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

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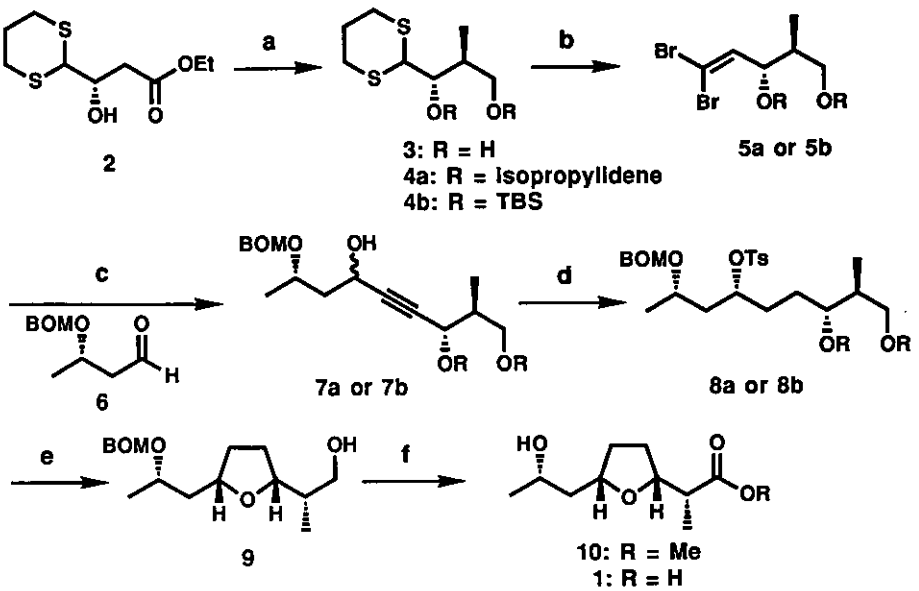
Abstract- A γ-dithio-β-hydroxy ester (**2**), prepared by microbial reduction with baker's yeast, was used as a chiral building block, for the synthesis of (-)-nonactic acid (**1**). It was converted to the lithium acetylide *via* **5**, of which 1,2-addition to the aldehyde (**6**) followed by reduction 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) ^nBuLi, 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) $^nBu_4NF$, 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 diasteroselectivity (*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 diasteromeric 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 reaction[10] 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.

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11. The relative stereochemistry of the tetrahydrofuran ring was assigned based on NOE measurement of the ring protons. ^{1}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}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° (c 1.10, $CHCl_3$).

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