Preparation of the Geranyl-α-pyrone (±)-Aurantiacone via a New Pyrone Synthesis

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Abstract: The structure of the leaf resin geranyl-α-pyrone aurantiacone isolated from *Mimulus* (= *Diplacus*) *aurantiacus* (Curtis) Jeps. (Scrophulariaceae) was confirmed through synthesis. The key step is lactonization of the sensitive 5-hydroxy-3-oxopent-4-enoic acid under mild conditions, which can be released from the corresponding bispotassium salt. The latter is accessible in a few steps from an *N*-acyl aziridine and an ethyl acetoacetate.

Key words: hydrolyses, cyclizations, lactones, heterocycles, natural products

Mimulus (= *Diplacus*) *aurantiacus* (Curtis) Jeps. (Scrophulariaceae) is a chaparral subshrub that mainly occurs in California. It produces striking amounts of leaf surface resins in excess of 30% of leaf dry weight.[1] This resin is remarkable since it reduces growth and survival of its primary herbivore, the larvae of *Euphydryas chalcedona*.[2] It consists of at least five geranyl flavonoids of known structure.[1,3] Additional compounds of the leaf surface resins have been isolated, but their structures have not been elucidated yet.[3a]

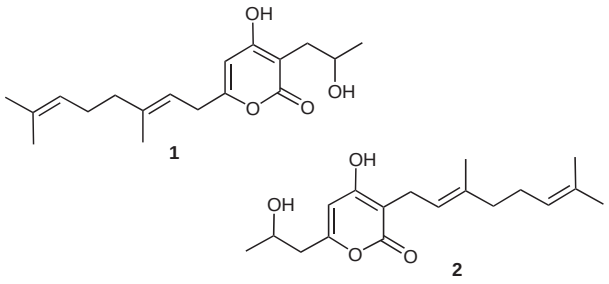
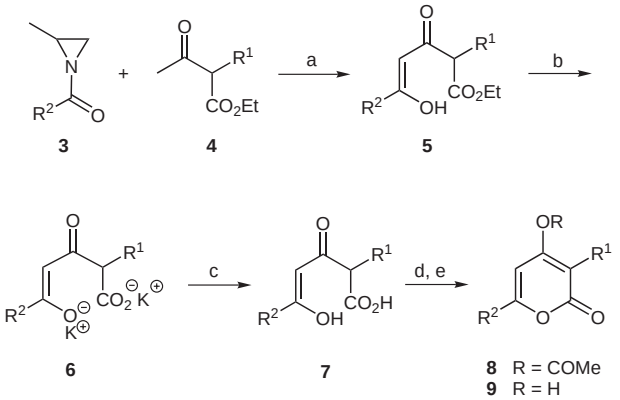


Figure 1 The two structural proposals for aurantiacone

In 1989, Wollenweber et al. were the first to report on the isolation of a geranyl-α-pyrone from the leaf resin of *Diplacus aurantiacus* with a molecular weight of 306.[3a] Based on the NMR spectroscopic data they proposed structure **1** but at the same time noted that structure **2** was also conceivable (Figure 1). Recently, this compound was again isolated from the leaf resin of *Mimulus* (= *Diplacus*) *aurantiacus* by Hare et al.[1b,c,4] Detailed NMR investigations led them to conclude that the initial structure assignment was incorrect. They suggested **2** as the structure of the natural product which was referred to as aurantiacone.

Biogenetic considerations also support structure **2**. Given that the biosynthesis of aurantiacone involves a triketo thioester cyclizing to produce an α-pyrone which then reacts with geranyl diphosphate, nothing else but **2** can be the correct structure, as **1** cannot be produced by this pathway.



Scheme 1 *Reagents and conditions*: (a) LDA (2 equiv), THF, –78 °C → 0 °C; NH_4Cl (aq); (b) KOH, EtOH, r.t.; (c) tartaric acid, 0 °C; (d) Ac_2O, py, –20 °C → 0 °C; (e) K_2CO_3, MeOH, r.t.

In order to confirm the structure of aurantiacone we performed a synthesis of this natural product. The procedure we applied relies on a method for the preparation of 4-hydroxy-2*H*-pyran-2-ones **9** (Scheme 1), which has recently been developed in our laboratory.[5] Our protocol is based on the assembly of 5-hydroxy-3-oxopent-4-enoic acid esters **5** through selective γ-acylation of the dianion of ethyl acetoacetates **4** with *N*-acyl-2-methyl aziridines **3**[6] and the transformation of **5** into the corresponding stable bispotassium salts **6**. The free 5-hydroxy-3-oxopent-4-enoic acid **7** is released from **6** by treatment with tartaric acid and cyclized under mild conditions with acetic anhydride–pyridine. The primarily formed *O*-acetyl derivatives **8** are finally hydrolyzed with potassium carbonate to give the 4-hydroxy-2*H*-pyran-2-ones **9**. In most cases **7** can be transformed into **9** in one synthetic step using trifluoroacetic acid–trifluoroacetic anhydride as a reagent. This method is suitable for the efficient synthesis of 6-substituted and 3,6-disubstituted 4-hydroxy-2*H*-pyran-2-ones. What distinguishes this method is that it employs the bispotassium salts **6** of 5-hydroxy-3-oxopent-4-enoic

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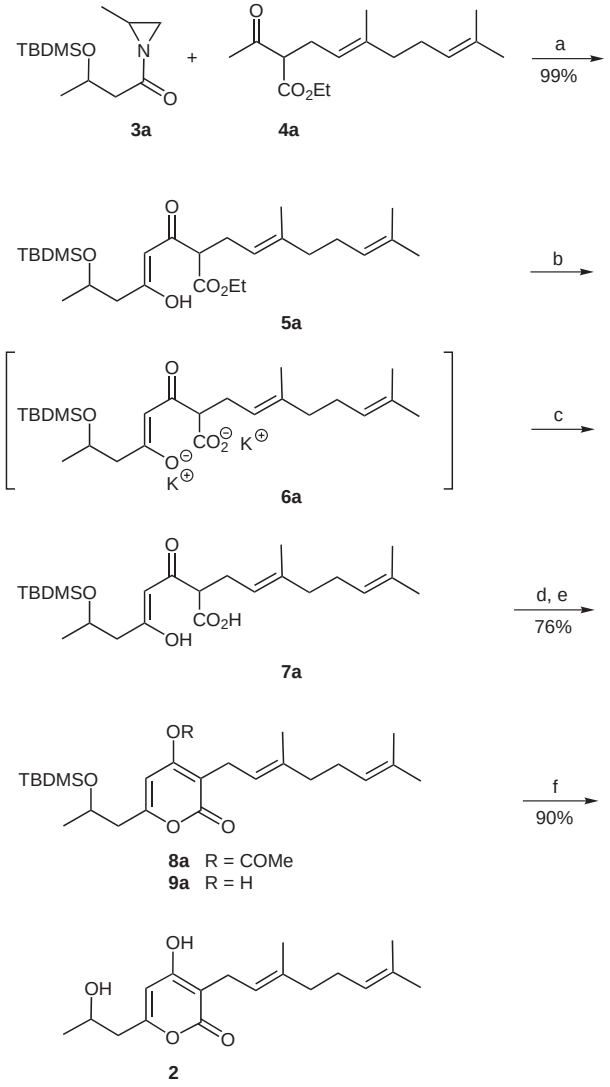
acids as a stable and easy to purify storage option for 5-hydroxy-3-oxopent-4-enoic acids **7**. If needed, **6** can be used to generate the very sensitive free 5-hydroxy-3-oxopent-4-enoic acids **7**, which in turn can be lactonized to give the substituted 4-hydroxy-2*H*-pyran-2-ones **9**.

In order to synthesize aurantiacone **2** the 5-hydroxy-3-oxopent-4-enoic acid ester **5a** was prepared according to Lygo's method[6] by reacting the dianion of the 2-geranyl substituted ethyl acetoacetate **4a** with the *N*-acyl-2-methyl aziridine **3a**[7] in 99% yield (Scheme 2).



Scheme 2 *Reagents and conditions:* (a) LDA (2 equiv), THF, –78 °C → 0 °C, 3 h; NH_4Cl (aq); (b) KOH, EtOH, r.t., 3 h; (c) tartaric acid, 0 °C, 10 min; (d) Ac_2O, py, –20 °C → 0 °C, 1 h; (e) K_2CO_3, MeOH, r.t., 2 h; (f) py·HF complex, THF, r.t., 12 h

The *N*-acyl-2-methyl aziridine **3a** was obtained through the conversion of 2-methyl aziridine and the corresponding carboxylic acid via DCC–DMAP activation in 83% yield. The substituted acetoacetate **4a** is accessible via alkylation of ethyl acetoacetate with geranyl chloride in 91% yield. 5-Hydroxy-3-oxopent-4-enoic acid ethyl ester **5a**[8] was transformed to produce the bispotassium salt **6a**. Though not isolated, **6a** was then treated with aqueous tartaric acid solution to yield the free 5-hydroxy-3-oxopent-4-enoic acid **7a**. The latter was then reacted with acetic anhydride–pyridine at temperatures between –20 °C and 0 °C to produce the *O*-acetyl derivative **8a**. Conversion of **8a** with potassium carbonate in methanol delivered the substituted 4-hydroxy-2*H*-pyran-2-one **9a** with 76% yield (4 steps).[9] The final cleavage of the silyl ether supplied **2** in 90% yield. Starting from **3a** and **4a** the natural product **2** was synthesized in over six steps with an overall yield of 68%.

As the structure of our synthetic sample is beyond doubt[10] and in agreement with that proposed by Hare et al.[4] we can validly conclude that the structure of aurantiacone is that shown in **2**.

References and Notes

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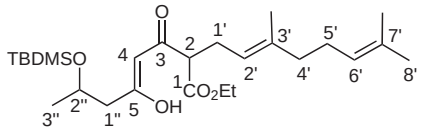
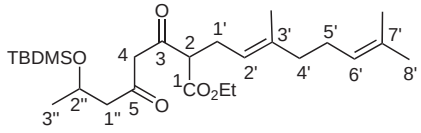
(7) Selected data for **3a** (mixture of two diastereomers D1 and D2): IR (ATR): 2957, 2929, 2856, 1696, 1471, 1405, 1374, 1255, 1179, 1134, 1076, 1002, 832, 810, 774 cm^{-1}. UV (MeCN): λ_{max} (log ε) = 243 (2.55) nm. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 3 H, $SiCH_3$),* 0.02 (s, 3 H, $SiCH_3$),* 0.07 (s, 6 H, 2 × $SiCH_3$),* 0.858 [s, 9 H, $SiC(CH_3)_3$],* 0.861 [s, 9 H, $SiC(CH_3)_3$],* 1.197 (d, ^3J = 6.1 Hz, 3 H, 4-H_3),* 1.202 (d, ^3J = 6.1 Hz, 3 H, 4-H_3),* 1.31 (d, ^3J = 5.3 Hz, 3 H, 2′-CH_3, D1), 1.32 (d, ^3J = 5.2 Hz, 3 H, 2′-CH_3, D2), 1.917 (d, ^3J = 3.1 Hz, 1 H, 3′-H_A, D2), 1.925 (d, ^3J = 2.9 Hz, 1 H, 3′-H_A, D1), 2.37 (d, ^3J = 5.9 Hz, 1 H, 3′-H_B, D2), 2.38 (d, ^3J = 6.2 Hz, 1 H, 3′-H_B, D1), 2.43 (dd, ^2J = 9.7 Hz, ^3J = 5.3 Hz, 1 H, 2-H_A),* 2.45 (dd, ^2J = 9.3 Hz, ^3J = 5.0 Hz, 1 H, 2-H_A),* 2.53 (overlapped, 2′-H, D1), 2.56 (overlapped, 2-H′, D2), 2.59 (overlapped, 2-H_B),* 2.61 (dd, ^2J = 10.1 Hz, ^3J = 7.7 Hz, 1 H, 2-H_B),* 4.29–4.37 (m, 1 H, 3-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.79 (2 × $SiCH_3$),* –4.73 ($SiCH_3$),* –4.71 ($SiCH_3$),* 17.72, 17.79 (2′-CH_3),* 17.92, 17.94 [$SiC(CH_3)_3$],* 23.92, 23.96 (C-4),* 25.79 [$SiC(CH_3)_3$], 31.12 (C-3′, D1), 31.69 (C-3′, D2), 32.18 (C-2′, D2), 32.72 (C-2′, D1), 47.44, 47.23 (C-2),* 66.09, 66.17 (C-3),* 183.68, 183.71 (C-1).* MS (EI, 70 eV): *m/z* (%) = 257.0 (<1%) [M^+], 242.0 (7) [M^+ – CH_3], 199.9 (100) [M^+ – C_4H_9], 142.9 (20) [M^+ – $C_6H_{14}Si$], 113.9 (35) [$C_6H_{17}Si^+$], 74.9 (30) [$C_2H_7OSi^+$]. * Unambiguous assignment was not possible.

(8) Selected data for **5a** (mixture of four isomers; for details see Figure 2): IR (ATR): 2928, 2856, 1738, 1601, 1444, 1375, 1255, 1132, 1096, 997, 834, 810, 775 cm^{-1}. UV (MeOH): λ_{max} (log ε) = 280 (3.92) nm. Tautomer T1: ^1H NMR (500 MHz, $CDCl_3$): δ = 0.002 (s, 6 H, 2 × $SiCH_3$),* 0.04 (s, 6 H, 2 × $SiCH_3$),* 0.855 [s, 9 H, $SiC(CH_3)_3$],* 0.858 [s, 9 H, $SiC(CH_3)_3$],* 1.19 (d, ^3J = 6.1 Hz, 3 H, 3′′-H_3), 1.25 (t,



T1 (exists as a mixture of two diastereomers D1 and D2)



T2 (exists as a mixture of two diastereomers D3 and D4)

Figure 2 Compound **5a** exists as a mixture of isomers in $CDCl_3$

^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$),* 1.27 (t, ^3J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$),* 1.59 (s, 3 H, 7′-CH_3), 1.63 (s, 3 H, 3′-CH_3), 1.68 (s, 3 H, 8′-H_3), 1.94–2.00 (m, 2 H, 4′-H_2), 2.01–2.08 (m, 2 H, 5′-H_2), 2.34 (dd, ^2J = 13.5 Hz, ^3J = 5.0 Hz, 1 H, 1″-H_A),* 2.35 (dd, ^2J = 13.5 Hz, ^3J = 5.0 Hz, 1 H, 1″-H_A),* 2.40 (dd, ^2J = 13.7 Hz, ^3J = 7.8 Hz, 1″-H_B),* 2.46–2.53 (overlapped, m, 1 H, 1′-H_A), 2.59–2.67 (overlapped, m, 1 H, 1′-H_B), 3.26 (dd, ^3J = 4.3 Hz, ^3J = 6.8 Hz, 1 H, 2-H),* 3.27 (dd, ^3J = 4.3 Hz, 1 H, ^3J = 6.8 Hz, 1 H, 2-H)*, 4.14–4.20 (overlapped, 2 H, OCH_2), 4.18–4.30 (m, 1 H, 2″-H), 5.02–5.09 (m, 2 H, 2′-H, 6′-H), 5.621 (s, 1 H, 4-H),* 5.623 (s, 1 H, 4-H),* 15.19 (br s, 1 H, enolic H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.11 (2 × $SiCH_3$), –4.71 ($SiCH_3$), –4.69 ($SiCH_3$), 14.09 ($CO_2CH_2CH_3$), 16.10 (3′-CH_3), 17.60 (7′-CH_3), 17.96 [$SiC(CH_3)_3$], 24.10, 24.12 (C-3″)*, 25.60 (C-8′), 25.72 [$SiC(CH_3)_3$], 26.57 (C-5′), 27.84, 28.00 (C-1′)*, 39.67 (C-4′), 47.79, 47.83 (C-1″),* 55.97, 56.03 (C-2),* 61.21, 61.23 (OCH_2),* 66.21 (C-2″), 100.47, 100.54 (C-4),* 119.78, 119.83 (C-2′)*, 123.97, 124.01 (C-6′),* 131.44, 131.50 (C-7′),* 138.28, 138.31 (C-3′),* 169.87, 169.88 (C-1),* 188.87, 189.06 (C-5),* 192.3 (C-3). Tautomer T2: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.52 (overlapped, 1″-H_A), 2.57 (overlapped, 2 H, 1′-H_2), 2.69 (overlapped, 1″-H_B), 3.56 (t, ^3J = 7.5 Hz, 1 H, 2-H),* 3.57 (t, ^3J = 7.5 Hz, 1 H, 2-H),* 3.61 (d, ^2J = 15.8 Hz, 1 H, 4-H_A, D3), 3.70 (s, 2 H, 4-H_2, D4), 3.77 (d, ^2J = 15.8 Hz, 1 H, 4-H_B, D3), 4.28 (overlapped, 2″-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.82 (C-1′), 39.64 (C-4′), 57.32, 57.36 (C-4),* 52.83 (C-1″), 59.49, 59.47 (C-2),* 65.38 (C-2″), 119.34, 119.36 (C-2′),* 138.34 (C-3′), 169.57 (C-1), 199.03 (C-3), 202.73 (C-5). MS (EI, 70 eV): *m*/*z* (%) = 466.0 (15) [M^+]. HRMS: *m*/*z* calcd for $C_{26}H_{46}O_5Si$: 466.31027; found: 466.30818. * Unambiguous assignment was not possible.

(9) **Synthesis of 9a from 5a**: A solution of **5a** (3.46 g, 7.43 mmol) in EtOH (15 mL) was treated with a solution of KOH (2.43 g, 41.0 mmol) in anhyd EtOH (30 mL) at r.t. and the resulting mixture was stirred for 3 h at r.t. The volatiles were removed in vacuo, the residue dissolved in distilled H_2O (ca. 30 mL) and then poured into a vigorously stirred mixture of CH_2Cl_2 (300 mL at –20 °C) and aq tartaric acid solution (10%, 200 mL at 4 °C). The reaction mixture was stirred for 10 min and the precipitated potassium hydrogen tartrate was filtered off. The filter cake was washed with CH_2Cl_2 (100 mL at –20 °C), the filtrates were combined and the organic phase was separated. The aqueous phase was saturated with solid NaCl and extracted twice with cold CH_2Cl_2. The organic phases were combined and dried over $MgSO_4$ and the volatiles were removed in vacuo (heating bath temperature: max. 5 °C). The crude product was immediately dissolved in cold Ac_2O (30 mL at –20 °C). Then pyridine (1 mL) was added and the resulting mixture was stirred for 2 h at 0 °C. The excess Ac_2O was removed in vacuo without heating and the residue was dissolved in MeOH (50 mL). After addition of K_2CO_3 (5.67 g, 41.0 mmol) the mixture was stirred for 2 h at r.t. The volatiles were removed in vacuo and the residue was dissolved in distilled H_2O (200 mL). The mixture was acidified with glacial AcOH to pH 3, saturated with solid NaCl and extracted with CH_2Cl_2 (3 ×). The combined organic phases were washed twice with H_2O and dried over $MgSO_4$. The volatiles were removed in vacuo (traces of AcOH were removed azeotropically with toluene) and the residue was submitted to flash chromatography (SiO_2; PE–EtOAc, 8:2). Pyrone **9a** (2.38 g, 76%) was obtained as a colorless oil that solidified on storage at –20 °C.

(10) Selected data for **2**: IR (ATR): 2965, 2913, 2726, 1667, 1579, 1431, 1409, 1273 cm^{-1}. UV (MeOH): λ_{max} (log ε) = 224 (4.21), 335 (4.40) nm. ^{1}H NMR (500 MHz, CD_3OD): δ = 1.23 (d, ^3J = 6.2 Hz, 3 H, 3″-H_3), 1.58 (s, 3 H, 7′-CH_3), 1.64 (s, 3 H, 8′-H_3), 1.73 (s, 3 H, 3′-CH_3), 1.94–1.99 (m, 2 H, 4′-H_2), 2.03–2.10 (m, 2 H, 5′-H_2), 2.53 (dd, ^2J = 14.4 Hz, ^3J = 7.7 Hz, 1 H, 1″-H_A), 2.58 (dd, ^2J = 14.5 Hz, ^3J = 5.3 Hz, 1 H, 1″-H_B), 3.08 (d, ^3J = 7.2 Hz, 2 H, 1′-H_2), 4.08–4.15 (m, 1 H, 2″-H), 5.07 (br t, ^3J = 7.0 Hz, 1 H, 6′-H), 5.17 (br t, ^3J = 7.0 Hz, 1 H, 2′-H), 6.06 (s, 1 H, 5-H). ^{13}C NMR (125 MHz, CD_3OD): δ = 16.27 (3′-CH_3), 17.71 (7′-CH_3), 22.79 (C-1′), 23.39 (C-3″), 25.86 (C-8′), 27.68 (C-5′), 40.84 (C-4′), 44.01 (C-1″), 66.19 (C-2″), 102.92 (C-5), 103.63 (C-3), 122.44 (C-2′), 125.38 (C-6′), 132.08 (C-7′), 136.54 (C-3′), 162.29 (C-6), 167.41 (C-4), 168.62 (C-2). MS (EI, 70 eV): *m*/*z* (%) = 306 (41) [M^+], 237 (28) [$M^+ - C_4H_5O$], 183 (36) [$M^+ - C_4H_{15}$], 139 (80) [$M^+ - C_{10}H_{15}O_2$], 123 (52) [$C_9H_{15}^+$], 69 (100) [$C_4H_3O^+$], 41 (90) [$C_3H_6^+$].