($CDCl_3$) δ 1.32 (3H, d, J = 6Hz, $CH_3CH$), 2.08 (2H, m, $SCH_2CH_2CH_2S$), 2.3 ~ 3.25 (6H, m, OH, OH, $SCH_2CH_2CH_2S$), 3.63 (1H, dd, J = 4.8Hz, $CH_3CH(OH)CH(OH)$), 3.9 ~ 4.4 (2H, m, $CH_3CHOH$, $CHS_2$); cf. R. P. Hatch, J. Shringarpure, and S. M. Weinreb, *J. Org. Chem.*, 43, 4172 (1978).
9. In contrast to the present reduction of the β-hydroxy-α-ketodithiane, the reduction of α-hydroxyketones with alkyl substituents with DIBAL or $Zn(BH_4)_2$ predominantly gave *anti*-diols, see; S. B. Bowles and J. A. Kazenellenbogen, *J. Org. Chem.*, 39, 3309 (1974); T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, 24, 2653 (1983).
10. H. R. Bollinger and P. Ulrich, *Helv. Chim. Acta*, 35, 93 (1952).
11. G. Fronza, C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, and C. Zirotti, *Tetrahedron Lett.*, 23, 4143 (1982).
12. C. Fronza, C. Fuganti, and P. Grasselli, *J. Chem. Soc., Chem. Commun.*, 1980, 442; C. Fuganti, P. Grasselli, S. Servi, F. Spreatico, and C. Zirotti, *J. Org. Chem.*, 49, 4087 (1984); C. Fuganti, S. Servi, and C. Zirotti, *Tetrahedron Lett.*, 24, 5285 (1983); W. R. Roush, D. J. Harris and B. M. Lesun, *ibid.*, 24, 2227 (1983).
13. In the case of using allylmagnesium bromide, the lower selectivity was observed (*anti* : *syn* = 70 : 30).


(Received in Japan 24 September 1985)