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An efficient total synthesis of chrysophanol and the sennoside C aglycon

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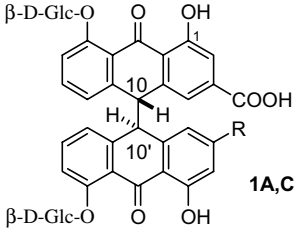
Abstract—A rapid synthetic approach to the naturally occurring chrysophanol and the sennoside C aglycon is reported. The method involves a three-step protocol starting with commercially available aloin-A to give the two title compounds.

Sennosides A–D **1A**–**D** and chrysophanol **2** are a family of polyphenolic compounds isolated from Senna plants including *Cassia acutifolia* or *Cassia angustifolia*.[1] *C. acutifolia* is native to Egypt and Sudan, while *C. angustifolia* is native to Somalia and Arabia. These plants have been used for centuries as an effective herbal laxative. They are clinically used to treat constipation and to clean bowels.[2] Despite the frequent use of cassia extracts it is so far unknown, which of the naturally occurring sennosides A–D (the sennosides A–D differ in their aromatic substitution pattern as well as in their C10–C10′ stereochemistry) is responsible for their biological activity, hence a reliable synthesis is required for their full biological evaluation.

Furthermore, the sennosides are currently under close scrutiny due to their reported tumour promoting activities.[3,4] The data, however, are inconclusive and under strong criticism and require pure synthetic material. Chrysophanol **2** has been extracted from *Cassia siamea*[5] and *Senna rugosa* plants[6] and synthesised biochemically from an octaketide,[7] and from emodin.[8] A multi-step chemical synthesis of chrysophanol **2** has also been reported.[9] The compound was shown to exhibit antifungal activity.[10,11]

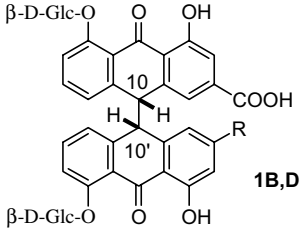
A synthesis of the sennoside C aglycon **1** has not been attempted previously. The original structure of the sennosides was reported in 1950 based on elegant chemical degradation procedures.[12,13]

In this letter, we report a short total synthesis of chrysophanol and the sennoside C aglycon. Starting from commercially available aloe emodin **3** oxidative cleavage using aqueous $FeCl_3$ afforded dianthron **4** in good yield. Reduction with $SnCl_2$ in HOAc produced



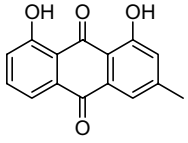
1A,C

C10-C10' *trans:*
Sennoside A R = COOH
Sennoside C R = CH_2OH



1B,D

C 10-C10' *cis (meso)*
Sennoside B R = COOH
Sennoside D R = CH_2OH



Chrysophanol **2**

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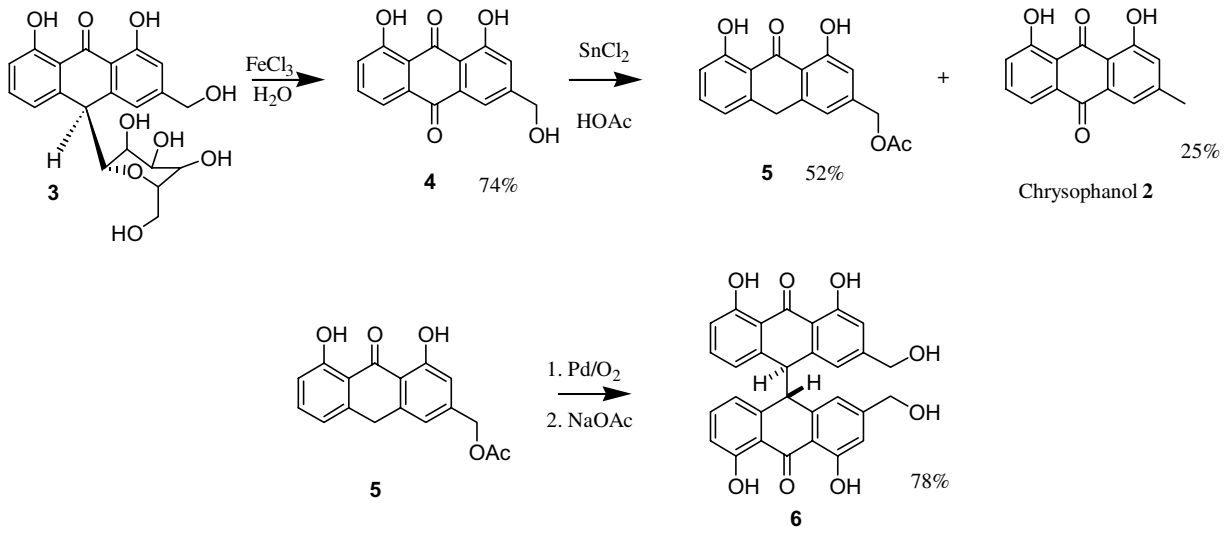

a 30:70 mixture of chrysophanol **2** and anthron **5** as judged from the ^{1}H NMR spectrum of a crude reaction mixture. The two compounds could be separated by column chromatography yielding chrysophanol **2** in a 25% isolated yield[14] and anthron **5** in a 52% isolated yield.[15] Similar selective reduction of the C-9 carbonyl as opposed to the C-1 carbonyl has been reported by Alexander et al. and was attributed to a protected Sn-chelate complex being formed between C-10 (C=O) and the neighbouring phenolic OH (either C-4 or C-5).[16,17]

The chrysophanol obtained showed identical spectroscopic data to those reported in the literature.[8]

Surprisingly, the $SnCl_2$ is able to act as a reducing agent for the benzylic alcohol functionality in **4**. We are not aware of any precedents for using $SnCl_2$ in the reduction of benzylic alcohols. This synthetic procedure allows the synthesis of large quantities of chrysophanol in only two synthetic steps.

The second major product of the reaction, anthron **5**, could be oxidatively coupled using palladium on charcoal in the presence of atmospheric oxygen to give the sennoside aglycon **6** as a single diastereoisomer as judged by ^{1}H and ^{13}C NMR spectroscopy. The surprisingly high diastereoselectivity can be tentatively explained by assuming π–π stacking between the two reacting anthrons **5** .The analytical data[18] confirms that the C_2-symmetric sennoside C aglycon is the product of the reaction as opposed to the *meso*-diastereomer.[12,13,19]

In conclusion, we have succeeded in developing a novel and rapid synthetic route to the naturally occurring sennoside C aglycon and chrysophanol from commercially available aloin A.

Acknowledgements

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14. A typical procedure for the preparation of **2** is as follows: To a solution of 0.8 g (2.96 mmol) aloe-emodin in a mixture of 6 ml of concentrated HCl and 24 ml of acetic acid was added 1.1 g (5.92 mmol) tin chloride and the resulting mixture was heated to 120 °C for 1 h. The reaction was cooled to room temperature, 50 ml of water was added to the mixture whereupon an orange solid precipitated. The solid precipitate was filtered and dried to recover 0.72 g of a mixture of products. The product was purified by column chromatography (SiO_2, diethyl ether–Lp (40–60 °C) 1:1) to give the title compound **2** as an orange solid (0.19 g, 25%); R_f 0.36 [ether–Lp (bp 40–60 °C) (1:1)]; δ_H (300 MHz, $CDCl_3$): 12.11 (1H, s, ArOH), 12.00 (1H, s, ArOH), 7.81 (1H, s, Ar), 7.64–7.67 (2H, m,

Ar), 7.28 (1H, d, *J* 8.5, Ar), 7.09 (1H, s, Ar), 2.46 (3H, s, Ar*CH*$_3$); δ_C (75 MHz, $CDCl_3$) 199.5 (CO), 193.1 (CO), 163.0, 162.7, 140.7, 138.6, 137.3, 135.4, 124.8, 124.7, 122.1, 121.7, 121.0, 120.2 (Ar), 30.1 (Ar*CH*$_3$). MS (ESI, negative ion mode), *m*/*z* 253 [M−H].

15. The analytical data of **5** are as follows: R_f 0.8 [diethyl ether–Lp (bp 40–60 °C) (1:1)]; mp 95–98 °C; ν_{max} (Nujol)/cm^{-1} 1667 (CO ketone), 1584 (C=C aromatic), 1242 (C–O); δ_H (300 MHz, $CDCl_3$) 12.29 (1H, s, OH), 12.28 (1H, s, OH), 7.48 (1H, t, *J* 7.4, Ar), 6.80–6.90 (4H, m, Ar), 4.73 (2H, s, Ar–*CH*$_2$–Ar), 4.34 (2H, s, *CH*$_2$COOCH$_3$), 2.16 (3H, s, CO*CH*$_3$); δ_C (125 MHz, $CDCl_3$) 193.8 (CO ketone), 170.8 (CO ester), 150.3, 145.9, 142.4, 142.0, 136.1, 135.4, 125.1, 121.6, 118.8, 116.5, 115.7, 113.1 (Ar), 65.3 (*CH*$_2$O), 32.9 (Ar*CH*$_2$Ar), 22.34 (CO*CH*$_3$); Found (CI) 299.0918 [M+H], $C_{17}H_{15}O_5$ requires 299.0914; *m*/*z* (EI) 299 (80%, M$^+$), 255 (20, M$^+$−COCH$_3$), 241 (100, M$^+$−CH$_2$COCH$_3$).
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18. A typical procedure for the preparation of **6** is as follows: To a solution of 0.05 g (0.15 mmol) anthrone **8** in 30 ml aqueous sodium hydroxide was added 25 mg of Pd on charcoal. Oxygen was bubbled through the solution for 2 h. at room temperature. Ten millilitres of hydrochloric acid (3 M) was added to the solution and the crude product was precipitated. The crude solid was filtered and dried to give the title compound **6** as an orange solid (0.03 g 78%); δ_H (500 MHz, $CDCl_3$): 7.81 (2H, d, *J* 7.4, Ar), 7.64–7.69 (4H, m, Ar), 7.28 (2H, d, *J* 8.4, Ar), 7.09 (2H, s, Ar), 4.81 (2H, s, Ar*CHCH*Ar), 4.46 (4H, *CH*$_2$OH); δ_C (125 MHz, $CDCl_3$) 193.2 (CO), 162.5, 150.1, 137.8, 133.9, 124.6, 124.3, 121.2, 121.1, 119.9, 118.1, 117.8, 116.5 (Ar), 78.1 (C–O), 74.5 (O*CH*$_2$), 63.1 (Ar*CHCH*Ar); *m*/*z* (CI) 511 (100%, M$^+$+H), 477 (10, M−2OH), 420 (50, 477−CO), 390 (477−COC$_6$H$_4$OH), 120 (5, COC$_6$H$_4$OH).
19. The synthetic material is identical by LC–MS^n to material assigned as sennoside C aglycone on comparison to authentic natural material (spiking of natural extract). For conditions see: Duez, P. *J. Chromatogr.* **1984**, *303*, 391–395.