Stereoselective synthesis of *cis*-fused hexahydro-isoindolones

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Dedicated to Professor Mieczysław Mąkosza on the occasion of his 70th birthday

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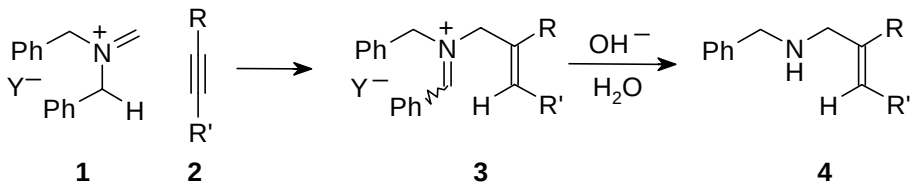
Abstract

Allylamines, readily accessible by ene reactions of *N*,*N*-dibenzyliminium pentachlorostannates with 1,3-enynes, undergo domino reactions with maleic anhydride or maleic imide to give *cis*-fused hexahydroisoindolones, which were characterized by x-ray analysis.

Keywords: Diels-Alder reactions, isoindolones, lactams, stereoselectivity, x-ray analysis

Introduction

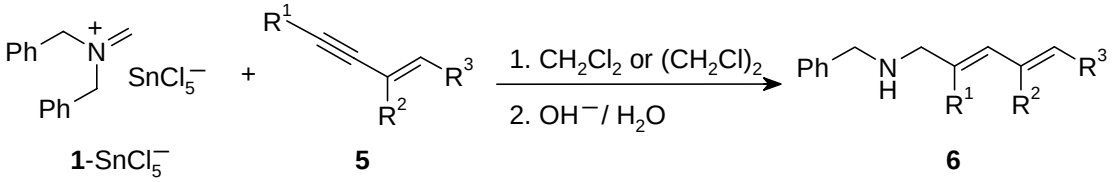
The reactions of iminium ions with alkynes provide a general access to allylamines.[1–3] *N*, *N*-dibenzylmethyleneammonium ions **1**, for example, undergo ene reactions with inverse electron demand with mono- and disubstituted acetylenes **2** to yield the iminium ions **3** which hydrolyze with formation of the N-benzyl protected allylamines **4** (Scheme 1).[2]



1 **2** **3** **4**

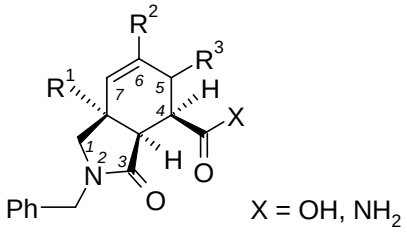
Scheme 1

Though ene reactions of iminium ions with CC-double bonds have also been reported,[4,5] CC-triple bonds are more reactive with the consequence that conjugated enynes **5** can selectively be converted into the corresponding dienylamines **6** (Equation 1).[2]



1-$SnCl_5^-$ **5** **6** **(1)**

We now report that the reactions of the dienylamines **6**, thus readily available, with maleic anhydride and maleic imide provide a straightforward access to partially hydrogenated N-benzyl-3-oxoisoindolone-4-carboxylic acid derivatives **7**,[6,7] a building block of a variety of natural products[8,9] and biologically active compounds.[10–12]



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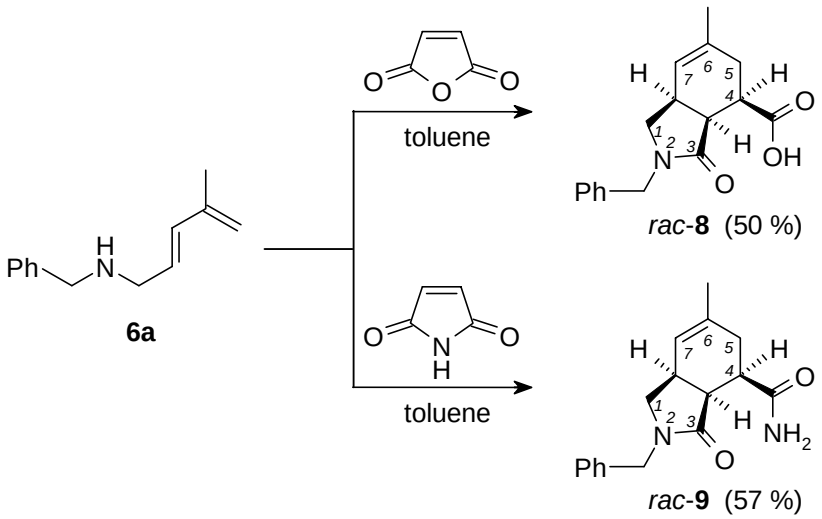
Results

Heating equimolar amounts of the 2,4-dienylamine **6a** with maleic anhydride or maleic imide in toluene gave rise to the formation of the bicyclic lactams *rac*-**8** and *rac*-**9**, respectively. The moderate yields of both reactions given in Scheme 2 were mainly caused by the consecutive crystallization procedure, and no attempt of optimization was undertaken.



Scheme 2

Vicinal coupling constants of $J_{3a,7a}$ = 6.8 Hz and 6.6 Hz were observed in the ^{1}H NMR spectra for the lactams **8** and **9**, respectively, and additional 2D NMR experiments indicated the formation of *cis*-fused ring systems. In order to unequivocally establish the molecular structures of **8** and **9**, crystals suitable for X-ray structure analysis were grown from ethyl acetate/petroleum ether mixtures. The ZORTEP plots in Figures 1 and 2 clearly demonstrate the *cis*-ring junction in both lactams *rac*-**8** and *rac*-**9**.

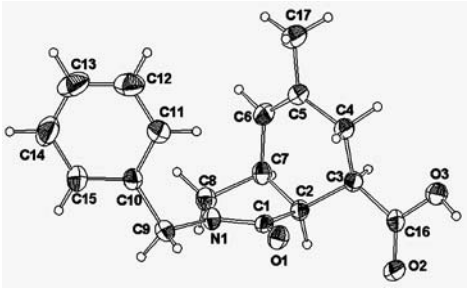


Figure 1. ZORTEP plot of **8**.

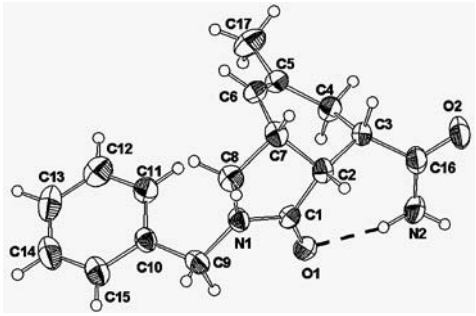


Figure 2. ZORTEP plot of **9**. The intramolecular hydrogen bond between N2 and O1 is shown by a dashed line.

The crystal structure of **9** reveals the presence of intermolecular hydrogen bonds between the free amido groups with O2–N2A distances of 288.9 pm. Further, a stronger intramolecular hydrogen bond between N2 and O1 (279.4 pm) can be found (Figure 2) which also persists in $CDCl_3$ solution and gives rise to separate NMR resonances at δ 5.64 and 9.10 for the protons of the -NH_2 group.

In the crystal structure of the analogous lactam **8** that carries a -COOH group, intramolecular hydrogen bonds could not be observed. However, intermolecular O-H — O hydrogen bonds also play an important role in the solid state of **8** and induce the pairing of enantiomers as shown in Figure 3.

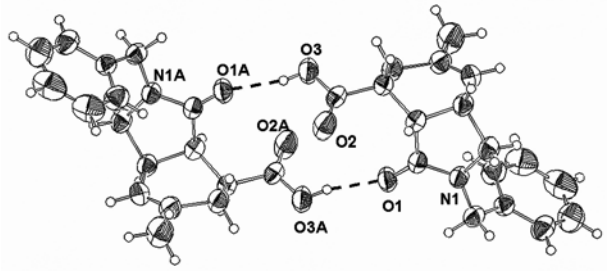
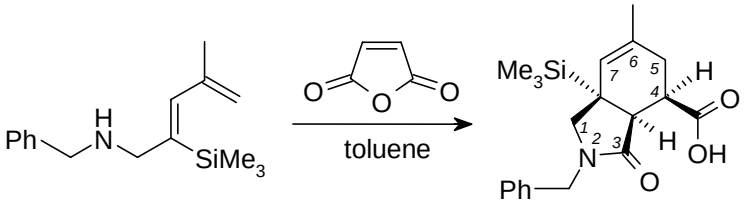


Figure 3. Intermolecular hydrogen bonding pattern in the crystals of racemic **8** (*d*(O1-O3A) = 265.8 pm).

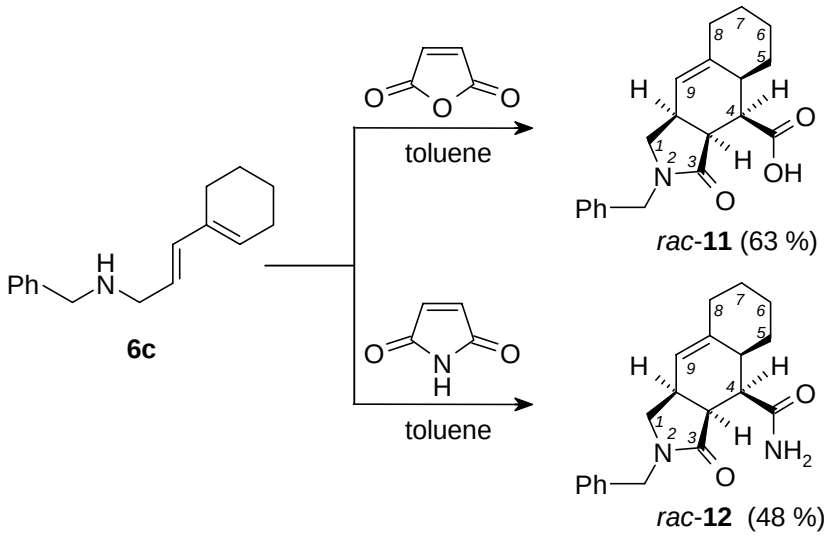
In an analogous reaction of **6b** with maleic anhydride, the silylated bicyclic lactam *rac*-**10** was obtained (Scheme 3). Though the quality of the crystals was not high enough for an X-ray analysis, the *cis*-fusion of the carbon skeleton could clearly be derived from the NOESY spectrum which showed signal enhancements for 1-H (δ 3.42), 3a-H, 4-H, and 7-H when the protons of the trimethylsilyl group were irradiated.



6b *rac*-**10** (65 %)

Scheme 3

The reactions of the dienylamine **6c** with maleic anhydride and maleic imide yielded the tricyclic lactams *rac*-**11** and *rac*-**12**, respectively (Scheme 4). The *cis*-annelation of the lactam and the cyclohexene ring was already indicated by the small vicinal coupling constant of $J_{3a,9a}$ = 6.3 Hz that was found in the ^{1}H NMR spectrum of **12**. Furthermore, the X-ray analysis of crystals of **12** that precipitated from a ethyl acetate/petrolem ether mixture proved that all protons of the central six-membered ring are located at the same face which gives rise to a bowl-shaped molecular structure (Figure 4). This finding is in accord with the observations by Crisp and Gebauer[7] who reported analogous reactions of chiral dienylamines with maleic anhydride.



Scheme 4

Similar to the molecular structure of **9**, the interatomic distance of 276.2 pm indicates the presence of an intramolecular hydrogen bond between the lactam oxygen O1 and the amido nitrogen N2 of **12**. Furthermore, each of the -$CONH_2$ groups is involved in a weaker intermolecular hydrogen bond (296.1 pm) between N2 and O2A. In agreement with the properties in the solid state, the ^{1}H NMR signals of the two protons bound to N2 are observed at chemical shifts that differ by 4.10 ppm.

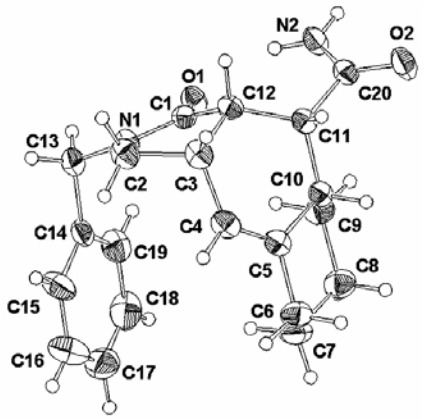
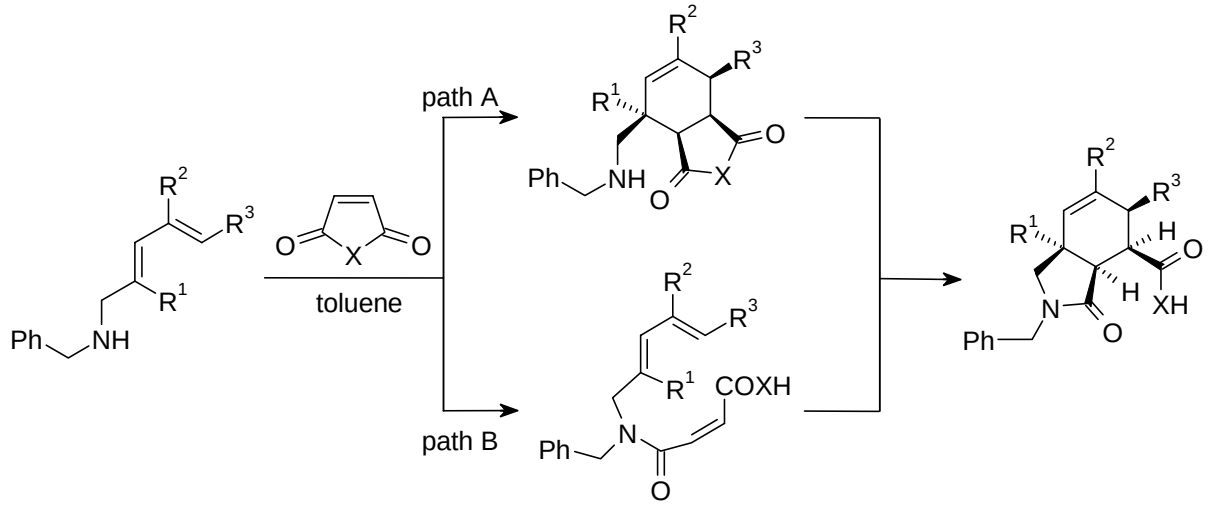


Figure 4. ZORTEP plot of **12** (*d*(O1-N2) = 276.2 pm).

Discussion

The isoindolone derivatives **8**–**12** which could be isolated in moderate yields from the reactions of maleic acid or maleic imine with dienylamines uniformly showed *cis*-annelation of the lactam ring to the adjacent cyclohexenyl ring though the presence of smaller amounts of *trans*-annelated products in the crude reaction products cannot be excluded. This observation contrasts the report by Mellor and Wagland[6] who described that the reaction of maleic anhydride with N-benzyl-hexa-2,4-dienylamine in toluene gave rise to the formation of a *trans*-fused hexahydroisoindolone (yield: 82 %) with a coupling constant of $J_{3a,7a}$ = 12.5 Hz.

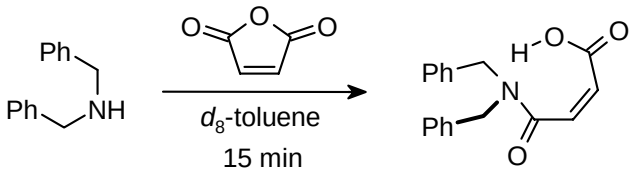
Because Diels-Alder reactions generally show preference for the formation of *endo*-products,[13] the observed *cis*-fusion of the bicyclic ring system in **8**–**12** can be rationalized by the two different reaction paths A and B in Scheme 5.



Scheme 5

Crisp and Gebauer demonstrated that Cbz-protected allylamines are not capable of attacking maleic anhydride. Therefore, they concluded that in the reactions of Cbz-protected dienylamines with maleic anhydride, the intermolecular Diels-Alder reaction precedes the N-attack on the anhydride, as suggested by path A in Scheme 5.[7a]

The situation is different for the N-benzyl substituted allylamines used in this work: When a solution of equimolar amounts of dibenzylamine (**14**) and maleic anhydride in d_8-toluene was kept at 20 °C for 15 min and analyzed by ^{1}H NMR,[14] quantitative conversion into amide **15** was observed (Scheme 6).



14 **15**

Scheme 6

As the corresponding intermolecular Diels-Alder reactions are considerably slower (4 d at 25 °C, 12 h at 40 °C)[7a] we can rule out path A as a major pathway in the domino reactions[15] of the N-benzyl-substituted dienylamines with maleic anhydride. Because of the lower electrophilicity of maleic imide, the sequence of the two reaction steps may be different from the reactions with maleic anhydride.

Experimental Section

General Procedures. Dienylamines **6a**–**c** were prepared as described before.[2] Maleic anhydride (> 99%, Fluka) and maleic imide (> 98 %, Merck) were used as purchased.
^{1}H NMR spectra (300, 400, or 600 MHz) and ^{13}C NMR spectra (75.5 or 100.6 MHz) refer to $CDCl_3$ (δ_H 7.24 ppm, δ_C 77.00 ppm). DEPT experiments were used to obtain information about the multiplicity of the ^{13}C resonances. Mass spectra (70 eV, EI) were obtained on a Finnigan MAT 95 Q.

2-Benzyl-6-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindole-4-carboxylic acid (8). A solution of **6a** (2.62 g, 14.0 mmol) and maleic anhydride (1.25 g, 12.7 mmol) in toluene (20 mL) was heated to reflux for 4 h. Removal of the solvent in vacuo yielded 3.78 g of a red viscous liquid oil. The crude product crystallized from a mixture of ethyl acetate and petroleum ether (1/1, v/v) to give **8** (1.82 g, 50 %) as colorless crystals; mp 161–163 °C.
NMR data: δ_H ($CDCl_3$, 300 MHz) 1.71 (s, 3 H, CH_3), 2.17–2.41 (m, 2 H, 5-H_2), 2.84–2.95 (m, 2 H, 4-H and 7a-H), 2.91 (d, ^2J = 10.1, 1 H, ½ × 1-H_2), 3.32 (dd, J = 6.8, J = 2.9, 1 H, 3a-H), 3.53 (dd, ^2J = 10.0, J = 6.2, 1 H, ½ × 1-H_2), 4.31, 4.59 (2 d, each ^2J = 14.9, 2 × 1 H, PhCH_2), 5.12 (s, 1 H, 7-H), 7.11–7.33 (m, 5 H, Ph), 12.15 (br s, COOH). δ_C ($CDCl_3$, 75.5 MHz) 23.4 (q, CH_3), 29.1 (t, C-5), 34.1 (d, C-7a), 41.3, 41.4 (2 d, C-3a and C-4), 46.6 (t, PhCH_2), 52.0 (t, C-1), 121.0 (d, C-7), 127.67, 127.73, 128.6 (3 d, Ph), 134.9, 136.5 (2 s, Ph and C-6), 175.2, 175.4 (2 s, COOH and CO). Signal assignments are based on ^{1}H,^{13}C-COSY and NOESY experiments. Anal. Calcd. for $C_{17}H_{19}NO_3$ (285.34): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.46; H, 6.77; N, 4.94.
2-Benzyl-6-methyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-carboxamide (9). A solution of **6a** (2.62 g, 14.0 mmol) and maleic imide (1.36 g, 14.0 mmol) in toluene (20 mL) was heated to reflux for 4 h. Removal of the solvent in vacuo yielded 3.98 g of a red viscous oil. The

crude product crystallized from a mixture of ethyl acetate and petroleum ether (1/1, v/v) to give **9** (2.27 g, 57 %) as colorless crystals; mp 131–134 °C.

NMR data: δ_H ($CDCl_3$, 400 MHz) 1.72 (s, 3 H, CH_3), 2.23–2.41 (m, 2 H, 5-H_2), 2.69–2.74 (m, 1 H, 4-H), 2.87 (d, ^2J = 9.8, 1 H, ½ × 1-H_2), 2.91 (br s, 1 H, 7a-H), 3.17 (br d, J = 6.6 Hz, 1 H, 3a-H), 3.46 (dd, ^2J = 9.6, J = 6.1, 1 H, ½ × 1-H_2), 4.29, 4.56 (2 d, each ^2J = 14.9, 2 × 1 H, PhCH_2), 5.10 (s, 1 H, 7-H), 5.64 (br, 1 H, ½ × $CONH_2$), 7.12–7.33 (m, 5 H, Ph), 9.10 (br, 1 H, ½ × $CONH_2$). δ_C ($CDCl_3$, 100.6 MHz) 23.3 (q, CH_3), 30.7 (t, C-5), 35.3 (d, C-7a), 42.1 (d, C-3a), 43.6 (d, C-4), 46.5 (t, PhCH_2), 51.3 (t, C-1), 121.5 (d, C-7), 127.6, 127.7, 128.5 (3 d, Ph), 135.6, 137.4 (2 s, Ph and C-6), 174.2, 177.0 (2 s, $CONH_2$ and CO). Signal assignments are based on ^{1}H,^{1}H-COSY and HETCOR experiments. Anal. Calcd. for $C_{17}H_{20}N_2O_2$ (284.36): C, 71.81; H, 7.09; N, 9.85. Found: C, 71.48; H, 6.98; N, 9.72.

2-Benzyl-6-methyl-3-oxo-7a-trimethylsilyl-2,3,3a,4,5,7a-hexahydro-1*H*-isoindol-4-carboxylic acid (10). A solution of **6b** (3.88 g, 15.0 mmol) and maleic anhydride (1.33 g, 13.6 mmol) in toluene (20 mL) was heated to reflux for 4 h. Removal of the solvent in vacuo yielded 3.55 g of a red viscous oil. The crude product crystallized from a mixture of ethyl acetate and petroleum ether (1/1, v/v) to give **10** (3.17 g, 65 %) as colorless crystals; mp 153–155 °C.

NMR data: δ_H ($CDCl_3$, 300 MHz) 0.06 (s, 9 H, $SiMe_3$), 1.75 (s, 3 H, CH_3), 2.26–2.47 (m, 2 H, 5-H_2), 2.85–2.91 (m, 1 H, 4-H), 2.89 (d, ^2J = 9.9, 1 H, ½ × 1-H_2), 3.20 (d, J = 2.5, 1 H, 3a-H), 3.42 (d, ^2J = 9.7, 1 H, ½ × 1-H_2), 4.18, 4.75 (2 d, each ^2J = 15, 2 × 1 H, PhCH_2), 5.04 (s, 1 H, 7-H), 7.11–7.43 (m, 5 H, Ph), 13.2 (br s, 1 H, COOH). δ_C ($CDCl_3$, 75.5 MHz) –3.5 (q, $SiMe_3$), 23.5 (q, CH_3), 29.4 (t, C-5), 33.6 (s, C-7a), 41.3 (d, C-4), 43.4 (d, C-3a), 46.6 (t, PhCH_2), 54.3 (t, C-1), 122.9 (d, C-7), 127.5, 127.7, 128.6 (3 d, Ph), 134.3, 134.9 (2 s, Ph and C-6), 175.42, 176.2 (2 s, COOH and CO). Signal assignments are based on ^{1}H,^{13}C-COSY and NOESY experiments. Anal. Calcd. for $C_{20}H_{27}NO_3Si$ (357.52): C, 67.19; H, 7.61; N, 3.92. Found: C, 67.22; H, 7.67; N, 3.91.

2-Benzyl-3-oxo-2,3,3a,4,4a,5,6,7,8,9a-octahydro-1*H*-benzo[f]isoindol-4-carboxylic acid (11). A solution of **6c** (1.05 g, 4.62 mmol) and maleic anhydride (0.41 g, 4.2 mmol) in toluene (10 mL) was heated to reflux for 90 min. Removal of the solvent in vacuo yielded 1.78 g of a red viscous oil. The crude product crystallized from a mixture of ethyl acetate and petroleum ether (1/1, v/v) to give **11** (948 mg, 63 %) as colorless crystals; mp 168–170 °C.

NMR data: δ_H ($CDCl_3$, 400 MHz) 1.18–1.25 (m, 1 H, ½ × 7-H_2), 1.37–1.45 (m, 2 H, ½ × 5-H_2 and ½ × 6-H_2), 1.83–2.04 (m, 4 H, ½ × 5-H_2, ½ × 6-H_2, ½ × 7-H_2 and ½ × 8-H_2), 2.17–2.22 (m, 1 H, ½ × 8-H_2), 2.49–2.52 (m, 1 H, 4a-H), 2.93–2.97 (m, 1 H, 9a-H), 3.03 (d, ^2J = 10.0, 1 H, ½ × 1-H_2), 3.20–3.23 (m, 2 H, 3a-H and 4-H), 3.53–3.57 (dd, ^2J = 10.0 Hz, J = 6.8 Hz, 1 H, ½ × 1-H_2), 4.16, 4.79 (2 d, each ^2J = 14.9, 2 × 1 H, PhCH_2), 5.02 (br s, 1 H, 9-H), 7.19–7.37 (m, 5 H, Ph), 14.7 (br s, 1 H, COOH). δ_C ($CDCl_3$, 100.6 MHz) 26.8 (t, C-6), 28.7 (t, C-7), 31.6 (t, C-5), 33.1 (d, C-9a), 36.5 (t, C-8), 39.1 (d, C-4a), 40.1 (d, C-3a), 46.2 (d, C-4), 46.9 (t, PhCH_2), 52.5 (t, C-1), 117.4 (d, C-9), 127.9, 128.1, 128.8 (3 d, Ph), 134.8 (s, Ph), 144.8 (s, C-8a), 174.5 (COOH), 177.0 (s, C-3). Signal assignments are based on gDQCOSY, gHSQC, gHMBC, and NOESY experiments.

MS data: *m*/*z* (%): 326 (11), 325 (M^+, 51), 281 (44), 280 (14), 279 (29), 278 (13), 147 (17), 146 (43), 145 (14), 131 (13), 120 (11), 118 (11), 105 (14), 92 (12), 91 (100).

2-Benzyl-3-oxo-2,3,3a,4,4a,5,6,7,8,9a-octahydro-1*H*-benz[f]isoindol-4-carboxamide (12). A solution of **6c** (1.11 g, 4.88 mmol) and maleic imide (0.437 g, 4.50 mmol) in toluene (10 mL) was heated in a sealed tube[16] to 120 °C for 2 h. Removal of the solvent in vacuo yielded 1.24 g of a red viscous liquid. The crude product crystallized from a mixture of ethyl acetate, diethyl ether, and tetrahydrofuran (1/1/1, v/v/v) to give **12** (759 mg, 48 %) as colorless crystals; mp 199–203 °C.

NMR data: δ_H ($CDCl_3$, 600 MHz) 1.24–1.27 (m, 1 H), 1.40–1.44 (m, 2 H), 1.81–1.87 (m, 2 H), 1.94–2.02 (m, 2 H), 2.19–2.21 (m, 1 H), 2.52 (br s, 1 H, 4a-H), 2.92 (br s, 1 H, 9a-H), 2.97 (d, J = 9.7, 1 H, ½ × 1-H_2), 3.00 (br s, 1 H, 4-H), 3.13 (dd, J = 6.3, J = 3.5, 1 H, 3a-H), 3.46 (dd, J = 9.5, J = 6.7, 1 H, ½ × 1-H_2), 4.10, 4.79 (2 d, each ^2J = 15.1, 2 × 1 H, PhCH_2), 5.01 (s, 1 H, 9-H), 5.68 (br s, 1 H, ½ × $CONH_2$), 7.20–7.34 (m, 5 H, Ph), 9.78 (br s, 1 H, ½ × $CONH_2$). δ_C ($CDCl_3$, 75.5 MHz) 26.8, 28.8, 31.0 (3 t), 34.2 (d, C-9a), 36.4 (t, C-8), 39.5 (d, C-4a), 41.0 (d, C-3a), 46.6 (t, Ph*C*H_2) 46.9 (d, C-4), 51.7 (t, C-1), 118.0 (d, C-9), 127.68, 127.74, 128.7 (3 d, Ph), 135.7, 145.3 (2 s, Ph and C-8a), 175.6, 176.4 (2 s, $CONH_2$ and CO). Signal assignments are based on ^{1}H,^{1}H-COSY90 and HETCOR experiments. Anal. Calcd. for $C_{20}H_{24}N_2O_2$ (324.43): C, 74.05; H, 7.46; N, 8.63. Found: C, 73.61; H, 7.47; N, 8.58.

X-Ray crystallography. Data for the crystal structure determinations were collected on a Nonius CAD4-MACH3 diffractometer. The SHELXS-86 software was used to determine the structures, and the refinement was performed using the SHELXL-93 software. The results of the crystal structure determinations and the crystallographic data of **8**, **9**, and **12** are summarized in Table 1.[17]

Table 1. Crystallographic data and parameters of the crystal structure determinations

Compound	**8**	**9**	**12**
Empirical formula	$C_{17}H_{19}NO_3$	$C_{17}H_{20}N_2O_2$	$C_{20}H_{24}N_2O_2$
Formula weight	285.33	284.35	324.41
Crystal size (mm)	0.53 × 0.47 × 0.13	0.53 × 0.43 × 0.33	0.53 × 0.30 × 0.13
Crystal System	monoclinic	orthorhombic	triclinic
Space group	C2/c	Pca21	P-1
a (Å)	28.762 (4)	28.774 (7)	6.668 (3)
b (Å)	8.8745 (13)	8.907 (4)	8.699 (2)
c (Å)	12.1980 (14)	6.089 (3)	15.628 (2)
α(°)	90	90	83.24 (2)
β (°)	109.272 (11)	90	79.40 (2)
γ(°)	90	90	74.43 (3)
V (Å^3)	2939.0 (7)	1560.6 (10)	856.1 (4)
Z	8	4	2
ρ_{calcd} (g cm^{-3})	1.290	1.210	1.258
μ(mm^{-1})	0.088	0.080	0.082
F(000)	1216	608	348
Temperature (K)	293 (2)	293 (2)	293 (2)
Wavelength Mo-K$_\alpha$ (Å)	0.71073	0.71073	0.71073
θ range (°)	2.48 to 23.97	2.29 to 23.97	2.44 to 23.99
Index ranges	$-32 \le h \le 0$	$-32 \le h \le 0$	$-7 \le h \le 7$
	$0 \le k \le 10$	$0 \le k \le 10$	$-9 \le k \le 8$
	$-13 \le l \le 13$	$-6 \le l \le 6$	$-17 \le l \le 17$
Reflections collected	2350	2438	2886
Independent reflections	2300	2434	2683
No. of restraints	0	1	0
No. of parameters	192	191	217
GooF on F^2	1.093	1.130	1.106
*R*1 [$I > 2\sigma$(I)]	0.0435	0.0478	0.0742
*wR*2 [$I > 2\sigma$(I)]	0.0976	0.1113	0.1697
*R*1 (all data)	0.0638	0.0702	0.1046
*wR*2 (all data)	0.1094	0.1373	0.1885
Resid. electron density (eÅ^{-3})	0.158 / –0.167	0.140 / –0.136	0.286 / –0.245

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References and Notes

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14. Dibenzylamine (1 mmol) and maleic anhydride (1 mmol) were dissolved in d_8-toluene (2 mL) and left at room temperature for 15 min. NMR data of **15**: δ_H (d_8-toluene, 400 MHz) 4.10, 4.42 (2 s, 2 × 2 H, NCH_2), 6.02, 6.11 (2 d, each J = 12.5 Hz, 2 × 1 H, -CH=CH-), 6.86–7.16 (m, 10 H, Ph), 13.40 (br s, 1 H, COOH).
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16. The reaction was carried out in a pressure tube that was equipped with a magnetic stir bar, sealed with a screw cap and heated in an aluminium block which was standing on the heating platform of a magnetic stirrer.

17. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-223583 for **8**, no. CCDC-223584 for **9** and no. CCDC-223585 for **12**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

