

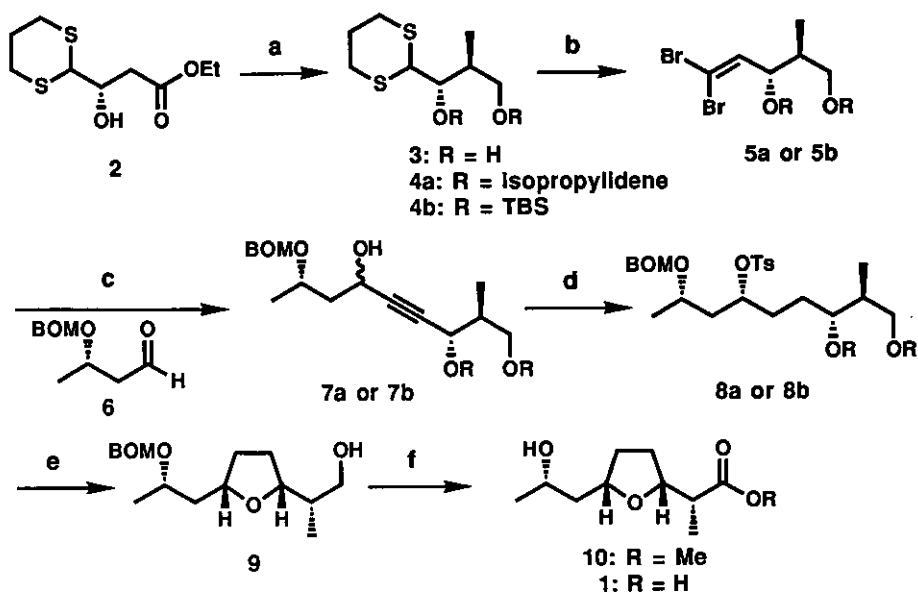
SYNTHESIS OF (-)-NONACTIC ACID: APPLICATION OF γ -DITHIO- β -HYDROXY
ESTER PREPARED BY MICROBIAL REDUCTION AS A CHIRAL BUILDING
BLOCK

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Abstract- A γ -dithio- β -hydroxy ester (2), prepared by microbial reduction with baker's yeast, was used as a chiral building block, for the synthesis of (-)-nonactic acid (1). It was converted to the lithium acetylide *via* 5, of which 1,2-addition to the aldehyde (6) followed by reduction gave the 3-silyloxy-6-tosyloxynonane (8b). On cleavage of the silyl ether, cyclization proceeded with complete inversion of configuration at C-6 to afford a *cis*-2,5-disubstituted tetrahydrofuran (9), which was led to 1.

The use of baker's yeast as a chiral reducing reagent is particularly advantageous because it is cheap and easily available. For example, optically active β -hydroxy esters, obtained by microbial reduction of the corresponding keto esters with baker's yeast,¹ have been efficiently employed as chiral building blocks.² We have demonstrated that various β -hydroxy esters can be produced asymmetrically by using microbial reduction.³ γ -Dithio- β -keto esters are also reduced by baker's yeast, and may provide good chiral building blocks for natural product synthesis.⁴ In this paper, we report an enantiospecific synthesis of (-)-nonactic acid (1),⁵ which is one of the subunits of the macrotetrolide antibiotic nonactin, from a γ -dithio- β -hydroxy ester *via* a 2,6-nonanediol derivative.



Reagents and conditions: (a) (i) LDA, THF, -78°C , then MeI, HMPA, -20°C , 65%; (ii) LiAlH_4 , 94%; (iii) 2,2-dimethoxypropane, *p*-TsOH, 81% for 4a; TBSCl, imidazole, 81% for 4b; (b) (i) MeI, CaCO_3 , H_2O /acetone, 73% for the a series; 86% for the b series; (ii) Ph_3P , CBr_4 , 68% for 5a; 99% for 5b; (c) $n\text{BuLi}$, THF, -78°C , then 6, HMPA, 65% for 7a; 73% for 7b; (d) (i) H_2 , 10% Pd-C, 65% for the a series; 82% for the b series; (ii) TsCl, DMAP, Et_3N , 85% for 8a; 89% for 8b; (e) $n\text{Bu}_4\text{NF}$, 82% from 8b; (f) (i) Jones oxidation; (ii) CH_2N_2 ; (iii) H_2 , 10% Pd-C, 43% from 9; (iv) KOH, 95%

(S)-Ethyl 3-(1,3-dithian-2-yl)-3-hydroxypropionate (2) was prepared by microbial reduction with baker's yeast (*Saccharomyces cerevisiae*) from the corresponding γ -dithio- β -keto ester (76% yield, 95% ee.). The β -hydroxy ester (2) was treated with 2 equiv. of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C followed by methylation with methyl iodide and hexamethylphosphoric triamide (HMPA) at -20°C to give an *anti*- β -hydroxy- α -methyl ester in 65% yield with high diastereoselectivity (*anti* : *syn* = 93 : 7).⁶ *anti*- β -Hydroxy- α -methyl ester was reduced to the diol (3) and it was protected as an isopropylidene to give the acetonide (4a). Cleavage of the dithioacetal ring of 4a followed by olefination with triphenylphosphine and carbon tetrabromide afforded the vinyl dibromide (5a). This was converted to the lithium acetylide,⁷ which was coupled with the aldehyde (6)⁸ in THF at -78°C to give a 1 : 1 diastereomeric mixture of 7a in 65% yield. This mixture was easily separated by column chromatography on silica gel to obtain the 6,8-*syn* and *anti*-isomers. The *syn*-7a was hydrogenated on 10% Pd-C and the resulting alcohol was tosylated to afford the 2,6-nonanediol derivative (8a). When 8a was

deprotected with a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in methanol at room temperature, cyclization proceeded, but the isolated product was a 1 : 1 mixture of *cis* and *trans*-2,5-disubstituted tetrahydrofuran, owing to epimerization at the C-6 position in **8a** under acidic conditions. Therefore, we examined cyclization of the 3-silyloxy-6-tosyloxynonane (**8b**), because it is known that the silyl ether is cleaved rapidly to alcohol by treatment with tetra-*n*-butylammonium fluoride.⁹ The silyl ether (**8b**) was derived from the diol (**3**) by the same procedure as before. Coupling of the vinyl dibromide (**5b**) with the aldehyde (**6**) also afforded a 1 : 1 diastereomeric mixture (**7b**) in 73% yield. After separation, the 6,8-*anti*-**7b** was converted to *syn*-**7b** by means of the Mitsunobu displacement reaction¹⁰ in 61% yield, and all the *syn*-**7b** was led to **8b**. As expected, treatment of **8b** with tetra-*n*-butylammonium fluoride in THF at room temperature caused deprotection with concomitant cyclization. The cyclization proceeded with complete inversion of configuration at C-6 in **8b** to afford the desired *cis*-2,5-disubstituted tetrahydrofuran (**9**)¹¹ as a single product in 82% yield. After oxidation of **9**, the resulting carboxylic acid was esterified with diazomethane, followed by hydrogenolysis on 10% Pd-C to give methyl nonactate (**10**)¹² in 45% yield. The structure of **10** was confirmed by comparison of spectral data with literature values.^{4d} Finally, hydrolysis of **10** gave (-)-nonactic acid (**1**) in 95% yield.

In summary, we have achieved the synthesis of (-)-nonactic acid from a γ -dithio- β -hydroxy ester (**2**). The γ -dithio- β -hydroxy ester (**2**) should also be useful as a chiral building block, for other purposes.

ACKNOWLEDGMENT

We thank Takasago Research Institute for a generous supply of (S)-methyl 3-hydroxybutanoate.

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11. The relative stereochemistry of the tetrahydrofuran ring was assigned based on NOE measurement of the ring protons. $^1\text{H-Nmr}$ (CDCl_3 , 400 MHz) δ : 0.80 (d, $J=6.9$ Hz, 3H), 1.21 (d, $J=6.2$ Hz, 3H), 1.45-1.78 (m, 4H), 1.92-2.05 (m, 2H), 3.45-3.60 (m, 2H), 3.61 (m, 1H), 3.93 (m, 1H), 4.06 (m, 1H), 4.60 (d, $J=11.8$ Hz, 1H), 4.63 (d, $J=11.8$ Hz, 1H), 4.76 (d, $J=6.9$ Hz, 1H), 4.83 (d, $J=6.9$ Hz, 1H), 7.25-7.40 (m, 5H).
12. $^1\text{H-Nmr}$ (CDCl_3 , 400 MHz) δ : 1.13 (d, $J=7.2$ Hz, 3H), 1.20 (d, $J=6.4$ Hz, 3H), 1.55-1.7 (m, 3H), 1.75 (ddd, $J=11.8, 7.7, 3.9$ Hz, 1H), 1.92-2.08 (m, 2H), 2.54 (dq, $J=8.5, 7.2$ Hz, 1H), 2.90 (br, 1H), 3.70 (s, 3H), 3.99 (m, 1H), 4.04 (m, 1H), 4.15 (m, 1H); ir (neat): 3430, 2950, 1735, 1455, 1370, 1255, 1195, 1080, 1055, 750 cm^{-1} ; $[\alpha]_D=-13.7^\circ$ (c 1.10, CHCl_3).

Received, 15th February, 1993