Short Communication

Microbial Asymmetric Reduction of Organometallic Ketones: Acetylferrocene and (Acetophenone)-tricarbonylchromium

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Enzymatic or microbiological transformation is one of the most powerful methods of asymmetric synthesis.¹⁾ Recently, we^{2a)} and other groups^{2b~d)} have started to expand the application of this method into the field of organometallic chemistry. Here we report the microbial reduction of metallocenyl ketones, which has been done to survey what microorganisms can reduce this specific class of ketones and secondly to find whether the compounds sensitive to light and air, e.g., tricarbonylchromium complexes, can be treated by a bioconversion process.

Initial screening was done of 57 species of yeasts (11 genera), 71 species of bacteria and actinomycetes (22 genera), and 67 species of fungi (29 genera), which were grown in shaking cultures in glucose-containing media.³⁾ The cells of each microorganism (4 ml of culture/strain) were suspended in a 1-ml mixture containing 2 mg acetylferrocene (**1**, Tokyo Kasei) in 0.1 M phosphate buffer (pH 7.5) with 1% ethanol and 1% glucose. After shaking at 28°C for 48 hr, the mixtures were extracted with ether (1 ml). The ether extracts were analyzed by TLC (on silicagel F₂₅₄ developed with 10% ethyl acetate/benzene). The samples for the following strains gave a clear spot corresponding to 1-hydroxyethylferrocene (**2**, Tokyo Kasei): *Candida tropicalis* IFO 199, *Pichia quercuum* IFO 949, *Saccharomyces cere-*

visiae IFO 305, *Saccharomyces rosei* IFO 428, *Torulopsis colliculosa* IFO 381, *Saccharomyces* sp. H-1 (FERM P-549), *Nocardia erythropolis* IFO 12320, IAM 1400, 1484 and 12122, and *Pseudomonas oleovorans* IFO 13583. Thus, the reductive activity is found mainly in yeasts and bacteria of *Nocardia* and *Pseudomonas*. Product (**2**) was isolated by preparative TLC and tested on its enantiomeric purity by HPLC with a chiral column (Cyclobond I, Astec Inc.) using 65% methanol in water as the solvent.⁴⁾ All the products had the *S* configuration and the enantiomeric purity was more than 96% e.e. for *C. tropicalis*, *S. cerevisiae*, *S. rosei*, *T. colliculosa* and *P. oleovorans*, 92% e.e. for *N. erythropolis* IAM 12122, 83% e.e. for H-1, and 23% e.e. for *P. quercuum*. Then, 200 mg of **1** were reduced by 39.5 g of the wet cells of *C. tropicalis* (23 hr old) suspended in 200 ml of phosphate buffer containing 2% glucose, 2% ethanol, and 0.02% Tween 80 at 28°C for 69 hr. After the usual workup and separation by preparative TLC, the crude product (27 mg) was recrystallized from hexane to afford 15 mg (7% yield) of (*S*)-(+)-**2** as yellow leaflets, mp 73~75°C, $[\alpha]_D^{28} +28^\circ$ ($c=0.5$, benzene)*¹ (lit.⁵⁾ for (*K*)-**2**, mp 72~73°C, $[\alpha]_D^{25} -30.5^\circ$ ($c=1.1$, benzene)). The enantiomeric purity was 96% e.e. as determined by the HPLC.

(Acetophenone)tricarbonylchromium (**3**) was synthesized by the published method.⁶⁾ A preliminary screening for the reduction of **3** was done with the strains described above. The most active strain was *Saccharomyces* sp. H-1, whose cells (5.6 g wet weight, 11.5 hr old) was suspended in a mixture of 36 mg of **3** in 9 ml of the phosphate buffer with 10% ethanol and 5% glucose. The vial was tightly sealed and wrapped with foil. The suspension was stirred with a magnetic stirrer at 28°C for 10 hr. Then, the whole content was extracted with ethyl acetate (60 ml × 4) after saturation with sodium chloride. This and the following operations were done in a dark room. The combined organic layer was dried over sodium sulfate, concentrated by an evaporator, and put on a silicagel

*¹ MS, IR and PMR spectra were consistent with the structure.

column (12 × 185 mm). Elution was done with 25 ml benzene and 25-ml mixtures of 5, 7.5, and 10% ethyl acetate in benzene. The 7.5% fraction was evaporated to afford 34 mg (94% yield) of (*S*)-tricarbonyl [(1,2,3,4,5,6- η)- α -methylbenzenemethanol]chromium (**4**) as a yellow gum, $[\alpha]_D^{25} + 17^\circ$ ($c = 3.4$, benzene) and $[\alpha]_D^{25} + 12^\circ$ ($c = 3.4$, CHCl_3) (lit.⁷⁾ $[\alpha]_D^{22} + 18^\circ$ ($c = 2.1$, CHCl_3), MS m/z : 257.9986 (M^+); Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_4\text{Cr} = 257.9984$.^{*1,*2} The enantiomeric purity of **4** was 73% *e.e.* as measured in the following way. An ether solution of **4** was left under a fluorescent lamp for 1.5 hr for decomplexation. Thus formed α -phenethyl alcohol (**5**, identified by GC) was analyzed by HPLC with a chiral column (Chiralcel OB, Daicel, with 10% isopropanol/hexane as the solvent and ($\pm$)- and (*R*)-(+)-**5** (Tokyo Kasei) as the authentic specimens), showing that this was (*S*)-**5** of 73% *e.e.* (*S*)-**4** was also obtained by the reduction of **3** with *S. rosei* (35% yield, >97% *e.e.*), *N. erythropolis* IAM 12122 (54% yield, 83% *e.e.*) and *C. tropicalis* (25% yield, 32% *e.e.*).

A preceding paper⁸⁾ describes how **1** was not reduced by baker's yeast in contrast to the rapid reduction of (trifluoroacetyl)ferrocene, but this work has shown that some strains of yeasts and bacteria did not need the fluorine substitution to reduce the ferrocenyl ketone. The reduction of **3** is the first report of the bioconversion of chromium-containing organometallic compounds. Although these com-

pounds are fairly unstable, the process using microorganisms was very effective for the transformation. Chiral ferrocenes^{9a)} and tricarbonylchromium complexes^{9b,c)} are often used as chiral auxiliaries in asymmetric synthesis. This work shows the feasibility of preparing such chiral organometallic compounds by enzymes or microorganisms more simply than by the conventional procedure based on derivatization and resolution as in the literature methods for optically active **2**⁵⁾ and **4**.⁷⁾ Finally it should be pointed out that all the products of these microbial reductions were formed by the hydrogen transfer to the *re*-face of carbonyl group, being consistent with Prelog's rule.¹⁾

REFERENCES

- 1) H. Maeda, Y. Yamazaki, K. Obuchi and S. Kajiura, "Fusei Gosei Bioreactor," Gakkai Shuppan Center, Tokyo, 1988, p. 7.
- 2) (a) Y. Yamazaki and K. Hosono, *Tetrahedron Lett.*, **29**, 5769 (1988); (b) N. W. Alcock, D. H. G. Crout, C. M. Henderson and S. E. Thomas, *J. Chem. Soc., Chem. Commun.*, **1988**, 746; (c) V. I. Sokolov, L. L. Toroitkaya and T. I. Rozhkova, *Gazz. Chim. Ital.*, **117**, 525 (1987) [*C.A.*, **108**, 109138a (1988)]; (d) C. Sylatk, H. Andree, A. Stoffregen, F. Wagner, B. Stumpf, L. Ernst, H. Zilch and R. Tacke, *Appl. Microbiol. Biotechnol.*, **27**, 152 (1987).
- 3) Y. Yamazaki and H. Maeda, *Agric. Biol. Chem.*, **49**, 3203 (1985).
- 4) D. W. Armstrong, W. DeMond and B. P. Czech, *Anal. Chem.*, **57**, 481 (1985).
- 5) G. W. Gokel, D. Marquarding and I. K. Ugi, *J. Org. Chem.*, **37**, 3052 (1972).
- 6) R. Riemschneider, O. Becker and K. Franz, *Monatsh. Chem.*, **90**, 571 (1959).
- 7) S. Top and G. Jaouen, *J. Org. Chem.*, **46**, 78 (1981).
- 8) A. Ratajczak and B. Misterkiewicz, *Chem. Ind.*, **1976**, 902.
- 9) (a) T. Hayashi, *Pure Appl. Chem.*, **60**, 7 (1988); (b) A. Solladié-Cavallo and D. Farkhani, *Tetrahedron Lett.*, **27**, 1331 (1986); (c) R. M. Moriarty, S. G. Engerer, O. Prakash, I. Prakash, U. S. Gill and W. A. Freeman, *J. Chem. Soc., Chem. Commun.*, **1985**, 1715.

*2 The PMR spectrum indicated this sample was little contaminated (only less than 2.5%) by the decomplexation product **5**.