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An Efficient Synthesis of *O*-Methyl Protected Emodin Aldehyde and Emodin Nitrile

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Summary. An efficient synthesis of tri-*O*-methylemodin aldehyde was achieved *via* bromination of tri-*O*-methylemodin utilizing *N*-bromosuccinimide yielding the monobromo and dibromo derivatives. *Sommelet* reaction of the monobromomethyl derivative as well as hydrolysis of the dibromomethyl analog with aqueous silver nitrate afforded the protected aldehyde in good yield. Accordingly, both bromo derivatives can be used even when they are obtained as a mixture of the bromination reaction, which could not be controlled easily to yield the bromo products selectively. From the aldehyde the tri-*O*-methylemodin nitrile was prepared in a one-pot reaction using hydroxylamine-*O*-sulfonic acid.

Keywords. Tri-*O*-methylemodin; *N*-Bromosuccinimide; *Sommelet* reaction; Silver nitrate; Hydrolysis.

Introduction

Emodin (**1**, 3-methyl-1,6,8-trihydroxyanthraquinone) has been shown to be a protein-tyrosine kinase inhibitor [1] as well as an anti-cancer agent [2]. On the one hand, syntheses of emodin analogues have become of recent interest with respect to increasing their biological activity [3, 4]. On the other hand, they might be used as intermediates to synthesize modified hypericines. Such are intended as photodynamic therapy agents [5–8]. Besides the fact that emodin aldehyde has been shown to possess anti-microbial and anti-tumour activity [9], it is thought to be a valuable synthon for the synthesis of hypericin anologs.

According to literature, only inconvenient, multi-step, and low yield protocols for its synthesis are available. The first one includes chromium trioxide oxidation of protected emodin to the emodic acid analog followed by subsequent reduction with diborane in alcohol. Alkaline hydrolysis or conversion to the corresponding acid chloride and reduction in presence of $Pd/BaSO_4$ has yielded emodin aldehyde in only up to 10% yield [10]. A slight modification of this procedure employing boron hydride in *THF* to reduce the emodic acid triacetate to the alcohol followed

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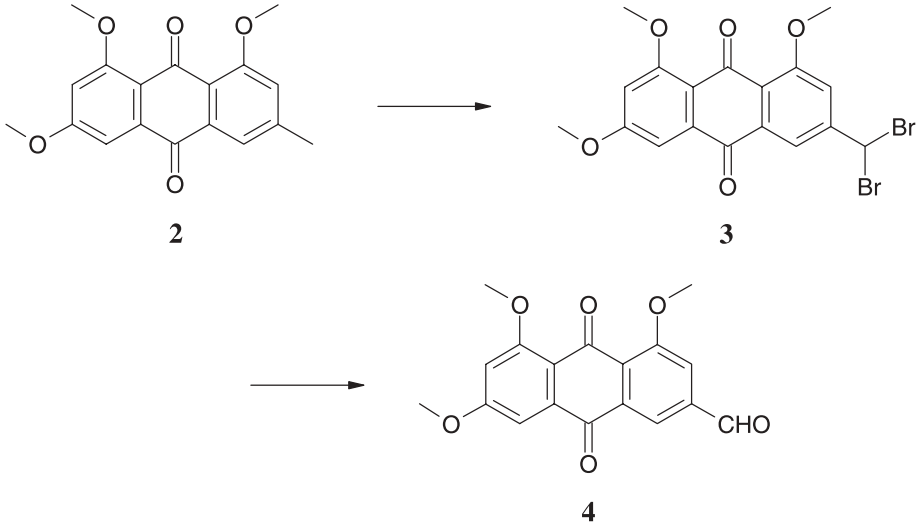
by *DMSO*/oxalyl chloride oxidation in *THF* and triethylamine at $-78°C$ has provided the aldehyde in somewhat higher yield [3]. The second one has been conceived by two independent groups who reported slightly different five-step syntheses of emodin aldehyde starting from emodin. *Thiem* and *Wessel* [11] reported bromination of emodin tri-*O*-acetyl to the 3-bromomethyl analogue, solvolysis with acetic anhydride/sodium acetate to the 3-acetoxy derivative, *N*-bromosuccinimide oxidation, and eventually acid hydrolysis to provide emodin aldehyde in 27% overall yield. An alternative two-step synthesis reported by the same authors, including chromium trioxide oxidation in an acetic anhydride/acetic acid mixture to the acetal and subsequent acid hydrolysis yielded the aldehyde in almost 11% yield. The other synthesis, reported by *Hirose et al.* [12], employed the former sequence to the 3-acetoxy derivative, alkaline hydrolysis to the alcohol followed by manganese dioxide oxidation to the aldehyde in 30% overall yield.

With respect to our aim to gain access to ω, ω'-derivatized hypericines, synthesis of a protected emodin aldehyde was more desirable than that of the free aldehyde itself. In particular, the methylated analog, hitherto prepared in a scarce yield only [10c], seemed to be promising in this context due to the instability of the acylated analogue [6] under the reaction conditions of hypericin formation. In addition, the corresponding nitrile could be envisaged as a convenient precursor of another series of hypericin derivatives. Therefore, we developed a high yield synthesis of tri-*O*-methyl emodin aldehyde as well as its transformation to the nitrile analog, which will be reported in this communication.

Results and Discussion

First, a straightforward strategy for the preparation of tri-*O*-methylemodin aldehyde (**4**) *via* oxidation of the methyl side chain of tri-*O*-methylemodin (**2**) [13, 14] was found to be unsuccessful. Several selective oxidation methods were investigated, including use of reagents such as chromium trioxide [15], ceric ammonium nitrate [16], and lead tetraacetate [17]. Unfortunately, none of these reagents yielded **4**, and **2** was recovered unchanged. Conversion of **2** to the bromomethyl analogue **5** as a precursor to the corresponding hydroxymethyl derivative, followed by oxidation to **4** was put aside as a multi-step approach.

N-Bromosuccinimide has been used to achieve benzylic bromination of some methylanthraquinone derivatives [13] forming either mono or dibromo derivatives depending on the molar ratio used as well as the substituents on the ring system. Consequently, we turned first to a benzylic dibromination. Reaction of **2** with 3.4 molar equivalents of *N*-bromosuccinimide and benzoyl peroxide as catalyst gave the dibromide **3** in 70% yield along with a small amount of the monobromide **5**. When only 1.2 mole of *N*-bromosuccinimide were used, **5** was obtained in 72% yield. Refluxing the dibromide **3** in aqueous acetic acid (1:4) for 22 h [13] yielded the aldehyde **4** in 79% yield. However, its purification was extremely difficult due to the similarity of the R_f values and the solubility of the contaminating unchanged **3**. In contrast to this result, drop-wise addition of a silver nitrate solution [18] to the refluxing solution of dibromide **3** in methoxyethanol gave **4** in 96% yield (67% based on **2**, Scheme 1, Experimental, method A).



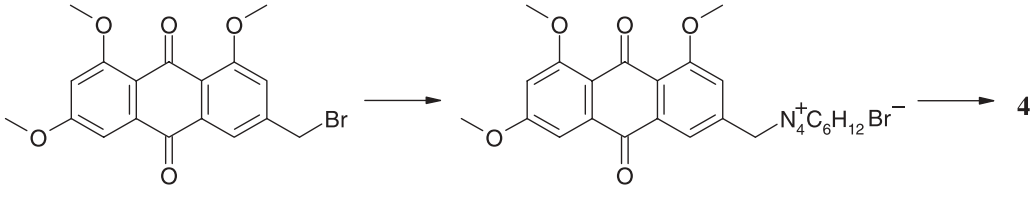
2 **3** **4**

Scheme 1

In addition, due to the readily accessible bromomethyl derivative **5**, a short approach to the aldehyde **4** *via* **5** seemed to be desirable. This was achieved by application of the *Sommelet* reaction [19–23]. Following the now well-established route to **5** [5], the latter was stirred under reflux with hexamethylenetetramine in chloroform for 2 h to give the *Sommelet* salt **6** in 92% yield. Upon refluxing **6** with hexamethylenetetramine in aqueous acetic acid (1:1) for 4–6 h the aldehyde **4** was obtained in 76% yield (50% based on **2**, Scheme 2, Experimental, method B).

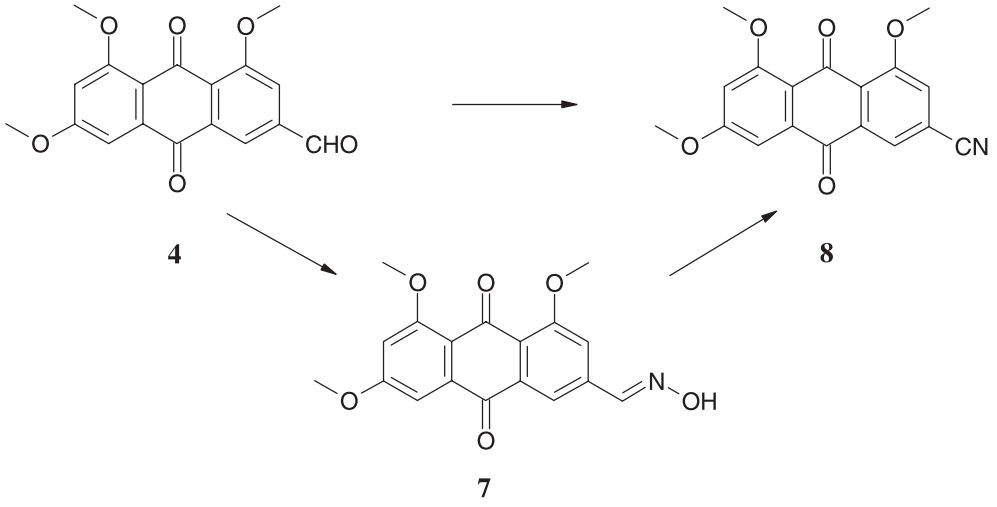
The *Sommelet* approach may also have a potential to be used for the synthesis of important naturally occurring anthraquinonoid compounds having a methyl side chain as well as for other anthraquinone aldehydes which are required to prepare porphyrin-quinones as models for the light-initiated charge separation in photosynthetic reaction centers [24].

Because bromination of protected emodin always gave a mixture of the mono- and dibromo-derivatives regardless of the *NBS* molar ratio [2, 4, 11], a combination of the both above mentioned procedures may be used for a more efficient preparation of the aldehyde **4**. Allowing the resulting mixture of the bromination with *NBS* to react with hexamethylenetetramine in refluxing chloroform, only the monobromide reacted to form the precipitating *Sommelet* salt leaving the unreacted dibromide in solution. Then, both of them could be hydrolysed according to the



5 **6**

Scheme 2



Scheme 3

procedures described above to the aldehyde **4**. It might be noted that the excess molar ratio of hexamethylenetetramine has no observable effect on the salt formation step. Using this approach particularly for large scale synthesis, **4** could be obtained from **2** in 52% overall yield (Experimental, method C).

Following our second goal, transformation of the aldehyde **4** to the corresponding nitrile **8** was also achieved. First, the synthesis of the nitrile **8** was carried out on the classical route by preparation of the oxime **7** from **4** and subsequent dehydration. Thus, refluxing the aldehyde with hydroxylamine hydrochloride and sodium acetate [25] in ethanol for 2 h gave the oxime **7** in 82% yield. Subsequent dehydration with acetic anhydride [25] under reflux for 3 h led to the nitrile **8** in only 58% yield (*i.e.* 48% based on **4**, Scheme 3), which led us to look for a more modern, higher yield, one-step aldehyde – nitrile conversion. However, neither stirring the aldehyde with triazidochlorosilane *in situ* [26] in acetonitrile at room temperature for 24 h nor heating with $NH_2OH \cdot HCl$ in *N*-methylpyrrolidone at 115°C [27] or under reflux in formic acid [28] yielded a significant amount of **8**. It was then obtained in a mere 34% yield when using a sodium acetate/formic acid mixture [29]. Eventually, the nitrile **8** could be prepared in a one-pot reaction in 74% yield by heating the aldehyde **4** with hydroxylamine-*O*-sulfonic acid (*HAS*) [30] in aqueous dimethylformamide (*DMF*) at 80–90°C for 12 h. It is noteworthy that no reaction occurred when using only water as the reaction medium as reported in Ref. [30], whereas the oxime **7** was exclusively isolated when using either aqueous ethanol or a CH_3CN:*NMP* (2:1) mixture as the solvent system.

Experimental

Solvents were of p. a. quality. Melting points are uncorrected. ^1H and ^{13}C NMR, IR, UV-Vis, and mass spectra were recorded using the Bruker DRX 500 and DPX 200, Bruker Tensor 27, Varian Cary 100 Bio UV/Vis, Hewlett Packard 59987 quadrupole, and Fisons MD 800 instruments. Assignments of the ^1H and ^{13}C NMR signals were achieved using 2D experiments (HSQC, HMBC, N*O*ESY) under standard instrument parameters. Tri-*O*-methylemodin (**2**) and the monobromo derivative **5** were

prepared according to Ref. [5]. All novel compounds were judged to be pure (>97%) by means of their ^{1}H NMR spectra and chromatography.

6-Dibromomethyl-1,3,8-trimethoxyanthraquinone (**3**, $C_{13}H_{14}Br_2O_3$)

A mixture of 400 mg of **2** (1.28 mmol), 797 mg of *N*-bromosuccinimide (4.48 mmol), 100 mg of benzoyl peroxide, and 30 cm^3 of CCl_4 was refluxed for 25 h. After cooling to room temperature the yellow solid was filtered off, washed with CCl_4, hot H_2O, dried, and triturated with acetone to give 420 mg (70%) of **3**. Mp 255–257°C (Ref. [2] 254–257°C); TLC: $R_f = 0.46$ ($CHCl_3$:$CH_3COOC_2H_5$ = 3:1), $R_f = 0.77$ ($CHCl_3$:CH_3OH = 20:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.92$ (d, $J = 1.5$ Hz, ar-H5), 7.56 (d, $J = 1.5$ Hz, ar-H7), 7.34 (d, $J = 2.4$ Hz, ar-H4), 6.80 (d, $J = 2.4$ Hz, ar-H2), 6.68 (s, $CHBr_2$), 4.07 (s, OCH_3), 3.98 (s, OCH_3), 3.97 (s, OCH_3) ppm; IR (KBr): $\bar{\nu}$ = 3020 (=CH), 2903, 2790 (OCH_3), 1663 (CO), 1596 (C=C), 1441, 1326, 1248, 941, 826, 750, 692 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 241$ (100), 281 (96), 405 (20) nm (rel. int.).

4,5,7-Trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (**4**, $C_{18}H_{14}O_6$)

Method A. A solution of 500 mg of $AgNO_3$ (2.94 mmol) in 10 cm^3 of distilled H_2O was added dropwise during 20 min to a refluxing solution of 70 mg of **3** (0.15 mmol) in 20 cm^3 of methoxyethanol. A precipitate of silver bromide formed immediately. Heating was continued for 10 min after which the mixture was cooled and diluted with 100 cm^3 of distilled H_2O. AgBr was filtered off and the aqueous filtrate was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give 47 mg (96%) of **4**. Mp 225–227°C (Ref. [10c] 221–223°C); TLC: $R_f = 0.43$ ($CHCl_3$:$CH_3COOC_2H_5$ = 3:1), $R_f = 0.79$ ($CHCl_3$:CH_3OH = 20:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 10.14$ (s, CHO), 8.32 (s, ar-H1), 7.97 (s, ar-H3), 7.37 (d, $J = 2.1$ Hz, ar-H8), 6.81 (d, $J = 2.1$ Hz, ar-H6), 4.07 (s, OCH_3), 4.02 (s, OCH_3), 3.99 (s, OCH_3) ppm; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 10.15$ (s, CHO), 8.18 (s, ar-H1), 7.93 (s, ar-H3), 7.21 (d, $J = 2.3$ Hz, ar-H8), 7.02 (d, $J = 2.3$ Hz, ar-H6), 3.99 (s, 4-OCH_3), 3.96 (s, 7-OCH_3), 3.92 (s, 5-OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 190.1$ (CHO), 183.4 (CO), 181.3 (CO), 164.5, 164.4, 162.1, 160.5, 139.6, 136.3, 135.7, 129.5, 122, 115.6, 105.8, 102.5, 57.1 (OCH_3), 56.8 (OCH_3), 56.2 (OCH_3) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 192.4$ (CHO), 182.5 (9-CO), 179.7 (10-CO), 163.7 (C7), 161.2 (C5), 159.3 (C4), 139.3, 135.5, 134.7, 127.1 (C2), 119.3 (C1), 117.6, 117.5 (C3), 105.1 (C6), 102.5 (C8), 56.6 (4-OCH_3), 56.4 (7-OCH_3), 56.0 (5-OCH_3) ppm; CI-MS (solid probe, CH_4 3.5): $m/z = 327$ ($[M + H]^+$); IR (KBr): $\bar{\nu}$ = 1703 (CHO), 1664 (CO), 1596 (C=C) cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 242$ (100), 276 (75), 404 (23) nm (rel. int.).

4,5,7-Trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-hexamethylenetetrammoniummethyl bromide (**6**, $C_{24}H_{27}BrN_4O_5$)

Method B. Sommelet Reaction: A mixture of 1.8 g of **5** (4.6 mmol), 1.0 g of hexamethylenetetramine (7.23 mmol), and 150 cm^3 of $CHCl_3$ was refluxed for 2 h. After cooling **6** was filtered off, washed with cold $CHCl_3$, and dried. Yield 2.24 g (92%); mp 213–215°C; TLC: $R_f = 0.0$ ($CHCl_3$:$CH_3COOC_2H_5$ = 3:1), $R_f = 0.0$ ($CHCl_3$:CH_3OH = 20:1), $R_f = 0.69$ (CH_3OH:NH_3 = 10:1); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 7.78$ (d, $J = 1.3$ Hz, ar-H1), 7.61 (d, $J = 1.3$ Hz, ar-H3), 7.16 (d, $J = 2.4$ Hz, ar-H8), 7.02 (d, $J = 2.4$ Hz, ar-H6), 5.14 (s, $3CH_2$), 4.61 (d, $J = 12.5$ Hz, 3H), 4.45 (d, $J = 12.5$ Hz, 3H), 4.18 (s, ar-CH_2), 3.97 (s, 4-OCH_3), 3.95 (s, 7-OCH_3), 3.92 (s, 5-OCH_3) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 182.3$ (2CO), 163.2 (C7), 160.8 (C5), 158.5 (C4), 135.0, 133.8, 131.2, 123.7 (C2), 122.4 (C3), 121.6 (C1), 116.9, 104.8 (C6), 102.1 (C8), 78.0 ($3CH_2$), 69.7 ($3CH_2$), 58.5 (ar-CH_2), 56.6 (4-OCH_3), 56.4 (5-OCH_3), 55.9 (7-OCH_3) ppm; ESI-MS (MeOH:*DMSO* = 4:1 + 5% HCOOH, positive ion mode): $m/z = 451$ ($[M - Br]^+$); IR (KBr): $\bar{\nu}$ = 3426, 2944, 2842, 1661, 1597, 1563, 1463, 1330, 1281, 1246, 1017, 823, 755, 649 cm^{-1}; UV-Vis (CH_3OH): $\lambda_{max} = 216$ (100), 279 (69), 402 (15) nm (rel. int.).

A mixture of 1.0 g of **6** (1.88 mmol) and 1.0 g of hexamethylenetetramine (7.14 mmol) was boiled for 6 h in 40 cm^3 of 50% acetic acid. After cooling the product was filtered off, washed with water, and dried. The filtrate was extracted with ethyl acetate. The extract was washed with 20% aqueous Na_2CO_3, twice with water, dried over Na_2SO_4, and the solvent was evaporated. The residue was washed with ether to give additional amounts of **4**. Yield 0.47 g (76%); mp, TLC, IR, and NMR spectra of the product were identical with that obtained by method A.

Method C. A mixture of 7.33 g of **2** (23.5 mmol), 12.08 g of *N*-bromosuccinimide (67.9 mmol), 1.26 g of benzoyl peroxide, and 540 cm^3 of CCl_4 was refluxed for 40 h. After cooling to room temperature, the yellow solid was filtered off, washed with CCl_4, hot H_2O, and dried to obtain 7.0 g of a mixture of **3** and **5**. To this solid, 3.20 g of hexamethylenetetramine (22.8 mmol) and 700 cm^3 of $CHCl_3$ were added and the mixture was refluxed for 5.5 h. After cooling, the salt was filtered off, washed with cold $CHCl_3$, and dried. Yield 4.35 g of **6**. The filtrate was evaporated to dryness and washed with acetone to provide 3.35 g of **3**. Hydrolysis of **3** and **6** according to method A and B gave 2.29 plus 1.73 g of **4** (52% overall yield). Mp, TLC, IR, and NMR spectra were identical with that obtained by methods A and B.

4,5,7-Trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde oxime (**7**, $C_{18}H_{15}NO_6$)

To a solution of 0.13 g of **4** (0.4 mmol) in 15 cm^3 of ethanol, a solution of 0.04 g of hydroxylamine hydrochloride (0.6 mmol) and 0.04 g of sodium acetate (0.49 mmol) in 3 cm^3 of H_2O was added and the reaction mixture was stirred under reflux for 2 h. After cooling to room temperature, the precipitate was filtered, washed with H_2O and ethanol, and dried. Recrystallization from acetone gave 0.11 g (82%) of **7**. Mp 228–230°C; TLC: $R_f = 0.10$ ($CHCl_3$:$CH_3COOC_2H_5 = 3{:}1$), $R_f = 0.30$ ($CHCl_3$:$CH_3OH = 20{:}1$); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 11.84$ (s, OH), 8.28 (s, CH=N), 7.89 (d, $J = 1.2$ Hz, ar-H1), 7.66 (d, $J = 1.2$ Hz, ar-H3), 7.17 (d, $J = 2.5$ Hz, ar-H8), 6.98 (d, $J = 2.5$ Hz, ar-H6), 3.94 (s, 7-OCH_3), 3.92 (s, 4-OCH_3), 3.90 (5-OCH_3) ppm; ^{13}C NMR (125 MHz, *DMSO*- d_6): $\delta = 183.0$ (9-CO), 179.7 (10-CO), 163.5 (C7), 161.1 (C5), 159.1 (C4), 147.1 (C=N), 138.1, 135.5, 134.3, 123.4 (C2), 117.7, 115.9 (C1), 115.8 (C3), 105.1 (C6), 102.3 (C8), 56.4 (5-OCH_3), 56.3 (4-OCH_3), 55.9 (7-OCH_3) ppm; ESI-MS (MeOH:$CHCl_3 = 2{:}1 + 5\%$ HCOOH, positive ion mode): $m/z = 342$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3527$, 3393 (OH), 3086, 2943, 2842 (CH-aliph.), 1655 (CO), 1597 (C=C), 1562, 1458, 1430, 1326, 1256, 1204, 1164, 983, 944, 880, 756 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 241$ (100), 284 (85), 407 (21) nm (rel. int.).

4,5,7-Trimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbonitrile (**8**, $C_{18}H_{13}NO_5$)

Method A. A solution of 100 mg of **7** (0.29 mmol) in 10 cm^3 of acetic anhydride was warmed slowly and then refluxed gently for 1 h. The cooled reaction mixture was poured onto 200 cm^3 of cold H_2O, extracted two times with ethyl acetate, and dried (Na_2SO_4). After removal of ethyl acetate, the residue was chromatographed using a chloroform:ethyl acetate (4:1) mixture as eluent to give 50 mg (58%) of **8**. Mp 274–276°C; TLC: $R_f = 0.37$ ($CHCl_3$:$CH_3COOC_2H_5 = 3{:}1$), $R_f = 0.75$ ($CHCl_3$:$CH_3OH = 20{:}1$); ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 7.99$ (s, ar-H1 and ar-H3), 7.17 (s, ar-H8), 7.01 (s, ar-H6), 3.96 (s, 4-OCH_3), 3.95 (s, 7-OCH_3), 3.91 (s, 5-OCH_3) ppm; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.11$ (s, ar-H), 7.49 (s, ar-H), 7.33 (s, ar-H), 6.81 (s, ar-H), 4.04 (s, OCH_3), 3.98 (s, 2OCH_3) ppm; ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 7.99$ (s, 2ar-H), 7.17 (s, ar-H), 7.01 (s, ar-H), 3.95 (s, 2OCH_3), 3.91 (s, OCH_3) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 181.7$ (9-CO), 179.1 (10-CO), 163.8 (C7), 161.2 (C5), 158.9 (C4), 135.2, 134.7, 126.4 (C2), 121.7 (C1 or C3), 121.5 (C3 or C1), 117.4, 117.3, 115.8 (CN), 105.2 (C6), 102.6 (C8), 57.0 (4-OCH_3), 56.5 (5-OCH_3), 56.0 (7-OCH_3) ppm; CI-MS (solid probe, CH_4 3.5): $m/z = 324$ ($[M + H]^+$); IR (KBr): $\bar{\nu} = 3083$, 2945 (CH-aliph.), 2236 (CN), 1662 (CO), 1597 (C=C), 1564, 1457, 1351, 1245, 1226, 1206, 1166, 1069, 1016, 874, 755 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 251$ (100), 349 (3), 405 (11) nm (rel. int.).

Method B. To a solution of 0.07 g of hydroxylamine-*O*-sulfonic acid (0.64 mmol) in 20 cm^3 of H_2O a solution of 0.15 g of **4** (0.46 mmol) in 15 cm^3 of *DMF* was added and the reaction mixture was stirred at 80–90°C for 14 h. The cooled reaction mixture was poured into 500 cm^3 of cold H_2O, extracted three times with $CHCl_3$, and dried (Na_2SO_4). After removal of $CHCl_3$, the crude product was purified by recrystallization from ether to give 0.11 g (74%) of **8**. Mp, TLC, IR, and NMR data were identical with that of the compound obtained by method A.

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