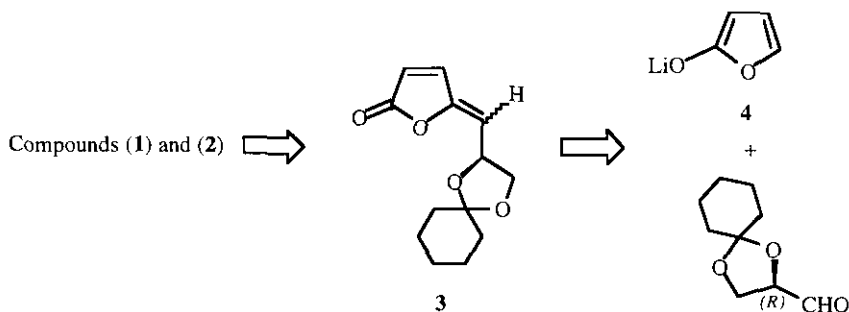


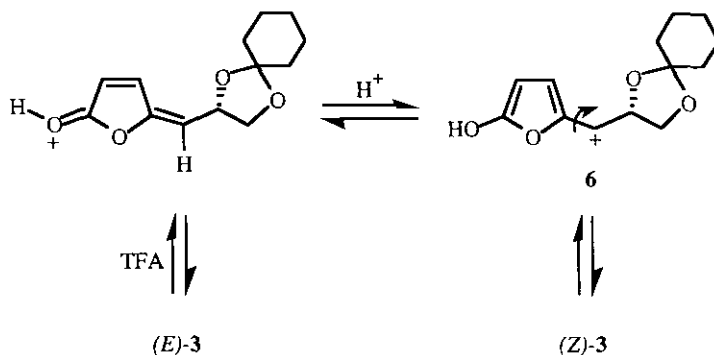
(4) with freshly prepared (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde⁹ at -78 °C for 1 h gave a crude product containing the desired γ -adduct along with other unidentified products. The crude reaction

Scheme 1



mixture was subjected to elimination without purification by employing methanesulfonyl chloride in pyridine or using methanesulfonyl chloride/triethylamine in dichloromethane followed by treatment with diisopropylamine.¹⁰ The pure (*Z*)-isomer (3) could be isolated in 22% yield by MPLC along with 5% yield of pure (*E*)-isomer (3) and 4% yield of a 71:29 mixture of the (*Z*)- and (*E*)-isomers. Hydrolysis of (*Z*)-3 to (*Z*)-diol (5) could be accomplished by using 90% aqueous trifluoroacetic acid at 0 °C or 0 °C to room temperature. All attempts led to moderate yield of the desired (*Z*)-diol (5) (47-57%) along with the recovered starting material ((*Z*)-3) (15-21% yield). The incomplete hydrolysis of (*Z*)-3 might be due to the fact that the reaction was reversible: cyclohexanone *in situ* generated could presumably react with (*Z*)-diol (5) in the presence of trifluoroacetic acid. The structure of (*Z*)-diol (5) was established on the basis of interpretation of 300 MHz ¹H NMR and NOE spectral data. The ¹H NMR data and the sign of the specific rotation of (*Z*)-diol (5) were consistent with those reported for the known (*S*)-(*Z*)-5-(2,3-dihydroxypropylidene)-2(5*H*)-furanone.⁶ Having succeeded in preparing the (*S*)-(*Z*)-diol (5), an attempt was made to hydrolyze the (*E*)-isomer (3) by employing the similar conditions for (*Z*)-3. It was found that treatment of the pure (*E*)-3 with 90% aqueous trifluoroacetic acid at 0 °C for 15-16 h provided a 74:26

Scheme 2



specific rotation of our synthetic melodorinol (**1**) [$[\alpha]_D^{25} +92.5^\circ$ (c 0.08, CHCl_3)] was concordant with (*S*)-(+)-melodorinol as previously synthesized by Shen⁶ [$[\alpha]_D^{22} +72^\circ$ (c 1.0 CHCl_3)] and Lu⁷ [$[\alpha]_D^{22} +86.4^\circ$ (c 0.95, CHCl_3)]. (*S*)-(+)-Acetylmelodorinol (**2**) could be finally prepared in 76% yield as a white solid by acetylation of (*S*)-(+)-melodorinol (**1**) with acetic anhydride and pyridine in dichloromethane at 0 °C to room temperature for 14 h. The spectral data including the sign of the specific rotation were found in good agreement with those published in the literature.^{6,7}

In summary, we have demonstrated the synthetic utility of the lithiated butenolide as a useful butenolide synthon for the preparation of (*S*)-(+)-melodorinol (**1**) and (*S*)-(+)-acetylmelodorinol (**2**).

EXPERIMENTAL

General: Melting points were determined either by an Electrothermal or a Buechi 510 Melting Point Apparatus and were uncorrected. ¹H NMR spectra were measured with a Bruker DPX300 Spectrometer, using TMS as an internal reference and reported in parts per million (ppm). IR spectra were recorded on a Jasco A-302 or a Perkin Elmer 2000 NIR FT Raman. MS spectra were obtained on a Finnigan MAT INCOS 50 Mass Spectrometer at 70 eV. Elemental analyses were performed by using a Perkin Elmer Elemental Analyzer 2400 CHN. All solvents were dried by using standard methods prior to use.

(*S*)-(*Z*)- and (*S*)-(*E*)-5-(2,3-*O*-Cyclohexylidene-2,3-dihydroxypropylidene)-2(5*H*)-furanone (**3**).

To a stirred (-78 °C) THF solution of LDA [prepared by reacting diisopropylamine (3.1 mL, 22 mmol) in THF (80 mL) with *n*-BuLi (1.03 M in hexane; 19.5 mL, 22 mmol) at -78 °C for 30 min] was added dropwise a THF (5 mL) solution of 2(5*H*)-furanone (1.68 g, 20 mmol). The resulting mixture was allowed to stir at -78 °C for 1 h. Freshly prepared 2,3-*O*-cyclohexylidene-D-glyceraldehyde (3.74 g, 22 mmol) in THF (5 mL) was added dropwise at -78 °C. The reaction mixture was kept stirring at this temperature for 1.5 h, and quenched with a saturated NH_4Cl solution (20 mL) at -78 °C. After warming up to rt, it was diluted with water (20 mL) and extracted with EtOAc (4 x 50 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 . Filtration and evaporation of the solvent gave a pale yellow viscous liquid of a crude product, which was used without further purification.

The crude product obtained was dissolved in dry pyridine (20 mL) under nitrogen atmosphere at 0 °C and treated with freshly distilled methanesulfonyl chloride (1.8 mL, 23 mmol) at 0 °C. After stirring at 0 °C for 20 min and then at rt for 2 h, the mixture was heated at 80-90 °C for 10 h. The reaction mixture was diluted with water and extracted with EtOAc (4x50 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was purified by MPLC (3.5 x 72 cm column on SiO_2 , 0-5% EtOAc in hexane) to give (*Z*)-**3** (1.03 g, 22%), a mixture of (*Z*)- and (*E*)-isomers (**3**) as a viscous liquid (71:29; 0.208 mg, 4%), and (*E*)-**3** (233 mg, 5%).

*Elimination employing MsCl/Et₃N/CH₂Cl₂/i-Pr₂NH.*¹⁰ The crude product obtained from the reaction of the lithiated butenolide (5.0 mmol) and 2,3-*O*-cyclohexylidene-D-glyceraldehyde (1.02 g, 6.0 mmol) was dissolved in CH₂Cl₂ (50 mL), to which was added triethylamine (1.41 mL, 10 mmol) and methanesulfonyl chloride (0.7 mL, 9.0 mmol) at -60 °C. After stirring at the same temperature for 30 min, the resulting mixture was quenched with a saturated NH₄Cl solution (20 mL) and extracted with CH₂Cl₂. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and evaporation to dryness to give a crude mesylate. This was dissolved in CH₂Cl₂ (50 mL), followed by the addition of diisopropylamine (3.95 mL, 28 mmol). The resulting reaction mixture was stirred at rt for 40 min, then quenched with a saturated NH₄Cl solution (20 mL) and extracted with CH₂Cl₂. The combined extracts were washed with water, brine and dried over anhydrous Na₂SO₄. Filtration and evaporation afforded a crude product (1.41 g), which was purified by MPLC (0-5% ethyl acetate in hexane) to give (*Z*)-**3** (168 mg, 14% yield), (*E*)-**3** (27.7 mg, 2% yield) and a mixture of (*Z*)- and (*E*)-isomers (70:30; 203 mg, 17% yield).

(*S*)-(-)-(*Z*)-**3**: as a viscous liquid. $[\alpha]_D^{26} - 35.6^\circ$ (*c* 0.23, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.39 (d, *J* = 5.4 Hz, 1H, COCH=CH-), 6.26 (d, *J* = 5.4 Hz, COCH=CH-), 5.37 (d, *J* = 8.4 Hz, 1H, =CHCHO-), 5.21-5.12 (m, 1H, =CHCHO-), 4.23 (dd, *J* = 8.2, 6.3 Hz, 1H, OCHCHHO-), 3.71 (dd, *J* = 8.2, 6.9 Hz, 1H, OCHCHHO-), 1.72-1.54 and 1.50-1.35 [each m, 10H, -(CH₂)₅]. IR (nujol): ν_{\max} 1772, 1740, 1676, 1560, 1450, 1370, 1299, 1236, 1166, 1097, 1039, 932, 873, 845 cm⁻¹. MS: *m/z* (%) relative intensity 236 (M⁺, 15), 206 (10), 193 (29), 177 (3), 165 (3), 149 (1), 138 (23), 122(100), 110 (10), 94 (60), 82 (16), 66 (44), 55 (65). Anal. Calcd for C₁₃H₁₆O₄: C, 66.08; H, 6.82. Found: C, 65.68; H, 6.80.

(*S*)-(-)-(*E*)-**3**: as a pale yellow solid. mp 80-82 °C (ether-hexane); $[\alpha]_D^{25} - 13.1^\circ$ (*c* 0.31, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 7.83 (d, *J* = 5.6 Hz, 1H, COCH=CH-), 6.29 (dd, *J* = 5.6, 1.6 Hz, 1H, COCH=CH-), 5.72 (dd, *J* = 7.8, 1.2 Hz, 1H, =CHCHO-), 4.92-4.82 (m, 1H, =CHCHO-), 4.21 (dd, *J* = 8.2, 6.2 Hz, 1H, OCHCHHO-), 3.72 (dd, *J* = 8.2, 7.4 Hz, 1H, OCHCHHO-), 1.72-1.56 and 1.50-1.35 [each m, 10H, -(CH₂)₅]. ¹³C NMR (75 MHz, CDCl₃): δ 168.84, 151.47, 140.35, 121.33, 112.10, 110.84, 71.05, 69.22, 36.14, 35.20, 24.89, 23.80, 23.73. IR (nujol): ν_{\max} 1779, 1753, 1670, 1560, 1459, 1450, 1370, 1162, 1119, 1066, 1052, 927, 884, 822 cm⁻¹. MS: *m/z* (%) relative intensity 236 (M⁺, 11), 206 (7), 193 (18), 177 (3), 164 (3), 149 (2), 138 (26), 122 (100), 110 (11), 94 (63), 82 (17), 66 (46), 55 (63). Anal. Calcd for C₁₃H₁₆O₄: C, 66.08; H, 6.82. Found: C, 65.90; H, 6.66.

Preparation of (*S*)-(+)-(*Z*)-**5**-(2,3-Dihydroxypropylidene)-2(5*H*)-furanone (**5**).

(*S*)-(*Z*)-**3** (0.116 g, 0.5 mmol) was dissolved in 90% trifluoroacetic acid (1 mL) at 0 °C. The solution was kept stirring at 0 °C for 1.5 h. After usual workup and chromatography, the desired (*S*)-(*Z*)-diol (**5**) (32.3 mg, 42%) as a colorless viscous liquid together with the starting material ((*S*)-(*Z*)-**3**) (31.2 mg, 27%) was obtained. When the reaction was carried out at 0 °C for 26 h, (*S*)-(*Z*)-diol (**5**) (44.8 mg, 57%) as a colorless viscous liquid was isolated along with the starting material ((*S*)-(*Z*)-**3**) (17.4 mg, 15%).

(*Z*)-Diol (**5**): $[\alpha]_{\text{D}}^{29} + 8^{\circ}$ (*c* 0.1, MeOH); lit.,⁶ $[\alpha]_{\text{D}}^{32} + 12^{\circ}$ (*c* 0.5, MeOH), lit.,⁷ $[\alpha]_{\text{D}}^{22} + 39^{\circ}$ (*c* 0.6, MeOH). ¹H NMR (300 MHz, CDCl₃): δ 7.42 (d, *J* = 5.5 Hz, 1H, COCH=CH-), 6.25 (d, *J* = 5.5 Hz, 1H, COCH=CH-), 5.40 (d, *J* = 8.1 Hz, 1H, =CHCHO-), 4.88-4.79 (m, 1H, =CHCHO-), 3.76 (dd, *J* = 11.4, 3.4 Hz, 1H, -OCHCHHO-), 3.59 (dd, *J* = 11.4, 6.9 Hz, 1H, -OCHCHHO-), 2.59 (br s, 2H, OH). ¹³C NMR (75 MHz, CDCl₃): δ 169.58, 149.51, 143.96, 120.47, 114.64, 67.63, 65.46. IR (CHCl₃): ν_{max} 3598, 3450, 3029, 3000, 2900, 1780, 1760, 1677, 1561, 1231, 1115, 1066, 941, 836 cm⁻¹. MS: *m/z* (%) relative intensity 156 (M⁺, 2), 139 (1), 125 (94), 109 (2), 97 (100), 82 (19), 79 (16), 69 (49), 65 (3), 61 (6), 54 (37).

Preparation of (*S*)-(+)-(*Z*)-5-(3-Benzoyloxy-2-hydroxypropylidene)-2(5*H*)-furanone (1**) (Melodorinol).**

Using PhCOCl/Et₃N/CH₂Cl₂ / 0 °C to rt (22 h).

To a cooled (0 °C) solution of (*S*)-(*Z*)-diol (**5**) (44.8 mg, 0.28 mmol) in dry CH₂Cl₂ (1 mL) were added triethylamine (0.2 mL) and a solution of PhCOCl (44.9 mg, 0.32 mmol) in CH₂Cl₂ (1 mL). The reaction mixture was kept in a refrigerator overnight (22 h), then diluted with water (10 mL) and extracted with EtOAc (4 x 20 mL). The combined extracts were washed with a cold 10% NaHCO₃ solution (10 mL), brine and dried over anhydrous Na₂SO₄. Filtration and evaporation of the solvent gave a crude product, which was purified by radial chromatography (SiO₂, 30-100 % EtOAc in hexane) to afford dibenzoate (**7**) (7.8 mg, 8%), melodorinol (**1**) (35.1 mg, 48%) and a mixture of **1** and **8** (36:64; 9.5 mg, 13%) along with the starting material ((*S*)-(*Z*)-diol **5**) (5.3 mg, 12%).

Using benzoyl cyanide/Et₃N/THF/-40 °C.

To a cooled (-40 °C) solution of (*S*)-(*Z*)-diol (**5**) (77 mg, 0.5 mmol) in THF (30 mL) were added sequentially triethylamine (0.2 mL, 1.5 mmol) and a solution of PhCOCN (0.2191 g, 1.67 mmol) in THF (5 mL). The reaction mixture was stirred at -40 °C for 2 h and quenched with MeOH (10 mL) in order to destroy the unreacted PhCOCN and allowed to warm to rt gradually. After removal of the solvents under reduced pressure, the residue was taken into EtOAc (100 mL). It was washed with a cold 5% NaHCO₃ solution (10 mL), water (10 mL), brine and dried over anhydrous Na₂SO₄. Filtration and evaporation provided a pale yellow viscous liquid, which was purified by radial chromatography (SiO₂) to give dibenzoate (**7**) (32.9 mg, 18%; hexane as an eluent) and melodorinol (**1**) (77.5 mg, 60%; 30-50% EtOAc-hexane elution). $[\alpha]_{\text{D}}^{25} + 92.5^{\circ}$ (*c* 0.08, CHCl₃); lit.,⁶ $[\alpha]_{\text{D}}^{22} + 72^{\circ}$ (*c* 1, CHCl₃), lit.,⁷ $[\alpha]_{\text{D}}^{22} + 86.4^{\circ}$ (*c* 0.95, CHCl₃). ¹H NMR (300 MHz, CDCl₃): δ 8.09-8.02 (m, 2H, ArH), 7.62-7.55 (m, 1H, ArH), 7.50-7.42 (m, 2H, ArH), 7.40 (d, *J* = 5.5 Hz, 1H, COCH=CH-), 6.27 (d, *J* = 5.5 Hz, 1H, COCH=CH-), 5.40 (d, *J* = 8.0 Hz, 1H, =CHCHO-), 5.18 (ddd, *J* = 8.0, 5.9, 4.5 Hz, 1H, OCHCH₂O-), 4.50 (dd, *J* = 11.7, 4.5 Hz, 1H, -OCHCHHO-), 4.46 (dd, *J* = 11.7, 5.9 Hz, 1H, -OCHCHHO-), 1.74 (br s, 1H, OH). ¹³C NMR (75 MHz, CDCl₃): δ 168.94, 166.69, 150.01, 143.67, 133.35, 129.72, 129.49, 128.46, 121.01, 113.18, 67.48, 65.80. IR (CHCl₃): ν_{max} 3472, 3030, 3020, 2940, 1779, 1750, 1721, 1690, 1603, 1562,

1453, 1317, 1273, 1178, 1113, 1067, 1027, 940, 879, 839 cm^{-1} . MS: m/z (%) relative intensity 260 (M^+ , 0.3), 243 (2), 230 (6), 215 (0.3), 177 (0.3), 165 (0.3), 154 (0.2), 138 (6), 125 (10), 110 (6), 105 (100), 97 (18), 91 (2), 82 (8), 77 (76), 69 (13), 65 (4), 55 (16), 51 (51).

(Z)-5-(2,3-Dibenzoyloxypropylidene)-2(5H)-furanone (7).

$[\alpha]_D^{27} - 60.8^\circ$ (c 0.34, CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 8.17-7.99 (m, 4H, ArH), 7.61-7.54 (m, 2H, ArH), 7.47-7.41 (m, 4H, ArH), 7.40 (d, $J = 5.4$ Hz, 1H, COCH=CH), 6.37 (ddd, $J = 8.1, 5.8, 4.5$ Hz, 1H, CHOCOPh), 6.30 (d, $J = 5.4$ Hz, COCH=CH), 5.45 (d, $J = 8.1$ Hz, 1H, =CHCHO-), 4.73 (dd, $J = 11.8, 5.8$ Hz, 1H, -OCHCHH-O), 4.68 (dd, $J = 11.8, 4.5$ Hz, 1H, -OCHCHHO-). ^{13}C NMR (75 MHz, CDCl_3): δ 168.41, 166.02, 165.37, 150.84, 143.27, 133.35, 133.25, 129.78, 129.69, 129.52, 129.47, 128.45, 121.65, 108.89, 67.99, 64.61. IR (CHCl_3): ν_{max} 3160, 3120, 3100, 3050, 3010, 2970, 2940, 2880, 1786, 1724, 1603, 1562, 1453, 1317, 1280, 1263, 1250, 1178, 1107, 1100, 1069, 1027, 942, 879, 832 cm^{-1} . MS: m/z (%) relative intensity 364 (M^+ , 3), 334 (2), 242 (30), 229 (1), 214 (1), 138 (1), 122 (4), 105 (100), 94 (3), 77 (65), 66 (6), 51 (38), 39 (10). Anal. Calcd for $\text{C}_{21}\text{H}_{16}\text{O}_6$: C, 69.22; H, 4.42. Found: C, 68.89; H, 4.38.

Preparation of (S)-(+)-(Z)-5-(2-Acetoxy-3-benzoyloxypropylidene)-2(5H)-furanone (2) (Acetylmelodorinol).

To a cooled (0°C) solution of melodorinol (**1**) (80 mg, 0.3 mmol) in dry CH_2Cl_2 (20 mL), were added dry pyridine (0.5 mL) and acetic anhydride (0.5 mL, 5.5 mmol). The reaction mixture was stirred at 0°C and slowly warmed up to rt gradually overnight (14 h). It was diluted with water (5 mL) and EtOAc (100 mL) was added. The resulting mixture was neutralized with a cold 2 N HCl solution (10 mL). The organic layer was washed with a saturated NaHCO_3 solution (10 mL), water (10 mL), brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure to give a crude product (77.8 mg) which was purified by radial chromatography (SiO_2 , 20% EtOAc in hexane) to afford a white solid of acetylmelodorinol (**2**) (68.9 mg, 76%; mp $78-80^\circ\text{C}$ from ether-hexane, lit.,⁶ mp $78-80^\circ\text{C}$ from *i*-PrOH-hexane). $[\alpha]_D^{27} + 31.9^\circ$ (c 0.23, CHCl_3); lit.,⁶ $[\alpha]_D^{22} + 32.5^\circ$ (c 2, CHCl_3), lit.,⁷ $[\alpha]_D^{22} + 41^\circ$ (c 0.33, CHCl_3), lit.,² $[\alpha]_D^{23} + 209^\circ$ (c 1, CHCl_3). ^1H NMR (300 MHz, CDCl_3): δ 8.07-8.01 (m, 2H, ArH), 7.63-7.55 (m, 1H, ArH), 7.51-7.43 (m, 2H, ArH), 7.38 (d, $J = 5.4$ Hz, 1H, COCH=CH), 6.28 (d, $J = 5.4$ Hz, COCH=CH), 6.15 (ddd, $J = 8.1, 5.8, 4.4$ Hz, 1H, CHOCOCH₃), 5.33 (d, $J = 8.1$ Hz, 1H, =CHCHO-), 4.58 (dd, $J = 11.8, 4.4$ Hz, 1H, -OCHCHHO-), 4.52 (dd, $J = 11.8, 5.8$ Hz, 1H, -OCHCHHO-), 2.11 (s, 3H, OCOCH₃). ^{13}C NMR (75 MHz, CDCl_3): δ 169.74, 168.42, 165.97, 150.66, 143.30, 133.26, 129.66, 129.48, 128.44, 121.55, 108.82, 67.24, 64.57, 20.85. IR (CHCl_3): ν_{max} 3029, 2930, 1786, 1755, 1725, 1690, 1603, 1563, 1452, 1373, 1273, 1240, 1178, 1108, 1067, 1028, 945, 877, 833 cm^{-1} . MS: m/z (%) relative intensity 302 (M^+ , 2), 272 (1), 258 (0.3), 243 (13), 230 (2), 215 (1), 180 (9), 167 (1), 152 (1), 138 (18), 125 (8), 110 (7), 105 (100), 97 (5), 77 (70), 66 (7), 51 (36), 43 (83).

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