# Stereoselective synthesis of (-)-pestalotin

**A. Shashidhar Kumar, Pushpal Bhaket, and B. Venkateswara Rao***

*Division of Organic Chemistry, Indian Institute of Chemical Technology*
*Hyderabad - 500 007, India*
*E-mail: venky@iict.res.in*

**Dedicated to Dr. A.V. Rama Rao on the occasion of his 70th birthday**

**(received 16 Jul 04; accepted 05 Nov 04; published on the web 12 Nov 04)**

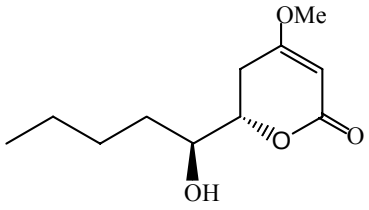
**Abstract**

The asymmetric synthesis of (-)-pestalotin is described using $OsO_4$-catalyzed asymmetric dihydroxylation and utilization of substituted aromatic system as a masked β-ketoester as the key steps in the reaction sequence.

**Keywords:** Asymmetric dihydroxylation, Birch reduction, ozonolysis

## Introduction

Pestalotin **1**, a gibberellin synergist, was first discovered by Kimura *et al*[1] from a culture broth of *Pestalotia Cryptomeriaecola* Sawada, which is a fungus pathogenic for the Japanese cedar, *Cryptomeria japonica*. Later, Ellestad *et al*[2] also isolated **1** as a minor metabolite from the fermentation culture P880, an unidentified penicillium species and gave the code LLP-880α. The 6-substituted 5,6-dihydro-2-pyrone skeleton in pestalotin **1** which also occurs in many natural products show diverse biological activity[3].




**(-)-Pestalotin 1**

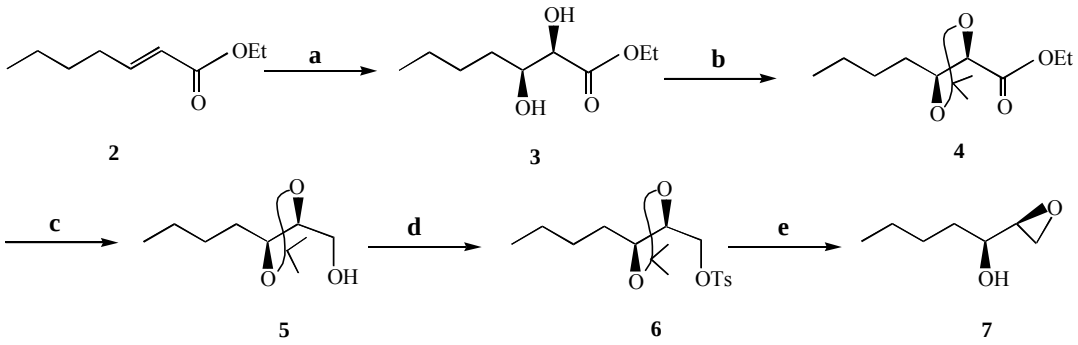
The presence of two contiguous stereogenic centers in (-)-pestalotin **1** has made it an attractive synthetic target since its discovery. Several synthesis of racemic[1c,4a-c] and optically active forms

[4d-p] of pestalotin have been reported. In most of these syntheses the two chiral centers were built stepwise and also in some cases low stereoselectivity was observed.

In connection with our interest in utilizing substituted aromatic system as masked, 1,3-dione or 1,3-diol and 1,5-dione in the synthesis of natural products[5], we report here a facile synthesis of (-)-pestalotin where the *m*-methoxy substituted benzene was utilized as a masked β-ketoester in turn to obtain the pyranone skeleton of compound **1**. Also in our approach the asymmetric dihydroxylation (AD) developed by Sharpless was used to get the two chiral centers present in **1**.

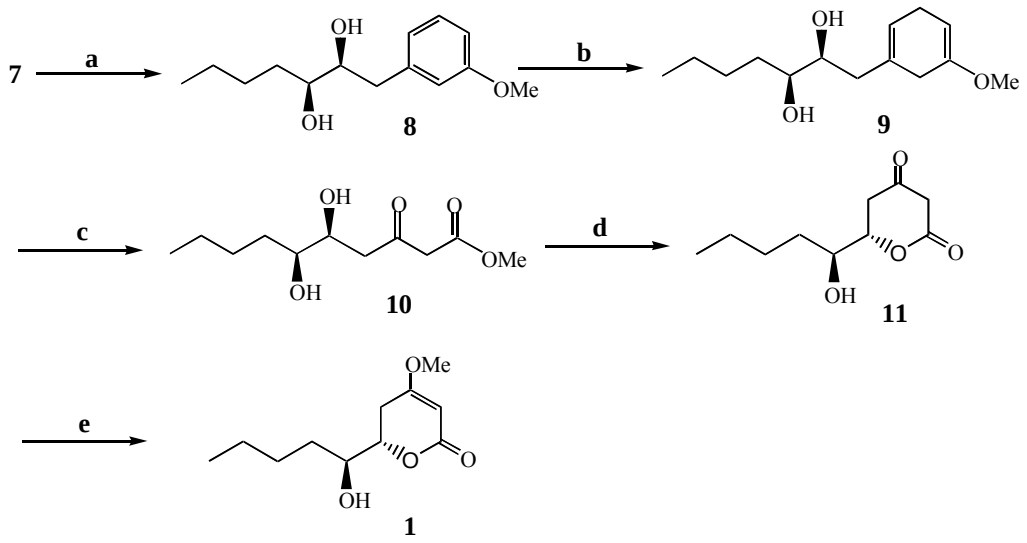
## Results and Discussion

Our synthesis commenced with the $OsO_4$ catalyzed asymmetric dihydroxylation (AD)[6a,b] of (E)-Ethyl-2-heptenoate[7] **2** using 1,4-bis(dihydroquinin-9-*O*-yl)phthalazine [$(DHQ)_2$-PHAL] as chiral ligand to afford the dihydroxyester **3** (scheme 1). It is well known that the straight chain α,β-unsaturated ester undergoes dihydroxylation with high enantioselectivity.[8] Compound **3** when exposed to 2,2-dimethoxy propane in the presence of catalytic PTSA gave **4**.




**Scheme 1.** *Reagents and conditions:* (a) $OsO_4$. $(DHQ)_2$-PHAL, $K_3FeCN_6$, $K_2CO_3$, $CH_3SO_2NH_2$, t-BuOH/$H_2O$ (1:1), 16 h, 0°C, 71%, 97.35% ee; (b) 2,2 DMP, cat. *P*-TsOH, $CH_2Cl_2$, rt, 16 h, 98%; (c) LiCl, $NaBH_4$, EtOH, THF, 0°C to rt, 16 h, 76%; (d) TsCl, $Et_3N$, cat. DMAP, $CH_2Cl_2$, 0°C to rt, 4 h, 85%; (e) i. *P*-TsOH, MeOH:$H_2O$ (4:1), rt, 20 h; ii.$K_2CO_3$, MeOH/$H_2O$ (6:1), 19 h, rt, 68% (for two steps).

The ester **4** was smoothly reduced by $LiBH_4$[9], generated in situ, to afford the alcohol **5**. The sulfonate ester **6** was readily prepared from **5** using *p*-toluene sulfonyl chloride, triethylamine and DMAP (catalytic).




**Scheme 2.** *Reagents and conditions:* (a) Mg, *m*-bromo anisole, cat. Cul, THF, -20°C, 3.5 h, 75.4%; (b) Li (80 eq)/liq.$NH_3$, THF, -78°C, EtOH, 1 h; (c) $O_3$, $CH_2Cl_2$, Sudan-III, -78°C, $Me_2S$, 30 min.; (d) NaOH, THF, rt, 1.5 h, 10% (overall yield for three steps, 47%, average yield for each step); (e) $Me_2SO_4$, $K_2CO_3$, $CH_3COCH_3$, rt, 14 h, 60%.

Deprotection of the isopropylidene moiety of **6** in acid medium followed by basification with $K_2CO_3$ in MeOH/$H_2O$ afforded the epoxy alcohol **7,** whose NMR spectral data ($^1H$ and $^{13}C$) was well in agreement with the reported data.[10] When compound **7** was subjected to nucleophilic epoxide ring opening with *m*-methoxyphenyl magnesium bromide in the presence of catalytic CuI[11], gave **8** (Scheme 2).

The crucial intermediate, β-keto ester **10** was unmasked from **8** via Birch reduction-ozonolysis sequence.[5,12] Accordingly, when **8** was treated with Li/liq.$NH_3$, EtOH the dihydroanisole intermediate **9** was produced. Ozonolytic cleavage[13,12d] was performed on the unpurified Birch product to give the β-keto ester **10,** which was carried to the next step without any purification. The δ- lactone **11** was obtained from **10** by treatment with 1N aqueous NaOH solution which was subsequently methylated using dimethyl sulphate to furnish, the (-)-pestalotin **1** as a white solid after recrystallization [Hexane:Benzene (1:1)]. The NMR ($^1H$,$^{13}C$) spectral data of the synthetic sample were consonant with those of the reported product.[1a,c,14]

## Conclusions

In summary, we have accomplished the synthesis of (-)-pestalotin using asymmetric dihydroxylation and Birch reduction-ozonolysis sequence of *m*-substituted anisyl ring as latent β-keto ester synthons for generating the 6-substituted 5,6-dihydro-2-pyrone unit. Use of *m*-Anisole

unit as a masked form of β-ketoester has an advantage it can be introduced easily in to the skeleton and can be converted to β-keto ester at an appropriate stage in two step sequence.

## Experimental Section

**General Procedures.** TLC was performed on Merck Kieselgel 60, $F_{254}$ plates (layer thickness 0.25mm). Column Chromatography was performed on silica gel (60-120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer RX-1FT-IR system, In the case of syrups and liquids IR spectra was recorded by adding a drop of solution of compound in chloroform on KBr pellet. $^1$H NMR (200 MHz), (400 MHz) and $^{13}$C NMR (50 MHz) spectra were recorded on Varian Gemini-200 MHz and Varian Unity 400 MHz spectrometers.$^{13}$C NMR (75 MHz and 125 MHz) spectra were recorded on Bruker Avance-300 MHz and DRX-500 MHz spectrometers. Optical rotations were measured with Jasco-Dip-360 digital polarimeter. The mass spectra were recorded on (VG MICROMASS-7070H) at 70 eV using a direct inlet system. The LSIMS (FAB) spectra were recorded on VG AUTOSPEC instrument at the structure (M+H) at m/z. Elemental analyses were performed by Elementar analyser ; Vario EL( Model)(Germany).

**Ethyl-2,3-dihydroxy-(2R, 3S)-heptanoate (3).** To a solution of $(DHQ)_2$-PHAL ligand (0.249 g, 0.32 mmol), potassiumferricyanide (31.63 g, 96.14 mmol), potassium carbonate (13.2 g, 96.15 mmol), $OsO_4$ (0.325 mL, 0.2 mol%) and methane sulfonamide (3.04 g, 32.04 mmol) in a 1:1 mixture of t-BuOH:$H_2O$ (50:50 mL) was added (E)-ethyl-2-heptenoate **2** (5 g, 32.05 mmol) at $0^0$C and the mixture was stirred for 16 h. The reaction was quenched by slow addition of sodium sulphite (20 g) and the suspension was warmed to room temperature, while stirring vigorously. After 45 min, EtOAc (40 mL) was added and the aqueous layer was further extracted with EtOAc ( 60 mL). The combined organic layers were washed with 2N aq KOH solution (56.11 g in 500 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc-hexane (1:4) to afford the pure product **3** (4.295 g, 71%) as a colourless liquid. $[\alpha]_D^{25}$ –9.21 (*c* 1, $CHCl_3$); IR (KBr, cm$^{-1}$) 3413, 2957, 2867.5, 1737, 1464, 1375, 1209, 1137, 1090, 1029; $^1$H NMR (200 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.0 Hz, $CH_3$ $(CH_2)_3$-), 1.22-1.65 (9H, m, $CH_3$ $(CH_2)_3$- and –$OCH_2CH_3$), 1.85 (1H, d, *J* = 8.0 Hz, OH), 3.02 (1H, d, -OH, *J* = 6.0 Hz), 3.72-3.88 (1H, m, -CH(OH)), 4.01 (1H, dd, *J* = 2.0, 6.0 Hz, -CH(OH)), 4.26 (2H, q, *J* = 7.0 Hz, -$OCH_2CH_3$);$^{13}$C NMR ( 75 MHz, $CDCl_3$ ) δ 13.87, 14.08, 22.50, 27.82, 33.36, 61.92, 72.52, 73.14, 173.62 ; MS (FAB) *m/z* : 191 (M+1). ; Anal. calcd for $C_9H_{18}O_4$ : C, 56.82 ; H, 9.54. Found: C, 56.84; H, 9.58.

**Ethyl 5-butyl-2,2-dimethyl-(4R, 5S)-1,3-dioxolane-4-carboxylate (4).** To a solution of the diol **3** (2.77 g, 14.57 mmol) in anhydrous $CH_2Cl_2$ (25 mL) were added 2,2-dimethoxypropane (2.3 mL, 18.95 mmol) and *p*-TsOH (0.015 g, 0.078 mmol ). The reaction was stirred for 16 h at room temperature. The reaction mixture was neutralised with $Et_3N$ (2 mL) and concentrated *in vacuo*.

The residue was purified by silica gel chromatography eluting with EtOAc-hexane (1:19) to afford **4** (3.27 g, 97.7%) as a coloured liquid. $[\alpha]_D^{25}$ -14.04 (*c* 1, $CHCl_3$); IR (KBr, $cm^{-1}$) 2988, 2936, 2870, 2127, 1759, 1458, 1376, 1265, 1192, 1097; $^1$H NMR (200 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 6.5 Hz, $CH_3$ $(CH_2)_3$-), 1.21-1.53 (13H, m, $CH_3$ $(CH_2)_2$,-$OCH_2CH_3$ and -$C(CH_3)_2$), 1.60-1.80 (2H, m, -$CH_2$-CH(O)), 4.00-4.10 (2H, m, -CH (O-)-CH(O-)), 4.22 (2H, q, *J* = 7.0 Hz, -$OCH_2CH_3$). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 13.59, 13.92, 22.34, 25.54, 27.01, 27.52, 33.07, 60.90, 79.13, 110.52, 170.73. EIMS *m/z:* 215 ($M^+$ -$CH_3$), 157, 144, 127, 119, 93, 81, 65; Anal. calcd for $C_{12}H_{22}O_4$ : C, 62.58 ; H, 9.62. Found: C, 62.73; H, 9.68.

**5-Butyl-2,2-dimethyl -(4S, 5S)-1,3-dioxolan-4-ylmethanol (5).** A ice cooled solution of anhydrous LiCl (1.50 g, 35.56 mmol) and $NaBH_4$ (1.34 g, 35.5 mmol) in dry ethanol (15 mL) was stirred for 30 min, to it ester **4** (3.27 g, 14.23 mmol) dissolved in dry THF (15 mL) was added over 10 min. The reaction mixture was brought to room temperature and stirred for 16 h. The solid precipitate was filtered and washed with EtOAc (3 x 50 mL) and EtOH (10 mL). The filtrate was concentrated *in vacuo* and the residue dissolved in EtOAc, treated with sat. $NH_4Cl$ (50 mL) at $0^0$C and extracted with EtOAc (3 x 50 mL). Combined organic layers were extracted with $H_2O$ and sat. NaCl, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc-hexane (7:93) to furnish the alcohol **5** (2.02 g, 76%) as a colourless oil. $[\alpha]_D^{25}$ -23.77 (*c* 1, $CHCl_3$); IR (KBr, $cm^{-1}$) 3460, 2986, 2933, 2870, 1460, 1375, 1219, 1168, 1104, 1048; $^1$H NMR (200 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.0 Hz, $CH_3$ $(CH_2)_3$-), 1.26-1.65 (12H, m, $CH_3$ $(CH_2)_3$ and -$C(CH_3)_2$), 1.92 (1H, br s, -OH), 3.52-3.92 (4H, m, -CH(O)-CH(O)$CH_2$OH); $^{13}$C NMR ( 75 MHz, $CDCl_3$) δ 13.85, 22.71, 27.03, 27.36, 28.06, 32.79, 62.19, 77.00, 81.58, 108.55; EIMS *m/z*: 173 ($M^+$ -$CH_3$), 157, 95,81, 69, 59; FAB-MS *m/z*:189( M+1).; Anal. calcd for $C_{10}H_{20}O_3$ : C, 63.80 ; H, 10.71. Found: C, 63.79; H, 10.70.

**5-Butyl-2,2-dimethyl-4-(4-methylphenylsulfonyloxymethyl)-(4S, 5S)-1,3-dioxolane (6).** To a stirred solution of compound **5** (1.95 g, 10.39 mmol) in dry $CH_2Cl_2$, were added triethylamine (2.9 mL, 20.78 mmol), *p*-toluene sulfonylchloride (2.17 g, 11.42 mmol) and DMAP (catalytic) at 0°C. After stirring at room temperature for 4 h, the reaction mixture was extracted with $H_2O$ and sat. NaCl, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc-hexane (3:97) to afford **6** (3.02 g, 85%) as a colourless oil. $[\alpha]_D^{25}$ –18.16 (*c* 1, $CHCl_3$); IR (KBr, $cm^{-1}$) 3417, 2941, 2871, 1744, 1705, 1598, 1456, 1371, 1220, 1189, 1098, 983, 818, 771.

$^1$H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.5 Hz, $CH_3$ $(CH_2)_3$ -), 1.23-1.42 (10H, m, $CH_3$ $(CH_2)_2$ $CH_2$- and -$C(CH_3)_2$), 1.45-1.60 (2H, m, -$CH_2$CH-(O)), 2.45 (3H, s, Ar-$CH_3$), 3.65-3.82 (2H, m, -CH(O)-CH(O)-), 4.05 (2H, d, *J* = 5.0 Hz, -$CH_2$-OAr), 7.35 (2H, d, *J* = 8.5 Hz, Ar-), 7.80 (2H, d, *J* = 8.5 Hz, Ar-); $^{13}$C NMR ( 75 MHz, $CDCl_3$ ) δ 13.83, 21.57, 22.58, 26.64, 27.23, 27.88, 32.69, 69.14, 77.75, 78.15, 109.23, 127.95, 129.81, 144.94; EIMS *m/z:* 327 ($M^+$ -$CH_3$), 213, 155, 95, 91; Anal. calcd for $C_{17}H_{26}O_5S$ : C, 59.62 ; H, 7.65. Found: C, 59.31; H, 7.57.

**1-[(2S)-Oxiran-2-yl]-(1S)-pentan-1-ol (7).** To a solution of compound **6** (2.93 g, 8.56 mmol) in MeOH: $H_2O$ (25.0 mL, 4:1) was added pTSA (0.295 g, 1.55mmol) and stirred at room temperature for 20 h. The reaction mixture concentrated *in vacuo* and extracted with $CH_2Cl_2$

(3x20 mL). The combined organic layers were washed with $H_2O$ then sat. NaCl (30 mL), dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*, to give diol tosyl derivative (2.05 g) which was used for subsequent reaction without purification.

To a solution of the diol tosyl derivative (2.05 g, 8.61 mmol) in MeOH (20 mL), $K_2CO_3$ (0.75 g, 5.42 mmol) was added to the reaction mixture till pH 9 and stirred at room temperature for 19 h. The methanol was removed on the rotavapor keeping the temperature of the water bath below $30^0$C. The residue was taken in $CH_2Cl_2$, washed with $H_2O$ then sat. NaCl, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc-hexane (5:95) to afford **7** (0.75 g, 68%), $[\alpha]_D^{25}$ +4.37 (*c* 1, $CHCl_3$) {lit.[4j] $[\alpha]_D^{23}$ +5.01 (*c* 1.39, $CHCl_3$ )}; $^1$H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.0 Hz, $CH_3$-), 1.30-1.54 (4H, m, $CH_3$ $(CH_2)_2$ -), 1.55-1.63 (2H, m, -$CH_2$-CH(OH)-), 1.71 (1H, d, *J* = 7.0 Hz, -OH), 2.67 (1H, m, $H_a$), 2.76 (1H, m, $H_b$), 2.92 (1H, m, $H_c$), 3.40 (1H, m, -CH(OH)-); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 13.91, 22.66, 27.45, 34.19, 45.10, 55.31, 71.66.; Anal. calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.56; H, 10.83.

**1-(3-Methoxyphenyl)-(2*S*, 3*S*)-heptane-2,3-diol (8).** A dried two necked round bottom flask (100 mL) was charged with activated magnesium (0.93 g, 38.42 mmol) in dry THF (15 mL) and 1,2-dibromoethane (0.05 mL) was added and stirred for 15 min. To this reaction mixture, *m*-bromoanisole (1.43 g, 7.68 mmol) in anhydrous THF (5 mL) was added drop wise over a period of 10 min and stirred for 30 min at the same temperature. The reaction mixture was cooled to –20°C, CuI (catalytic) and compound **7** (0.5 g, 3.84 mmol) in dry THF (5 mL) was added. The reaction was allowed to stir for 3.5 h at room temperature. The reaction mixture was quenched with sat. $NH_4Cl$ (30 mL) at 0°C and extracted with EtOAc (3 x 25 mL). The combined organic solution was washed with $H_2O$ and sat. NaCl, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo.* The residue was purified by silica gel chromatography eluting with EtOAc-hexane (1:9) to furnish **8** (0.69 g, 75.4%) as a white solid. mp 50-52.4°C; $[\alpha]_D^{25}$ –20.06.(*c* 1, $CHCl_3$); IR (KBr,$cm^{-1}$) 3251, 2936, 1587, 1486, 1266, 1156, 1042, 1002, 844, 693.$^1$H NMR (200 MHz, $CDCl_3$) δ 0.98 (3H, t, -$CH_3$, *J* = 7.3 Hz), 1.22-1.62 (6H, m, $CH_3$-$(CH_2)_3$), 1.83, 1.98 (2H, 2 br s, 2 OH), 2.7 (1H, dd, *J* = 10, 14.6 Hz, H-1), 2.85 (1H, dd, *J* = 4.4, 14.6Hz, H-1'), 3.42 (1H, m, H-2), 3.62 (1H, m, H-3), 3.81 (3H, s, $OCH_3$), 6.70-6.84 (3H, m, Ar-H), 7.15-7.28 (1H, m, Ar-H); $^{13}$C NMR ( 75 MHz, $CDCl_3$ ) δ 13.96, 22.70, 27.82, 33.44, 40.35, 55.16, 73.60, 74.89, 111.90, 115.16, 121.67, 129.60, 139.78, 159.86 ; MS *m/z* % 238(M+), 151, 122, 121, 91; FAB-MS *m/z*: 261 (M+Na), 239 (M+1), 238 (M+). ; Anal. calcd for $C_{14}H_{22}O_3$ : C, 70.55 ; H, 9.30. Found: C, 70.51; H, 9.38.

**6-[1-Hydroxy-(1S)-pentyl]-(6S)-2*H*, 3*H*, 4*H*, 5*H*-2,4-pyrandione (11).** To a solution of lithium (1.17 g, 168 mmol) in liq. ammonia (100 mL) at –78°C (cooling was maintained by acetone/dry ice in the cold finger bath) was added compound **8** (0.5 g, 2.1 mmol) dissolved in dry THF (15 mL). After the addition the acetone/dry ice bath was replaced by $CCl_4$/dry ice bath and stirred for 2 h, again cooled to –78°C and treated with dry EtOH (6 mL). The blue solution was stirred for 1 h and solid $NH_4OAc$ (5 g) was added after which the reaction mixture was brought to room temperature. After all ammonia had evaporated the residue was partitioned between EtOAc/

$H_2O$. The aqueous layer was separated extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with $H_2O$ then sat. NaCl, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo* to afford **9** (0.463 g) as a colourless oil which was further carried for the next step without any purification.

To a solution of crude dihydroanisole **9** (0.457 g, 1.904 mmol) in dry $CH_2Cl_2$ (15 mL), were added MeOH (4 mL), pyridine (0.3 mL) and a catalytic amount of sudan III. The pink solution was treated with a dilute stream of ozone in oxygen at $-78^0$C for 30min untill it turned light yellow, at which point dimethylsulfide (3 mL) was added. The mixture was stirred at room temperature for 2 h after which the reaction was partitioned between EtOAc and $H_2O$. The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, concentrated *in vacuo* to afford β-keto ester **10** (0.243 g,), which was used for subsequent reaction without purification.

To a solution of the β- keto ester **10** (0.243 g, 1.04 mmol) in dry THF (8 mL), was added aqueous NaOH (1N, 6.4 mL, 6.4 mmol) and stirred at room temperature for 1.5 h. To it aqueous $NH_4Cl$ was added and the pH was brought to ~ 4 by adding dilute HCl. The reaction mixture was partitioned between EtOAc and $H_2O$. The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic solution was washed with $H_2O$ then sat. NaCl, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification of the residue by silica gel chromatography eluting with EtOAc-hexane (2:3) gave **11** (0.042 g, 10% overall yield for 3 steps, 47% average yield for each step) as a thick syrup. $[\alpha]_D^{25}$ –69.39 (*c* 1.18, MeOH); IR (KBr,$cm^{-1}$) 3390, 2932, 2868, 1723, 1667, 1409, 1278, 1226, 1137, 1059, 888, 832, 755; $^1$H NMR (200 MHz, $CDCl_3$) δ 0.95 (3H, t, -$CH_3$, $J$ = 7.8Hz), 1.25-1.51 (4H, m, $CH_3$ $(CH_2)_2$ -$CH_2$), 1.51-1.75 (2H, m, $CH_3$ $(CH_2)_2$ -$CH_2$), 2.23 (1H, br s, -OH), 2.66-2.76 (2H, m, H-5), 3.47 (2H, s, -CO-$CH_2$-CO-), 3.65 (1H, m, H-1'), 4.55 (1H, m, H-6); MS *m/z* %: 156, 155, 141, 114, 101, 86.; Anal. calcd for $C_{10}H_{16}O_4$ : C, 59.98 ; H, 8.05. Found: C, 59.97; H, 8.09.

**6-[1-Hydroxy-(1*S*)-pentyl]-4-methoxy-(6*S*)-2H, 5H-2-pyranone (1).** To a solution of δ-lactone **11** (0.042 g, 0.21 mmol) in anhydrous acetone (10 mL) were added dimethylsulfate in acetone (0.55 M, 0.4 mL, 0.209 mmol) and potassium carbonate (0.043 g, 0.314 mmol). The resulting slurry was stirred at room temperature for 14 h. Acetone was removed in the rotavapor and the residue was partitioned between EtOAc and $H_2O$ (20 mL, 3:1). The organic layer was separated and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic layers was washed with $H_2O$ then sat. NaCl, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with EtOAc-hexane (3:7) to afford **1.** After recrystalisation in Hexane: Benzene (2 mL, 1:1) as a white solid (0.027g, 60%): m.p: 76-79°C ; $[\alpha]_D^{25}$ – 94.76 (*c* 1, MeOH) {lit.[2] $[\alpha]_D^{25}$ –86.2 (*c* 0.14, MeOH )}; IR (KBr, $cm^{-1}$) 3434, 2950, 1705, 1619, 1236 . $^1$H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, $J$ = 7.4 Hz, -$CH_3$), 1.28-1.68 (6H, m, $CH_3$-$(CH_2)_3$), 2.1 (1H, br s, OH), 2.24 (1H, dd, $J$ = 4, 16.6 Hz, H-5a), 2.82 (1H, dd, $J$ = 12, 16.6 Hz, H-5b), 3.60 (1H, m, H-1'), 3.79 (3H, s, $OCH_3$), 4.28 (1H, m, H-6), 5.14 (1H, s, H-3): $^{13}$C NMR (50 MHz, $CDCl_3$) δ 13.90, 22.54, 27.57, 29.54, 32.33, 56.09, 72.37,

78.37, 89.96, 166.64, 173.10; FAB-MS *m/z*: 237(M+Na), 215(M+1), 197, 127, 109, 95, 81, 69, 55 ; Anal. calcd for $C_{11}H_{18}O_4$ : C, 61.66 ; H, 8.46. Found: C, 61.65; H, 8.44.

## Acknowledgments

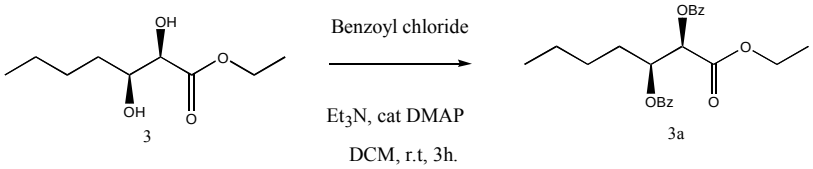
ASK thanks CSIR, New Delhi for a research fellowship (S.R.F). One of the author (PB) thanks the UGC, New Delhi for financial assistance. We thank Dr. J. S. Yadav for his support and encouragement.

## References and Notes

IICT Communication Number: 0407010

1. (a) Kimura, Y.; Katagiri, K.; Tamura, S. *Tetrahedron Lett.* **1971**, *33,* 3137. (b) Kimura, Y.; Katagiri, K.; Inoue, T.; Tamura, S. *Agric. Biol. Chem.* **1971**, *35*, 1313. (c) Kimura, Y.; Tamura, S. *Agric. Biol. Chem.* **1972**, *36*, 1925.
2. Ellestad, G. A.; McGahren, W. J.; Kunstmann, M. P. *J. Org. Chem.* **1972**, *37*, 2045.
3. Davies-Coleman, M. T.; Rivett, D. E. A. *Progress in the Chemistry of Organic Natural Products,* Herz, W.; Grisebach, H.; Kirby, G. W.; Tamm, Ch., Eds.; Springler-Verlag, 1989**,** Vol. *55*, pp 1-35.
4. (a) Carlson, R. M.; Oyler, A. R. *Tetrahedron Lett.* **1974**, *30*, 2615. (b) Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1978**, 409. (c) Honda, T.; Okuyama, A.; Hayakawa, T.; Kondoh, H.; Tsubuki, M. *Chem. Pharm. Bull*. **1991**, *39,* 1866. (d) Meyer, H.; Seebach, D. *Liebigs Ann Chem*. **1975**, 2261. (e) Seebach, D.; Meyer, H. *Angew. Chem., Int. Ed*. **1974**, *13*, 77. (f) Mori, K.; Oda, M.; Matsui, M. *Tetrahedron Lett.* **1976**, *36*, 3173. (g) Takeda, A.; Amano, E.; Tsuboi, S. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2191. (h) Kirihata, Y.; Ohta, K.; Yamamoto, S.; Ichimoto, I.; Ueda, H. *Abstract of Papers, Annual Meeting of the Agricultural Chemical Society of Japan* 1980, Fukuoka, p 211. (i) Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc*. **1984**, *106*, 4294. (j) Mori, K.; Otsuka, T.; Oda, M. *Tetrahedron* **1984**, *40*, 2929. (k) Masaki, Y. ;Nagata, K.; Serizawa, Y.; Kaj, K. *Tetrahedron Lett.* **1984**, *25*, 95. (l) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Chem. Commun*. **1986**, 860. (m) Zhang, J. C.; Curran, D. P. *J. Chem. Soc., Perkin Trans I* **1991**, 2627. (n) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Perkin Trans I* **1992**, 693. (o) Wang, Z.; Shen, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3393. (p) Mayer, S. F.; Steinreiber, A.; Goriup, M.; Saf, R.; Faber, K. *Tetrahedron: Asymmetry* **2002**, *13*, 523.
5. (a) Rao, B.V.; Rao, A. S. *Synth. Commun*. **1995**, 1531. (b) Shashidhar Kumar, A.; Haritha, B.; Rao, B. V. *Tetrahedron Lett*. **2003**, *44*, 4261. (c) Naveen Kumar, D.; Rao, B. V. *Tetrahedron Lett*. **2004**, *10*, 2227.

6. (a) Kolb. H. C.; Van Nieuwenhze. M. S.; Sharpless. K. B. *Chem. Rev*. **1994**, 94, 2483. (b) Sharpless. K. B.; Ambeng, W.; Benanni, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Morikawa, H. L.; Wang, Z-M.; Xu, D.; Zhang, Z-I. *J. Org .Chem*. **1992**, *57*, 2768.
7. (*E*)-Ethyl-2-heptenoate (**2**) was prepared by the Wittig-olefination reaction of 1-pentanal and (carbethoxymethylidene)triphenylphosphorane. The *trans*-ester was isolated by silica gel chromatography eluting with AcOEt-hexane (1:99).
8. Enantiomeric purity of **(3)** were estimated to be 97.35% ee, by HPLC analysis of the corresponding dibenzoate **(3a)** $\{[\alpha]_D^{26.5}$ = -67.71 (C 1.03, $CHCl_3$) using a chiralcel OD (semi prep) column. (1% i- propanol /n- hexane, flow rate 2.0mL/min, λ =225 nm, range: 0.05000AUFS).




9. (a) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *Inorg. Chem*. **1981**, *20*, 454. (b) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604.
10. Mayer, S. F.; Steinreiber, A.; Orru, R. V. A.; Faber, K. *Eur. J. Org .Chem*. **2001**, 4537.
11. Huynh, C.; Dergnini-Bonmechal, D.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503.
12. (a) Birch, A. J.; Fitton, P.; Smith, D. C. C.; Steere, D. E.; Stelfox, A. R. *J. Chem. Soc*. **1963**, 2209. (b) Kirkeno, C. L.; White, J. D. *J. Org. Chem.* **1985**, 1316. (c) Bringmann, G.; *Liebigs Ann. Chem*. **1985**, 2105. (d) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741.
13. For the use of dyes in ozonolysis see: Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.
14. Kimura, Y.; Suzuki, A.; Tamura, S. *Agric. Biol. Chem.* **1980**, *44*, 451.