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Synthesis of (−)-mellein, (+)-ramulosin, and related natural products

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Abstract—(−)-Mellein, (+)-ramulosin, (−)-*O*-methylmellein, (−)-6-hydroxymellein, (−)-6-methoxymellein, and (+)-6-hydroxyramulosin were synthesized as optically active forms using one-pot esterification–Michael addition–aldol reaction of δ-hydroxy-α,β-unsaturated aldehyde and diketene as a key step.

1. Introduction

A lot of related compounds to isocoumarin have been isolated from fungal metabolites and other natural sources. Most of these compounds are aromatic derivatives such as mellein, while relatively few compounds are non-aromatic derivatives such as ramulosin. Many of naturally occurring 8-hydroxy-3-methyl-3,4-dihydroisocoumarins (mellein or ramulosin derivatives) exhibit a variety of biological activities. Mellein (**1**) (Fig. 1),[1–7] which plays a pheromonal role, was isolated from many fungi and several insects. The derivatives of mellein, *O*-methylmellein (**2**),[8] 6-hydroxymellein (**3**),[9–14] and 6-methoxymellein (**4**)[12–19] were isolated from phytopathogen, fungi or plant and showed cytotoxicity, phytotoxicity, and phytoalexin activities. On the other hand, ramulosin (**5**),[20–22] which has antigerminating and antimicrobial activities, was isolated from several fungi. Its derivative, 6-hydroxyramulosin (**6**),[22,23] was also isolated from several fungi and showed antimicrobial activity. These dihydro- and hexahydroisocoumarins have been synthesized in various ways till date.[24–36] Herein, we describe the synthesis of these optically active isocoumarin derivatives (**1**–**6**) in a short and efficient way.

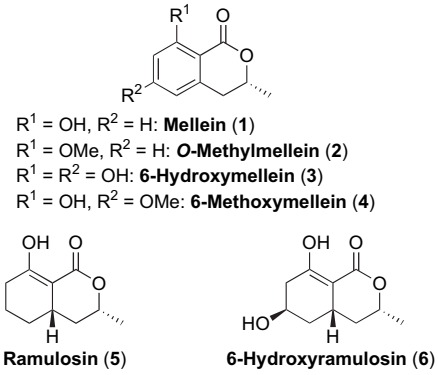

Figure 1.

2. Results and discussion

We have already reported a novel method for one-pot esterification–Michael addition–aldol reaction of δ-hydroxy-α,β-unsaturated aldehyde and diketene, and the synthesis of the insecticidal tetrahydroisocoumarin, (3*R*,4*S*,4a*R*)-4,8-dihydroxy-3-methyl-3,4,4a,5-tetrahydro-1*H*-2-benzopyran-1-one.[37,38] The synthesis of mellein (**1**), ramulosin (**5**), and other derivatives (**2**, **3**, **4**, **6**) was considered to be possible by employing our one-pot procedure (Scheme 1). We expected the key intermediate (**B**) to be constructed from two building blocks, diketene (**C**) and δ-hydroxy-α,β-unsaturated aldehyde (**D**) by successive esterification (a) to open the diketene β-lactone to give an acetoacetate, Michael addition (b) of the enolate, and aldol condensation (c) of the methyl ketone to the aldehyde. In the Michael addition step, the angular hydrogen atom would be controlled to be in an axial orientation by proceeding via the chair-form transition state with all equatorial substituents. Separation of diastereomers of **B** would give 6-hydroxyramulosin (**6**). Other compounds (**1**–**5**) would be synthesized via intermediate **A**, which would be obtained by dehydration of **B**.

The synthesis of δ-hydroxy-α,β-unsaturated aldehyde **9** is shown in Scheme 2. Starting from enantiomerically pure ethyl (*R*)-3-hydroxybutyrate **7**,[39,40] δ-hydroxy-α,β-unsaturated

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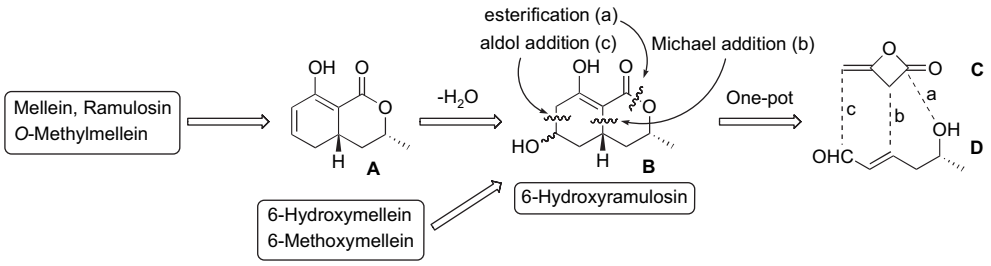
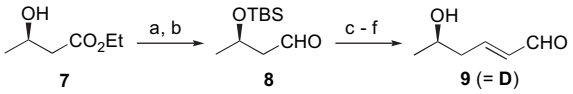


Scheme 1. Synthetic plan.

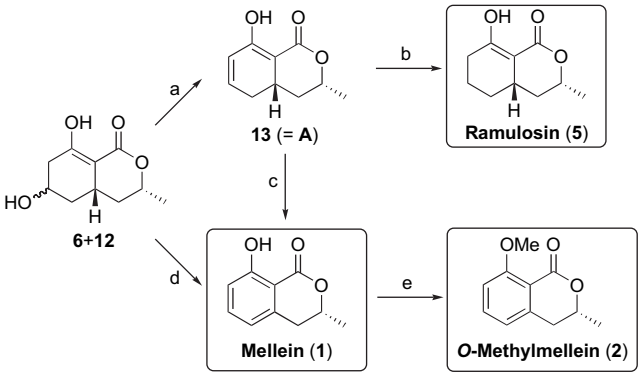
aldehyde **9** (=**D**) was prepared via C_2 elongation by the modified method of the reported one.[41]



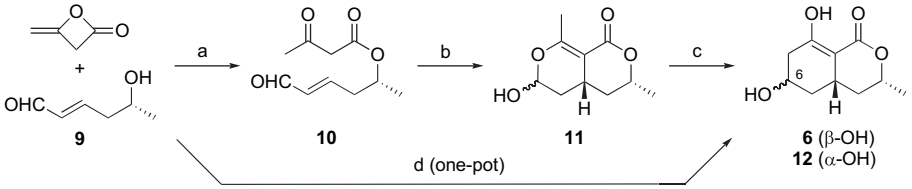
Scheme 2. Synthesis of (*R*,*E*)-5-hydroxyhex-2-enal (**9**). Reagents and conditions: (a) TBSCl, imid., CH_2Cl_2, quant; (b) DIBAL, CH_2Cl_2, 98%; (c) Ph_3PCHCO_2Me, CH_2Cl_2, 88%; (d) DIBAL, CH_2Cl_2, 96%; (e) MnO_2, CH_2Cl_2, 97%; (f) aq HF, CH_3CN, 94%.

One-pot reaction to afford the key intermediate **B** is shown in Scheme 3. At first, the step-by-step reaction was examined. Esterification of **9** with diketene was promoted by catalytic amount of 4-(dimethylamino)pyridine at room temperature to give β-keto ester **10**. When **10** was treated with potassium carbonate and 18-crown-6 at room temperature, the desired Michael addition occurred to afford hemiacetal **11** (inseparable mixture of α- and β-hydroxy isomers in a 1:2.4 ratio). Treatment of hemiacetal **11** with potassium carbonate and 18-crown-6 again at higher temperature effected reopening of hemiacetal ring and aldol reaction to give the desired bicyclic compounds **6**+**12** (=**B**) in a high yield as a 3.4:1 mixture. Now that the step-by-step reaction was successful, we then tried the one-pot esterification–Michael addition–aldol reaction from **9** to **6**+**12**. With 1.05 equiv of diketene, DMAP-catalyzed esterification proceeded smoothly also in benzene. Subsequent addition of a catalytic amount of potassium carbonate and 18-crown-6 and heating lead to the further reactions to give **6**+**12** (3.4:1) successfully in one-pot. In this reaction, concentration dependence was observed. When one-pot reaction was performed with 0.028 M of **9**, bicyclic products were obtained in good yield (74%), while the higher concentrations (0.42 M, 0.084 M) gave moderate yield of products (34%, 59%, respectively). Thus, we succeeded in carrying out the key one-pot reaction to obtain intermediates (**6**+**12**) efficiently. The diastereomers at C-6 were easily separated by preparative thin layer chromatography (SiO_2) to give (+)-6-hydroxyramulosin (**6**), whose spectral data were identical to those of natural 6-hydroxyramulosin.[23] Its mp and specific rotation were 134–135 °C and $[\alpha]_D^{24}$ +91 (*c* 0.43, MeOH), respectively {lit.[23] mp 132–133 °C, $[\alpha]_D^{25}$ +91.6 (*c* 1, MeOH)}.

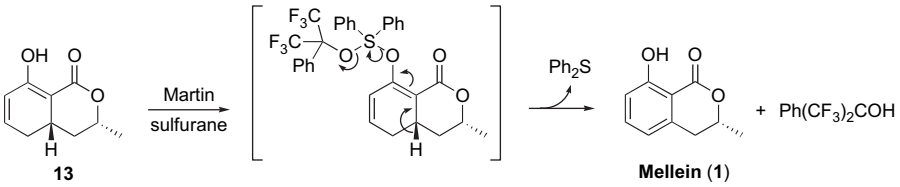
Next, we examined the dehydration of **6**+**12** for the synthesis of mellein and ramulosin (Scheme 4). Although treatment with 2-fluoro-*N*-methylpyridinium tosylate[42] gave dehydrated product **13** in a moderate yield, treatment with Martin sulfurane[43] (1 equiv) gave **13** in higher yield. The synthesis of (+)-ramulosin (**5**) was succeeded by the selective reduction[29] of **13** and the synthesis of (−)-mellein (**1**) was also succeeded by the oxidative aromatization of **13** with DDQ in excellent yield. Interestingly, when the alcohol **12** was treated with excess amount of Martin sulfurane, mellein (**1**) was obtained unexpectedly in a one-step reaction via dehydration and aromatization. Similarly, the treatment of **13** with excess amount of Martin sulfurane gave mellein. During this aromatization with Martin sulfurane, formation of Ph_2S was observed. We therefore suppose the reaction mechanism of the aromatization to be as shown in Scheme 5. We considered that the enolic oxygen of **13** would attack



Scheme 4. Synthesis of mellein, ramulosin, and *O*-methylmellein. Reagents and conditions: (a) Martin sulfurane (1 equiv), $CHCl_3$, 74%; (b) Ph_2SiH_2, $ZnCl_2$, $Pd(PPh_3)_4$, $CHCl_3$, 81%; (c) DDQ, benzene, 98% or Martin sulfurane (excess), $CHCl_3$, 75%; (d) Martin sulfurane (excess), $CHCl_3$, 72%; (e) Me_2SO_4, K_2CO_3, acetone, quant.



Scheme 3. Synthesis of key intermediates **6** and **12**. Reagents and conditions: (a) DMAP, benzene, 83%; (b) K_2CO_3, 18-crown-6, benzene, 60%; (c) K_2CO_3, 18-crown-6, benzene, reflux, 94%; (d) DMAP, benzene, then K_2CO_3, 18-crown-6, rt, then reflux, 71–74% (one-pot).



Scheme 5. Mechanism of aromatization by Martin sulfurane.

the sulfur of Martin sulfurane and then reductive removal of Ph_2S and $Ph(CF_3)_2COH$ was followed by aromatization to give mellein. Thus we succeeded in the effective synthesis of (+)-ramulosin (**5**) and (–)-mellein (**1**), which was subjected to methylation to give another natural product, (–)-*O*-methylmellein (**2**) quantitatively. Spectral data of synthetic (–)-mellein, (+)-ramulosin, and (–)-*O*-methylmellein were identical to the reported data.[5,20,8] Their mps and specific rotations were as follows: (–)-mellein: mp 55–56 °C, $[\alpha]_D^{22}$ −102 (*c* 0.53, $CHCl_3$) {lit.[5] mp 56 °C, $[\alpha]_D^{25}$ −102.5 (*c* 1.0, $CHCl_3$)}; (+)-ramulosin: mp 118–119 °C, $[\alpha]_D^{21}$ +19 (*c* 0.50, EtOH) {lit.[20] mp 120–121 °C, $[\alpha]_D^{25}$ +18 (*c* 2.9, EtOH)}; *O*-methylmellein: mp 87–88 °C, $[\alpha]_D^{26}$ −252 (*c* 0.55, $CHCl_3$) {lit.[3] mp 88–89 °C, $[\alpha]_D^{15}$ −250 (*c* 0.50, $CHCl_3$)}.

Finally, we examined the conversion of the intermediates (**6+12**) to 6-hydroxymellein (**3**) and 6-methoxymellein (**4**). Oxidation of **6+12** was found to be slightly difficult. Oxidation with IBX, Dess Martin periodinane, PCC, TPAP, TEMPO or Swern condition gave no desired compound, but PDC oxidation afforded a trace amount of 6-hydroxymellein (**3**). The best result was obtained employing Jones condition, which gave the mixture of (–)-6-hydroxymellein (**3**, 8%), ketone **14** (7%), mellein (**1**, 8%), and starting material **6+12** (19%) (Scheme 6). (–)-6-Hydroxymellein (**3**) was separated and subjected to mono-methylation to give (–)-6-methoxymellein (**4**) in good yield. Spectral data of synthetic (–)-6-hydroxymellein and (–)-6-methoxymellein were identical to the reported data.[11,18] Their mps and specific rotations were as follows: (–)-6-hydroxymellein: mp 201–203 °C, $[\alpha]_D^{18}$ −51 (*c* 0.10, MeOH) {lit.[11] mp 211–214 °C, $[\alpha]_D^{26}$ −49 (*c* 1.0, MeOH)}; (–)-6-methoxymellein: mp 76–77 °C, $[\alpha]_D^{25}$ −55 (*c* 0.23, MeOH) {lit.[15] mp 75–76 °C, $[\alpha]_D^{24}$ −56 (*c* 1, MeOH)}.

In summary, (–)-mellein, (+)-ramulosin, (–)-*O*-methylmellein, (–)-6-hydroxymellein, (–)-6-methoxymellein, and (+)-6-hydroxyramulosin were synthesized in short steps as optically active forms. The overall yields were (–)-mellein: 51% (in two steps), (+)-ramulosin: 43% (in three steps), (–)-*O*-methylmellein: 51% (in three steps), (–)-6-hydroxymellein: 6% (in two steps), (–)-6-methoxymellein: 5% (in three steps), and (+)-6-hydroxyramulosin: 55% (in one step) from the known δ-hydroxy-α,β-unsaturated aldehyde **9**. The key step, one-pot esterification–Michael addition–aldol reaction from **9** to **6+12**, was succeeded in a high yield and in a stereoselective manner. This reaction would be applicable to the synthesis of other isocoumarins.

3. Experimental

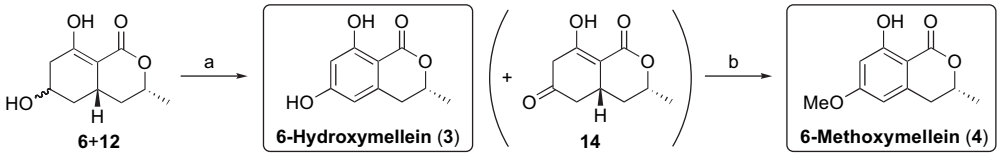
3.1. General

Optical rotations were recorded with a JASCO DIP-1000 polarimeter. IR spectra were measured with a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM AL300. Chemical shifts (δ) were referenced to the residual solvent peak as the internal standard ($CDCl_3$: δ_H=7.26, δ_C=77.0; CD_3OD: δ_H=3.30, δ_C=49.0; acetone-d_6: δ_C=29.8). Mass spectra were recorded on JEOL JMS-700T. Column chromatography was performed using Merck silica gel 60 (0.060–0.200 mm). TLC was carried out on Merck glass plates precoated with silica gel 60 F_{254} (0.25 mm). Melting points are uncorrected values.

3.2. Synthetic studies

3.2.1. (1*R*,3*E*)-1-Methyl-5-oxopent-3-enyl 3-oxobutanoate (10). 4-(Dimethylamino)pyridine (2.6 mg, 5 mol %) was added to a solution of hydroxyl aldehyde **9** (48.5 mg, 0.425 mmol) in dry benzene (1 ml). After 8 min, it was cooled to <10 °C and then a solution of diketene (38 mg, 0.45 mmol) in benzene (1 ml) was added. After 30 min, the reaction was quenched with saturated NH_4Cl (1 ml) solution and the mixture was extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine and dried with $MgSO_4$. After filtration, the solvent was evaporated and the residue was subjected to silica gel column chromatography. Elution with *n*-hexane/ethyl acetate (7:3) gave ester **10** (70 mg, 83%) as a colorless oil.

IR (film): ν=3441 (br), 2981, 2935, 2826, 1739, 1714, 1692, 1411, 1361, 1314, 1269, 1151, 1060, 978 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.32 (3H, d, *J*=6.3 Hz), 2.26 (3H, s), 2.63 (2H, ddd, *J*=7.2, 6.0, 1.2 Hz), 3.46 (2H, s), 5.16 (1H, m), 6.15 (1H, ddd, *J*=15.6, 7.8, 1.2 Hz), 6.80 (1H, dt, *J*=15.6, 7.2 Hz), 9.52 (1H, d, *J*=7.8 Hz). ^{13}C NMR



Scheme 6. Synthesis of 6-hydroxymellein and 6-methoxymellein. Reagents and conditions: (a) Jones reagent, acetone, **3** (8%), **14** (7%), **1** (8%); (b) Me_2SO_4, K_2CO_3, acetone, 88%.

(75 MHz in $CDCl_3$): δ=19.6, 30.1, 38.6, 49.9, 69.3, 135.4, 152.2, 166.3, 193.5, 200.3. ESI-HRMS *m/z* calcd for $C_{10}H_{14}O_4Na$ $[M+Na]^+$ 221.0784, found 221.0753.

3.2.2. (3*R*,4a*R*)-6-Hydroxy-3,8-dimethyl-4,4a,5,6-tetrahydro-1*H*,3*H*-pyrano[3,4-*c*]pyran-1-one (11). To a stirring solution of ester **10** (108 mg, 0.545 mmol) in dry benzene (3 ml) was added K_2CO_3 (2.6 mg, 3.5 mol %) and 18-crown-6 (23 mg, 16 mol %) at room temperature. After 2.5 h, solvent was evaporated in vacuo and the residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (7:3–1:1) afforded hemiacetal **11** (65 mg, 60%, β-OH/α-OH=2.4:1) as a white solid.

IR ($CDCl_3$ solution): 3256 (br), 2983, 2935, 2862, 1674, 1583, 1387, 1283, 1257, 1158, 1133, 1106, 1045, 999, 959, 943, 882, 837 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$) for β-OH-isomer: δ=1.37 (3H, d, *J*=6.3 Hz), 1.26–1.51 (2H, m), 1.90–2.29 (2H, m), 2.36 (3H, s), 2.84 (1H, m), 4.45 (1H, m), 5.59 (1H, br s). ^1H NMR (300 MHz in $CDCl_3$) for α-OH-isomer: δ=1.36 (3H, d, *J*=6.3 Hz), 1.26–1.51 (2H, m), 1.90–2.29 (2H, m), 2.35 (3H, s), 2.71 (1H, m), 4.42 (1H, m), 5.36 (1H, m).

3.2.3. 6,8-Dihydroxy-3-methyl-3,4,4a,5,6,7-hexahydro-1*H*-isochromen-1-one [12 and (+)-6-hydroxyramulosin (6)]—stepwise reaction. To a stirring solution of hemiacetal **11** (48 mg, 0.24 mmol) in dry benzene (3 ml) was added K_2CO_3 (1.2 mg, 3.5 mol %) and 18-crown-6 (10.2 mg, 16 mol %). This mixture was then refluxed for 2 h and cooled to room temperature. The solvent was evaporated in vacuo and the residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (1:1) afforded a mixture of **6** and **12** (45 mg, 94%, **6**/**12**=3.4:1) as a white solid. Diastereomers were separated by preparative TLC using diethyl ether as the developing solvent to afford **6** (35 mg, 73%) and **12** (4.1 mg, 8.6%). Both of the isomers were recrystallized from ethyl acetate/*n*-hexane to give colorless needles.

*(+)-6-Hydroxyramulosin (**6**)*: mp 134–135 °C. $[\alpha]_D^{24}$ +91 (*c* 0.43, MeOH). IR (KBr): ν=3448, 3000–2840, 1639, 1599, 1444, 1401, 1352, 1289, 1257, 1233, 1166, 1145, 1107, 1062, 1028, 944, 867, 830 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.25–1.46 (2H, m), 1.40 (3H, d, *J*=6.3 Hz), 1.66 (1H, d, *J*=3.0 Hz), 1.92 (1H, m), 2.01 (1H, m), 2.41 (1H, d, *J*=19.5 Hz), 2.66 (1H, ddd, *J*=19.5, 4.5, 2.4 Hz), 2.92 (1H, br t, *J*=11.1 Hz), 4.37 (1H, br s), 4.52 (1H, m), 13.18 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.7, 26.4, 35.7, 36.8, 37.5, 63.7, 76.8, 96.4, 171.4, 171.6. ESI-HRMS *m/z* calcd for $C_{10}H_{14}O_4Na$ $[M+Na]^+$ 221.0784, found 221.0812. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.42; H, 6.87.

*Compound **12***: mp 127–128 °C. $[\alpha]_D^{18}$ +21 (*c* 0.07, MeOH). IR (KBr): ν=3400 (br), 3000–2840, 1639, 1599, 1411, 1295, 1231, 1176, 1105, 1058, 870 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.21–1.45 (2H, m), 1.39 (3H, d, *J*=6.6 Hz), 1.67 (1H, d, *J*=4.8 Hz), 1.97 (1H, m), 2.12 (1H, m), 2.35 (1H, ddd, *J*=18.3, 9.9, 2.4 Hz), 2.60 (1H, br t, *J*=11.1 Hz), 2.80 (1H, dd, *J*=18.3, 6.3 Hz), 4.04 (1H, m), 4.46 (1H, m), 13.14 (1H, s). ESI-HRMS *m/z* calcd for $C_{10}H_{14}O_4Na$ $[M+Na]^+$ 221.0784, found 221.0744.

3.2.4. 6,8-Dihydroxy-3-methyl-3,4,4a,5,6,7-hexahydro-1*H*-isochromen-1-one (6+12)—one-pot reaction. 4-(Dimethylamino)pyridine (35 mg, 5.6 mol %) was added to a solution of hydroxyl aldehyde **9** (583 mg, 5.11 mmol) in dry benzene (110 ml). After 8 min, a solution of diketene (465 mg, 5.52 mmol) in benzene (90 ml) was added to the reaction mixture through cannula over 15 min at 10 °C and it was stirred for further 30 min. Then K_2CO_3 (75 mg, 11 mol %) and 18-crown-6 (414 mg, 30.7 mol %) were added and stirring was continued for 2.5 h at room temperature. After completion of Michael addition, the mixture was refluxed for 3 h to give aldol product. After cooling down to room temperature, the reaction mixture was quenched with H_2O (15 ml) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (300 ml). Both of the benzene part and the dichloromethane part were washed with brine (10 ml) separately and the combined brine part was re-extracted with dichloromethane (50 ml). Combined organic layer was then dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo and the residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (1:1–4:5) afforded a mixture of **6** and **12** (715 mg, 71%, **6**/**12**=3.4:1) as a white solid, whose spectral data were identical to those of the product obtained by stepwise reactions.

3.2.5. 8-Hydroxy-3-methyl-3,4,4a,5-tetrahydro-1*H*-isochromen-1-one (13). To a stirring solution of bicyclic diol **6+12** (135 mg, 0.681 mmol) in chloroform (12 ml) was added Martin sulfurane (1 equiv) at 0 °C. After 3 h, solvent was evaporated in vacuo and the residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (4:1) afforded **13** (91 mg, 74%) as a white solid.

Mp 83–84 °C. $[\alpha]_D^{26}$ +174 (*c* 0.40, $CHCl_3$). IR (KBr): ν=3435, 3000–2800, 1647, 1575, 1388, 1313, 1248, 1185, 1146, 1092, 873, 799 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.41 (3H, d, *J*=6.3 Hz), 1.51 (1H, m), 1.92–2.07 (2H, m), 2.34 (1H, dt, *J*=17.1, 6.3 Hz), 2.87 (1H, m), 4.39 (1H, m), 6.07 (1H, dd, *J*=9.9, 3.3 Hz), 6.44 (1H, ddd, *J*=9.9, 6.9, 2.1 Hz), 12.84 (1H, s). ^{13}C NMR (75 MHz in $CDCl_3$): δ=21.3, 29.8, 30.5, 36.6, 74.7, 92.5, 124.5, 139.4, 168.0, 171.8. ESI-HRMS *m/z* calcd for $C_{10}H_{12}O_3Na$ $[M+Na]^+$ 203.0679, found 203.0699.

3.2.6. (3*R*,4a*S*)-(+)-Ramulosin (5). According to the method of Pietrusiewicz,[29] reduction of diene **13** (=**A**) (45.5 mg, 0.253 mmol) afforded **5** (37.1 mg, 81%) as a white solid.

Mp 118–119 °C. $[\alpha]_D^{21}$ +19 (*c* 0.50, EtOH). IR (KBr): ν=3422, 3000–2800, 1643, 1618, 1446, 1407, 1387, 1354, 1304, 1273, 1235, 1172, 1145, 1105, 1065, 1019, 957, 892, 831, 774 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.09–1.34 (2H, m), 1.38 (3H, d, *J*=6.3 Hz), 1.62 (1H, m), 1.85–1.96 (3H, m), 2.38 (2H, m), 2.52 (1H, m), 4.46 (1H, m), 13.26 (1H, s). ^{13}C NMR (75 MHz in $CDCl_3$): δ=20.9, 21.7, 29.0, 29.5, 32.9, 37.4, 76.0, 96.8, 171.8, 174.7. ESI-HRMS *m/z* calcd for $C_{10}H_{14}O_3Na$ $[M+Na]^+$ 205.0835, found 205.0853.

3.2.7. (*R*)-(−)-Mellein (1).

3.2.7.1. Aromatization by DDQ. To a stirring solution of diene **13** (26.1 mg, 0.144 mmol) in dry benzene (2 ml)

was added DDQ (60 mg, 0.26 mmol) at room temperature. After 3 h, the reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was chromatographed over silica gel. Elution with *n*-hexane/ether (5:2) afforded **1** (25 mg, 98%) as a white solid.

3.2.7.2. Aromatization by Martin sulfurane. To a stirring solution of diene **13** (12.2 mg, 0.068 mmol) in chloroform (1.5 ml) was added Martin sulfurane (91.5 mg, 0.136 mmol) at 0 °C and then the reaction mixture was allowed to warm to room temperature. After 7 h, solvent was evaporated in vacuo and the residue was chromatographed over silica gel. Elution with *n*-hexane/ether (5:2) afforded **1** (9.1 mg, 75%) as a white solid.

3.2.7.3. Dehydration and aromatization by Martin sulfurane. To a stirring solution of bicyclic diol **12** (16 mg, 0.08 mmol) in chloroform (1.2 ml) was added Martin sulfurane (161 mg, 0.24 mmol) at 0 °C and then the reaction mixture was slowly allowed to warm to room temperature. After 15 h, the solvent was evaporated in vacuo and the residue was chromatographed over silica gel. Elution with *n*-hexane/ether (5:2) afforded **1** (10.3 mg, 72%) as a white solid. Recrystallization from *n*-hexane gave colorless needles.

Mp 55–56 °C. $[\alpha]_D^{22}$ −102 (*c* 0.53, $CHCl_3$). IR (KBr): ν=3430, 3000, 1672, 1619, 1465, 1366, 1325, 1293, 1237, 1225, 1168, 1118, 1049, 956, 898, 805, 783, 756, 715, 696, 680 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.53 (3H, d, *J*=6.3 Hz), 2.93 (2H, d, *J*=7.2 Hz), 4.73 (1H, m), 6.69 (1H, d, *J*=7.2 Hz), 6.89 (1H, d, *J*=8.4 Hz), 7.41 (1H, dd, *J*=8.4, 7.2 Hz), 11.03 (1H, s). ^{13}C NMR (75 MHz in $CDCl_3$): δ=20.7, 34.5, 76.2, 108.2, 115.9, 117.9, 136.1, 139.3, 162.1, 169.9. ESI-HRMS *m*/*z* calcd for $C_{10}H_{10}O_3Na$ $[M+Na]^+$ 201.0522, found 201.0492.

3.2.8. (*R*)-(−)-*O*-Methylmellein (2). To a stirring solution of (*R*)-(−)-mellein **1** (29 mg, 0.16 mmol) in acetone (5 ml) was added Me_2SO_4 (25 μl, 0.26 mmol) and K_2CO_3 (136 mg, 0.984 mmol) at room temperature. The mixture was warmed to 40 °C and kept up to complete conversion. The solvent was evaporated in vacuo and ethyl acetate was added to the residue. After filtration, the filtrate was concentrated in vacuo to give almost pure product, which was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (1:1) afforded **2** (31.2 mg, quant). Recrystallization from ether/*n*-hexane gave colorless prisms.

Mp 87–88 °C. $[\alpha]_D^{21}$ −252 (*c* 0.55, $CHCl_3$). IR (KBr): ν=3100–2840, 1712, 1597, 1589, 1476, 1457, 1435, 1353, 1300, 1274, 1238, 1117, 1084, 1057, 948, 900, 802, 776, 702 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.48 (3H, d, *J*=6.3 Hz), 2.87 (2H, m), 3.95 (3H, s), 4.55 (1H, m), 6.80 (1H, d, *J*=7.5 Hz), 6.92 (1H, d, *J*=8.4 Hz), 7.45 (1H, dd, *J*=8.4, 7.5 Hz). ^{13}C NMR (75 MHz in $CDCl_3$): δ=20.6, 36.0, 56.0, 74.1, 110.7, 113.5, 119.1, 134.4, 141.8, 161.0, 162.7. ESI-HRMS *m*/*z* calcd for $C_{11}H_{12}O_3Na$ $[M+Na]^+$ 215.0679, found 215.0635. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.53; H, 6.08.

3.2.9. 6-Hydroxymellein (3). To a stirring solution of bicyclic diol **6+12** (30 mg, 0.15 mmol) in acetone (1.5 ml) was added Jones reagent (76 μl) at 0 °C and stirring was continued for 45 min. After evaporation in vacuo, the residue was diluted with ether and filtered through Celite pad. The filtrate was concentrated in vacuo to give the crude product, which was purified by preparative TLC using chloroform/methanol (30:1) as the developing solvent to afford **3** (2.3 mg, 7.8%) as a white solid, ketone **14** (2.0 mg, 6.7%), mellein **1** (2.1 mg, 7.8%), and starting material **12** (5.7 mg, 19%).

*6-Hydroxymellein (**3**)*: mp 201–203 °C. $[\alpha]_D^{18}$ −51 (*c* 0.10, MeOH). IR (KBr): ν=3600–2800, 1651, 1632, 1587, 1503, 1477, 1386, 1290, 1257, 1221, 1195, 1170, 1120, 1067, 854, 796, 737 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.51 (3H, d, *J*=6.3 Hz), 2.87 (2H, m), 4.68 (1H, m), 6.21 (1H, d, *J*=2.1 Hz), 6.31 (1H, d, *J*=2.1 Hz), 11.22 (1H, s). ^{13}C NMR (75 MHz in acetone-d_6): δ=20.8, 35.0, 76.3, 101.6, 101.9, 107.4, 143.2, 165.3, 165.3, 170.7. ESI-HRMS *m*/*z* calcd for $C_{10}H_{10}O_4Na$ $[M+Na]^+$ 217.0471, found 217.0469. Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.81; H, 5.00.

*Ketone **14***: IR ($CDCl_3$ solution): ν=3100–2840, 1728, 1651, 1604, 1407, 1313, 1285, 1259, 1215, 1175, 1138, 1087, 855 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.44 (3H, d, *J*=6.3 Hz), 1.49 (1H, m), 2.10 (1H, ddd, *J*=13.5, 4.5, 1.8 Hz), 2.22 (1H, dd, *J*=15.0, 12.3 Hz), 2.68 (1H, dd, *J*=15.0, 4.2 Hz), 2.89 (1H, m), 3.25 (2H, s), 4.47 (1H, m), 13.26 (1H, s).

3.2.10. 6-Methoxymellein (4). To a solution of (−)-6-hydroxymellein (**3**, 14.8 mg, 0.076 mmol) in acetone (1.5 ml) was added K_2CO_3 (52 mg, 0.38 mmol) and Me_2SO_4 (7.5 μl, 0.078 mmol) at 0 °C and the mixture was stirred at 4 °C for 36 h. The solvent was evaporated in vacuo and H_2O (2 ml) and dichloromethane (20 ml) were added to the residue. After separation of the organic layer, the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with *n*-hexane/ethyl acetate (7:3) afforded **4** (14 mg, 88%) as a white solid. Recrystallization from *n*-hexane/ether gave colorless needles.

Mp 76–77 °C. $[\alpha]_D^{25}$ −55 (*c* 0.23, MeOH). IR (KBr): ν=3600–2840, 1664, 1635, 1583, 1510, 1440, 1372, 1247, 1205, 1157, 1115, 1095, 1069, 1037, 964, 849, 828, 800, 709 cm^{-1}. ^1H NMR (300 MHz in $CDCl_3$): δ=1.50 (3H, d, *J*=6.2 Hz), 2.86 (2H, m), 3.82 (3H, s), 4.67 (1H, m), 6.24 (1H, s), 6.37 (1H, s), 11.25 (1H, s). ^{13}C NMR (75 MHz in $CDCl_3$): δ=20.7, 34.8, 55.5, 75.5, 99.4, 101.5, 106.2, 140.9, 164.5, 165.7, 169.9. ESI-HRMS *m*/*z* calcd for $C_{11}H_{12}O_4Na$ $[M+Na]^+$ 231.0628, found 231.0588. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.85; H, 6.12.

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