Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 8, pp. 2313-2320, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00286-8

Chemoenzymatic Synthesis of a Versatile Cyclopentenone: (+)-(3a*S*,6a*S*)-2,2-Dimethyl-3aβ,6aβ-dihydro-4*H*-cyclopenta-1,3-dioxol-4-one

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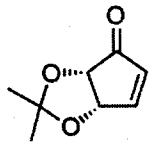
Abstract: The title cyclopentenone has been prepared by enzymatic resolution of *cis*-4-phenyloxy- and *cis*-4-(4-methoxyphenyloxy)-cyclopent-2-en-1-ol in isopropenyl acetate using *Pseudomonas cepacia* lipase. The use of a 4-methoxyphenyloxy-alcohol intermediate enabled the use of both enzymatically resolved enantiomers in the synthesis of the desired (+)-enone. Copyright © 1996 Elsevier Science Ltd

Enantiomerically pure enone (+)-**1** has seen many synthetic applications. For example, it has been used as a centerpiece in prostaglandin synthesis,[1] in the preparation of nucleoside analogues and 4-substituted riboses[2a,b] or sugar analogues.[3]

Various syntheses of enone (+)-**1** and its enantiomer have been developed in our and in other laboratories.[4a-f] The syntheses of the enantiopure enone (+)-**1** starting from cyclopentadiene described herein are based on modifications of the procedure from Siddiqi *et al.*[5] and make use of an enzymatic resolution of racemic aryloxy-alcohol intermediates **2**. These routes, amenable to large scales, represent convenient alternatives to the asymmetrization of the meso product of singlet oxygen addition to cyclopentadiene followed by thiourea reduction of the endoperoxide.[1,4d]



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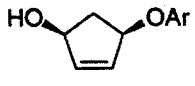
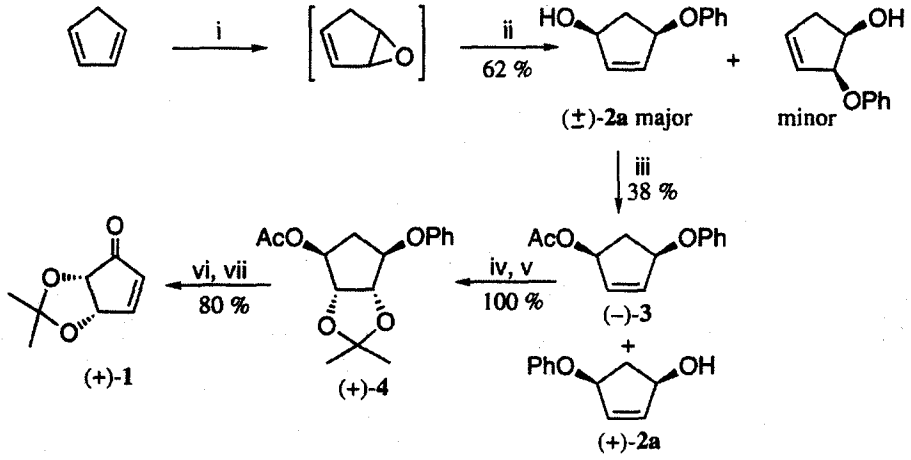


(±)

2a Ar = phenyl
b Ar = 4-methoxyphenyl

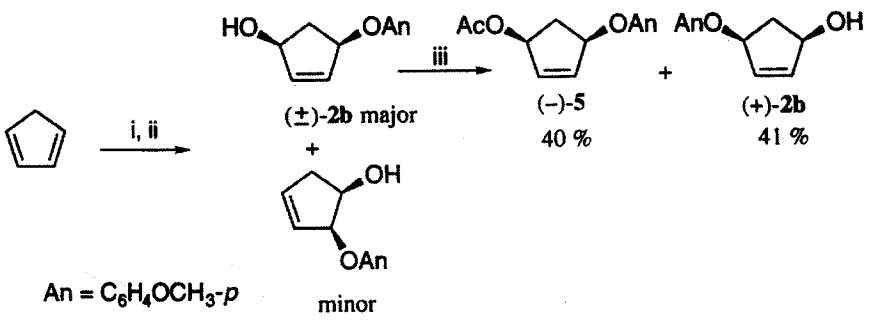
In the first synthesis,[6] cyclopentadiene was treated with peracetic acid to afford the intermediate epoxide, which was treated in situ with phenol in the presence of catalytic Pd(0), to afford the racemic phenoxy-alcohol **2a** in 62 % yield (Scheme 1). A minor product was observed in 7 % yield, with spectral data compatible with the structure, *cis*-2-phenoxycyclopent-3-en-1-ol.[7] The slightly impure phenoxy alcohol **2a** obtained after distillation of the crude mixture was treated with *Pseudomonas cepacia* lipase (Amano PS-30) (10 % by weight) in 1.6:1 hexanes:isopropenyl acetate, to provide a mixture of enantiomerically enriched phenoxy acetate (–)-**3** (95-97 % ee) and phenoxy alcohol (+)-**2a**. These products were separated by a combination of crystallization and chromatography. The phenoxy acetate (–)-**3** ($[\alpha]^{25}_D$ -32.5 (*c*1.0, acetone)) was obtained as a pure enantiomer after a single recrystallization from hexanes. Acetate (–)-**3** was quantitatively converted to the intermediate (+)-**4** by osmium-catalyzed *N*-methylmorpholine *N*-oxide (NMO) dihydroxylation and diol protection. The enone (+)-**1** ($[\alpha]^{25}_D$ +68.7 (*c*1.0, $CHCl_3$)) was obtained upon cleavage of the acetate moiety and subsequent chromium-based oxidation of the resulting alcohol using a catalytic amount of pyridine to favor the elimination of phenol.



Scheme 1 *Reagents and Conditions:* i, AcOOH, Na_2CO_3, 0 °C; ii, $Pd(PPh_3)_4$, PhOH; iii, Amano PS-30 lipase, isopropenyl acetate, 50 °C; iv, OsO_4, NMO; v, dimethoxypropane, acetone, TsOH; vi, KOH, MeOH; vii, PCC, cat. pyridine.

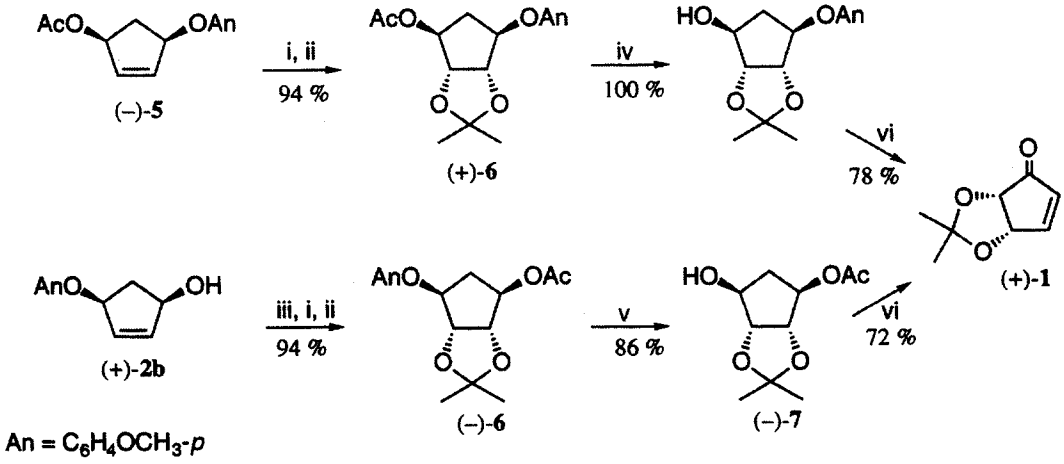
However convenient the above method may be, it suffers the drawback of conversion of only 50 % at best of the racemic material **2a** to enone (+)-**1**. A further refinement was devised that allows use of both pure enantiomers issuing from the enzymatic resolution towards the synthesis of the enone (+)-**1**.

In a sequence similar to that previously mentioned, the epoxide formed from cyclopentadiene was treated with *p*-methoxyphenol in the presence of Pd(0) to afford the racemic intermediate **2b** in 51 % yield. As in the previous case, a minor unwanted isomer was also observed in 11 % yield.[7] The pure racemic **2b** obtained after distillation and recrystallization was then treated with Amano PS-30 lipase (20 % by weight) in a 50:1 mixture of isopropenyl acetate and acetonitrile at 50 °C. The enantiomerically enriched *p*-methoxyphenyloxy acetate (–)-**5** and alcohol (+)-**2b** were isolated (Scheme 2).



Scheme 2 *Reagents and Conditions:* i, AcOOH, Na_2CO_3, 0 °C; ii, $Pd(PPh_3)_4$, 4-methoxyphenol; iii, Amano PS-30 lipase, isopropenyl acetate, 50 °C.

The alcohol (+)-**2b** was converted to the corresponding acetate (+)-**5**. The initial enantiomeric excesses of 87 to 90 % were improved by recrystallization of (–)-**5** and (+)-**5** from pentane, to obtain pure enantiomers ($[\alpha]^{25}_D$ -33.6 (*c*2.15, acetone) and $[\alpha]^{25}_D$ +34.3 (*c*1.84, acetone), respectively). The advanced intermediates (+)-**6** and (–)-**6** were then obtained using OsO_4/NMO in the key oxidation step; (+)-**5** was converted to (–)-**6** ($[\alpha]^{25}_D$ -6.69 (*c*2.03, acetone))and (–)-**5** to (+)-**6** ($[\alpha]^{25}_D$ +6.51 (*c*1.95, acetone)). (+)-**6** was transformed into enone (+)-**1** ($[\alpha]^{25}_D$ +68.6 (*c*1.1, $CHCl_3$)) upon cleavage of the acetate group and oxidation of the resulting secondary alcohol by PCC/pyridine, followed by recrystallization. The intermediate (–)-**6** was first converted to the hydroxy acetate (–)-**7** upon cleavage of the *p*-methoxyphenyl moiety using ceric ammonium nitrate.[8] The enone (+)-**1** ($[\alpha]^{25}_D$ +68.1 (*c*1.1, $CHCl_3$)) was obtained after oxidation of (–)-**7** by PCC/pyridine and recrystallization (Scheme 3).



Scheme 3 *Reagents and Conditions:* i, OsO_4, NMO; ii, dimethoxypropane, acetone, TsOH; iii, Ac_2O, pyridine; iv, KOH, MeOH; v, ceric ammonium nitrate, H_2O-MeCN; vi, PCC, cat. pyridine.

The phenol based synthesis of enone (+)-**1** is an obvious improvement, since it is not only efficient, but also convenient. However, the overall yield from the racemic phenoxy alcohol **2a** is only 34 %, a drawback

inherent to the enzymatic resolution. The further improved method using *p*-methoxyphenol (Scheme 2) seems even more promising; by making use of both enantiomers, the overall yield of enone (+)-**1** is increased to 60 % from the racemic intermediate **2b**.

EXPERIMENTAL SECTION

(±)-*cis*-4-Phenyloxy-2-cyclopenten-1-ol (2a). Dicyclopentadiene (400 g) was heated at 160-170 °C in a distillation apparatus. Cyclopentadiene was distilled at 40 to 55 °C at a rate of approximately 0.5 g/min, and immediately cooled to -78 °C in the receiving flask; 187 g (2.83 mol) of the monomer was collected. Excessive heating was avoided in order to minimize distillation of the dimer.

To peracetic acid (500 mL, 32 wt%, 2.17 mol) was added sodium acetate (25 g) and the mixture was set aside until dissolution was complete. To a 5-L flask equipped with a mechanical stirrer, an addition funnel and a Dry Ice condenser was added CH_2Cl_2 (1.8 L) and Na_2CO_3 (1 Kg), the mixture was cooled to 0 °C in an ice bath. To this cooled solution was added cold cyclopentadiene (187 g, 2.83 mol) and then the buffered peracetic acid solution was added dropwise via the addition funnel over a period of 2 h (a short induction period was observed then rapid CO_2 evolution occurred with extensive solvent condensation on the condenser). After the addition was complete, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 2 h, at which time gas evolution had ceased. The suspension was filtered and the salts were washed with CH_2Cl_2 (700 mL). The filtrate, containing the crude cyclopentadiene monoepoxide, was dried over $MgSO_4$, filtered, degased with bubbling nitrogen and cooled to 0 °C. To a flame dried 5-L flask was added $(Ph_3P)_4Pd$ (2.0 g), phenol (235 g, 2.44 mol) and dry THF (1.5 L); the mixture was cooled to 0 °C. To this cooled mixture under nitrogen, the cooled mixture containing the monoepoxide was then added via canula, and the reaction mixture was stirred for 12 h. Air was then bubbled through the solution for a few minutes and the solution was concentrated. The residue was distilled 0.05 to 0.1 mmHg; phenol was collected between 45 and 80 °C and the mixture of desired *cis*-1,4-phenoxy alcohol **2a** and unwanted (±)-*cis*-2-phenyloxy-3-cyclopenten-1-ol in a 15:1 ratio was collected between 110 and 130 °C (237 g, 1.35 mol, 62 %). The composition of the distillate fractions was determined by GC. The mixture of **2a** (mp 43-44 °C) and (±)-*cis*-2-phenyloxy-3-cyclopenten-1-ol (mp 47 °C) (15:1) could be separated on smaller scales by column chromatography (hexanes and EtOAc, 10:1 to 4:1).

(2a): ^{1}H NMR ($CDCl_3$) 1.79 (dt, 1H, J = 3.9, 14.4 Hz), 2.65 (d, 1H, J = 8.4 Hz), 2.87 (ddd, 1H, J = 7.5, 7.5, 15.0 Hz), 4.71-4.77 (m, 1H), 5.09-5.13 (m, 1H), 6.12-6.16 (m, 2H), 6.90-7.00 (m, 3H), 7.76-7.33 (m, 2H). ^{13}C NMR ($CDCl_3$) 41.1, 74.6, 79.8, 115.5, 120.7, 129.4, 132.6, 138.2,157.7.

(±)-*cis*-2-phenyloxy-3-cyclopenten-1-ol: ^{1}H NMR ($CDCl_3$) 2.47-2.55 (m, 1H), 2.65-2.69 m, 1H), 2.70-2.73 (d, 1H, J = 6.6 Hz), 4.54-4.62 (m, 1H), 5.06-5.10 (d, 1H), 5.92-5.97 (m, 1H), 6.07-6.12 (m, 1H), 6.97-7.03 (m, 3H), 7.28-7.34 (m, 2H). ^{13}C NMR ($CDCl_3$) 39.9, 70.9, 81.7, 115.8, 121.5, 128.4, 129.6, 134.9, 157.9.

(±)-*cis*-4-(4-Methoxyphenyloxy)-2-cyclopenten-1-ol (2b). The same procedure as above was followed dicyclopentadiene (100 g) and *p*-methoxyphenol (76 g, 0.61 mol) instead of phenol. Distillation at 1.5 mmHg gave a first fraction containing *p*-methoxyphenol at 110 °C, a second fraction containing the desired aryloxy alcohol **2b** between 120 and 150 °C, and a mixture of the desired **2b** and unwanted (±)-*cis*-2-(4-

Methoxyphenyl)-3-cyclopenten-1-ol (mp 128 °C) between 150 and 170 °C. The second fraction containing *p*-anisyloxy alcohol **2b**, mp 72-73 °C, (57 g, 51 %) was found to be contaminated with 8 % *p*-methoxyphenol but no trace of 1,2 isomer was observed.

(2b): ^{1}H NMR ($CDCl_3$) 1.78 (dt, 1H, J = 3.8, 14.4 Hz), 1.98 (d, 1H, J = 8.9 Hz), 2.83 (ddd, 1H, J = 7.2, 7.3, 14.5 Hz), 3.77 (s, 3H), 4.73 (m, 1H), 5.03 (ddd, 1H, J = 0.7, 3.7, 6.7 Hz), 6.13 (s, 2H), 6.84 (d, 4H, J = 1.89 Hz). ^{13}C NMR ($CDCl_3$) 41.3, 55.7, 75.1, 80.8, 114.7, 116.7, 133.3, 138.1, 151.9, 154.0.

(±)-*cis*-2-(4-Methoxyphenyl)-3-cyclopenten-1-ol: ^{1}H NMR (CD_3OD) 2.36-2.43 (m, 1H), 2.63-2.73 (m, 1H), 3.69 (s, 3H), 4.18-4.21 (m, 1H), 4.62 (td, J = 2.2, 5.8 Hz), 5.74-5.77 (m, 1H), 5.91-5.95 (m, 1H), 6.60-6.72 (m, 4H). ^{13}C NMR (CD_3OD) 42.5, 52.0, 56.1, 74.1, 113.5, 116.5, 130.6, 133.1, 150.6, 154.4.

(–)-(1*S*,4*R*)- and (+)-(1*R*,4*S*)-4-Phenyloxy-2-cyclopenten-1-yl Acetate (3). To the crude phenoxy alcohols (128 g, 730 mmol) containing 90 % 1,4-phenoxy alcohol **2a**, 5 % 1,2-phenoxy alcohol and 3 % phenol (as determined by GC) was added isopropenyl acetate (500 mL) and hexanes (800 mL) and PS-30 Lipase (13 g). The suspension was heated at 40-45 °C and stirred for 24 h. The chemical conversion was determined by gas chromatography using a packed column (5 % phenyl 95 % methyl polysiloxane on Chromasorb W) after filtration of a small aliquot through Celite and rinsing with EtOAc. The time required for the resolution to be completed varied between 12 and 24 h. When the GC area% of the acetate to that of the alcohol reached 57:43 (as it is the case in a previously prepared standard mixture of racemic **2a** and **3** in a 1:1 molar ratio) the enzymatic resolution was stopped; the suspension was filtered through Celite and concentrated to dryness to give a semi-solid. Chiral HPLC showed that both (–)-**3** and (+)-**2a** had an enantiomeric excess superior to 95 % (column ChiralcelOB, 1.5 % EtOAc in hexanes).[9] The residue was dissolved in hot ethanol (600 mL) to which was added hot water (300 mL); crystals formed as the mixture was allowed to cool slowly. Filtration and washing the crystals with a mixture of cold ethanol and water (1:1) gave the phenoxy acetate (–)-**3** (47 g, 30 %). The mother liquor was concentrated and extracted with CH_2Cl_2. Column chromatography gave additional phenoxy acetate (–)-**3** (17 g, 11 %), and 1,4 alcohol (+)-**2a** (62 g, 48 %), $[\alpha]_D^{20}$ +5.6 (*c* 1.0, acetone). A single recrystallisation of the combined fractions of phenoxy acetate (–)-**3** from hot hexanes yielded a product with ee>98 %, $[\alpha]_D^{20}$ -32.5 (*c* 1.0, acetone), mp 75 °C, in 38 % yield. The pure acetate enantiomer (+)-**3**, $[\alpha]_D^{20}$ +32.9 (*c* 1.0, acetone), mp 75 °C, (64.8 g, 298 mmol, 40 % from the racemic phenoxy alcohol) was obtained from the phenoxy alcohol (+)-**2a** (62 g, 352 mmol) by acylation with Ac_2O (42 mL), triethylamine (78 mL) in CH_2Cl_2 with a catalytic amount of dimethylaminopyridine, followed by recrystallization from hot hexanes.

(3): ^{1}H NMR ($CDCl_3$) 1.90 (dt, 1H, J = 4.0, 14.4 Hz), 2.06 (s, 3H), 2.99 (ddd, J = 7.2, 7.2, 14.4 Hz), 5.20 (m, 1H), 5.62 (m, 1H), 6.14 (m, 1H), 6.25 (m, 1H), 6.92-7.00 (m, 3H), 7.28-7.33 (m, 2H). ^{13}C NMR ($CDCl_3$) 21.0, 37.9, 76.7, 79.5, 115.3, 120.9, 129.5, 134.0, 135.0, 157.7, 171.0.

(–)-(1*S*,4*R*)- and (+)-(1*R*,4*S*)-4-(4-Methoxyphenyloxy)-2-cyclopenten-1-yl Acetate (5). To the phenoxy alcohol **2b** (30 g, 146 mmol) containing 8 % *p*-methoxyphenol (as determined by GC) was added isopropenyl acetate (250 mL), acetonitrile (5 mL) and PS-30 lipase (6 g).[10] The suspension was heated at 50-55 °C and stirred for 15 h. The chemical conversion was determined by gas chromatography using a packed column (5 % phenyl 95 % methyl polysiloxane on Chromasorb W) after filtration of a small aliquot through

Celite and rinsing with EtOAc. The time required for the resolution to be completed varied between 14 and 16 h. When the GC area% of the acetate to that of the alcohol reached 51:49 (as it is the case in a previously prepared standard mixture of racemic **2b** and **5** in a 1:1 molar ratio) the enzymatic resolution was stopped: the suspension was filtered through Celite and concentrated to dryness to give a semi-solid. Column chromatography (petroleum ether : ethyl acetate 6:1 to 2:3) gave (+)-**2b** (15 g, 50 %) and a mixture of (–)-**5** and *p*-methoxyphenol. This mixture was dissolved in EtOAc, washed with 1N NaOH (2 x 50 mL), dried and concentrated to give (–)-**5** (17.4 g, 48 %). The aryloxy acetate (–)-**5** obtained was shown to have an enantiomeric excess of 85 % by chiral HPLC. The enantiomeric excess was improved upon a single recrystallization from pentane: (–)-**5**, mp 48-49 °C, $[\alpha]_D^{20}$ -31.0 (*c* 2.0, acetone), chiral HPLC indicated an optical purity superior to 99 % ee, was obtained in 40 % yield based on the starting racemic material. The aryloxy alcohol (+)-**2b** (15 g, 73 mmol) was quantitatively converted to the corresponding acetate (+)-**5** upon treatment with triethylamine (15.2 mL, 109 mmol), acetic anhydride (8.4 mL, 88 mmol) in THF (300 mL). The (+)-**5** thus obtained had an optical purity of 86% ee (chiral HPLC), which was improved to over 99% after a single recrystallization from pentane: (+)-**5**, mp 48-49 °C, $[\alpha]_D^{20}$ +31.3 (*c* 1.5, acetone) was obtained in a 41 % overall yield from the starting racemic aryloxy alcohol **2b**.

(–)-(**5**): ^{1}H NMR ($CDCl_3$) 1.87 (dt, 1H, *J* = 3.9, 14.6 Hz), 2.05 (s, 3H), 2.93 (ddd, 1H, *J* = 7.4, 7.4, 14.6 Hz), 3.77 (s, 3H), 5.08 (m, 1H), 5.59 (m, 1H), 6.10 (m, 1H), 6.22 (m, 1H), 6.84 (m, 4H). ^{13}C NMR ($CDCl_3$) 21.1, 37.9, 55.6, 76.7, 80.5, 114.4, 114.7, 116.7, 133.8, 135.3, 151.9, 154.1, 170.7. HRMS 248.1048 (exp.) 248.1054 (found).

(+)-(3a*R*,6a*S*,4*S*,6*R*)-2,2-Dimethyl-6-phenyloxy-3aβ,6aβ,5,6-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-yl Acetate (4). To the phenoxy acetate (–)-3 (46.5 g, 213 mmol) was added acetone (300 mL), water (100 mL), *N*-methylmorpholine-*N*-oxide (85 mL, 436 mmol) and OsO_4 (9 mL of 0.01 g/mL in THF). The solution slowly became homogeneous and was stirred for 24 h. Acetone was then removed under reduced pressure, EtOAc (100 mL) was added and again the reaction mixture was concentrated. The residue was cooled to 0 °C and saturated sodium bisulfite (100 mL) was added and the mixture was stirred for 15 min., then extracted with EtOAc (6 x 150 mL). The combined organics were dried ($MgSO_4$) and concentrated. To the crude diol was added dimethoxypropane (175 mL), acetone (175 mL) and TsOH (1g), and the solution was stirred for 18 h. A saturated solution of $NaHCO_3$ (5 mL) was added and the mixture was concentrated. The residue was dissolved in hexanes/ether (500 mL, 1:1) and was washed with water (3 x 25 mL) and dried. Filtration through 30 g of silica gel, rinsing with ether and concentration gave 62.2 g (100 %) of the very stable and crystalline intermediate (+)-**4**, $[\alpha]_D^{20}$ +10.7 (*c* 2.1, acetone), mp 58-60 °C.

(+)-(**4**): ^{1}H NMR ($CDCl_3$) 1.31 (s, 3H), 1.49 (s, 3H), 2.16 (dd, 1H, *J* = 1.5, 15.3 Hz), 2.45 (dt, 1H, *J* = 5.4, 15.5 Hz), 4.68-4.75 (m, 3H), 5.13 (d, 1H, *J* = 5.1 Hz), 6.89-7.00 (m, 3H), 7.28-7.33 (m, 2H). ^{13}C NMR ($CDCl_3$) 21.1, 24.0, 26.4, 34.1, 78.8, 81.2, 84.0, 84.4, 111.0, 115.4, 121.1, 129.6.

(+)-(3a*R*,6a*S*,4*S*,6*R*)-2,2-Dimethyl-6-(4-methoxyphenyl-oxy)-3aβ,6aβ,5,6-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-yl Acetate and (–)-(3a*R*,6a*S*,4*S*,6*R*)-2,2-Dimethyl-4-(4-methoxyphenyl-oxy)-3aβ,6aβ,5,6-tetrahydro-4*H*-cyclopenta-1,3-dioxol-6-yl Acetate (6). The same procedure as above was followed on both enantiomers (+)-**5** and (–)-**5**, affording the corresponding

intermediates (–)-**6** (mp 46-47 °C, $[\alpha]_D^{20}$ -6.7 (*c* 2.0, acetone)) and (+)-**6** ($[\alpha]_D^{20}$ +6.9 (*c* 2.0, acetone)) respectively, in a yield of 94 % on 60 mmol scales.

(**6**): ^{1}H NMR ($CDCl_3$) 1.30 (s, 3H), 1.47 (s, 3H), 2.05 (s, 3H), 2.12 (dt, 1H, *J* = 1.5, 15.3 Hz), 2.40 (dt, 1H, *J* = 5.45, 15.4 Hz), 3.77 (s, 3H), 4.64-4.73 (m, 3H), 5.10 (d, 1H, *J* = 5.0 Hz), 6.83 (s, 4H). ^{13}C NMR ($CDCl_3$) 21.1, 24.0, 26.3, 34.0, 55.6, 78.8, 81.95, 84.0, 84.4, 111.0, 114.7, 116.5, 151.0, 154.1, 170.2. HRMS: 322.1416 (exp.), 322.1417 (found).

(–)-(3a*R*,6a*S*,4*S*,6*R*)-2,2-Dimethyl-6-acetoxy-3aβ,6aβ,5,6-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-ol (7).

Acetate(–)-**6** (4.0 g, 12.4 mmol) was dissolved in 200 mL of a mixture of acetonitrile:water (4:1) and cooled to 0 °C. Ceric ammonium nitrate (17 g, 31 mmol) was added in one portion, and the reaction mixture was stirred at 0 °C for 5 min., and then was partitioned between 200 mL of EtOAc and 200 mL of brine. The phases were separated, the aqueous phase was extracted with 2 portions of 250 mL EtOAc. Column chromatography (2.5:1 petroleum ether:EtOAc) afforded (–)-**7** (2.3 g, 86 % yield, $[\alpha]_D^{20}$ -25.7 (*c* 2.0, acetone)) as a thick colorless oil.

(–)-(**7**): ^{1}H NMR ($CDCl_3$) 1.26 (s, 3H), 1.39 (s, 3H), 1.85 (dm, 1H, *J* = 15.3 Hz), 2.05 (s, 3H), 2.32 (dt, 1H, *J* = 5.2, 15.3 Hz), 2.82 (bs, 1H), 4.21 (d, 1H, *J* = 4.9 Hz), 4.59 (m, 2H), 5.11 (d, 1H, *J* = 5.4 Hz). ^{13}C NMR ($CDCl_3$) 21.1, 23.8, 26.2, 36.2, 76.8, 79.55, 84.2, 86.2, 110.7, 169.7.

(+)-(3a*S*,6a*S*)-2,2-Dimethyl-3aβ,6aβ-dihydro-4*H*-cyclopenta-1,3-dioxol-4-one (1).

(a) From 4. To **4** (5.00 g, 17 mmol) was added MeOH (60 mL) and KOH (5 pellets). The solution was stirred for 30 min. at room temperature, and neutralized with 2M HCl, then concentrated. The crude alcohol was dissolved in Et_2O (30 mL) and filtered through a pad of silica gel and concentrated to give 4.33 g (100 %) of alcohol. To this alcohol was added CH_2Cl_2 (150 mL), activated powdered molecular sieves (20 g), PCC (10 g) and pyridine (1 mL). After completion, addition of an equivalent volume of Et_2O was added and the mixture was filtered through a layer of sand and Florisil. Rinsing with Et_2O (100 mL), concentration and column chromatography gave phenol and enone **1** (2.39 g, 15.5 mmol, 91 %). Recrystallization from hexanes and CH_2Cl_2 gave 2.1 g (80 % yield), of colorless needles, mp 69-70 °C, $[\alpha]_D^{20}$ +68.7 (*c* 1.0, chloroform) (lit[4d] $[\alpha]_D^{20}$ +71.8, *c* 0.92, $CHCl_3$).

(+)-(**1**): ^{1}H NMR ($CDCl_3$) 1.39 (s, 6H), 4.44 (d, 1H, *J* = 5.5 Hz), 5.25 (dd, 1H, *J* = 1.95, 5.5 Hz), 6.19 (d, 1H, *J* = 5.85 Hz), 7.59 (dd, 1H, *J* = 2.25, 6.0 Hz). ^{13}C NMR ($CDCl_3$) 26.1, 27.3, 76.4, 78.5, 115.5, 134.2, 159.6, 202.9.

(b) From (+)-6. The same procedure was followed from (+)-**6** (5.5 g, 17 mmol) to afford enone (+)-**1**, $[\alpha]_D^{20}$ +68.6 (*c* 1.2, chloroform), in 72 % yield. After filtration and evaporation, the crude mixture was dissolved in 100 mL CH_2Cl_2 and washed with 2 portions of 50 mL of 2N NaOH before chromatography to eliminate most of the *p*-methoxyphenol formed in the reaction.

(c) From 7. The aforementioned oxidation conditions were repeated on the enone precursor (–)-**7** (5.5 g, 25 mmol), and afforded the enone (+)-**1**, $[\alpha]_D^{20}$ +68.1 (*c* 1.1, chloroform), in 78 % yield.

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7. The spectral data provide an easy method of identification of the minor and the major product of the reaction. The signals for the two olefinic protons coincide in the major components **2a** and **2b** (6.12-6.16 ppm and 6.13 ppm, respectively), indicating a sense of symmetry absent in the minor components, in which either of the olefinic proton has a distinct chemical shift..

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9. When conducting this reaction, two points should be noted. Although the alcohol (+)-**2a** $[\alpha]_D^{20}$ +5.6 (*c* 1.0, acetone) and (±)-*cis*-2-phenyloxy-3-cyclopenten-1-ol $[\alpha]_D^{20}$ -152 (*c* 1.0, acetone) are separable by chromatography, the corresponding acetates are not; therefore, optical rotation can not be used to check the ee of the crude solid phenoxy acetate (–)-**3** obtained directly from the enzyme reaction by column chromatography, since a small amount of *vic*-phenoxy acetate ($[\alpha]_D^{20}$ +188 (*c* 1.0, acetone)) can significantly alter the observed rotation. Chiral HPLC analysis shows the crude phenoxy acetate (–)-**3** to be 95 to 97% ee, and indicates that the *vic*-phenoxy acetate, both enantiomers of the phenoxy acetate **3** and traces of phenol are contained only in the mother liquor.

10. The phenoxy alcohol **2b** does not have sufficient solubility in the hexanes:isopropenyl acetate system that was used for the enzymatic resolution of the phenoxy alcohol **2a**. Therefore the system isopropenyl acetate:acetonitrile was chosen, in which the amount of acetonitrile used is the minimal amount required to achieve dissolution of the substrate and maintain a comparable substrate concentration

(*Received in USA* 13 *May* 1996; *accepted* 18 *June* 1996)