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A facile synthetic approach to the core structure of 6,7-didehydrocarnosoic acid type derivatives

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Abstract—In this paper we report on the development of a flexible and efficient synthetic approach towards 6,7-didehydrocarnosoic acid type analogues. The elaboration of the required *trans*-decalin system, the installation of the carboxylic acid in the angular position as well as the generation of the C_6–C_7 double bond to afford the 6,7-didehydrocarnosoic acid scaffold as it was found in **2** and **3** is described.

1. Introduction

6,7-Didehydrocarnosoic acid **1** is an abietane type diterpenoid which is discussed to play a key role in the biosynthesis of highly oxidized abietane type diterpenes.[1,2] In 1965 Wenkert and co-workers[1] expected **1** to be an essential intermediate in the formation of rosmaricine, an alkaloid which was allegedly isolated from *Rosmarinus officinalis* L. in 1962,[3] as well as further γ-lactone artifacts. To date the isolation of some 6,7-didehydrocarnosoic acid type natural compounds is described in the literature. In 1978, Saleh and co-workers[4] separated the carboxylic acid **2** form *Salvia lanigera* Poir. and González et al.[5] reported on the isolation of the methyl ester **3** form *Salvia canariensis* L. in 1987. Due to the evidence for **3** and further research work Luis and co-workers[2] postulated a biosynthetic pathway to highly oxidized abietane type diterpenoids like rosmanol, isorosmanol, epirosmanol and rosmadial in which the reaction of 6,7-didehydrocarnosoic acid with singlet oxygen would be essential. The synthesis of the analogues **4a** and **4b** was published by Jones and co-workers[6] in 1994 using a Diels–Alder reaction as the key step. As part of our research project to study synthetic strategies towards carnosol type derivatives[7] we developed a flexible and efficient synthetic route to the core structure of 6,7-didehydrocarnosoic acid type derivatives. This strategy is supposed to give us access to a wide range of analogues to **1** as well as to further abietane type compounds with interesting biological properties. Applying a synthetic route to amide **10** derivatives reported by Yardley and Rees[8] in 1985 as a key strategic element to install the required *trans*-decalin scaffold with a carboxylic acid functionality in the angular position we wish to describe the synthesis of the simplified carboxylic acid **5** as a model compound in this paper (Fig. 1).

2. Results and discussion

According to our previously reported retrosynthetic considerations[7] we started our synthesis with the reaction of the α,β-unsaturated methyl ester **6** with the 3,5-dimethoxy phenyl acetonitrile **7** in the presence of sodium hydride in THF (Scheme 1). In a Michael addition combined with a S_N-reaction the nitrile methyl ester **8** was formed in 78% yield. Additional saponification of the methyl ester function provided the corresponding carboxylic acid **9** in 89% yield. To elaborate the ketonitrile **11** with the *trans*-decalin structure and the nitrile functionality in the angular position, two synthetic pathways were to be pursued. Once the amide **10** was synthesized by treating the nitrile carboxylic acid **9**

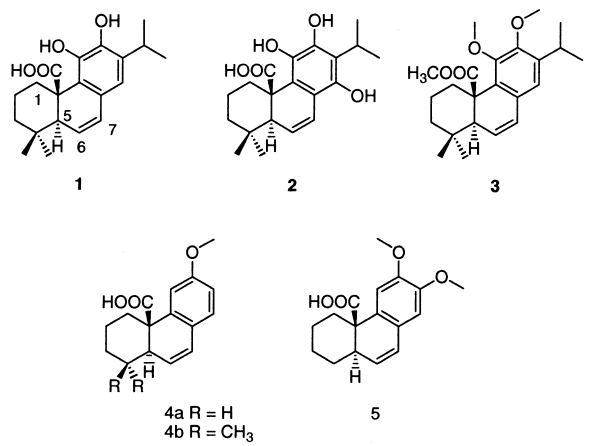

Figure 1.

Keywords: 6,7-didehydrocarnosoic acid; natural product; diterpene; synthesis; analogues.

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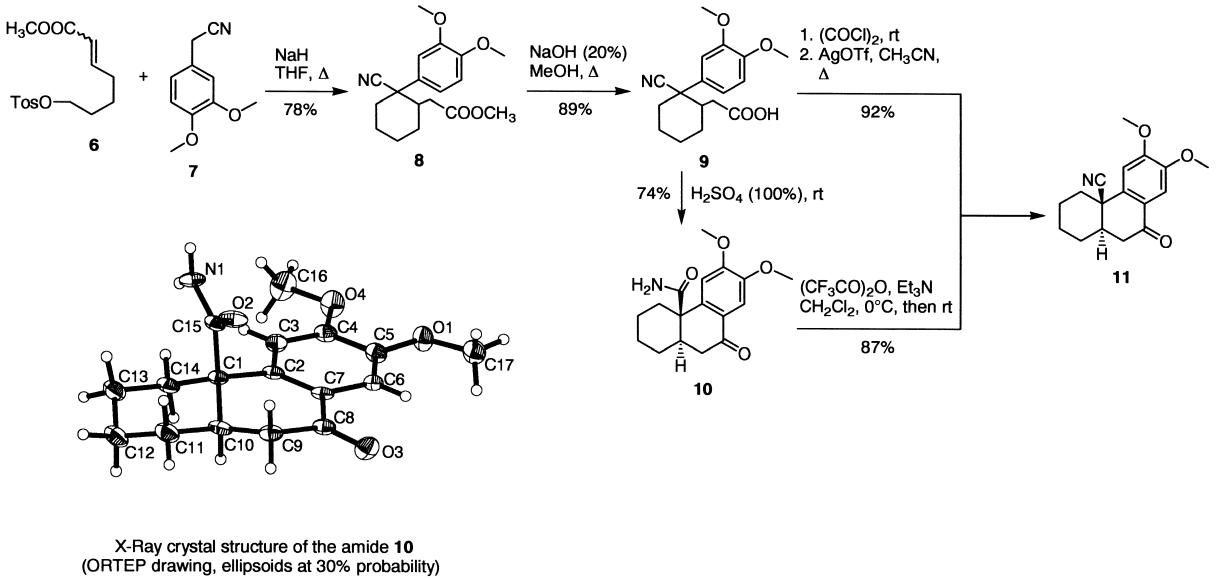
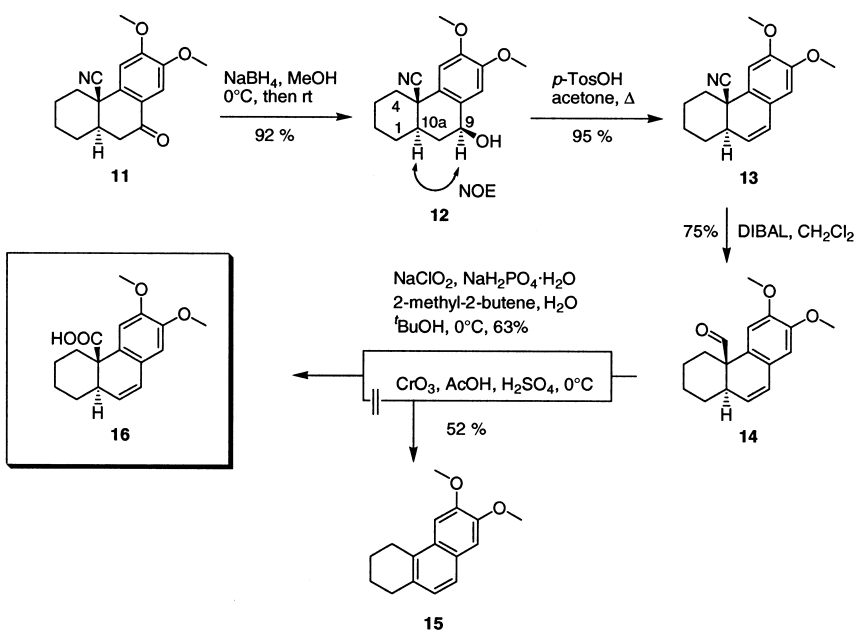


X-Ray crystal structure of the amide **10**
(ORTEP drawing, ellipsoids at 30% probability)

Scheme 1.

with concentrated sulfuric acid first. The installation of the required *trans*-decalin structure in **10** was confirmed by X-ray crystallographic analysis (Scheme 1). Subsequent dehydration of the amide group with TFAA[9] gave the desired ketonitrile **11** in 64% yield in two steps. Alternatively, we employed a method described by Effenberger et al.[10] Thus, the carboxylic acid function in **9** was transformed into the corresponding acid chloride first and subsequently refluxed in acetonitrile in the presence of silver trifluoromethanesulphonic acid, so that the ketonitrile **11** was obtained in 92% yield in only one step. Reduction of the carbonyl functionality in **11** with $NaBH_4$ in methanol[11] led to the hydroxy nitrile **12** in 92% yield (Scheme 2). As the β-oriented nitrile function prevents a reduction from the upper side of the molecule, the β-directed benzylic alcohol was formed only. The resulting three-dimensional structure of **12** was determined from the NOESY correlation between the benzylic proton at C_9 and the bridgehead proton at C_{10a} as well as by X-ray crystallographic analysis (Fig. 2). Elimination of water by refluxing **12** in acetone in the presence of *p*-TosOH[12] provided the nitrile **13** with the required C_6–C_7 double bond in 95% yield. The generation of the corresponding aldehyde **14** was achieved in 75% yield by the treatment of the nitrile function in **13** with DIBAL[13] in dichloromethane at low temperatures. We tried to oxidize the aldehyde **14** to the desired carboxylic acid **16** using the Jones oxidation[14] or the PDC method.[15] Despite several attempts the acid **16** could not be isolated. Either the starting material was recovered unchanged or decarboxylation to **15** occurred. In the case of the Jones oxidation **15** was



Scheme 2.

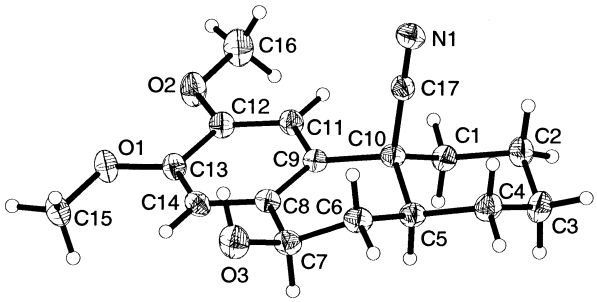


Figure 2. X-Ray crystal structure of the hydroxy nitrile **12** (ORTEP drawing, ellipsoids at 30% probability).

separated in 52% yield. Applying the PDC method 23% of **15** were afforded. Finally, the oxidation of the aldehyde **14** to the desired carboxylic acid **16** was performed using the Lindgren protocol.[16] Thus **14** was treated with $NaClO_2$ in the presence of 2-methyl-2-butene so that **16** was accomplished in 63% yield and from **7** in 29% overall-yield in seven steps.

3. Conclusions

In summary, we developed an appropriate and concise synthetic route to the model compound **5**. The synthesis of **5** was accomplished in 29% overall-yield in seven steps and features the construction of the required *trans*-decalin system, the installation of the carboxylic acid functionality in the angular position as well as the formation of the C_6–C_7 double bond. Our strategy is efficient, flexible and should enable us to synthesize various 6,7-didehydrocarnosoic acid type derivatives.

4. Experimental

4.1. General information

Melting points were obtained on a Büchi apparatus (Dr Tottoli) and are uncorrected. Infrared spectra were measured on a Beckmann Acculab 8 and a Bio-Rad Excalibur FTS 3000 spectrometer (FT-IR). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as the internal standard. Mass spectra and accurate mass data were obtained on either a Finnigan MAT 90 (CI, 120 eV, methane) or a Varian MAT 311 (EI, 70 eV) instrument. X-Ray diffraction analyses were carried out by Dr Volker Huch at the Department of Inorganic Chemistry at Saarland University with a STOE (Image Plate (IPDS)) Area Detector Diffractometer apparatus. Elemental microanalyses were performed with a Leco CHNS-932. All reactions were monitored by thin layer chromatography (TLC) using 0.2 mm silica gel (Merck Kieselgel 60 F_{254}) precoated aluminium roll. Column chromatography was performed on J. T. Baker silica gel (particle size 63–260 μm). All solvents were purified and dried by standard techniques or used as supplied from commercial sources as appropriate. Reactions in dry solvents were carried out under an atmosphere of nitrogen.

The α,β-unsaturated methyl ester **6** was prepared according to the procedure described in Ref. 7.

4.1.1. Methyl [2-cyano-2-(3,4-dimethoxyphenyl)cyclohexyl]-acetate (8). A solution of the 3,4-dimethoxy phenyl acetonitrile **7** (9.12 g, 51.4 mmol) in dry THF (110 ml) was added dropwise to a suspension of sodium hydride (60% in mineral oil; 2.21 g, 55.3 mmol) in dry THF (120 ml) at rt. The reaction mixture was stirred at rt for further 1.5 h. Subsequently, a solution of the α,β-unsaturated methyl ester **6** (15.0 g, 48.1 mmol) in dry THF (110 ml) was added dropwise at rt and the reaction mixture was refluxed for additional 48 h. After being cooled to rt, acetic acid (7.60 ml) was added. The solvent was evaporated to small volume, the residue was diluted with water (300 ml) and extracted with diethyl ether (4×100 ml). The organic layers were combined, washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (silica gel, diethyl ether/petroleum ether 7:3) to yield 11.9 g (78%) of **8** as a colourless oil. IR (film) 2985, 2930, 2845, 2220, 1770, 1625, 1545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, J_1=8.4 Hz, J_2=2.2 Hz, 1H), 6.99 (d, J=1.8 Hz, 1H), 6.87 (d, J=8.8 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.57 (s, 3H), 2.46–2.37 (m, 1H), 2.22–2.15 (m, 2H), 2.13–2.04 (m, 1H), 2.01–1.92 (m, 1H), 1.91–1.75 (m, 4H), 1.60–1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.57, 149.30, 148.77, 131.65, 120.60, 118.34, 111.53, 109.35, 56.06, 55.97, 51.59, 49.86, 41.87, 39.95, 37.06, 29.81, 25.26, 23.70; MS (EI) *m/z* (%) 318 (M^++1, 15), 317 (M^+, 65), 286 (16), 285 (39), 214 (14), 190 (17), 189 (100), 177 (27), 176 (18), 41 (25).

4.1.2. [2-Cyano-2-(3,4-dimethoxyphenyl)cyclohexyl]acetic acid (9). A solution of the nitrile methyl ester **8** (11.8 g, 37.2 mmol) in methanol (135 ml) was refluxed with a 20% aqueous NaOH solution (37 ml) for 3 h. The reaction mixture was cooled to rt and the methanol was distilled off to small volume. The residue was diluted with water (250 ml) and extracted with diethyl ether (2×90 ml). The ethereal extracts were discarded. Subsequently, the aqueous solution was acidified to pH 1 by the dropwise addition of 37% HCl and the resulting acidic suspension was extracted with diethyl ether (4×100 ml). The combined organic extracts were washed with brine and dried over $MgSO_4$. Finally, the solvent was evaporated to give 10.1 g (89%) of **9** as a colourless solid. An analytical sample was obtained by recrystallization from water/ethanol. Mp 131–133°C. IR (KBr) 3070, 2940, 2860, 2235, 1710, 1590, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, J_1=8.4 Hz, J_2=2.2 Hz, 1H), 6.97 (d, J=1.8 Hz, 1H), 6.86 (d, J=8.4 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 2.41–2.34 (m, 1H), 2.30–2.17 (m, 2H), 2.13–1.97 (m, 2H), 1.92–1.76 (m, 4H), 1.61–1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.03, 149.36, 148.87, 131.48, 120.47, 118.37, 111.63, 109.38, 56.06, 55.95, 49.77, 41.76, 39.89, 37.03, 29.73, 25.25, 23.66; MS (EI) *m/z* (%) 304 (M^++1, 36), 303 (M^+, 100), 285 (25), 214 (17), 202 (16), 196 (25), 189 (57), 176 (23), 166 (16), 151 (41), 149 (15), 83 (15), 81 (18), 73 (19), 71 (21), 69 (32), 60 (18), 59 (15), 57 (31), 55 (27). Anal. calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found C, 67.24; H, 6.95; N, 4.56.

4.1.3. 6,7-Dimethoxy-9-oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrene-carboxylic acid amide (10). The nitrile carboxylic acid **9** (5.00 g, 16.5 mmol) was stirred with concentrated sulfuric acid (160 ml) at rt for 24 h. The reaction mixture was poured onto ice and the resulting crystalline solid was filtered off, dried in vacuo over $CaCl_2$

and purified by column chromatography (silica gel, ethyl acetate) to give 3.69 g (74%) of **10** as a colourless solid. Mp 232–233°C. IR (KBr) 3430, 3300, 3195, 3015, 2935, 2915, 2860, 1655, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 6.94 (s, 1H), 5.62 (s_b, 1H, NH_2), 5.14 (s_b, 1H, NH_2), 3.98 (s, 3H), 3.93 (s, 3H), 2.96 (dd, J_1=18.6 Hz, J_2=13.7 Hz, 1H), 2.67–2.62 (m, 1H), 2.52 (dd, J_1=18.6 Hz, J_2=4.0 Hz, 1H), 2.26–1.98 (m, 3H), 1.93–1.76 (m, 2H), 1.72–1.63 (m, 1H), 1.55–1.48 (m, 1H), 1.43–1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.84, 175.52, 153.80, 148.74, 142.11, 126.38, 109.96, 106.95, 56.24, 56.11, 48.59, 43.63, 42.68, 35.49, 28.56, 25.58, 22.65; MS (EI) *m/z* (%) 304 (M^++1, 14), 303 (M^+, 64), 260 (60), 259 (100), 231 (30), 217 (42), 191 (70), 189 (18), 151 (18), 115 (17), 77 (14), 44 (24). Anal. calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found C, 67.43; H, 6.92; N, 4.66.

4.1.4. 6,7-Dimethoxy-9-oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrene-carbonitrile (11). *Method A*. To a suspension of the amide **10** (3.50 g, 11.5 mmol) and dry Et_3N (3.22 ml, 23.1 mmol) in dry CH_2Cl_2 (70 ml) were added dropwise TFAA (1.93 ml, 13.9 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1.5 h and at rt for further 4 h. Subsequently, a 10% Na_2CO_3 solution (85 ml) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 ml). The organic extracts were combined and dried over $MgSO_4$. Finally, the solvent was removed and the residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:1) to afford 2.86 g (87%) of **11** as a colourless solid.

Method B. The nitrile carboxylic acid **9** (2.00 g, 6.59 mmol) was stirred with oxalyl chloride (11.5 ml, 132 mmol) at rt for 24 h. The excessive oxalyl chloride was removed in vacuo. The formed acid chloride was dissolved in dry acetonitrile (72 ml), silver trifluoromethanesulfonic acid (1.17 g, 5.30 mmol) was added and the reaction mixture was heated to reflux for 24 h. Subsequently, the solvent was distilled off to small volume, the residue was taken up in water (140 ml) and extracted with CH_2Cl_2 (3×50 ml). The combined organic extracts were dried over $MgSO_4$, concentrated and the residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:1) to give 1.73 g (92%) of **11** as a colourless solid. Mp 154–156°C. IR (KBr) 3095, 3000, 2935, 2865, 2835, 2225, 1665, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.94 (s, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 2.83–2.71 (m, 2H), 2.63 (dd, J_1=17.7 Hz, J_2=3.5 Hz, 1H), 2.17–2.06 (m, 1H), 2.05–1.83 (m, 3H), 1.82–1.58 (m, 3H), 1.46–1.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.19, 154.16, 149.45, 136.17, 125.63, 119.87, 109.51, 106.88, 56.24, 56.14, 42.80, 42.13, 34.66, 29.86, 24.83, 23.21; MS (EI) *m/z* (%) 286 (M^++1, 22), 285 (M^+, 100), 242 (18), 216 (46), 189 (17), 137 (31), 91 (21), 79 (15), 55 (14), 45 (20), 43 (20). Anal. calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found C, 71.68; H, 7.00; N, 4.84.

4.1.5. 9-Hydroxy-6,7-dimethoxy-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrene-carbonitrile (12). A solution of the nitrile **11** (2.80 g, 9.81 mmol) in methanol (75 ml) was cooled to 0°C and $NaBH_4$ (1.48 g, 39.3 mmol) was added portionwise at this temperature. The reaction mixture was stirred at 0°C for further 15 min and at rt for another 3 h. Subsequently, water (30 ml) was added, most of the methanol was evaporated and the residue was extracted with diethyl ether (3×15 ml). The ethereal extracts were combined, washed with brine and dried over $MgSO_4$. The solvent was evaporated and the obtained colourless solid was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:1) to yield 2.58 g (92%) of **12** as a colourless solid. Mp 155–156°C. IR (KBr) 3520, 3020, 2940, 2865, 2225, 1605, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.82 (s, 1H), 4.73 (dd, J_1=10.6 Hz, J_2=6.2 Hz, 1H), 3.87 (s, 6H), 2.67–2.60 (m, 1H), 2.21 (s_b, 1H, OH), 2.11 (dd, J_1=12.8 Hz, J_2=6.6 Hz, 1H), 1.96–1.86 (m, 4H), 1.74–1.58 (m, 3H), 1.51–1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.36, 148.86, 132.69, 127.77, 121.79, 110.36, 107.88, 68.84, 56.06, 55.94, 43.35, 41.77, 38.39, 35.63, 30.01, 25.19, 23.41; MS (EI) *m/z* (%) 288 (M^++1, 20), 287 (M^+, 100), 286 (20), 180 (84). Anal. calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found C, 71.23; H, 7.29; N, 4.93.

4.1.6. 6,7-Dimethoxy-*trans*-1,3,4,10a-tetrahydro-4a(2*H*)-phenanthrenecarbonitrile (13). A solution of the hydroxy nitrile **12** (1.00 g, 3.48 mmol) and a catalytic amount of *p*-TosOH (20 mg) in acetone (95 ml) were refluxed for 24 h. After being cooled to rt, most of the solvent was evaporated and the residue was taken up in water (50 ml). Subsequently, the aqueous layer was extracted with ethyl acetate (3×20 ml). The organic extracts were combined, washed with saturated $NaHCO_3$ solution, brine and dried over $MgSO_4$. Finally, the solvent was evaporated and the residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:2) to give 891 mg (95%) of **13** as a colourless solid. Mp 146–147°C. IR (KBr) 3020, 2930, 2855, 2225, 1605, 1570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.71 (s, 1H), 6.53 (dd, J_1=9.5 Hz, J_2=2.5 Hz, 1H), 5.71 (dd, J_1=9.5 Hz, J_2=2.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.70–2.62 (m, 1H), 2.31–2.22 (m, 1H), 2.01–1.66 (m, 6H), 1.45–1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.12, 148.65, 130.21, 127.59, 127.35, 126.83, 121.21, 110.80, 107.56, 56.26, 56.06, 42.28, 41.70, 32.72, 28.84, 25.35, 23.12; MS (EI) *m/z* (%) 270 (M^++1, 24), 269 (M^+, 100), 227 (21), 226 (72), 86 (22), 84 (34), 43 (18); Anal. calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found C, 75.97; H, 6.99; N, 5.11.

4.1.7. 6,7-Dimethoxy-*trans*-1,3,4,10a-tetrahydro-4a(2*H*)-phenanthrenecarbaldehyde (14). To a solution of the nitrile **13** (850 mg, 3.16 mmol) in dry toluene (42 ml) was added dropwise DIBAL (1.5 M in toluene; 2.31 ml, 3.47 mmol) at −78°C. It was stirred at this temperature for one additional hour. The reaction mixture was allowed to warm to −10°C. After being stirred at −10°C for 1 h, the mixture was cooled to −78°C again, ethyl acetate (1 ml) was added and the mixture was allowed to warm to rt. Subsequently, the mixture was poured into water (80 ml) and a saturated K–Na tartrate solution was added until the formed precipitate was completely dissolved. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×40 ml). The organic extracts were combined, washed with brine, dried over Na_2SO_4 and the solvent was evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:2) to yield 643 mg (75%) of **14** as a colourless solid. Mp 102–103°C. IR (KBr) 2990, 2905, 2830, 2705, 1740, 1600,

1540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 6.78 (s, 1H), 6.64 (s, 1H), 6.32 (dd, J_1=9.7 Hz, J_2=3.1 Hz, 1H), 5.76 (dd, J_1=9.7 Hz, J_2=2.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.70–2.56 (m, 2H), 1.88–1.63 (m, 4H), 1.51–1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.71, 148.87, 148.75, 131.32, 128.78, 127.52, 126.60, 110.49, 108.83, 56.16, 55.98, 52.66, 41.03, 29.52, 28.77, 26.13, 22.97; MS (EI) *m/z* (%) 272 (M^+, 23), 244 (54), 243 (100), 228 (25), 212 (27), 201 (67), 171 (15), 157 (23), 141 (22), 139 (14), 129 (17), 128 (34), 127 (17), 115 (33). Anal. calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found C, 74.89; H, 7.31.

4.1.8. 6,7-Dimethoxy-1,2,3,4-tetrahydrophenanthrene (15). To a solution of the aldehyde **14** (130 mg, 0.48 mmol) in acetone (3 ml) were added dropwise a solution of CrO_3 (71.7 mg, 0.72 mmol) and concentrated sulfuric acid (0.11 ml) in water (2.15 ml) at 0°C. After being stirred at this temperature for 1 h, the mixture was stirred at rt for one additional hour. Water (20 ml) and 2-propanol (3 ml) were added. After extraction with diethyl ether (3×10 ml) the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was distilled off and the residue was chromatographed on silica gel (ethyl acetate/cyclohexane 1:2) to afford 60.1 mg (52%) of **15** as a colourless solid. Mp 146–147°C. IR (KBr) 3000, 2920, 2835, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J=8.3 Hz, 1H), 7.17 (s, 1H), 7.07–7.03 (m, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.04–2.98 (m, 2H), 2.90–2.84 (m, 2H), 1.99–1.90 (m, 2H), 1.89–1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.29, 148.48, 132.72, 130.17, 128.04, 127.61, 126.55, 124.16, 107.19, 102.19, 55.75, 30.35, 26.01, 23.41, 23.08; MS (EI) *m/z* (%) 243 (M^++1, 16), 242 (M^+, 100), 214 (21), 211 (19), 65 (27).

4.1.9. 6,7-Dimethoxy-*trans*-1,3,4,10a-tetrahydro-4a(2*H*)-phenanthrenecarboxylic acid (16). To a mixture of the aldehyde **14** (600 mg, 2.20 mmol), $NaH_2PO_4 \cdot H_2O$ (304 mg, 2.20 mmol), 2-methyl-2-butene (4.66 ml, 44.1 mmol), water (7 ml) and ^{t}BuOH (23 ml) was added portionwise $NaClO_2$ (678 mg, 7.49 mmol) at 0°C. After being stirred at 0°C for further 2 h, water (50 ml) was added and it was extracted with diethyl ether (3×30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:1) to give 399 mg (63%) of **16** as a colourless solid. 114 mg (18%) of 6,7-Dimethoxy-1,2,3,4-tetrahydrophenanthrene **15** were isolated as by-product (colourless solid). Mp 94–96°C. IR (KBr) 2910, 2845, 2635, 2585, 1720, 1635, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.58 (s, 1H), 6.27 (dd, J_1=9.3 Hz, J_2=3.1 Hz, 1H), 5.75 (dd, J_1=9.3 Hz, J_2=2.2 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 2.81–2.73 (m, 1H), 2.50–2.42 (m, 1H), 2.13–2.00 (m, 1H), 1.87–1.71 (m, 3H), 1.64–1.53 (m, 1H), 1.51–1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.68, 148.42, 148.22, 133.03, 130.11, 127.87, 125.15, 110.05, 109.50, 56.19, 55.94, 49.33, 42.05, 34.51, 28.22, 26.03, 23.64; MS (CI) *m/z* (%) 289 (M^++1, 15), 288 (M^+, 42), 276 (18), 258 (34), 244 (19), 243 (59), 242 (100), 211 (15). Anal. calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found C, 70.96; H, 7.06.

The spectroscopic data of 6,7-dimethoxy-1,2,3,4-tetrahydrophenanthrene **15** were completely identical with those described for compound **15** in Section 4.1.8.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 209214 for **10** and CCDC 209215 for **12**. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44-(0)-1223336033 or e-mail: deposit@ccdc.cam.ac.uk).

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