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An efficient regioselective synthesis of endocrocin and structural related natural anthraquinones starting from emodin

Mario Waser, Bernd Lackner, Joachim Zuschrader, Norbert Müller and Heinz Falk*

Institute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstr. 69, 4040 Linz, Austria

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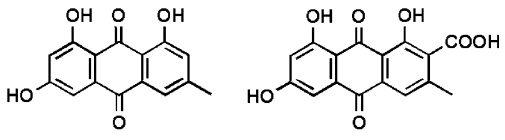
Abstract—Endocrocin and related naturally occurring anthraquinone pigments like cinnalutein could be synthesized regioselectively via a Marschalk type reaction, starting from the natural hydroxy anthraquinone emodin. Furthermore, the new tri-*O*-methyl protected emodin-2-carbaldehyde may serve as a promising synthon for new bathochromically shifted, higher generation photodynamically active hypericin derivatives.

1. Introduction

The hydroxylated anthraquinones emodin (1,6,8-trihydroxy-3-methyl-9,10-anthraquinone)[1] (**1**) and endocrocin (1,6,8-trihydroxy-3-methyl-9,10-anthraquinone-2-carboxylic-acid) (**2**) are natural pigments mainly occurring in fungi and lichens[2] and are biosynthesized on a polyketide pathway.[3] Contrary to previous assumptions,[4] **2** is not the biosynthetic precursor of **1**.[5] It has also been found, that decarboxylation of similar anthraquinone carboxylic acids by conventional means is hardly possible on the stage of the anthraquinone but on the corresponding anthrone[6] (see Fig. 1).

Synthesis pathways for **2** include total synthesis of the anthraquinone skeleton via Friedel–Crafts acylations[7] as well as rather tedious modifications of 2,3-dimethyl-anthraquinones.[8] We have now found a way to regioselectively substitute the emodin moiety in position 2, affording not only the carboxylic acid **2** in a six step synthesis, but also other structurally related compounds like cinnalutein (1,8-dihydroxy-3-methyl-6-methoxy-9,10-anthraquinone-2-carboxylicacid) (**3**) and 1,6,8-trimethoxy-2-formyl-3-methyl-9,10-anthraquinone (**4**). The latter is of particular interest in our search for potential precursors for a new generation of photodynamically active hypericin derivatives.[9] It might serve as a promising synthon for new 9,12-substituted hypericin derivatives with a bathochromically shifted long wavelength absorption overcoming dimerization problems which occurred in the case of 3-stilbenoid-substituted emodin derivatives.[10]



1 **2**

Figure 1. Structures of emodin (**1**) and endocrocin (**2**).

2. Results and discussion

The main challenge in this work was to regioselectively substitute the emodin skeleton in position 2 in a simple and reliable way. We have recently shown,[11] that substitution of this position via an intramolecular Friedel–Crafts acylation is possible in principle, but with an unsatisfying regioselectivity. Thus, conventional electrophilic substitutions like Friedel–Crafts and Gattermann type reactions seem to be not the methods of choice, not only because of the missing regioselectivity but also because of the severe deactivation of the anthraquinone system with respect to an electrophilic attack.

Our approach was to introduce a hydroxymethyl group via a Marschalk type reaction,[12] followed by subsequent

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* Corresponding author. Tel.: +43 732 2468 8748; fax: +43 732 2468 8747; e-mail addresses: heinz.falk@jku.at; mario.waser@jku.at

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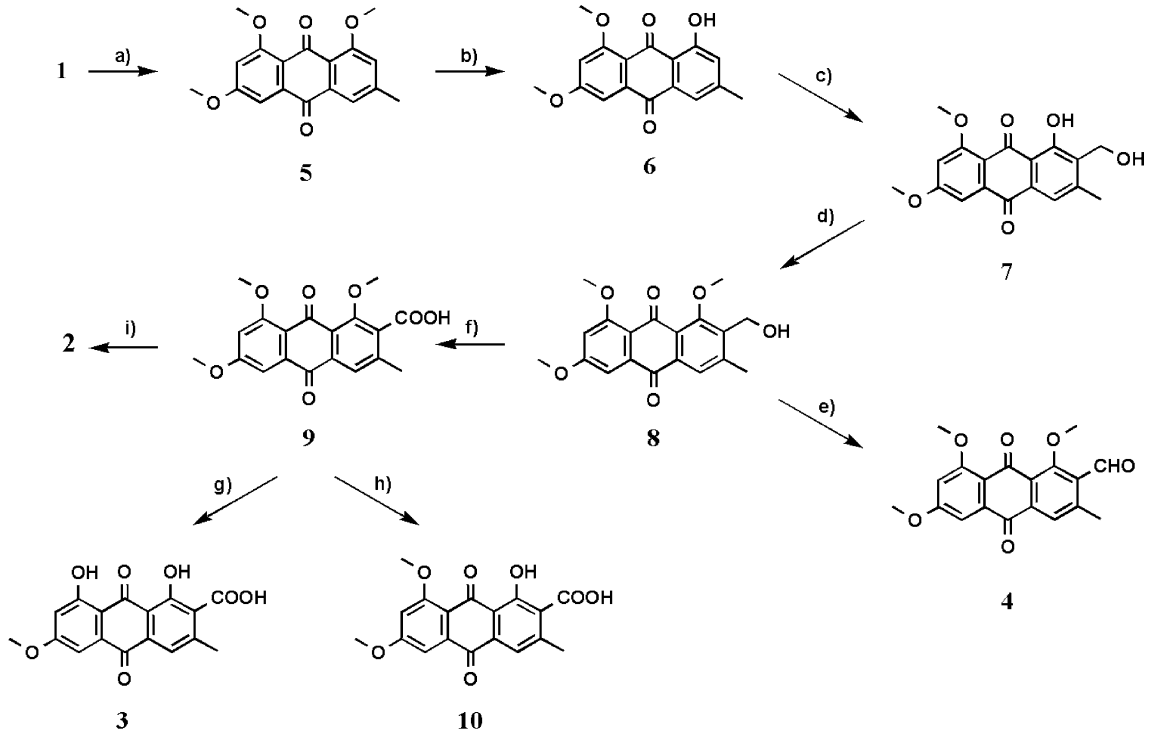
oxidation to the aldehyde and eventually to the carboxylic acid. Marschalk type reactions are quite common in the syntheses of anthracyclinone type antibiotics,[13] as the electrophilic attack always occurs *ortho* to a phenolic group. Accordingly, it was necessary to selectively protect the hydroxyl groups in position 6 and 8. We therefore converted **1** to tri-*O*-methyl emodin (**5**) by microwave assisted synthesis (cf. Ref. 14; 98%), followed by a selective ether cleavage, using an improved procedure of Hassall's deprotection[15] (starting at −5 °C instead of −70 °C increases the yield) to obtain the 1-hydroxy-6,8-dimethoxy-3-methyl-9,10-anthraquinone (**6**) in 93% yield. Due to the high reactivity of the intermediate *ortho*-quinone methide[13] hydroxymethylation of **6** required a rather short reaction time (40 min) and low temperature (0 °C). After purification and separation of by-products by column chromatography 6,8-dimethoxy-1-hydroxy-2-hydroxymethyl-3-methyl-9,10-anthraquinone (**7**) was obtained in 63% yield. Benzylic oxidation of **7** by means of pyridiniumchlorochromate (PCC) or CrO_3 to the corresponding mono-deprotected aldehyde and carboxylic acid proceeded with insufficient selectivity and rather low yields, especially in the case of the carboxylic acid, which might be due to the unprotected phenolic group. Furthermore, with respect to the aldehyde as a suitable starting point for extensions of the chromophoric system, a protection of the hydroxyl group seems to be necessary anyway.

Thus, a selective etherification of the phenolic hydroxyl group leaving the primary alcohol untouched was carried out affording the 1,6,8-trimethoxy-2-hydroxymethyl-3-methyl-9,10-anthraquinone (**8**) in 90% yield. Subsequent oxidation of **8** with PCC gave the aldehyde **4** in 87% yield. Accordingly, the promising synthon **4** could be obtained from **1** in a five step synthesis with an overall yield of 45%.

Tri-*O*-methyl endocrocin (**9**) could be obtained via a Jones oxidation of **8** in 78% yield. Due to the fact, that not only the non-methylated **2**, but also the monomethyl ether **3** and the dimethyl ether **10** (1-hydroxy-6,8-dimethoxy-3-methyl-9,10-anthraquinone-2-carboxylicacid) are interesting naturally occurring pigments,[2] we also investigated the selective deprotection of **9** to **3** and **10**. According to the procedure used for the synthesis of **6**, a BBr_3 mediated deprotection of **9** gave the mono-deprotected **10** in 72% yield, whereas a HBr/AcOH mediated deprotection selectively yielded the dideprotected compound cinnalutein (**3**) in 85% yield (35% overall yield).

The few published procedures,[7,15,16] describing the direct total deprotection of methyl ether protected 1,6,8-hydroxylated anthraquinones, give either rather low yields, or lead to a decarboxylation[16] of carboxylic acid derivatives. This is also in accordance with our experience. Thus we always observed either a destruction of the compound under rather harsh conditions (e.g., HI in boiling AcOH, $AlCl_3$/NaCl melt), or only a dideprotection, leaving the 6-*O*-methyl ether untouched, under 'softer' conditions (e.g., HBr). Steglich and Reininger[7] described the total *O*-demethylation of **10** by means of BBr_3. In our case, treatment of **9** with an excess of



Scheme 1. Reagents and conditions: (a) cf. Ref. 14: Me_2SO_4/K_2CO_3/tetrabutylammonium bromide, 600 W (75 °C), 20 min, 98%; (b) BBr_3/CH_2Cl_2, −5 to 25 °C, 1.5 h, 93%; (c) $Na_2S_2O_4/CH_2O$ (37%)/MeOH/NaOH (1 N), 0 °C, 40 min, subsequent H_2O_2 oxidation, 63%; (d) Me_2SO_4/K_2CO_3/acetone, reflux, 16 h, 90%; (e) PCC/CH_2Cl_2, 2 h, 87%; (f) CrO_3/H_2SO_4/acetone, 0–10 °C, 1.5 h, 78%; (g) HBr/AcOH, reflux, 30 min, 85%; (h) BBr_3/CH_2Cl_2, −5 to 5 °C, 0.5 h, 72%; (i) BBr_3/CH_2Cl_2, reflux, 10 h, 78%.

BBr_3 in boiling CH_2Cl_2 for 10 h was the only possibility found to obtain **2** in a reasonable yield of 78%. Accordingly, endocrocin (**2**) could be obtained from emodin (**1**) in a six step synthesis with an overall yield of 32% (see Scheme 1).

In conclusion, we found an efficient way to regioselectively substitute emodin in position 2, yielding endocrocin-like naturally occurring pigments as well as the promising hypericin precursor **4** in satisfying overall yields, with a Marschalk type reaction as the key step. All compounds were fully characterized on basis of their IR, UV/vis, MS, and NMR spectra, particularly by 2D NMR measurements including HSQC, HMBC, and NOESY experiments.[18] Compound **5** displayed spectroscopic data in accordance to Ref. 14. Melting points of **2**, **3**, **6**, and **10** were according to literature.[7,15,17]

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References and notes

1. This numbering, although arbitrary, was chosen for a better illustration of the regioselectivity in this work.
2. Thomson, R. *Naturally Occuring Quinones III*; Chapman and Hall Ltd.: London, 1987, pp 403–457.
3. For reviews see: (a) Han, Y.-S.; Van der Heijden, R.; Verpoorte, R. *Plant Cell Tiss. Org. Cult.* **2001**, *67*, 201–220; (b) Gill, M.; Steglich, W. In *Progress in the Chemistry of Organic Natural Products*; Springer, Wien, 1987; Vol. 51, pp 147–149.
4. (a) Birch, A. J.; Donovan, F. W. *Aust. J. Chem.* **1953**, *6*, 360–368; (b) Robinson, R. *Structural Relations of Natural Products*; Clarendon: Oxford, 1955, pp 10.
5. Steglich, W.; Arnold, R.; Lösel, W.; Reininger, W. *J. Chem. Soc., Chem. Commun.* **1972**, *2*, 102–103.
6. Yamaguchi, M.; Hasebe, K.; Higashi, H.; Uchida, M.; Irie, A.; Minami, T. *J. Org. Chem.* **1990**, *55*, 1611–1623.
7. Steglich, W.; Reininger, W. *J. Chem. Soc., Chem. Commun.* **1970**, *3*, 178.
8. Joshi, B. S.; Ramanathan, S.; Venkataraman, K. *Tetrahedron Lett.* **1962**, *21*, 951–955.
9. (a) Falk, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3136–3316; (b) Falk, H. *Angew. Chem.* **1999**, *111*, 3306–3326.
10. Obermüller, R. A.; Hohenthanner, K.; Falk, H. *Photochem. Photobiol.* **2001**, *74*, 211–215.
11. Waser, M.; Falk, H. *Monatsh. Chem.* **2005**, DOI:10.1007/S00706-004-0263-X.
12. Marschalk, C.; Koenig, F.; Ouroussoff, N. *Bull. Soc. Chim. Fr.* **1936**, *3*, 1545–1575.
13. For a review see: Krohn, K. *Tetrahedron* **1990**, *46*, 291–318.
14. Lackner, B.; Popova, Y.; Etzlstorfer, C.; Klampfl, C.; Smelcerovic, A.; Falk, H. *Monatsh. Chem.*, in press.
15. Hassall, C. H.; Morgan, B. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2853–2861.
16. Kelly, T. R.; Xu, W.; Ma, Z.; Bushan, V. *J. Am. Chem. Soc.* **1993**, *115*, 5843–5844.
17. Steglich, W.; Reininger, W. *Chem. Ber.* **1972**, *105*, 2922–2927.
18. Selected properties of compound **2**: Mp: decomp $\geqslant$ 310 °C. ^{1}H NMR (500 MHz, δ, DMSO-d_6, 30 °C): 2.38 (s, 3H, ar-CH_3), 6.64 (d, 1H, J = 2.14 Hz, ar-H7), 7.17 (d, 1H, J = 2.14 Hz, ar-H5), 7.60 (s, 1H, ar-H4), 11.44 (s, 1H, 3-OH), 11.92 (br s, 1H, COOH), 11.95 (s, 1H, 8-OH), 12.37 (s, 1H, 1-OH) ppm. ^{13}C NMR (125 MHz, δ, DMSO-d_6, 30 °C): 19.4 (ar-CH_3), 107.9 (C7), 108.9 (C5), 109.1 (C8a), 114.9 (C9a), 120.5 (C4), 129.1 (C2), 130.5 (C4a), 144.0 (C3), 157.9 (C1), 164.5 (C8), 165.7 (C6), 181.8 (C10) ppm, C9, C10a, and –COOH not observed due to insufficient solubility. ESI-MS (neg. ion mode): m/z = 313 ($[M-H]^-$). IR (KBr): 3445, 2954, 2924, 2854, 1740, 1713, 1463, 1377, 1262, 1208, 1071, 801, 722 cm^{-1}. UV–vis ($CHCl_3$): λ_{max} = 242 (100), 284 (69), 443 (20) nm (rel. int.); compound **3**: Mp: 275–278 °C. ^{1}H NMR (500 MHz, δ, DMSO-d_6, 30 °C): 2.42 (s, 3H, ar-CH_3), 3.94 (s, 3H, 6-OCH_3), 6.89 (d, 1H, J = 2.20 Hz, ar-H7), 7.21 (d, 1H, J = 2.20 Hz, ar-H5), 7.57 (s, 1H, ar-H4), 12.14 (s,1H, –OH), 12.29 (br s, 2H, –OH and –COOH) ppm. ^{13}C NMR (125 MHz, δ, DMSO-d_6, 30 °C): 19.7 (ar-CH_3), 56.4 (6-OCH_3), 106.6 (C7), 107.7 (C5), 110.0 (C8a), 114.0 (C9a), 120.5 (C4), 130.4 (C2 or C3), 132.5 (C4a), 134.8 (C10a), 143.9 (C2 or C3), 164.4 (C1 and C8), 166.2 (C6), 167.0 (–COOH), 180.9 (C10), 189.6 (C9) ppm. ESI-MS (neg. ion mode): m/z = 327 ($[M-H]^-$). IR (KBr): 2924, 2854, 1709, 1675, 1601, 1465, 1394, 1285, 1244, 1216, 1174, 1100, 958, 766 cm^{-1}. UV–vis ($CHCl_3$): λ_{max} = 268 (93), 290 (100), 442 (40) nm (rel. int.); compound **4**: Mp: 246–248 °C. ^{1}H NMR (500 MHz, δ, DMSO-d_6, 30 °C): 2.67 (s, 3H, ar-CH_3), 3.98 (s, 3H, 6-OCH_3), 4.00 (s, 3H, 8-OCH_3), 4.08 (s, 3H, 1-OCH_3), 6.81 (d, 1H, J = 2.14 Hz, ar-H7), 7.35 (d, 1H, J = 2.14 Hz, ar-H5), 7.87 (s, 1H, ar-H4), 10.65 (s, 1H, –CHO) ppm. ^{13}C NMR (125 MHz, δ, DMSO-d_6, 30 °C): 21.9 (ar-CH_3), 56.3 (6-OCH_3), 57.0 (8-OCH_3), 65.2 (1-OCH_3), 102.8 (C5), 105.9 (C7), 118.3 (C8a), 125.9 (C4), 126.4 (C9a), 134.2 (C2), 136.7 (C10a), 136.8 (C4a), 146.8 (C3), 162.4 (C8), 164.7 (C6), 164.9 (C1), 180.9 (C9), 183.6 (C10), 192.9 (–CHO) ppm. ESI-MS (pos. ion mode): m/z = 341 ($[M+H]^+$). IR (KBr): 2940, 2849, 1686, 1676, 1599, 1456, 1427, 1377, 1324, 1257, 1209, 985 cm^{-1}. UV–vis ($CHCl_3$): λ_{max} = 282 (100), 346 (14) nm, 405 (14) (rel. int.); compound **6**: Mp: 204–205 °C. ^{1}H NMR (500 MHz, δ, $CDCl_3$, 25 °C): 2.43 (s, ar-CH_3), 3.99 (s, 8-OCH_3), 4.03 (s, 6-OCH_3), 6.79 (d, J = 2.3 Hz, ar-H7), 7.08 (s, ar-H2), 7.46 (d, J = 2.3 Hz, ar-H5), 7.57 (s, ar-H4), 13.09 (s, 1-OH) ppm. ^{13}C NMR (125 MHz, δ, $CDCl_3$, 25 °C): 22.19 (ar-CH_3), 56.27 (8-OCH_3), 56.84 (6-OCH_3), 104.2 (C5), 104.9 (C7), 115.0 (C9a), 115.5 (C8a), 120.2 (C4), 125.0 (C2), 132.5 (C4a), 137.9 (C10a), 147.1 (C3), 162.9 (C1), 163.3 (C6), 165.5 (C8), 183.2 (C10), 187.7 (C9) ppm. ESI-MS (pos. ion mode): m/z = 299 ($[M+H]^+$). IR (KBr): 3083, 2945, 2846, 1670, 1630, 1593, 1555, 1493, 1460, 1364, 1326, 1263, 1230, 1202, 1163, 1135, 1060, 1012, 946, 885, 838, 757, 611 cm^{-1}. UV–vis ($CHCl_3$): λ_{max} = 272 (100), 280 (96), 426 (36) nm (rel. int.); compound **7**: Mp: 237–240 °C. ^{1}H NMR (500 MHz, δ, DMSO-d_6, 30 °C): 2.49 (s, 3H, ar-CH_3), 3.97 (s, 3H, 8-OCH_3), 3.98 (s, 3H, 6-OCH_3), 4.60 (d, 2H, J = 5.19 Hz, ar-CH_2–), 4.92 (t, 1H, J = 5.19 Hz, –OH), 7.02 (d, 1H, J = 2.14 Hz, ar-H7), 7.29 (d, 1H, J = 2.14 Hz, ar-H5), 7.46 (s, 1H, ar-H4), 13.68 (s, 1H, 1-OH) ppm. ^{13}C NMR (125 MHz, δ, DMSO-d_6, 30 °C): 19.4 (ar-CH_3), 53.1 (ar-CH_2–), 56.1 (8-OCH_3), 56.6 (6-OCH_3), 104.4 (C7), 104.5 (C5), 113.9 (C8a), 114.1 (C9a), 119.7 (C4), 130.5 (C4a), 134.8 (C2), 136.6 (C10a), 146.5 (C3), 160.0 (C1), 163.1 (C8), 165.1 (C6), 181.8 (C10), 186.7 (C9) ppm. ESI-MS (pos. ion mode): m/z = 329 ($[M+H]^+$). IR (KBr): 3472, 3335, 2920, 2850, 1699, 1618, 1489, 1457 1376, 1321, 1268,

1220, 1160, 1058, 1017 cm^{-1}. UV–vis ($CHCl_3$): λ_{max} = 273 (100), 425 (32) nm (rel. int.); compound **8**: Mp: 249–252 °C. ^1H NMR (500 MHz, δ, DMSO-d_6, 30 °C): 2.52 (s, 3H, ar-CH_3), 3.84 (s, 3H, 1-OCH_3), 3.93 (s, 3H, 8-OCH_3), 3.95 (s, 3H, 6-OCH_3), 4.60 (d, 2H, J = 5.19 Hz, ar-CH_2–), 5.03 (t, 1H, J = 5.19 Hz, –OH), 7.00 (d, 1H, J = 2.14 Hz, ar-H7), 7.20 (d, 1H,J = 2.14 Hz, ar-H5), 7.73 (s, 1H, ar-H4) ppm. ^{13}C NMR (125 MHz, δ, DMSO-d_6, 30 °C): 19.4 (ar-CH_3), 54.2 (ar-CH_2–), 55.9 (6-OCH_3), 56.5 (8-OCH_3), 62.9 (1-OCH_3), 102.5 (C5), 105.0 (C7), 117.2 (C8a), 123.4 (C4), 125.5 (C9a), 132.6 (C4a), 135.7 (C10a), 141.4 (C2 or C3), 145.0 (C3 or C2), 158.0 (C1), 161.4 (C8), 163.6 (C6), 180.2 (C9), 182.8 (C10) ppm. ESI-MS (pos. ion mode): m/z = 343 ($[M+H]^+$). IR (KBr): 3481, 2925, 2853, 1669, 1593, 1458, 1328, 1263, 1162 cm^{-1}. UV–vis ($CHCl_3$): λ_{max} = 278 (100), 349 (15) nm, 393 (16) (rel. int.); compound **9**: Mp: 228–232 °C. ^1H NMR (500 MHz, δ, DMSO-d_6, 30 °C): 2.38 (s, 3H, ar-CH_3), 3.83 (s, 3H, 1-OCH_3), 3.94 (s, 3H, 8-OCH_3), 3.96 (s, 3H, 6-OCH_3), 7.02 (d, 1H, J = 2.14 Hz, ar-H7), 7.22 (d, 1H, J = 2.14 Hz, ar-H5), 7.80 (s, 1H, ar-H4), 13.65 (br s, 1H, –COOH) ppm. ^{13}C NMR (125 MHz, δ, DMSO-d_6, 30 °C): 18.9 (ar-CH_3), 55.9 (6-OCH_3), 56.5 (8-OCH_3), 62.7 (1-OCH_3), 102.7 (C5), 105.0 (C7), 116.9 (C8a), 123.5 (C4), 125.2 (C9a), 131.8 (C4a), 135.7 (C10a), 138.6 (C2 or C3), 140.0 (C3 or C2), 155.7 (C1), 161.6 (C8), 163.8 (C6), 167.6 (–COOH), 179.5 (C9), 182.4 (C10) ppm. ESI-MS (neg. ion mode): m/z = 355 ($[M-H]^-$). IR (KBr): 3502, 2923, 2855, 1687, 1673, 1598, 1458, 1394, 1353, 1255, 1213, 1163, 1151, 1084, 1042, 984, 750 cm^{-1}. UV–vis ($CHCl_3$): λ_{max} = 276 (100), 344 (19), 396 (20) nm (rel. int.); compound **10**: Mp: 273–275 °C. ^1H NMR (500 MHz, δ, DMSO-d_6, 30 °C): 2.39 (s, 3H, ar-CH_3), 3.97 (s, 3H, 8-OCH_3), 4.00 (s, 3H, 6-OCH_3), 7.05 (d, 1H, J = 2.14 Hz, ar-H7), 7.32 (d, 1H, J = 2.14 Hz, ar-H5), 7.53 (s, 1H, ar-H4), 13.45 (s, 1H, 1-OH), 13.55 (br s, 1H, –COOH) ppm. ^{13}C NMR (125 MHz, δ, DMSO-d_6, 30 °C): 19.4 (ar-CH_3), 56.2 (6-OCH_3), 56.7 (8-OCH_3), 104.5 (C5), 104.8 (C7), 113.9 (C8a), 114.7 (C9a), 119.4 (C4), 128.6 (C10a), 131.5 (C3), 131.6 (C10a), 142.2 (C3), 158.0 (C1), 163.2 (C8), 165.3 (C6), 167.2 (–COOH), 181.6 (C10), 186.3 (C9) ppm. ESI-MS (neg. ion mode): m/z = 341 ($[M-H]^-$). IR (KBr): 3421, 2924, 2854, 1735, 1685, 1627, 1559, 1508, 1363, 1254, 972, 748 cm^{-1}. UV–vis ($CHCl_3$): λ_{max} = 284(100), 432 (36) nm (rel. int.).