Total Synthesis of Chaetoquadrins H and I

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Abstract: The first total syntheses of the chromone-containing natural products chaetoquadrins H and I are reported, using an aldol reaction and an acid-catalyzed deprotection/cyclization/elimination sequence. Chaetoquadrin H was isolated from the ascomycete *Chaetomium quadrangulatum* and exhibits potent mouse liver monoamine oxidase (MAO) inhibitory activity. Chaetoquadrin I was not isolated in sufficient quantity to enable biological evaluation. The synthesis of the title compounds provides a useful starting point for a medicinal chemistry program focused on chaetoquadrin natural products.

Key words: monoamine oxidase inhibitors, natural products, spiroketal compounds, aldol reaction

In 2002 Fujimoto and co-workers reported the structures of five chromone-containing natural products, chaetoquadrins A–E, that exhibit monoamine oxidase (MAO) inhibitory properties.[1] A second publication in 2003 reported six additional MAO-inhibiting natural products named chaetoquadrin F–K.[2] Our ongoing interest in the synthesis of aromatic spiroketals[3] prompted our recently reported synthesis of chaetoquadrins A–C.[4] The comparatively potent MAO inhibitory activity of chaetoquadrin H (**4**; IC_{50} 2.3×10^{-4} M) and the limited amount of chaetoquadrin I (**5**) available from natural sources also attracted our attention, hence we embarked on the synthesis of these bis-pyranone chaetoquadrins H (**4**) and I (**5**) (Figure 1).

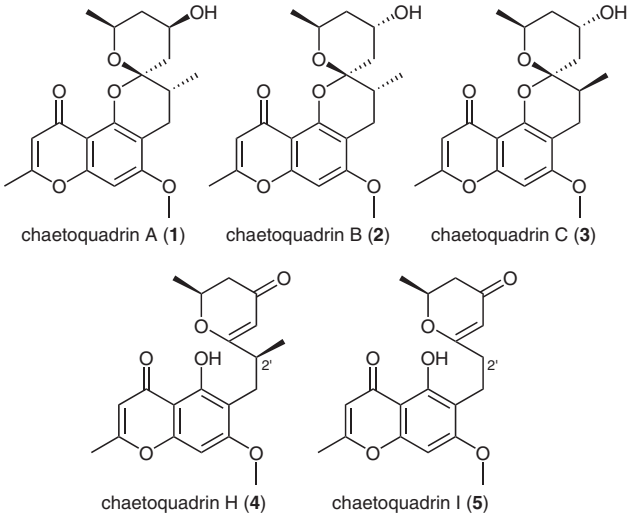

Figure 1 Structures of chaetoquadrins A–C (**1**–**3**) and chaetoquadrins H (**4**) and I (**5**)

Our strategy to prepare the bis-pyranone chaetoquadrins H (**4**) and I (**5**) was similar to our approach to prepare the spiroketal chaetoquadrins A–C (**1**–**3**).[3] The retrosynthetic analysis for chaetoquadrin I (**5**) is illustrated below (Scheme 1). We envisaged constructing the pyranone ring through an acid-catalyzed deprotection/cyclization/elimination sequence applied to 1,3-diketone **6**. In turn, the latter would be assembled by aldol reaction of aldehyde **7** with ketone **8**. Aldehyde **7** would be accessible through hydroboration-oxidation of terminal olefin **9**, which can be prepared from noreugenin (**10**) in three steps.[4] Wacker oxidation of a protected derivative of terminal olefin **11** enables access to methyl ketone **8**.

Our initial target was ethoxymethyl ether (EOM) protected aldehyde **7**. The acid labile EOM protecting group[5] was chosen with the final acid-catalyzed deprotection/cyclization/elimination sequence in mind. Phenol **9** was treated with EOM-Cl to furnish EOM-protected olefin **12** in good yield (Scheme 2). The subsequent hydroboration-oxidation of **12** using $Me_2S{\cdot}BH_3$ afforded primary alcohol **13** in moderate yield. Throughout the course of this work, the hydroboration-oxidation of compounds related to olefin **12** proved to be challenging, often resulting in low yields and decomposition of the starting olefins. It was crucial to perform the oxidative peroxide workup as quickly as possible. The subsequent oxidation of alcohol **13** with 2-iodoxybenzoic acid (IBX)[6] in dimethyl sulfoxide (DMSO) smoothly afforded the desired aldehyde **7**.

With aldehyde **7** in hand, our attention turned to the synthesis of the requisite aldol partner, methyl ketone **8**. Towards this end, (*S*)-pent-4-en-2-ol (**11**) was protected with EOM-Cl to afford EOM-protected olefin **14** in good yield. Subjection of terminal olefin **14** to Wacker oxidation conditions[7] provided methyl ketone **8** in reasonable yield (Scheme 3).

With aldehyde **7** and ketone **8** in hand, we were then set to execute the key aldol coupling. Disappointingly, aldol reactions mediated by lithium diisopropylamide (LDA) or potassium hexamethyldisilazide (KHMDS) as the base were unsuccessful. Fortunately, use of Paterson's aldol conditions[8,9] delivered the desired β-hydroxy ketone **15** in moderate yield (Scheme 4). Initial attempts to oxidize β-hydroxy ketone **15** under a variety of standard conditions (Swern, IBX-DMSO, DMP, TPAP/NMO) led to poor yields and/or elimination of the sensitive hydroxyl moiety. Eventually, application of the oxidation protocol developed specifically for β-hydroxy ketones involving IBX

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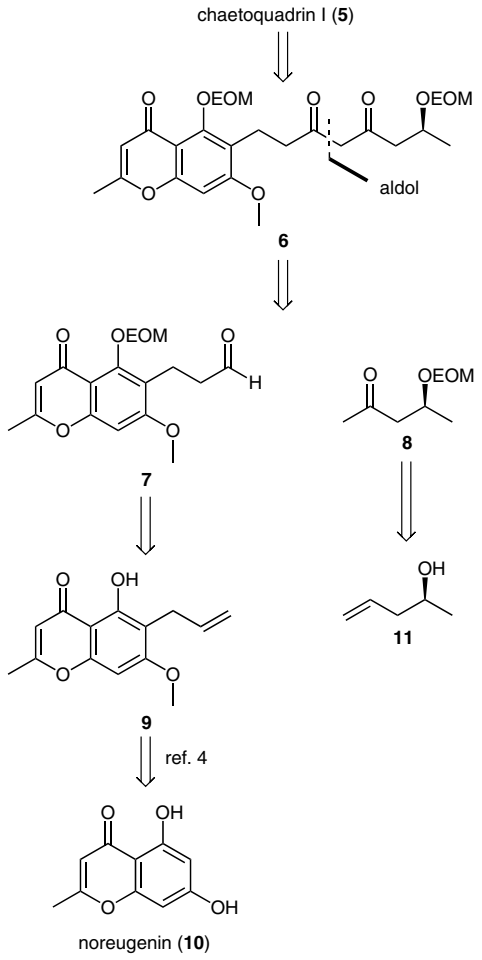
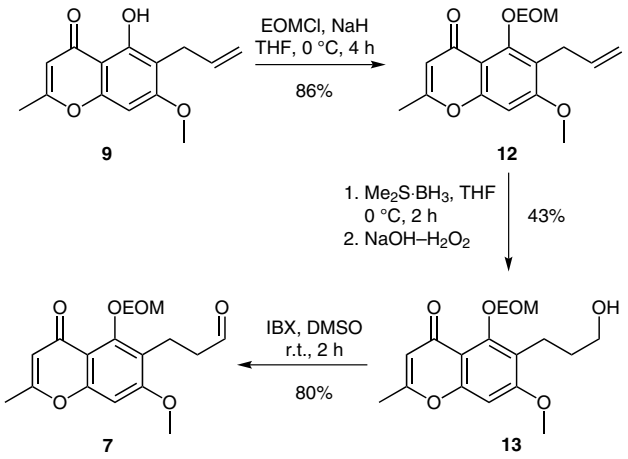
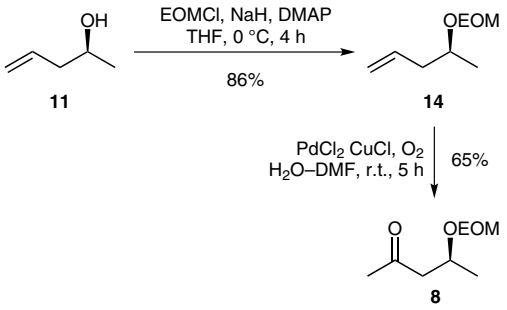


Scheme 1 Retrosynthetic analysis of chaetoquadrin I (**5**)



Scheme 2 Synthesis of aldehyde **7**

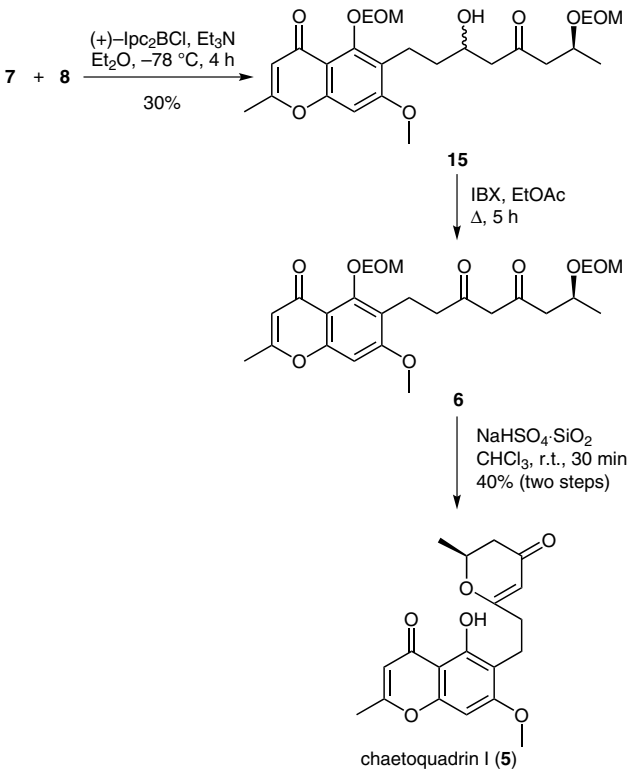
in ethyl acetate at reflux[10] efficiently delivered 1,3-diketone **6**, which could be used without further purification. Gratifyingly, acid-catalyzed double EOM deprotection/cyclization/elimination in the presence of $NaHSO_4{\cdot}SiO_2$[11] afforded the desired natural product chaetoquadrin I (**5**).[12] No oxa-Michael addition of the weakly nucleophilic hydrogen-bonded phenol of **5** to the pyranone was observed and this transformation also did not



Scheme 3 Synthesis of methyl ketone **8**

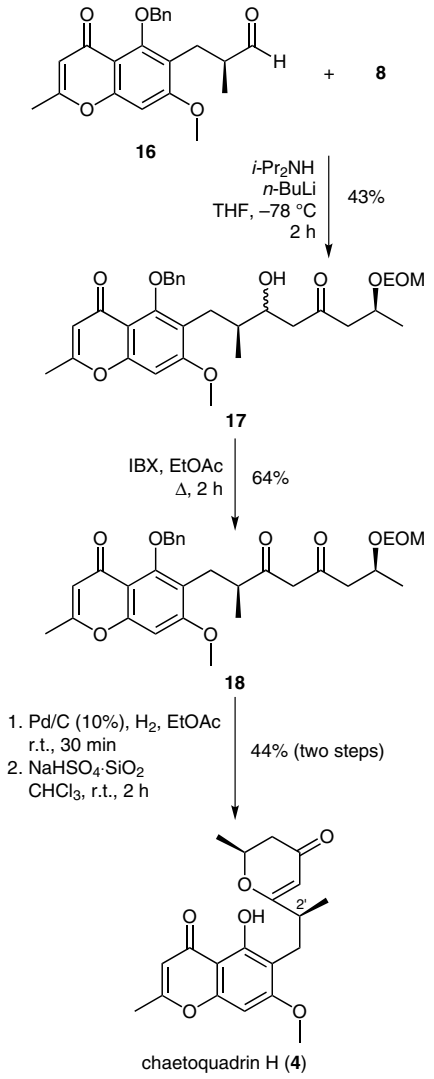
proceed under a wide range of acidic or basic conditions. Pleasingly, the spectroscopic data obtained for synthetic chaetoquadrin I (**5**) were in good agreement with those reported for the natural product.[2]

The structure of chaetoquadrin H (**4**) features an additional methyl group at C-2' in comparison to chaetoquadrin I (**5**). Accordingly, a similar strategy for the synthesis of chaetoquadrin I (**5**) was employed to complete the total synthesis of chaetoquadrin H (**4**; Scheme 5). Aldol reaction between enantiopure α-methyl aldehyde **16**[4] and methyl ketone **8** mediated by LDA as the base, afforded β-hydroxy ketone **17** in moderate yield.[13] IBX-mediated oxidation[10] of **17** then furnished 1,3-diketone **18**. Hydrogenolysis using 10% Pd/C as catalyst followed by treatment with $NaHSO_4{\cdot}SiO_2$[11] effected the EOM deprotection/cyclization/elimination sequence, affording chaetoquadrin H (**4**).[14] The spectroscopic data for synthet-



Scheme 4 Total synthesis of chaetoquadrin I (**5**)

ic chaetoquadrin H (**4**) were again in excellent agreement with those reported in the literature.[2]



Scheme 5 Total synthesis of chaetoquadrin H (**4**)

In conclusion, the first total synthesis of the bis-pyranone natural products chaetoquadrins H (**4**) and I (**5**) are reported herein. An aldol reaction was used to unite the two key fragments. Oxidation of the resulting β-hydroxy ketones **15** and **18** followed by execution of a deprotection/cyclization/elimination sequence enabled facile synthesis of the two natural products, chaetoquadrins H (**4**) and I (**5**).

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References and Notes

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(9) **Aldol reaction between 7 and 8:** A two-necked, round-bottom flask was charged with (+)-Ipc_2BCl (210 mg, 0.66 mmol) and placed under high vacuum for 1 h to remove traces of HCl. Et_2O (2 mL) was added and the mixture was cooled to –78 °C. NEt_3 (0.1 mL, 0.72 mmol) was added followed by a solution of ketone **8** (100 mg, 0.63 mmol) in Et_2O (1 mL). The resultant white suspension was warmed to 0 °C and stirred for 40 min. The reaction mixture was cooled to –78 °C and aldehyde **7** (100 mg, 0.31 mmol) in Et_2O (2 mL) was added. The reaction mixture was stirred at –78 °C for 4 h then quenched by addition of aqueous pH 7 buffer solution (1 mL), MeOH (0.5 mL) and 30% H_2O_2 solution (0.5 mL), warmed to r.t. and stirred for 1 h. The mixture was then diluted with H_2O (10 mL) and EtOAc (10 mL), the layers separated, and the aqueous layer was further extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by flash chromatography (EtOAc–hexanes, 2:1) to yield β-hydroxy ketone **15** (44 mg, 30%) as an inseparable mixture of diastereoisomers (1:1) and as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13–1.30 (m, 9 H), 1.60–1.78 (m, 2 H), 2.29 (s, 3 H), 2.40–2.63 (m, 3 H), 2.69–2.98 (m, 3 H), 3.55 (q, *J* = 7.24 Hz, 2 H), 3.81–3.92 (m, 2 H), 3.89 (s, 3 H), 3.93–4.04 (m, 1 H), 4.11–4.28 (m, 1 H), 4.63–4.72 (m, 2 H), 5.12–5.23 (m, 2 H), 5.99 (s, 1 H), 6.63 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0 (CH_3), 15.2 (CH_3), 19.6 (CH_2), 19.9 (CH_3), 20.6 (CH_3), 35.9 (CH_2), 36.0 (CH_2*), 50.4 (CH_2), 50.5 (CH_2*), 50.9 (CH_2), 51.0 (CH_2*), 56.0 (CH_3), 63.3 (CH_2), 65.7 (CH_2), 67.2 (CH), 67.3 (CH*), 69.6 (CH), 69.7 (CH*), 93.7 (CH_2), 93.8 (CH_2*), 95.3 (CH), 100.5 (CH_2), 111.2 (C), 111.5 (CH), 122.0 (C), 155.2 (C), 158.1 (C), 161.8 (C), 163.5 (C), 177.0 (C), 209.6 (C), 209.7 (C*). IR (film): 2974, 1709, 1655, 1600, 1446, 1388, 1341, 1260, 1177, 1107, 1046, 990 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{37}O_9^+$: 481.2432; found: 481.2417.
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(12) **Synthesis of Chaetoquadrin I (5):** To a solution of β-hydroxyketone **15** (19 mg, 0.04 mmol) in EtOAc (2 mL) was added 2-iodoxybenzoic acid (100 mg, 0.36 mmol) and the reaction mixture was heated to reflux for 5 h. The reaction mixture was then allowed to cool to r.t. and filtered through a plug of cotton wool. The solvent was removed in vacuo to give 1,3-diketone **6**, which was dissolved in $CHCl_3$ (1 mL). $NaHSO_4{\cdot}SiO_2$[11] (20 mg) was added and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through cotton wool and the filtrate loaded directly on a preparative TLC plate (EtOAc–hexanes, 2:1) to yield chaetoquadrin I (**5**; 5.5 mg, 40% over two steps). $[\alpha]_D^{20}$ –10.8 (*c* 0.05, $CHCl_3$) {lit.[2] $[\alpha]_D^{20}$ –40.8 (*c* 0.05, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.1 Hz, 3 H), 2.33–2.39 (m, 2 H), 2.36 (s, 3 H), 2.43–2.50 (m, 2 H), 2.83–3.02 (m, 2 H), 3.88 (s, 3 H), 4.38–4.53 (m, 1 H), 5.22 (s, 1 H), 6.05 (s, 1 H), 6.36 (s, 1 H), 12.8 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6

(CH_2), 20.6 (CH_3), 20.6 (CH_3), 33.8 (CH_2), 42.8 (CH_2), 56.0 (CH_3), 75.8 (CH), 89.5 (CH), 104.2 (CH), 105.2 (C), 109.1 (CH), 111.3 (C), 157.0 (C), 159.0 (C), 163.2 (C), 166.6 (C), 177.8 (C), 182.6 (C), 193.5 (C). IR (film): 2928, 1660, 1493, 1448, 1343, 1174 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}O_6^+$: 345.1333; found: 345.1341.

(13) **Aldol reaction between 16 and 8:** A solution of diisopropylamine (0.04 mL, 0.25 mmol) in THF (1 mL) was cooled to –78 °C. *n*-BuLi (1.6 M in hexanes, 0.24 mmol, 0.15 mL) was carefully added by using a syringe and the mixture was stirred for 1 h at the same temperature. The reaction mixture was then warmed to 0 °C for 10 min, then cooled to –78 °C. A solution of ketone **8** (39 mg, 0.24 mmol) in THF (1 mL) was cooled to –78 °C and added to the LDA mixture by using a cannula, maintaining the temperature of all of the reactants at –78 °C. The solution of aldehyde **16** (36 mg, 0.11 mmol) in THF (1 mL) was then cooled to –78 °C and added to the mixture dropwise by using a cannula. The reaction mixture was stirred at this temperature for 2 h, then NH_4Cl (4 mL) was added and reaction mixture was allowed to warm to r.t. The reaction mixture was extracted with EtOAc (3 × 4 mL) and the combined organic extracts were washed with brine (6 mL), dried over $MgSO_4$, and purified by flash column chromatography (EtOAc–hexanes, 1.5:1) to yield β-hydroxy ketone **17** (22 mg, 43%) as an inseparable mixture of diastereomers (1:1) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 7.14 Hz, 1.5 H), 0.84 (d, *J* = 6.76 Hz*, 1.5 H), 1.14–1.22 (m, 6 H), 1.73–1.98 (m, 2 H), 2.23–2.71 (m, 6 H), 2.31 (s, 1.5 H), 2.32 (s*, 1.5 H), 3.47–3.59 (m, 2 H), 3.76–3.87 (m, 1 H), 3.88 (s, 1.5 H), 3.90 (s*, 1.5 H), 4.07–4.19 (m, 1 H), 4.59–4.69 (m, 2 H), 4.87–4.95 (m, 1 H), 4.99–5.09 (m, 1 H), 6.04 (s, 0.5 H), 6.05 (s*, 0.5 H), 6.65 (s, 0.5 H), 6.67 (s*, 0.5 H), 7.29–7.44 (m, 3 H), 7.56–7.66 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7 (CH_3), 15.1 (CH_3), 15.2 (CH_3*), 15.4 (CH_3), 20.0 (CH_3), 20.7 (CH_3*), 25.9 (CH_2), 27.3 (CH_2*), 38.1 (CH), 38.6 (CH*), 46.6 (CH_2), 48.1 (CH_2*), 50.8 (CH_2), 50.9 (CH_2*), 56.0 (CH_3), 56.1 (CH_3*), 63.3 (CH_2), 63.4 (CH_2*), 69.0 (CH), 69.6 (CH), 69.7 (CH*), 71.2 (CH*), 77.0 (CH_2), 93.8 (CH_2), 93.9 (CH_2*), 95.4 (CH), 95.7 (CH*), 111.9 (CH), 112.2 (C), 121.0 (C), 121.4 (C*), 128.2 (CH), 128.3 (CH*), 128.5 (CH), 128.6 (CH*), 129.0 (CH), 129.1 (CH*), 137.2 (C), 137.5 (C*), 156.7 (C), 156.8 (C*), 158.3 (C), 158.4 (C*), 162.2 (C), 162.3 (C*), 163.4 (C), 163.5 (C*), 176.9 (C), 177.0 (C*), 209.6 (C), 210.7 (C*). IR (film): 2971, 2932, 1709, 1655, 1600, 1444, 1389, 1341, 1202, 1129, 1034 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{39}O_8^+$: 527.2639; found: 527.2622.

(14) **Synthesis of chaetoquadrin H (4):** 1,3-diketone **18** (10 mg, 0.02 mmol) was taken up in EtOAc (1 mL), 10% Pd/C (16 mg) was added, and the reaction mixture was stirred under an atmosphere of hydrogen for 30 min. The mixture was filtered through cotton wool and the solvent was removed in vacuo. The crude product was dissolved in $CHCl_3$ (1 mL), $NaHSO_4{\cdot}SiO_2$[11] (15 mg) was added, and the mixture was stirred for 2 h. The reaction mixture was filtered through cotton wool and the filtrate was loaded directly on a preparative TLC plate (EtOAc–hexanes, 3:1) to yield chaetoquadrin H (**4**; 3 mg, 44% over two steps). $[\alpha]_D^{20}$ –41.3 (*c* 0.15, $CHCl_3$) {lit.[2] $[\alpha]_D^{20}$ –57.2 (*c* 0.2, $CHCl_3$)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.7 Hz, 3 H), 1.44 (d, *J* = 6.5 Hz, 3 H), 2.24–2.42 (m, 2 H), 2.35 (s, 3 H), 2.63–2.81 (m, 2 H), 2.89–3.05 (m, 1 H), 3.87 (s, 3 H), 4.29–4.45 (m, 1 H), 5.11 (s, 1 H), 6.04 (s, 1 H), 6.34 (s, 1 H), 12.85 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 27.3 (CH_2), 39.1 (CH), 42.9 (CH_2), 56.0 (CH_3), 75.8 (CH), 89.5 (CH), 103.3 (CH), 105.2 (C), 109.1 (CH), 110.8 (C), 157.0 (C), 159.2 (C), 163.4 (C), 166.6 (C), 181.3 (C), 182.7 (C), 193.7 (C). IR (film): 2935, 1661, 1598, 1494, 1449, 1343, 1127 cm^{-1}. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{23}O_6^+$: 359.1489; found: 359.1487.

