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Total synthesis of both enantiomers of melodorinol. Redetermination of their absolute configurations

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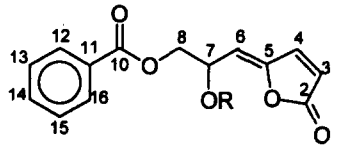
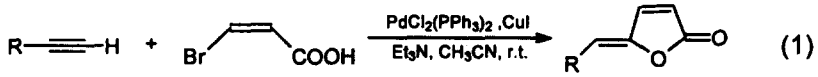
Abstract: Both enantiomers of the natural products, melodorinol and acetylmelodorinol, have been synthesized by a palladium catalyzed enyne coupling methodology. Their absolute configurations are redetermined. © 1997 Elsevier Science Ltd

It has been reported that there is an important group of natural antitumor compounds which were isolated from *Melodorum fruticosum* Lour. (Annoaceae).[1–4] Many members of this class contain the γ-(*Z*)-alkylidenebutenolide structural unit, such as melodorinol **1** and acetylmelodorinol **2**. In 1990, McLaughlin assigned the configuration of C-7 in melodorinol and acetylmelodorinol as the *S* configuration and in 1996, the first total syntheses of (*S*)-melodorinol and (*S*)-acetylmelodorinol from D-(+)-mannitol were reported by Shen *et al.*, which gives rise to confusion because of the difference in specific rotations.[5]



melodorinol (1, R=H)
acetylmelodorinol (2, R=Ac)

Recently, a convenient synthesis of γ-(*Z*)-alkylidenebutenolides starting from propiolic acid was reported from this laboratory (eq. 1).[6] It occurred to us that by this method, the stereocontrolled syntheses of both enantiomers of melodorinol and acetylmelodorinol may be fulfilled, thus the problem encountered in their specific rotations may be resolved.



(1)

Our synthesis of **1** started from the enantiomerically pure 2,3-O-isopropylidene glyceraldehyde **3**. In this procedure, both enantiomers of **3** were transformed into **5** in two steps, which were then coupled with (*Z*)-3-bromopropenoic acid[7] under the catalysis of palladium to yield γ-(*Z*)-alkylidenebutenolides **6**. Hydrolysis and benzoylation of the product **7** afforded melodorinol **1**. Further acetylation of **1** yielded acetylmelodorinol **2** (Scheme 1). The synthetic **1** and **2** provided spectral data that are consistent with those reported.[1,3–5] Both enantiomers of **1** and **2** were determined by chiral HPLC as enantiomerically pure (Figs 1 and 2).

The specific rotation values of melodorinol and acetylmelodorinol mentioned in the literature together with the data from our synthesis are summarized in Table 1. From the table, it can be seen that just as with the results obtained by Shen *et al.*,[5] the specific rotations of both synthetic compounds **1** and **2** by our work are not concordant with those of the natural ones, not only in their values, but also

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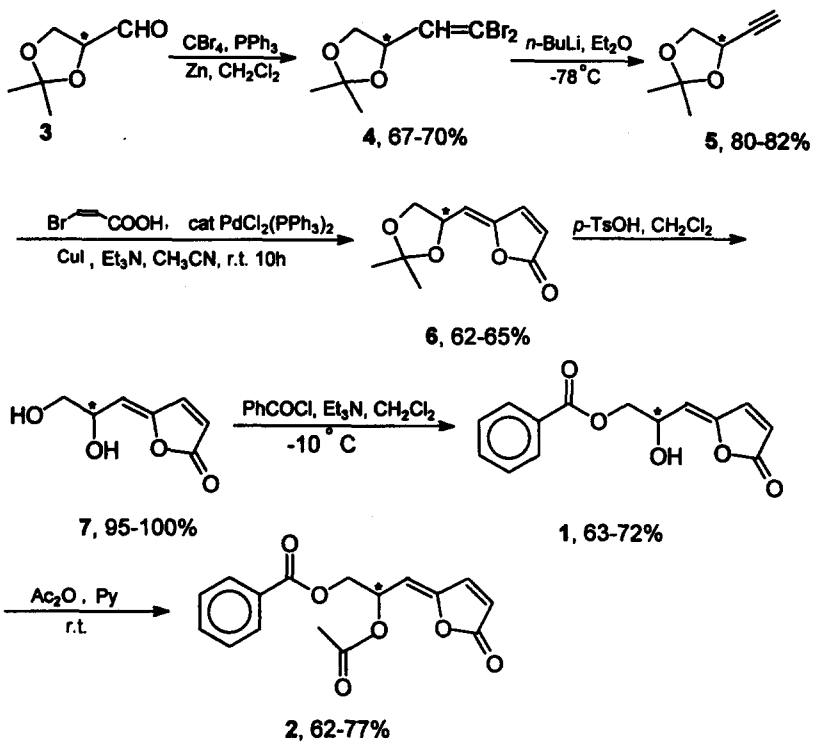

Scheme 1.

in their signs. According to the specific rotations of the synthetic pure enantiomers, we can conclude that the isolated natural melodorinol should be in *R* configuration with an e.e. value of about 45%.

The absolute configurations of isolated natural melodorinol and acetylmelodorinol were once assigned by McLaughlin *et al.*,[3] using Horeau's chemical method (partial resolution or kinetic resolution for secondary alcohols).[8] They concluded from the 2-phenylbutanioc acid obtained from the resolution [(−) *R*, $[\alpha]^{23}=-0.23$, in C_6H_6; optical yield 3.4%] that the isolated natural melodorinol is a partial racemic mixture with a higher concentration of the *S* isomer, although the enantiomeric excess is quite low. As we know, Horeau's chemical method is an empirical rule, it describes the relationship between the sign of the isolated 2-phenylbutyric acid and the absolute configuration of the alcohol used in the reaction based on the sizes of the groups.[8] However, as pointed out by Horeau himself,[8] this method can not be used to assign *R* or *S* configuration of compounds directly because of the difficulty in determining the relationship between the priority of *R* groups in Cahn–Ingold–Prelog nomenclature and their sizes. Thus, it is doubtful to predict the absolute configuration of melodorinol in this way.

While the exact *e.e.* value of the isolated natural acetylmelodorinol is difficult to assess since there is no unanimous report on its specific rotation, its absolute configuration should also be *R*.

In summary, we have developed a highly stereocontrolled synthesis of both enantiomers of melodorinol and acetylmelodorinol in which the key step is a palladium catalyzed enyne coupling and successive cyclization reaction. The absolute configurations of natural products were redetermined.

Experimental

Infrared spectra were obtained with a Shimadzu IR-440 instrument. Proton magnetic resonance spectra were recorded with a Varian EM-390 or Bruker AM-300 spectrometer and were reported in ppm downfield of internal tetramethylsilane (δ units). Mass spectra data were taken on a Finnigan

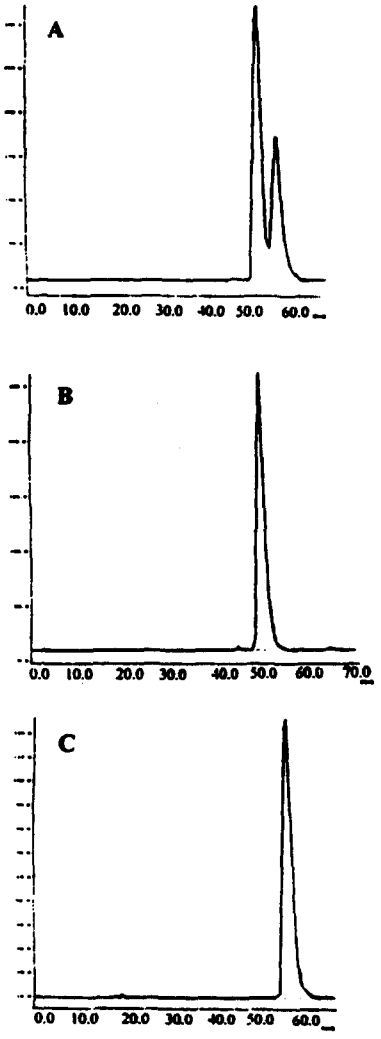

Figure 1. Chiral HPLC analysis of synthetic melodorinol. (A) (*R*)-isomer plus (*S*)-isomer; (B) (*R*)-isomer; (C) (*S*)-isomer. Analyses were performed using chiralcel OJ column, under *c*-C_6H_{12}/*i*-PrOH=70/30, 0.7ml/min, UV 254 nm.

4021 spectrometer. Optical rotations were measured on a Perkin–Elmer 241 MC instrument. Elemental analyses were run on a Carlo-Erba 1106 instrument.

(*R*)-2,3-O-Isopropylideneglyceraldehyde, (*R*)-**3**, and (*S*)-2,3-O-isopropylideneglyceraldehyde, (*S*)-**3**, were prepared according to literature procedure from D-(+)-mannitol[9,10] and vitamin C,[11] respectively. (*S*)-1,1-Dibromo-3,4-O-isopropylidene-3,4-dihydroxybutene, (*S*)-**4**, and (*R*)-1,1-dibromo-3,4-O-isopropylidene-3,4-dihydroxybutene, (*R*)-**4**, were synthesized according to literature procedure[10] from (*R*)-**3** and (*S*)-**3**, respectively. (*S*)-3,4-O-Isopropylidene-3,4-dihydroxybutyne, (*S*)-**5**, and (*R*)-3,4-O-isopropylidene-3,4-dihydroxybutyne, (*R*)-**5**, were prepared from (*S*)-**4** and (*R*)-**4**, respectively, according to the literature procedure.[12]

[S-(Z)]-5-(2,3-O-Isopropylidene-2,3-dihydroxypropylidene)-2(5H)-furanone, (S)-6

A mixture of (*S*)-**5** (189 mg, 1.5 mmol), (*Z*)-3-bromopropenoic acid (151 mg, 1 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (5.7 mg, 0.03 mmol), Et_3N (202 mg, 2 mmol) and acetonitrile (8 ml) was stirred at rt under N_2 and monitored by TLC. After 10 h, the mixture was filtered, washed with ether

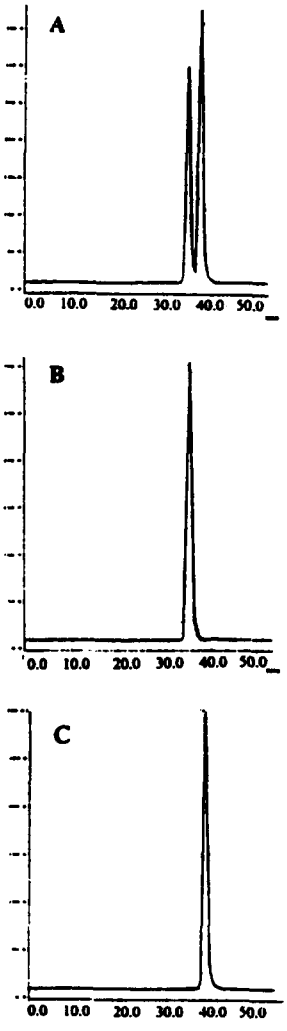

Figure 2. Chiral HPLC analysis of synthetic acetylmelodorinol. (A) (*R*)-isomer plus (*S*)-isomer; (B) (*R*)-isomer; (C) (*S*)-isomer. Analyses were performed using chiralpak AD column, under *c*-C_6H_{12}/*i*-PrOH=90/10, 0.7ml/min, UV 254 nm.

Table 1.

Compound	Isolated Natural Product			Synthetic Product		
	Tuchinda[4]	McLaughlin[3]	McLaughlin[1]	Shen[5]	our results	absolute configuration
Melodorinol 1	$[\alpha]_D^{20}$ - 40.0 (c 0.26,$CHCl_3$)	$[\alpha]_D$ -37 (c 1, $CHCl_3$)		$[\alpha]_D^{22}$ +72 (c 1, $CHCl_3$)	$[\alpha]_D^{22}$ +86.4 (c 0.95,$CHCl_3$)	S
					$[\alpha]_D^{22}$ - 88.0 (c 1.36,$CHCl_3$)	R
Acetyl-melodorinol 2	$[\alpha]_D^{20}$-7.8 (c 0.17, $CHCl_3$)		$[\alpha]_D$ +209 (c 1, $CHCl_3$)	$[\alpha]_D^{22}$ +32.5 (c 2, $CHCl_3$)	$[\alpha]_D^{22}$ +41.0 (c 0.33,$CHCl_3$)	S
					$[\alpha]_D^{22}$ -38.8 (c 1.25,$CHCl_3$)	R

and concentrated. The residue was purified by column chromatography on silica gel (eluent: petroleum ether:ethyl acetate=5:1) to afford the desired product (*S*)-**6** (128 mg, 65%), oil, $[\alpha]_D^{20}$+42.3 (c 0.82, $CHCl_3$); IR (neat) 3144, 2989, 1785, 1679, 1561, 1382, 1227, 1110, 1061, 936 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, *J*=5.48 Hz, 1H), 6.23 (d, *J*=5.48 Hz, 1H), 5.35 (d, *J*=8.38 Hz, 1H), 5.20–5.10 (m, 1H), 4.25–4.19 (m, 1H), 3.20–3.15 (m, 1H), 1.50 (s, 3H), 1.40 (s, 3H); MS m/e (%) 196 (M^+, 1.33), 181 (26.27), 166 (96.31), 139 (100.00), 121 (59.25), 72 (52.76), 43 (77.30); HRMS calcd for $C_{10}H_{12}O_4$ 196.0735, found 196.0723.

Similarly, (*R*)-**6** was prepared from (*R*)-**5**. (*R*)-**6**: oil, $[\alpha]_D^{22}$−39.4 (c 1.8, $CHCl_3$); IR (neat) 3144, 2989, 1785, 1382, 1227, 1061, 936 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, *J*=5.46 Hz, 1H), 6.28 (d, *J*=5.46 Hz, 1H), 5.42 (d, *J*=8.29 Hz, 1H), 5.24–5.16 (m, 1H), 4.30–4.25 (m, 1H), 3.25–3.18 (m, 1H), 1.50 (s, 3H), 1.40 (s, 3H); MS m/e (%) 196 (M^+, 0.90), 181 (17.36), 166 (72.20), 139 (83.87), 121 (44.42), 72 (49.22), 43 (100.00); HRMS calcd for $C_{10}H_{13}O_4$ (M^++1) 197.0814, found 197.0808.

[S-(Z)]-5-(2,3-Dihydroxypropylidene)-2(5H)-furanone, (S)-7

A mixture of (*S*)-**6** (158 mg, 0.8 mmol), TsOH·H_2O (20.3 mg, 0.1 mmol), and MeOH (10 ml) was stirred at rt. After the reaction was completed as monitored by TLC, the MeOH was evacuated and the residue was purified with preparative TLC on silica gel (eluent: ethyl acetate:MeOH:$CHCl_3$=6:1:6) to give (*S*)-**7** as a pale yellow solid (97 mg, 80%); mp 87–89°C, $[\alpha]_D^{20}$+53.1 (c 0.42, acetone), $[\alpha]_D^{22}$+39.0 (c 0.6, MeOH) [Lit.[5] $[\alpha]_D^{22}$+12 (c 0.5, MeOH)]; IR (Nujol) 3448, 3333, 1778, 1748, 1402, 1121, 1028, 949, 879, 850 cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.58 (d, *J*=5.43 Hz, 1H), 6.20 (d, *J*=5.43 Hz, 1H), 5.45 (d, *J*=8.49 Hz, 1H), 5.10–4.90 (s, br, 2H), 4.70 (ddd, *J*=8.49, 5.43, 2.40 Hz, 1H), 3.60–3.40 (m, 2H); MS m/e (%) 156 (M^+, 0.74), 139 (8.4), 125 (100.00), 97 (79.10), 82 (11.95), 77 (23.96), 69 (9.95), 54 (7.77), 43 (18.16); HMRS calcd for $C_7H_8O_4$ 156.0422, found 156.0433.

Similarly, (*R*)-**7** was prepared from (*R*)-**6**. (*R*)-**7**: mp 87–89°C, $[\alpha]_D^{22}$−52.0 (c 0.44, acetone); IR (Nujol) 3334, 1778, 1403, 1121, 1078, 1028, 950, 879, 850 cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) δ 7.78 (d, *J*=5.44 Hz, 1H), 6.30 (d, *J*=5.44 Hz, 1H), 5.50 (d, *J*=8.65 Hz, 1H), 4.72 (ddd, *J*=8.65, 5.44, 2.40 Hz, 1H), 3.55–3.65 (m, 2H), 3.30–3.40 (m, 2H); MS m/e (%) 156 (M^+, 0.72), 139 (M^+–OH, 8.09), 125 (100.00), 97 (76.04), 82 (24.99), 69 (9.28), 54 (22.97), 43 (20.71); HRMS calcd for $C_7H_8O_4$ 156.0422, found 156.0398.

(+)-Melodorinol, (S)-1

To a solution of (*S*)-**7** (46.5 mg, 0.3 mmol) in CH_2Cl_2 (6 ml) was dropped slowly at −10°C a solution of benzoyl chloride (0.038 ml, 0.31 mmol) in CH_2Cl_2 (3 ml) under N_2. The reaction mixture was stirred at −10°C and monitored by TLC. After the reaction was completed, a saturated water solution of NaCl (5 ml) was added and separated. The water layer was extracted with CH_2Cl_2 (4×10 ml) and the organic layer was combined and dried (Na_2SO_4). After distilling off the solvent, the residue was purified by preparative TLC on silica gel (eluent: petroleum ether:ethyl acetate=5:1) to yield (*S*)-**1** as a pale yellow oil (56 mg, 72%); $[\alpha]_D^{22}$+86.4 (c 0.95, $CHCl_3$); IR (neat) 3462, 2959, 1779, 1751, 1720, 1452, 1274, 1114, 1070, 877, 841, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2H), 7.60 (m, 1H), 7.55–7.45 (m, 2H), 7.40 (d, *J*=5.35 Hz, 1H), 6.25 (d, *J*=5.35 Hz, 1H), 5.40 (d, *J*=8.02 Hz, 1H), 5.18 (ddd, *J*=8.02, 5.35, 4.70 Hz, 1H), 4.50 (m, 2H), 3.10–2.90 (s, br, 1H); MS m/e (%) 260 (M^+, 0.57), 243 (M^+–OH, 88.53), 138 (7.03), 122 (8.55), 105 (100.00), 77 (47.37), 51 (16.01), 43 (5.12); HRMS calcd for $C_{14}H_{12}O_5$ 260.0735, found 260.0730.

Similarly, (*R*)-**1** was synthesized from (*R*)-**7**. (*R*)-**1**: oil, $[\alpha]_D^{20}$−88.0 (c 1.36, $CHCl_3$); IR (neat) 3463, 1781, 1779, 1751, 1452, 1316, 1274, 1114, 1020, 937, 877, 807 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 7.39 (d, *J*=5.42 Hz, 1H), 6.25 (d, *J*=5.42 Hz, 1H), 5.42 (d, *J*=8.18 Hz, 1H), 5.20 (ddd, *J*=8.18, 5.45, 4.80 Hz, 1H), 4.50 (m, 2H), 3.20 (s, br, 1H); MS m/e (%) 243 (M^+–OH, 0.42), 138 (6.80), 105 (100.00), 77 (38.61), 51 (11.40), 43 (3.61); HRMS calcd for $C_{14}H_{11}O_5$ (M^+-1) 259.0606, found 259.0642.

(+)-Acetylmelodorinol, (S)-2

To a solution of (*S*)-**1** (29 mg, 0.11 mmol) in CH_2Cl_2 (3 ml) was added at 0°C under N_2 a solution of acetic anhydride (265 mg, 1.0 mmol) and pyridine (252 mg, 3.25 mmol) in CH_2Cl_2 (4 ml). The reaction mixture was stirred at rt and monitored by TLC. After the reaction was completed, a saturated solution of NaCl (5 ml) was added. The organic layer was washed successively with 2N HCl, saturated $NaHCO_3$ solution and saturated NaCl solution and dried (Na_2SO_4). The residue after evaporating off the solvent was purified with preparative TLC on silica gel (eluent: petroleum ether:ethyl acetate=3:1) to afford a yellow solid. Recrystallization from *i*-PrOH/*n*-hexane gave a colorless crystal of (*S*)-**2** (19 mg, 62%); mp 78–80°C, $[\alpha]_D^{22}$+41.0 (c 0.33, $CHCl_3$); IR (Nujol) 2926, 1781, 1740, 1717, 1286, 1270, 1232, 1106, 940, 880, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2H), 7.55 (m, 1H), 7.50–7.40 (m, 2H), 7.36 (d, *J*=5.44 Hz, 1H), 6.28 (d, *J*=5.44 Hz, 1H), 6.12 (ddd, *J*=8.06, 5.44, 4.30 Hz, 1H), 5.30 (d, *J*=8.06 Hz, 1H), 4.50 (m, 2H), 2.10 (s, 3H); MS m/e (%) 302 (M^+, 0.49), 180 (8.15), 138 (23.28), 105 (100.00), 77 (37.10), 43 (25.04); HRMS calcd for $C_{16}H_{14}O_6$ 302.0790, found 302.0791.

Similarly, (*R*)-**2** was synthesized from (*R*)-**1**. (*R*)-**2**: 79–80°C, $[\alpha]_D^{20}$−38.8 (c 1.25, $CHCl_3$); IR (Nujol) 2916, 1779, 1755, 1734, 1717, 1564, 1451, 1282, 1269, 1230, 1107, 940, 882, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05 (m, 2H), 7.60 (m, 1H), 7.45 (m, 2H), 7.38 (d, *J*=5.48 Hz, 1H), 6.29 (d, *J*=5.48 Hz, 1H), 6.15 (ddd, *J*=8.05, 5.48,4.30 Hz, 1H), 5.32 (d, *J*=8.05 Hz, 1H), 4.55 (m, 2H), 2.10 (s, 3H); MS m/e (%) 302 (M^+, 0.49), 149 (18.43), 138 (12.15), 105 (100.00), 77 (28.22), 43 (27.28); HRMS calcd for $C_{16}H_{14}O_6$ 302.0790, found 302.0770.

Acknowledgements

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