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Stereocontrolled Synthesis of the 4-Hydroxy-5-methyl-2(3H)-dihydrofuranone Isomers

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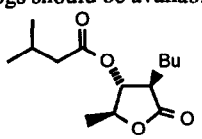
Abstract: A synthesis of all four stereoisomers of 4-hydroxy-5-methyl-2(3H)-dihydrofuranone was achieved in 6 or 7 steps with an overall yield of 19% to 23% from a common starting material. The source of chirality being derived from stereoselective bakers' yeast reductions of carbonyl groups.

Several 4-hydroxy-5-methyl-2(3H)-dihydrofuranone moieties and their O-acetyl derivatives, substituted at C-3 by alkyl or alkylidene chains, such as in the polyketide natural products (+)-blastimycinone **1**, litsenolide **2** and dihydromahubalactone **3**[1], are found as metabolites from differing natural sources . This widespread distribution has generated an enormous amount of interest in the synthesis and configurational assignments of variously di- and tri-substituted butyrolactones[2]. The biological activity of these compounds is such that the synthesis of these compounds is still of great interest. In principle they can be prepared from the corresponding hydroxy γ-butyrolactones by stereoselective alkylation or alkylidination. All of these natural products and unnatural analogs should be available having the stereoisomeric hydroxybutyrolactones **16-19** in hand.



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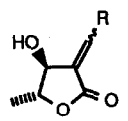
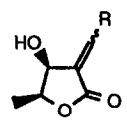


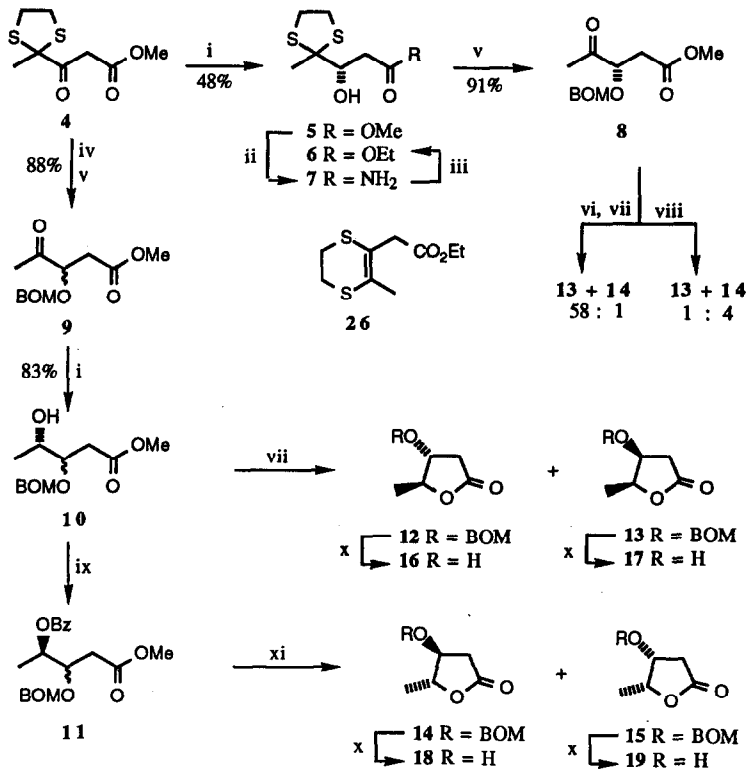
2 R = $(CH_2)_{13}CH{:}CH_2$



3 R = $(CH_2)_{13}CH_2CH_3$

We describe here a simple procedure for the synthesis of all four stereoisomers **16, 17, 18** and **19** of the basic title ring system, starting from the readily available monodithioacetal **4**[3] (scheme 1). The critical steps involve asymmetric reductions of carbonyl groups by bakers' yeast (*Saccharomyces cerevisiae*) a 'reagent' which has recently been widely employed in organic synthesis[4]. The enzymic reduction of some simple α-ketothioacetals[3,5] and α-alkoxyketones and derivatives[6] have been reported and structural limitations are indicated.

The bakers' yeast reduction of the ketone **4** afforded the alcohol **5** in 48%[7] chemical yield with an e.e. of 95%[8]. Reduction of the corresponding ethyl ester gave lower chemical yields of an alcohol with an e.e. of only 87% and having the same configuration. The (S) configuration was assigned by converting the ethyl ester of **5** into known ethyl 3-(R)-hydroxypentanoate[9] by using Raney Ni. Enantiomeric enrichment of (S)-**6** was achieved by recrystallisation of the amide **7** from pet. ether/ethyl acetate and then reconverting it to the ester by acid catalysed hydrolysis. The overall process is efficient and the amide is a readily available derivative for the enantiomeric enrichment of hydroxyesters. Traces of the dihydrodithiin **26** were detected after the acid alcoholysis and was an expected product since the known 1,2-sulphur migration processes can occur under these conditions [3]. Substantial rearrangement was fortunately never observed.



Scheme 1 (i) bakers' yeast (0.4 g/ml), **4** (45 mM), 21 °C, 48 h; (ii) MeOH/NH_3, rt, 72 h, recrystallised from pet. ether 40-60°C/ethyl acetate, 96%, ee (S) > 97%; (iii) EtOH/HCl, reflux, 18 h, 80 %; (iv) $NaBH_4$, EtOH, rt, 2h; (v) a: i-Pr_2NEt/BOMCl (3 eq), CH_2Cl_2, rt, 48 h; b: HgO/BF_3OEt_2 (2 eq), THF/H_2O (85:15), rt, 2 h, 91% (2 steps); (vi) K-Selectride® (1 eq), THF, -100 °C, 30 min, 60%; (vii) 0.4M HCl in Me_2CO/H_2O (3:1), rt, 3 days; (viii) $Zn(BH_4)_2$ (3 mol excess), Et_2O, rt, 4 days, **13** 15%, **14** 60%; (ix) Ph_3P/DEAD/$PhCO_2H$ (1.5 eq), Et_2O, rt, 24 h, 82%; (x) H_2, 10% Pd/C, EtOH, rt, 36h, 86% to 96%; (xi) $Ti(OiPr)_4$ (1.9 eq), EtOH, reflux, 16 h, **14** 37%, **15** 40%.

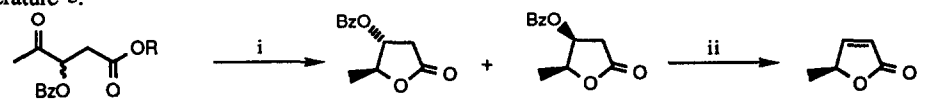
The ketone **8** was obtained in 91% overall yield from **5** by sequential protection of the hydroxyl with a BOM group followed by deprotection of the carbonyl group using mercury reagents.

The optically active protected lactone **13**[10] was obtained, in the ratio 58:1 **13**:**14**, by reduction of **8** with K-Selectride® followed by acid catalysed lactonization. At higher temperatures (-80 C) the reducing agent was

sufficiently basic to eliminate the benzyloxymethoxy group, indicated by the formation of benzyl alcohol, thus affording only moderate yields of the required lactone **13**. On the other hand, the epimeric lactone **14**[10] was also selectively formed, in a ratio of 1:4 of **13**:**14**, by reduction of **8** with $Zn(BH_4)_2$[11].

Another approach to the synthesis of **13** involved enzymic reduction of racemic hydroxy ketone **9** which was prepared in 88% overall yield from **4** by $NaBH_4$ reduction and then using the same sequence described for the (S)-**8** isomer. Bakers' yeast reduction of **9** gave exclusively **10** in 83% yield with a ~1:1 ratio of epimers at the 3- position each diastereoisomer being optically pure. Acid catalysed lactonization gave the lactones **12** and **13** in nearly quantitative yield. Finally, deprotection of the hydroxyl group with 10% Pd/C[12] afforded optically pure lactones (e.e. > 97%) **16** and **17**[13] in 86 to 96% yield. The remaining lactone isomers were obtained by inversion of the C-4 chiral center. A diastereomeric mixture of benzoates **11** was prepared in 82% yield using the Mitsunobu method,[14] the separated isomers were subsequently converted to the lactones **14** and **15** in respectively 37% and 40% yield by a $Ti(OiPr)_4$ catalysed transesterification[15]. By catalytic hydrogenolysis, the optical pure hydroxylactones (e.e. > 97%) **18** and **19**[13] were prepared efficiently from compounds **14** and **15** respectively.

We have also prepared the optical pure lactones **23** and **24**[16] by using the same strategies which involve bakers' yeast reductions of the corresponding optically active or racemic α-benzoyloxyketones (scheme 2). These have been converted into the corresponding (+) (S)-β-angelica lactone **25**, using procedures described in the literature[2g].



	23 e.e.>97%	**24** e.e.>97%	**25** e.e.>97%
20 R = Me e.e. (S)- 95%	2%	76%	
21 R = Me racemic	42%	30%	
22 R = Et racemic	33%	28%	

Scheme 2 (i) a: bakers' yeast (0.4 g/ml), ketone (45 mM), 23 °C, 48 h; b: 0.4M HCl in Me_2CO/H_2O (3:1), rt, 2.5 days; (ii) literature procedure[2g]; $MeOH/NH_3$.

The route presented provides a simple means of preparing all of the stereoisomers of 4-hydroxy-5-methyl-dihydrofuranone from **4** in 6 or 7 steps with an overall yield of 19 to 23% involving the introduction of chirality by a simple bakers' yeast (enzymic) reduction[17]. β- Angelicalactone is also accessible through the same scheme and although the synthesis of only one enantiomer is described in the present work, both enantiomers are available.

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Experimental Section

Reagent quality solvents were distilled prior to use. Pyridine was dried by distillation from sodium hydroxide. Anhydrous carbon tetrachloride was prepared by distillation from phosphorus pentoxide under argon. Anhydrous dichloromethane was prepared by distillation from calcium hydride under argon. Benzene and diethyl ether were dried by standing over sodium wire. N,N-diisopropylethylamine was dried by distillation from calcium hydride. Anhydrous tetrahydrofuran was prepared by distillation from sodium/benzophenone ketyl under argon. (R)-MTPA (Sigma) was converted to the acid chloride using a literature procedure[18],

followed by Kugelrohr distillation. Column chromatography was performed using Silica gel Merck 60 H (Art. 7736) and aluminum-backed silica gel Merck 60 F_{254} plates for analytical TLC. Melting points (uncorrected) were determined on a Electrothermal Mod. IA 6304 capillary melting point apparatus. Microanalyses were carried out by LNETI using a Carlo Erba model 1106 analyser. Mass spectra (MS) and exact masses (HRMS) were obtained using a Kratos MS 25 RF and AEI/VG MS 9 mass spectrometers. Infra-red spectra (IR) were recorded on a Perkin-Elmer model 157 G infra-red spectrophotometer. ^{1}H NMRwere recorded on Perkin-Elmer R12B (60 MHz) and Bruker CXP300 (300 MHz) spectrometers. Chemical shifts are reported as δ values relative to tetramethylsilane (δ = 0 ppm). Observed rotations at the Na-D line were measured at 25°C using a Perkin-Elmer 241 polarimeter.

Preparation of methyl 3(S)-hydroxy-4-oxopentanoate-4-ethylenedithioacetal (5). Fresh commercial baker's yeast (404 g) was suspended in a stirred solution of sucrose (424 g) in tap water (1009 ml). The mixture was allowed to stand at 21 °C during 1hr (gas evolution). The ketone (4)[3] (10.00 g, 45.39 mmol) was added and stirring was continued (48 hr). The mixture was then saturated with NaCl and filtered through celite. The solid was washed with ethyl acetate (2 x 500 ml) and the aqueous filtrate was extracted with diethyl ether (4 x 500 ml). The combined organic phases were dried ($MgSO_4$), filtered, evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 8:2 to 1:1) to afford in order of elution starting material (4) (4.20 g, 42 % recovery) and (5) (4.82 g 48 %) as a clear colourless oil; spectral data identical to that described for a racemic sample[3]; e.e. determined by prior transterification of (5) (0.062 g, 0.28 mmol) in absolute ethanol (1 ml) and acetyl chloride (0.04 ml) (reflux, 3 hr, usual work-up and silica gel column (eluents: petroleum ether 40/60 : dichloromethane 1:1)) to afford the ethyl ester (6) (0.055g, 83%) as a clear colourless oil; e.e. 95 % determined by ^{1}H NMR(300 MHz, 0.035 M in $CDCl_3$) spectra for (R) and (S) enantiomers signals of C-5 Me (respectively 2.38 and 2.63 ppm) and OCH_2CH_3 (respectively 1.41 and 1.29 ppm) in the presence of 0.64:1 molar ratio Eu(tfc)3/substrate; ^{1}H NMR(300 MHz, $CDCl_3$) δ: 1.279(3H, t J=7.4 Hz, OCH_2CH_3), 1.758(3H, s, H-5), 2.549(1H, dd J=16.1, 10.3 Hz, H-2), 2.828(1H, d J=16.1 Hz, H-2), 3.199(1H, br, OH), 3.284-3.362(4H, m, $S(CH_2)_2S$), 4.148-4.220(1H, CHOH, masked by q of OEt), 4.183(2H, q J=7.4 Hz, OCH_2Me); IR (film): 3480(br, OH), 2980(m), 2940(m), 2880(w), 1730(m, C=O), 1450(m), 1380(s), 1285(s), 1180(s), 1100(m), 1045(s), 950(w), 910(w), 890(w), 855(m), 760(w), cm-1.

Preparation of ethyl 3(R)-hydroxypentanoate. To a stirred solution of (6) (1.006 g, 4.26 mmol, e.e. (S) 92 %), in absolute ethanol (220 ml) was added Raney Ni (prepared by the described method[19] starting from 30 g of 1:1 aluminum-nickel) and refluxed for 6 hr. The mixture was filtered, and the filtrate was washed with ethanol (2 x 30 ml). The solvent was evaporated and the residue was distilled (kugelrohr) 115-120 °C/20 mmHg to afford **ethyl 3(R)-hydroxypentanoate** (0.471 g, 76 %); $[\alpha]^{25}_D$ = -29.3° (c 1.1, $CHCl_3$), e.e. 89 % determined by optical rotation comparison; lit.[9a] for e.e. (S) 100 % $[\alpha]^{25}_D$ = +33.1° (c 0.88, $CHCl_3$); lit.[9b] for e.e. (S) 84 % $[\alpha]^{25}_D$ = +28° ($CHCl_3$).

Preparation of 3(S)-hydroxy-4-oxopentanamide-4-ethylenedithioacetal (7). Into a solution of (5) (1.268 g, 5.70 mmol, e.e. 95 %) in absolute methanol (40 ml) at -60 °C was passed ammonia to a total volume of 55 ml and the mixture was closed and allowed to stand at room temperature for 3 days. The ammonia was then slowly evaporated, and the remaining solvent removed under vacuum. The residue was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : ethyl acetate from 1:1 to 0:1) to afford (7) (1.135 g, 96 %), solid, Rf = 0.36 (ethyl acetate). Enantiomerically pure amide was obtained after two crystallizations from petroleum ether 40/60 : ethyl acetate; m.p. 118.5-119 °C; $[\alpha]^{25}_D$ = -41.1° (c 1.0 ethanol); ^{1}H NMR(60 MHz, $CDCl_3$)δ: 1.75(3H, s, H-5), 2.52(1H, d J=9 Hz, H-2), 2.65(1H, d J=3 Hz, H-2), 3.35(4H, s, $S(CH_2)_2S$), 3.40(3H, br, OH and NH_2), 4.12(1H, dd J=3, 9 Hz, CHOH); IR (nujol): 3390(m, NH and OH), 3350(m, NH and OH), 3290(m, NH and OH), 3240(m, NH and OH), 3180(m, NH and OH), 2720(m), 1660(s, C=O), 1610(m), 1305(m), 1275(m), 1245(m), 1190(s), 1160(m), 1100(m), 1090(m), 1055(s), 1025(s), 975(m), 885(w), 875(m), 850(m), 760(m), 720(s), cm^{-1}; MS m/e: 207(M^+), 189(M^+-H_2O), 171, 156, 145, 119($C_4H_7S_2^+$, base), 97; Anal. Calcd for $C_7H_{13}NO_2S_2$: C 40.56, H 6.32, N 6.76%; Found:C 40.50, H 6.41, N 6.65%.

Preparation of ethyl 3(S)-hydroxy-4-oxopentanoate-4-ethylenedithioacetal (6) (e.e. > 97 %) from (7). A previous prepared solution of absolute ethanol (75 ml) and acetyl chloride (5.1 ml, 72.1 mmol) was added to crystallized (7) (3.738

g, 18.03 mmol) then stirred and refluxed for 18 hr under a dry atmosphere. Solid sodium bicarbonate was carefully added, the ethanol was evaporated and ether (50ml) and water (50ml) was added to the residue. The aqueous phase was separated and extracted with more ether (3x50ml). The combined organic phases were dried ($MgSO_4$), filtered, evaporated to dryness, and chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 1:1 to 0:1) to afford in order of elution **3-methyl-2-ethoxycarbonylmethyl-5,5-dihydro-1,4-dithiine (26)** (0.492 g, 13 %), clear colourless oil; elemental analysis as reported[20]; ^1H NMR(60 MHz, CCl_4)δ: 1.30(3H, t J=7 Hz, $CO_2CH_2CH_3$), 1.92(3H, s, C-3 Me), 3.10(2H, s, CH_2CO_2Et), 3.20(4H, s, $S(CH_2)_2S$), 4.18(2H, q J=7 Hz, CO_2CH_2Me); IR (film): 2980(m), 2920(m), 2860(w), 1735(s, C=O), 1600(w, C=C), 1445(w), 1415(m), 1390(w), 1365(m), 1325(m), 1290(m), 1255(m), 1180(s), 1120(w), 1095(w), 1030(m), 975(w), 925(w), 870(w), cm^{-1}; and **(6)** (3.397 g, 80 %); clear colourless oil, $[\alpha]^{25}_D$ = -35.2 (c 1.2, $CHCl_3$), e.e. > 97 % determined as described above.

Preparation of methyl 3(S)-benzyloxymethoxy-4-oxopentanoate (8). Benzyl chloromethyl ether (2.0 ml, 3 eq.) was added dropwise (5 min) to a stirred solution of **(5)** (1.072 g, 4.82 mmol e.e. (S) = 94%) and dry diisopropylethylamine (2.5 ml, 3 eq.) in anhydrous dichloromethane (10 ml) at room temperature under argon. After 48 hr the reaction was poured onto to a saturated aqueous solution of ammonium chloride (25 ml) and extracted with diethyl ether (4 x 25 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness yielding a yellow oil which was dissolved in tetrahydrofuran (4 ml) and added dropwise to a strong stirred suspension of red mercury (II) oxide (2.089 g, 2 eq.) and boron trifluoride etherate (1.2 ml, 2 eq.) in aqueous tetrahydrofuran (15%, 10 ml) at room temperature. After 2 hr the reaction was quenched by the addition of saturated aqueous bicarbonate (10 ml) with formation of a white precipitate. The mixture was then filtered, washed with diethyl ether (20 ml) and the aqueous phase extracted with diethyl ether (4 x 15 ml). The combined organic layers were dried ($MgSO_4$), filtered, evaporated to dryness and chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 8:2 to 0:1) to afford **(8)**, (1.165 g, 91%), clear colourless oil; Rf = 0.43 (dichloromethane); $[\alpha]_D^{25}$ = -6.6 (c.1.9, chloroform); ^1H NMR(60 MHz, CCl_4)δ: 2.16(3H, s, COMe), 2.68(2H, dd J=5, 0.5 Hz, H-2), 3.62(3H, s, CO_2Me), 4.30(1H, dd J=5, 5.5 Hz, CHOBOM), 4.60(2H, s, OCH_2Ar), 4.80(2H, s, OCH_2O), 7.30(5H, s, Ar); IR (film): 3100(w, Ar), 3070(w, Ar), 3040(w, Ar), 3020(w, Ar), 2960(m), 2900(m), 1745(s, C=O), 1725(s, C=O), 1610(w, Ar), 1590(w, Ar), 1500(m), 1460(m), 1445(s), 1420(m), 1360(s), 1280(s), 1270(s), 1210(s), 1170(s), 1120(s), 1050(s), 1030(s), 960(m), 910(w), 855(w), 745(s, Ar), 700(s, Ar), cm^{-1}; MS m/e: 267(M^++1), 237, 223(M^+-MeCO), 207, 193, 194, 181, 119, 91($C_7H_7^+$, base).

Preparation of methyl 3(R,S)-benzyloxymethoxy-4(S)-hydroxypentanoate (10). The ketone (9)[21](0.500 g, 1.88 mmol) was subjected to bakers' yeast reduction in a manner similar to that described earlier. Purification by flash chromatography (eluents: petroleum ether 40/60 : dichloromethane 1:1) gave **(10)** (0.419 g, 83%) as a clear colourless oil; ^1H NMR(60 MHz, CCl_4)δ: 1.12(3H, d J=6 Hz, $CHOHCH_3$), 2.45(2H, dd J=7, 1 Hz, H-2), 2.76(1H, br, OH), 3.60(3H, s, CO_2Me), 3.68-4.0(2H, m, CHOH and CHOBOM), 4.60(2H, s, OCH_2Ar), 4.78(2H, s, OCH_2O), 7.32(5H, s, Ar); IR (film): 3500(br, OH), 3100(w, Ar), 3080(w, Ar), 3040(w, Ar), 2990(s), 2970(s), 2950(s), 2910(s), 1745(s, C=O), 1610(w, Ar), 1590(w, Ar), 1500(m), 1460(s), 1440(s), 1410(m), 1380(s), 1340(m), 1290(s), 1200(s), 1165(s), 1100(s), 1040(s), 1050(m), 905(m), 855(m), 745(s, Ar), 700(s, Ar), cm^{-1}.

Preparation of methyl 4(R)-benzoyloxy-3(R,S)-benzyloxymethoxypentanoate (11). Diethyl azodicarboxylate (0.53 ml, 1.5 eq.) was added dropwise during 5 min to stirred solution of **(10)** (0.599 g, 2.23 mmol), triphenylphosphine (0.878 g, 1.5 eq.) and benzoic acid (0.409 g, 1.5 eq.) in dry diethyl ether (10 ml) under argon at room temperature. After 24 hr water (15 ml) was added and the aqueous phase was extracted with diethyl ether (3 x 15 ml). The combined organic phases were dried ($MgSO_4$), evaporated to dryness, and chromatographed on a silica gel column (eluents: petroleum ether 40/60 : dichloromethane from 1:0 to 1:1) to afford **(11)** (0.678 g, 82%), as a clear oil, Rf = 0.54 (dichloromethane); $[\alpha]_D^{25}$ = -42.4 (c.0.74, chloroform); ^1H NMR(60 MHz, CCl_4)δ: 1.30(3H, d J=7 Hz, $CHOBzCH_3$), 2.55(2H, dd J=5, 0.5 Hz, H-2), 3.52(s) and 3.56(s)(3H, CO_2Me), 4.12-4.38(1H, m, CHOBOM), 4.58(2H, s, OCH_2Ar), 4.80(2H, s, OCH_2O), 5.14-5.45(1H, m, CHOBz), 7.28(5H, s, OCH_2Ar), 7.45-7.6(3H, m,

Bz), 8.0-8.2(2H, m, Bz); IR (film): 3100(w, Ar), 3080(w, Ar), 3040(w, Ar), 3000(m), 2960(m), 2900(m), 1745(s, CO_2Me), 1725(s, CO_2Ar), 1610(m, Ar), 1590(m, Ar), 1500(m), 1460(s), 1445(m), 1385(m), 1320(m), 1280(s), 1220(m), 1210(m), 1165(m), 1120(m), 1080(m), 1045(m), 1030(m), 1005(m), 945(w), 890(w), 850(w), 810(w), 780(w), 740(m, Ar), 720(s, Ar), 705(m, Ar), cm^{-1}.

Preparation of 4(R)-benzyloxymethoxy-5(S)-methyl-2(3H)-dihydrofuranone (12) and 4(S)-benzyloxymethoxy-5(S)-methyl-2(3H)-dihydrofuranone (13) from (10). Hydrochloric acid 37% (0.22 ml, 2 eq.) was added dropwise to a stirred solution of (10) (0.348 g, 1.30 mmol) in acetone/water (3:1, 6.5 ml) at room temperature. After 3 days the reaction was neutralized by the addition of sodium bicarbonate and the acetone was then evaporated *in vacuo* . The mixture was diluted with water (10 ml) and extracted with diethyl ether (4 x 10 ml). The combined organic phases were dried ($MgSO_4$), filtered, evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : ethyl acetate from 9.5:0.5 to 8:2) to afford in order of elution (12) (0.162 g, 44%) as a clear colourless oil; Rf = 0.43 (7:3 petroleum ether 40/60 : ethyl acetate); $[\alpha]_D^{25}$ = -27.4 (c.1.0, chloroform), $[\alpha]_D^{25}$ = -28.6 (c.1.3, chloroform); ^1H NMR(300 MHz, $CDCl_3$)δ: 1.356(3H, d J=7.0 Hz, $CHC\underline{H}_3$), 2.591(1H, dd $J_{2,3}$=4.0 Hz, $J_{2,2'}$=18.0 Hz, H-2), 2.851(1H, dd $J_{2,3}$=7.2 Hz, $J_{2,2'}$=18.0 Hz, H-2), 4.113-4.161(1H, m, C<u>H</u>OBOM), 4.519-4.582(1H, m, C<u>H</u>Me or d, $J_{3,4}$=2.7 Hz on irradiating the d. at 1.356ppm), 4.657(2H, s, OCH_2Ar), 4.807(1H, d J=8.0 Hz, OCH_2O), 4.834(1H, d J=8.0 Hz, OCH_2O), 7.285-7.390(5H, m, Ar); IR (film): 3100(w, Ar), 3080(w, Ar), 3050(m, Ar), 2990(m), 2950(m), 2910(m), 1790(s, C=O), 1615(w, Ar), 1595(w, Ar), 1505(m), 1460(m), 1415(m), 1390(m), 1365(m), 1320(m), 1300(m), 1250(m), 1215(m), 1180(s), 1170(s), 1115(s), 1085(s), 1055(s), 1035(s), 995(m), 950(m), 910(m), 850(w), 830(w), 745(s, Ar), 705(s, Ar), cm-1; MS m/e: 237(M^++1), 236(M^+), 223, 206, 198, 180, 179, 167, 109, 108, 107; HRMS calcd for $C_{13}H_{16}O_4$: 236.10485, found:236.10590; and (13) (0.164 g, 45%) as a clear colourless oil; Rf = 0.31 (7:3 petroleum ether 40/60 : ethyl acetate); $[\alpha]_D^{25}$ = +10.7 (c. 1.0, chloroform), $[\alpha]_D^{25}$ = +11.1 (c.0.7, chloroform); ^1H NMR(300 MHz, $CDCl_3$)δ: 1.431(3H, d J=6.1 Hz, $CHC\underline{H}_3$), 2.662(1H, dd $J_{2,3}$=2.9 Hz, $J_{2,2'}$=17.5 Hz, H-2), 2.747(1H, dd $J_{2,3}$=5.3 Hz, $J_{2,2'}$=17.5 Hz, H-2), 4.402-4.444(1H, m, C<u>H</u>OBOM), 4.588-4.663(1H, m, C<u>H</u>Me or d, (4.651 ppm) $J_{3,4}$=6.0 Hz on irradiating the d. at 1.431 ppm), 4.641(2H, s, OCH_2Ar), 4.791(1H, d J=7.4 Hz, OCH_2O), 4.831(1H, d J=7.4 Hz, OCH_2O), 7.316-7.362(5H, m, Ar); IR (film): 3100(w, Ar), 3080(m, Ar), 3050(m, Ar), 3000(m), 2960(s), 2910(s), 1785(s, C=O, 1615(w, Ar), 1595(w, Ar), 1505(m), 1460(s), 1415(m), 1395(s), 1350(m), 1300(m), 1250(m), 1220(s), 1165(s), 1110(s), 1100(s), 1050(s), 975(m), 950(s), 910(m), 855(m), 825(m), 750(s, Ar), 705(s, Ar), cm^{-1}; MS m/e: 236(M^+), 206, 167, 122, 118, 108(base), 107, 98, 91, 79; HRMS calcd for $C_{13}H_{16}O_4$: 236.10485, found: 236.10530.

Preparation of 4(S)-benzyloxymethoxy-5(R)-methyl-2(3H)-dihydrofuranone (14) and 4(R)-benzyloxymethoxy-5(R)-methyl-2(3H)-dihydrofuranone (15) from (11). Freshly distilled tetraisopropyl titanate (0.39 ml, 1.94 eq.) was added to a stirred solution of (11) (0.250 g, 0.67 mmol) in absolute ethanol (5 ml) under argon at room temperature. The reaction mixture was then refluxed during 16 h. The solvent was evaporated *in vacuo* , diluted with 1 M hydrochloric acid (10 ml) and extracted with diethyl ether (3.x 10 ml). The etheral solution was washed with saturated aqueous bicarbonate (20 ml) and the combined organic phases were dried ($MgSO_4$), filtered, evaporated and the crude product was chromatographed on a silica gel column (eluents: petroleum ether 40/60 : ethyl acetate from 1:0. to 8:2) to afford in order of elution (14) (0.059 g, 37%) as a clear colourless oil; spectral data identical to those reported earlier for its enantiomer; $[\alpha]_D^{25}$ = +26.5 (c.1.08, chloroform), $[\alpha]_D^{25}$ = +27.0 (c.1.5, chloroform), $[\alpha]_D^{25}$ = +26.9 (c. 0.93, chloroform), $[\alpha]_D^{25}$ = +26.9 (c.1.1, chloroform) and (15) (0.064, 40%) as a clear colourless oil; spectral data identical to those reported earlier for its enantiomer; $[\alpha]_D^{25}$= -10.6 (c.1.1, chloroform), $[\alpha]_D^{25}$ = -10.6 (c.0.6, chloroform).

Preparation of 4(R)-hydroxy-5(S)-methyl-2(3H)-dihydrofuranone (16). 10% Palladium on carbon (0.215 g, 154.7 mg/mmol) was added to a solution of (12) (0.328 g, 1.39 mmol) in ethanol (9 ml). The solution was degassed and then stirred vigorously under a slight positive-pressure hydrogen atmosphere (balloon) at room temperature. After 1.5 days methanol (15 ml) and

hydrochloric acid 37% (1 drop) was added. After stirring for 1 hr the reaction was filtered, washed with methanol (50 ml) and the filtrate was evaporated to dryness and the crude product chromatographed on a silica gel column (eluents: petroleum ether 40/60 : ethyl acetate from 7:3 to 0:1) to afford (16) (0.155 g, 96%) as a clear colourless oil; spectral data (IR, ^{1}H NMR) consistent with those reported[2i,d]; e.e. > 97%; $[\alpha]_D^{25}$ = -11.6 (c. 2.5, $CHCl_3$), lit.[2d] $[\alpha]_D^{25}$ = -10.81 (c. 1.85, $CHCl_3$). The Mosher's ester derivative was prepared following the literature procedure [18] using (16) (11 mg), dry carbon tetrachloride (284 µl), dry pyridine (284 µl) (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (25 µl), rt, 18 hr and further purification by preparative TLC (eluents: 1:1 petroleum ether 40/60 : ethyl acetate) to remove baseline material; ^{1}H NMR(300 MHz, $CDCl_3$)δ: 1.469(3H, d J=7.0 Hz, $CHC\underline{H}_3$), 2.568(1H, dd J=2.1, 17.8 Hz, H-2), 3.014(1H, dd J=7.3, 17.8 Hz, H-2), 3.534(3H, s, OMe), 4.676(1H, q J=7.0 Hz, C<u>H</u>Me), 5.242(1H, d J=7.3 Hz, C<u>H</u>OMTPA), 7.421-7.494(5H, m, Ar).

Preparation of 4(S)-hydroxy-5(S)-methyl-2(3H)-dihydrofuranone (17). The lactone (13) (0.364 g, 1.54 mmol) was deprotected in a similar manner to that described earlier. Purification by flash chromatography (eluents: petroleum ether 40/60 : ethyl acetate 7:3 to 0:1)) gave (17) (0.154 g, 86%).as a clear colourless oil; spectral data (IR, ^{1}H NMR) consistent with those reported[2d,]; e.e. > 97%; $[\alpha]_D^{25}$ = -73.7 (c.1.67, ethanol), $[\alpha]_D^{25}$ = -73.5 (c.0.93, ethanol), lit.[2d] $[\alpha]_D^{20}$ = -73.7 (c. 1.6, ethanol). The Mosher's ester derivative was prepared in a similar manner to that described earlier; ^{1}H NMR(300 MHz, $CDCl_3$)δ: 1.245(3H, d J=6.6 Hz, $CHC\underline{H}_3$), 2.653(1H, d J=18 Hz, H-2), 3.001(1H, dd J=6.0, 18 Hz, H-2), 3.539(3H, s, OMe), 4.721-4.756(1H, m, C<u>H</u>Me), 5.604(1H, t J=5.1 Hz, C<u>H</u>OMTPA), 7.400-7.513(5H, m, Ar).

Preparation of 4(S)-hydroxy-5(R)-methyl-2(3H)-dihydrofuranone (18). The lactone (14) was deprotected in a similar manner to that described earlier for its enantiomer. Purification by flash chromatography (eluents: petroleum ether 40/60 : ethyl acetate 7:3 to 0:1)) gave (17) as a clear colourless oil; spectral data (IR, ^{1}H NMR) consistent with those reported[2i,d]; e.e. > 97%; $[\alpha]_D^{25}$ = +11.0 (c. 1.4, $CHCl_3$), lit.[2d] $[\alpha]_D^{20}$ = +10.2 (c. 2.6, $CHCl_3$), lit.[2i] $[\alpha]_D^{20}$ = +10.87 (c. 2.42, $CHCl_3$). The Mosher's ester derivative was prepared in a similar manner to that described earlier; ^{1}H NMR(300 MHz, $CDCl_3$)δ: 1.448(3H, d J=6.9 Hz, $CHC\underline{H}_3$), 2.656(1H, dd J=2.6, 16.7 Hz, H-2), 3.045(1H, dd J=6.5, 16.7 Hz, H-2), 3.520(3H, s, OMe), 4.578(1H, q J=6.9 Hz, C<u>H</u>Me), 5.258(1H, dd J=2.6, 6.5 Hz, C<u>H</u>OMTPA), 7.362-7.494(5H, m, Ar).

Preparation of 4(R)-hydroxy-5(R)-methyl-2(3H)-dihydrofuranone (19). The lactone (15) was deprotected in a similar manner to that described earlier for its enantiomer. Purification by flash chromatography (eluents: petroleum ether 40/60 : ethyl acetate 7:3 to 0:1)) gave (19) as a clear colourless oil; spectral data (IR, ^{1}H NMR) consistent with those reported[2d,16,]; e.e. > 97%; $[\alpha]_D^{20}$ = +73.2 (c. 1.1, EtOH), lit.[22] $[\alpha]_D^{25}$ = +75 (c. 0.25, EtOH). The Mosher's ester derivative was prepared in a similar manner to that described earlier; ^{1}H NMR(300 MHz, $CDCl_3$)δ: 1.370(3H, d J=6.6 Hz, $CHC\underline{H}_3$), 2.570(1H, d J=18.3, Hz, H-2), 2.976(1H, dd J=6.6, 18.3 Hz, H-2), 3.506(3H, s, OMe), 4.744-4.780(1H, m, C<u>H</u>Me), 5.599(1H, t J=5.0 Hz, C<u>H</u>OMTPA), 7.423-7.505(5H, m, Ar).

Preparation of 4(S)-benzyloxymethoxy-5(S)-methyl-2(3H)-dihydrofuranone (13) and 4(S)-benzyloxymethoxy-5(R)-methyl-2(3H)-dihydrofuranone (14) from (8). a) <u>Reduction of (8) with K-Selectride®</u>: K-Selectride® (1.0 M in tetrahydrofuran, 1.5 ml, 1 eq.) was added dropwise (10 min) *via* syringe to a stirred solution of (8) (0.396 g, 1.49 mmol e.e. (S) 95%) in dry tetrahydrofuran (6 ml) at -100 °C under argon. After 30 min the reaction was quenched by addition of saturated ammonium chloride (5 ml). The mixture was allowed to warm to ambient temperature and was then extracted with diethyl ether (4 x 5 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness to give a yellow oil which was treated with HCl/acetone/water as described earlier. Purification by flash chromatography (eluents: petroleum ether 40/60 : ethyl acetate 9.5:0.5 to 8:2)) gave in order of elution (14) (0.004 g, 1%) and (13) (0.204 g, 58%). Deprotection of lactone (13) as described earlier gave the hydroxylactone (17); $[\alpha]_D^{25}$ = -66.4 (c.1.74, ethanol).

b) <u>Reduction of (8) with zinc borohydride</u>: Zinc borohydride[11] (0.13 M in diethyl ether, 2.6 ml, 0.34 mmol) was added dropwise (5 min) *via* syringe to a stirred solution of (8) (0.154 g, 0.68 mmol, e.e. (S) 95%) in dry diethyl ether (2 ml) at room temperature under argon. Successive additions of zinc borohydride (3 x 2.6 ml) were made after 1, 2 and 3 days. After 4 days the mixture was

partitioned between diethyl ether (7 ml) and water (5 ml) and the aqueous phase extracted with diethyl ether (3 x 7 ml). The combined organic phases were dried ($MgSO_4$), filtered, evaporated and the crude product was chromatographed by preparative TLC (eluents: 8:2 petroleum ether 40/60 : ethyl acetate) to afford in order of elution starting material (**8**) (0.014 g, 9% recovery), (**14**) (0.096 g, 60%), e.e. 94% determined by conversion into the Mosher's ester derivative of corresponding hydroxylactone as described earlier and NMR analysis; and (**13**) (0.024 g, 15%), e.e. 93% determined as above.

Preparation of methyl 3-(S)-benzoyloxy-4-oxopentanoate (20). Benzoyl chloride (1.1 ml, 1.5 eq.) was added to a stirred solution of (**5**) (1.402 g, 6.31 mmol, e.e. (S) = 95%) and dry pyridine (1.5 ml, 3 eq.) in dry benzene (6 ml) at room temperature under argon. After 2.5 days 1M hydrochloric acid (10 ml) was added and this mixture extracted with diethyl ether (3 x 15 ml). The etheral solution was washed with saturated aqueous bicarbonate (30 ml) and the combined organic phases were dried ($MgSO_4$), filtered, evaporated and the crude product, a colourless oil, was treated with mercury (II) oxide/trifluoride etherate in a similar manner to that described earlier. Purification by flash chromatography (eluents: petroleum ether 40/60 : dichloromethane from 8:2 to 0:1) gave (**20**) (1.262 g, 80%).as a clear colourless oil; Rf = 0.34 (dichloromethane); $[\alpha]_D^{25}$ = -6.3 (c. 0.80, chloroform); ^{1}H NMR(60 MHz, CCl_4)δ: 2.25(3H, s, MeCO), 2.95(2H, d J=5 Hz, H-2), 3.70(3H, s, CO_2Me), 5.55(1H, t J=5 Hz, CHOBz), 7.48-7.70(3H, m, Ar), 8.05-8.25(2H, m, Ar); IR (film): 3070(w, Ar), 3010(w, Ar), 2960(m), 1725(s, C=O), 1610(m, Ar), 1590(w, Ar), 1500(w), 1460(s), 1445(s), 1370(s), 1320(m), 1280(s), 1210(s), 1180(s), 1120(s), 1080(s), 1030(m), 1010(m), 995(m), 970(m), 900(w), 850(w), 810(w), 715(s, Ar), cm^{-1}. The racemic sample (**21**) was prepared as described above starting from racemic (**5**)[3].

Preparation of ethyl 3-(R,S)-benzoyloxy-4-oxopentanoate (22). The racemic α-hydroxythioacetal ethyl ester (**6**) (1.200 g, 5.12 mmol) was subjected to hydroxyl protection (benzoate ester) and carbonyl deprotection in a similar manner to that described earlier. Purification by flash chromatography (eluents: petroleum ether 40/60 : ethyl acetate from 1:0 to 8:2) gave (**22**) (1.064 g, 78%) as a clear colourless oil; R_f = 0.43 (dichloromethane); ^{1}H NMR(60 MHz, CCl_4)δ: 1.24(3H, t J=7 Hz, $OCH_2\underline{CH_3}$), 2.24(3H, s, COMe), 2.90(2H, d J=5 Hz, H-2), 4.12(2H, q J=7 Hz, $OC\underline{H_2}Me$), 5.52(1H, t J=5 Hz, CHOBz), 7.45-7.65(3H, m, Ar), 8.0-8.2(2H, m, Ar); IR (film): 3080(w, Ar), 2990(m), 2950(m), 2920(w), 1725(s, C=O), 1610(m, Ar), 1590(m, Ar), 1460(s), 1400(m), 1380(s), 1360(s), 1320(s), 1280(s), 1180(s), 1120(s), 1075(s), 1030(s), 1005(m), 970(w), 940(w), 850(w), 810(w), 760(w), 710(s, Ar) cm^{-1}; HRMS calcd for $C_{14}H_{16}O_5$: 264.09976, found: 264.09972; MS m/e: 264(M^+), 221(M^+-COMe), 219(M^+-OEt), 127, 105($PhCO^+$, base), 97, 77($C_6H_5^+$).

Preparation of 4(R)-benzoyloxy-5(S)-methyl-2(3H)-dihydrofuranone (23) and 4(S)-benzoyloxy-5(S)-methyl-2(3H)-dihydrofuranone (24). General procedure: The ketone (**21**) (1.737 g, 6.91 mmol) was subjected to bakers' yeast reduction (23 °C) and lactonization with HCl/acetone/water (2.5 days) in a similar manner to that described earlier. Purification by flash chromatography (eluents: petroleum ether 40/60 : dichloromethane from 1:1 to 1:9) gave in order of elution (**23**) (0.642 g, 42%) as a white solid; Rf = 0.54 (dichloromethane); mp. 103 - 103.5°C (petroleum ether 40/60/carbon tetrachloride); lit.[2i] for its enantiomer 100.5 - 101.5°C (diethyl ether/petroleum ether 40/60); $[\alpha]_D^{25}$ = +41.6 (c. 1.1, chloroform), $[\alpha]_D^{25}$ = +41.4 (c. 0.87, chloroform), lit.[2i] for its enantiomer $[\alpha]_D$ = -42.5 (c. 1.0, chloroform); e.e.> 97%, determined by optical shift comparison; spectral data (IR, ^{1}H NMR) consistent with those reported for its enantiomer[2i]; MS m/e: 220(M^+), 202(M^+-H_2O), 176(M^+- CO_2 or M^+-CH_2CO), 148, 123, 105($PhCO^+$, base), 98, 83, 77; Anal. Calcd. for $C_{12}H_{12}O_4$: C 65.45, H 5.49%. Found:C 65.36, H 5.44% and (**24**) (0.455 g, 30%) as a colourless solid; R_f = 0.43 (dichloromethane); mp. 101-102°C (petroleum ether 40/60/carbon tetrachloride); $[\alpha]_D^{25}$ = -47.4 (c.1.0, chloroform), $[\alpha]_D^{25}$ = -47.8 (c.0.55, chloroform); e.e. > 97% determined by ^{1}H NMR(300 MHz, 0.02 M in $CDCl_3$) of (**24**) and its enantiomer in a racemic sample based on signals for the C-4 Me (d, J =18 Hz) (respectively at δ 2.98 and 3.00 ppm) in the presence of 1.2:1 molar ratio Eu(tfc)$_3$/substrate; ^{1}H NMR(300 MHz, $CDCl_3$)δ: 1.475(3H, d J=6.0 Hz, C-4 Me), 2.754(1H, d $J_{22'}$=18.2 Hz, H-2), 3.035(1H, dd $J_{22'}$=18.2 Hz, J_{23}=6.0 Hz, H-2), 4.794-4.872(1H, m, H-4, q J=6.0 Hz, if irradiated the dd (5.710 ppm) of H-3), 5.710(1H, dd J_{34}=5.0 Hz, J_{23}=6.0 Hz, H-3), 7.471(2H, t J=7.5 Hz,

m-Ar), 7.612(1H, t J=7.5 Hz, p-Ar), 8.040(2H, d J=7.5 Hz, o-Ar); IR (nujol): 1780(s, C-1 C=O), 1720(s, OBz C=O), 1600(m, Ar), 1355(s), 1315(s), 1275(s), 1245(s), 1210(s), 1170(s), 1140(s), 1110(s), 1100(s), 1060(s), 1025(s), 980(s), 950(s), 920(s), 875(m), 850(m), 810(m), 730(s, Ar), 715(s, Ar) cm^{-1}; MS m/e: 220(M^+), 176(M^+-CO_2 or M^+-CH_2CO), 148, 105($PhCO^+$, base), 98, 83, 77; Anal. Calcd for $C_{12}H_{12}O_4$: C 65.45, H 5.49%. Found:C 65.22, H 5.48%.

Preparation of (+)-(S)-β-angelica lactone (25) from (24): The lactone (24) (0.078 g, 0.35 mmol) was treated with MeOH/NH_3 using literature procedure[2g]. Purification by flash chromatography (eluents: petroleum ether 40/60 : dichloromethane from) gave (25) (0.030 g, 88%) as a clear colourless oil; spectral data (IR, ^1H NMR) consistent with those reported[2d,i]; $[\alpha]_D^{25}$ = +104.8 (c. 0.65, chloroform); lit.[2d] $[\alpha]_D^{20}$ = +93.83 (c. 0.5, chloroform); for its enantiomer lit.[2i] $[\alpha]_D$ = -107.0 (c. 1.61, chloroform), lit.[2d] $[\alpha]_D^{20}$ = -95.9 (c. 0.7, chloroform); e.e.> 97%, determined by optical rotation comparison.

From (23):(+)-(S)-β-angelica lactone (25) was prepared as described above, $[\alpha]_D$ = +104.0 (c. 0.6, chloroform), e.e.> 97%, determined by optical rotation comparison.

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