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Baker's yeast mediated mono-reduction of 1,3-cyclohexanediones bearing two identical C(2) substituents

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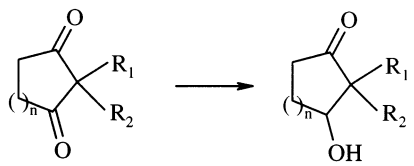
Abstract—Baker's yeast mediated transformation of a series of 1,3-cyclohexanediones with two identical substituents at C(2) was investigated and the results of the biotransformation were found to depend on the size of the substituents at C(2). 1,3-Cyclohexanediones with less sterically demanding C(2) substituents could be mono-reduced to provide the corresponding ketols in good yields and excellent enantiomeric excesses.

1. Introduction

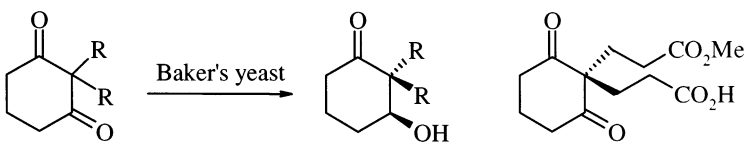
The baker's yeast (*Saccharomyces cerevisiae*) mediated asymmetric reduction of ketones has been widely used to obtain chiral building blocks because it is cheap, versatile and easy to perform.[1] Brooks et al.[2] have successfully used baker's yeast in the reduction of prochiral 2,2-disubstituted 1,3-cycloalkanediones to give ketol products with two stereogenic centers, which are valuable chiral intermediates in enantioselective natural product synthesis ($R_1 \neq R_2$) (Scheme 1). However, the microorganism mediated mono-reduction of 1,3-cycloalkanediones with two identical C(2) substituents to provide enantiomeric cycloalkanoid ketols is less well known, and except for the simple substrate, 2,2-dimethyl-1,3-cyclohexanedione **1**,[3] has not been investigated. Since homochiral cycloalkanoid ketols are potentially useful precursors in natural product synthesis, we thought it worthwhile investigating the baker's yeast mediated biotransformation of 1,3-cycloalkanediones in more depth.



Scheme 1.

2. Results and discussion

2,2-Disubstituted 1,3-cyclohexanediones **1**,[4] **2**,[5] and **3**[6] were prepared from their corresponding monosubsti-



1 R = CH_3
2 R = $CH_2C{\equiv}CH$
3 R = $CH_2CH{=}CH_2$
4 R = $CH_2CH_2CH_3$
5 R = $CH_2CH_2CO_2Me$

6 R = CH_3
7 R = $CH_2C{\equiv}CH$
8 R = $CH_2CH{=}CH_2$
9 R = $CH_2CH_2CH_3$

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Scheme 2.

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Table 1. Baker's yeast mediated transformation of 1,3-cyclohexanediones **1**–**5**

Entry	Substrate	R =	Product	Yield[a] (%)	$[\alpha]_D$	E.e. (%)	Config.
1	**1**	CH_3	**6**	48 (22)	+22.5	>96[b]	*S*[b]
2	**2**	$CH_2C{\equiv}CH$	**7**	41 (12)	−3.5	>96[c]	*S*[d]
3	**3**	$CH_2CH{=}CH_2$	**8**	14 (24)	+11	98.4[e]	*S*[f]
4	**4**	$CH_2CH_2CH_3$	**9**	<3 (25)	–	–	–
5	**5**	$CH_2CH_2CO_2CH_3$	**10**	61	–	–	–

[a] Isolated yield; figure in the parentheses is the yield of recovered substrate.
[b] Based on the reported specific rotation.
[c] Determined by ^{1}H NMR analysis of its Mosher ester.
[d] Determined by the improved Mosher method developed by Kusumi et al.
[e] Determined by chiral HPLC analysis.
[f] Assigned by X-ray crystallographic analysis of **12**.

tuted 1,3-cyclohexanediones by introducing another identical substituent at C(2) according to the reported procedure. 2,2-Dipropyl-1,3-cyclohexanedione **4** was prepared by catalytic hydrogenation of **3**.[6] The dicarboxylic ester **5** was readily prepared by Michael addition of the corresponding 2,6-dioxo-cyclohexanepropanoic acid methyl ester[7] with excess methyl acrylate in triethylamine under reflux. The 1,3-cyclohexanedione derivatives **1**–**5** were then incubated with baker's yeast for 2 days (Scheme 2);[8] the results of these reactions are summarized in Table 1.

As shown in Table 1, 2,2-dimethyl-1,3-cyclohexanedione **1** and 2,2-di(prop-2-ynyl)-1,3-cyclohexanedione **2** could be well reduced by baker's yeast to provide ketol **6** in a 48% yield with an e.e. of over 96%. Ketol **7** was formed in 41% yield with excellent e.e. of over 96% (Table 1, entries 1 and 2). The reduction of **1** using bakers's yeast was found to be similar to reported results.[3] Though baker's yeast could still reduce the dialkenic ketone **3** to provide ketol **8** in 14% yield with e.e. of 98.4% (entry 3), incubation of 2,2-dipropyl-1,3-cyclohexanedione **4** with baker's yeast for 2 days provided only trace reduced product **9** (entry 4) and, interestingly, when diketone **5** was incubated with baker's yeast for 2 days, the sole product obtained was mono-hydrolyzed product **10** in a 61% yield (entry 5).

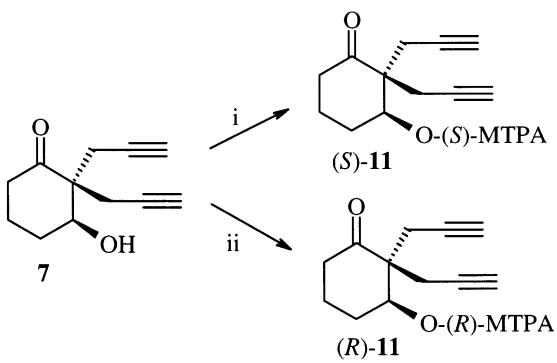
The enantiomeric excess of **6** was determined by comparison of its specific rotation with the reported value.[3b]

The optical purity of **7** was determined by ^{1}H NMR analysis of its (*R*)-(+)-MTPA ester.[9] The absolute configuration of **7** was determined as (*S*) by the improved Mosher method developed by Kusumi et al.[10] using the MTPA esters of **7** (Scheme 3, Fig. 1).

The enantiomeric excess of **8** was directly determined by chiral HPLC analysis detected at $UV_{214\ nm}$ using its racemic compounds as comparison. Its absolute configuration was assigned by X-ray crystallographic analysis after transformation into the corresponding camphor sulfonate **12**, by treatment with (+)-camphor-10-sulfonyl chloride. As shown in Fig. 2, the configuration of the hydroxymethylene carbon of **8** was unambiguously established as (*S*).

It can be seen from Table 1 that the baker's yeast mediated reduction of the 1,3-cyclohexanediones **1**–**5** depends strongly on the size of the two C(2) substituents. For the series propyl, allyl, propynyl and methyl, there was a similar trend of increased reactivity during baker's yeast mediated reduction. 1,3-Cyclohexanediones with two less sterically demanding substituents, methyl or propynyl, at C(2) could be readily reduced to afford ketols in high enantiomeric purity. With increasing size of the C(2) substituents reactivity diminished; hence, the relatively bulky allyl substituted diketone **3** could be reduced, but the more bulky propyl diketone **4** was much less reactive to baker's yeast. The limits of the system are shown in the reaction of diketone **5**, where no reduction occurred.

The effects of size of the two C(2) substituents on the mono-reduction of 1,3-cyclohexanediones can be interpreted as follows. When both substituents at C(2) are bulky, they 'shield' both faces of the two identical prochiral carbonyl groups. Therefore, oxidoreductase(s) in yeast cells might be prevented from approaching the carbonyl groups and, as a result, cannot catalyze the reduction efficiently. Therefore, if one of the C(2) substituents is less sterically demanding, for example a methyl group, the steric hindrance on one side of the cyclohexane plane would be lowered, which would favor oxidoreductase(s) approaching one of the carbonyl groups from this side and reducing the corresponding 2,2-disubstituted 1,3-cycloalkanedione efficiently. This has been proved by the results of



Scheme 3. (i) (*S*)-(−)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 12 h. (ii) (*R*)-(+)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 12 h.

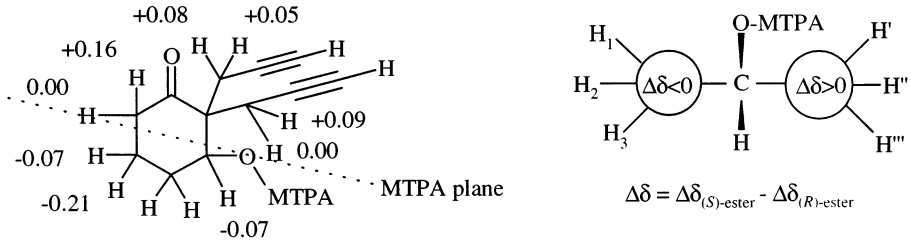


Figure 1.

Brooks et al.,[2] who have successfully accomplished the baker's yeast mono-reduction of various 2,2-disubstituted 1,3-cycloalkanediones with a methyl group at C(2).

Considering the small coupling constants (<8.0 Hz) of the protons geminal to the hydroxy groups, it is interesting to find that the hydroxy groups of the obtained ketol products **6**–**8** prefer the axial conformation. Furthermore, after the hydroxy group was converted to the corresponding carboxy group, it still prefers the axial conformation. This could obviously be seen from the X-ray analysis diagram of the camphorsulfonate **12** (Fig. 2). According to the studies of Gorthey et al.[11] and Bowen et al.[12] on conformational analysis of β-heteroatom-substituted cyclohexanones, the axial preference of the hydroxy or the carboxy groups in **6**–**8** and **12** is probably due to the electrostatic or dipole–dipole interactions which serve as stabilizing influences.

3. Experimental

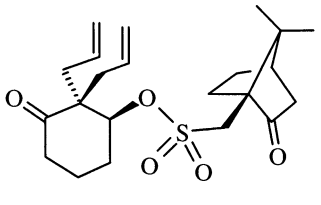
All melting points are uncorrected. IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on an HP-5989 A mass spectrometer and high resolution mass spectra (HRMS) were recorded on a Finnigan MAT-4021 instrument. ^{1}H NMR spectra were recorded on a Bruker AMX-300 spectrometer with tetramethylsilane as the internal standard. Optical rotation was measured on a Perkin–Elmer 241 polarimeter. TLC was carried out using HSG F_{254} silica gel plates and silica gel (200–400 mesh) was used for chromatography. Organic extracts were dried over anhydrous sodium sulfate. Baker's yeast was obtained from a local store.

3.1. Preparation of 3-[1-(2-methoxycarbonylethyl)-2,6-dioxocyclohexyl]propionic acid methyl ester 5

A mixture of 3-(2,6-dioxocyclohexyl)propionic acid methyl ester (3 g, 15 mmol),[7] triethylamine (20 mL), and methyl acrylate (15 mL) was refluxed for 20 h. After cooling to room temperature, the mixture was evaporated under reduced pressure to remove triethylamine and excess methyl acrylate. The residue obtained was purified by chromatography over silica gel with petroleum ether–ethyl acetate (5:1) to provide **5** as colorless oil (2.8 g, 65%). IR (KBr): ν_{max} 2950, 1725 (br), 1695, 1435, 1370, 1180 (br), 1025, 850 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (s, 6H), 2.62 (t, 4H, J=6.7 Hz), 2.20–2.10 (m, 4H), 2.05–1.90 (m, 6H). MS m/z (rel. intensity): 284 (M^+, 4.6), 221 (56.5), 192 (35.5), 164 (35.3), 151 (42), 137 (40.1), 55 (100), 42 (48.9). Anal. calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.89; H, 7.23%.

3.2. Baker's yeast mediated transformation of 1–5. General procedure

A mixture of baker's yeast (10 g) in 20% glucose solution (50 mL) was shaken at 30°C for 1 h. The substrate (1 mmol) in DMF (if it is solid, 0.5 mL) was added slowly. The mixture was continuously shaken at 30°C for 2 days. After that baker's yeast was removed by centrifugation and washed with ethyl acetate. The supernatant solution was saturated with sodium chloride and extracted with ethyl acetate (3×50 mL). The organic layers were combined and washed with brine, dried, filtered and evaporated under reduced pressure. The residue was purified by chromatography to provide the product as follows.



12

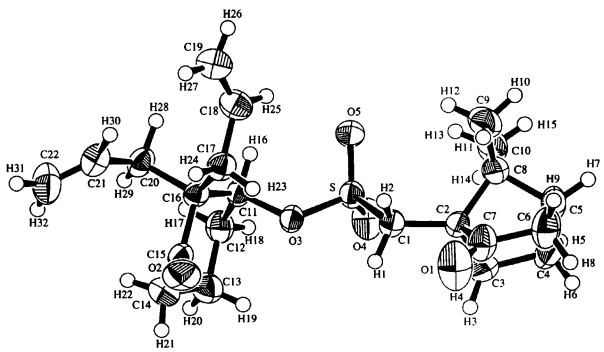


Figure 2. The molecular structure of **12**.

3.2.1. (*S*)-3-Hydroxy-2,2-di(prop-2-ynyl)cyclohexanone 7. White solid, mp 104–106°C; 96%, $[\alpha]_D^{20}$ −3.5 (*c* 2.0, $CHCl_3$). IR (KBr): ν_{max} 3450, 3300, 2950, 1700, 1430, 1350, 1280, 1210, 1130, 1070, 1000, 945, 640, 560 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.18 (dd, 1H, $J=6.2$, 3.0 Hz), 2.80–2.50 (m, 5H), 2.50–2.30 (m, 2H), 2.10–1.90 (m, 4H), 1.85–1.75 (m, 1H), 1.75–1.60 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.47, 79.85, 79.55, 73.87, 72.08, 71.81, 56.16, 37.84, 28.32, 22.92, 20.56, 19.97. Anal. calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.69; H, 7.48.

3.2.2. (*S*)-2,2-Diallyl-3-hydroxycyclohexanone 8. White solid, e.e.: 98.4%, $[\alpha]_D^{20}$ +11 (*c* 2.2, $CHCl_3$). IR (KBr): ν_{max} 3450, 2940, 1685, 1640, 1340, 1275, 1215, 1110, 980, 920 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.70–5.50 (m, 2H), 5.10–4.90 (m, 4H), 3.92 (dd, 1H, $J=7.1$, 3.1 Hz), 2.50–2.20 (m, 7H), 2.10–1.75 (m, 3H), 1.70–1.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.39, 133.93, 133.47, 118.34, 118.06, 73.96, 57.46, 38.25, 36.82, 34.07, 28.23, 20.48. Anal. calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.88; H, 9.66. The enantiomeric excess was determined by HPLC analysis using Chiralpak AD column (0.46×25 cm) detected at UV 214 nm; eluent: hexane–2-propanol (9:1); rate of flow: 0.7 mL/min.

3.2.3. 3-[1-(2-Carboxylethyl)-2,6-dioxocyclohexyl]-propionic acid methyl ester 10. White solid, mp 87–89°C. IR (KBr): ν_{max} 3400, 2900 (br), 1710 (br), 1450, 1410, 1330, 1290, 1210, 1170, 1030, 995, 910 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.82 (br s, 1H), 3.70 (s, 3H), 2.90–2.50 (m, 4H), 2.50–2.20 (m, 4H), 2.20–1.90 (m, 6H). MS *m*/*z* (rel. intensity): 271 ($[M+1]^+$, 12.7), 253 (33.9), 224 (45.2), 221 (100), 192 (54.7), 179 (44.2), 164 (38.2), 151 (52.4), 137 (45.2), 123 (38.5), 55 (78.3). Anal. calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.45; H, 6.67.

3.3. Determination of the absolute configuration of ketol 7

To a stirred solution of **7** (15 mg, 0.14 mmol) in methylene chloride (2 mL) was added dicyclohexylcarbodiimide (80 mg), 4-dimethylaminopyridine (3 mg), and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (40 mg, 0.21 mmol). The mixture was stirred at room temperature for 2 days, then filtered and the filtrate was diluted with ethyl acetate (20 mL). The organic phase was washed with saturated aqueous sodium bicarbonate and brine, dried, filtered, and condensed under reduced pressure. The residue was purified by chromatography over silica gel with petroleum ether–ethyl acetate (7:1) to provide (*R*)-**11** (30 mg, 94%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.53–7.39 (m, 5H), 5.60 (dd, 1H, $J=5.2$, 3.0 Hz), 3.51 (s, 3H), 2.86 (dd, 1H, $J=6.9$, 2.5 Hz), 2.71 (dd, 1H, $J=7.5$, 2.6 Hz), 2.63–2.37 (m, 2H), 2.29–2.16 (m, 2H), 2.13–2.03 (m, 4H), 1.94–1.80 (m, 2H). MS *m*/*z* (rel. intensity): 407 ($[M+1]^+$, 0.7), 406 (M^+, 0.4), 189 (100).

(*S*)-**11** was similarly prepared according to the above procedure, yield 90%. ^1H NMR (300 MHz, $CDCl_3$): δ 7.52–7.38 (m, 5H), 5.53 (t, 1H, $J=3.5$ Hz), 3.51 (s, 3H), 2.86 (dd, 1H, $J=7.0$, 2.6 Hz), 2.75 (dd, 1H, $J=7.5$, 2.6 Hz), 2.60–2.46 (m, 2H), 2.38–2.29 (m, 2H), 2.18–2.03 (m, 4H), 1.85–1.77 (m, 1H), 1.70–1.60 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.9, 165.7, 131.8, 129.9, 128.6, 127.5, 79.1, 78.2, 77.5, 77.3, 72.9, 72.7, 55.4, 54.1, 37.7, 24.9, 23.4, 20.6, 20.4.

3.4. Determination of the configuration of the ketol 8

To the solution of optically pure ketol **8** (20 mg, 0.1 mmol), obtained from baker's yeast reduction of **3** in methylene chloride (1 mL), and pyridine (0.5 mL) at 0°C was added (+)-camphor-10-sulfonyl chloride (120 mg, 0.5 mmol). The mixture was warmed to room temperature and stirred for a day. After that the mixture was diluted with ethyl acetate and the organic layer was washed with brine, dried, filtered, and condensed. Purification of the residue by chromatography with petroleum ether–ethyl acetate (10:1) provided the corresponding (+)-camphorsulfonates **12** (35 mg, 83%) as a white solid: mp 90–91°C. $[\alpha]_D^{20}$ +43.6 (*c* 0.2, $CHCl_3$). IR (KBr): ν_{max} 2973, 1738, 1709, 1446, 1339, 1175, 895, 870 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.77–5.57 (m, 2H), 5.19–5.13 (m, 4H), 5.06 (dd, 1H, $J=6.2$, 3.7 Hz), 3.63 and 3.03 (AB, 2H, $J=14.9$ Hz), 2.60–2.27 (m, 9H), 2.14–1.93 (m, 4H), 1.88–1.75 (m, 1H), 1.68–1.61 (m, 2H), 1.49–1.43 (m, 1H), 1.13 (s, 3H), 0.88 (s, 3H). Anal. calcd for $C_{22}H_{32}O_5S$: C, 64.68; H, 7.89; S, 7.85. Found: C, 64.66; H, 7.90; S, 8.07.

Crystals of **12** suitable for X-ray analysis were cultured from methylene chloride–petroleum ether. Data were collected on a Rigaku AFC7R diffractometer using the ω–2θ scan technique at 293 K. The intensities were corrected for Lorentz-polarization effects. The structure was solved by direct methods[13] and expanded using Fourier techniques.[14] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. All calculations were performed using the teXsan crystallographic software package.[15] Crystal data: colorless prismatic monoclinic crystal (0.20×0.20×0.30 mm) in space group $P2_1$ (#4); $a=11.204(2)$ Å, $b=7.9105(9)$ Å, $c=13.093(3)$ Å, $\beta=111.86(1)°$, $V=1077.0(3)$ $Å^3$; $Z=2$; $D_{calcd}=1.260$ g cm^{-3}; $F(000)=440.00$; Mo Kα ($\lambda=0.71069$ Å), $\mu=1.79$ cm^{-1}; reflections measured = 2769, unique reflections = 2641 ($R_{int}=0.015$); observations [$I>2\sigma(I)$] = 2236; parameters = 253; goodness-of-fit = 1.68; $R=0.041$, $Rw=0.047$.

Acknowledgements

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8. It is noteworthy that when the C(2) monosubstituted 1,3-cyclohexanedione was incubated with baker's yeast no reduced product was isolated.
9. The (*R*)-(+)-MTPA ester derived from racemic **7** showed two signals at 5.53 and 5.61 ppm, while only the signal at 5.53 ppm was observed in the ^{1}H NMR spectrum of the (*R*)-(+)-MTPA ester of **7**. Therefore, the e.e. of **7** obtained from baker's yeast mono-reduction of **2** was considered to be over 96% e.e.
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