spectra on a Perkin-Elmer 521; mass spectra on an AEI MS 902 by direct insertion; NMR spectra on a Varian A-60 using Me_4Si as an internal standard. The following abbreviations are used: (br) broad, (w) weak, (ex) exchangeable with D_2O, (s) singlet, (t) triplet, (q) quartet, (m) multiplet.

The following procedures are illustrative of the reductions carried out.

DL-**Mandelic Acid Methyl Ester (3b).** To a solution of methyl phenylglyoxalate (**3a**) (1.6 g, 10 mmol) in THF (25 mL) was added potassium carbonate (2 g, 14 mmol) and Pd/C (5%, 50:50 water wet, 300 mg). The stirring mixture was heated to reflux, and a solution of sodium hypophosphite (2 g, 18 mmol) in water (20 mL) was added dropwise. The reaction mixture was stirred overnight, and the next day, a TLC analysis (70:20:10 toluene/CH_2Cl_2/EtOAc) showed the reaction to be complete. The reaction mixture was cooled and filtered and the filtrate diluted with diethyl ether. The organic layer was separated, washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated to yield DL-mandelic acid methyl ester (**3b**) ~1.2 g (~75%), mp 53–54 °C. The product could be recrystallized from cyclohexane to yield material which was identical (IR, NMR, mp) with an authentic reference standard: IR (CH_2Cl_2) 3550 (br), 3080, 1740 (s) cm^{-1}; NMR ($CDCl_3$) δ 7.4 (s, 5, Ar), 4.3 (Ab q, 1, CH), 3.7 (s, 3, OCH_3).

3-Chloro-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (15b). A mixture of the dichloro lactam **15a**[6] (20 g, 0.087 mol), Pd/C (10%, 1.2 g), sodium acetate (20 g, 0.24 mol), and sodium hypophosphite (9.2 g, 0.244 mol) in glacial acetic acid (200 mL) was heated to 56 °C for 24 h. The reaction mixture was filtered and the filtrate concentrated to a residue; water (200 mL) was added, and this was stirred as the product precipitated out. The product **15b** was filtered, washed with water, and dried in vacuum to yield 15.1 g (~89% 1st crop), mp 164–167 °C.; this material contained ~1.7% lactam which was completely reduced and no detectable starting material: NMR ($CDCl_3$) δ 8.8 (m, 4, Ar), 4.5 (m, 1, CH), 2.8–2.5 (m, 4, aliphatics).

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Registry No. **1a**, 38743-17-8; **2a**, 98-86-2; **2b**, 98-85-1; **3a**, 1603-79-8; **3b**, 4358-88-7; **4a**, 100-52-7; **4b**, 100-51-6; **5a**, 104-53-0; **5b**, 122-97-4; **6a**, 110-83-8; **6b**, 110-82-7; **7a**, 872-05-9; **7b**, 124-18-5; **8a**, 1613-37-2; **8b**, 91-22-5; **9a**, 23162-18-7; **9b**, 110-89-4; **10a**, 86499-24-3; **10b**, 86499-35-6; **11a**, 286-20-4; **11b**, 108-93-0; **12a**, 100-47-0; **13a**, 100-44-7; **13b**, 108-88-3; **14a**, 108-90-7; **14b**, 71-43-2; **15a**, 86499-22-1; **15b**, 86499-23-2; **16a**, 116-54-1; **16b**, 96-34-4; **17a**, 56-23-5; **17b**, 67-66-3; **18a**, 542-18-7; **19a**, 836-43-1; **19b**, 623-05-2; **20a**, 32563-40-9; **20b**, 15028-44-1; **21a**, 4360-47-8; **21b**, 645-59-0; **22a**, 97351-55-8; **22b**, 81763-85-1; **23a**, 836-42-0; **23b**, 834-25-3; sodium hypophosphite, 7681-53-0.

Microbial Reduction of Prochiral 2,2-Disubstituted 1,3-Cycloheptanediones

Dee W. Brooks,*† Hormoz Mazdiyasni, and Peter Sallay

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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We have pursued a research program directed toward applying the ability of enzymes to make prochiral distinctions as a useful element of synthetic strategy to obtain optically pure intermediates for the total synthesis of natural products. Asymmetric microbial reduction with common bakers' yeast (*Saccharomyces cerevisiae*) of 2,2-disubstituted 1,3-cyclopentane- and 1,3-cyclohexanediones has proved to be a synthetically useful method.[1] We have further examined the scope and generality of yeast-mediated reductions of medium sized (seven-, eight-, and nine-membered) diones and herein report these results.

The 2-methyl 1,3-diones **3**, **6**, and **9** were prepared by applying the method reported for **3**, by Okamura,[2] as outlined in Scheme I.

Treatment of the 2-methyl diones **3**, **6**, and **9** with 1 N NaOH (1 equiv) followed by 3-bromopropene (10 equiv) at 25 °C for 64 h gave the allyl diones **15** (60%), **30** (50%), and **35** (50%). Reaction of **3** with 3-chloropropyne (5 equiv) and triethylamine (10 equiv) at reflux for 24 h gave **20** (65%). Similar treatment of **3** with 3-chloro-2-methylpropene gave **25** (75%). Hydrogenation of **15** with PtO_2 catalyst at 1 atm in ethanol for 2 h at 25 °C gave **10** (98%).

The diones **10**, **15**, **20**, **25**, **30**, and **35** were subjected to microbial reduction with bakers' yeast and the results are summarized in Table I. The enantiomeric composition of the chiral ketols produced by yeast reduction was determined by analysis and comparison of the ^1H NMR (470 MHz) of the corresponding (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters[3] with those derived from the racemic ketols prepared by reduction with $NaBH_4$ (1 equiv, 0.1 M in ethanol, 0 °C, 3 h). In each case the singlets of the 2-methyl group and the methine proton α to the MTPA derivatized hydroxyl group were clearly resolved. In all cases the ketols generated by yeast reduction were found to have >98% enantiomeric excess.[4] The assignment of structure and absolute configuration for the chiral cycloheptanoids was established by comparison of the ^1H NMR spectra of the propyl (+)-MTPA esters **11** and **13** of known absolute configuration which were peviously reported[1c] with the same propyl (+)-MTPA esters derived from catalytic hydrogenation of the (+)-MTPA esters of **16**, **21**, and **23** obtained by yeast reduction. The structure of the microbial ketol products derived from diones **25** and **30** were not proven but assigned on the basis of comparison of their spectral data with those of the analogous (+)-MTPA esters of the correlated products.

The medium-size rings are not as efficiently reduced by bakers' yeast as the five- or six-membered diones.[1] Substrates **20** and **25** provide synthetically useful conversions to novel chiral functionalized cycloheptanoids. In each case the ketols derived by yeast reduction were >98% enantiomerically pure regardless of the conversion efficiency. Attempts to optimize the fermentation conditions to provide better conversions were not carried out.

The completely opposite stereoselectivity in the yeast reduction of the propyl dione **10** (entry 1) vs. the allyl dione **15** (entry 3) and the lack of stereoselectivity for the methylallyl dione **25** (entry 7) is very interesting. The stereoselectivity of the yeast reduction closely parallels that of the $NaBH_4$ reduction of these substrates.[6] Microbial

†Current address: Department 47K AP10, Abbott Laboratories, Abbott Park, IL 60064.

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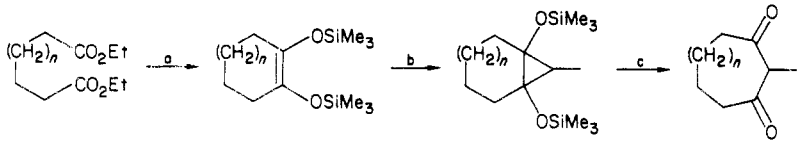
(4) A control experiment established a practical limit of detection of 1.5% of a MTPA diastereomer in a mixture by ^1H NMR at 470 MHz.

(5) The use of MTPA derivatives for assignment of absolute configurations has been reported, see: (a) Dale, J. A.; Mosher, A. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

0022-3263/85/1950-3411$01.50/0

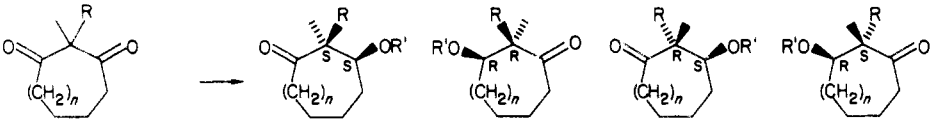
Scheme I[a]



n=1	1	2	3
n=2	4	5	6
n=3	7	8	9

[a] (a) Na (5 equiv), Me_3SiCl (5 equiv), toluene reflux, 18 h; (b) CH_3CHI_2 (2 equiv), $ZnEt_2$ (2 equiv), benzene, reflux, 3 h; (c) $FeCl_3$ (2 equiv) DMF, 60 °C, 3 h.

Table I[a]



10, n = 1 R = $CH_2CH_2CH_3$	11	12	13	14
15, n = 1 R = $CH_2CH{=}CH_2$	16	17	18	19
20, n = 1 R = $CH_2C{\equiv}CH$	21	22	23	24
25, n = 1 R = $CH_2C(CH_3){=}CH_2$	26	27	28	29
30, n = 2 R = $CH_2CH{=}CH_2$	31	32	33	34
35, n = 3 R = $CH_2CH{=}CH_2$	36	37	38	39

entry	dione	reduction method	ketol products (% composition)	yield,[b] %	recovered dione, %
1	**10**	yeast	**11**, **13** (2, 98)	10	75
2	**10**	$NaBH_4$	**11**, **12**; **13**, **14** (2, 98)	60	15
3	**15**	yeast	**16** (100)	20	60
4	**15**	$NaBH_4$	**16**, **17**; **18**, **19** (95, 5)	65	10
5	**20**	yeast	**21**, **23** (71, 29)	60	30
6	**20**	$NaBH_4$	**21**, **22**; **23**, **24** (7, 93)[6]	15	15
7	**25**	yeast	**26**, **28**, (55, 45)	40	50
8	**25**	$NaBH_4$	**26**, **27**; **28**, **29** (53, 47)	65	10
9	**30**	yeast	**31**, **33** (82, 18)	5	75
10	**30**	$NaBH_4$	**31**, **32**, **33**, **34** (88, 12)	60	15
11	**35**	yeast	no ketol product	0	80
12	**35**	$NaBH_4$	**36**, **37**; **38**, **39** (85, 15)	60	15

[a] The compound number followed by **a** indicates R′ = (+)-MTPA otherwise R′ = H. [b] Isolated yield of ketols.

reduction of the cyclooctanedione **30** proceeded slowly to give a poor conversion to ketols **31** and **33**. No ketol product could be isolated from attempted yeast reduction of the cyclononanedione **35** under the conditions employed. These results suggest that bakers' yeast mediated reduction of prochiral eight- and nine-membered rings may not be a viable preparative method. Microbial reduction of these substrates with other microorganisms is another recourse.

Experimental Section

All experiments requiring anhydrous conditions were conducted under a dry nitrogen atmosphere. Reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F-254 plates (0.25 mm). The plates were visualized by spraying or dipping with a *p*-anisaldehyde solution (1350 mL of ethanol, 50 mL of concentrated H_2SO_4, 15 mL of glacial acetic acid, 37 mL of *p*-anisaldehyde) followed by heating the plate (125–150 °C). Chromatography was performed by the flash method as described by Still[8] with 230–400 mesh silica gel. Solvents were evaporated on a rotary evaporator at aspirator pressure (ca. 20 mm). Nuclear magnetic resonance (NMR) spectra were acquired on a Perkin-Elmer R-32 and Nicolet 470-MHz NMR instruments for proton and a Varian XL-200 instrument for carbon and fluorine nuclei. Chemical shifts are reported in ppm downfield relative to tetramethylsilane as standard.

General Procedure for the Preparation of Enediol Bis(silyl ethers) 1, 4, and 7.[7] A solution of diester (57 mmol) in dry toluene was added dropwise to a stirred suspension of molten sodium (299 mmol) and trimethylsilyl chloride (311 mmol) in dry toluene (200 mL) at 40–50 °C, under N_2, over a 3-h period. After the addition was complete, the mixture was heated at reflux overnight. The reaction mixture was cooled to 20 °C, and the solids were filtered and washed with dry toluene (25 mL). Evaporation of the solvent and purification by distillation at reduced pressure afforded the corresponding bis(silyl ethers) **1** [bp 110 °C (10 mm), 82%], **4** [bp 97 °C (3 mm), 76%], and **7** [bp 80 °C (0.5 mm), 49%].

General Procedure for the Preparation of the Ring-Expanded Diones 3, 6, and 9 from the Enediol Bis(silyl ethers) 1, 4, and 7.[2] To a solution of bis(silyl ether) **1**, **4**, or **7** (89 mmol) and diethylzinc (178 mmol) in dry benzene (400 mL) was added dropwise 1,1-diiodoethane (178 mmol) over a 0.5-h period, and then the mixture was refluxed for 3 h. The cooled mixture was poured into saturated aqueous NH_4Cl (200 mL) and then extracted with benzene (3 × 100 mL). The organic phase was washed with saturated aqueous NH_4Cl (200 mL) and saturated aqueous NaCl (100 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification by distillation at reduced pressure afforded the corresponding methylcyclopropylbicycle **2**, **5**, or **8**, which was dissolved in DMF (50 mL), and added to a solution of anhydrous $FeCl_3$ (162 mmol, 2 equiv) in DMF (25 mL) at 25 °C. The mixture was heated at 60 °C for 3 h. The DMF was evaporated at reduced pressure, and after cooling, the residue was poured into cold 10% aqueous HCl (25 mL) and extracted with chloroform (6 × 20 mL). The chloroform extract was washed with 10% aqueous HCl (25

(6) Efficient selective monoreduction with $NaBH_4$ was not practical for the alkynyl dione **20**, providing 15% ketol, 15% dione, and 60% diol; therefore the stereoselectivity observed for the ketol products may be biased by the possible differences in rates for further reduction of the diasteromeric ketols to diol.

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(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

mL) and water (25 mL) and then dried over Na_2SO_4. Evaporation of the solvent and purification by flash chromatography (fc)[8] (silica gel, 30% ethyl acetate in hexane) afforded the corresponding cyclic 1,3-diones **3**[2] (56%), **6** (40%), or **9** (28%). **6**: ^1H NMR ($CDCl_3$, 90 MHz) 1.3 (3 H, d, J = 7 Hz, CH_3), 1.5–2.0 (6 H, m), 2.4–2.6 (4 H, m), 3.6 (1 H, q, CH). **9**: ^1H NMR ($CDCl_3$, 90 MHz) 1.25 (3 H, d, J = 7 Hz, CH_3), 1.3–1.5 (4 H, m), 1.6–1.8 (4 H, m), 2.4–2.6 (4 H, m), 3.8 (1 H, q, CH).

Preparation of 2,2-Disubstituted 1,3-Cycloalkanediones 15, 30, and 35. To a solution of dione **3**, **6**, or **9** (11 mmol) in aqueous 1 N NaOH (15 mL) was added 3-bromopropene (35 mmol) at 25 °C. After 1 week, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was washed with saturated aqueous NaCl (15 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification by fc (silica gel, 30% ethyl acetate in hexane) afforded the corresponding diones. **15** (61%): ^1H NMR ($CDCl_3$, 470 MHz) 1.18 (3 H, s, CH_3), 1.86 (4 H, m), 2.43 (4 H, m), 2.50 (2 H, d, J = 8 Hz), 5.01 (1 H, d , J = 10 Hz), 5.04 (1 H, br s), 5.58 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 18.37 (CH_3), 27.91 (2 CH_2), 38.49 (CH_2), 41.44 (2 CH_2), 64.65 (C2), 118.78 (=CH_2), 132.41 (CH=), 212.10 (C1 and C3). **30** (51%): ^1H NMR ($CDCl_3$, 90 MHz), 1.25 (3 H, s, CH_3), 1.3 (2 H, m), 1.6 (4 H, m), 2.4 (4 H, m), 2.6 (2 H, d, J = 8 Hz), 5.0 (1 H, m), 5.16 (1 H, m), 5.5 (1 H, m). **35**(48%): ^1H NMR ($CDCl_3$, 470 MHz), 1.24 (3H, s, CH_3), 1.31 (4 H, m), 1.63 (4 H, m), 2.38 (4 H, m), 2.58 (2 H, d, J = 7.5 Hz), 5.0 (1 H, d, J = 10 Hz), 5.04 (1 H, d, J = 14 Hz), 5.50 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 16.98 (CH_3), 21.97 (2 CH_2), 24.07 (2 CH_2), 36.11 (2 CH_2), 37.90 (CH_2), 70.18 (C2), 119.36 (=CH_2), 133.34 (CH=), 210.61 (C1 and C3).

Preparation of 2,2-Disubstituted 1,3-Cycloalkanediones 20 and 25. To a solution of dione **20** or **25** (10 mmol) in triethylamine (50 mmol) was added 3-chloropropyne or 3-chloro-2-methylpropene (30 mmol), and the mixture was heated at 50 °C for 1 week. Dichloromethane (50 mL) was added, and the organic phase was washed with 1 N HCl (2 × 30 mL) and saturated aqueous NaCl (30 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification by fc (silica gel, 30% ether in hexane) gave the dione **20** (46%) or **25** (70%). **20**: ^1H NMR ($CDCl_3$, 470 MHz) 1.3 (3 H, s, CH_3), 1.88 (4 H, m), 2.02 (1 H, t, J = 2.5 Hz), 2.48 (4 H, m), 2.65 (2 H, d, J = 2.5 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 18.68 (CH_3), 24.11 (CH_2), 27.94 (2 CH_2), 41.24 (2 CH_2), 63.70 (C2), 71.95 (≡CH), 78.6 (C≡), 210.60 (C1 and C3). **25**: ^1H NMR ($CDCl_3$, 90 MHz), 1.18 (3 H, s, CH_3), 1.6 (3 H, br s, CH_3), 1.8–2.0 (4 H, m), 2.4–2.6 (4 H, m), 2.6 (2 H, br s), 4.6 (1 H, s), 4.7 (1 H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz), 18.25 (CH_3), 23.52 (CH_3), 27.96 (2 CH_2), 41.08 (2 CH_2), 41.58 (CH_2), 65.24 (C2), 115.53 (=CH_2), 140.44 (C=), 212.03 (C1 and C3).

2-Methyl-2-propyl-1,3-cycloheptanedione (10). Excess hydrogen gas was added to a solution of dione **15** (335 mg, 1.9 mmol) in dry ethanol (10 mL) containing PtO_2 (5 mg). After 30 min, the solution was filtered through Celite, and the solvent was evaporated. Purification by fc (silica gel, 25% ether in hexane) afforded 335 mg of **10** (98%): ^1H NMR ($CDCl_3$, 470 MHz) 0.88 (3 H, t, CH_3), 1.14 (2 H, m), 1.20 (3 H, s, CH_3), 1.74 (2 H, m), 1.83 (2 H, m), 2.02 (2 H, m), 2.59 (2 H, m), 2.70 (2 H, m).

General Procedure for the Microbial Reduction of 2,2-Disubstituted 1,3-Cycloalkanediones. The following procedure was used for the microbial reduction of diones **10**, **15**, **20**, **25**, **30**, and **35**. To a solution of 200 mL of pH 7 phosphate buffer, 20 g of D-glucose, and 1.0 g of yeast extract, warmed to 35 °C, was added 20 g of dry active bakers' yeast (Fleischmann's from Standard Brands Inc.), and the mixture was stirred at 35 °C for 30 min, after which 0.5 g of dione dissolved in 0.5 mL of ethanol was added. The mixture was vigorously stirred at 25–30 °C for 24–48 h and the continuously extracted with dichloromethane for 48 h providing a crude product after evaporation of the solvent, which consisted mainly of ketol and unreacted dione. The products were purified by fc, and the results are outlined in Table I.

(2*S*,3*S*)-2-Allyl-3-hydroxy-2-methylcycloheptanone (16). Purified by fc (silica gel, 30% ethyl acetate in hexane): ^1H NMR ($CDCl_3$, 470 MHz) 1.10 (3 H, s, CH_3), 1.46–2.05 (6 H, m), 2.30–2.80 (5 H, m), 3.70 (1 H, d, J = 7.0 Hz), 5.12 (2 H, m), 5.85 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 21.26 (CH_3), 22.87 (CH_2), 25.02 (CH_2), 32.23 (CH_2), 40.08 (CH_2), 41.70 (CH_2), 55.51 (C2), 73.68 (CHOH), 118.08 (=CH_2), 135.21 (CH=), 215.59 (C1).

(2*S*,3*S*)- and (2*R*,3*S*)-3-Hydroxy-2-methyl-2-propynylcycloheptanone (21, 23). Purified by fc (30% ether in hexane). **21**: ^1H NMR ($CDCl_3$, 470 MHz) 1.2 (3 H, s, CH_3), 1.6 (7 H, m), 2.4–2.6 (5 H, m), 4.05 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 21.13 (CH_3), 23.05 (CH_2), 24.60 (CH_2), 24.94 (CH_2), 32.22 (CH_2), 41.92 (CH_2), 54.91 (C2), 72.79 (≡CH), 72.97 (CHOH), 81.62 (C≡), 214.23 (C1). **23**: ^1H NMR ($CDCl_3$, 470 MHz) 1.3 (3 H, s, CH_3), 1.6–2.1 (7 H, m), 2.4–2.6 (5 H, m), 4.75 (1 H, m); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 16.68 (CH_3), 25.59 (CH_2), 25.93 (CH_2), 27.31 (CH_2), 34.02 (CH_2), 42.16 (CH_2), 63.66 (C2), 72.79 (≡CH), 72.98 (CHOH), 81.62 (C≡), 215.56 (C1).

(2*S*,3*S*)- and (2*R*,3*S*)-3-Hydroxy-2-isobutenyl-2-methylcycloheptanone (26, 28). Purified by fc (25% ether in hexane). **26**: ^1H NMR ($CDCl_3$, 90 MHz) 1.1 (3 H, s, CH_3), 1.5–2.2 (6 H, m), 1.7 (3 H, br s, CH_3), 2.3–2.9 (5 H, m), 3.75 (1 H, br t , J = 6.0 Hz), 4.78 (1 H, br s), 4.84 (1 H, br s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 22.32 (CH_3), 22.43 (CH_2), 24.38 (CH_3), 24.56 (CH_2), 31.95 (CH_2), 42.07 (CH_2), 44.70 (CH_2), 55.67 (C2), 74.30 (CHOH), 114.97 (=CH_2), 144.34 (C=), 215.93 (C=O). **28**: ^1H NMR ($CDCl_3$, 90 MHz) 1.1 (3 H, s, CH_3), 1.5–2.2 (6 H, m), 1.67 (3 H, br s, CH_3), 2.3–2.8 (5 H, m), 4.07 (1 H, m), 4.71 (1 H, br s), 4.86 (1 H, br s); ^{13}C NMR ($CDCl_3$), 50.3 MHz) 15.36 (CH_3), 24.28 (CH_3), 27.05 (CH_2), 27.14 (CH_2), 34.76 (CH_2), 41.42 (CH_2), 46.31 (CH_2), 56.38 (C2), 75.40 (CHOH), 115.28 (=CH_2), 142.16 (C=), 215.86 (C=O).

General Procedure for $NaBH_4$ Reduction of 2,2-Disubstituted 1,3-Cycloalkanediones. To a solution of dione (5 mmol) in dry ethanol (3 mL) was added $NaBH_4$ (1.4 mmol). The reaction stirred for 3 h at 25 °C. The solution was adjusted to pH 2 with 1 N HCl, and the ethanol was evaporated at reduced pressure. The residue was diluted with ether (15 mL), washed with brine (10 mL), and dried over ($MgSO_4$). Evaporation of the solvent and purification by fc (silica gel, 10–30% ethyl acetate in hexane) afforded the corresponding racemic ketols.

General Procedure for the Preparation of MTPA Esters of Chiral and Racemic Ketols. To ketol (1 mmol) were added pyridine (3 mmol), (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.1 mmol), and a catalytic amount of (dimethylamino)pyridine. The mixture was stirred overnight, after which ether (10 mL) and 1 N HCl (5 mL) were added. The organic phase was washed with 10% $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification by fc afforded the corresponding (+)-MTPA esters.

(2*S*,3*S*)- and (2*R*,3*S*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-methyl-2-propylcycloheptanone (11a, 13a). Authentic correlated material was available from a previous study.[2c] **11a**: ^1H NMR ($CDCl_3$), 470 MHz) 0.78 (3 H, t, J = 7 Hz, CH_3), 1.08 (3 H, s, CH_3), 1.05–1.80 (9 H, m), 2.17 (1 H, m), 2.34 (1 H, m), 2.60 (1 H, m), 3.55 (3 H, s, OCH_3), 5.13 (1 H, d, J = 8 Hz), 7.4 (3 H, m), 7.55 (2 H, m). **13a**: ^1H NMR ($CDCl_3$, 470 MHz) 0.76 (3 H, t, J = 7 Hz, CH_3), 1.05 (3 H, s, CH_3), 1.05–1.8 (9 H, m), 2.17 (1 H, m), 2.34 (1 H, m), 2.60 (1 H, m), 3.58 (3 H, s, OCH_3), 5.38 (1 H, dd, J = 9, 2 Hz), 7.4 (3 H, m), 7.55 (2 H, m).

General Hydrogenation Procedure for Correlation of the (+)-MTPA Esters of 16, 21, and 23. Excess hydrogen gas was added to a solution of MTPA ester (0.2 mmol) in dry ethanol (2 mL) containing PtO_2 (1 mg). The reaction was monitored by TLC. After 30 min, there was no starting material remaining. The solution was filtered through Celite, and the solvent was evaporated and purified by fc (25% ethyl acetate in hexane) to give **11a** and/or **13a**.

(2*S*,3*S*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)-acetoxy]-2-allyl-2-methylcycloheptanone (16a). Purified by fc (25% ethyl acetate in hexane): ^1H NMR ($CDCl_3$, 470 MHz) 1.06 (3H, s, CH_3), 1.5–1.8 (5 H, m), 2.25 (3 H, m), 2.5 (2 H, m), 3.53 (3 H, s, OCH_3), 4.96 (1 H, d, J = 15 Hz), 5.03 (1 H, d, J = 10 Hz), 5.17 (1 H, d, J = 8 Hz), 5.63 (1 H, m), 7.4 (3 H, m), 7.55 (2 H, m).

(2*S*,3*S*)- and (2*R*,3*R*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-allyl-2-methylcycloheptanone (16a, 17a; 1:1). Purified by fc (25% ethyl acetate in hexane): ^1H NMR ($CDCl_3$, 470 MHz) 1.06 (3 H, s, CH_3), 1.1 (3 H, s, CH_3), 2.25 (6 H, m), 2.5 (4 H, m), 3.53 (3 H, s, OCH_3), 3.54 (3 H, s, OCH_3), 4.94 (1 H, d, J = 15 Hz), 4.96 (1 H, d, J = 15 Hz), 5.03 (2 H, d, J = 10 Hz), 5.12 (1 H, d, J = 8 Hz), 5.17 (1 H, d, J = 8 Hz), 7.4 (6 H, m), 7.55 (4 H, m).

(2*S*,3*S*)- and (2*R*,3*S*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-methyl-2-(2-propynyl)cycloheptanone (21a, 23a). Purified by fc (30% ether in hexane). **21a**: ^{1}H NMR ($CDCl_3$, 470 MHz) 1.25 (3 H, s, CH_3), 1.5–2.0 (6 H, m), 2.02 (1 H, t, J = 2.5 Hz), 2.3 (1 H, dd, J = 15, 2.5 Hz), 2.39 (1 H, dd, J = 15, 2.5 Hz), 2.4–2.7 (2 H, m), 3.53 (3 H, s, OCH_3), 5.43 (1 H, d, J = 8 Hz), 7.4 (3 H, m), 7.55 (2 H, m). **23a**: ^{1}H NMR ($CDCl_3$, 470 MHz) 1.11 (3 H, s, CH_3), 1.5–2.0 (6 H, m), 2.10 (1 H, t, J = 2.5 Hz) 2.21 (2 H, d, J = 2.5 Hz), 2.4–2.7 (2 H, m), 3.58 (3 H, s, OCH_3), 5.70 (1 H, t, J = 6.5 Hz), 7.4 (3 H, m), 7.55 (2 H, m).

(2*R*,3*S*)- and (2*S*,3*R*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-methyl-2-(2-propynyl)cycloheptanone (23a, 24a; 1:1). Purified by fc (30% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$, 470 MHz) 1.11 (3 H, s, CH_3), 1.12 (3 H, s, CH_3), 1.5–2.0 (12 H, m), 2.15 (1 H, t, J = 2.5 Hz), 2.21 (2 H, d, J = 2.5 Hz), 2.35 (1 H, dd, J = 14, 2.5 Hz), 2.37 (1 H, dd, J = 14, 2.5 Hz), 2.5–2.7 (4 H, m), 3.51 (3 H, s, OCH_3), 3.58 (3 H, s, OCH_3), 5.64 (1 H, dd, J = 8, 2 Hz), 5.71 (1 H, t, J = 6 Hz), 7.4 (6 H, m), 7.55 (4 H, m).

(2*S*,3*S*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-isobutenyl-2-methylcycloheptanone (26a) and (2*R*,3*S*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-isobutenyl-2-methylcycloheptanone (28a). Purified by fc (20–30% ether in hexane). **26a**: ^{1}H NMR ($CDCl_3$, 470 MHz) 1.06 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 1.5–1.8 (5 H, m), 2.11 (1 H, d, J = 14 Hz), 2.15 (1 H, m), 2.34 (1 H, d, J = 14 Hz), 2.37 (1 H, m), 2.64 (1 H, m), 3.54 (3 H, s, OCH_3), 4.57 (1 H, s), 4.79 (1 H, s), 5.13 (1 H, d, J = 8 Hz), 7.4 (3 H, m), 7.55 (2 H, m). **28a**: ^{1}H NMR ($CDCl_3$, 470 MHz) 1.08 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 1.5–1.9 (6 H, m), 2.02 (1 H, d, J = 14 Hz), 2.28 (1 H, d, J = 14 Hz), 2.40 (1 H, m), 2.65 (1 H, dt, J = 11, 2.5 Hz), 3.57 (3 H, s, OCH_3), 4.48 (1 H, s), 4.82 (1 H, s), 5.37 (1 H, d, J = 10 Hz), 7.4 (3 H, m), 7.55 (2 H, m).

(2*S*,3*S*)- and (2*R*,3*R*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-isobutenyl-2-methylcycloheptanone (26a, 27a; 1:1) and (2*R*,3*S*)- and (2*S*,3*R*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-isobutenyl-2-methylcycloheptanone (28a, 29a; 1:1). Purified by fc (20-30% ether in hexane). **26a, 27a**: ^{1}H NMR ($CDCl_3$, 470 MHz) 1.06 (3 H, s, CH_3), 1.11 (3 H, s, CH_3), 1.56 (6 H, br s, 2 CH_3), 1.5–1.8 (10 H, m), 2.07 (1 H, d, J = 13 Hz), 2.11 (1 H, d, J = 14 Hz), 2.15 (2 H, m), 2.34 (1 H, d), J = 14 Hz), 2.37 (2 H, m), 2.43 (1 H, d, J = 13 Hz), 2.64 (2 H, m), 3.54 (3 H, s, OCH_3), 3.56 (3 H, s, OCH_3), 4.55 (1 H, s), 4.57 (1 H, s), 4.79 (2 H, s), 5.07 (1 H, d, J = 8 Hz), 5.13 (1 H, d, J = 8 Hz), 7.4 (6 H, m), 7.55 (4 H, m). **28a, 29a**: ^{1}H NMR ($CDCl_3$, 470 MHz) 1.07 (3 H, s, CH_3), 1.08 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 1.59 (3 H, s, CH_3), 1.5–1.9 (12 H, m), 2.02 (1 H, d, J = 14 Hz), 2.10 (1 H, d, J = 14 Hz), 2.28 (1 H, d, J = 14 Hz), 2.35 (1 H, d, J = 14 Hz), 2.4 (2 H, m), 2.65 (2 H, br t , J = 11 Hz), 3.5 (3 H, s, OCH_3), 3.57 (3 H, s, OCH_3), 4.48 (1 H, s), 4.55 (1 H, s), 4.82 (1 H, s), 4.85 (1 H, s), 5.36 (1 H, d, J = 10 Hz), 5.37 (1 H, d, J = 10 Hz), 7.4 (6 H, m), 7.55 (4 H, m).

(2*S*,3*S*)- and (2*R*,3*S*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-allyl-2-methylcyclooctanone (31a, 33a). Purified by fc (25% ethyl acetate in hexane). **31a**: ^{1}H NMR ($CDCl_3$, 470 MHz) 0.89 (3 H, s, CH_3), 1.5–2.0 (8 H, m), 2.15 (1 H, dd, J = 14, 8 Hz), 2.33 (1 H, m), 2.50 (1 H, dd, J = 14, 6 Hz), 2.77 (1 H, m), 3.55 (3 H, s, OCH_3), 4.90 (1 H, s), 4.93 (1 H, d, J = 6.0 Hz), 5.78 (1 H, dd, J = 9, 4 Hz), 5.82 (1 H, m), 7.4 (3 H, m), 7.55 (2 H, m). **33a**: ^{1}H NMR ($CDCl_3$, 470 MHz) 1.02 (3 H, s, CH_3), 1.5–2.0 (8 H, m), 2.1–2.9 (4 H, m), 3.45 (3 H, s, OCH_3), 4.84 (1 H, d, J = 15 Hz), 4.97 (1 H, d, J = 10 Hz), 5.8 (2 H, m), 7.4 (3 H, m), 7.55 (2 H, m).

(2*S*,3*S*)- and (2*R*,3*R*)-3-[(+)-α-Methoxy-α-((trifluoromethyl)phenyl)acetoxy]-2-allyl-2-methylcyclooctanone (31a, 32a; 1:1). Purified by fc (30% ethyl acetate in hexane): ^{1}H NMR ($CDCl_3$, 470 MHz) 0.89 (3 H, s, CH_3), 1.5–2.0 (16 H, m), 2.15 (2 H, m), 2.33 (2 H, m), 2.50 (2 H, m), 2.77 (2 H, m), 3.55 (3 H, s, OCH_3), 3.58 (3 H, s, OCH_3), 4.92 (4 H, m), 5.8 (4 H, m), 7.4 (6 H, m), 7.55 (4 H, m).

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Supplementary Material Available: 470-MHz ^{1}H NMR spectra of the (+)-MTPA esters of the ketols derived from microbial and $NaBH_4$ reduction (12 pages). Ordering information is given on any current masthead page.

Chemical Reactions by Polyethylene Glycol Modified Enzymes in Chlorinated Hydrocarbons

Katsunobu Takahashi, Ayako Ajima, Takayuki Yoshimoto, Masato Okada, Ayako Matsushima, Yutaka Tamaura, and Yuji Inada*

Laboratory of Biological Chemistry, Tokyo Institute of Technology, Ookayama, Meguroku, Tokyo 152, Japan

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Generally native enzymes never dissolve in organic solvents. Recently, we have reported that a modified enzyme, whose surface was covalently attached to polyethylene glycol (PEG), dissolved in various organic solvents such as benzene, toluene, acetone, ethanol, and dimethylformamide in a transparent state.[1] This modified enzyme can be used as a catalyst of chemical reactions that take place in organic solvents such as benzene and toluene. The modified peroxidase, lipase, catalase, and chymotrypsin specifically catalyze oxidation reactions,[2] ester syntheses,[3] hydrogen peroxide decomposition,[4] and acid–amide bond formation,[5] respectively, in a transparent benzene solution.

In the present paper, we have studied the ester synthesis (eq 1), acid–amide bond formation (eq 2), and H_2O_2 decomposition (eq 3) reactions by the polyethylene glycol modified enzymes in chlorinated hydrocarbons, aiming the wide application of the modified enzymes in various organic solvents.

lauryl alcohol + lauric acid → lauryl laurate + H_2O (1)

N-benzoyl-L-tyrosine ethyl ester + *n*-butylamine → *N*-benzoyl-L-tyrosine butylamide + ethanol (2)

$$2H_2O_2 \rightarrow 2H_2O + O_2 \quad (3)$$

Table I shows the activity and solubility for the reactions (eq 1–3) by PEG-modified enzymes [lipase (eq 1), chymotrypsin (eq 2), and catalase (eq 3)] in chlorinated hydrocarbons. The PEG-modified enzymes dissolved in a

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