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# The first stereospecific approach to both enantiomers of mellein

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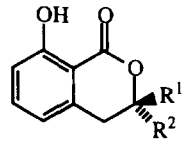
***Abstract:*** (*R*)-(−)-Mellein **1** and its (*S*)-(+)-antipode **2** are prepared in six steps and *ca.* 30% overall yield from (*R*)- and (*S*)-propylene oxide, **3** and *ent*-**3**, respectively. © 1997 Elsevier Science Ltd

Mellein (8-hydroxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran-1-one) is the parent of an extensive class of naturally occurring dihydroisocoumarins that collectively display a wide range of biological activity.[1] Racemic[2] mellein **1+2** has been synthesised many times[1] but there exists to date only one report of a synthesis of mellein in homochiral form. Thus, fifty-two years after the first report of mellein as a metabolite of *Aspergillus melleus*,[3] Mori and Gupta[4] reported a synthesis of (*R*)-(−)-mellein **1** in 7.3% yield over nine steps from ethyl (*R*)-3-hydroxybutanoate. It is interesting in the context of the current paper that Mori had earlier made "several unsuccessful attempts to utilise optically active propylene oxide as the chiral source".[4] We report here details of the synthesis of both enantiomers, **1** and **2**, of mellein, each one in *ca.* 30% yield over six steps from the appropriate enantiomer of propylene oxide.[5] The method is further applicable in principle to the synthesis of many substituted mellein derivatives in either stereochemical form.




**1** $R^1$ = H, $R^2$ = Me
**2** $R^1$ = Me, $R^2$ = H

(*R*)-(−)-Mellein **1** is now known to be widespread in Nature having been isolated, *inter alia*, from many fungi[1] and several insects[6] in which it appears to play a pheromonal role. (*S*)-(+)-Mellein **2** is also a fungal metabolite, one source being the marine fungus *Helicascus kanaloanus*.[7]

Our synthesis of (*R*)-(−)-mellein **1** is summarised in Scheme 1. Commercially available (*R*)-propylene oxide **3** was treated with the ethylenediamine complex of lithium acetylide to afford (*R*)-pent-4-yn-2-ol **4**, $[\alpha]_D$ −17.7 (*c* 0.13, $CHCl_3$), which was derivatised under standard conditions to give the silyl ether **5**, $[\alpha]_D$ +0.67 (*c* 10.7, $CHCl_3$), in 58% yield from **3**. Metallation of **5**, followed by exposure of the resulting acetylide anion to methyl chloroformate, gave the (*R*)-hexynoate ester **6**, $[\alpha]_D$ −6.8 (*c* 0.63, $CHCl_3$) in 81% yield over the two steps. We have previously employed the (*S*)-enantiomer of **6** as the dienophile in several regioselective Diels–Alder cycloaddition reactions with naphthoquinonoid dienophiles.[8] In the present context, reaction between the hexynoate **6** and 1-methoxy-1,3-cyclohexadiene, in the presence of a trace of 2,3-dichloromaleic anhydride and *N*-phenyl-β-naphthylamine, gave a mixture consisting of the benzoate **7**, $[\alpha]_D$ −30.1 (*c* 0.76, $CHCl_3$), and unchanged ester **6** that could be conveniently separated by filtration of the crude reaction mixture through a pad of silica gel followed by fractional distillation. Recovered ester **6** obtained in this way was sufficiently pure for recycling without further purification. The yield of the benzoate **7** based on the quantity of alkynoate consumed in a single cycle is typically 75–80%. 1-Methoxy-1,3-cyclohexadiene

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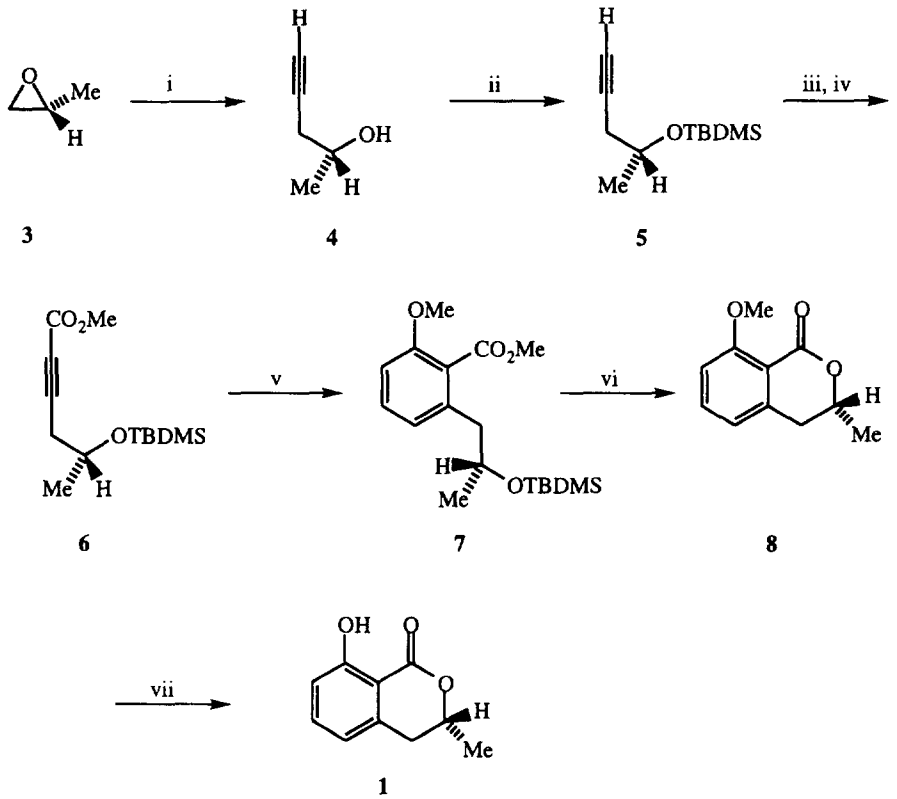
is available commercially in admixture with its 1,4-diene isomer in a ratio of 65:35. Addition of 2,3-dichloromaleic anhydride to this reaction mixture promotes *in situ* conjugation of the 1,4-diene.[9]




**Scheme 1.** *Reagents*: (i) LiC≡CH: $H_2N(CH_2)_2NH_2$ complex, DMSO, 0°C to r.t., 16 h, 65%; (ii) TBDMSCl, imidazole, DMF, r.t., 16 h, 89%; (iii) *n*-BuLi, −78°C, 30 min; (iv) $ClCO_2Me$, −78°C to r.t., 2 h, 81% over two steps; (v) 1-methoxy-1,3-cyclohexadiene, dichloromaleic anhydride, *N*-phenyl-β-naphthylamine, sealed tube, 185°C, 26 h, 79%; (vi) *p*-TsOH, $CH_2Cl_2$, r.t., 25 h, 84%; (vii) HBr, AcOH, reflux, 4 h, 97%.

Hydrolysis of the silyl ether group of the benzoate **7** with subsequent lactonisation of the secondary hydroxy group afforded (*R*)-8-*O*-methylmellein **8**,[10] m.p. 87–87.5°C (lit.[11] 88–89°C), $[\alpha]_D$ −259.0 (*c* 0.50, $CHCl_3$) {lit.[11] $[\alpha]_D$ −250 (*c* 0.50, $CHCl_3$)}, which is itself a natural product having been isolated from the phytopathogen *Septoria nodorum*.[10]

Demethylation of (*R*)-8-*O*-methylmellein **8** under acidic conditions gave (*R*)-(−)-mellein **1**, m.p. 55.5–56°C (lit.[4] 55–56°C), $[\alpha]_D$ −101.3 (*c* 0.07, $CHCl_3$) {lit.[4] $[\alpha]_D$ −100.8 (*c* 1.01, $CHCl_3$)}, in 30.2% yield from (*R*)-propylene oxide **3**. The synthetic material displayed physical and spectroscopic properties identical with those reported for the natural product.[12]

In a completely analogous fashion, (*S*)-propylene oxide *ent*-**3** was transformed *via* the (*S*)-hexynoate *ent*-**6**[8] to (*S*)-(+)-mellein **2**, m.p. 55–56°C (lit.[13] 56–57°C), $[\alpha]_D$ +88.6 (*c* 0.27, MeOH) {lit.[14] $[\alpha]_D$ +88 (*c* 1.03, MeOH)}, which proved to be identical in all other respects with the (*R*)-antipode **1**. This is the first synthesis of (*S*)-(+)-mellein **2** to be reported in the literature.

Thus, both of the naturally occurring enantiomers of mellein, **1** and **2**, are made available from inexpensive, readily available starting materials. Moreover, the methodology developed has the potential to lead to a variety of biologically-active mellein derivatives in homochiral form.

## Experimental

NMR spectra were recorded either at 300 MHz ($^1$H) and 75 MHz ($^{13}$C) or 400 MHz ($^1$H) and 100 MHz ($^{13}$C) on Varian Unity 300 or JEOL JNM-GX-400 spectrometers for solutions in deuteriochloroform with chloroform (7.26 ppm $^1$H and 77.0 ppm $^{13}$C) as internal references. Chemical shifts are given in ppm relative to tetramethylsilane with multiplicities indicated as s (singlet), d (doublet), m (multiplet) in the usual fashion. Coupling constants are reported in Hertz (Hz). Infrared spectra were obtained as KBr discs for solids and between NaCl plates for liquids by using a Perkin–Elmer 983 G grating spectrometer. Electron impact mass spectra were obtained on a JEOL JMS-AX505H spectrometer operating with an ionisation energy of 70 eV. Only ions of relative intensity greater than 20% of the base peak are reported, unless they are of particular significance. Specific rotations were measured by using a Perkin–Elmer MC 241 polarimeter with concentrations (*c*) quoted in g/100 ml in the solvent cited in each case. Melting points were determined on a Kofler hot-stage and are uncorrected. All reactions requiring anhydrous conditions were performed in oven and flame dried glassware under an atmosphere of dry nitrogen. Flash column and vacuum pad chromatography were performed over Merck Kieselgel 60 silica gel. Preparative thin layer chromatography employed Merck Kieselgel $GF_{254}$ (20×20 cm coated glass plates, 1.0 mm thickness) silica gel. Tetrahydrofuran was distilled from potassium benzophenone ketyl under nitrogen immediately prior to use. Other solvents were purified immediately prior to use by published procedures. Light petroleum refers to the hydrocarbon fraction boiling in the range 40–60°C.

*(R)-(−)-Pent-4-yn-2-ol* ***4***

To a suspension of lithium acetylide–ethylenediamine complex (2.85 g) in dimethyl sulfoxide (40 ml) cooled to 0°C under nitrogen was added dropwise (*R*)-(+)-propylene oxide (1.87 ml, 26.7 mmol). After complete addition the suspension was allowed to warm slowly to room temperature and the mixture was stirred overnight. The reaction mixture was poured onto ice (40 ml) and the product was extracted into ether (3×50 ml). The combined extracts were washed sequentially with brine (3×30 ml) and water (2×25 ml) and dried ($MgSO_4$). Evaporation of the solvent followed by distillation of the residue yielded the (*R*)-(−)-alcohol **4** (1.45 g, 65%) as a colourless liquid, b.p. 126°C; $[\alpha]_D^{26}$ −17.7 (*c* 0.13, $CHCl_3$), $[\alpha]_D^{26}$ +21.7 (*c* 0.57, ether) (Found: C, 71.38; H, 9.63. $C_5H_8O$ requires C, 71.38; H, 9.60%). IR $\upsilon_{max}$ 3356, 3296, 2973, 2931, 2913, 936, 643 cm$^{-1}$. $^1$H-NMR δ (300 MHz) 3.96 (1H, m, 2-H), 2.39 (1H, ddd, *J* 16.6, 5.2, 2.6 Hz, 3-H), 2.31 (1H, ddd, *J* 16.6, 6.6, 2.6 Hz, 3-H′), 2.05 (1H, t, *J* 2.6 Hz, 5-H), 1.25 (3H, d, *J* 6.1 Hz, 1-$H_3$). $^{13}$C-NMR δ (75 MHz) 80.9 (C-4), 70.6 (C-5), 66.1 (C-2), 28.8 (C-3), 22.1 (C-1).

*(S)-(+)-Pent-4-yn-2-ol* ent-***4***

The title compound was prepared as described above in 60% yield from (*S*)-(−)-propylene oxide *ent*-**3**; b.p. 126°C (lit.[8] 126°C); $[\alpha]_D^{26}$ +17.5 (*c* 0.16, $CHCl_3$), $[\alpha]_D^{26}$ −21.3 (*c* 0.55, ether) {lit.[8] $[\alpha]_D^{26}$ +17.8 (*c* 0.22, $CHCl_3$), $[\alpha]_D^{26}$ −21.2 (*c* 0.35, ether)}. All other spectroscopic data are identical with those quoted for **4**.

*(R)-(+)-4-*tert*-Butyldimethylsiloxypent-1-yne* ***5***

A solution of (*R*)-(−)-pent-4-yn-2-ol **4** (1.45 g, 17.2 mmol), imidazole (2.35 g, 34.5 mmol) and *tert*-butylchlorodimethylsilane (2.86 g, 19.0 mmol) in *N,N*-dimethylformamide (15 ml) was stirred overnight. The mixture was diluted with water (30 ml) and stirred for 30 min. The product was extracted into ether (3×30 ml) and the combined extracts were washed with brine (6×25 ml), dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Kügelrohr distillation of the residue yielded the (*R*)-(+)-silyl ether **5** (3.06 g, 89%) as a colourless liquid, b.p. 70–72°C/19 mmHg; $[\alpha]_D^{26}$ +0.67 (*c* 10.7, $CHCl_3$) (Found: C, 66.51; H, 11.41. $C_{11}H_{22}OSi$ requires C, 66.58; H, 11.20%). IR $\upsilon_{max}$ 3310, 2121 cm$^{-1}$. $^1$H-NMR δ (300 MHz) 3.96 (1H, m, 4-H), 2.36 (1H, ddd, *J* 16.6, 5.6, 2.7 Hz, 3-H), 2.24 (1H, ddd, *J* 16.6, 7.1, 2.7 Hz, 3-H′), 1.98 (1H, t, *J* 2.7 Hz, 1-H), 1.23 (3H, d, *J* 6.1 Hz, 5-$H_3$), 0.89

(9H, s, $SiCMe_3$), 0.08 and 0.07 (each 3H, s, SiMe). $^{13}$C-NMR δ (75 MHz) 81.9 (C-2), 69.7 (C-1), 67.5 (C-4), 29.4 (C-3), 25.8 ($SiCMe_3$), 23.2 (C-5), 18.1 ($SiCMe_3$), −4.7 and −4.8 (SiMe).

*(S)-(−)-4-*tert*-Butyldimethylsiloxypent-1-yne* ent-**5**

The title compound was prepared as described above in 93% yield from (*S*)-(+)-pent-4-yn-2-ol *ent*-**4**; b.p. 70–71°C/19 mmHg (Kügelrohr) (lit.[8] 70°C/20 mmHg); $[\alpha]_D^{26}$ −0.70 (*c* 10.7, $CHCl_3$) {lit.[8] $[\alpha]_D^{26}$ −0.68 (*c* 10.7, $CHCl_3$)}. All other spectroscopic data are identical with those obtained for **5**.

*Methyl (R)-(−)-5-*tert*-butyldimethylsiloxyhex-2-ynoate* **6**

To a stirred solution of the silyl ether **5** (1.20 g, 6.1 mmol) in tetrahydrofuran (20 ml) at −78°C was added *n*-butyllithium (4.54 ml, 1.6 M in hexane, 7.3 mmol). After 30 min methyl chloroformate (0.56 ml, 7.3 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After 2 h the reaction mixture was diluted with water (20 ml) and extracted with ether (3×20 ml). The combined extracts were washed with brine (3×20 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (light petroleum-ether, 95:5) followed by Kügelrohr distillation to yield the (*R*)-(−)-hexynoate **6** (1.26 g, 81%) as a colourless liquid, b.p. 98–101°C/0.6 mmHg; $[\alpha]_D^{26}$ −6.83 (*c* 0.63, $CHCl_3$) (Found: C, 60.91; H, 9.52. $C_{13}H_{24}O_3Si$ requires C, 60.88; H, 9.45%). IR $\upsilon_{max}$ 2241, 1717 $cm^{-1}$. $^1$H-NMR δ (300 MHz) 4.02 (1H, m, 5-H), 3.75 (3H, s, $CO_2Me$), 2.49 (1H, dd, *J*, 17.0, 6.0 Hz, 4-H), 2.38 (1H, dd, *J* 17.0, 6.6 Hz, 4-H′), 1.24 (3H, d, *J* 5.8 Hz, 6-$H_3$), 0.88 (9H, s, $SiCMe_3$), 0.08 and 0.07 (each 3H, s, SiMe). $^{13}$C-NMR δ (75 MHz) 154.1 (C-1), 87.1 (C-3), 74.1 (C-2), 66.8 (C-5), 52.5 ($CO_2$**Me**), 29.6 (C-4), 25.7 ($SiCMe_3$), 23.6 (C-6), 18.0 ($SiCMe_3$), −4.7 and −4.9 (SiMe). MS *m/z* 256 ($M^+$, 0.2%), 199 (26), 159 (49), 155 (75), 133 (71), 89 (100), 73 (84), 58 (20).

*Methyl (S)-(+)-5-*tert*-butyldimethylsiloxyhex-2-ynoate* ent-**6**

The title compound was prepared as above in 75% yield from (*S*)-(−)-4-*tert*-butyldimethylsiloxypent-1-yne *ent*-**5**; b.p. 89–91°C/0.45 mmHg (Kügelrohr) [lit.[8] 89–90°C/0.5 mmHg (Kügelrohr)]; $[\alpha]_D^{26}$ +6.76 (*c* 0.68, $CHCl_3$) {lit.[8] $[\alpha]_D^{22}$ +6.5 (*c* 0.57, $CHCl_3$)}. All other spectroscopic data are identical with those obtained for **6**.

*Methyl (R)-(−)-2-(2-*tert*-butyldimethylsiloxypropyl)-6-methoxybenzoate* **7**

A mixture of the hexynoate **6** (1.05 g, 4.1 mmol), 1-methoxy-1,3-cyclohexadiene (a commercial mixture of the 1,3-diene and the 1,4-diene in a 65:35 ratio, 0.97 ml, 8.2 mmol), dichloromaleic anhydride (2.5 mg) and *N*-phenyl-β-naphthylamine (20 mg) was heated in a sealed tube, with stirring, at 185°C for 26 h. Flash vacuum pad chromatography using a graded solvent system (light petroleum-ether), followed by Kügelrohr distillation afforded the starting material **6** (0.62 g) and the (*R*)-(−)-benzoate ester **7** (0.45 g, 79%) as a viscous colourless oil, b.p. 138–140°C/0.25 mmHg; $[\alpha]_D^{22}$ −30.1 (*c* 0.76, $CHCl_3$). IR $\upsilon_{max}$ 2927, 1727, 1468, 1263, 829 $cm^{-1}$. $^1$H-NMR δ (300 MHz) 7.26 (1H, m, 4-H), 6.85 (1H, d, *J* 7.8 Hz, 3-H), 6.78 (1H, d, *J* 8.6 Hz, 5-H), 4.00 (1H, m, 2′-H), 3.90 (3H, s, OMe), 3.81 (3H, s, $CO_2Me$), 2.71 (1H, dd, *J* 13.4, 7.3 Hz, 1′-H), 2.62 (1H, dd, *J* 13.4, 5.6 Hz, 1′-H′), 1.12 (3H, d, *J* 6.1 Hz, 3′-$H_3$), 0.83 (9H, s, $SiCMe_3$), −0.08 and −0.19 (each 3H, s, SiMe). $^{13}$C-NMR δ (75 MHz) 168.8 ($CO_2$**Me**), 156.4, 137.9, 129.8, 124.1, 123.6 and 108.9 (all Ar), 69.2 (C-2′), 56.0 (OMe), 52.1 ($CO_2$**Me**), 43.7 (C-1′), 25.8 ($SiCMe_3$), 23.9 (C-3′), 18.0 ($SiCMe_3$), −5.0 and −5.1 (Si**Me**). MS *m/z* 281 (22), 280 (100), 249 (43), 175 (75), 159 (34), 115 (20), 111 (26), 89 (34), 75 (26), 73 (89), 58 (20).

*Methyl (S)-(+)-2-(2-*tert*-butyldimethylsiloxypropyl)-6-methoxybenzoate* ent-**7**

The title compound was prepared as above in 81% yield from methyl (*S*)-(+)-5-*tert*-butyldimethylsiloxyhex-2-ynoate *ent*-**6**; b.p. 140–145°C/0.35 mmHg (Kügelrohr); $[\alpha]_D^{26}$ +30.9 (*c* 0.23, $CHCl_3$). All other spectroscopic data are identical with those obtained for **7**.

*(R)-(−)-Mellein methyl ether* ***8***

A solution of the benzoate ester **7** (280 mg, 0.83 mmol) in dichloromethane (10 ml) containing *p*-toluenesulfonic acid (10 mg) was stirred at room temperature for 25 h. The reaction mixture was diluted with water (15 ml), extracted with dichloromethane (3×20 ml) and the combined extracts were washed with water (20 ml) and dried ($MgSO_4$). After removal of solvent under reduced pressure the residue was purified by preparative thin layer chromatography (ether, 100%). (*R*)-(−)-Mellein methyl ether **8** (134 mg, 84%) was obtained as colourless prisms from ether/hexane, m.p. 87–87.5°C (lit.[11] 88–89°C); $[\alpha]_D^{26}$ −259 (*c* 0.50, $CHCl_3$) {lit.[11] $[\alpha]_D^{15}$ −250 (*c* 0.5, $CHCl_3$)} (Found: C, 68.71; H, 6.40. $C_{11}H_{12}O_3$ requires C, 68.72; H, 6.31%). IR $\upsilon_{max}$ 2949, 1710, 1593, 1472, 1236 $cm^{-1}$. $^1$H-NMR δ (300 MHz) 7.45 (1H, m, 6-H), 6.92 (1H, d, *J* 8.5 Hz, 5-H), 6.80 (1H, d, *J* 7.3 Hz, 7-H), 4.55 (1H, m, 3-H), 3.95 (3H, s, OMe), 2.87 (2H, m, 4-$H_2$), 1.48 (3H, d, *J* 6.1 Hz, 3-Me). $^{13}$C-NMR δ (100 MHz) 162.7 (C-1), 161.1, 141.9, 134.4, 119.1, 113.6 and 110.8 (all Ar), 74.1 (C-3), 56.1 (OMe), 36.1 (C-4), 20.7 (3-Me). MS *m/z* 192 ($M^+$, 87%), 149 (34), 148 (100), 147 (21), 146 (64), 131 (29), 118 (22), 106 (24), 105 (38), 91 (48), 90 (64), 79 (24), 77 (41).

*(S)-(+)-Mellein methyl ether* ent-***8***

The title compound was prepared as above in 91% yield from methyl (*S*)-(+)-2-(2-*tert*-butyldimethylsiloxypropyl)-6-methoxybenzoate *ent*-**7**; m.p. 86.5–87.5°C (ether/hexane); $[\alpha]_D^{26}$ +261 (*c* 0.52, $CHCl_3$) (Found: C, 68.72; H, 6.30. $C_{11}H_{12}O_3$ requires C, 68.72; H, 6.31%). All other spectroscopic data are identical with those obtained for **8**.

*(R)-(−)-Mellein* ***1***

The methyl ether **8** (65 mg, 3.38 mmol) was dissolved in a solution of hydrobromic acid in glacial acetic acid (45% w/v, 3 ml) and the solution was heated at reflux for 4 h. The mixture was cooled to room temperature, diluted with water (10 ml) and neutralised with solid sodium hydrogen carbonate. The product was extracted into dichloromethane (3×10 ml) and the combined extracts were washed with satd. aq. sodium hydrogen carbonate (10 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by preparative thin layer chromatography (ether, 100%). (*R*)-(−)-Mellein **1** (58 mg, 97%) was obtained as colourless prisms from ether/hexane, m.p. 55.5–56°C [lit.[4] 55–56°C (hexane)]; $[\alpha]_D^{26}$ −101.3 (*c* 0.07, $CHCl_3$) {lit.[4] $[\alpha]_D^{22}$ −100.8 (*c* 1.01, $CHCl_3$)} (Found: C, 67.35; H, 5.69. $C_{10}H_{10}O_3$ requires C, 67.40; H, 5.67%). IR $\upsilon_{max}$ 3421, 1678, 1617, 1460, 1235 $cm^{-1}$. $^1$H-NMR δ (300 MHz) 11.03 (1H, s, OH), 7.41 (1H, m, 6-H), 6.89 (1H, d, *J* 8.3 Hz, 5-H), 6.69 (1H, d, *J* 7.3 Hz, 7-H), 4.73 (1H, m, 3-H), 2.93 (2H, d, *J* 7.3 Hz, 4-$H_2$), 1.53 (3H, d, *J* 6.3 Hz, 3-Me). $^{13}$C-NMR δ (75 MHz) 169.9 (C-1), 162.1, 139.3, 136.1, 117.9, 116.2 and 108.2 (all Ar), 76.1 (C-3), 34.6 (C-4), 20.8 (3-Me). MS *m/z* 178 ($M^+$, 100%), 160 (47), 135 (23), 134 (98), 106 (25), 105 (22), 104 (23), 78 (36), 77 (32).

*(S)-(+)-Mellein* ***2***

The title compound was prepared as above in 96% yield from (*S*)-(+)-mellein methyl ether *ent*-**8**; m.p. 55–56°C (ether/hexane) [lit.[13] 56–57°C (light petroleum)]; $[\alpha]_D^{26}$ +88.6 (*c* 0.27, MeOH) {lit.[14] $[\alpha]_D^{25}$ +88 (*c* 1.03, MeOH)} (Found: C, 67.19; H, 5.59. $C_{10}H_{10}O_3$ requires C, 67.40; H, 5.67%). All other spectroscopic data are identical with those obtained for **1**.

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