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# PRODUCT STEREOSPECIFICITY IN THE MICROBIAL REDUCTION OF IMIDAZOL-1-YL METHYL ARYL KETONES

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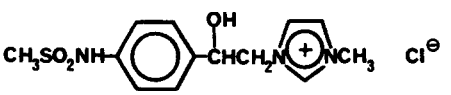
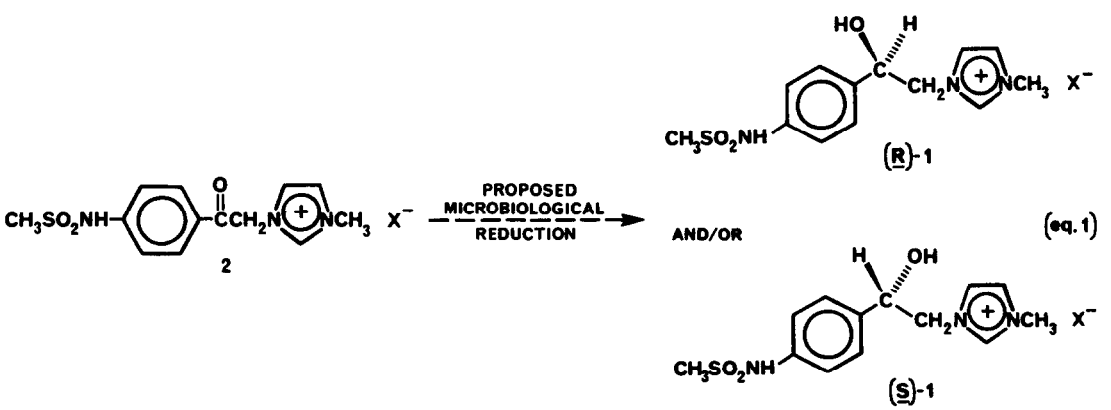
**Abstract:** Various microorganisms can be used to reduce ketoimidazole **3** to hydroxyimidazole **4**. Only one enantiomer (i.e., (R)-**4**) is produced. In contrast, ketoimidazolium salt **2** is not reduced under identical conditions.

The importance of racemic imidazolium salt **1** as an active Class III antiarrhythmic agent[1] prompted us to investigate syntheses of its'



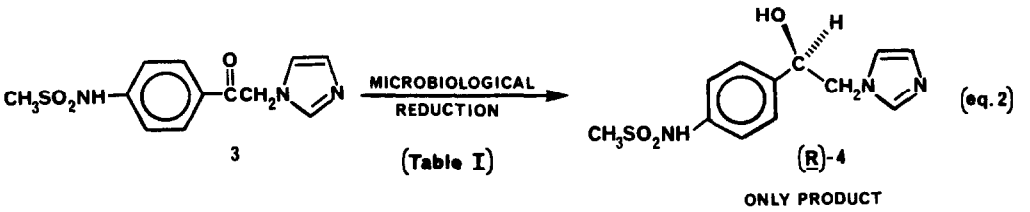
**1**

enantiomers. One possible route would be via the microbiological reduction of ketoimidazolium salt **2** to give (R)-**1** and/or (S)-**1** (eq. 1).




**2**

Attempted reduction of 2, using over 60 microbial organisms, was unsuccessful and afforded only recovered starting material. In contrast, reduction of ketoimidazole 3 with various microorganisms proved to be quite effective and afforded only one enantiomer[2] (i.e. (R)-4, vide infra) regardless of the microorganism used (eq. 2). High enantioselectivity has also been reported in the microbiological reductions of other aryl ketones.[3]




The results of the microbial reduction of 3 are summarized in Table I. The extent of reduction and chemical yield were determined by HPLC analysis of the crude lyophilized broths.[4]

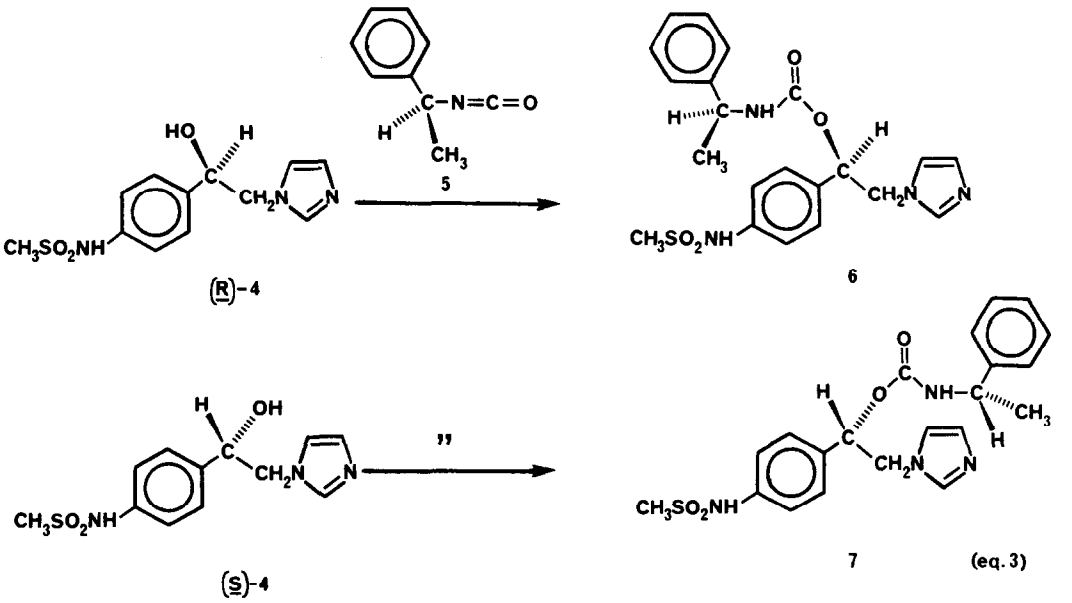
**TABLE I: Result of the Microbial Reduction of 3**

| Reduction Medium | Time (hr) | Starting Ketone 3 Remaining | Yield* |
|---|---|---|---|
| Saccharomyces carlsbergensis, immobilized | 232 | 15% | 16% |
| Kloeckera magna, immobilized | 232 | 2% | 21% |
| Hansenula subpelliculosa, distilled water resting cell, 3-fold | 332 | 3% | 27% |
| Hansenula subpelliculosa, distilled water resting cell, 5-fold | 188 | 1% | 36% |
| Kloeckera magna, distilled water resting cell, 3-fold | 236 | 11% | 69% |
| Kloeckera magna, distilled water resting cell, 5-fold | 332 | 24% | 69% |
| Kloeckera magna (Tris buffer), resting cell, 5-fold | 188 | 0% | 43% |
| Kloeckera jensenii (Tris buffer), resting cell, 3-fold | 332 | 11% | 45% |

* $\text{Yield} = 100 \times \frac{\text{mol of alcohol}}{\text{mol of starting ketone-mole of recovered ketone}}$

The enantiomers of 4[5] have been prepared and their absolute configurations established by a single-crystal X-ray of the (-)-l-camphorsulfonic acid salt of (S)-4.[1] Derivatization of these enantiomers with (S)-(-)-α-methylbenzyl

isocyanate (MBI) 5 gave the corresponding diastereomeric carbamates 6 and 7 (eq 3), which were also analyzed by HPLC.[6] Treating the lyophilized broths[7] in Table I with (S)-(-)-α-MBI afforded only carbamate 6 by HPLC analysis.




This indicates that only (R)-4 is produced from the microbial reduction of 3. This result is also consistent with Prelog's rule[8] for predicting the stereochemistry of alcohols prepared by microbial reduction of their ketone precursors.

In conclusion, it is possible to prepare enantiomerically pure (R)-4 (and therefore (R)-1)[2] using various microbiological methods.

General Procedure of Microbiological Reduction: The yeast strains were cultivated in an aqueous nutrient medium containing per liter: glucose 50 g, and corn steep 20 g (pH 6.5). After inoculation, the flasks were agitated at 28°C for 70 h. Cells were harvested by centrifugation and resuspended for fermentation in distilled water or 0.1 M Tris/HCl buffer (pH 7.5). In addition, cells were entrapped by suspending in sodium alginate solution and dropping the mixture into $CaCl_2$ solution. The alginate beads were resuspended in aqueous transformation medium containing 10 g $CaCl_2$ per liter. After incubation on a rotary shaker at 28°C (substrate concentration 200 mg per liter) the cells and the alginate beads were filtered and the filtrate lyophilized.

## REFERENCES AND NOTES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2. Previous studies (ref 1) have shown that (R)-4 and (S)-4 can be converted into (R)-1 and (S)-1, respectively.

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4. HPLC Chromatographic Conditions: Column: Phenyl-4.6 mm X 250 mm, 5 micron, spherical (Chromegabond-Alkyl Phenyl, ES Industries, Marlton, NJ), Mobile Phase: 2/98 v/v 2-propanol/0.025 M ammonium acetate adjusted to pH 4.0 with $H_2SO_4$, Flow Rate: 1.5 mL/min, Temp.: 40°C, Detection: UV at 225 nm, Typical Retention Times: 3:$t_r$ = 8.17 min; 4: $t_r$ = 5.44 min.

5. Enantiomers (R)-4 and (S)-4 were prepared by the method described in reference 1.

   (R)-4: CD ($CH_3OH$) $\lambda$ = 276 nm, $\Delta\varepsilon$ = -0.132;
   $\lambda$ = 224 nm, $\Delta\varepsilon$ = -0.92
   $[\alpha]^{23}$ = -59.5° (1N HCl)

   (S)-4: CD ($CH_3OH$) $\lambda$ = 276 nm, $\Delta\varepsilon$ = + 0.135
   $\lambda$ = 223 nm, $\Delta\varepsilon$ = + 1.90
   $[\alpha]^{23}$ = +59.7° (1N HCl)

6. HPLC Chromatographic Conditions: Column: $C_8$ - 4.6 mm x 250 mm, 5 micron, spherical (Chromegabond-$C_8$, ES Industries, Marlton, NJ), Mobile Phase: 12/88 V/V 2-propanol/0.05 M ammonium acetate adjusted to pH 2.5 with $H_2SO_4$, Flow Rate: 1.5 mL/min., Temp: 50°C, Detection: U.V. at 254 nm, Typical Retention Times 6: $t_r$ = 7.12 min.; 7: $t_r$ = 8.48 min.

7. The crude lyophilized broths were purified by preparative TLC prior to derivatization. The carbamates were prepared by treating (R)-4 and (S)-4 with (S)-(-)α-methylbenzyl isocyanate (MBI) in 1-methyl-2-pyrrolidinone. Purification prior to derivatization minimizes interferences in the HPLC chromatogram.

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