Structural Revision and Synthesis of Altechromone A

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The chromone "altechromone A" was synthesized as a substructure in the course of natural product synthesis. Its architecture was verified by X-ray analysis, but spectroscopic data showed a strong deviation from the reported data. By comparison with the synthesized isomers the structure of altechromone A was revised.

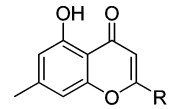
In 1992 a chromone derivative was isolated from *Alternaria* sp. and consequently named altechromone A (**1**) (Figure 1). The structural assignment was performed by a complete set of ^{1}H and ^{13}C NMR data. Additional NOE data made the suggestion of this rather simple natural product plausible.[1] Further analytical data such as UV and IR spectra as well as microanalysis confirmed its identity. 5-Hydroxy-2,7-dimethylchromone (**1**) was first mentioned by Ahluwalia and Kumar 16 years earlier.[2] Although **1** was claimed to be synthesized, only the melting point and IR data were published. More recently, altechromone A was isolated from several fungi including *Hypoxylon truncatum*,[3] *Ascomycota* sp.,[4] and *Alternaria brassicicola*.[5] The isolated compound showed remarkable biological activity such as root growth promotion[1] and inhibition of bacterial proliferation.[4] These authors referred to **1**, which was isolated almost 20 years ago.[1]

Several natural products originating from fungal sources contain **1** as substructure. Chloromonilicin (**3**) was isolated from *Monilia fructicola* in 1985,[6] coniochaeton A (**4**) from *Coniochaeta sacerdoi,*[7] and remisporin A (**5**) from the marine fungus *Remispora maritima* (Figure 2).[8]

In the course of our synthetic efforts on **3**−**5** we envisaged using altechromone A as an intermediate. Our synthesis of **1** commenced with 2,6-dihydroxy-4-methylacetophenone (**6**), which is readily available by a simple Friedel−Crafts acylation of orcinol.[9] The bis(trimethylsilyl) ether **7** is formed almost quantitatively under the prevailing conditions (Scheme 1).

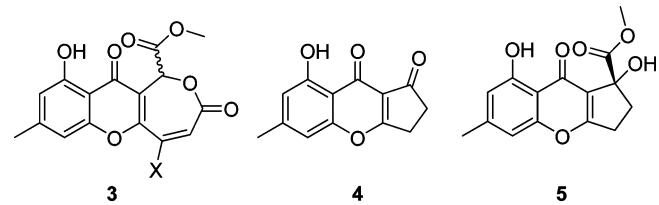
Aldol reaction of **7** with ethyl acetate affords chromone **1** directly after acidic workup and purification by column chromatography on silica. This represents rapid access to the chromone derivative. Compound **1** was properly characterized. In addition, suitable single crystals of **1** allowed X-ray analysis, which confirmed the anticipated molecular structure.[10] Since the chromone system is planar (mean deviation from the least-squares plane 0.023 Å), the molecules form close π-stacks parallel to the *a*-axis with alternating intermolecular distances of 3.33 and 3.45 Å. The piles are cross-linked via weak intermolecular hydrogen bonds involving the carbonyl oxygen, acting as a trifurcating acceptor atom. Furthermore, the molecular structure confirms the hydrogen bonding between the C-4 carbonyl functionality and the 5-hydroxy group (O5−H5 0.84(2) Å, H5−O4 1.82(2) Å, O5−O4 2.599(1) Å, O5−H5−O4 155(2)°) (Figure 3).

However, since the NMR data of **1** strongly deviated from the reported data of altechromone A,[1] we were prompted to synthesize



1 R = CH_3
2 R = CH_2COCH_3

Figure 1. Originally assigned structures of altechromone A (**1**) and altechromone B (**2**).

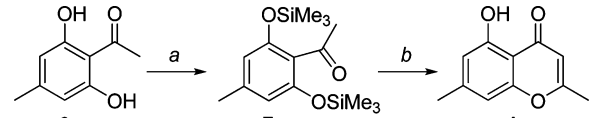


3 **4** **5**

X = Cl; Br

Figure 2. Secondary metabolites containing the altechromone substructure.

Scheme 1. Synthesis of 5-Hydroxy-2,7-dimethylchromone (**1**)[a]



6 **7** **1**

[a] Reagents and conditions: (*a*) HMDS, TMSCl, 140 °C, 5 h, > 99%; (*b*) NaH, EtOAc, THF, 75 °C, 6 h, then rt, 16 h, 69%.

isomeric congeners of **1**. First, the aromatic substituents were switched. Starting with 2,4-dihydroxy-6-methylacetophenone **8**, a synthetic approach similar to the previous one was employed (Scheme 2). Compound **8** is accessible by a Gattermann-type acetylation reaction of orcinol with acetonitrile and zinc chloride.[11] Blocking of the hydroxy moieties by trimethylsilyl groups is accomplished in quantitative yield. The subsequent aldol reaction and cyclization via acidic conditions furnished 7-hydroxy-2,5-dimethylchromone (**10**) in good yield (61%, two steps).

In order to exclude the possibility of a coumarin architecture, we synthesized the analogous coumarin derivative **11** (Figure 4). 5-Hydroxy-4,7-dimethylcoumarin (**11**) was accessible in low yield by a Von Pechmann-type condensation of orcinol with methyl acetoacetate.[12] Since the analytical data of **11** and altechromone A showed distinct differences, this coumarin can definitely be excluded as a candidate structure.

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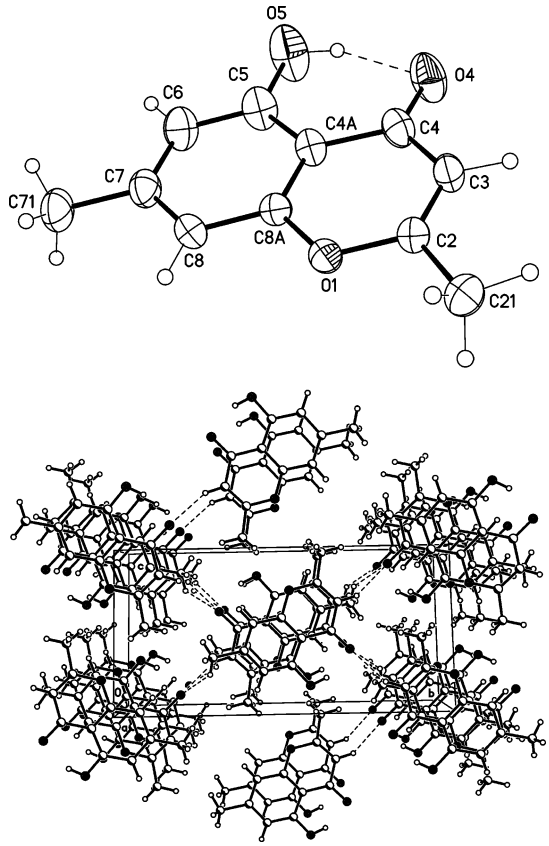
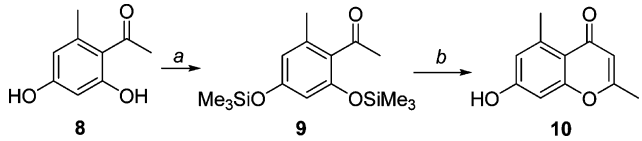


Figure 3. (Top) Molecular structure of **1** showing the intramolecular hydrogen bond (displacement parameters are drawn at 50% probability). (Bottom) Crystal packing of **1** showing the weak intermolecular hydrogen bonds.[10]

Scheme 2. Preparation of Isomeric Chromone **10**[a]



[a] Reagents and conditions: (*a*) 1. HMDS, TMSCl, 140 °C, 5 h, > 99%; (*b*) 1. NaH, EtOAc, THF, 75 °C, 6 h, then rt, 16 h, 2. HCl conc., THF, rt, 16 h, 61% (two steps).

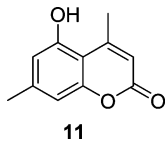


Figure 4. Related coumarin derivative **11**.

The best fit of ^{1}H and ^{13}C NMR data with the isolated compound of Kimura et al.[1] is given by **10**. In contrast, the data of **1** do not fit those of altechromone A at all. Most striking is the signal at 12.53 ppm, which indicates an intramolecular hydrogen bonding. The melting point reported by Kimura et al.[1] (250−252 °C) only deviates slightly from the one originally reported by Ahluwalia (245−248 °C, dec).[2] The melting point we determined for **1** is totally different (82−83 °C). Further reports dealing with **1**[3−5] did not report melting points for altechromone A. In contrast, 5-hydroxy-4,7-dimethylcoumarin (**11**) melts at 243 °C with decomposition. Consequently, the melting points and NMR data support our hypothesis that the structure of altechromone A has to be revised to 7-hydroxy-2,5-dimethylchromone (**10**).

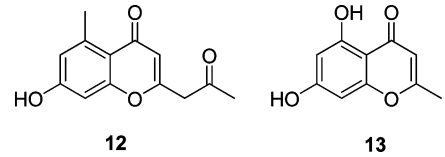


Figure 5. Chromones from plant material.

7-Hydroxy-2,5-dimethylchromone (**10**) is a well-known constituent of plant material. First synthesized and characterized in 1974,[13] it was recently isolated from different plant families such as *Polygonaceae*, *Lamiaceae*, *Fabaceae*, and *Hypericaceae*.[14] Although the structural similarity to aleosone (**12**) and 5,7-dihydroxy-2-methylchromone (**13**) (Figure 5), both products of the polyketide pathway, is obvious, 7-hydroxy-2,5-dimethylchromone as a typical fungal metabolite presumably has its origin in endophytic fungi.

This seems possible as recent reports describe the compound as a fungal secondary metabolite ("altechromone A").[3−5] These species often exist in mutualistic interaction with a host plant, protecting it from grazing livestock, invertebrate herbivores, and pathogenic microorganisms.

In conclusion, the structure of altechromone A has to be reassigned as 7-hydroxy-2,5-dimethylchromone. A fast and reliable synthesis of **1** was established in 67% overall yield starting from 2-acetyl orcinol. The use of this intermediate in the synthesis of other natural products will be reported in due course.

Experimental Section

General Experimental Procedures. All reagents were used in analytical grade. Solvents were dried if necessary by standard methods. Melting points were determined with an SMP 3 melting point apparatus (Bibby Sterilin LTD, Stone, Staffordshire) and were uncorrected. Microanalysis was performed with a Vario EL (Elementar-Analysensysteme, Hanau, Germany). NMR spectra were recorded with a Bruker AM 300 and AM 400 (Analytische Messtechnik, Karlsruhe, Germany) by calibration in $CHCl_3$ with $\delta = 7.26$ or DMSO-d_6 ($\delta = 2.50$) for ^{1}H NMR; chemical shifts were expressed in ppm. Mass spectra were obtained on a MAT8200 (Finnigan, Bremen, Germany) employing EI or on a MS50 (Kratos, Manchester, England) or MAT95XL (Finnigan, Bremen, Germany) employing HRMS. All reactions were monitored by TLC, and visualization was effected by UV and heating with a 1% aqueous solution of $Ce(SO_4)_2 \cdot 4H_2O$ containing 2.5% of molybdatophosphoric acid and 6% of H_2SO_4. Column chromatography was performed on silica gel (particle size 63−200 μm, Merck, Darmstadt, Germany) using mixtures of cyclohexane with EtOAc as eluents.

5-Hydroxy-2,7-dimethylchromone (1): colorless solid; 69% yield; mp 82−83 °C; R_f (cyclohexane−EtOAc, 90:10) 0.26; ^{1}H NMR and ^{13}C NMR data see Table 1; HREIMS *m/z* 190.0637 (calcd for $C_{11}H_{10}O_3$, 190.0630); *anal*. C 69.46, H 5.30%, calcd for $C_{11}H_{10}O_3$, C 69.14, H 5.12%.

Crystal Data for 1: formula $C_{11}H_{10}O_3$, $M = 190.19$, $a = 6.9503(2)$ Å, $b = 16.4718(4)$ Å, $c = 8.2909(2)$ Å, $\beta = 102.266(1)°$, $V = 927.51(4)$ Å^3, $\rho_{calc} = 1.362$ g cm^{-3}, $\mu = 0.099$ mm^{-1}, no absorption correction, $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $T = 123$ K, ω and φ scans, 15 639 reflections collected, 2112 unique ($R_{int} = 0.0591$); 132 parameters, 1 restraint, $R = 0.0602$, $wR_2 = 0.1479$ (both for all data), max. residual electron density 0.322 (−0.252) e Å^{-3}. The hydrogen atoms were localized by difference Fourier synthesis and refined using a riding model. H(O) was refined free.

7-Hydroxy-2,5-dimethylchromone (10): light yellow solid; 61% yield; mp 252 °C; ^{1}H NMR and ^{13}C NMR data see Table 1; HREIMS *m/z* 190.0633 (calcd for $C_{11}H_{10}O_3$, 190.0630).

5-Hydroxy-4,7-dimethylcoumarin (11): light brown solid; 8% yield; mp 243 °C (dec); ^{1}H NMR and ^{13}C NMR data see Table 1; HREIMS *m/z* 190.0628 (calcd for $C_{11}H_{10}O_3$, 190.0630).

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Table 1. Comparison of NMR Data

^{1}H NMR Shifts (400 MHz for **1** and **10**, 300 MHz for **11**, DMSO-d_6)

	altechromone A	**1**	**10**	**11**
entry	δ_H (J in Hz)	δ_H (J in Hz)	δ_H (J in Hz)	δ_H (J in Hz)
1	2.27, s	2.34, s	2.26, d (0.8)	2.27, dd (0.7, 0.7)
2	2.67, d (0.5)	2.37, s	2.64, b	2.54, d (1.3)
3	5.97, s	6.23, s	5.96, s	6.04, q (1.3)
4	6.60, d (1.5)	6.58, d (0.6)	6.61, dq (0.8, 2.3)	6.57, dq (0.7, 1.7)
5	6.62, d (1.5)	6.78, d (0.6)	6.65, d (2.3)	6.62, dq (0.7, 1.7)
6	10.53, s	12.53, s	10.55, b	10.50, s

^{13}C NMR Shifts (100 MHz for **1** and **11**, 75 MHz for **10**, DMSO-d_6)

	altechromone A	**1**	**10**	**11**
entry	δ_C, mult.	δ_C, mult.	δ_C, mult.	δ_C
1	19.3, CH_3	20.0, CH_3	19.3, CH_3	21.0
2	22.3, CH_3	21.7, CH_3	22.4, CH_3	23.3
3	100.5, CH	107.3, CH	100.5, CH	106.4
4	110.7, CH	107.6, C	110.7, CH	107.6
5	114.2, C	108.4, CH	114.2, C	111.8
6	116.4, CH	111.5, CH	116.5, CH	111.9
7	141.4, C	147.0, C	141.4, C	142.6
8	159.1, C	156.1, C	159.1, C	154.4
9	160.8, C	159.6, C	160.9, C	154.7
10	163.7, C	168.5, C	163.8, C	156.4
11	178.2, C	182.6, C	178.3, C	159.7

Supporting Information Available: Full experimental details, copies of the spectra, and the crystallographic information file (CCDC-783508 (**1**)). This material is available free of charge via the Internet at http://pubs.acs.org.

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