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SYNTHESIS OF FUNCTIONALIZED CHIRAL SYNTHONS VIA MICROBIOLOGICAL REDUCTION

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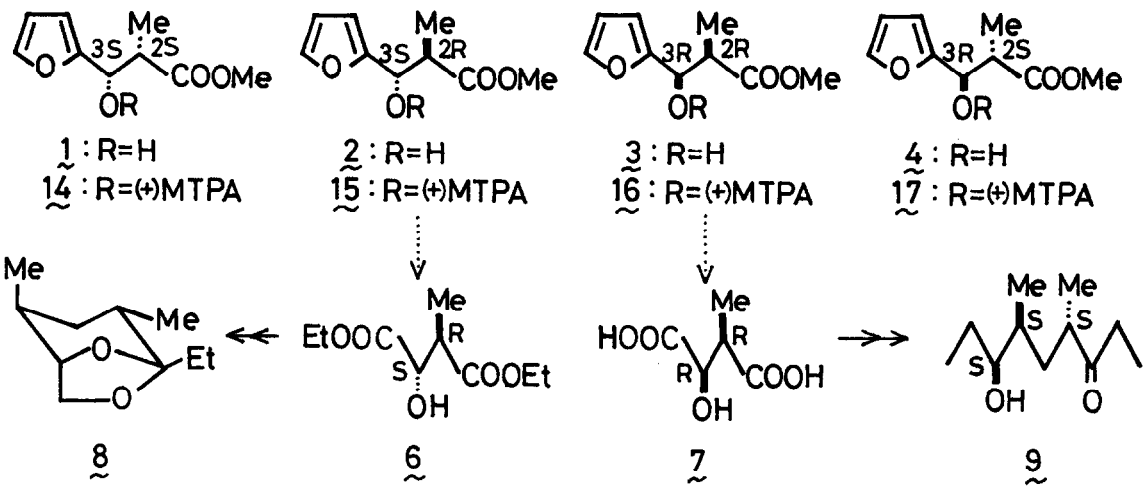
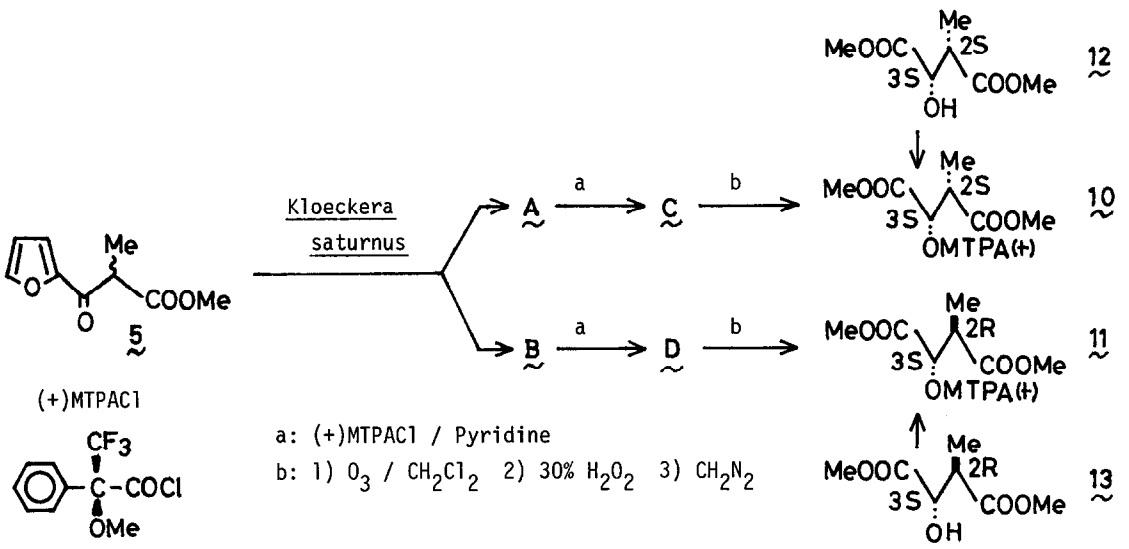
Summury: Four functionalized chiral synthons 1-4 having high optical purity were prepared by microbiological asymmetric reduction.

In the field of synthesis of polyoxoantibiotics or the related polyfunctional natural products, the use of optically active compounds as a starting material is known to be quite advantageous[3]. We now report the synthesis of four functionalized optically active building blocks 1, 2, 3 and 4 based on the asymmetric reduction of the corresponding ketone 5 by yeast[4]. The furylpropionates 1-4 involving two chiral centers were selected as target compounds because the 2-methyl, 3-hydroxy moiety involved in them frequently appear in a variety of natural products such as erythromycins[5], oudemansin[6] and other polyoxoantibiotics[7] and furan group is convertible, after reduction by yeasts, into a carboxylic acid or its congeners. In fact, dicarboxylic acid derivatives 6 , 7 expected to be obtained from 2 and 3 have already been converted to optically active insect pheromones, δ-multistriatin (8)[8] and serricornin (9)[9], respectively.



An attempted reduction of the ketone 5 with usual active fermenting baker's yeast (Saccharomyces cerevisiae) gave only a starting material. However, when reduction was continued using some selected yeasts, Kloeckera saturnus was found to reduce this particular ketone producing two isomeric alcohols A ($[\alpha]_D$ = -10.73°) and B ($[\alpha]_D$ = -27.29°) as main products. For the purpose of determining the stereostructure and optical purity, A and B were separately



condensed with (+)-α-methoxy-α-trifluoromethyl-phenylacetic acid chloride ((+)-MTPACl)[10] and the resulting esters C and D were ozonolyzed and then esterified with diazomethane to yield the corresponding esters 10 and 11. Comparison of the NMR data (400 MHz) of 10 and 11 with those of the authentic samples prepared from alcohols, 12 and 13, whose absolute configuration had been already established[11] reveals that the absolute configurations of 10 and thence A and C are 2S, 3S (therefore, A=1, C=14) and those of 11 and thence B and D are 2R, 3S (B=2, D=15).

In order to prepare the four possible stereoisomers 1-4, the ketone 5 was reduced with $NaBH_4$ and the products were directly converted to the (+)-MTPA esters 14, 15, 16 and 17. The signals due to four methyl protons appeared in distinctly different field (δ 3.513, 3.596, 3.640 and 3.686) in 400 MHz NMR spectrum without adding any shift reagent. Among them, the signals appeared in δ 3.640 and 3.686 could be ascribed to that of 14 (2S, 3S) and 15 (2R, 3S) by direct comparison with those of the authentic specimen obtained above. Then, the ketone 5 was reduced with $Zn(BH_4)_2$ which was known to give predominantely syn-isomers[12] 1 and 3. The reduction products were converted to the (+)-MTPA esters as usual. Only two peaks appeared in the ester methyl reagion as expected and one of the peaks was identified as that of 14 and consequently the other peak (δ 3.596) could be ascribed to that of the another syn-isomer 16. Thus, the remaining unassigned peak in δ 3.513 should be due to that of the another anti-isomer 17. The relation of signals and the structures was shown in scheme 1. From the small peaks due to isomers present in 14 and 15, optical yields of 14 and 15 were calculated as 68% ee and 46% ee, respectively.

Thus, we succeeded in the development of a facile method for determining a stereostructure and optical purity of the reduction products by means of 400 MHz NMR spectroscopy. Therefore, with an intension of finding a more effective microorganisms, we then carried out a reduction using a variety of yeasts and found that several yeasts actually possess a desired reduction

Scheme 1

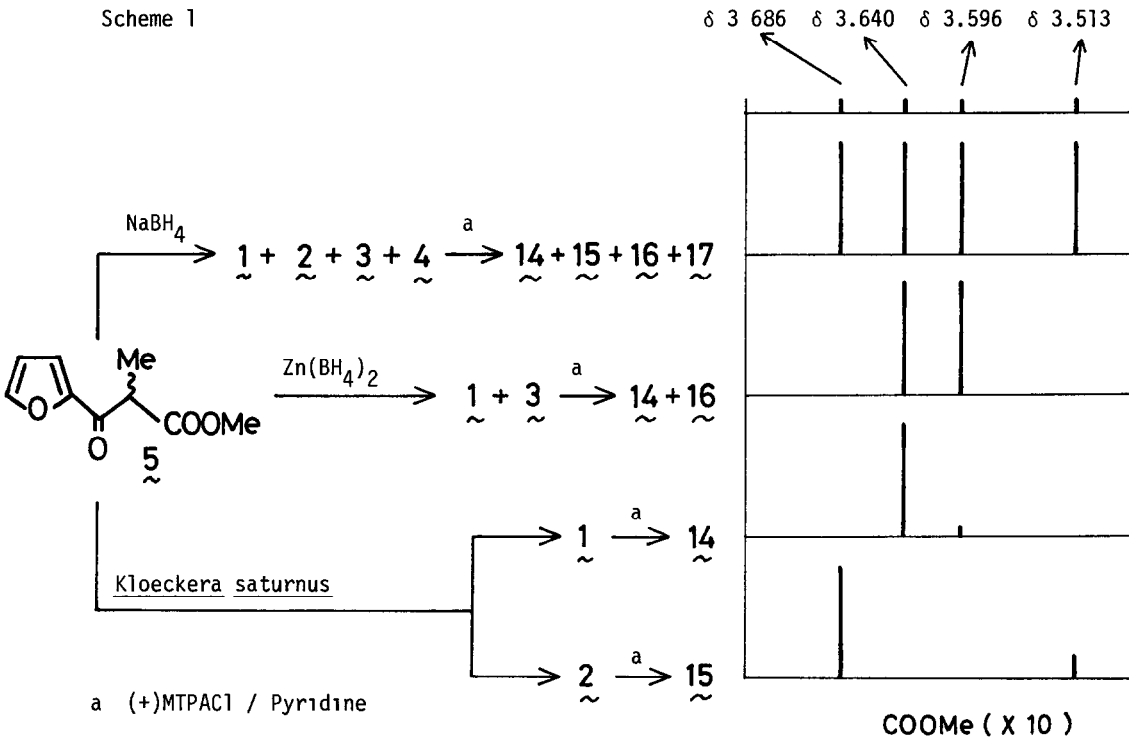


Table 1[a]

Entry	Yeast	chemical yield (%) (as (+)-MTPA ester)	syn/anti	optical purity (% ee)
1	Kloeckera saturnus	29 (12)[b]	47/53 (54/46)[b]	syn 1 68 (87)[b] anti 2 46 (53)[b,c]
2	Saccharomyces delbrueckii	43 (50)[b]	39/61 (41/59)[b]	syn 3 90 (99)[b] anti 4 91 (94)[b]
3	Saccharomyces fermentati	21 (36)[b]	40/60 (44/56)[b]	syn 3 84 (99)[b] anti 4 86 (98)[b]

a. Yeasts were incubated to 100 ml of liquid medium and the mixtures were shaken for three days at 30°C, to which ca. 50 mg of substrate 5 was added and the whole was again shaken for three days at 30°C.

b Data obtained in the cases where yeast cells were used

c In a preliminary experiment using a jar-fermentor, (5, 4.7 g), both of chemical yield (1, 39% , 2, 33%) and optical purity (1, 83% ee , 2, 73% ee) were significantly improved (cf. entry 1, table 1).

ability. In particular, Saccharomyces delbrueckii and Saccharomyces fermentati were found to give 3 and 4 under high optical purity. In cases where yeast cells were used, optical yield was significantly improved in each case. A part of the results were shown in table 1.

The particular feature of the present asymmetric reduction is that alcohols having opposite absolute configuration were obtained depending on the species of yeasts used, that is, Kloeckera saturnus produces (S)-alcohols whereas all of other effective yeasts afford (R)-alcohols, (R)-configuration[13] being expected from the results of the reduction by usual fermenting baker's yeast. Moreover, syn (1, 3)- and anti (2, 4)-isomers directly obtained after reduction are separable by usual silica gel chromatography. Therefore, it become possible to prepare all four isomers by combining the above two features. Now, mass production of 1-4 is being undertaken in this laboratory.

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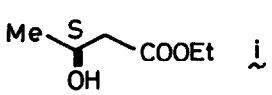
References and Notes

1. Synthetic Organic Chemistry Laboratory.
2. Laboratory of Bacteriology and Ecology.
3. a) H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M. R. Johnson, Y. Kishi, J. Am. Chem. Soc., 102, 7962 (1980). b) Y. Kishi, Aldrichim. Acta., 13, 23 (1980). c) D. A. Evans, C. E. Sacks, W. A. Kleschick, T. R. Taber, J. Am. Chem. Soc., 101, 6789 (1979). d) D. B. Collum, J. H. MaDonald, III, W. C. Still, J. Am. Chem. Soc., 102, 2120 (1980). e) A. I. Meyers, R. A. Amos, J. Am. Chem. Soc., 102, 870 (1980).
4. B. S. Deol, D. D. Ridley and G. W. Simpson, Aust. J. Chem., 29, 2459 (1976) and references cited therein.
5. Structure (X-ray): D. R. Harris, S. G. McGeachin, H. H. Mills, Tetrahedron Lett., 1965, 679 and references cited therein.
6. T. Anke, H. J. Hecht, G. Schramm, and W. Steglich, J. Antibiotics, 32, 1112 (1979).
7. S. Masamune, G. S. Bates, J. W. Corcoran, Angew. Chem. Int. Ed. Engl., 16, 585 (1977).
8. K. Mori and H. Iwasawa, Tetrahedron, 36, 87 (1980).
9. H. Nomi, K. Mori, T. Chuman, and K. Kato, Abstructs of papers, the Annual Meeting of Agricultural Chemical Society of Japan, page 133, Tokyo, 1982.
10. a) J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969). b) J. A. Dale, and H. S. Mosher, J. Am. Chem. Soc., 95, 512 (1973).
11. a) S. Tatsumi, M. Imaida, and Y. Izumi, Bull. Chem. Soc. Japan, 39, 1818 (1966). b) D. Seebach and D. Wasmuth, Helv. Chim. Acta., 63, 197 (1980). c) K. Mori, H. Nomi, T. Chuman, M. Kohno, K. Kato, and M. Noguchi, Tetrahedron Lett., 22, 1127 (1981).
12. T. Nakata and T. Oishi, Tetrahedron Lett., 21, 1641 (1980).
13. Reduction of ethyl acetoacetate by baker's yeast is known to afford (S)-alcohol i[4]. According to the rule, the configuration of alcohols in 3 and 4 should be reprsented by the symbol R.



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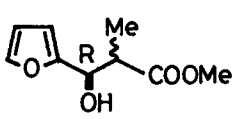

3 or 4

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