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A BIOCATALYTIC APPROACH TO NONRACEMIC 2-METHYL-3-(2-THIOPHENE)-1-PROPANOLS AS CHIRAL BUILDING BLOCKS FOR THE SYNTHESIS OF PYRIDINE ALKALOIDS

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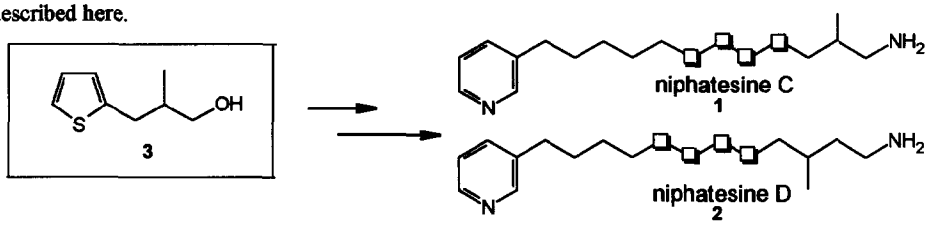
Abstract: (S)-2-Methyl-3-(2-thiophene)-1-propanol was prepared by an improved baker's yeast-mediated asymmetric reduction of the corresponding 2,3-unsaturated aldehyde. (R)-2-Methyl-3(2-thiophene)-1-propanol was obtained by enzymatic kinetic resolution of the racemic alcohol in an organic solvent. Both enantiomers are versatile chiral building blocks for the synthesis of 3-alkyl pyridine alkaloids.

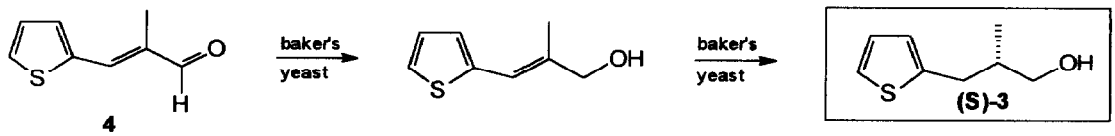
Numerous pyridine alkaloids with antimicrobial and cytostatic activity have been isolated from molluscs and sponges in the last few years[1]. The *niphatesines C* (1) and *D* (2) are chiral representatives of this group of substances[2]. For the total synthesis of both related alkaloids a single homochiral building block was to be used for the introduction of the stereogenic centre. As the homochiral building block the thienylalcohol 3 was employed, which allows the formation of pyridine alkaloids by connection with an 3-alkylpyridine derivative, reductive desulfurization, and functional group transformation.[3-5] The preparation of both enantiomers of 3 is described here.



(The carbon atoms derived from the thiophene ring of 3 are marked with squares)

(S)-(-)-2-Methyl-3-(2-thiophene)-1-propanol ((S)-3) was prepared by enantioselective reduction of E-2-methyl-3-(2-thiophene)propenal (4) with baker's yeast. The original procedure[6] for this microbial transformation had the severe disadvantage to be restricted to small amounts of substrate not exceeding three grams, if substantial decreases in reaction rate and yield should be avoided.[7] Chemical and optical yields of this reaction were strongly depending from aeration,[6] thus indicating supply of oxygen as the limiting factor.

For improving the aeration a 10 l stirred tank reactor with a three stage flat-blade stirrer was used. A commercial brand of *Saccharomyces cerevisiae* was used for the microbial transformation of the unsaturated aldehyde **4**. After inoculation for 2 h in a nutrient solution[8] the substrate **4** was added. The culture was fed with glucose after 26 h of fermentation. The fermentation broth was worked up by continous extraction to give (S)-**3** (75 % yield, 94 % ee) after distillation.[9] This procedure permits the large scale conversion of **4**.

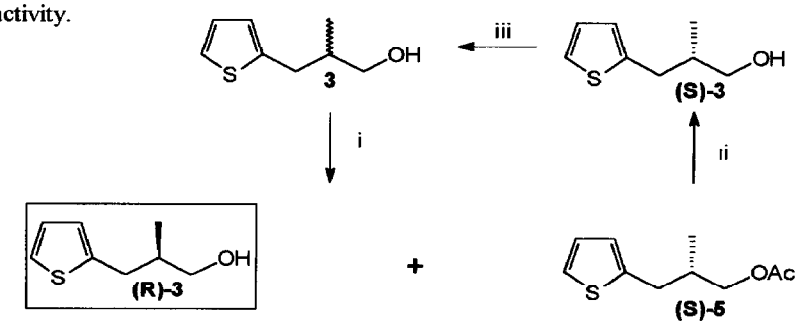


4

The racemic alcohol **3** was prepared by reduction of aldehyde **4** with lithium aluminium hydride or *via* a malonic ester synthesis starting from 2-chloromethylthiophene.[4]

Kinetic resolutions of 2-methyl-1-alkanols have been achieved in good yields by transesterification with vinyl acetate by lipase from *Pseudomonas fluorescens* in organic media.[10,11] (R)-(+)-2-methyl-3-(2-thiophene)-1-propanol ((R)-**3**)[12] was obtained in good enantiomeric excess and chemical yield (42 % yield, 96 % ee) by kinetic resolution of **3** with lipase PS (Amano) in *tert*-butyl methyl ether.[13] The reaction was stopped at 57 % conversion followed by GLC.[14]

The undesired ester (S)-**5** (55 % yield, 75 % ee) can be isomerized to give racemic starting material **3** by subsequent saponification (67 % yield) and racemization with sodium and benzophenone in toluene[11] (73 % yield). Under these conditions the thiophene ring is remarkably stable. Only small amounts of decomposition products were detected by TLC. The enzyme applied to the resolution can be used several times without loss of catalytic activity.



Reagents and conditions: i, lipase PS, vinyl acetate, tBuOMe; ii, KOH, EtOH / water, reflux; iii, toluene, benzophenone, sodium

Alternatively to the preparation of (R)-3 by kinetic resolution a microbial asymmetric decarboxylation of an appropriate disubsubstituted malonic acid was attempted. Though (R)-α-aryl propionates are obtained in good yields from the corresponding α-methyl aryl malonic acids with *Alcaligenes bronchisepticus*[15] no decarboxylation was detected with the homologous methyl 2-thenyl malonic acid employing this bacterium.[16]

The enantiomeric excesses of (R)-3 and (S)-3 were determined after *Jones* oxidation and formation of the (R)-phenyl ethylamide derivatives[6] by GLC.[17] This derivatization proceeds without racemization.[6,11] The determination of the enantiomeric excess using ^{19}F-NMR spectroscopy of the MTPA derivatives is of lower accuracy than GLC of the phenyl ethylamides. The diastereomeric MTPA derivatives could not be separated by GLC. On commercial chiral stationary GLC phases (Chirasil-Val™, cyclodextrin G-PN Astec™) no separation of the enantiomers was achievable.

The absolute configuration of both enantiomers of 3 was referred to the sense of specific rotation given in literature[6] for (S)-3 .

The enantiomeric pure alcohols (R)-3 and (S)-3 are useful homochiral building blocks for the preparation of homochiral, nonracemic pyridine alkaloids.[5]

Acknowledgments.
We thank Mitsubishi International Co., Tokyo for the gift of lipase Amano PS. We are grateful to Dr. H. Ohta, Department of Chemistry, Keio University Yokohama (Japan) for running the experiments with *Alcaligenes* with our substrate. Financial support of this work by the Fonds der Chemischen Industrie is greatly acknowledged. We thank Ms. Tanja Stenzig for preparing the manuscript of this work.

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9. After dissolving glucose (500 g) in a nutrient solution[8] (10 l) baker's yeast (1.3 kg, commercial brand) was inoculated for 2 h at 30 °C with 600 rpm and 0.5 vvm aeration at pH 6.3 in a 10 l laboratory fermenter (Biostat E™, Braun-Melsungen) fitted with a three stage flat-blade stirrer. Then a solution of 4 (25 g, 162 mmol) in ethanol (15 ml) was added. The culture was fed with glucose (250 g) after 26 h of fermentation. Polypropyleneglycol was added as antifoam when needed. The fermentation broth was worked up by continuous extraction with ethyl acetate (3 l) after 50 h to give 15 g of (S)-3 (75 %, 94 % ee) after distillation ($b.p._{0.2}$ 68 °C).
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11. Barth, S.; Effenberger, F. *Tetrahedron: Asymmetry* **1993**, *4*, 823-833.
12. The spectroscopic data of (R)-3 are in complete agreement with the values published[6] for (S)-3.
13. 96 g of 3 (613 mmol), vinyl acetate (107 g, 1250 mmol) and Lipase PS (Amano) (6.15 g, 184500 U) were added to *t*-BuOMe (1.2 l) and stirred at 30 °C. The reaction was followed by GLC. At a conversion of 57 % the reaction was stopped by filtering off the enzyme. Products were separated by flash column chromatography to yield 40 g of (R)-3 (42 %, 96 % ee) and 67 g of (S)-5 (55 %, 75 % ee).
14. GLC conditions: column AT-1™ (15 m, 0.53 mm I.D., 1.2 µm film), 1.5 m retention gap (phenyl methylsilicon), 150 to 181 °C, gradient 5 K / min; carrier: hydrogen, 50 cm / s; detection: FID; injection: on-column, 60 to 170 °C, 80 K / min, 170 to 195 °C, 7 K / min; t_R: 1.63 min ((R)-3), 2.37 min ((S)-5), 5.70 min (heptadecane).
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16. We thank Dr. H. Ohta, Department of Chemistry, Keio University Yokohama for carrying out this experiment.
17. GLC conditions: column AT-50™ (30 m, 0.25 mm I.D., 0.25 µm film), 220 °C isothermal; carrier: hydrogen, 1.125 kp / cm^2, 50 cm / s; detection: FID; injection: split 1:33, 270 °C; t_R: 6.29 min (derivative of (R)-3), 6.77min (derivative of (S)-3).

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