Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 3297–3305

TETRAHEDRON

The synthesis of carnosol derivatives

Andreas Luxenburger*

Institut für Organische Chemie, Universität des Saarlandes, Im Stadtwald, P.O. Box 151150, D-66041 Saarbrücken, Germany

Received 14 January 2003; accepted 13 March 2003

Abstract—In this paper we report on the development of an efficient and flexible synthetic strategy towards the synthesis of carnosol type derivatives. The strategy involves the construction of the required *trans*-decalin structure with a carboxylic functionality in the angular position as well as the elaboration of the lactone ring to afford the tetracyclic core structure of the natural compound **1**.

1. Introduction

Carnosol **1** (Fig. 1.) is an abietane type diterpene lactone which exhibits a variety of biological activities. Apart from antiseptic and anti-inflammatory[1] effects it shows strong antioxidant[2] as well as anticarcinogenic properties.[3] In 1942 White and Jenkins isolated carnosol from *Salvia carnosa* for the first time.[4] In an independent research work Brieskorn and Fuchs separated another bitter tasting compound named pricrosalvin[5] from *Salvia officinalis*, *Salvia triloba* and *Rosmarinus officinalis* 20 years later. Comparing the physical and chemical properties both compounds proved to be identical.[6] In 1971 Meyer and co-workers[7] reported on the first total synthesis of the carnosol dimethyl ether. The exact structure was confirmed by the X-ray crystallographic analysis in 1990.[8]

Due to the biological activities and the unique tetracyclic core structure our interest arose in developing a general and concise methodology making a wide variety of carnosol type analogues readily available. Such a strategy should provide first the lactone **2a** as a model compound and should then be applied to the synthesis of further derivatives. To establish the tetracyclic core structure the installation of the required *trans*-fused decalin system as well as a carboxylic functionality in the angular position would be a key task. A first approach towards the model compound **2a** was attempted by Jones et al.[9] in 1996 using a Diels–Alder reaction as a key step. As a result of their strategy the desired *trans*-lactone **2a** could only be isolated as a by-product while the *cis*-configurated isomer was obtained as the main product. In 1985 Yardley and Rees[10] described a synthetic sequence in which the amide **7b** with the required *trans*-decalin structure was generated and that was used in the synthesis towards the D-normorphinan **3**. Applying this sequence as a key strategic element, we wish to report herein a concise and efficient approach to the model compound **2a** as well as to the methoxy substituted derivative **2b**.

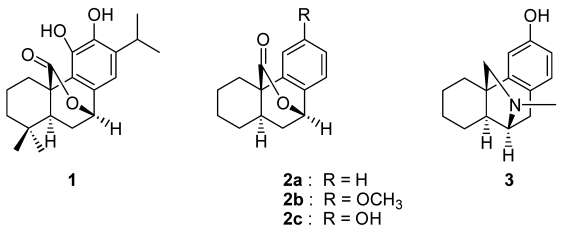


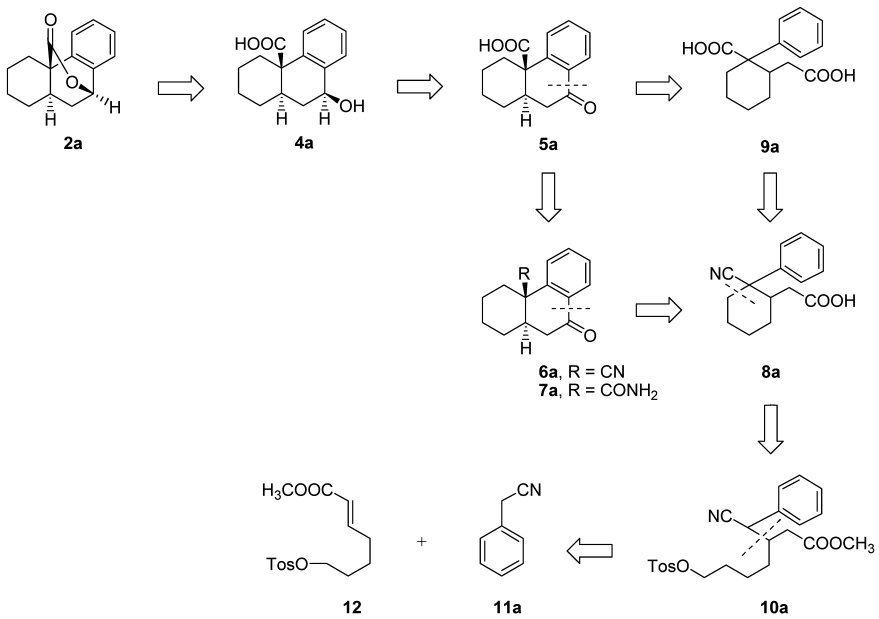
Figure 1.

The retrosynthetic analysis for the lactone **2a** is outlined in Scheme 1. Initial opening of the lactone bridge provided the hydroxy carboxylic acid **4a** which was oxidised to the corresponding ketocarboxylic acid **5a**. At this point two possible retrosynthetic strategies were to be discussed. Once, the carboxylic acid function in **5a** has to be generated either by hydrolysis of a corresponding amide or a nitrile group. Subsequent disconnection in the resulting ketonitrile **6a** in the sense of a retro-Friedel–Craft's acylation provided the nitrile carboxylic acid **8a**. To perform the second retrosynthetic pathway a bond disconnection in **5a** would lead to the dicarboxylic acid **9a** which can be readily obtained from the nitrile carboxylic acid **8a**. Further retrosynthetic steps required the conversion of the carboxylic acid function in **8a** into the corresponding methyl ester. Retro-S_N-reaction and subsequent retro-Michael addition led to the α,β-unsaturated methyl ester **12** as well as the commercially available phenyl acetonitrile **11a** as starting materials.

Keywords: carnosol; natural product; diterpene; lactone; synthesis; analogues.

* Address: Institut für Pharmazie, Johannes Gutenberg-Universität, Staudinger Weg 5, D-55099 Mainz, Germany. Tel.: +49-61313925728; fax: +49-61313923062; e-mail: luxenburger@freenet.de

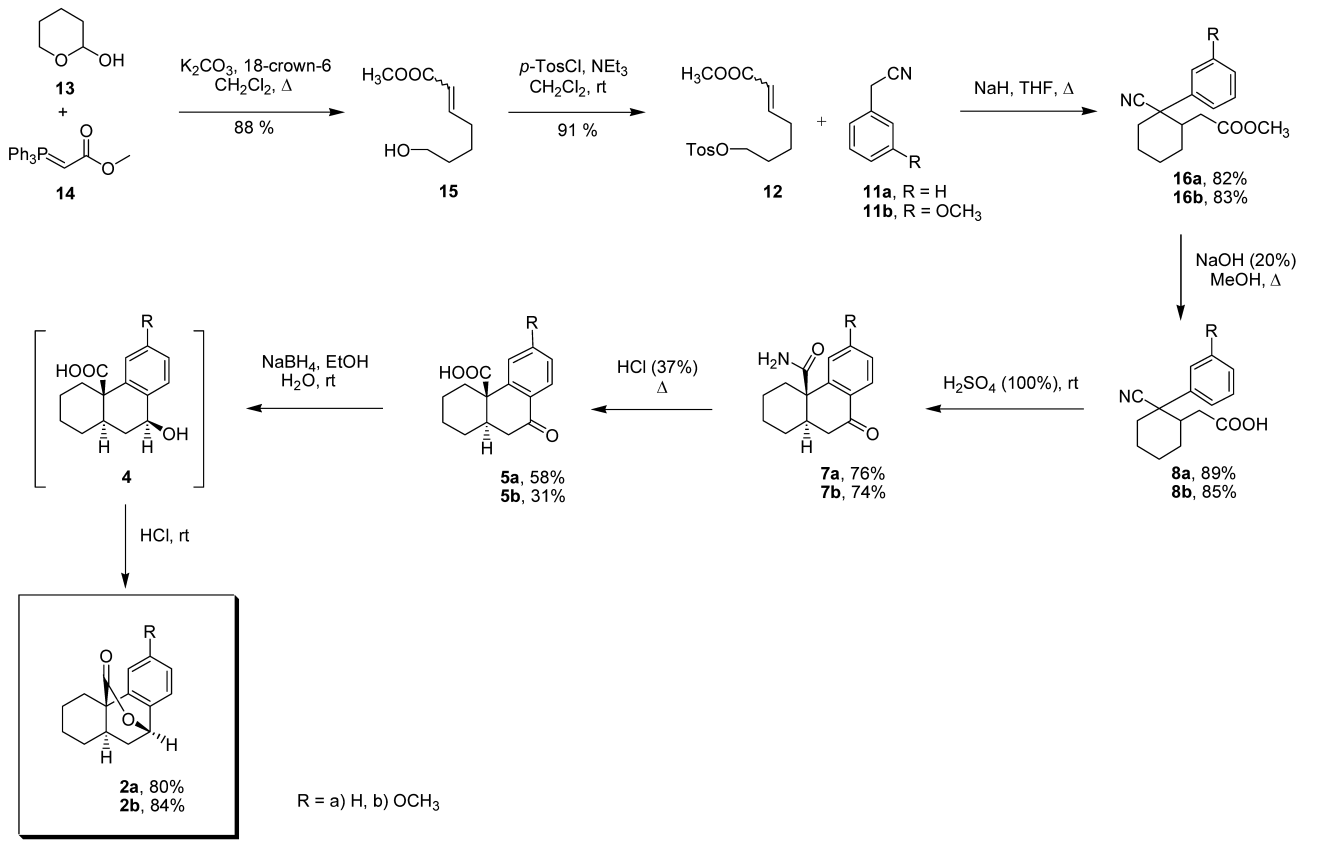
0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00412-5



Scheme 1.

2. Results and discussion

We started our first approach towards the lactone **2a** with the preparation of the α,β-unsaturated methyl ester **12**[10] (Scheme 2). In a first step methyl (triphenylphosphoranylidene)acetate **14**[11] was reacted with 2-hydroxy-tetrahydropyrane **13**[12] in a Wittig-reaction according to Boden's protocol[13] to afford the hydroxy methyl ester **15** in 88% yield as *E*/*Z*-mixture of isomeres. Additional tosylation with *p*-toluenesulphochloride in the presence of triethylamine and DMAP[15] gave the α,β-unsaturated methyl ester **12** in 91% yield. Subsequent Michael addition combined with a simultaneously occurring S_N-reaction of **12** with phenylacetonitrile **11a** in THF in the presence of sodium hydride afforded the nitrile methyl ester **16** in 82% yield. Saponification of the methyl ester group led to the



Scheme 2.

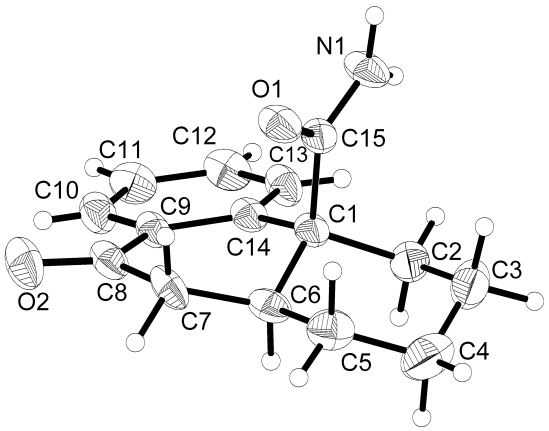


Figure 2. X-Ray crystal structure of amide **7a** (ORTEP drawing, ellipsoids at 30% probability).

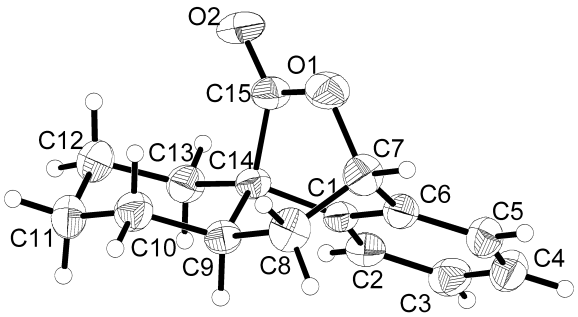
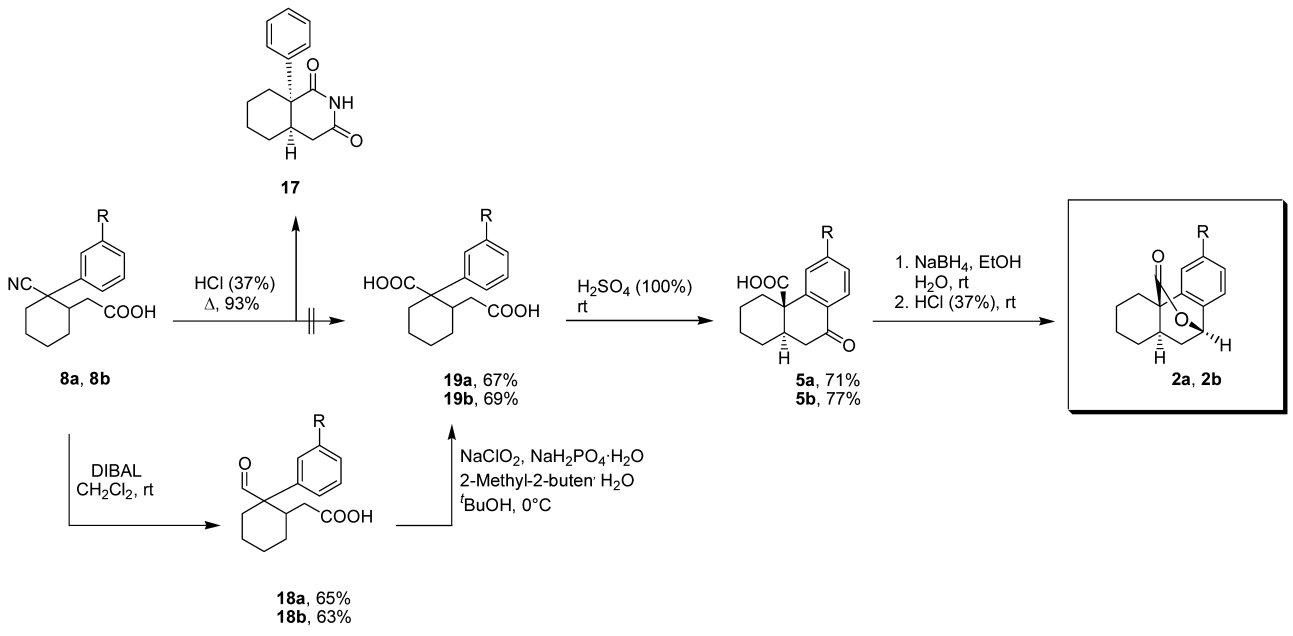


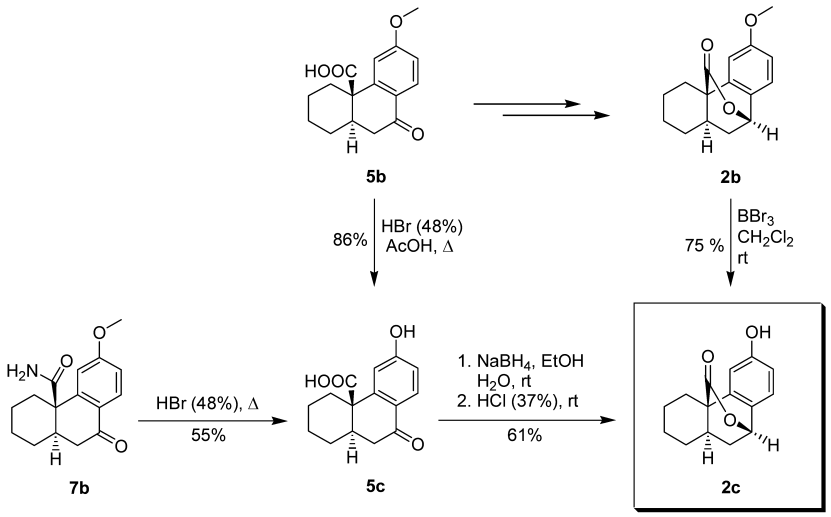
Figure 3. X-Ray crystal structure of lactone **2a** (ORTEP drawing, ellipsoids at 30%).

corresponding carboxylic acid **8a** in 89% yield. Further treatment of **8a** with concentrated sulphuric acid at room temperature provided the desired ketoamide **7a**.[10] The assignment of the required *trans*-decalin system was confirmed by single-crystal X-ray crystallographic analysis (Fig. 2.). Acidic hydrolysis of the amide **7a** gave the corresponding carboxylic acid **5a** in 58% yield. Subsequent reduction of the carbonyl group with $NaBH_4$ resulted in the hydroxy carboxylic acid **4a** as an intermediate which was not isolated. Due to the β-direction of the angular carboxylic acid the hydride can only attack the carbonyl function from the α-side elaborating the necessary β-oriented benzylic alcohol in **4a**. Finally, the hydroxy carboxylic acid **4a** was stirred with hydrochloric acid at room temperature so that the desired lactone **2a** was accomplished in 80% from **11a** and in an overall-yield of 26% for six steps. The three-dimensional structure of the lactone **2a** was determined by single-crystal X-ray crystallographic analysis (Fig. 3.). Applying the same sequence, the methoxy substituted lactone **2b** was obtained in an overall-yield of 14% as well.

To elaborate the second synthetic pathway (Scheme 3) we envisaged the direct conversion of the nitrile function in **8a** into the carboxylic acid group of the dicarboxylic acid **19a**. First we attempted the hydrolysis of the nitrile group by refluxing **8a** in concentrated hydrochloric acid. As a result only the imide **17** could be isolated in a very good yield of 93%. As the acid mediated hydrolysis did not lead to the desired dicarboxylic acid **19a** we alternatively tried to generate the carboxylic function using potassium hydroxide. Despite several attempts **19a** could not be isolated. Either the starting material was recovered unchanged or decomposition occurred at the elevated temperatures employed. Due to these results we decided to use an additional reaction step. Thus, the nitrile carboxylic acid was reduced to the corresponding aldehyde acid **18a** by treatment with DIBAL in dichloromethane.[16] Subsequent Lindgren oxidation[17] with $NaClO_2$ in the presence of 2-methyl-2-butene provided the desired dicarboxylic acid **19a** in a yield of 44% in two steps. Cyclisation of **19a** by treatment with concentrated sulphuric acid led to the



Scheme 3.



Scheme 4.

ketocarboxylic acid **5a** with the required *trans*-decalin system. Further reduction of the carbonyl group using $NaBH_4$ and final reaction with hydrochloric acid provided the desired lactone **2a** for seven steps in 18% overall-yield. According to this second synthetic strategy the methoxy substituted lactone **2b** too was synthesised in an overall-yield of 20%.

As the biological properties of carnosol **1** depend also on its two free phenolic hydroxy groups we investigated strategies to synthesise the lactone **2c** with one free phenolic hydroxy function. Therefore, we persued two synthetic pathways (Scheme 4): Once we started from the amide **7b** which was hydrolysed with simultaneously cleavage of the methyl ether resulting in formation of the hydroxy carboxylic acid **5c** in a yield of 55%. Further reduction of the carbonyl function by $NaBH_4$ led to the corresponding dihydroxy carboxylic acid which was finally lactonised to **2c** with the unprotected phenolic hydroxy group by exposure to hydrochloric acid at room temperature in 61% and in 18% overall-yield for seven steps. The unprotected carboxylic acid **5c** could also be prepared in a yield of 86% by cleaving the methyl ether refluxing in 48% hydrobromic acid. Alternatively, the lactone **2c** was generated by treating the methyl ether protected lactone **2b** with BBr_3 at low temperatures[18] in a yield of 75%.

3. Conclusions

In summary, we developed two appropriate procedures for the preparation of the lactones **2a** and **2b**. Due to the sluggish hydrolysis step of **7b** to **5b** the second approach, via the cyclisation of the dicarboxylic acid **19** to the ketocarboxylic acid **5** with the required *trans*-fused decalin structure and the carboxylic acid function in the angular position, is to be preferred. In addition, the lactone **2c** with one free phenolic hydroxy function was synthesised either by the BBr_3 method or via the acidic hydrolysis of amide **7a**. Our synthesis is concise, efficient and easily modifiable for the synthesis of various carnosol 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). ^1H NMR- and ^{13}C NMR-Spectra were recorded on an 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 analysis 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 micro-analyses 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). Preparative TLC was carried out on Macherey–Nagel DC-plates 20×20 cm^2 SIL G-200 UV_{254}. 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.

Methyl (triphenylphosphoranylidene)acetate **14** was prepared according to the procedure described in Ref. 11 and 2-hydroxytetrahydropyrane **13** as reported in Ref. 12.

4.1.1. Methyl (7-hydroxy-2-heptenoate) (15). Methyl (triphenylphosphoran-ylidene)acetate[11] **14** (103 g, 248 mmol) was dissolved in dry CH_2Cl_2 (510 ml). Subsequently, 2-hydroxytetrahydropyrane[12] **13** (18.0 g, 177 mmol), dry K_2CO_3 (43.9 g, 318 mmol) and a catalytic amount of 18-crown-6 were added and the mixture was refluxed for 48 h. After being cooled to rt, inorganic salts were filtered off and most of the solvent was evaporated. The residue was stirred with a 7:3 mixture of diethyl ether and petroleum

ether (350 ml) at rt for 1 h. The precipitate was sucked off and washed with the 7:3 mixture of diethyl ether and petroleum ether. The solvents were removed and the crude product was chromatographed (silica gel, diethyl ether/petroleum ether 7:3) to give 24.5 g (88%) of **15** (*Z*/*E* ratio was determined to 1:6 from the ^{1}H NMR spectrum) as a colourless oil. The spectroscopical data for **15** were completely identical with those reported for compound **15**.[14]

4.1.2. Methyl [7-(*p*-toluenesulfonyl)-2-heptenoate] (12). To a solution of **15** (24.5 g, 155 mmol) in dry CH_2Cl_2 (750 ml) were added dry triethylamine (43.2 ml, 310 mmol), *p*-TosCl (34.0 g, 178 mmol) and a catalytic amount of DMAP at rt. The mixture was stirred at rt for further 24 h. Subsequently, the solvent was distilled off to small volume, the residue was taken up in water (300 ml) and extracted with diethyl ether (4×90 ml). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (silica gel, diethyl ether/petroleum ether 7:3) to yield 44.0 g (91%) of **12** as a colourless oil. An analytical sample of each isomer was obtained using preparative TLC.

E-Isomer.[10] IR (film) 2935, 2860, 1755, 1690, 1635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 6.87 (dt, J_1=15.5 Hz, J_2=7.1 Hz, 1H), 5.76 (d, J=15.5 Hz, 1H), 4.03 (t, J=6.2 Hz, 2H), 3.72 (s, 3H), 2.45 (s, 3H), 2.20–2.12 (m, 2H), 1.72–1.63 (m, 2H), 1.54–1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.82, 148.19, 144.84, 133.23, 129.91, 127.87, 121.57, 70.04, 51.38, 31.31, 28.25, 23.90, 21.59; MS (CI) *m*/*z* (%) 314 (M^++2, 22), 313 (M^++1, 100), 281 (15).

Z-Isomer. IR (film) 2925, 2845, 1750, 1675, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 6.14 (dt, J_1=11.5 Hz, J_2=7.5 Hz, 1H), 5.78 (d, J=11.5 Hz, 1H), 4.04 (t, J=6.2 Hz, 2H), 3.69 (s, 3H), 2.66–2.58 (m, 2H), 2.45 (s, 3H), 1.73–1.64 (m, 2H), 1.53–1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.66, 149.30, 144.68, 133.37, 129.85, 127.91, 120.04, 70.25, 51.02, 28.45, 28.11, 24.79, 21.61; MS (CI) *m*/*z* (%) 314 (M^++2, 81), 313 (M^++1, 5), 282 (70), 281 (54), 229 (55), 228 (15), 213 (48), 202 (35), 170 (16), 169 (14), 156 (33), 142 (41), 128 (15), 111 (31), 109 (23), 108 (100), 91 (51), 81 (65), 80 (37), 79 (14), 65 (17), 55 (14).

4.1.3. Methyl (2-cyano-2-phenyl-cyclohexyl)-acetate (16a). A solution of the phenyl acetonitrile **11a** (5.92 ml, 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 **12** (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 distilled off 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 afford **16a** (10.1 g, 82% yield) as a colourless oil. IR (film) 3010, 2915, 2845, 2210, 1770, 1630, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.48 (m, 2H), 7.42–7.36 (m, 2H), 7.34–7.28 (m, 1H), 3.55 (s, 3H), 2.49–2.42 (m, 1H), 2.21–2.17 (m, 2H), 2.11–2.06 (m, 1H), 2.00–1.77 (m, 5H), 1.61–1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.46, 139.15, 129.13, 128.11, 126.03, 120.39, 51.58, 50.29, 41.70, 39.85, 37.06, 29.71, 25.31, 23.63; MS (CI) *m*/*z* (%) 258 (M^++1, 9), 257 (M^+, 63), 226 (40), 225 (100), 224 (17), 197 (20), 196 (16), 183 (15), 170 (16), 157 (14), 130 (19), 129 (62), 116 (14), 115 (23), 103 (14), 69 (18).

4.1.4. (2-Cyano-2-phenyl-cyclohexyl) acetic acid (8a). A solution of the nitrile methyl ester **16a** (10.0 g, 38.9 mmol) in methanol (140 ml) was refluxed with a 20% aqueous NaOH solution (39.0 ml) for 3 h. The reaction mixture was cooled to rt and evaporated to small volume. The residue was diluted with water (250 ml) and extracted with diethy 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 yield 8.42 g (89%) of **8a** as a colourless solid. Mp 139–140°C; IR (KBr) 3035, 2950, 2860, 2230, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J=8.0 Hz, 2H), 7.41–7.35 (m, 2H), 7.32–7.27 (m, 1H), 2.45–2.37 (m, 1H), 2.22–2.18 (m, 2H), 2.11–2.06 (m, 1H), 2.05–1.97 (m, 1H), 1.93–1.76 (m, 4H), 1.62–1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.03, 139.00, 129.18, 128.20, 125.96, 120.24, 50.16, 41.54, 39.79, 36.96, 29.62, 25.26, 23.60; MS (EI) *m*/*z* (%) 243 (M^+, 11), 225 (37), 136 (47), 130 (25), 129 (76), 117 (13), 116 (15), 115 (25), 103 (20), 92 (56), 91 (100), 89 (16), 86 (64), 85 (16), 81 (14), 79 (16), 77 (21), 71 (18), 68 (22), 65 (29), 63 (23), 58 (14), 57 (16), 55 (19), 51 (21), 45 (19), 44 (18), 43 (30), 42 (19), 41 (58). Anal. calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found C, 74.12; H, 6.98; N, 5.74.

4.1.5. 9-Oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylic acid amide (7a). The nitrile carboxylic acid **8a** (5.00 g, 20.6 mmol) was stirred with concentrated sulphuric acid (200 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 3.80 g (76%) of **7a** as a colourless solid. Mp 195–197°C; IR (KBr) 3400, 3300, 3185, 2920, 2865, 1670, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J_1=8.0 Hz, J_2=1.3 Hz, 1H), 7.60 (td, J_1=7.5 Hz, J_2=1.3 Hz, 1H), 7.52 (d, J=7.5 Hz, 1H), 7.42 (dd, J_1=7.5 Hz, J_2=1.3 Hz, 1H), 5.58 (s_b, 1H, NH_2), 5.14 (s_b, 1H, NH_2), 3.09 (dd, J_1=18.6 Hz, J_2=13.2 Hz, 1H), 2.72–2.65 (m, 1H), 2.55 (dd, J_1=18.6 Hz, J_2=4.4 Hz, 1H), 2.29–2.06 (m, 2H), 2.02–1.77 (m, 3H), 1.72–1.63 (m, 1H), 1.58–1.50 (m, 1H), 1.42–1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.04, 175.43, 147.44, 133.95, 132.90, 128.43, 127.97, 124.62, 48.83, 42.97, 42.88, 35.56, 28.71, 25.59, 22.68; MS (EI) *m*/*z* (%) 244 (M^++1, 7), 243 (M^+, 37), 201 (18), 200 (31), 199 (100), 198 (24), 181 (24), 171 (18), 158 (46), 157 (55), 143 (20), 141 (19), 131 (94), 130 (19), 129 (61), 128 (39), 127

(17), 117 (14), 115 (45), 103 (20), 91 (35), 77 (24), 67 (24), 55 (21), 51 (18), 44 (26), 43 (26). Anal. calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found C, 73.98; H, 7.15; N, 5.81.

4.1.6. 9-Oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylic acid (5a). The amide **7a** (2.00 g, 8.22 mmol) was heated to reflux with 37% HCl (100 ml) for 48 h. The mixture was cooled to rt, water (100 ml) was added and extracted with diethyl ether (3×70 ml). The combined organic layers were extracted with saturated $NaHCO_3$ solution (4×80 ml). The aqueous $NaHCO_3$ extracts were combined, acidified to pH 1 by the dropwise addition of 37% HCl and subsequently extracted with diethyl ether (3×100 ml). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and concentrated to yield 1.16 g (58%) of **5a** as a colourless solid. An analytical sample was obtained by recrystallisation from water/ethanol. Mp 152–154°C; IR (KBr) 3070, 2925, 2860, 1725, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J=8.0 Hz, 1H), 7.60–7.52 (m, 2H), 7.38 (td, J=7.1, 1.8 Hz, 1H), 3.30 (dd, J_1=18.6 Hz, J_2=14.1 Hz, 1H), 3.01–2.96 (m, 1H), 2.51 (dd, J_1=18.6 Hz, J_2=5.1 Hz, 1H), 2.22–2.13 (m, 1H), 1.90–1.31 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.96, 178.90, 144.72, 133.63, 132.71, 127.91, 127.78, 126.29, 49.46, 42.03, 35.53, 29.44, 25.62, 23.66; MS (EI) m/z (%) 244 (M^+, 12), 199 (20), 198 (55), 197 (100), 196 (18), 170 (23), 169 (96), 168 (25), 167 (14), 166 (17), 165 (45), 142 (19), 141 (45), 139 (14), 131 (21), 115 (51), 91 (23), 89 (15), 50 (15), 41 (15), 39 (32). Anal. calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found C, 73.82; H, 6.69.

4.1.7. *trans*-1,3,4,9,10,10a-Hexahydro-4a(2*H*),9-phenanthrenecarbolactone (2a). To a solution of the keto-carboxylic acid **5a** (1.15 g, 4.71 mmol) dissolved in a 2:1 mixture of ethanol and water (120 ml) was added $NaBH_4$ (1.07 g, 28.3 mmol) in portions at 0°C. The reaction mixture was stirred for further 24 h at rt and 37% HCl (14.5 ml) was dropwise added (ice-cooling). After being stirred for further 1.5 h at rt, water (100 ml) was added and the mixture was extracted with chloroform (3×70 ml). The combined organic layers were dried over $MgSO_4$, the solvent was evaporated and the crude product was purified by column chromatography (silica gel, chloroform) to give 860 mg (80%) of **2a** as a colourless solid. Mp 116°C (Ref. 9 79–80°C); The spectroscopical data for **2a** were completely identical with those published for compound **2a**.[9]

4.1.8. Methyl [2-cyano-2-(3-methoxyphenyl)cyclohexyl]-acetate (16b). Using the procedure described for the preparation of **16a**, a solution of the (3-methoxyphenyl)-acetonitrile **11b** (7.01 ml, 51.4 mmol) in dry THF (110 ml) and NaH (60% in mineral oil; 2.21 g, 55.3 mmol) suspended in dry THF (120 ml) were reacted with a solution of the α,β-unsaturated methyl ester **12**[10] (15.0 g, 48.1 mmol) in dry THF (110 ml) to give 11.4 g (83%) of **16b** as a colourless oil. IR (film) 3000, 2935, 2855, 2235, 1735, 1600, 1585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J=8.0 Hz, 1H), 7.10–7.04 (m, 2H), 6.86–6.82 (m, 1H), 3.82 (s, 3H), 3.56 (s, 3H), 2.47–2.39 (m, 1H), 2.21–2.17 (m, 2H), 2.11–2.06 (m, 1H), 1.99–1.92 (m, 1H), 1.90–1.74 (m, 4H), 1.59–1.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.44, 160.16, 140.77, 130.15, 120.39, 118.19, 113.30, 112.27, 55.35, 51.58, 50.31, 41.67, 39.72, 37.05, 29.65, 25.26, 23.62; MS (CI) m/z (%) 288 (M^++1, 8), 287 (M^+, 27), 181 (19), 180 (100), 121 (60), 91 (20).

4.1.9. [2-Cyano-2-(3-methoxyphenyl)cyclohexyl]acetic acid (8b). A solution of the nitrile methyl ester **16b** (10.7 g, 37.3 mmol) in methanol (135 ml) was reacted with 20% aqueous NaOH solution (37 ml) according to the procedure outlined for the preparation of **8a**. The crude product was recrystallised from water/ethanol to yield 8.45 g (85%) of **8b** as a colourless solid. Mp 119–118°C; IR (KBr) 3010, 2950, 2860, 2230, 1710, 1610, 1585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J=8.0 Hz, 1H), 7.09–7.01 (m, 2H), 6.86–6.81 (m, 1H), 3.81 (s, 3H), 2.43–2.37 (m, 1H), 2.24–2.18 (m, 2H), 2.13–2.06 (m, 1H), 2.04–1.97 (m, 1H), 1.93–1.76 (m, 4H), 1.61–1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.02, 160.18, 140.61, 130.22, 120.26, 118.15, 113.34, 112.26, 55.35, 50.19, 41.51, 39.68, 36.96, 29.57, 25.23, 23.57; MS (EI) m/z (%) 273 (M^+, 24), 227 (18), 166 (69), 159 (57), 122 (23), 121 (100), 91 (53), 79 (16), 78 (28), 77 (31), 71 (21), 65 (17), 55 (18), 51 (21), 45 (42), 43 (16), 41 (32). Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found C, 70.21; H, 7.07; N, 5.22.

4.1.10. 6-Methoxy-9-oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylic acid amide (7b). Using the procedure described for the preparation of **7a**, the nitrile carboxylic acid **8b** (5.00 g, 18.3 mmol) was treated with concentrated sulphuric acid (175 ml) to afford 3.72 g (74%) of **7b** as a colourless solid. Mp 219–220°C (Ref. 10 225–228°C) ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J=8.8 Hz, 1H), 6.99 (d, J=2.7 Hz, 1H), 6.92 (dd, J_1=8.8 Hz, J_2=2.6 Hz, 1H), 5.31 (s_b, 1H, NH_2), 5.15 (s_b, 1H, NH_2), 3.90 (s, 3H), 3.01 (dd, J_1=18.6 Hz, J_2=13.7 Hz, 1H), 2.66–2.59 (m, 1H), 2.51 (dd, J_1=18.6 Hz, J_2=4.0 Hz, 1H), 2.21–2.19 (m, 1H), 2.14–1.64 (m, 5H), 1.56–1.49 (m, 1H), 1.41–1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.89, 175.07, 164.08, 149.87, 131.02, 126.45, 112.40, 110.97, 55.62, 48.95, 43.07, 42.74, 35.47, 28.63, 25.57, 22.62.

4.1.11. 6-Methoxy-9-oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylic acid (5b). The amide **7b** (2.00 g, 7.32 mmol) was reacted with 37% HCl (100 ml) according to the procedure described for the preparation of **5a** to yield 625 mg (31%) of **5b** as a colourless solid. Mp 184–185°C; IR (KBr) 2935, 2865, 1710, 1640, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J=8.8 Hz, 1H), 7.03 (d, J=2.7 Hz, 1H), 6.88 (dd, J_1=8.8 Hz, J_2=2.7 Hz, 1H), 3.86 (s, 3H), 3.26 (dd, J_1=18.6 Hz, J_2=13.7 Hz, 1H), 2.96–2.89 (m, 1H), 2.46 (dd, J_1=18.6 Hz, J_2=4.9 Hz, 1H), 2.20–2.09 (m, 1H), 1.89–1.56 (m, 5H), 1.53–1.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.01, 178.71, 163.88, 147.14, 130.25, 126.34, 113.24, 111.79, 55.51, 49.66, 42.18, 41.86, 35.56, 29.44, 25.62, 23.69; MS (EI) m/z (%) 275 (M^++1, 50), 274 (M^+, 100), 231 (25), 230 (68), 229 (87), 228 (28), 215 (17), 211 (15), 204 (24), 201 (37), 188 (23), 187 (48), 177 (19), 162 (20), 161 (61), 159 (34), 128 (21), 121 (19), 115 (29), 91 (17), 77 (19), 74 (28), 59 (38), 45 (36). Anal. calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found C, 70.01; H, 6.72.

4.1.12. 6-Methoxy-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*),9-phenanthrenecarbolactone (2b). According to the procedure described for **2a**, a solution of the ketocarboxylic acid **5b** (1.30 g, 4.74 mmol) in a 2:1 mixture of ethanol and water (123 ml) was treated with $NaBH_4$ (1.08 g, 28.4 mmol) and 37% HCl (14.6 ml). 1.03 g (84%) of **2b** were obtained as a colourless solid. Mp 122–124°C; IR (KBr) 2995, 2940, 2855, 1740, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J=8.0 Hz, 1H), 6.82 (d, J=2.2 Hz, 1H), 6.75 (dd, J_1=8.0 Hz, J_2=2.2 Hz, 1H), 5.46 (dd, J_1= 3.6 Hz, J_2=1.3 Hz, 1H), 3.81 (s, 3H), 2.61–2.53 (m, 1H), 2.09 (ddd, J_1=13.2 Hz, J_2=10.2 Hz, J_3=1.8 Hz, 1H), 2.05–1.77 (m, 6H), 1.65–1.56 (m, 1H), 1.33–1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.30, 160.31, 141.98, 130.32, 123.81, 111.27, 108.85, 76.93, 55.51, 48.89, 37.00, 35.95, 33.28, 26.66, 25.80, 21.82; MS (EI) *m/z* (%) 259 (M^++1, 13), 258 (M^+, 44), 215 (47), 214 (100), 213 (29), 212 (23), 186 (14), 185 (23), 184 (15), 173 (27), 172 (75), 171 (81), 159 (15), 158 (17), 153 (14), 141 (25), 129 (22), 128 (34), 127 (14), 115 (36), 77 (14), 51 (15). Anal. calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found C, 74.33; H, 6.96.

4.1.13. 8a-Phenyl-*cis*-hexahydro-2*H*, 4*H*-isoquinoline-1,3-dion (17). The nitrilecarboxylic acid **8a** (500 mg, 2.06 mmol) was refluxed with 37% HCl (50 ml) for 24 h. The reaction mixture was cooled to rt, water (150 ml) was added and extracted with diethyl ether (3×80 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (ethyl acetate/cyclohexane 1:1) to give 464 mg (93%) of **17** as a colourless solid. Mp 136–137°C; IR (film) 3205, 3085, 2940, 2860, 1720, 1695, 1600 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (s_b, 1H, NH), 7.37–7.23 (m, 5H), 2.60–2.48 (m, 3H), 2.36–2.28 (m, 1H), 1.89–1.65 (m, 3H), 1.55–1.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.51, 172.08, 141.37, 129.14, 127.54, 125.69, 53.02, 37.44, 37.21, 36.34, 29.81, 25.35, 23.46; MS (EI) *m/z* (%) 244 (M^+, 14), 243 (100), 201 (54), 188 (25), 172 (34), 159 (17), 158 (93), 157 (18), 156 (24), 143 (34), 130 (52), 129 (53), 128 (31), 117 (23), 116 (16), 115 (54), 104 (15), 103 (17), 91 (44), 78 (14), 77 (30), 65 (14), 51 (19). Anal. calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found C, 74.37; H, 7.08; N, 5.69.

4.1.14. (2-Formyl-2-phenylcyclohexyl)acetic acid (18a). To a solution of the nitrilecarboxylic acid **8a** (4.00 g, 16.4 mmol) in dry CH_2Cl_2 (50 ml) was dropwise added DIBAL (1.0 M in CH_2Cl_2; 37.8 ml, 37.8 mmol) at −78°C. The reaction mixture was stirred for further 2 h at −78°C and allowed to warm up to rt overnight. After being recooled to −78°C, ethyl acetate (7.5 ml) was added. The mixture was stirred for 15 min at this temperature, warmed up to rt and poured into water (200 ml) under stirring. The mixture was acidified to pH 1 by adding dropwise 37% HCl dissolving the precipitate and stirred for one more hour at rt. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×80 ml). The combined organic layers were extracted with saturated $NaHCO_3$ solution (4×80 ml). The aqueous extracts were acidified to pH 1 by adding dropwise 37% HCl and extracted with diethyl ether (3×100 ml). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. 2.63 g (65%) of the dicarboxylic acid **18a** were obtained as a colourless solid. Mp 82–84°C; IR (KBr) 3040, 2930, 2850, 2810, 2705, 1715, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.39–7.34 (m, 2H), 7.29–7.21 (m, 3H), 2.60 (dd, J_1=15.5 Hz, J_2=10.2 Hz, 1H), 2.52–2.45 (m, 1H), 2.41 (dd, J_1=15.5 Hz, J_2=2.2 Hz, 1H), 2.20–2.14 (m, 1H), 1.93–1.66 (m, 4H), 1.58–1.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.61, 179.13, 140.04, 129.17, 127.45, 127.09, 57.79, 39.62, 35.59, 34.00, 28.54, 25.32, 22.99; MS (CI) *m/z* (%) 248 (M^++1, 11), 247 (M^+, 62), 234 (16), 233 (90), 230 (14), 229 (71), 217 (17), 215 (14), 159 (17), 158 (100), 157 (31), 139 (56), 91 (20). Anal. calcd for $C_{15}H_{18}O_3$ C, 73.15; H, 7.37. Found C, 72.98 H, 7.25.

4.1.15. 2-Carboxymethyl-1-phenyl-cyclohexanecarboxylic acid (19a). To a mixture of the aldehyde carboxylic acid **18a** (2.60 g, 10.6 mmol), $NaH_2PO_4 \cdot H_2O$ (1.46 g, 10.6 mmol), 2-methyl-2-butene (22.4 ml, 211 mmol), water (16.5 ml) and ^{t}BuOH (54.5 ml) were added $NaClO_2$ (3.25 g, 35.9 mmol) portionwise at 0°C. After being stirred for further 2 h at 0°C, water (20 ml) and saturated $Na_2S_2O_3$ solution (5 ml) were added. The mixture was acidified to pH 1 by the dropwise addition of 37% HCl and extracted with diethyl ether (3×35 ml). The combined organic layers were extracted with saturated $NaHCO_3$ solution (4×40 ml). The aqueous extracts were combined, acidified to pH 1 by adding dropwise 37% HCl and extracted with diethyl ether (3×50 ml). The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo to give 1.85 g (67%) of **19a** as a colourless resin. IR (film) 3045, 2925, 2855, 2645, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 2.67 (dd, J_1= 16.6 Hz, J_2=10.4 Hz, 1H), 2.56–2.46 (m, 1H), 2.40 (dd, J_1=16.8 Hz, J_2=1.3 Hz, 1H), 2.35–2.27 (m, 1H), 1.93–1.67 (m, 4H), 1.62–1.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.73, 180.07, 141.97, 128.76, 127.16, 126.48, 56.53, 41.40, 36.56, 31.00, 28.87, 25.28, 23.63; MS (CI) *m/z* (%) 262 (M^+, 9), 159 (14), 158 (100), 157 (15), 91 (18).

4.1.16. 9-Oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylic acid (5a). The dicarboxylic acid **19a** (1.80 g, 6.86 mmol) was stirred with concentrated sulphuric acid (67 ml) at rt for 24 h. Subsequently, the reaction mixture was poured onto ice and extracted with diethyl ether (3×100 ml). The organic layers were combined and extracted with saturated $NaHCO_3$ solution (4×100 ml). The combined aqueous extracts were acidified to pH 1 by adding dropwise 37% HCl and extracted with diethyl ether (3×110 ml). The ethereal extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated to provide 1.19 g (71%) of **5a** as a colourless solid. An analytical sample was achieved by recrystallisation from water/ethanol. Mp 152–154°C; The spectroscopical data for **5a** were completely identical with those described for compound **5a** in Section 4.1.6

4.1.17. [2-Formyl-2-(3-methoxyphenyl)cyclohexyl]acetic acid (18b). The nitrilecarboxylic acid **8b** (4.00 g, 14.5 mmol) was dissolved in dry CH_2Cl_2 (44 ml) and reduced with DIBAL (1.0 M in CH_2Cl_2; 33.3 ml, 33.3 mmol) using the procedure described for the preparation of **18a** to afford 2.51 g (63%) of **18b** as a colourless

solid. An analytical sample was obtained by recrystallisation from water/ethanol. Mp 141–144°C; IR (KBr) 3050, 2935, 2860, 2735, 1705, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.31–7.25 (m, 1H), 6.83–6.76 (m, 3H), 3.79 (s, 3H), 2.58 (dd, J_1=16.4 Hz, J_2=11.0 Hz, 1H), 2.51–2.41 (m, 2H), 2.21–2.15 (m, 1H), 1.90–1.66 (m, 4H), 1.57–1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.41, 178.96, 160.27, 141.65, 130.09, 119.42, 113.41, 112.50, 57.77, 55.28, 39.62, 35.60, 34.04, 28.56, 25.32, 22.98; MS (CI) *m/z* (%) 277 (M^++1, 47), 276 (M^+, 51), 260 (30), 259 (85), 249 (34), 248 (100), 229 (24), 201 (34), 189 (30), 188 (95), 187 (42). Anal. calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found C, 69.65; H, 7.36.

4.1.18. 2-Carboxymethyl-1-(3-methoxyphenyl)cyclohexanecarboxylic acid (19b). Using the procedure for the preparation of **19a**, a mixture of the aldehyde carboxylic acid **18a** (2.50 g, 9.05 mmol), $NaH_2PO_4 \cdot H_2O$ (1.25 g, 9.05 mmol), 2-methyl-2-butene (19.2 ml, 181 mmol), water (35.4 ml) and ^{t}BuOH (117 ml) was treated with $NaClO_2$ (2.78 g, 30.8 mmol) to afford 1.82 g (69%) of **19b** as a colourless solid. An analytical sample was achieved by recrystallisation from water/ethanol. Mp 147–148°C; IR (KBr) 3030, 2940, 2615, 1700, 1605, 1580 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.23 (t, J=8.0 Hz, 1H), 6.93–6.86 (m, 2H), 6.80 (dd, J_1=8.0 Hz, J_2=2.4 Hz, 1H), 3.78 (s, 3H), 2.56 (dd, J_1=16.4 Hz, J_2=10.6 Hz, 1H), 2.49–2.39 (m, 1H), 2.30–2.19 (m, 2H), 1.88–1.41 (m, 7H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.81, 177.64, 161.33, 146.04, 130.50, 120.11, 114.10, 113.01, 57.85, 55.74, 42.96, 38.77, 37.81, 30.10, 26.62, 24.94; MS (CI) *m/z* (%) 293 (M^++1, 40), 292 (M^+, 86), 275 (42), 248 (34), 246 (16), 229 (23), 201 (16), 189 (18), 188 (100), 187 (20). Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found C, 65.67; H, 6.81.

4.1.19. 6-Methoxy-9-oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylic acid (5b). The dicarboxylic acid **19b** 1.80 g (6.16 mmol) was treated with concentrated sulphuric acid (60 ml) according to the procedure for the preparation of **5a**. 1.30 g (77%) of **5b** were obtained as a colourless solid. The spectroscopical data of **5b** were completely identical with those for compound **5b** in Section 4.1.11.

4.1.20. 6-Hydroxy-9-oxo-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*)-phenanthrenecarboxylic acid (5c). *Method A*. The amide **7b** (2.00 g, 7.32 mmol) was refluxed with 48% HBr (200 ml) for 48 h. The reaction mixture was cooled to rt, water (300 ml) was added and extracted with diethyl ether (4×200 ml). The combined organic layers were extracted with saturated $NaHCO_3$ solution (4×210 ml) and filtered. The combined aqueous extracts were acidified to pH 1 by adding dropwise 37% HCl and extracted with diethyl ether (3×300 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was taken up in less chloroform and crystallised. The solid was sucked off and dried in vacuo over $CaCl_2$. 1.05 g (55%) of **5c** were obtained as a colourless solid.

Method B. The ketocarboxylic acid **5b** (100 mg, 0.37 mmol) was refluxed for 24 h with a mixture of acetic acid (1 ml) and 48% HBr (10 ml). The reaction mixture was cooled to rt, water (30 ml) was added and extracted with diethyl ether (3×15 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated. The crude product was taken up in a small volume of chloroform and crystallised. The obtained solid was sucked off and dried in vacuo over $CaCl_2$ to give 81.5 mg (86%) of **5c** as a colourless solid. Mp 243–244°C; IR (KBr) 3290, 2935, 2865, 1685, 1655, 1575 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 7.77 (d, J=8.4 Hz, 1H), 6.91 (d, J=2.2 Hz, 1H), 6.78 (dd, J_1=8.4 Hz, J_2=2.2 Hz, 1H), 3.11 (dd, J_1=18.1 Hz, J_2=13.7 Hz, 1H), 2.82–2.73 (m, 1H), 2.33 (dd, J_1=18.1 Hz, J_2=5.0 Hz, 1H), 2.14–2.02 (m, 1H), 1.83–1.68 (m, 2H), 1.66–1.45 (m, 3H), 1.42–1.27 (m, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 195.54, 174.06, 162.07, 148.13, 129.28, 124.39, 114.72, 112.11, 48.80, 41.48, 41.19, 34.69, 29.12, 25.03, 23.40; MS (EI) *m/z* (%) 261 (M^++1, 48), 260 (M^+, 100), 216 (29), 215 (65), 214 (17), 191 (14), 187 (17), 173 (28), 147 (34), 145 (22), 131 (12), 115 (17), 104 (18), 76 (16). Anal. calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found C, 69.02; H, 6.32.

4.1.21. 6-Hydroxy-*trans*-1,3,4,9,10,10a-hexahydro-4a(2*H*),9-phenanthrenecarbolactone (2c). *Method A*. The lactone **2b** (500 mg, 1.94 mmol) was dissolved in dry CH_2Cl_2 (16 ml), cooled to −78°C and BBr_3 (1.0 M in CH_2Cl_2; 4.26 ml, 4.26 mmol) were dropwise added. The reaction mixture was stirred for further 30 min at this temperature. Subsequently, the mixture was warmed to rt over 2 h and stirred at rt for further 1.5 h. Saturated $NaHCO_3$ solution (50 ml) was added and the mixture was extracted with diethyl ether (3×20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/cyclohexane 1:1) to give 356 mg (75%) of **2c** as a colourless solid. 61.3 mg (16%) of 5,6,7,8-tetrahydro-3-phenanthreneol were isolated as by-product.

Method B. Using the procedure outlined for the preparation of **2a**, a solution of the ketocarboxylic acid **5c** (1.00 g, 3.84 mmol) in a 2:1 mixture of ethanol and water (100 ml) was treated with $NaBH_4$ (872 mg, 23.1 mmol) and subsequently with 37% HCl (11.8 ml). Extraction was performed with chloroform instead of previously used diethyl ether. The crude product was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1:1) to yield 571 mg (61%) of **2c** as a colourless solid. Mp 131–133°C; IR (KBr) 3255, 2940, 2855, 1710, 1610 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.14 (d, J=8.0 Hz, 1H), 6.73 (d, J=2.2 Hz, 1H), 6.67 (dd, J_1=8.0 Hz, J_2=2.2 Hz, 1H), 5.50 (dd, J_1=3.5 Hz, J_2=1.8 Hz, 1H), 2.48–2.40 (m, 1H), 2.11 (ddd, J_1=13.3 Hz, J_2=10.2 Hz, J_3=1.8 Hz, 1H), 1.98–1.69 (m, 6H), 1.66–1.56 (m, 1H), 1.39–1.25 (m, 1H), 1.16–1.04 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 177.48, 159.53, 143.05, 130.38, 125.17, 114.31, 110.32, 78.96, 50.12, 38.28, 37.11, 34.56, 27.69, 26.81, 23.07; MS (EI) *m/z* (%) 245 (M^++1, 7), 244 (M^+, 20), 201 (34), 200 (100), 199 (34), 198 (22), 172 (12), 171 (21), 169 (16), 159 (21), 158 (73), 157 (98), 145 (15), 144 (18), 128 (21), 127 (14), 115 (25), 47 (22). Anal. calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found C, 73.81; H, 6.68. 5,6,7,8-tetrahydro-3-phenanthreneol IR (film) 3375, 3035, 2920, 2845, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=8.9 Hz, 1H), 7.52 (d, J=8.0 Hz, 1H), 7.25 (s, 1H), 7.06–7.00 (m, 2H), 3.01–2.95 (m, 2H), 2.91–2.85 (m, 2H), 2.00–1.78 (m, 4H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 153.52, 135.09, 133.91, 130.28, 130.05, 127.46, 126.06, 125.43, 116.08, 105.55, 30.52, 25.77, 23.28, 22.97.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 201076 for **7a**, CCDC 201077 for **17**, CCDC 201074 for **2a** and CCDC 201075 for **2b**. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK. (fax: +44-1223336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

A. L. thanks Professor Dr Dr h.c. T. Eicher for generous support.

References

1. Moujir, L.; Navarro, G. M. A.; Andres, L. S.; Luis, J. G. *Phytochemistry* **1993**, *34*, 1493–1495.
2. (a) Brieskorn, C. H.; Dömling, H.-J. *Z. Lebensm. Unters. Forsch.* **1969**, *141*, 10–16. (b) Wu, J. W.; Lee, M.-H.; Ho, C.-T.; Chang, S. S. *J. Am. Oil Chem. Soc.* **1982**, *59*, 339–345. (c) Inatani, R.; Nakatani, N.; Fuwa, H. *Agric. Biol. Chem.* **1983**, *47*, 521–528. (d) Schwarz, K.; Ternes, W.; Schmauderer, E. Z. *Lebensm. Unters. Forsch.* **1992**, *195*, 104–107. (e) Aruoma, O. I.; Halliwell, B.; Aeschbach, R.; Löligers, J. *Xenobiotica* **1992**, *22*, 257–268. (f) Cuvelier, M.-E.; Berset, C.; Richard, H. *J. Agric. Food Chem.* **1994**, *42*, 665–669. (g) Haraguchi, H.; Saito, T.; Okamura, N.; Yagi, A. *Planta Med.* **1995**, *61*, 333–336. (h) Hopia, A. I.; Huang, S.-W.; Schwarz, K.; German, J. B.; Frankel, E. N. *J. Agric. Food Chem.* **1996**, *44*, 2030–2036. (i) Pearson, D. A.; Frankel, E. N.; Aeschbach, R.; German, J. G. *J. Agric. Food Chem.* **1997**, *45*, 578–582.
3. (a) Jones, C. *Nutr. Sci. News* **1998**, *March*. (b) Huang, M.-T.; Ho, C.-T.; Wang, Z. Y.; Ferraro, T.; Lou, Y.-R.; Stauber, K.; Ma, W.; Georgiadis, C.; Laskin, J. D.; Conney, A. H. *Cancer Res.* **1994**, *54*, 701–708. (c) Chan, M. M.-Y.; Ho, C.-T.; Huang, H.-I. *Cancer Lett.* **1995**, *96*, 23–29. (d) Offord, E. A.; Macé, K.; Ruffieux, C.; Malnoe, A.; Pfeifer, A. M. A. *Carcinogenesis* **1995**, *16*, 2057–2062. (e) Singletary, K.; MacDonald, C.; Wallig, M. *Cancer Lett.* **1996**, *104*, 43–48. (f) Singletary, K. W. *Cancer Lett.* **1996**, *100*, 139–144. (g) Offord, E. A.; Macé, K.; Avanti, O.; Pfeifer, A. M. A. *Cancer Lett.* **1997**, *114*, 275–281.
4. White, A. I.; Jenkins, G. L. *J. Am. Pharm. Assoc., Sci. Ed.* **1942**, 33–43.
5. Brieskorn, C. H.; Fuchs, A. *Chem. Ber.* **1962**, *95*, 3034–3041.
6. Brieskorn, C. H.; Fuchs, A.; Bredenberg, J. B.; McChesney, J. D.; Wenkert, E. *J. Org. Chem.* **1964**, *29*, 2293–2298.
7. Meyer, W. L.; Manning, R. A.; Schindler, E.; Schroeder, R. S.; Shew, D. C. *J. Org. Chem.* **1976**, *41*, 1005–1015.
8. Gajhede, M.; Anthoni, U.; Nielsen, P. H.; Pedersen, E. J.; Christophersen, C. J. *Crystallogr. Spectrosc. Res.* **1990**, *20*, 165–171.
9. Jones, D. W.; Nongrum, F. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 705–713.
10. Yardley, J. P.; Rees, R. W. *Can. J. Chem.* **1985**, *63*, 1013–1017.
11. Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 6044–6050.
12. Murphy, P. J.; Williams, H. L.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron* **1996**, *52*, 8315–8332.
13. Boden, R. M. *Synthesis* **1975**, 784.
14. Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* **1981**, *37*, 4371–4383.
15. Smith, A. B., III.; Codon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947–961.
16. (a) Nicolaou, K. C.; Petasis, N. A.; Li, W. S.; Ladduwahetty, T.; Randall, J. L.; Webber, S. E.; Hernandez, P. E. *J. Org. Chem.* **1983**, *48*, 5403–5404. (b) Zhang, W.-Y.; Jakiela, D. J.; Maul, A.; Knors, C.; Lauher, J. W.; Helquist, P.; Enders, D. *J. Am. Chem. Soc.* **1988**, *110*, 4652–4660.
17. (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890. (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583–4592. (c) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567–569.
18. Luis, J. G.; Andrés, L. S.; Fletcher, W. Q.; Lahlou, E. H.; Perales, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2207–2211.