Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis B: Enzymatic 45 (2007) 68–72
JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC
www.elsevier.com/locate/molcatb

Biotransformation of α-bromo and α,α′-dibromo alkanone to α-hydroxyketone and α-diketone by *Spirulina platensis*

Takamitsu Utsukihara, Shinnosuke Okada, Nakahide Kato, C. Akira Horiuchi *

Department of Chemistry, Rikkyo (St. Paul's) University, Nishi-Ikebukuro, Toshima-Ku, Tokyo 171-8501, Japan

Received 2 November 2006; received in revised form 5 December 2006; accepted 8 December 2006
Available online 15 December 2006

Abstract

Biotransformation of α-bromo and α,α′-dibromo alkanones were investigated with alga of *Spirulina platensis*. Biotransformation of α-bromo ketone with *S. platensis* gave the corresponding α-hydroxyketone in good yields (80–95%). It was found that α,α′-dibromo ketone biotransforms into α-diketone and then converts α-hydroxy ketone. However, in the case of diosphenol, it seems that alkyl group at the α-position of carbonyl group prevents reduction into α-hydroxy ketone. We compared to five algae (*Cyanidioschyzon merolae*, *Cyanidium caldarium*, *Synechoccus elongatus* PCC 7942, *Synechosystis* sp. PCC 6803 and *S. platensis*) for the biotransformation of 2-bromo cyclohaxanone (**2**). Among the algae, *S. platensis* gave the corresponding 2-hydroxycyclohexanone (**2a**) in best result (89% yield) for short reaction time (24 h). This reaction affords a new, eco-friendly and convenient method for α-hydroxyketones.

Keywords: *Spirulina platensis*; Biotransformation; Bromo cycloalkanone; Dibromo cycloalkanone; α-Hydroxyketone

1. Introduction

In the synthesis of various natural products and pharmacologically active compounds, α-hydroxycarbonyl compounds are potential valuable synthethic intermediates for preparation of a range of compounds of biological products, such as substituted 2-amino-1-aryletanols [1].

α-Hydroxyketones are usually prepared by one of the following methods: α-hydroxylation by treatment of their enolate forms with a molybdenum peroxide reagent in THF-hexane at −70 °C [2], transformation of the enamine derivatives of ketones to α-hydroxy derivatives by molecular oxygen [3], and α-hydroxylation of silyl enol ethers with *m*-chloroperbenzoic acid [4], or with certain other oxidizing agents [5].

It is known that there has been considerable interest in the development of direct methods for the synthesis of α-hydroxyketones using nontoxic hypervalent iodine reagents, which involve the following methods: reaction of ketone with iodobenzene diacetate in the presence of potassium hydroxide in methanol and then hydrolysis of the dimethylacetals [6]; oxidation of enol silyl ether of acetophenone using the system iodosobenzene/boron trifluoride etherate/water in methylene chloride at −40 °C [7] and reaction of ketones with [bis(trifluoroacetoxy)] iodobenzene and trifluoroacetic acid in acetonitrile-water under acidic conditions [8].

We have been investigating the organic synthesis from the viewpoint of green chemistry. In our previous paper, we found that a novel reaction of α-halo ketone (α-bromo and α-chloro ketone) with irradiation under microwave gives the corresponding α-hydroxyketone and pyrazine derivative in good yields [9]. And in the case of α,α′-dibromo ketone, α-diketone was obtained. These methods are sometimes said to result from the viewpoint of "green chemistry" as synthesis. However, we tried much more synthetic method as compared with microwave method. We have been reported that biotransformation of a synthetic substance into a more useful substance by plant cultured-cells is an important reaction in synthetic chemistry [10–13]. Plant cultured-cells have the ability of regio- and stereoselective hydroxylation, oxidation, reduction, hydrogenation, glycosylation and hydrolysis for various organic compounds [14].

Furthermore, many biocatalytic enantio- and regioselective reduction of α-diketone have reported as methods using baker's yeast [15–17] and some fungi [18,19].

* Corresponding author. Tel.: +81 3 3985 2397; fax: +81 3 3985 2397.
E-mail addresses: horiuchi@rikkyo.ac.jp, cahoriuchi@nifty.com (C.A. Horiuchi).

1381-1177/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcatb.2006.12.001

More recently, we reported that the reduction of acetophenone derivatives, (+)- and (−)-camphorquinones and steroidal ketones using red algae (*Cyanidioshyzon merolae* 10D and *Cyanidium caldarium*) [20]. Moreover, (+)-camphorquinone was reduced to high stereoselectivity by cyanobacteria (*Synechococcus elogatus* PCC 7942 and *Synechosystis* sp. PCC 6803) to provide (−)-3*S*-*exo*-hydroxycamphor (94%) [21].

There is only very little information on the biotransformation of α-bromo and α,α′- dibromo ketones. Here, we report on convenient and simple procedure for the preparation of α-hydroxyketones from α-bromo and α,α′-dibromo alkanone with *Spirulina platensis* under mild conditions.

2. Experimental

2.1. Analytical and substrates

GC–MS: Shimadzu GCMS-QP5050 (EI-MS 70 eV) using DB1 (0.25 mm × 30 m, 0.25 μm) capillary column GC; GC: GC-17A. ^{1}H NMR: Jeol GSX 400 spectrometer. $CDCl_3$ with tetramethylsilane as the internal standared was used. The IR spectra were measured on Jasco FT-IR 230. *S. platensis* NIES-39 was obtained from the National Institute for Environmental Studies (NIES-Collection).

2.2. Cultivation

S. platensis was grown in SOT medium (pH 10.0) under continuous illumination provided by fluorescent lamps (2000 lx) with air-bubbling at 25 °C.

2.3. General reaction conditions

Substrates (100 mg) were added to suspended culture of *S. platensis* (adjusted pH 7.0, 1 g/L as dry weight) in SOT medium (100 ml). The mixture was treated with a shaker (120 rpm) at 25 °C in the light (2000 lx). The end of the reaction, *S. platensis* was filtered from algae, and the resulting mixture was extracted with EtOAc–Et_2O (1:1). All the products were determined by IR, ^{1}H NMR and GC–MS analyses.

2.4. Synthesis of α-bromo alkanone [22]

Alkanone (1 mmol), dioxane-dibromide [23] (1.1 mmol) and silica gel (60 mesh, 3 g) were taken in round flask (100 ml). The round flask was introduced in the domestic microwave oven National NE-S330F (170 W) for 2 min. After irradiation, the contents were cooled to room temperature and extracted ethyl acetate (50 ml). The resulting residue was applied to a silica gel column and eluted with *n*-hexane-Et_2O (1:1).

2.5. Synthesis of α,α′- dibromo alkanone [24]

In 30 ml of anhydrous ether, alkanone (61 mmol) was brominated at −10 °C by adding bromine (122 mmol) dropwise under stirring. The reaction mixture was washed with saturated aqueous NaCl, then twice with saturated aqueous $NaHCO_3$, and finally with saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and ether was evaporated to give α,α′- dibromo alkanone.

2.6. Preparation of microbial culture

SOT medium was prepared by mixing $NaHCO_3$ (16.8 g), K_2HPO_4 (0.5 g), $NaNO_3$ (2.5 g), K_2SO_4 (1 g), NaCl (1 g), $MgSO_4{\cdot}7H_2O$ (0.2 g), $CaCl_2{\cdot}2H_2O$ (0.04 g), $FeSO_4{\cdot}7H_2O$ (0.01 g), Na_2EDTA (0.08 g) and A5 solution (1 ml) in distilled H_2O (1 L).

A5 solution was H_3BO_3 (286 mg), $MnSO_4{\cdot}7H_2O$ (250 mg), $ZnSO_4{\cdot}7H_2O$ (22.2 mg), $CuSO_4{\cdot}5H_2O$ (7.9 mg) and $Na_2MoO_4{\cdot}2H_2O$ (2.1 mg) dissolved in distilled H_2O (100 ml).

2.6.1. Compound **2a**: 2-hydroxycyclohexanone [25a]

Colorless oil; IR (NaCl) = 3473 cm^{-1} (O–H) and 1714 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm) = 4.15 (ddd, 1H, *J* = 1.6, 4.6, 8.8 Hz), 3.66 (brs, 1H), 2.30–2.50 (m, 2H) and 1.50–2.15 (m, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 211.4, 75.3, 39.5, 36.7, 27.5 and 23.4; MS (EI) *m*/*z* 114 (M^+), 96 ([M−H_2O]$^+$), 85, 70, 57 and 44.

2.6.2. Compound **3a**: 2-hydroxycycloheptanone [25b]

Pale-yellow oil; IR (NaCl) = 3469 cm^{-1} (O–H) and 1699 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm) = 4.29 (dt, 1H, *J* = 6.2, 2.1 Hz), 3.86 (brd, 1H), 2.72 (dddd, 1H, *J* = 0.9, 2.2, 4.8, 7.1 Hz), 2.47 (ddd, 1H, *J* = 3.8, 11.3, 18.2 Hz), 2.01–2.09 (m, 1H), 1.74–1.93 (m, 3H), 1.54–1.73 (m, 3H) and 1.29–1.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 213.2, 77.2, 40.0, 33.6, 29.4, 26.5 and 23.2; MS (EI) *m*/*z* 128 (M^+), 110 ([M−H_2O]$^+$), 99, 81, 57 and 44.

2.6.3. Compound **4a**: 2-hydroxycyclooctanone [25b]

Pale-yellow oil; IR (NaCl) = 3475 cm^{-1} (O–H) and 1701 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm) = 4.19 (dd, 1H, *J* = 1.9, 4.3 Hz), 3.79 (brs, 1H), 2.71 (dt, 1H, *J* = 2.6, 8.5 Hz), 2.30–2.45 (m, 2H), 1.91–2.08 (m, 2H), 1.62–1.87 (m, 4H) 1.32–1.45 (m, 2H) and 0.85–0.97 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 217.6, 76.1, 37.4, 29.2, 28.3, 25.7, 24.8 and 22.1; MS (EI) *m*/*z* 142 (M^+), 124 ([M−H_2O]$^+$), 113, 98, 81, 57 and 41.

2.6.4. Compound **5a**: 2-hydroxyacetophenone [25c]

Pale-yellow needles; mp 85–86 °C; IR (KBr) = 3428 cm^{-1} (O–H) and 1687 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm) = 7.92 (d, 2H, *J* = 7.6 Hz), 7.61 (t, 1H, *J* = 7.4 Hz),7.49 (t, 2H, *J* = 7.7 Hz), 4.88 (s, 2H) and 3.54 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 198.4, 134.2, 133.3, 128.9, 127.6 and 65.4; MS (EI) *m*/*z* 136 (M^+), 105, 77 and 51.

2.6.5. Compound **6a**: 4′-methyl-2-hydroxyacetophenone [25d]

Pale-yellow needles; mp 82–83 °C; IR (KBr) = 3428 cm^{-1} (O–H) and 1681 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm) = 7.82 (m, 2H), 7.27 (m, 2H), 4.85 (s, 2H) and 3.59 (brs, 1H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 197.9, 145.3, 130.8, 129.6,

127.7, 65.2 and 21.8; MS (EI) *m/z* 150 (M^+), 119, 105, 91, 77, 65 and 51.

2.6.6. Compound **7a**: 4′-fluoro-2-hydroxyacetophenone [25e]

Pale-yellow needles; mp 109–110 °C, IR (KBr) = 3429 cm^{-1} (O–H) and 1684 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ (ppm) = 7.96 (dd, 2H, J = 5.5, 8.8 Hz), 7.19 (t, 2H, J = 8.8 Hz), 4.86 (s, 2H) and 3.60 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 196.8, 167.6, 129.8, 116.4 and 65.3; MS (EI) *m/z* 154 (M^+), 123, 95, 75 and 50.

2.6.7. Compound **8a**: 4′-chloro-2-hydroxyacetophenone [25d]

Pale-yellow needles; mp 115–116 °C, IR (KBr) = 3423 cm^{-1} (O–H) and 1681 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ (ppm) = 7.85 (d, 2H, J = 8.4 Hz), 7.48 (d, 2H, J = 8.4 Hz), 4.85 (s, 2H) and 3.42 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 197.2, 140.8, 131.6, 129.4, 129.0 and 65.3; MS (EI) *m/z* 172 (M^+), 170, 141, 139, 113, 111, 75 and 50.

2.6.8. Compound **9a**: 4′-bromo-2-hydroxyacetophenone [25d]

Pale-yellow needles; mp 133–134 °C, IR (KBr) = 3411 cm^{-1} (O–H) and 1681 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ (ppm) = 7.78 (d, 2H, J = 8.8 Hz), 7.65 (d, 2H, J = 8.8 Hz), 4.85 (s, 2H) and 3.48 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) = 197.5, 132.4, 132.0, 129.6, 129.1 and 65.4; MS (EI) *m/z* 216 (M^+), 214, 185, 183, 157, 155, 135, 104, 75 and 50.

2.6.9. Compound **10a**: 3-hydroxy-4-heptanone [25a]

Colorless oil; IR (NaCl) = 3473 cm^{-1} (O–H) and 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ (ppm) = 4.16 (dd, 1H, J = 5.6, 8.1 Hz), 2.45 (t, 2H, J = 7.60 Hz), 2.05 (brs, 1H), 1.86–1.96 (m, 2H), 1.56–1.72 (m, 2H) and 0.94 (t, 6H, J = 7.20 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) = 212.3, 60.4, 39.7, 26.7, 17.0, 13.6 and 8.80; MS (EI) *m/z* 216 (M^+), 214, 185, 183, 157, 155, 135, 104, 75 and 50; MS (EI) *m/z* 130 (M^+), 113, 101, 88, 71, 59 and 43.

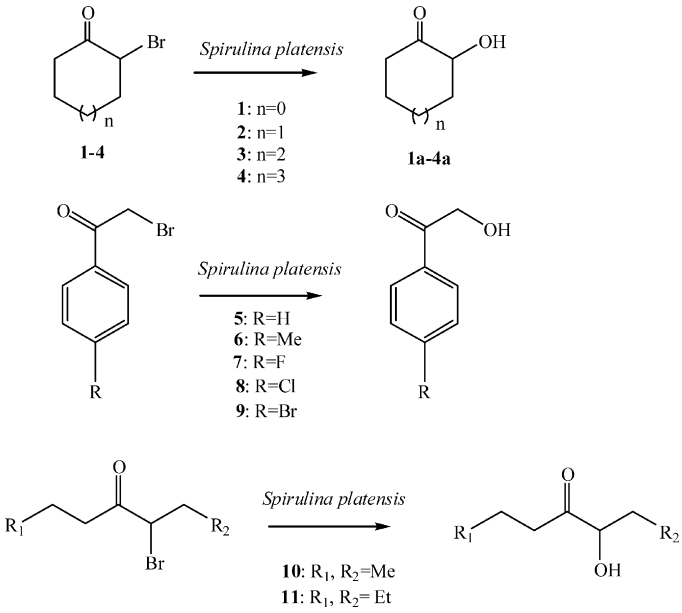
3. Results and discussion

3.1. Biotransformation of α-bromo alkanone

Simple cyclic, aromatic and aliphatic α-bromo ketones were targeted for biotransformation using *S. platensis* in SOT medium (adjusted pH 7.0). The biotransformation of α-bromo cycloalkanones (**1**–**4**) by *S. platensis* gave α-hydroxycycloalkanones (**1a**–**4a**) with in 88–95 yields. These results are summarized in Table 1, and are shown in Fig. 1.

The versatility of *S. platensis* hydroxylation system is further exemplified by α-bromo aromatic ketone as substrates. 2-Bromo acetophenone (**5**) gave 2-hydroxyacetophenone with in 55% yield. However, 2-bromo-4′-methylacetophenone (**6**) gave 2-hydroxy-4′-methylacetophenone (**6a**) with in 35% yield. Furthermore, biotransformation of 2-bromo-4′-chloroacetophenone (**8**) and 2-bromo-4′-bromoacetophenone (**9**) gave the corresponding α-hydroxy compounds in 11 and 6% yield, respectively. Biotransformation of simple aliphatic ketones, 3-bromo-4-heptanone (**10**) and 4-bromo-5-nonanone (**11**) with *S. platensis* gave the corresponding α-hydroxy compound in 91% and 60% yield, respectively. On the basis of these results, it was found that the biotransformation of **1–11** occurs biocatalytic hydrolysis of α-bromo ketones, which gave α-hydroxy ketone from the viewpoint of "green chemistry".

Table 1
Biotransformation of α-bromo cycloalkanones by *Spirulina platensis*



Run	Substrate	Day	Product	Yield (%)[a]
1	**1**	1	**1a**	92
2	**2**	1	**2a**	89
3	**3**	1	**3a**	95
4	**4**	5	**4a**	88
5	**5**	3	**5a**	55
6	**6**	3	**6a**	35
7	**7**	3	**7a**	80
8	**8**	3	**8a**	11
9	**9**	3	**9a**	6
10	**10**	1	**10a**	91
11	**11**	3	**11a**	60

Reaction conditions: substrate (100 mg), algae (dry weight 1 g/L) and medium (100 ml) were employed.
[a] Yields were determined by GLC.

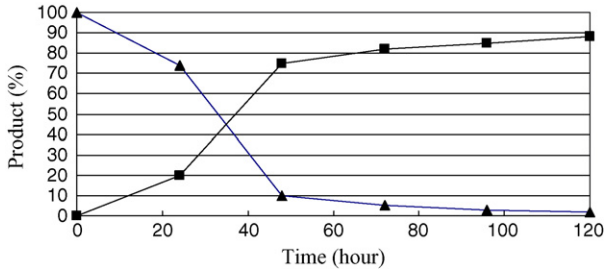


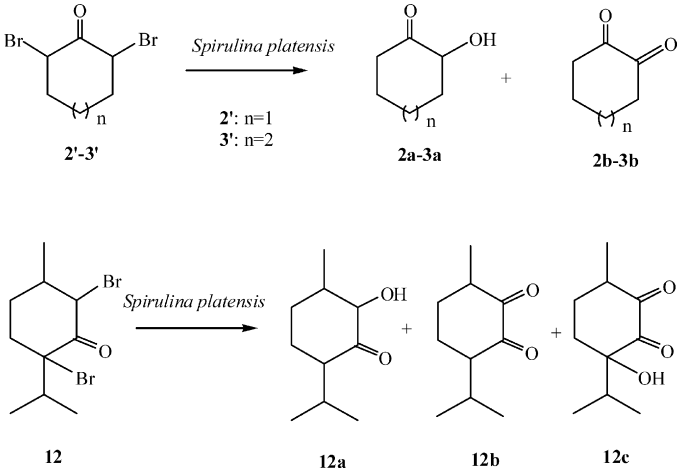
Fig. 1. Biotransformation of 2-bromo cycloheptanone by *Spirulina platensis*: (▲), 2-bromo cycloheptanone; (■), 2-hydroxycycloheptanone.

The cultivation of photosynthetic microorganisms can be an advantage process for the production of high biological value protein for human and animal [26]. *S. platensis* is blue-green photoautotrophic and unicellular microalga inhabiting in alkaline (pH 10). This alga has been used as human food in Mexico and Africa. Approximately 70% of *S. platensis* biomass is constituted of proteins and all the amino acids. The amino acids are contained in *S. platensis* recommended by FAO (Food and Agriculture Organization), except for methionine [27,28]. This microorganism is considered as important material from the medical [29,30]. Furthermore, *S. platensis* contains a high percentage of vitamins, especially B_{12}, and several pigments like carotenoids, xantophylls, phycobiliproteins and chlorophyll *a* [31].

3.2. Biotransformation of α,α′-dibromo cycloalkanones

There is only very little information on the reaction of α,α′-dibromo ketones using biocatalyst. Recently, we have reported that a novel reaction of α,α′-dibromo ketone with irradiation under microwave gives the corresponding diketone in good yields [9]. So, we tried biotransformation of α,α′-dibromo cycloalkanones by *S. platensis*. These results are shown in Table 2. 2,6-Dibromo cyclohexanone (**2′**) and 2,7-dibromo cyclohepanone (**3′**) gave the corresponding α-diketone and α-hydroxy compounds. In order to investigate the time course of the reactions, 2,7-dibromo cycloheptanone (**3′**) using *S. platensis* was examined. In the case of α,α′-dibromo cycloheptanone (**3′**), substrate disappeared after 120 h incubation (Fig. 2). 2,7-Dibromo cycloheptanone (**3′**) by *S. platensis* was transformed to α-diketone **3b** after 24 h incubation. After 5 days, it was found that **3′** and **3b** were converted into 2-hydroxycycloheptanone

Table 2
Biotransformation of α,α′-dibromo cycloalkanones by *Spirulina platensis*



Run	Substrate	Day	Yield (%)[a]		
1	**2′**	3	**2a** (92)	**2b** (3)	
2	**3′**	5	**3a** (42)	**3b** (1)	
3	**12**	3	**12a** (4)	**12b** (58)	**12c** (15)

Reaction conditions: substrate (100 mg), algae (dry weight 1 g/L) and medium (100 ml) were employed.
[a] Yields were determined by GLC.

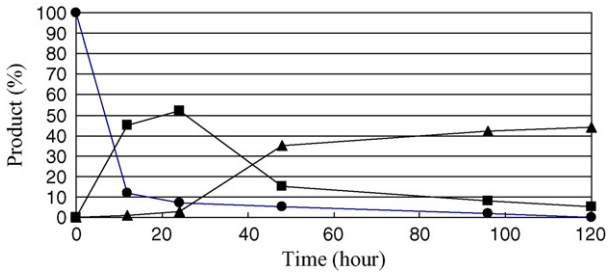


Fig. 2. Biotransformation of 2,7-dibromo cycloheptanone by *Spirulina platensis*: (●), 2,7-dibromo cycloheptanone; (■), 1,2-cycloheptanedione; (▲), 2-hydroxycycloheptanone.

(**3a**). From these results, it was found that only hydroxy ketones were ultimately obtained not diols.

It was found that the biotransformation of α-bromo and α,α′-dibromo cycloalkanone using *S. platensis* can be obtained α-hydroxy ketone efficiently. Example, 1,2-cyclohexanedione as intermediates was converted the corresponding α-hydroxy compound (Fig. 3).

Moreover, 2,6-dibromo menthone (**12**) was transformed to diosphenol (**12b**) and 6-hydroxy-3-methyl-6-isopropylcyclohexane-1,2-dione (**12c**) after 3 days incubation. The biotransformation of diosphenol (**12b**) with *S. platensis* resulted in the recovery of the starting material.

On the basis of these results, it was found that first α,α′-dibromo ketone biotransforms into α-diketone and then converts α-hydroxy ketone. However, in the case of diosphenol, it seems that alkyl group at the α-position of carbonyl group prevents reduction into α-hydroxy ketone.

3.3. Comparison with other algae

In order to discuss biotransformation of α-bromo ketone (**2**) for algae, we tried to carry out the following experiment for five algae. *C. merolae* and *C. caldarium* have a simple cellular structure, with each cell having one plastid and one nucleus plus other organelles, such as Golgi bodies, endoplasmic reticulum and microbodies. These red algae (*C. merolae* and *C. caldarium*) are extremely characteristic algae inhabiting sulfate-rich hot springs (pH 2.5). On the other hand, cyanobacteria (*Synechoccus elongatus* PCC 7942 and *Synechosystis* sp. PCC 6803) are microbe categories. In other words, they are plant-like photosynthetic bacteria. It is known that aryl methyl ketones are reduced to the corresponding *S*-alcohols by *S. elongatus* PCC 7942 with high enatioselectivity [32].

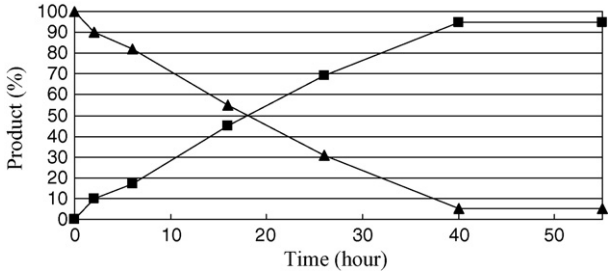
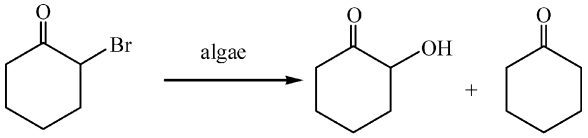


Fig. 3. Biotransformation of 1,2-cyclohexanedione by *Spirulina platensis*: (▲), 1,2-cyclohexanedione; (■), 2-hydroxycyclohexanone.

Table 3
Biotransformation of 2-bromo cyclohexanone by various algae



2 **2a** **2c**

Run	Algae	Product[a]	
1	*Cyanidioschyzon merolae*	**2a** (19)	**2c** (22)
2	*Cyanidium caldarium*	**2a** (21)	**2c** (20)
3	*Synechococcus elongatus* PCC 7942	**2a** (48)	**2c** (25)
4	*Synechosystis sp.* PCC 6803	**2a** (52)	**2c** (25)
5	*Spirulina platensis*[b]	**2a** (89)	**2c** (8)

Reaction conditions: substrate (100 mg), algae and medium (100 ml) were employed for 3 days.
[a] Yields were determined by GLC.
[b] Reaction time: 24 h.

Biotransformation of 2-bromo cyclohexanone (**2**) using various algae gave corresponding α-hydroxy compound. These results are summarized in Table 3. *S. elongatus* PCC 7942 and *S.* sp. PCC 6803 afforded **2a** in moderate yield (48% and 52%). However, *C. merolae* and *C. caldarium* afforded **2a** in low yield. These red algae proceed to cyclohexanone (**2c**) for by-product material. On the other hand, *S. platensis* gave the best result (89% yield) for short reaction time (24 h).

Among the microbes, *S. platensis* gave the best result (89% yield). This result indicated that *S. platensis* is efficient biocatalyst for synthesis of α-hydroxy ketones from α-bromo ketons.

4. Conclusion

This is the first time that the bioreaction of α-bromo and α,α′-dibromo ketone using *S. platensis* has been successfully accomplished. Although enatioselective α-hydroxy ketone can not be obtained, it was found that the hydroxyl biotransformation of α-bromo and α,α′-dibromo ketone using *S. platensis* affords a new synthetic method, which is more convenient, cleaner, and low energy than the chemical method used heretofore. Biotransformation for α-hydroxy ketone from α-bromo ketone is no doubt attributable to the special properties of *S. platensis* system.

Acknowledgments

This work was partially supported by Frontier Project "Adaptation and Evolution of Extremophile" and a Grant-in-Aid for Scientific Research (no. 18550142).

References

[1] (a) E.J. Corey, J.O. Link, Tetrahedron Lett. 31 (1990) 601;
(b) E.J. Corey, J.O. Link, J. Org. Chem. 56 (1991) 442;
(c) P.V. Ramachandran, B. Gong, H.C. Brown, Chilrality 7 (1995) 103;
(d) J. Elks, C.R. Ganelli, Dictionary of Drugs, Chapman and Hall, 1990, p. 1160;
(e) P. Taggart, P. Sutton, R. Donaldson, Clin. Sci. 69 (1985) 631;
(f) Z.-L. Wei, Z.-Y. Li, G.-Q. Lin, Tetrahedron 54 (1998) 13059.
[2] (a) E. Vedejs, J. Am. Chem. Soc. 96 (1974) 5944;
(b) E. Vedejs, J.E. Telschow, J. Org. Chem. 41 (1976) 740;
(c) E. Vedejs, S. Larsen, Org. Synth. Collect. VII (1990) 277;
(d) R. Gamboni, C. Tamm, Tetrahedron Lett. 27 (1986) 3999.
[3] T. Cuvigny, G. Valette, M. Larcheveque, H. Normant, J. Organomet. Chem. 155 (1978) 147.
[4] (a) G.M. Rubottom, M.A. Vazquez, D.R. Pelegrina, Tetrahedron Lett. (1974) 4319;
(b) Y. Horiguchi, E. Nakamura, I. Kuwajima, Tetrahedron Lett. 30 (1989) 3323.
[5] (a) T. Takai, T. Yamada, O. Rhode, T. Mukaiyama, Chem. Lett. (1991) 281;
(b) F.A. Davis, A.C. Sheppard, J. Org. Chem. 52 (1987) 954.
[6] R.M. Moriarty, H. Hu, S.C. Gupta, Tetrahedron Lett. 22 (1981) 1283.
[7] R.M. Moriaty, M.P. Duncan, O. Prakash, J. Chem. Soc. Perkin Trans. 1 (1987) 1781.
[8] R.M. Moriarty, B.A. Berglund, R. Penmasta, Tetrahedron Lett. 33 (1992) 6065.
[9] T. Utsukihara, H. Nakamura, M. Watanabe, C.A. Horiuchi, Tetrahedron Lett. 47 (2006) 9359.
[10] Y. Matsuura, W. Chai, E. Endoh, J. Suhara, H. Hamada, C.A. Horiuchi, Phytochemistry 61 (2002) 669.
[11] H. Sakamaki, S. Kitanaka, W. Chai, Y. Hayashida, Y. Takagi, C.A. Horiuchi, J. Nat. Prod. 64 (2001) 630.
[12] W. Chai, H. Sakamaki, S. Kitanaka, C.A. Horiuchi, Bull. Chem. Soc. Jpn. 76 (2003) 177.
[13] W. Chai, H. Hamada, J. Suhara, C.A. Horiuchi, Phytochemistry 57 (2001) 669.
[14] K. Ishihara, H. Hamada, T. Hirata, N. Nakajima, J. Mol. Catal. B: Enzym. 23 (2003) 145.
[15] K. Nakamura, S. Kondo, Y. Kawai, K. Hida, K. Kitano, A. Ohno, Tetrahedron: Asymmetry 7 (1996) 409.
[16] J. Cui, T. Ema, T. Sakai, M. Utaka, Tetrahedron: Asymmetry 9 (1998) 2692.
[17] Y. Kawai, K. Hida, M. Tsujimoto, S. Kondo, K. Kitano, K. Nakamura, A. Ohno, Bull. Chem. Soc. Jpn. 72 (1999) 99.
[18] A.S. Demir, H. Hamamci, P. Ayhan, A.N. Duygu, A.C. İgdir, D. Capanoglu, Tetrahedron: Asymmetry 15 (2004) 2579.
[19] J.D. Carballeira, E. Àlvarez, M. Campillo, L. Pardo, J.V. Sinisterra, Tetrahedron: Asymmetry 15 (2004) 951.
[20] T. Utsukihara, O. Misumi, N. Kato, T. Kuroiwa, C.A. Horiuchi, Tetrahedron: Asymmetry 17 (2006) 1179.
[21] T. Utsukihara, W. Chai, N. Kato, K. Nakamura, C.A. Horiuchi, J. Mol. Catal. B: Enzym. 31 (2004) 19.
[22] S. Paul, V. Gupta, R. Gupta, A. Loupy, Tetrahedron Lett. 44 (2003) 439.
[23] Dioxane-dibromide was prepared by adding drop wise bromine (8 ml) to dioxane (5 ml), until a yellow solid product was obtained. It was filtered dried in vacuum and stored in refrigerator (yield 10 g).
[24] M. Utaka, S. Matsushita, A. Takeda, Chem. Lett. (1980) 779.
[25] (a) A.K. El-Qisairi, H.A. Qaseer, J. Organomet. Chem. 659 (2002) 50;
(b) S. Matsubara, K. Takai, H. Nozaki, Bull. Chem. Soc. Jpn. 56 (1983) 2029;
(c) J.S. Yadav, B.V.S. Reddy, A.K. Basak, A.V. Narsaiah, Tetrahedron 60 (2004) 2131;
(d) Y.-Y. Xuan, Z.-C. Chen, Synth. Commun. 32 (2002) 1875;
(e) M.V.S. Elipe, S.W. Huskey, B. Zhu, J. Pharm. Biomed. Anal. 30 (2003) 1431.
[26] R. Henrikson, Earth Food Spirulina, Ronore Enterprises Inc., California, 1989, p. 180.
[27] J.C. Dillon, A.P. Phuc, J.P. Dubacq, World Rev. Nutr. Diet. 77 (1995) 32.
[28] O. Ciferri, O. Tiboni, Annu. Rev. Microbiol. 39 (1985) 503.
[29] S. Aaronson, T. Berner, Z. Dubinsky, Microalgae as a Source of the Chemicals and Natural Products. In: Algae Biomass, Biochemical Press, Elsevier, 1980, p. 575.
[30] A. Richmond, in: M.A. Borowitzka, L.J. Borowitzka (Eds.), Microalgal Biotechnology, Cambridge University Press, Cambridge, 1988, p. 85.
[31] B.S. Henry, in: G.A.F. Hendry, J.D. Houghton (Eds.), Natural Food Colorants, Blackil Academic Professional, London, 1996, p. 40.
[32] K. Nakamura, R. Yamanaka, K. Tohi, H. Hamada, Tetrahedron Lett. 41 (2000) 6799.