(80), 263 (85), 161 (100), 133 (20). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.84; H, 6.45.

3-Methoxyphenyl monochloroacetate (24): yellow oil; IR (film) 2980, 1780, 1620, 1490, 1280, 1160, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3 H, OCH_3), 4.34 (s, 2 H, CH_2Cl), 6.8–7.3 (m, 4 H, H arom); MS m/z 200 (18), 124 (100), 109 (72), 95 (18). Anal. Calcd for $C_9H_9ClO_3$: C, 53.88; H, 4.52; Cl, 17.67. Found: C, 53.80; H, 4.45; Cl, 17.52.

ω,ω-Dichloro-2-hydroxy-3-*tert*-butyl-5-methylacetophenone (27): yellow crystals; mp 55–59 °C; IR (KBr) 2980, 1640, 1440, 1280, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9 H, $(CH_3)_3C$), 2.32 (s, 3 H, CH_3), 6.63 (s, 1 H, $CHCl_2$), 7.39 (s, 1 H, H-4), 7.44 (s, 1 H, H-6), 12.14 (s, 1 H, OH); MS m/z 274 (30), 259 (50), 191 (100), 175 (8). Anal. Calcd for $C_{13}H_{16}Cl_2O_2$: C, 56.74; H, 5.86; Cl, 25.77. Found: C, 56.62; H, 5.94; Cl, 25.92.

2-*tert*-Butyl-4-methylphenyl dichloroacetate (28): pale yellow oil; IR (film) 2980, 1770, 1500, 1190, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 9 H, $(CH_3)_3C$), 2.35 (s, 3 H, CH_3), 6.17 (s, 1 H, $CHCl_2$), 6.89 (d, 1 H, H-6, J = 8.2 Hz), 7.04 (dd, 1 H, H-3, J = 1.8 Hz); MS m/z 274 (54), 259 (100), 241 (30), 164 (25), 149 (78). Anal. Calcd for $C_{13}H_{16}Cl_2O_2$: C, 56.74; H, 5.86; Cl, 25.77. Found: C, 56.60; H, 5.70; Cl, 25.58.

2-*tert*-Butyl-5-methylphenyl dichloroacetate (30): pale yellow oil; IR (film) 2990, 1680, 1520, 1240, 1090, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H, $(CH_3)_3C$), 2.32 (s, 3 H, CH_3), 6.17 (s, 1 H, $CHCl_2$), 6.81 (d, 1 H, H-6, J = 1.8 Hz), 7.03 (dd, 1 H, H-4, J = 8.1 and 1.8 Hz), 7.30 (d, 1 H, H-3, J = 8.1 Hz); MS m/z 274 (34), 259 (100), 241 (20), 176 (14), 149 (26). Anal. Calcd for $C_{13}H_{16}Cl_2O_2$: C, 56.74; H, 5.86; Cl, 25.77. Found: C, 56.68; H, 5.95; Cl, 25.88.

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Registry No. **5** (R = 2-Bu-*t*), 88-18-6; **6a**, 75-36-5; **6b**, 79-04-9; **6c**, 79-36-7; **6d**, 76-02-8; **6e**, 354-32-5; **6f**, 645-45-4; **6g**, 102-92-1; **6h**, 7299-58-3; **9a**, 114299-91-1; **9b**, 39068-23-0; **9c**, 41769-06-6; **9d**, 36359-98-5; **9e**, 127354-48-7; **9f**, 127354-30-7; **9g**, 127354-49-8; **9h**, 5797-27-3; **9i**, 127354-31-8; **9l**, 127354-50-1; **10**, 127354-32-9; **11**, 127354-33-0; **12**, 127354-34-1; **16a**, 35770-74-2; **16b**, 55960-09-3; **16c**, 127354-51-2; **16d**, 127354-52-3; **17a**, 620-73-5; **17b**, 119929-84-9; **17c**, 127354-35-2; **17d**, 63573-05-7; **18a**, 53074-73-0; **18b**, 60965-23-3; **18c**, 127354-36-3; **19b**, 75717-59-8; **20a**, 3245-25-8; **20c**, 127354-37-4; **20d**, 127354-39-6; **20f**, 40123-27-1; **20g**, 127354-41-0; **20h**, 127354-43-2; **21a**, 24242-55-5; **21c**, 127354-38-5; **21d**, 111422-36-7; **21e**, 111422-37-8; **21f**, 127354-40-9; **21g**, 127354-42-1; **21h**, 127354-44-3; **23**, 127354-55-6; **24**, 30287-15-1; **26a**, 118967-71-8; **26c**, 127354-53-4; **27**, 127354-45-4; **28**, 127354-46-5; **29b**, 53863-60-8; **29d**, 127354-54-5; **30**, 127354-47-6.

Stereoselective Reduction of Diketones by a Novel Carbonyl Reductase from *Candida parapsilosis*

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An NADPH-linked carbonyl reductase purified from *Candida parapsilosis* IFO 0708 can reduce a variety of diketone compounds such as analogues of 1*H*-indole-2,3-dione (**3**), dihydro-4,4-dimethyl-2,3-furandione (**1a**), and 1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-dione (**2**). Electron-donating substituents at the 5 position on the ring of **3** increased the reduction velocity; however, a 1-methyl group had no effect on it. Analogues of **1a** carrying bulky substituents at the 4 or 5 position of the lactone ring were reduced at lower rates than that of **1a**, although they showed higher affinities for the enzyme. Ones carrying less bulky substituents were reduced at higher rates, but had lower K_m values. On reduction, 4,4-diethyldihydro-2,3-furandione (**1c**), (*R*)- and (*S*)-dihydro-4,4-dimethyl-5-(1-methylethyl)-2,3-furandione (**1e**), and (*R*)-(−)- and (S)-(+)-**2**, **3**, and 1-methyl-1*H*-indole-2,3-dione (**4**) all gave *R* alcohols.

The stereospecific reduction of prochiral α-diketones is of synthetic importance. Several enzymatic reactions have been shwon to be promising in giving good enantiomeric excesses of the reduction products. The reduction of dihydro-4,4-dimethyl-2,3-furandione (**1a**) has been reported to give (*R*)-(−)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone,[2] which is a key intermediate in the synthesis of (*R*)-*N*-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)-β-alanine (D-pantothenic acid), and the reduction of 2-(6-carbomethoxyhexyl)cyclopentane-1,3,4-trione gives important intermediates of (−)-prostaglandin E_1 and (−)-prostaglandin E_2.[3] Furthermore, this type of reduction is involved in the metabolism of C_{18}-steroid hormones such as in the reduction of 3-hydroxyestra-1,3,5(10)-triene-16,17-dione (16-oxoestrone).[4] Many kind of ketols exist in nature and play important physiological roles.[5] In a previous paper, we reported that a fungus, *Mucor ambiguus*, produces a new type of carbonyl reductase showing strict specificity for only conjugated polyketone compounds.[6] The following studies demonstrated that similar enzymes are widely distributed in a variety of microorganisms.[7] For example, the carbonyl reductases of *Candida parapsilosis* and *Saccharomyces cerevisiae* also exhibit broad substrate specificities toward only conjugated polyketones.[7b,c] These results suggest that they can be grouped into a new carbonyl reductase family, which has not been reported previously. However, the two yeast enzymes (i.e., *Candida*

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	R^1	R^2	R^3
a	Me	Me	H
b	Me	Et	H
c	Et	Et	H
d	Me	Pr	H
e	Me	Me	Me_2CH
f	Me	Et	MeEtCH
g	Et	Et	Et_2CH
h	Me	Pr	MePrCH
i	Me	Me	Et_2CH
j	Me	Me	MePrCH

Figure 1.

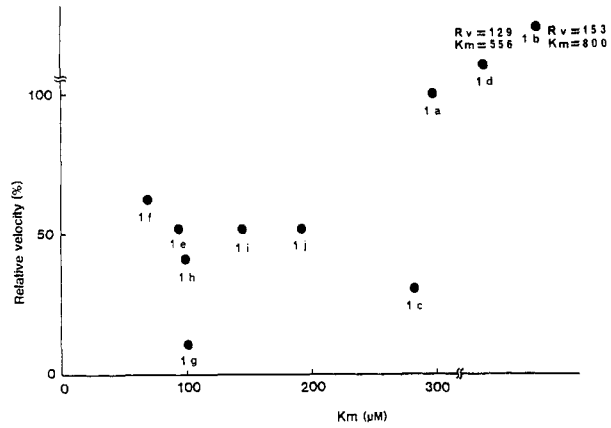

Figure 2. Substrate specificity for analogues of dihydro-4,4-dimethyl-2,3-furandione of *Candida* carbonyl reductase. Enzyme activity was measured as described in the Experimental Section. The ordinate represents the V_{max}, and the V_{max} with dihydro-4,4-dimethyl-2,3-furandione (**1a**, 481 units/mg enzyme) was taken as 100%.

and *Saccharomyces* carbonyl reductases) seemed to be different from the mold enzyme (i.e., *Mucor* carbonyl reductase) in their stereospecificities. The former enzymes gave the *R*-(−) enantiomer of dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone on reduction of **1a**, but the latter gave the *S*-(+) enantiomer. Because of their broad substrate specificities for various prochiral α-diketone compounds, these enzymes seem to be highly suitable as tools for general synthetic studies. Here we report the stereoselective reduction of several diketones such as analogues of **3** and **1a** and (*R*)- and (*S*)-**2** by the *Candida* enzyme, with emphasis on identification of the carbonyl group that can be reduced, demonstration of the absolute configurations of the reduction products, and the effects of the insertion of several aliphatic substituents into the substrate molecules on the kinetics of the enzyme reaction.

Results

Substrate Specificity. In addition to **1a**, several of its derivatives were also examined as substrates (Figure 1). The results are schematically presented in Figure 2. Most of the derivatives carrying bulky substituents at the 4 or 5 position of the lactone ring were reduced at lower rates than that of **1a**, although they showed higher affinities for the enzyme than did **1a**. Among them, **1e** was the best substrate, as judged from the fact that it showed the highest pseudo-second-order rate constant ratio (V_{max}/K_m). On the other hand, **1b** and **1d**, which carry bulkier substituents than does **1f**, showed higher V_{max} but lower K_m values than **1a**.

The reduction velocities for analogues of **3** increased when the substituent group was electron donating. The K_m (μM) and V_{max} (unit/mg) are as follows: 5-NO_2, 21, 211; 5-Br, 9, 244; no substituent group (i.e. isatin), 12, 306; 5-Me, 35, 353; 1-Me, 19, 302.

Identification of the Products. Table I and Figure 3 show the results of the reduction of α-diketones. In the case of compounds **6** and **7**, **a** and **b** indicate the order of elution. The ^1H NMR data for the products showed that they were pure, with the exceptions of **8** and **9**, and that they were derived through the reduction of one carbonyl group. **7a** and **7b** were estimated to be more than 98% ee from the ^1H NMR data of non-bridgehead methyne proton. **8** and **9** included small amounts of **3** and **4**, respectively, which were formed through the air oxidation of **8** and **9**, respectively, during concentration of aliquots of the respective column chromatography fractions. The derivatives of **5**, **6a**, **6b**, and **9** with chloroformic acid

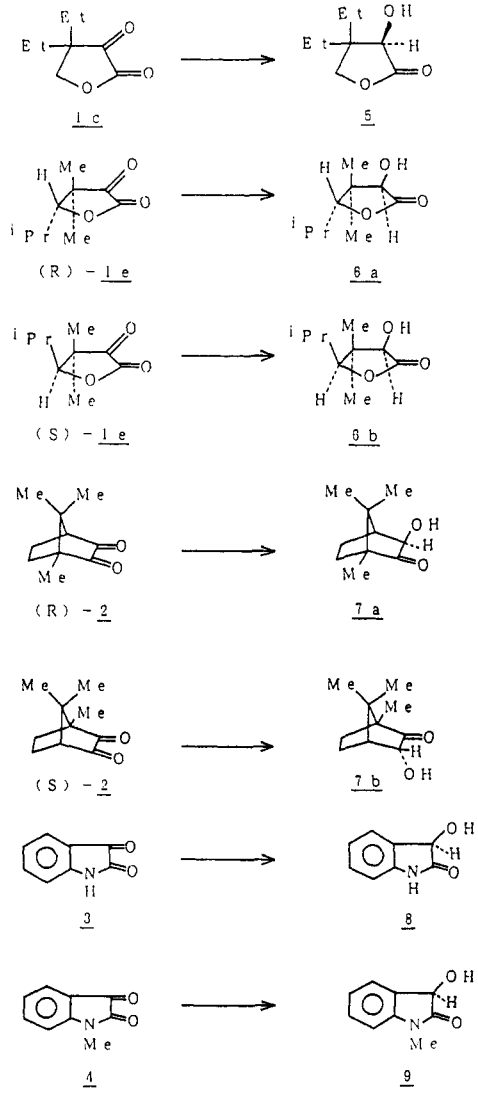

Figure 3.

Table I. Stereoselective Reduction of Polyketones by *Candida* Carbonyl Reductase

substr	incubtn time, h	product	isoltd wt, mg	yield,[a] %	(*RS*)[d]	ee, %
1c	1	**5**	21.3	63	(*R*)	>99[e]
(*RS*)-**1e**	1	**6a**	12.9	38	(*R*)	>99[e]
		6b	9.1	27	(*R*)	>99[e]
(*RS*)-**2**	3	**7a**	8.0	24	(*R*)	>98[f]
		7b	11.3	34	(*R*)	>98[f]
3	1	**8**	13.5[b]	40[b]	(*R*)	
4	1	**9**	9.3[c]	28[c]	(*R*)	>99[e]

[a] Molar yields based on added NADPH. Molar conversions of each substrate to the respective products were **1c**, 42%; **1e**, 44%; **2**, 38%; **3**, 27%; and **4**, 18%. [b] Values corrected by subtraction of the isatin formed through oxidation of the product during evaporation in the isolation step. [c] Values corrected by subtraction of the 1-methylisatin formed through oxidation of the product during evaporation in the isolation step. [d] Configurations of the products were determined according to the method of Horeau[8] using cyclohexanol as a standard compound. (*R*)-(−)-Dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone was determined to be of the *R* configuration. [e] Values are based on the GLC analysis of the derivatives of the product with chloroformic acid (1*R*,2*S*,5*R*)-(−)-5-methyl-2-(1-methylethyl)cyclohexanol ester.[7a] [f] Values are based on ^{1}H NMR analysis.

(1*R*,2*S*,5*R*)-(−)-5-methyl-2-(1-methylethyl)cyclohexanol ester[7a] each gave a single peak on gas–liquid chromatography (GLC), with retention times of 13.1, 13.1, 15.2, and 6.3 min, respectively, indicating that the products were optically pure (>99% ee). All the alcohols formed were determined to be of the *R* configuration by Horeau's method,[8] because in all cases the ratio of the areas of the two peaks, 8.1 min (retention time) vs 8.8 min, on the gas–liquid chromatograms was greater than that in the case of cyclohexanol (standard compound). The peak increments (%) of the peak (retention time, 8.1 min) were as follows: **5**, +1.3; **6a**, +2.1; **6b**, +1.3; **7a**, +1.2; **7b**, +1.7; **8**, +1.3; **9**, +1.1. Determinations of the configuration of **8** and **9** were based on that of (−)-mandelic acid.[8b] Furthermore, **6a** and **6b** were determined to have 3*R*,5*R* and 3*R*,5*S* form structures, respectively, from the coupling constant of the hydrogen at the 5 position carbon, because the dihedral angles for H–C(5)–C(methylethyl)–H calculated with the MOPAC (A General Molecular Orbital Package for Semi-Empirical MO-SCF Calculation) program[9] were 56° and 160°, respectively. Thus, the structures of the reduction products were determined to be **5**, **6a**, and **6b**. The structures of **7a** and **7b** were determined on the basis of their ^{1}H NMR spectral data, compared with those in the literature.[10]

Discussion

The results described here indicate that the polyketone reductase of *C. parapsilosis* catalyzes the reduction of a variety of diketones, including analogues of **1a** and **3**, and **2**, to give *R* alcohols. *R* alcohol **5** derived from **1c** has negative optical rotation, as has (*R*)-(−)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone. The reduction of (*RS*)-**1e** also proceeded well, *R* alcohols being yielded. These results suggest that ethyl groups at the 4 position and a methylethyl group at the 5 position of the lactone ring do not greatly affect the reduction velocity. On the contrary, the bridgeheaded methyl group of **2** seemed to disturb the reduction, since the reduction of **2** only occurred on the opposite side of the carbonyl group from the methyl group. Ohno et al.[11] showed that the reduction with a model compound of NADPH, (4*R*)-*N*-[(*R*)-α-methylbenzyl]-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide, yielded (*R*)-**7b** from (*S*)-(+)-**2** as a major product; however, the *S* alcohol of **7a**, but not the *R* alcohol of **7a**, was obtained from (*R*)-(−)-**2**. These results indicate that the model of NADPH only recognized endo and exo sites of **2**. On the contrary, the enzyme from *C. parapsilosis* recognized the whole molecule, an *R* alcohol being yielded from each enantiomer of **2**. **3** and **4** gave **8** and **9**, respectively, which are difficult to synthesize through chemical reduction of **3** and have not been reported.

As the carbonyl reductase of *C. parapsilosis* has a broad substrate specificity and gives *R* alcohols with full stereospecificity as products, the enzyme is thought to be useful for the general synthesis of chiral α-hydroxy ketones.

Experimental Section

Materials. **1a** was synthesized as reported previously.[12] Analogues of **1a** were obtained from Seitetsu Kagaku Kogyo (Japan). NADPH was from Oriental Yeast (Japan). All other reagents, of analytical grade, were commercially available.

Preparation of the Enzyme. A homogeneous preparation of conjugated polyketone reductase (ketopantoyl lactone reductase) was prepared from *Candida parapsilosis* IFO 0708 as described previously.[7b] The enzyme showed a specific activity of 175 μmol/min/mg protein for **1a**, when assayed as described below.

Enzyme Assay. The reaction mixture consisted of 200 mM potassium phosphate buffer (pH 7.0), 0.32 mM NADPH, polyketone reductase, and 0.4 mM each substrate, in a total volume of 2.5 mL. The reactions were initiated by the addition of the substrate and the decrease in absorbance at 340 nm was monitored spectrophotometrically at 30 °C. Analogues of **3** were assayed by measuring the decrease in maximum absorbance between 414 and 441 nm because they showed absorbance at 340 nm. One unit of the enzyme is defined as the change in absorbance corresponding to the oxidation of 1 μmol of NADPH in the presence of **1a** as a substrate.

Substrate Specificity. The substrate specificity was determined, adding various substrates instead of **1a**, in the same manner as for the "enzyme assay". The K_m and V_{max} values were determined from Lineweaver–Burk double reciprocal plots.

Isolation of the Enzymatically Synthesized Products. Reaction Method. A 6-mL mixture, containing 50 mg of substrate, NADPH (0.67 molar ratio, to the substrate), 3 mmol of potassium phosphate buffer (pH 7.0), and 170 μg of the enzyme, was incubated for a prescribed period, as shown in Table I, at 30 °C. When the substrates were **1c** and **1e**, 10 μL of a 16.7 w/v % substrate solution in 0.1 N HCl (aq) was added every min 30 times to prevent hydrolysis of the lactone ring, with incubation for a prescribed period, as mentioned above.

The resultant mixture was extracted with five portions of 5 mL of acetic acid ethyl ester after heating with 1.0 mL of 6 N HCl for 10 min in boiling water. The combined organic layer was evaporated in vacuo after being dried over anhydrous sodium sulfate. The residual mass was dissolved in a minimal amount of benzene and then applied on a column of silica gel (Wacogel C-200, 2.5 × 20 cm, Wako Pure Chemicals, Japan). A linear gradient of benzene (150 mL)–acetic acid ethyl ester (150 mL) was used for elution. Products in the fractions were monitored with a UV lamp (254 nm) after being developed on a silica gel sheet (Kieselgel 60F_{254}, Merck F.R.G.) with a solvent system of benzene/acetic acid ethyl ester (volume ratio, 3/1). Fractions containing a product were combined and dried in vacuo.

Characterization of the Products. Quantitative analysis of the products was carried out with a Shimadzu GC-7AF gas–liquid chromatograph equipped with a flame ionization detector.

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A column (1 m long, 3.0 mm i.d.) packed with silicone OV-1 (3%) was used. The operation conditions were as follows: injection port, 160 °C; column, 150 °C for isatins and their reduced products and 110 °C for other substrates and their reduced products; helium as a carrier, 70 mL/min; hydrogen, 0.6 kg/cm^2; air, 0.6 kg/cm^2. The retention times (min) of the substrates and products were as follows: **1c**, 3.5; **5**, 4.0; **1e**, 2.2; **6a**, 2.5; **6b**, 2.2; **2**, 3.4; **7a**, 2.3; **7b**, 2.3; **3**, 4.0; **8**, 3.5; **4**, 2.7; **9**, 2.1. The purity of the products, **5**, **6a**, **6b**, **7a**, and **7b**, was judged to be larger than 95% by this GLC determination, and **8** and **9** were found to include only **3** and **4**, respectively, as impurities. ^{1}H NMR spectra were obtained at 360 MHz. The purities of **8** and **9** were determined to be 88 and 92%, respectively, based on the intensity of their 3-H signal in the ^{1}H NMR spectra.

The optical purities of the reduction products were determined by GLC after derivatization with chloroformic acid (1*R*,2*S*,5*R*)-(−)-5-methyl-2-(1-methylethyl)cyclohexanol ester.[7a] The absolute configurations of the formed alcohols were determined according to the method of Horeau.[8] The method is as follows: after heating a mixture containing 1 μmol of a compound to be assayed, 4 μL of dry pyridine, and 2 μL of (*RS*)-2-phenylbutanoic acid anhydride for 90 min at 40 °C, 4 μmol of (*R*)-1-phenylethylamine was added to the mixture. After heating for 15 min at 40 °C, 60 μL of ethyl acetate was added and the resulting solution was analyzed by GLC as to the area ratio of the formed (*S*)-1-phenylethylamide of (*R*)-(−)-2-phenylbutyric acid and the (*S*)-1-phenylethylamide of (*S*)-(+)-2-phenylbutyric acid. The analytical conditions were the same as described above except for the following changes: silicone OV-17 (1%) on Gas Chrom Q (100–120 mesh); carrier N_2, 50 mL/min; injection port, 250 °C; detector port, 250 °C; column, 215 °C. The retention times of the (*S*)-1-phenylethylamide of (*R*)-(−)-2-phenylbutyric acid and the (*S*)-1-phenylethylamide of (*S*)-(+)-2-phenylbutyric acid were 8.1 and 8.8 min, respectively.

Determination of the molecular shapes of **6a** and **6b** derived from (*RS*)-**1e** was carried out by calculation with the MOPAC program (QCPE (Quantum Chemistry Program Exchange, Indiana University) #455) using the AM1 (Austin Model 1) option.[9]

The analytical data for the reduction products were as follows.

5. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.7; H, 8.9. ^{1}H NMR ($CDCl_3$, δ): 0.83 (Me, t, J = 7.6 Hz, 3 H), 0.91 (Me, t, J = 7.6 Hz, 3 H), 1.48 (CH_2, m, J = 7.2 Hz, 4 H), 3.80 and 4.08 (CH_2, each d, J = 9.4 Hz, 2 H), 2.8 (OH, br s, 1 H). IR (film): 3450 (br), 2980, 1785, 1465, 1195, 1120, 1010, 885 cm^{-1}. Mass spectrum (m/e): 156, 86, 85 (base), 71, 55, 43, 40. Optical rotation: $[\alpha]^{25}_D$ −13° (c = 18 MeOH).

6a. ^{1}H NMR ($CDCl_3$, δ): 0.95 (Me, d, J = 6.8 Hz, 3 H), 0.99 (Me, d, J = 6.8 Hz, 3 H), 1.09 (Me, s, 3 H), 1.10 (Me, s, 3 H), 1.95 (H, m, 1 H), 3.95 (H, d, J = 6.5 Hz, 1 H), 4.05 (H, s, 1 H), 2.7 (OH, br s, 1 H). IR (film): 3450 (br), 2975, 2940, 1775, 1475, 1225, 1120, 995, 975 cm^{-1}. Mass spectrum (m/e): 101, 86, 85 (base), 83, 73, 72, 57, 55, 44, 43, 40, 39. Optical rotation: $[\alpha]^{25}_D$ +48° (c = 1, MeOH).

6b. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.6; H, 9.3. ^{1}H NMR ($CDCl_3$, δ): 0.88 (Me, s, 3 H), 0.92 (Me, d, J = 6.7 Hz, 3 H), 1.03 (Me, d, J = 6.7 Hz, 3 H), 1.21 (Me, s, 3 H), 1.87 (H, m, 1 H), 3.57 (H, d, J = 10.4 Hz, 1 H), 4.01 (H, s, 1 H), 2.5 (OH, br s, 1 H). IR (KBr): 3410 (br), 2980, 2930, 2890, 1760, 1485–1440, 1400–1200, 1180, 1150, 1020, 985 cm^{-1}. Mass spectrum (m/e): 101, 86, 85 (base), 83, 73, 72, 57, 55, 44, 43, 40, 39. Mp: 121–2 °C. Optical rotation: $[\alpha]^{25}_D$ −25° (c = 1, MeOH).

7a. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.2; H, 9.4. ^{1}H NMR ($CDCl_3$, δ): 0.85 (Me, s, 3 H), 0.88 (Me, s, 3 H), 0.92 (Me, s, 3 H), 2.02 (H, d, J = 4.3 Hz, 1 H), 3.65 (H, s, 1 H), 2.4 (OH, br s, 1 H), 1.9, 1.6 and 1.3 (m, 4 H). IR (KBr): 3450 (br), 2960, 1775, 1460, 1400, 1380, 1320, 1295, 1105, 1080, 1020, 835 cm^{-1}. Mp: 207–9 °C. Mass spectrum (m/e): 168, 125, 95, 84, 83 (base), 69, 55, 43, 40, 39. Optical rotation: $[\alpha]^{25}_D$ +85° (c = 1, MeOH).

7b. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.4; H, 9.6. ^{1}H NMR ($CDCl_3$, δ): 0.82 (Me, s, 3 H), 0.97 (Me, s, 3 H), 0.95 (Me, s, 3 H), 2.20 (H, dd, J_1 = 4.7 Hz, J_2 = 4.0 Hz, 1 H), 4.13 (H, d, J = 4.0 Hz, 1 H), 2.4 (OH, br s, 1 H), 1.9, 1.7 and 1.3 (m, 4 H). IR (KBr): 3460 (br), 2960, 1745, 1480, 1460, 1400, 1380, 1110, 1085, 1005, 980 cm^{-1}. Mass spectrum (m/e): 168, 125, 95, 84, 83 (base), 69, 55, 43, 40, 39. Mp: 109–10 °C. Optical rotation: $[\alpha]^{25}_D$ −2° (c = 1, MeOH).

8. ^{1}H NMR (2-propanone-d_6, δ): 3.63 (H, s, 1 H), 5.03 (OH, br d, J = 6.1 Hz, 1 H), 7.25–6.75 (Ar H, 4 H), 9.07 (NH, br s, 1 H). IR (KBr): 3440 (br), 1710, 1635, 1480, 1360, 1270, 1200, 1180, 1115, 750 cm^{-1}. Mass spectrum (m/e): 147, 119 (base), 93, 92, 64, 40. Optical rotation: $[\alpha]^{25}_D$ +7° (c = 1, MeOH).

9. ^{1}H NMR ($CDCl_3$, δ): 3.18 (Me, s, 3 H), 3.52 (H, s, 1 H), 5.01 (OH, s, 1 H), 6.67–7.56 (Ar H, 4 H). IR (KBr): 3420 (br), 1720, 1620, 1500, 1215, 760 cm^{-1}. Mass spectrum (m/e): 161, 133, 105, 104 (base), 92, 78, 63, 50, 44, 39. Optical rotation: $[\alpha]^{25}_D$ +3° (c = 1, MeOH).

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Registry No. **1a**, 13031-04-4; (±)-**1b**, 39748-47-5; **1c**, 96909-86-3; (±)-**1d**, 124402-14-8; (±)-**1e**, 124402-15-9; (*R*)-**1e**, 124508-43-6; (*S*)-**1e**, 124508-44-7; **1f**, 116340-03-5; **1g**, 124402-16-0; **1h**, 96909-84-1; **1i**, 124402-17-1; **1j**, 96909-82-9; (±)-**2**, 10373-78-1; (*R*)-**2**, 10334-26-6; (*S*)-**2**, 2767-84-2; **3**, 91-56-5; **3** (R = 5-NO_2), 611-09-6; **3** (R = 5-Br), 87-48-9; **3** (R = 5-Me), 608-05-9; **4**, 2058-74-4; **5**, 108100-41-0; **6a**, 124402-18-2; **6b**, 124402-19-3; **7a**, 28357-11-1; **7b**, 80513-78-6; **8**, 124508-45-8; **9**, 124508-46-9; dihydro-3-((2-isopropyl-5-methylcyclohex-1-yl)carbonyldioxy)-4,4-diethyl-2(3*H*)-furanone, 124402-20-6; dihydro-3-((2-isopropyl-5-methylcyclohex-1-yl)carbonyldioxy)-4,4-dimethyl-5-isopropyl-2(3*H*)-furanone (stereoisomer 1), 124402-21-7; dihydro-3-((2-isopropyl-5-methylcyclohex-1-yl)carbonyldioxy)-4,4-dimethyl-5-isopropyl-2-(3*H*)-furanone (stereoisomer 2), 124508-47-0; dihydro-3-((2-isopropyl-5-methylcyclohex-1-yl)carbonyldioxy)-*N*-methyl-2*H*-indol-2-one, 124402-22-8; polyketone reductase, 37211-75-9; chloroformic acid (1*R*,2*S*,5*R*)-(−)-5-methyl-2-(1-methylethyl)cyclohexanol ester, 14602-86-9; *N*-(1-phenylethyl)-2-phenylbutyramide (stereoisomer 1), 60418-69-1; *N*-(1-phenylethyl)-2-phenylbutyramide (stereoisomer 2), 17430-18-1.