Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 11, pp. 3141-3146, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00415-6

Total Synthesis of Acetylmelodorinol

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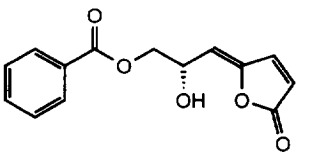
Abstract: An enantioselective total synthesis of bioactive melodorinol and acetylmelodorinol starting from 2,3-*O*-isopropylidene-D-glyceraldehyde and an alkoxyfuran is reported. Lithiation of the alkoxyfuran and subsequent reaction with the glyceraldehyde provided two diastereomers. These two adducts were treated with *p*-toluenesulfonic acid in aqueous THF to give a γ-propylidene butenolide, which was converted to melodorinol and acetylmelodorinol by acylation.

Melodorinol (**1**) and acetylmelodorinol (**2**) are two bioactive compounds, which were isolated from *Melodorum fruticosum* Lour. (Annonaceae).[1-3] Both compounds are heptene derivatives possessing a novel seven-carbon skeleton and showed cytotoxic activities in several human tumor cell lines including breast carcinoma, lung carcinoma, and colon adenocarcinoma. This paper presents the first total synthesis of these two compounds.



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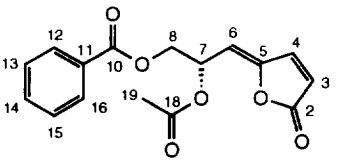
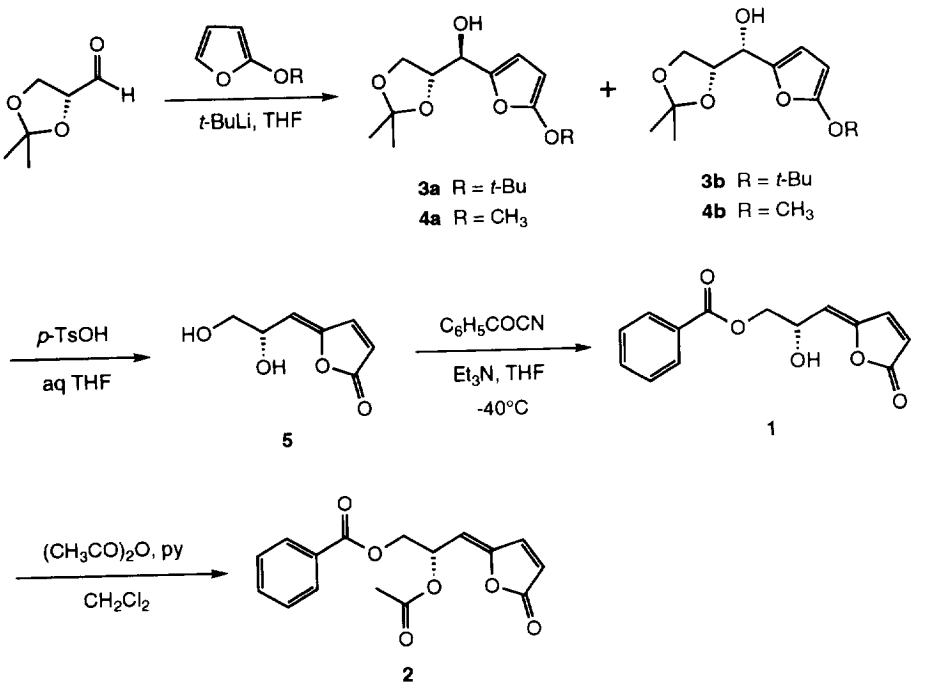


2

RESULTS AND DISCUSSION

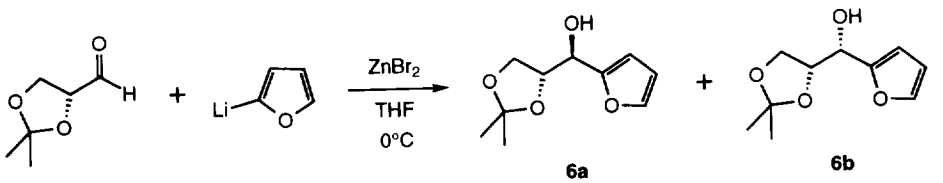
Our synthetic sequence shown in scheme 1 started from 2,3-*O*-isopropylidene-D-glyceraldehyde, which has the same *S*-configuration as acetylmelodorinol. After metallation of 2-*tert*-butoxyfuran at C-5 by *tert*-butyllithium, the furyllithium compound was treated with 2,3-*O*-isopropylidene-D-glyceraldehyde to

Scheme 1



afford two diastereomers, **3a** and **3b**, in a ca. 1:1 ratio.[4] The use of 2-methoxyfuran gave the corresponding methoxy products but the yield was lower. The aldol condensation of this glyceraldehyde was also attempted with 2-(trimethylsilyloxy)furan in the presence of $TiCl_4$,[5,6] $BF_3{\cdot}Et_2O$, or trimethylsilyl trifluoromethanesulfonate[7] but no desired butenolide was obtained.

In order to determine the configuration of the newly formed stereogenic center in **3a** and **3b**, we prepared similarly constituted chiral compound **6a**, (1*R*,2*R*)-1-(2-furyl)-2,3-*O*-isopropylidene-1,2,3-propanetriol, by the procedure of Suzuki et al.[8] In the presence of $ZnBr_2$, 2-furyllithium stereoselectively reacted with 2,3-*O*-isopropylidene-D-glyceraldehyde in THF at 0°C to afford *anti*-adduct **6a** predominantly.[9] The signal at 4.04 ppm in its ^1H NMR spectrum was assigned as the methylene protons of the 1,3-dioxolane ring, whereas these protons of *syn*-adduct **6b** resonated at a higher field (3.71 and 3.91 ppm). For compounds **3a** and **3b**, the methylene protons appeared at 4.02, 4.04 and 3.70, 3.90 ppm, respectively. Thus, by comparison of ^1H NMR spectra of compounds **3a**, **3b**, **6a**, and **6b**, we tentatively assigned the *anti*-configuration for **3a** and the *syn*-configuration for **3b**. Likewise, the stereochemistry of compounds **4a** and **4b** was determined.



Treatment of the diastereomeric mixture **3** or **4** with *p*-toluenesulfonic acid in aqueous THF cleaved the acetonide protecting group and transformed the alkoxyfuran to γ-propylidene butenolide **5**. Use of dilute hydrochloric acid instead of *p*-toluenesulfonic acid gave a lower yield. The geometry of the trisubstituted exocyclic double bond in **5** was determined by an NOE difference spectroscopy experiment. Irradiation of the H-4 signal at 7.37 ppm enhanced the H-6 signal at 5.37 ppm by 3%, which indicates the *Z*-geometry in **5**. Selective benzoylation of the primary alcohol in **5** was accomplished with benzoyl cyanide[10,11] in THF at -40° C in the presence of triethylamine to give melodorinol. In its HMBC spectrum the protons of H-8 at 4.43 ppm showed three-bond coupling to C-10 at 166.65 ppm, which indicated that the benzoyl group was attached to the primary alcohol. Finally the synthesis of acetylmelodorinol was achieved by acetylation of **1** with acetic anhydride and pyridine in CH_2Cl_2. The possibility of acyl migration in acetylation was excluded by the HMBC experiment of **2**. The carbon signal at 169.77 ppm was assigned as the carbonyl carbon (C-18) of acetyl group due to its two-bond coupling to the methyl protons (δ_H 2.08 ppm). Furthermore, the HMBC spectrum showed three-bond couplings of H-8 (δ_H 4.50 and 4.55 ppm) and H-7 (δ_H 6.12 ppm) to C-10 (δ_C 165.99 ppm) and C-18 (δ_C 169.77 ppm), respectively. This correlation indicated that the acetoxy group was located at C-7 and the benzoxy group at C-8; thus the structure of **2** was confirmed.

The ^1H and ^{13}C NMR data of melodorinol and acetylmelodorinol are identical to those reported in literature except the ^{13}C assignments of C-7 and C-8 in melodorinol. In the paper of Jung et al.[2] C-7 and C-8 signals of melondorinol appeared at 67.48 ppm and 65.88 ppm, respectively; however, Tuchinda et al.[3] reported that C-7 resonated at 65.78 ppm and C-8 at 67.40 ppm. Through the spectral analysis of DEPT and ^1H–^{13}C direct HETCOR experiments we confirmed that the signals at 65.74 and 67.44 ppm should be assigned as C-7 and C-8, respectively.

EXPERIMENTAL

General.

All reagents and solvents were purchased from commercial sources and used as received unless otherwise noted. Tetrahydrofuran was dried and freshly distilled from sodium benzophenone ketyl under Ar. Dichloromethane was dried by distillation under Ar from calcium hydride. ^1H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50.3 MHz on a Varian Gemini-200 spectrometer. All chemical shifts are reported in ppm on the δ scale. The HMBC experiment was performed using a Bruker microprogram on a Bruker AC-300 spectrometer at 300 MHz and 8 Hz of long-range ^{13}C–^1H coupling was set. Infrared spectra were recorded on a Bio-Rad FTS-7 spectrometer using CH_2Cl_2 as the solvent and peaks are reported in cm^{-1}. Mass spectra were acquired on Finnigan TSQ-46C, Jeol JMS-SX/SX 102A, or Jeol JMS-HX110 instruments. Optical rotations were taken on a JASCO DIP-370 polarimeter.

(1R,2R)-1-(5-tert-Butoxy-2-furyl)-2,3-O-isopropylidene-1,2,3-propanetriol (3a) and (1S,2R)-1-(5-tert-Butoxy-2-furyl)-2,3-O-isopropylidene-1,2,3-propanetriol (3b).

To a stirred solution of 2-*tert*-butoxyfuran[12] (1.60 g, 11.4 mmol) in 20 mL of THF was added dropwise 6.3 mL of *tert*-butyllithium (1.7 M solution in pentane, 10.7 mmol) at -40°C under an atmosphere of Ar and the resulting solution was kept stirring at this temperature. After 1 h, a solution of 1.00 g (7.68 mmol) of 2,3-*O*-isopropylidene-D-glyceraldehyde in 5 mL of THF was introduced dropwise to the yellow solution at -40°C. The reaction mixture was stirred at -40°C for 1 h and allowed to warm to room temperature gradually before

adding 2 mL of saturated aqueous NH_4Cl solution and then 30 mL of H_2O. The products were extracted into Et_2O and washed with brine. After drying over anhydrous $MgSO_4$ and evaporation of the volatiles, the residue was chromatographed on a silica gel column eluting with hexanes-EtOAc (3:1) to give 1.43 g (69%) of products as a mixture of two diastereomers in a ca. 1:1 ratio. Further separation of this mixture with MPLC resulted in the isolation of these two compounds, **3a** and **3b**, in eluting sequence.

3a: $[\alpha]_D^{22}$ +27 (*c* 1, CH_2Cl_2); IR 3589, 2935, 1616, 1568, 1371, 1222, 1154, 1061; ^1H NMR (CD_3COCD_3) 6.15 (1H, dd, *J* = 3.1 and 0.5 Hz, H-3'), 5.38 (1H, d, *J* = 3.1 Hz, H-4'), 4.44 (2H, m, H-1 and OH), 4.27 (1H, m, H-2), 4.04 (1H, dd, *J* = 8.3 and 5.8 Hz, H-3), 4.02 (1H, dd, *J* = 8.3 and 6.3 Hz, H-3), 1.32 (12H, s, *t*-Bu and Me), 1.26 (3H, q, *J* = 0.6 Hz, Me); ^{13}C NMR (CD_3COCD_3) 157.59 (C-5'), 147.51 (C-2'), 109.67 (O–C–O),108.50 (C-3'), 92.11 (C-4'), 82.54 (*C*Me$_3$), 78.22 (C-2), 68.85 (C-1), 67.05 (C-3), 28.45 (CH_3 of *t*-Bu), 26.96 (Me), 25.62 (Me); EIMS (70 eV) *m/z* (%) 270 (5, M^+), 157 (72), 139 (65), 113 (100), 101 (86); HRMS *m/z* calcd for $C_{14}H_{22}O_5$ (M^+) 270.1467, obsd 270.1469.

3b: $[\alpha]_D^{22}$ +6 (*c* 0.5, CH_2Cl_2); IR 3572, 2936, 1617, 1568, 1371, 1216, 1153, 1068, 852; ^1H NMR (CD_3COCD_3) 6.19 (1H, dd, *J* = 3.1 and 0.6 Hz, H-3'), 5.39 (1H, d, *J* = 3.1 Hz, H-4'), 4.44 (1H, ddd, *J* = 6.8, 5.0, and 0.6 Hz, H-1), 4.32 (1H, q, *J* = 6.5 Hz, H-2), 4.26 (1H, d, *J* = 5.0 Hz, OH), 3.90 (1H, dd, *J* = 8.3 and 6.5 Hz, H-3), 3.70 (1H, dd, *J* = 8.3 and 6.4 Hz, H-3), 1.32 (12H, s, *t*-Bu and Me), 1.29 (3H, q, *J* = 0.6 Hz, Me); ^{13}C NMR (CD_3COCD_3) 157.67 (C-5'), 146.82 (C-2'), 110.00 (O–C–O), 108.79 (C-3'), 92.22 (C-4'), 82.63 (*C*Me$_3$), 78.97 (C-2), 69.80 (C-1), 66.57 (C-3), 28.44 (CH_3 of *t*-Bu), 26.96 (Me), 25.63 (Me); EIMS (70 eV) *m/z* (%) 270 (3, M^+), 157 (37), 139(29), 113 (100), 101 (90); HRMS *m/z* calcd for $C_{14}H_{22}O_5$ (M^+) 270.1467, obsd 270.1472.

(1R,2R)-2,3-O-Isopropylidene-1-(5-methoxy-2-furyl)-1,2,3-propanetriol (4a) and (1S,2R)-2,3-O-Isopropylidene-1-(5-methoxy-2-furyl)-1,2,3-propanetriol (4b).

To a stirred solution of 2-methoxyfuran (1.13 g, 11.5 mmol) in 20 mL of THF was added dropwise 6.3 mL of *tert*-butyllithium (1.7 M solution in pentane, 10.7 mmol) at -40°C under an atmosphere of Ar. After 1 h, a solution of 1.00 g (7.68 mmol) of 2,3-*O*-isopropylidene-D-glyceraldehyde in 5 mL of THF was introduced dropwise to the yellow solution at -40°C. The reaction mixture was stirred at -40°C for 1 h and allowed to warm to room temperature gradually before adding 2 mL of saturated aqueous NH_4Cl solution and then 30 mL of H_2O. The products were extracted into Et_2O and washed with brine. After drying over anhydrous $MgSO_4$ and evaporation of the volatiles, the residue was chromatographed on a silica gel column eluting with hexanes-EtOAc (3:1) to give 0.893 g (51%) of products as a mixture of two diastereomers in a ca. 1:1 ratio. Further separation of this mixture with MPLC resulted in the isolation of these two compounds, **4a** and **4b,** in eluting sequence.

4a: $[\alpha]_D^{22}$ +17 (*c* 1, CH_2Cl_2); IR 3599, 2936, 1616, 1584, 1373, 1216, 1062; ^1H NMR (CD_3COCD_3) 6.16 (1H, dd, *J* = 3.2 and 0.4 Hz, H-3'), 5.15 (1H, d, *J* = 3.2 Hz, H-4'), 4.41 (2H, m, H-1 and OH), 4.27 (1H, m, H-2), 4.06 (1H, dd, *J* = 8.3 and 5.9 Hz, H-3), 4.01 (1H, dd, *J* = 8.3 and 6.0 Hz, H-3), 3.81 (3H, s, OMe), 1.31 (3H, q, *J* = 0.6 Hz, Me), 1.26 (3H, q, *J* = 0.6 Hz, Me); ^{13}C NMR (CD_3COCD_3) 162.19 (C-5'), 145.72 (C-2'), 109.69 (O–C–O), 109.31 (C-3'), 80.27 (C-4'), 77.92 (C-2), 68.77 (C-1), 67.20 (C-3), 57.94 (OMe), 26.95 (Me), 25.57 (Me).

4b: $[\alpha]_D^{22}$ +10 (*c* 0.5, CH_2Cl_2); IR 3561, 2929, 1617, 1583, 1373, 1215, 1067; ^1H NMR (CD_3COCD_3) 6.20 (1H, dd, *J* = 3.2 and 0.6 Hz, H-3'), 5.16 (1H, d, *J* = 3.2 Hz, H-4'), 4.42 (1H, ddd, *J* = 6.8, 5.0, and 0.6 Hz, H-1), 4.32 (1H, q, *J* = 6.5 Hz, H-2), 4.21 (1H, d, *J* = 5.0 Hz, OH), 3.91 (1H, dd, *J* = 8.4 and 6.4 Hz, H-3), 3.80

(3H, s, OMe), 3.67 (1H, dd, J = 8.4 and 6.3 Hz, H-3), 1.33 (3H, q, J = 0.6 Hz, Me), 1.29 (3H, q, J = 0.6 Hz, Me); ^{13}C NMR (CD_3COCD_3) 162.27 (C-5'), 145.04 (C-2'), 110.04 (O–C–O), 109.43 (C-3'), 80.35 (C-4'), 78.76 (C-2), 69.53 (C-1), 66.64 (C-3), 58.03 (OMe), 26.93 (Me), 25.64 (Me).

[S-(Z)]-5-(2,3-Dihydroxypropylidene)-2(5H)-furanone (5).

A solution of **3** (1.33 g of diastereomers, 4.92 mmol) and *p*-toluenesulfonic acid monohydrate (0.160 g, 0.841 mmol) in 25 mL of THF containing 1.5 mL of H_2O was stirred at room temperature. After 2 d, the volatiles were removed under reduced pressure and the residue was chromatographed on a silica gel column with EtOAc as the eluent to afford 0.572 g (74%) of **5** as a colorless liquid. An analytical sample was further purified by MPLC. $[\alpha]_D^{22}$ +12 (*c* 0.5, MeOH); IR 3686, 3597, 2926, 1779, 1422; ^{1}H NMR ($CDCl_3$) 7.37 (1H, d, J = 5.5 Hz, H-4), 6.23 (1H, d, J = 5.5 Hz, H-3), 5.37 (1H, d, J = 8.0 Hz, H-6), 4.85 (1H, ddd, J = 8.0, 6.8, and 3.5 Hz, H-7), 3.79 (1H, dd, J = 11.3 and 3.5 Hz, H-8), 3.60 (1H, dd, J = 11.3 and 6.8 Hz, H-8), 2.35 (2H, br s, OH); ^{13}C NMR ($CDCl_3$) 169.07 (C-2), 149.76 (C-5), 143.71 (C-4), 120.72 (C-3), 113.94 (C-6), 67.85 (C-7), 65.62 (C-8); EIMS (70 eV) *m/z* (%) 156 (1.5, M^+), 125 (82), 82 (100); HRMS *m/z* calcd for $C_7H_8O_4$ (M^+) 156.0422, obsd 156.0426.

Hydrolysis of 4.

A solution of **4** (500 mg of diastereomers, 2.19 mmol) and *p*-toluenesulfonic acid monohydrate (63.0 mg, 0.331 mmol) in 10 mL of THF containing 0.5 mL of H_2O was stirred at room temperature. After 2 d, the volatiles were removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with EtOAc to afford 100 mg (29%) of **5**.

Melodorinol (1).

To a stirred solution of **5** (78 mg, 0.50 mmol) in 25 mL of THF was added benzoyl cyanide (200 mg in 5 mL of THF) and triethylamine (150 mg in 5 mL of THF) at -50°C under an Ar atmosphere. The resulting solution was stirred at -40°C for 2 h and then the unreacted benzoyl cyanide was decomposed by addition of MeOH. After evaporation of volatiles, the product was extracted into Et_2O and washed successively with 2N HCl, saturated aqueous $NaHCO_3$, H_2O, and brine. After drying over anhydrous $MgSO_4$ and evaporation of the solvent, the residue was chromatographed on a silica gel column eluting with hexanes-EtOAc (3:2) to give 71 mg (54%) of **1**. $[\alpha]_D^{22}$ +72 (*c* 1, $CHCl_3$); IR 3594, 2927, 1782, 1722, 1111, 1067; ^{1}H NMR ($CDCl_3$) 8.01 (2H, dt, J = 6.9 and 1.4 Hz, H-12 and H-16), 7.55 (1H, tt, J = 7.3 and 1.4 Hz, H-14), 7.46-7.34 (3H, m, H-4, H-13, and H-15), 6.21 (1H, d, J = 5.5 Hz, H-3), 5.39 (1H, d, J = 8.1 Hz, H-6), 5.15 (1H, ddd, J = 8.1, 5.7, and 4.8 Hz, H-7), 4.43 (1H, d, J = 4.8 Hz, H-8), 4.43 (1H, d, J = 5.7 Hz, H-8), 2.90 (1H, br s, OH); ^{13}C NMR ($CDCl_3$) 168.93 (C-2), 166.65 (C-10), 149.97 (C-5), 143.66 (C-4), 133.31 (C-14), 129.68 (C-12 and C-16), 129.45 (C-11), 128.42 (C-13 and C-15), 120.96 (C-3), 113.17 (C-6), 67.44 (C-8), 65.74 (C-7); EIMS (70 eV) *m/z* (%) 230 (5), 138 (6), 105 (100), 77 (32); HRMS *m/z* calcd for $C_{14}H_{12}O_5$ (M^+) 260.0685, obsd 260.0672.

Acetylmelodorinol (2).

To a stirred solution of **1** (71 mg, 0.27 mmol) in 10 mL of CH_2Cl_2 was added acetic anhydride (560 mg in 5 mL of CH_2Cl_2) and pyridine (440 mg in 5 mL of CH_2Cl_2) at 0°C under an atmosphere of Ar. The resulting solution was allowed to warm to room temperature and stirred overnight. After quenching by adding water, the organic layer was washed successively with 2N HCl, saturated aqueous $NaHCO_3$, H_2O, and brine.

After drying over anhydrous $MgSO_4$ and evaporation of volatiles, the residue was chromatographed on a silica gel column eluting with hexanes-EtOAc (2:1) to provide 51 mg (63%) of **2**. $[\alpha]_D^{22}$ +32.5 (*c* 2, $CHCl_3$) [lit. $[\alpha]_D$ +209 (*c* 1, $CHCl_3$),[1] -7.8 (*c* 0.17, $CHCl_3$)[3]]; IR 2926, 1786, 1746, 1723, 1372, 1229, 1108; ^1H NMR ($CDCl_3$) 8.01 (2H, m, H-12 and H-16), 7.56 (1H, tt, J = 7.5 and 1.4 Hz, H-14), 7.43 (2H, m, H-13 and H-15), 7.35 (1H, d, J = 5.5 Hz, H-4), 6.26 (1H, d, J = 5.5 Hz, H-3), 6.12 (1H, ddd, J = 8.0, 5.8, and 4.5 Hz, H-7), 5.31 (1H, d, J = 8.0 Hz, H-6), 4.55 (1H, dd, J = 11.8 and 4.5 Hz, H-8), 4.50 (1H, dd, J = 11.8 and 5.8 Hz, H-8), 2.08 (3H, s, Me); ^{13}C NMR ($CDCl_3$) 169.77 (C-18), 168.45 (C-2), 165.99 (C-10), 150.66 (C-5), 143.29 (C-4), 133.28 (C-14), 129.68 (C-12 and C-16), 129.49 (C-11), 128.46 (C-13 and C-15), 121.59 (C-3), 108.85 (C-6), 67.26 (C-7), 64.60 (C-8), 20.89 (C-19); EIMS (70 eV) *m/z* (%) 180 (5), 105 (100), 77 (25); HRMS *m/z* calcd for $C_{16}H_{14}O_6$ (M^+) 302.0791, obsd 302.0793.

ACKNOWLEDGMENTS

This work was supported by the National Science Council of the Republic of China (NSC 83-0208-M-077-002).

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(*Received in Japan* 29 *July* 1996; *accepted* 9 *September* 1996)