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A short synthesis of phenanthro[2,3-*d*]imidazoles from dehydroabietic acid. Application of the methodology as a convenient route to benzimidazoles

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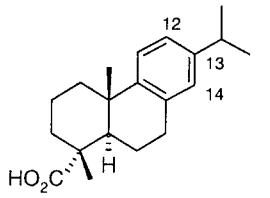
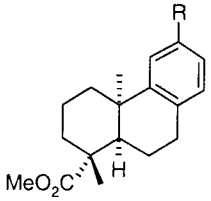
Abstract—Methyl *cis*-deisopropyldehydroabietate was selectively nitrated at the 12-position by reaction with 'claycop', a montmorillonite clay impregnated with copper(II) nitrate. The 12-nitro compound was reduced to the corresponding amine and this was subjected to a combined acylation and *ortho* nitration. The compounds so produced were further converted into octahydro-1*H*-phenanthro[2,3-*d*]imidazoles by reductive cyclization. The same acylation-*ortho* nitration methodology was shown to provide a short synthesis of 2-substituted benzimidazoles from aniline. © 2001 Elsevier Science Ltd. All rights reserved.

Dehydroabietic acid **1**, the main constituent of disproportionated rosin, and several of its derivatives show antibacterial or antifungal activity.[1] Methyl dehydroabietate is readily transformed into methyl *cis*-deisopropyldehydroabietate **2** by reaction with aluminium trichloride[2] and this compound provides a convenient starting material for the construction of other derivatives. Some of these derivatives lacking the isopropyl group are also antimicrobial agents.[3] The discovery that 'claycop', a montmorillonite clay impregnated with copper(II) nitrate, could act as a selective nitrating agent for activated aromatic compounds[4] led us to investigate the selective nitration of the ester **2**.[5] It was found that the selectivity for the formation of the 12-nitro derivative **3** over the 13-nitro and 14-nitro isomers was significantly improved when this reagent was used.

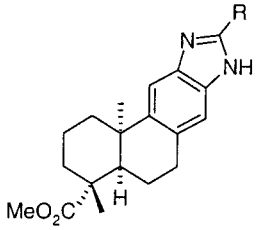
The aim of the present work was to construct imidazoles fused to the aromatic ring of the dehydroabietic acid skeleton with this 12-nitro derivative **3** as the starting material. Benzimidazoles are known to have diverse biological activity and, by combining the imidazole ring system with the dehydroabietic acid skeleton, there seemed a good possibility that the new compounds would show useful antibacterial or antifungal properties. An efficient route to a series of phenanthro[2,3-*d*]imidazole derivatives having the general structure **4** has been developed. The key step is a one pot acylation and *ortho* nitration procedure starting from the amine **5** (Scheme 1). This procedure had previously been carried out successfully with aniline and acetic anhydride[4] and we have now shown that this is also a general and convenient method for the synthesis of benzimidazoles from aniline (Scheme 2).



1



2 R = H
3 R = NO_2
5 R = NH_2
7 R = NHCOPh



4a R = Me
b R = Pr
c R = CF_3
d R = H
e R = Ph

Keywords: diterpenes; resin acids; benzimidazoles.
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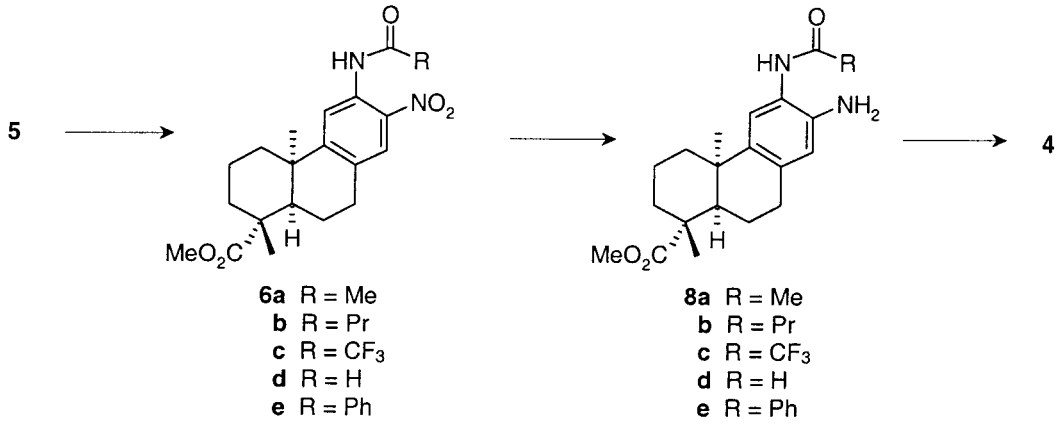
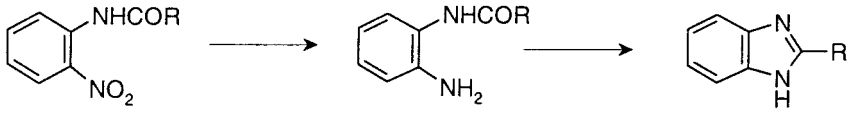


6a R = Me
b R = Pr
c R = CF_3
d R = H
e R = Ph

8a R = Me
b R = Pr
c R = CF_3
d R = H
e R = Ph

Scheme 1.



9a R = Me
b R = Pr
c R = CF_3
d R = H
e R =Ph

10a R = Me
b R = Pr
c R = Ph

11a R = Me
b R = Pr
c R =CF_3
d R = H
e R = Ph

Scheme 2.

1. Phenanthro[2,3-*d*]benzimidazole derivatives

The nitroarene **3** was obtained in 43% yield as a yellow crystalline solid from methyl *cis*-deisopropyldehydroabietate **2** by nitration with 'claycop' followed by recrystallization from methanol. It was reduced in high yield to the amine **5** by catalytic hydrogenation. The combined acylation and nitration of the amine **5** was carried out by adding the amine to a cooled suspension of 'claycop' and the appropriate carboxylic acid anhydride in carbon tetrachloride. By this means three 12-acylamino-13-nitro- compounds **6a–c** were prepared and isolated in 60–70% yield. The formamide **6d** was prepared (59%) by a slight modification of the general procedure. The procedure did not succeed when benzoic anhydride was used so the benzamide **6e** was prepared in two steps, and in good overall yield, by benzoylation of the amine **5** to give the amide **7** followed by nitration.

2-Nitro-*N*-acylanilines are well established as intermediates in the synthesis of 2-substituted benzimidazoles.[6] The reaction sequence is reduction of the nitro group to an amino group followed by cyclodehydration. With the nitro compounds **6** catalytic hydrogenation of the nitro group required forcing conditions. The reactions were best carried out under a pressure of 50–100 psi over a palladium catalyst. When the hydrogenation was performed at rt the corresponding amines **8** were isolated and these were then cyclized to the imidazoles **4** by heating in a mixture of xylenes and acetic acid. Alternatively when the catalytic hydrogenation was carried out at 120°C and in the presence of a catalytic amount of montmorillonite clay (K10) as an acid catalyst, the imidazoles **4** could be obtained directly as the major or exclusive products.

Preliminary assays have shown that the imidazoles **4** possess both antimicrobial and antifungal activity. These results will be reported separately.

2. Benzimidazoles

Having established this route as an efficient method for the preparation of the phenanthro[2,3-*d*]imidazoles **4** the methodology was briefly applied to the conversion of aniline into 2-substituted benzimidazoles (Scheme 2). The 2-nitro-*N*-acylanilines **9a–e** were prepared in one step by the reaction with the appropriate acid anhydride and 'claycop'. This method worked well with acetic, butyric, acetic-formic and benzoic anhydrides but the yield of the amide **9c** was low (40%) in the reaction with trifluoroacetic anhydride because the major product (52%) was 4-nitrotrifluoroacetanilide. These amides were then converted into benzimidazoles **11** by either of the two procedures described above for compounds **4**. The yields were usually higher when the two step procedure, involving isolation of the amines **10** and subsequent cyclization, was used although benzimidazole **11d** and 2-trifluoromethylbenzimidazole **11c** were prepared in good yield by the one step method.

3. Experimental

3.1. Materials and methods

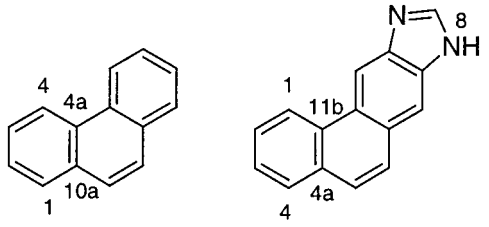
All reagents were of analytical grade, dried and purified when necessary. Dehydroabietic acid **1** was obtained from commercially disproportionated rosin and was purified by

repeated crystallization of the ethanolamine salt.[7] Methyl dehydroabietate[8] was prepared from the acid by reaction with diazomethane. 'Claycop' was prepared by impregnation of an acidic montmorillonite clay (K10), commercially available, with cupric nitrate, according to a published procedure.[9] Light petroleum refers to the fraction bp 40–60°C.

^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75.5 MHz, on a Varian Gemini 300 instrument. Mass spectra were recorded on a VG micromass 7070E instrument under electron impact at 70 eV. Microanalyses were performed in the University of Liverpool microanalysis laboratory.

3.2. Nomenclature

Compounds derived from dehydroabietic acid have been named systematically in the Section 3 as derivatives of phenanthrene (**A**) or of phenanthro[2,3-*d*]imidazole (**B**). The systematic numbering of the two ring systems is shown.



3.2.1. Methyl (1*R*,4a*R*,10a*R*)-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydro-phenanthrene-1-carboxylate (methyl *cis*-deisopropyldehydroabietate) 2. Aluminium trichloride (94.43 g, 0.71 mol) was added carefully to a solution of methyl dehydroabietate (42 g, 0.12 mol) in toluene (500 mL), with vigorous stirring, under N_2, at rt. The reaction was followed by GC analysis. After the reaction was complete (4.5 h) water and sodium hydroxide pellets were added to the reaction mixture, maintained in an ice bath. The separated organic layer was washed with water and dried with anhydrous sodium sulfate. The aqueous layer was extracted with diethyl ether, washed with water and dried with anhydrous sodium sulfate. The combined organic layers were evaporated to dryness. The residue obtained was dissolved in light petroleum and treated with charcoal and filtered after 24 h. The solution was dried and evaporated to leave a yellow gum. By recrystallization, methyl *cis*-deisopropyldehydroabietate **2** was obtained as colourless crystals, mp 90–92°C (from methanol) (lit.[2] 93–94°C); IR (Nujol) ν_{max} 1721 and 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (3H, s, 1-Me), 1.21 (3H, s, 4a-Me), 1.20–1.22 (1H, m, 2-H$_\alpha$), 1.50–1.66 (3H, m; 4-H$_\alpha$, 3-H$_\beta$ and 10-H$_\beta$); 1.75–1.82 (2H, m, 4-H$_\beta$ and 3-H$_\alpha$), 1.99–2.04 (2H, m, 2-H$_\beta$ and 10-H$_\alpha$), 2.35 (1H, dd, *J*=11.1 Hz, 10a-H), 2.84–2.89 (2H, m, 2×9-H), 3.68 (3H, s, COOC*H*$_3$), 7.02–7.16 (3H, m; 6-H, 7-H and 8-H) and 7.27 (1H, d, *J*=7.2 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.7 (C-3), 20.1 (C-10), 26.0 (C-1-Me), 27.5 (C-4a-Me), 30.3 (C-9), 32.2 (C-2), 36.8 (C-4), 38.6 (C-4a), 45.4 (C-1), 46.0 (C-10a), 51.6 (COO*C*H$_3$), 125.3 (C-5), 125.9 (C-6), 126.2 (C-7), 128.7 (C-8), 136.1 (C-8a), 146.3 (C-4b) and 179.5 (*C*OOCH$_3$); MS *m*/*z* 272 [M]$^+$ (12%), 257 (17%) and 197 (100%). Anal. Calcd for $C_{18}H_{24}O_2$ C 79.37, H 8.88; found C 79.13, H 8.87%.

3.2.2. Methyl (1*R*,4a*R*,10a*R*)-1,4a-dimethyl-6-nitro-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate 3. The ester **2** (4.01 g, 14.7 mmol) was added to a suspension of 'claycop' (3.94 g, 17.1 mmol) in carbon tetrachloride (23 mL) and acetic anhydride (12.5 mL), in an ice-bath. The mixture was vigorously stirred at rt and the reaction followed by TLC, until completion, and then filtered. The filter cake was washed with diethyl ether and the combined organic extracts were washed with water followed by aq. sodium hydrogen carbonate, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure (5.29 g). Analysis by GC showed **3** (51%), 7-nitrophenanthrene (28%) and 8-nitrophenanthrene (19%). By recrystallization compound **3** (2.0 g, 6.3 mmol, 43%) was isolated as yellow crystals, mp 108–110°C (from methanol) (lit.[5] 109–110°C); FT-IR (KBr) ν_{max} 1726, 1517, 1346 and 1137 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (3H, s), 1.26 (3H, s), 1.24–1.28 (1H, m), 1.48–1.69 (3H, m); 1.78–1.88 (2H, m), 2.02–2.17 (2H, m), 2.39 (1H, dd, *J*=10.4 and 3.3 Hz), 2.93–2.97 (2H, m), 3.69 (3H, s), 7.18 (1H, d, *J*=8.5 , 8-H), 7.92 (1H, dd, *J*=8.4 and 2.3 Hz, 7-H) and 8.17 (1H, d, *J*=2.3 Hz, 5-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.4, 19.6, 25.6, 27.7, 30.3, 32.2, 36.8, 38.9, 45.1, 45.2, 51.8, 120.4, 121.6, 129.7, 144.2, 146.8, 148.0 and 179.2; MS *m*/*z* 317 [M]$^+$(6%), 300 (5%), 242 (100%) and 176 (35%). Anal. Calcd for $C_{18}H_{23}NO_4$ C 68.12, H 7.30, N 4.41; found C 68.28, H 7.32, N 4.34%.

3.2.3. Methyl (1*R*,4a*R*,10a*R*)-6-amino-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate 5. A mixture of the nitro compound **3** (2.20 g, 6.94 mmol) and Pd/C 5% (238 mg) in ethanol (66.5 mL) was stirred in a pressure reactor at rt under H_2 (100 psi). The reaction was followed by TLC and at the end the reaction mixture was filtered over Celite and the catalyst washed with dichloromethane. After the solvent was evaporated under reduced pressure, the amine **5** (2.00 g, 6.66 mmol, 96%) was obtained as white crystals, mp 115–117°C (from ethanol); IR (KBr) ν_{max} 3465, 3372, 1708, 1629, 1257 and 1192 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (3H, s), 1.17 (3H, s), 1.18–1.20 (1H, m), 1.43–1.61 (3H, m); 1.72–1.83 (2H, m), 1.94–2.03 (2H, m), 2.29 (1H, dd, *J*=10.6 and 3.6 Hz), 2.72–2.77 (2H, m), 3.40 (2H, brs), 3.67 (3H, s), 6.46 (1H, dd, *J*=8.0 and 2.4 Hz), 6.60 (1H, d, *J*=2.4 Hz) and 6.82 (1H, d, *J*=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.5, 20.2, 25.7, 27.5, 29.3, 32.2, 36.6, 38.4, 45.1, 45.9, 51.5, 112.9, 113.3, 126.4, 129.5, 144.2, 147.2 and 179.8; MS *m*/*z* 287 [M]$^+$(70%), 272 (5%), 228 (4%) and 212 (100%). Anal. Calcd for $C_{18}H_{25}NO_2$ C 75.22, H 8.77, N 4.87; found C 74.99, H 8.88, N 4.79%.

3.2.4. Methyl (1*R*,4a*R*,10a*R*)-6-acetamido-1,4a-dimethyl-7-nitro-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate 6a. The amine **5** (213 mg, 0.75 mmol) was added to a suspension of 'claycop' (350 mg, 1.53 mmol) in carbon tetrachloride (2.5 mL) and acetic anhydride (0.9 mL, 9.38 mmol) with vigorous stirring, in an ice-bath. The reaction mixture was warmed to rt, and the reaction followed by TLC. At the end (1.5 h), the 'claycop' was

filtered off and the filter cake washed with diethyl ether. The organic phases were washed with water followed by sodium hydrogen carbonate and dried over anhydrous sodium sulfate. After evaporation of the solvent an orange residue (372 mg) was obtained that was purified by silica column chromatography with light petroleum–ethyl acetate (6:4) as eluent. After recrystallization, yellow crystals of the acetamide **6a** (160 mg, 0.51 mmol, 68%) were obtained, mp 101.5–103.5°C (from light petroleum); IR (KBr) ν_{max} 3378, 1726, 1701, 1655, 1579 and 1339 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (3H, s), 1.24 (3H, s), 1.23–1.25 (1H, m), 1.54–1.62 (3H, m); 1.81–1.86 (2H, m), 1.99–2.13 (2H, m), 2.27 (3H, s), 2.37 (1H, dd, J=8.0 and 3.3 Hz), 2.86–2.91 (2H, m), 3.70 (3H, s), 7.91 (1H, s), 8.74 (1H, s) and 10.21 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.3, 19.8, 25.2, 25.6, 27.7, 29.1, 32.5, 36.4, 39.6, 45.3, 51.8, 120.1, 125.3, 132.3, 132.7, 134.1, 156.1, 169.1 and 179.1; MS m/z 374 $[M]^+$(33%), 332 (53%), 328 (59%), 317 (36%), 299 (14%), 257 (55%), 59 (25%) and 43 (100%). Anal. Calcd for $C_{20}H_{26}N_2O_5$ C 64.16, H 7.00, N 7.48; found C 64.09, H 7.02, N 7.47%.

3.2.5. Methyl (1*R*,4a*R*,10a*R*)-6-butyramido-1,4a-dimethyl-7-nitro-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate 6b. Under the conditions described for the preparation of the amide **6a**, the amine **5** (200 mg, 0.70 mmol), 'claycop' (584 mg, 2.6 mmol), butyric anhydride (0.8 mL, 4.88 mmol) and carbon tetrachloride (2.5 mL) gave, after 3.5 h, an oil (314 mg) that was purified by silica chromatography using light petroleum–ethyl acetate (8:2) as eluent. The amide **6b** was obtained as a yellow oil (169 mg, 0.42 mmol, 60%), IR (film) ν_{max} 3369, 1727, 1620, 1579, 1503, 1335, 1252, and 1136 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (3H, t, J=7.3 Hz), 1.06 (3H, s), 1.24 (3H, s), 1.19–1.29 (1H, m), 1.50–1.66 (3H, m), 1.72–1.84 (4H, m), 1.98–2.11 (2H, m), 2.36 (1H, dd, J=11.4 and 3.6 Hz), 2.45 (2H, t, J=7.3 Hz), 2.83–2.85 (2H, m), 3.69 (3H, s), 7.90 (1H, s), 8.77 (1H, s) and 10.25 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.7, 18.7, 19.3, 19.7, 25.4, 27.5, 29.2, 32.2, 36.3, 39.5, 40.4, 45.1, 45.3, 51.8, 120.0, 125.2, 132.0, 132.6, 133.8, 156.1, 172.1 and 179.1; MS m/z 402 $[M]^+$(23%), 356 (67%), 332 (100%), 317 (21%), 257 (60%), 71 (54%) and 43 (77%). HRMS: Calcd for $C_{22}H_{30}N_2O_5$ 402.21545; found 402.21490.

3.2.6. Methyl (1*R*,4a*R*,10a*R*)-1,4a-dimethyl-7-nitro-1,2,3,4,4a,9,10,10a-octahydro-6-trifluoroacetamidophenanthrene-1-carboxylate 6c. Under the conditions described for the amide **6a**, the amine **5** (202 mg, 0.71 mmol), 'claycop' (255 mg, 1.11 mmol), trifluoroacetic anhydride (0.5 mL, 3.58 mmol) and carbon tetrachloride (2.5 mL) gave, after 1 h, an oil (399 mg) that was purified by silica column chromatography using light petroleum–ethyl acetate (8:2) as eluent. The amide **6c** was obtained as a yellow oil (213 mg, 0.49 mmol, 70%); IR (Nujol) ν_{max} 3315, 1732, 1619, 1592, 1510, 1345, 1301, 1252, and 1141 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (3H, s), 1.26 (3H, s), 1.23–1.29 (1H, m), 1.51–1.67 (3H, m), 1.76–1.87 (2H, m), 2.00–2.15 (2H, m), 2.39 (1H, dd, J=10.3 and 3.6 Hz), 2.89–2.94 (2H, m), 3.70 (3H, s), 7.99 (1H, s), 8.67 (1H, s) and 11.30 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.5, 19.7, 25.6, 27.4, 29.4, 32.0, 36.4, 39.6, 45.1, 45.2, 51.9, 120.1, 125.8, 129.6, 134.4, 134.6, 155.1, 156.7 and 178.9; MS m/z 428 $[M]^+$ (10%), 353 (60%), 305 (52%), 287 (31%), 69 (100%), 55 (82%) and 41 (99%). HRMS: Calcd for $C_{20}H_{23}F_3N_2O_5$ 428.15588, found 428.15516.

3.2.7. Methyl (1*R*,4a*R*,10a*R*)-1,4a-dimethyl-6-formamido-7-nitro-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate 6d. Acetic-formic anhydride was generated under N_2 by the dropwise addition of 98% formic acid (0.14 mL, 3.58 mmol) to acetic anhydride (0.28 mL, 2.91 mmol) maintained at 0°C followed by gentle heating (50–60°C, 2 h). The reaction mixture was cooled to rt and carbon tetrachloride (5 mL) was added. The amine **5** (296 mg, 1.03 mmol) in carbon tetrachloride (5 mL) was added dropwise to the reaction mixture. After checking that the amine had been consumed (TLC), 'claycop' (592.8 mg, 2.62 mmol) followed by acetic anhydride (1.6 mL, 16.7 mmol) were added. The reaction was complete in 2.25 h. After workup as for amide **6a** the solid residue (385 mg) was purified by silica column chromatography using light petroleum ether–ethyl acetate (6:4) as eluent. After recrystallization, yellow crystals of the amide **6d** (219 mg, 0.60 mmol, 59%) were obtained, mp 127.9–130°C (from light petroleum–diethyl ether); IR (film) ν_{max} 3358, 1724, 1618, 1578, 1502, 1337, 1254, 1137 and 733 $^{-1}$; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (3H, s), 1.25 (3H, s), 1.18–1.29 (1H, m), 1.50–1.66 (3H, m), 1.78–1.85 (2H, m), 1.91–2.05 (2H, m), 2.38 (1H, dd, J=10.0 and 3.6 Hz), 2.87–2.91 (2H, m), 3.70 (3H, s), 7.93 (1H, s), 8.55 (1H, s), 8.76 (1H, s) and 10.18 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.4, 19.8, 25.4, 27.6, 29.2, 32.3, 36.4, 39.6, 45.3, 51.8, 120.7, 125.5, 131.5, 133.0, 134.0, 156.1, 159.4 and 179.1; MS m/z 360 $[M]^+$ (32%), 345 (3%), 285 (100%), 173 (91%), 115 (67%) and 41 (77%). Anal. Calcd for $C_{19}H_{24}N_2O_5$ C 63.45, H 6.69, N 7.74; found C 63.60, H 6.95, N 7.56%.

3.2.8. Methyl (1*R*,4a*R*,10a*R*)-6-benzamido-1,4a-dimethyl-7-nitro-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate 6e. *(a) Benzoylation of the Amine 5.* Benzoyl chloride (0.3 mL, 2.30 mmol), the amine **5** (625 mg, 2.13 mmol) and *N*,*N*-diisopropylethylamine (0.27 mL, 2.84 mmol) in dry diethyl ether (52 mL) gave methyl (1*R*,4a*R*,10a*R*)-6-benzamido-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylate **7** (723 mg, 1.85 mmol, 87%) as a white solid, mp 165–167°C (from heptane–diethyl ether); IR ν_{max} 3328, 2943, 1725, 1649, 1311 and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (3H, s), 1.25 (3H, s), 1.24–1.30 (1H, m), 1.48–1.65 (3H, m), 1.74–1.84 (2H, m), 1.98–2.09 (2H, m), 2.34 (1H, dd, J=10.4 and 3.3 Hz), 2.82–2.86 (2H, m), 3.68 (3H, s), 7.03 (1H, d, J=8.1 Hz), 7.36 (1H, dd, J=8.1 and 2.1 Hz), 7.43–7.53 (3H, m), 7.55 (1H, d, J=2.1 Hz), 7.83 (1H, brs) and 7.86 (2H, dd, J=7.0 and 1.5 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.6, 20.1, 25.7, 27.7, 29.7, 32.3, 36.7, 38.7, 45.3, 45.8, 51.6, 117.9, 118.2, 127.0, 128.8, 129.3, 131.7, 132.7, 135.3, 135.9, 147.1, 165.7 and 179.6; MS m/z 391 $[M]^+$ (30%), 376 (9%), 316 (38%), 105 (100%) and 77 (55%). Anal. Calcd for $C_{25}H_{29}NO_3$ C 76.70, H 7.47, N 3.58; found C 76.96, H 7.58, N 3.42%.

(b) Nitration. By the procedure used for the amide **6a**, the amide **7** (150 mg, 0.38 mmol), 'claycop' (142 mg,

0.62 mmol), acetic anhydride (0.8 mL, 8.34 mmol), and carbon tetrachloride (2.5 mL) gave after 0.5 h, yellow crystals of the amide **6e** (160 mg, 0.366 mmol, 96%), mp 161–162°C (from diethyl ether); IR ν_{max} 3364, 1725, 1684, 1580, 1501, 1335, 1259, 1136 and 732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (3H, s), 1.18–1.24 (1H, m), 1.30 (3H, s), 1.55–1.71 (3H, m), 1.83–1.91 (2H, m), 2.00–2.15 (2H, m), 2.40 (1H, dd, J=10.0 and 3.6 Hz), 2.88–2.93 (2H, m), 3.70 (3H, s), 7.50–7.62 (3H, m), 7.98 (1H, s), 7.98–8.00 (2H, m), 8.99 (1H, s) and 11.24 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.4, 19.8, 25.3, 27.8, 29.2, 32.4, 36.5, 39.7, 45.4, 51.8, 120.0, 125.5, 127.3, 129.1, 132.5, 133.1, 134.2, 134.4, 156.4, 165.9 and 179.2; MS m/z 436 $[M]^+$ (8%), 390 (37%) and 105 (100%). Anal. Calcd for $C_{25}H_{28}N_2O_5$ C 68.79, H 6.46, N 6.42; found C 68.67, H 6.62, N 6.35%.

3.2.9. Methyl (4*R*,4a*R*,11b*R*)-2,3,4,4a,5,6,8,11b-octahydro-4,9,11b-trimethyl-1*H*-phenanthro[2,3-*d*]imidazole-4-carboxylate 4a. *(a) Reduction.* A mixture of the nitroacetamide **6a** (73 mg, 0.19 mmol), Pd/C 10% (21 mg) and ethanol (8 mL) was hydrogenated (H_2, 50 psi) in a pressure reactor at rt. After the reaction was complete (TLC), the reaction mixture was filtered over Celite, washed with dichloromethane and the solution evaporated to dryness. The residue obtained (73 mg) was purified by silica column chromatography using dichloromethane–methanol (9:1) to give the amine **8a** (56 mg, 0.16 mmol, 84%) as an oil; IR (film) ν_{max} 3345, 2933, 1723, 1661, 1509, 1248, 1134 and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (3H, s), 1.14 (3H, s), 1.19–1.26 (1H, m), 1.41–1.61 (3H, m), 1.68–1.80 (2H, m), 1.93–2.01 (2H, m), 2.14 (3H, s), 2.26 (1H, dd, J=10.6 and 3.5 Hz), 2.72–2.77 (2H, m), 3.67 (3H, s), 3.68 (2H, brs), 6.45 (1 H), 7.00 (1H, s) and 7.37 (1H, brs); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.7, 20.1, 23.5, 26.1, 27.6, 29.9, 32.0, 37.0, 37.9, 45.1, 45.8, 51.6, 117.7, 122.8, 123.3, 135.4, 138.0, 138.4, 169.0 and 179.7; MS m/z 344 $[M]^+$ (43%), 329 (43%), 269 (100%) and 251 (47%). HRMS: Calcd for $C_{20}H_{28}N_2O_3$ 344.20996; found 344.21052.

(b) Cyclization. A mixture of the amine **8a** (302 mg, 0.88 mmol), xylene (6 mL) and acetic acid (2 mL) was heated under reflux for 15 min. The solution was evaporated to dryness. After purification of the residue by silica column chromatography using dichloromethane–methanol (9.5:0.5), the imidazole **4a** (221 mg, 0.68 mmol, 77%) was obtained by recrystallization; mp 133–135°C (from toluene); IR ν_{max} 2938, 1727, 1463, 1248, 1194, 1135 and 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.00 (3H, s), 1.24 (3H, s), 1.26–1.30 (1H, m), 1.55–1.68 (3H, m), 1.71–1.79 (2H, m), 1.82–2.00 (1H, m), 2.03–2.12 (1H, m), 2.38 (1H, dd, J=9.4 and 3.0 Hz), 2.58 (3H, s), 2.94–2.98 (2H, m), 3.68 (3H, s), 7.17 (1H, s) and 7.45 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.8, 19.5, 20.5, 24.1, 29.6, 30.0, 33.6, 37.7, 38.7, 46.2, 51.5, 111.5, 113.1, 131.2, 136.5, 138.0, 140.8, 150.9 and 179.5; MS m/z 326 $[M]^+$ (18%), 311 (27%), 251 (100%) and 84 (31%). Anal. Calcd for $C_{20}H_{26}N_2O_2$ C 73.59, H 8.03, N 8.58; found C 73.29, H 8.06, N 7.97%. HRMS: Calcd for $C_{20}H_{26}N_2O_2$ 326.19943; found 326.19931.

3.2.10. Methyl (4*R*,4a*R*,11b*R*)-4,11b-dimethyl-2,3,4,4a,5,6,8,11b-octahydro-9-propyl-1*H*-phenanthro[2,3-*d*]imidazole-4-carboxylate 4b. *(a) Reduction.* By the procedure described for reduction of the nitroamide **6a**, the nitroamide **6b** (53 mg, 0.13 mmol) was reduced over Pd/C 5% (21 mg) in ethanol (5 mL) under H_2 (100 psi) at rt for 4 h. The residue obtained (65 mg) was purified by silica column chromatography using dichloromethane–methanol (24:1); the amine **8b** was isolated as a white foam (50 mg, 0.125 mmol, 96%); IR ν_{max} 3345, 1724, 1660, 1651, 1515, 1255, 1135, 732, and 666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (3H, t, J=7.4 Hz), 1.07 (3H, s), 1.14 (3H, s), 1.18–1.22 (1H, m), 1.45–1.62 (3H, m), 1.70–1.81 (2H, m), 1.70–1.82 (2H, m), 1.97–2.00 (2H, m), 2.27 (1H, dd, J=9.1 and 3.0 Hz), 2.34 (2H, t, J=7.3 Hz), 2.73–2.77 (2H, m), 3.67 (3H, s), 3.68 (2H, brs), 6.46 (1H, s), 7.03 (1H, s) and 7.22 (1H, brs); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.8, 19.2, 19.7, 20.1, 26.1, 27.6), 29.9, 32.1, 37.0, 37.9, 38.9, 45.1, 45.8, 51.6, 117.8, 123.0, 127.1, 135.1, 137.3, 138.2, 171.8 and 179.7; MS m/z 372 $[M]^+$ (22%), 357 (21%), 297 (40%), 279 (100%) and 43 (30%). Anal. Calcd for $C_{22}H_{32}N_2O_3$ C 70.94, H 8.66, N 7.52; found C 70.60, H 8.75, N 7.43%. HRMS: Calcd for $C_{22}H_{32}N_2O_3$ 326.19943; found 326.19931.

(b) Cyclization. The amine **8b** (50 mg, 0.125 mmol), xylene (3 mL), and acetic acid (1 mL) were heated under reflux for 40 min. The solution was evaporated to dryness after cooling the reaction mixture to rt. After purification of the reaction mixture by silica column chromatography using dichloromethane–methanol (19.1), a white foam of the imidazole **4b** (30 mg, 0.085 mmol, 67%) was obtained; IR ν_{max} 2940, 1726, 1462, 1250, 1194, 1135, and 731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.96 (3H, t, J=7.3 Hz), 1.00 (3H, s), 1.22 (3H, s), 1.18–1.29 (1H, m), 1.51–1.63 (3H, m), 1.72–1.76 (1H, m), 1.85 (2H, q, J=7.3 Hz), 1.91–1.95 (2H, m), 1.99–2.09 (1H, m), 2.36 (1H, dd, J=9.4 and 3.6 Hz), 2.88 (2H, t, J=7.3 Hz), 2.94–2.99 (2H, m), 3.67 (3H, s), 7.18 (1H, s) and 7.46 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.8, 19.6, 20.4, 21.6, 25.1, 28.8, 30.9, 32.0, 32.6, 37.5, 38.7, 45.5, 46.0, 51.7, 111.7, 112.9, 131.1, 135.7, 137.2, 141.0, 155.1 and 179.6; MS m/z 354 $[M]^+$ (17%), 339 (22%) and 279 (100%). HRMS: Calcd for $C_{22}H_{30}N_2O_2$ 354.23071; found 354.23031.

3.2.11. Methyl (4*R*,4a*R*,11b*R*)-4,11b-dimethyl-2,3,4,4a,5,6,8,11b-octahydro-9-trifluoromethyl-1*H*-phenanthro-[2,3-*d*]imidazole-4-carboxylate 4c. The nitroamide **6c** (111 mg, 0.26 mmol), K10 (211 mg), Pd/C 10% (29 mg) and ethanol (7 mL) were heated under H_2 (150 psi) at 120°C for 17 h. The imidazole **4c** (95 mg, 0.25 mmol, 97%) was obtained as a white foam; IR ν_{max} 2927, 1727, 1461, 1251, and 1139 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (3H, s), 1.25 (3H, s), 1.25–1.32 (1H, m), 1.53–1.66 (3H, m), 1.76–1.78 (1H, m), 1.96–2.01 (2H, m), 2.11–2.16 (1H, m), 2.41 (1H, dd, J=9.0 and 4.8 Hz), 3.00–3.02 (2H, m), 3.70 (3H, s), 7.36 (1H, s) and 7.65 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.4, 20.6, 23.5, 29.8, 30.0, 33.8, 37.7, 38.9, 45.9, 46.4, 51.6, 113.8, 114.7, 117.4 (t, J=271 Hz), 135.8, 137.8, 141.2 (q, J=43.1 Hz), 143.5 and 179.6; MS m/z 380 $[M]^+$ (10%), 365 (11%), 361 (3%), 333 (4%), and 305 (100%). HRMS: Calcd for $C_{20}H_{23}N_2O_2F_3$ 380.17114; found 380.17102.

3.2.12. Methyl (4*R*,4a*R*,11b*R*)-4,11b-dimethyl-2,3,4,4a,5,6,8,11b-octahydro-1*H*-phenanthro[2,3-*d*]imidazole-4-

carboxylate 4dA mixture the formamide **6d** (70 mg, 0.194 mmol), K10 (175 mg), Pd/C 10% (20 mg) and ethanol (10 mL) was hydrogenated (H_2, 100 psi) at 120°C overnight (16.5 h) with vigorous stirring. After cooling to rt, the reaction mixture was filtered over Celite and washed with dichloromethane, that after evaporation to dryness gave a white foam of the imidazole **4d** (58 mg, 0.186 mmol, 96%); IR ν_{max} 2943, 1723, 1583, 1462, 1249, 1194, 1135 and 731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (3H, s), 1.26 (3H, s), 1.26–1.32 (1H, m), 1.50–1.68 (3H, m), 1.68–1.78 (1H, m), 1.91–1.99 (2H, m), 2.01–2.14 (1H, m), 2.39 (1H, dd, J=9.1 and 4.0 Hz), 2.99–3.03 (2H, m), 3.69 (3H, s), 7.29 (1H, s), 7.58 (1H, s) and 8.00 (1H, s, 9-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.6, 20.5, 24.7, 29.2, 30.3, 33.0, 37.6, 38.8, 45.8, 46.0, 51.7, 112.6, 113.9, 132.0, 135.4, 137.1, 140.7, 141.7 and 179.7; MS m/z 312 $[M]^+$ (12%), 297 (20%) and 237 (100%). HRMS: Calcd for $C_{19}H_{24}N_2O_2$ 312.18378; found 312.18365.

3.2.13. Methyl (4*R*,4a*R*,11b*R*)-4,11b-dimethyl-2,3,4,4a,5,6,8,11b-octahydro-9-phenyl-1*H*-phenanthro[2,3-*d*]imidazole-4-carboxylate 4e. *(a) Reduction.* The nitroamide **6e** (150 mg, 0.38 mmol) and Pd/C 10% (36 mg) in ethanol (10 mL) was hydrogenated under H_2 (60 psi) at rt for 2 h. Column chromatography using dichloromethane–methanol (24:1) gave the amine **8c** as a white foam (131 mg, 0.32 mmol, 85%); IR ν_{max} 3343, 2943, 1723, 1649, 1516, 1256, 1136, and 731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (3H, s), 1.16 (3H,s), 1.20–1.26 (1H, m), 1.43–1.63 (3H, m), 1.69–1.82 (2H, m), 1.96–2.03 (2H, m), 2.28 (1H, dd, J=10.4 and 3.0 Hz), 2.74–2.80 (2H, m), 3.67 (3H, s), 3.73 (2H, brs), 6.50 (1H, s), 7.20 (1H, s), 7.46 (1H, brs), 7.43–7.56 (3H, m) and 7.81–7.91 (2H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.7, 20.1, 26.0, 27.7, 29.9, 32.2, 37.0, 37.9, 45.1, 45.8, 51.6, 118.0, 122.9, 123.1, 127.4, 128.8, 131.8, 134.4, 135.2, 138.1, 138.2, 165.9 and 179.7; MS m/z 406 $[M]^+$ (10%), 373 (19%), 313 (100%), 105 (61%) and 77 (27%). HRMS: Calcd for $C_{25}H_{30}N_2O_3$ 406.22562; found 406.22538.

(b) Cyclization. The amine **8c** (87 mg, 0.21 mmol), xylene (3 mL) and acetic acid (0.5 mL) were heated under reflux and under nitrogen for 1 h. The solution was evaporated to dryness after cooling the reaction mixture to rt. After purification by silica column chromatography using dichloromethane–methanol (24:1), yielded the imidazole **4e** (72 mg, 0.18 mmol, 88%) as a white foam; IR ν_{max} 2947, 1726, 1463, 1194, 1136, and 732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (3H, s), 1.19 (3H, s), 1.21–1.26 (1H, m), 1.45–1.62 (3H, m), 1.62–1.75 (1H, m), 1.84–1.99 (2H, m), 2.04–2.14 (1H, m), 2.36 (1H, dd, J=9.0 and 4.0 Hz), 2.86–3.00 (2H, m), 3.68 (3H, s), 7.19 (1H, s), 7.33–7.37 (3H, m), 7.49 (1H, s) and 8.10–8.13 (2H, m); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.5, 20.5, 24.6, 29.2, 30.2, 33.1, 37.5, 38.7, 45.8, 46.0, 51.7, 112.5, 113.5, 126.9, 129.0, 129.9, 130.2, 131.9, 137.0, 138.9, 141.5, 152.3 and 179.8; MS m/z 388 $[M]^+$ (25%), 373 (21%) and 313 (100%). HRMS: Calcd for $C_{25}H_{28}N_2O_2$ 388.21506; found 388.21534.

3.2.14. 2-Nitroacetanilide 9a. Aniline (0.2 mL, 2.19 mmol) was added with vigorous stirring to a mixture of claycop (1.06 g, 4.6 mmol), acetic anhydride (3.3 mL, 34.4 mmol) and carbon tetrachloride (6.6 mL) in an ice-bath. The reaction was followed by TLC and after it was complete (1 h) the claycop was filtered off and the filter cake was washed with dichloromethane. The organic phases were washed with water followed by sodium hydrogencarbonate and dried over anhydrous sodium sulfate. After evaporation of the solvents the solid residue (477 mg) was purified by silica column chromatography using dichloromethane–ethyl acetate (9:1) as eluent. Yellow crystals of 2-nitroacetanilide (355 mg, 1.97 mmol, 90%) were obtained, mp 91–92°C (lit.[10] 91–92°C).

3.2.15. 2-Nitrobutyranilide 9b. A solution of aniline (0.2 mL, 2.19 mmol) in carbon tetrachloride (3 mL) was added with vigorous stirring to butyric anhydride (0.5 mL, 3 mmol) in carbon tetrachloride (4 mL) in an ice-salt bath. After the aniline had been consumed (TLC), 'claycop' (1.55 g, 6.72 mmol), followed by acetic anhydride (3.5 mL, 36.6 mmol) were then added, with vigorous stirring. The ice bath was removed and the reaction continued at rt. After 2 h, the reaction was worked-up as for **9a** to give a solid residue (509 mg) that was purified by silica column chromatography using dichloromethane. Yellow crystals of 2-nitrobutyranilide **9b** (373 mg, 1.79 mmol, 82%) were obtained, mp 49–49.5°C (lit.[11] 50–51°C).

3.2.16. 2-Nitrotrifluoroacetanilide 9c. By the procedure described for the amide **9b**, TFAA (0.35 mL, 2.5 mmol), aniline (0.2 mL, 2.19 mmol), carbon tetrachloride (7 mL), 'claycop' (1.55 g, 6.72 mmol) and acetic anhydride (3.5 mL, 36.6 mmol) gave (2 h) a solid product (453 mg). By silica column chromatography with dichloromethane-light petroleum (3:2) as eluent, 2-nitrotrifluoroacetanilide **9c** was eluted first to give yellow crystals (205 mg, 0.86 mmol, 40%), mp 86–87°C (lit.[12] 86–87°C).

Further elution with dichloromethane gave 4-nitrotrifluoroacetanilide (267 mg, 1.14 mmol, 52%) as a yellow solid, mp 150–152°C (lit.[13] 151–153°C).

3.2.17. 2-Nitroformanilide 9d. Acetic-formic anhydride was prepared in situ from formic acid (0.17 mL, 4.35 mmol) and acetic anhydride (0.42 mL, 4.38 mmol). Carbon tetrachloride (5 mL) was added followed by dropwise addition of aniline (0.4 mL, 4.35 mmol) in carbon tetrachloride (5 mL) at −10°C. After the aniline had reacted (TLC) 'claycop' (2.33 g, 10.13 mmol) then acetic anhydride (6.5 mL, 67.9 mmol) were added to the reaction mixture. After 2.5 h the 'claycop' was filtered off. After workup, the solid residue (883 mg) was purified by silica column chromatography using light petroleum–ethyl acetate (3:2). Pale yellow crystals of 2-nitroformanilide **9d** (498 mg, 3.0 mmol, 69%) were obtained, mp 118.5–119.5°C (lit.[14] 122–123°C).

3.2.18. 2-Nitrobenzanilide 9e. Benzoic anhydride (509 mg, 2.25 mmol), aniline (0.2 mL, 2.19 mmol) and carbon tetrachloride (10 mL), 'claycop' (2.09 g, 9.1 mmol) and acetic anhydride (5.66 mL, 59.18 mmol) reacted for 4 h as described for the preparation of amide **9b**. The solid obtained was purified by silica column chromatography using dichloromethane–light petroleum (3:2) to give 2-nitrobenzanilide **9e** (317 mg, 1.31 mmol, 60%), mp 92.4–93.3°C (lit.[15] 94–95°C).

3.3. Two step conversion of amides 9 into benzimidazoles

3.3.1. General procedure. The appropriate amide in ethanol was hydrogenated over 10% Pd/C at rt under hydrogen (50 psi). The amine obtained was isolated and cyclized by heating under reflux in xylene–acetic acid (13:1) for 0.5–2 h.

The following compounds were prepared in this way:

2-Aminoacetanilide 10a (91% from **9a**), mp 124–126°C (lit.[10] 130–131°C).

2-Methylbenzimidazole 11a (97% from **10a**), mp 170–172°C (lit.[16] 175–176°C).

2-Aminobutyranilide 10b (81% from **9b**), mp 123–124°C (lit.[17] 131°C).

2-Propylbenzimidazole 11b (81% from **10b**) mp 152–153°C (lit.[18] 156–157.5°C).

2-Aminobenzanilide 10c (95% from **9e**), mp 145–147°C (lit.[19] 148–151°C).

2-Phenylbenzimidazole 11e (54% after column chromatography), mp 295°C (lit.[20] 295°C).

3.4. One step conversion of amides 9 into benzimidazoles

The following benzimidazoles were prepared directly from the appropriate amides **9**.

3.4.1. 2-Trifluoromethylbenzimidazole 11c. 2-Nitrotrifluoroacetanilide **9c** (102 mg, 0.44 mmol), K10 (306 mg) and Pd/C 10% (49 mg) were heated in ethanol (10 mL) under H_2 (130 psi) at 120°C for 18 h. 2-Trifluoromethylbenzimidazole **11c** (71 mg, 0.38 mmol, 88%) was obtained as a white precipitate after evaporation of the solvent; mp 205–208°C (lit.[12] 209–210°C).

3.4.2. Benzimidazole 11d. 2-Nitroformanilide **9d** (45 mg, 0.297 mmol), K10 (266 mg), and Pd/C 10% (30 mg) were heated in ethanol (10 mL) under H_2 (150 psi), at 120°C for 16 h. After evaporation of the solvent, **11d** (24 mg, 0.21 mmol, 70%) was obtained as a white precipitate; mp 170–171°C (lit.[21] 173–174°C).

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