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A Synthesis of Emodin Anthrone

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Summary. A novel high yield (74% overall) synthesis of five steps to prepare emodin anthrone, which serves as a valuable precursor of hypericin, was devised using the benzamide *ortho* lithiation strategy for the key step.

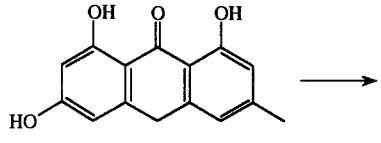
Keywords. Emodin anthrone; Hypericin; Synthesis; Regioselective lithiation.

Eine Synthese von Emodinanthron

Zusammenfassung. Es wird eine neue Syntheseroute zur Darstellung von Emodinanthron, welches einen wichtigen Synthesevorläufer der Hypericinsynthese darstellt, beschrieben; sie verwendet als Schlüsselreaktion eine Benzamid-*ortho*-Lithiierungsreaktion und verläuft in fünf Stufen mit einer Gesamtausbeute von 74%.

Introduction

Emodin anthrone (**1**) serves as the immediate precursor in the course of hypericin synthesis [1]. A recent interest in hypericin (**2**), sparked by its antiviral and antiretroviral properties [2], spurred a search for efficient methods to improve its synthetic accessibility. According to literature, **2** may be either isolated from natural sources, as for instance *Hypericum perforatum* and *Hypericum hirsutum* [3], or it can be obtained by dimerization procedures starting from emodin derivatives [1, 4, 5]. However, accessibility using these roads suffers from rather long and low yield synthesis routes [1, 4–6] or the tedious isolation from natural sources [3,



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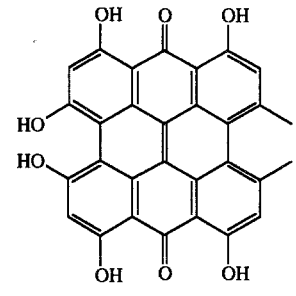

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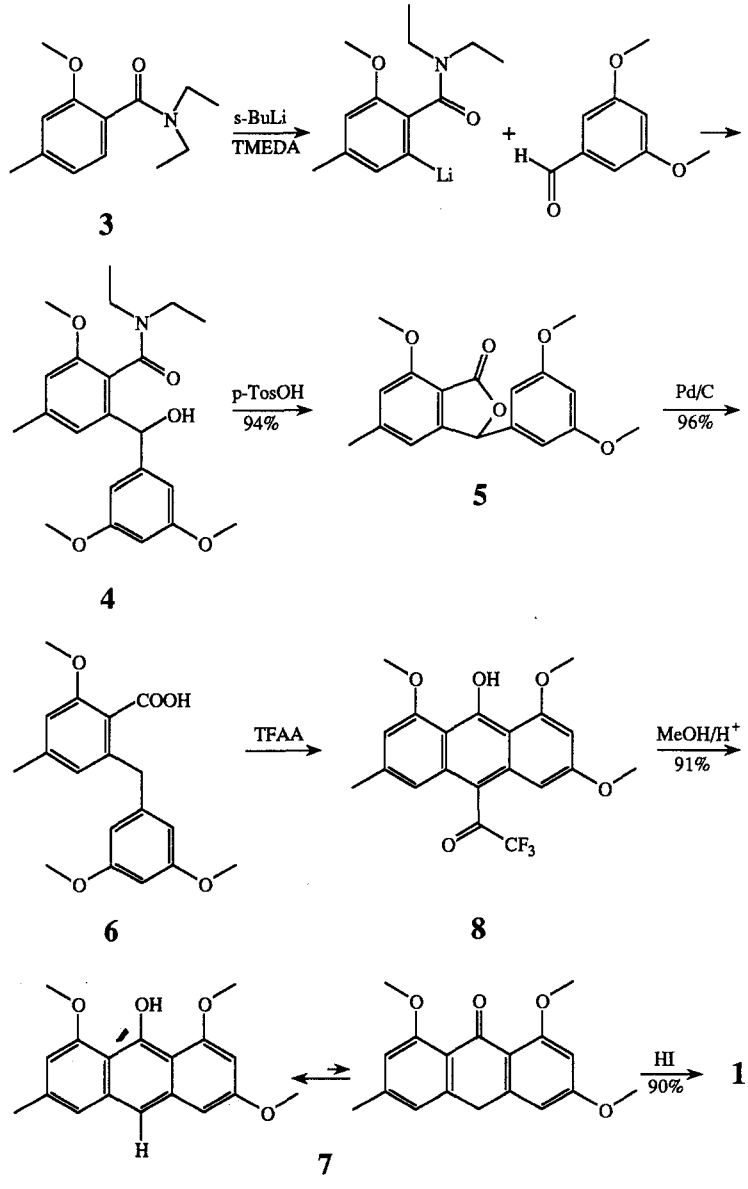
* Dedicated to Prof. K. Schaffner on the occasion of his 60th birthday

7]. We therefore developed a high yield synthetic route to prepare emodin anthrone as the key precursor of **2**, which will be reported in this communication.

Results and Discussion

Lithiation of the readily accessible amide **3** (in two steps from the commercially available *meta*-cresotinic acid) following a recently described [8] strategy for benzamide–*ortho*-metallation is observed to be strictly regioselective for position 6. This was proven by the nearly quantitative deuterium substitution of this position on treatment of the lithiation product of **3** with deuterium oxide. Reaction of the lithiation product of **3** with 3,5-dimethoxy-benzaldehyde and refluxing of the resulting crude carbinol **4** with *p*-toluenesulfonic acid in toluene afforded the lactone **5** in 94% overall yield. Upon hydrogenation of **5** using activated palladium on



charcoal as the catalyst the acid **6** was obtained in nearly quantitative yield. Cyclization of **6** by means of trifluoroacetic anhydride produced in good yield trimethyl emodin anthrone (**7**) which is exclusively present in solution as its 9-anthracenol tautomer. This was proven by the intensity and the chemical shift of its ^{1}H-NMR -H-10 signal, which are characteristic of *one aromatic* proton. The trifluoroacetyl derivative **8** could be isolated as a stable product of the acetylation of **7** by trifluoroacetic anhydride when the latter was used in a one molar excess. It was easily cleaved in high yield by hydrochloric acid in methanol to give **7**. As **8** is found also as a by-product, diminishing the yield of the desired product **7** even when equimolar amounts of trifluoroacetic anhydride are used, it seemed to be preferable to execute the sequence from **6** via **8** to **7** as a one-pot procedure using a one molar excess of the trifluoroacetic anhydride. Demethylation of **7** by means of hydroiodic acid in acetic acid (in analogy to the preparation of emodin anthrone from trimethyl emodin [9]) produced **1** in a 90% yield. Thus, a reaction sequence was generated which affords emodin anthrone (**1**) starting from readily accessible **3** in five steps – the overall yield of this synthesis was 74%.

Experimental Part

Melting points were taken by means of a Kofler hot stage microscope (Reichert, Vienna). ^{1}H-, ^{13}C-, IR-, UV-VIS-, and M-spectra were recorded using the Bruker-WM-360, and AC-200, Biorad-FT-IR-45, Hitachi-U-3210, and Finnigan-MAT-115 instruments. Tetrahydrofurane and benzene were dried by means of sodium benzophenone – their water contents were monitored by Karl Fischer titrations. *Sec*-butyl lithium solutions in *n*-pentane (Aldrich) were used after analysing their content by titration with *sec*-butanol in absol. benzene using 1,10-phenanthroline as the indicator.

N,N-Diethyl-2-methoxy-4-methylbenzamide (**3**; $C_{13}H_{19}NO_2$)

3 was prepared by methylation and amidation according to standard preparation methods of benzamides [10, 11] from 2-hydroxy-4-methyl-benzoic acid (Fulka) in 90% yield as white crystals of m.p. 58 – 61°C and b.p. 128°C/0.35 mm. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 7.06 (X-part of AMX-system, $J_{AX} = J_{MX} = 8$ Hz, aryl-H 6), 6.77 (M-part of AMX-system, $J_{AX} = J_{MX} = 8$ Hz, $J_{AM} = 2$ Hz, aryl-H 5), 6.71 (A-part of AMX-system, $J_{AM} = 2$ Hz, aryl-H 3), 3.80 (s, CH_3O), 3.55 (q, broadened, $J = 7$ Hz, CH_2CH_3), 3.14 (q, $J = 7$ Hz, CH_2CH_3), 2.36 (s, CH_3), 1.23 (t, $J = 7$ Hz, CH_2CH_3), 1.02 (t, $J = 7$ Hz, CH_2CH_3) ppm. IR (KBr): 1 620, 1 500 cm^{-1}.

N,N-Diethyl-2-methoxy-4-methyl-6-[(3,5-dimethoxyphenyl)-hydroxymethyl]-benzamide (**4**; $C_{22}H_{29}NO_5$)

4 was prepared by regioselective lithiation of **3** in analogy to Ref. [10] and reaction with 3,5-dimethoxybenzaldehyde (Merck). Into a thoroughly flamed three-necked reaction flask 36 ml absol. tetrahydrofurane was introduced under argon atmosphere and cooled to – 80°C. After introduction of 664 µl (4.4 mmol) of tetramethylethylenediamine, 3.14 ml of a 1.4 molar *sec*-butyl lithium solution in pentane was added and the mixture was stirred for 10 min. To this intensively yellow colored solution of the complex a solution of 884 mg (4 mmol) of **3** in 4 ml tetrahydrofurane was slowly added and the resultant mixture stirred for 20 min. After fast addition of a solution of 731 mg (4.4 mmol) 3,5-dimethoxy-benzaldehyde (Merck) in 4 ml absol. tetrahydrofurane still at – 80°C the reaction mixture was stirred for additional 20 min and afterwards quenched by addition of 2 ml water. The reaction mixture was acidified with 5% HCl, tetrahydrofurane evaporated in vacuo by means of a rotatory evaporator, and the resulting aqueous phase extracted three times with chloroform. Washings of the

chloroform phase with satd. NaCl solution, drying with Na_2SO_4, and evaporation of solvent resulted in 1 550 mg of the practically pure raw product (100% yield) which can be used immediately in the following step. A yield of 1 455 mg (94%) of white crystals was obtained on crystallization from toluene; m. p. 142–143°C. ^{1}H-NMR ($CDCl_3$, 360 MHz, δ): 6.90 and 6.67 (2 s, broadened, aryl-H 3, aryl-H 5), 6.52 (d, J=2.2 Hz, aryl-H 2′, aryl-H 6′), 6.29 (t, 1 H, aryl-H 4′), 5.57 (d, J=10 Hz, CH-OH), 5.21 (d, J=10 Hz, CH-OH), 3.76 (s, CH_3O), 3.74 (s, 2 CH_3O), 3.28–2.55 (m, broadened, J=7.15 Hz, CON(CH_2CH_3)$_2$), 2.38 (s, CH_3), 0.95 (t, J=7.15 Hz, CH_2CH_3), 0.85 (t, J=7.15 Hz, CH_2CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz, δ): 168.7 (s, CO*N*Et_2), 160.5 (s, 2 C, C 3′, C 5′), 155.9 (s, C 6), 146.5, 143.0, 140.5 (3 s, C 1, C 2, C 4, C 1′), 123.6, 111.0 (C 3, C 5), 104.0 (C 2′, C 6′), 98.9 (C 4′), 76.4 (CHOH), 55.3 (3 CH_3O), 43.0, 38.5 (2 CH_2CH_3), 21.7 (CH_3), 12.9, 12.4 (2 CH_2CH_3) ppm. The assignments were achieved using DEPT and ^{1}H–^{13}C-COSY experiments.

N,N-Diethyl-6-deutero-2-methoxy-4-methylbenzamide ($C_{13}H_{18}DNO_2$)

This compound was prepared according to the procedure described above to test for regioselective metallation by providing D_2O instead of the dimethoxybenzoic aldehyde as the electrophile. Yield 99% of white crystals of m. p. 60°C. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 6.77 (A-part of AM system, J_{AM}=2 Hz, aryl-H 5), 6.71 (M-part of AM system, J_{AM}=2 Hz, aryl-H 3), 3.80 (s, CH_3O), 3.55 (q, broadened, J=7 Hz, CH_2CH_3), 3.14 (q, J=7 Hz, CH_2CH_3), 2.36 (s, CH_3), 1.23 (t, J=7 Hz, CH_2CH_3), 1.02 (t, J=7 Hz, CH_2CH_3) ppm. MS (25°C, 70 eV): *m/e* (%)=222 (12, M^+), 220 (10), 151 (10), 150 (100), 92 (10).

5-Methyl-7-methoxy-3-(3,5-dimethoxyphenyl)-3 H-isobenzofuranone (**5**; $C_{18}H_{18}O_5$)

400 mg (1.03 mmol) crude **4** (as prepared above) and 30 mg *p*-toluenesulfonic acid were refluxed in 100 ml toluene (p. a.) for 2 h. The resulting solution was extracted twice with Na_2CO_3 (5% solution) followed by washings with water, HCl (5%) and satd. NaCl solution. After drying over Na_2SO_4 the organic layer was evaporated and the residue crystallized from toluene. Yield 306 mg (94% overall yield from amide **3**!) of white crystals of m. p. 160–161°C. ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 6.73 (s, aryl-H 4 or H 6), 6.68 (s, aryl-H 4 or H 6), 6.43 (s, aryl-H 2′, H 6′, H 4′), 6.16 (s, H 3), 4.0 (s, CH_3O), 2.76 (s, 2 CH_3O), 2.40 (s, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz, δ): 168.0 (CO), 161.2 (C 3′, C 5′), 158.2 (C 7), 152.7, 148.3, 139.2, 115.0 (C 1′, C 3 a, C 5, C 7 a), 111.9 (C 4, C 6), 104.5 (C 2′, C 6′), 100.8 (C 4′), 81.2 (C 3), 56.0 (2 CH_3O), 55.4 (CH_3O), 22.5 (CH_3) ppm. The assignments were achieved using a ^{1}H–^{13}C-COSY experiment. MS (90°C, 70 eV): *m/e* (%)=316 (2, M+2), 315 (21, M+1), 314 (100, M^+), 285 (4), 284 (19), 241 (5), 177 (7), 149 (26), 148 (6), 142 (5). IR (KBr): 1 750, 1 610, 1 590 cm^{-1}.

2-Methoxy-4-methyl-6-[(3,5-dimethoxyphenyl)-methyl]-benzoic Acid (**6**; $C_{18}H_{20}O_5$)

800 mg lactone **5** (2.545 mmol) were dissolved in 50 ml absolute tetrahydrofurane + 50 µl conc. H_2SO_4. After addition of 50 mg activated Pd/C (10%) the solution was agitated for 6 h under a hydrogen atmosphere of 5 bar at 45°C. The activation of Pd/C was achieved by treatment with 10% sulfuric acid for 5 min and washings with water, methanol and absol. tetrahydrofurane. The filtered solution was evaporated and crystallized from toluene. 774 mg white crystals of m. p. 260–262°C were obtained (96% yield). ^{1}H-NMR ($CDCl_3$, 200 MHz, δ): 10.12 (s, broadened, COOH), 6.63 (s, aryl-H 5), 6.61 (s, aryl-H 3), 6.38 (d, J=2.2 Hz, aryl-H 2′, H 6′), 6.29 (t, J=2.2 Hz, aryl-H 4′), 4.03 (s, CH_2), 3.85 (s, CH_3O), 2.72 (s, 2 CH_3O), 2.28 (s, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 50 MHz, δ): 172.1 (COOH), 160.6 (C 3′, C 5′), 157.0 (C 6), 142.6, 141.8, 140.7 (C 4, C 2, C 1′), 123.6 (C 3), 110.1 (C 5), 107.2 (C 2′, C 6′), 98.2 (C 4′), 56.0 (CH_3O), 55.1 (2 CH_3O), 39.3 (CH_2), 21.7 (CH_3) ppm. The assignments were achieved using ^{1}H–^{13}C-COSY and DEPT experiments. MS (70°C, 70 eV): *m/e* (%)=316 (100, M^+), 298 (12, M-H_2O), 283 (12), 149 (12), 99 (12), 97 (12), 85 (12), 83 (12), 77 (12), 73 (12), 71 (50), 69 (12), 60 (12), 59 (100), 57 (100), 55 (12). IR (KBr): 1 700, 1 600, 1 460 cm^{-1}.

1,3,8-Trimethoxy-6-methylanthracen-9-ol (**7**; $C_{18}H_{18}O_4$)

(a) 500 mg (1.27 mmol) of the trifluoroacetyl derivative **8** were dissolved in 600 ml methanol under an argon atmosphere. After addition of 20 µl concentrated HCl the mixture was agitated at 45°C for 2 h. The solution was neutralized by means of satd. aqueous sodium carbonate, filtered off and evaporated. Crystallization from methanol resulted in 344 mg (91%) **7**; yellow crystals, m. p. 161°C. ^{1}H-NMR ($CDCl_3$, 360 MHz, δ): 10.76 (s, 1 H, fast exchange upon addition of CD_3OD, OH), 7.48 (s, broadened, fast exchange upon addition of CD_3OD, H 10), 7.14 and 6.43 (2 s, broadened, H 5 and H 7), 6.65 and 6.35 (AX system, $J_{AX} = 2.0$ Hz, H 2 and H 4), 4.05, 4.03, 3.91 (3 s, 3 CH_3O), 2.44 (s, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 90 MHz, δ): 158.9, 157.7, 157.3, 153.4 (C 1, C 3, C 8, C 9), 135.8, 135.5 (C 4 a, C 10 a), 135.7 (C 6), 119.2 (C 7), 113.7 (C 5), 104.1 (C 4), 96.93, 96.90 (C 2, C 10), 109.4, 108.4 (C 9 a, C 8 a), 56.13, 56.08, 55.34 (3 CH_3O), 22.04 (CH_3) ppm. UV-VIS (ethanol): 372 (8 600), 265 (79 800), 231 (19 200) nm (ε). MS (90°C, 70 eV): *m/e* (%) = 300 (20.9), 299 (47.6), 298 (100, M^+), 283 (40), 255 (45), 240 (32), 225 (31), 197 (19), 149 (43). IR (KBr): 3 300, 1 620 cm^{-1}.

(b) 600 mg (1.896 mmol) benzoic acid **6** were dissolved in 70 ml absolute dichloromethane under an argon atmosphere. After addition of 528 µl trifluoroacetic anhydride (3.78 mmol) the mixture was agitated at room temperature for 6 h. Then the solvent was evaporated and procedure (a) as given above was followed to yield 514 mg **7** (91% yield of the one-pot synthesis of **7** from **6**).

10-Trifluoroacetyl-1,3,8-trimethoxy-6-methylanthracen-9-ol (**8**; $C_{20}H_{17}F_3O_4$)

Following procedure (b) of the synthesis of **7**, after evaporation of the solvent, the trifluoroacetic acid is removed at 0.01 torr at room temperature and the raw material is crystallized from absolute ethanol. From 600 mg acid **6** 710 mg **8** (95%) are obtained as orange crystals; m. p. 174 – 176°C. ^{1}H-NMR ($CDCl_3$, 360 MHz, δ): 11.27 (s, OH), 6.91 and 6.53 (2 s, broadened, H 5 and H 7), 6.38 and 6.37 (2 s, broadened, H 2 and H 4), 4.07 (s, CH_3O), 4.04 (s, CH_3O), 3.87 (s, CH_3O), 2.44 (s, CH_3) ppm. ^{13}C-NMR ($CDCl_3$, 90 MHz, δ, 5% chromium acetylacetonate as relaxation reagent): 191.1 (q, $J = 35.5$ Hz, $COCF_3$), 159.9, 159.6, 158.0. 157.9 (C 1, C 3, C 8, C 9), 139.2 (C 6), 134.1, 133.5 (C 4 a, C 10 a), 115.2 (C 7), 108.8, 107.6 (C 9 a, C 8 a), 104.9 (C 5), 97.4 (C 4), 93.5 (C 2), 96.8 (C 10), 56.4 (2 CH_3O), 55.2 (CH_3O), 22.5 (CH_3) ppm; the CF_3 quartet could not be localized. UV-VIS (ethanol): 437 (7 000), 323 (10 100), 265 (46 000), 223 (20 100) nm (ε). IR (KBr): 3 300, 1 620, 1 580 cm^{-1}. MS (90°C, 70 eV): *m/e* (%) = 396 (11), 395 (53), 394 (78, M^+), 326 (60), 325 (100, M-CF_3), 298 (58, M-$COCF_3$), 297 (53), 282 (54), 197 (41).

Emodin Anthrone (**1**; $C_{15}H_{12}O_4$)

200 mg **7** (0.67 mmol) were dissolved in 18 ml acetic acid and 8 ml HI (ρ = 1.50) and the mixture kept under reflux for 4 h. Upon cooling the product crystallized from the reaction mixture. It was rinsed with water and dried [9]. 154 mg of **1** were obtained (90%); m. p. 254 – 258°C (250 – 258°C [9]). ^{1}H-NMR (*DMSO-d_6*, 200 MHz, δ): 12.36 and 12.19 (2 s, OH 1 and OH 8), 10.82 (s, broadened, OH 3), 6.73 and 6.64 (2 s, broadened, H 5 and H 7), 6.37 and 6.20 (AM system, $J_{AM} = 2.2$ Hz, H 2 and H 4), 4.26 (s, CH_2), 2.29 (s, CH_3) ppm. ^{13}C-NMR (*DMSO-d_6*, 50 MHz, δ): 191.0 (s, C = O), 164.9, 164.5, 161.6 (3 s, C 1, C 3, C 8), 146.9, 144.8, 141.9 (3 s, C 4 a, C 6, C 10 a), 112.7, 108.3 (2 s, C 9 a, C 8 a), 119.8 (d, C 7), 115.1 (d, C 5), 107.3 (d, C 4), 100.9 (d, C 2), 32.2 (CH_2), 21.5 (CH_3) ppm. Assignments were achieved by means of a ^{1}H – ^{13}C-COSY experiment. IR (KBr): 1 620 cm^{-1}. UV (ethanol): 379 (18 300), 271 (15 300), 225 (26 200) nm(ε). MS (90°C, 70 eV): *m/e* (%) = 300 (21), 299 (48), 298 (100, M^+), 283 (40), 255 (45), 240 (32), 225 (31), 197 (19), 149 (43).

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