Intramolecular cycloadditions with 1-aminoisobenzofurans: a simple entry into the field of polycyclic aza-compounds

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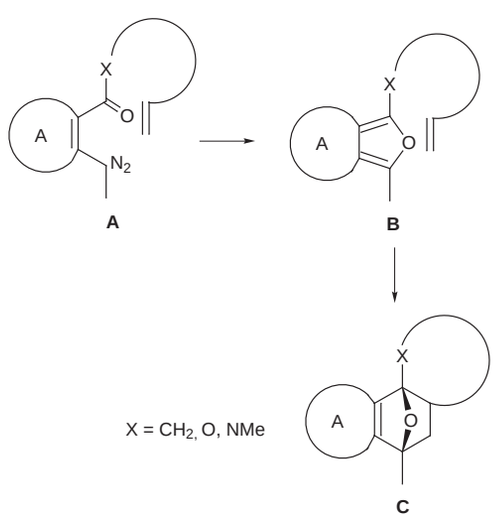
Starting with 6-methoxyisochromane-1,3-dione (**1**) isobenzofuran **5** was generated *in situ* using the Hamaguchi–Ibata methodology. Intramolecular cycloaddition with subsequent transformations provides benzo[*h*]quinolines of type **7**, **8** and **9**. In a similar manner 11-azasteroid analogues (**22**–**26**) were obtained, starting with **1** and amine **18**. Density functional theoretical (DFT) studies of various *inter*- and *intra*molecular Diels–Alder reactions are reported.

Introduction

The synthesis of polycyclic systems from readily available starting materials remains an important goal in organic chemistry.[1] The Diels–Alder reaction especially has been used for this purpose in near countless cases.[2] Isobenzofurans (benzo[*c*]furans)[3] and heteroanalogues thereof have been frequently employed as reactive dienes.

The importance of these systems stems from the fact that alkenes (and alkynes) may undergo both inter- and intramolecular cycloaddition reactions giving a wide variety of interesting new compounds.[3,4,5,7] Recently we succeeded in the preparation of oxasteroids using benzo[*c*]furans of type **B** (Scheme 1, A = benzo, X = O) as intermediates[9] and we anticipated that azapolycyclic systems may be accessible using a similar methodology with 1-aminoisobenzofurans (**B**, Scheme 1, A = benzo, X = N-) as starting materials. The *in situ* generation of, and *inter*molecular cycloaddition with, compounds of this type has been described for the first time by Beak and coworkers.[10] In this paper we describe *intra*molecular Diels–Alder reactions with 1-aminoisobenzofurans[11,12,13] and some computational results concerning the reactivity of various substituted *c*-annulated furans.

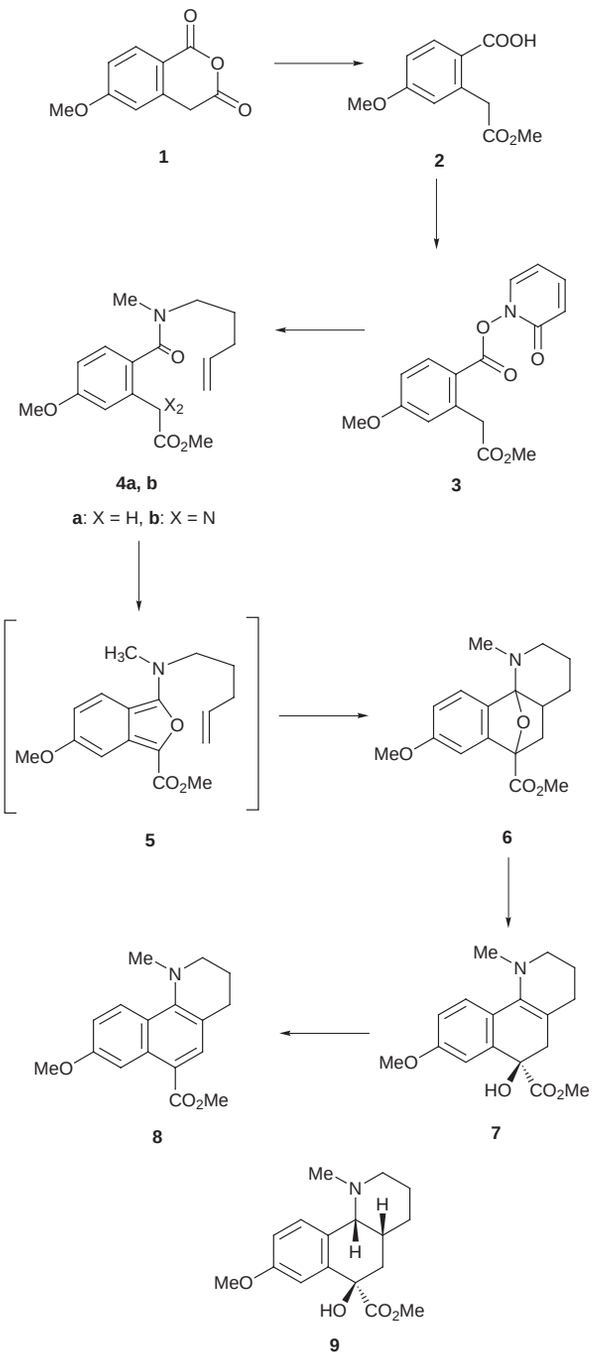


Scheme 1

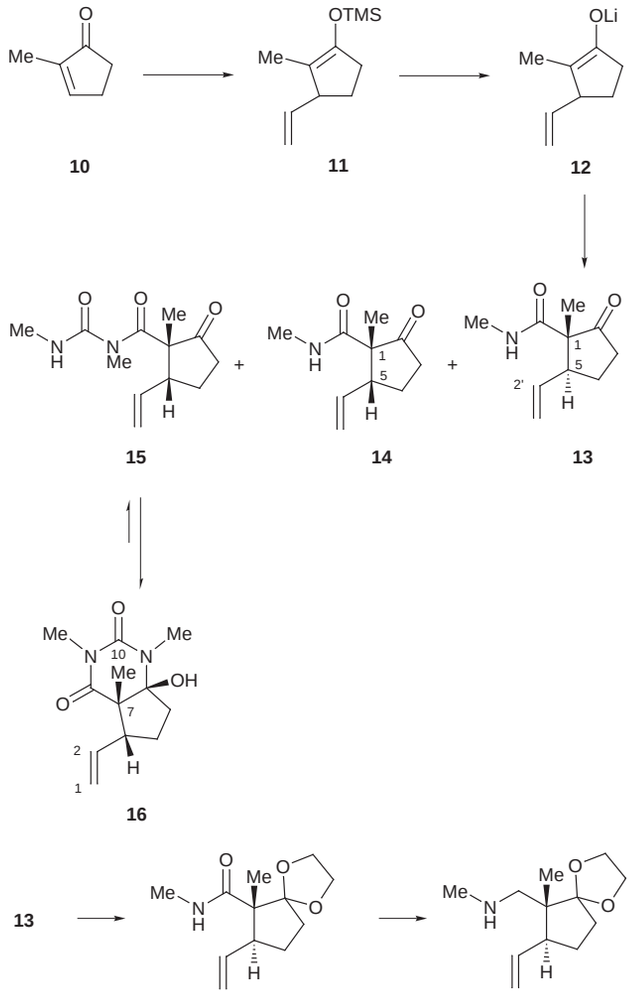
Preparative results

Beak and co-workers devised several routes for the preparation of 1-aminoisobenzofurans,[10] besides others the transition metal induced decomposition of vinylogous diazo amides of type **A** (Scheme 1, A = benzo, X = N-). This methodology is based on the work of Buchardt[14] and Ibata[15] and has also been proved to be of value in our studies.[14c] In our first experiments a model study was undertaken to investigate the reactivity of a suitably substituted 1-aminoisobenzofuran **5** (Scheme 2) against an unactivated olefin moiety. Compound **5** was prepared as follows. Regioselective ring opening of anhydride **1**[16,17,18] with methanol yields—within the line of expectations (see below)—monoester **2**,[19] which on reaction with *N*-hydroxy-2-pyridone–DCC gives the activated ester **3**.[20] Treatment of this compound with *N*-(methyl)pentenylamine[21,22] yields amide **4a**. Diazo transfer can be accomplished by the Regitz procedure.[24] The diazoester **4b** was obtained in 99% yield as a stable yellow oil. Transition metal catalyzed decomposition with only a minimal amount (0.05%) of copper hexafluoroacetylacetonate[25] gives—even under these conditions—a ring opened product **7**. The primary cycloadduct **6** was not isolated and underwent facile rearrangement to α-hydroxy ester **7**, presumably through nitrogen lone-pair-assisted opening of the oxygen bridge,[26] facilitated by the transition metal catalyst.[27] The dehydration of **7** with toluene-*p*-sulfonic acid furnished the benzoquinoline **8**, isolated in 62% yield. Hydrogenation of the double bond in **7** was achieved with palladium on charcoal. The addition of hydrogen occurs from the less hindered side and gives **9** in 35% yield. The structure of **9** was confirmed by an X-ray crystal structure analysis (see Experimental).[28] In conclusion it can be stated that 1-aminoisobenzofurans of type **5** react even with unactivated olefins in an intramolecular Diels–Alder reaction to give benzo[*h*]quinolines.

In order to extend this synthetic methodology for the preparation of 11-azasteroidal analogues[29] it was necessary to prepare a suitable C–D building block **18** (Scheme 3). The synthesis of **18** starts with 2-methylcyclopentenone **10**.[30] Treatment of **10** with vinylmagnesium bromide–copper(I) iodide and subsequent trapping with TMSCl yields **11**.[31] Cleavage of this silyl ether with methyl lithium (to **12**) and addition of a cooled ethereal solution of methyl isocyanate[32] at −100 °C gave **13**, **14** and **16** in 41, 0.5 and 0.3% yield, respectively. The structures of these compounds could be clarified unequivocally by NMR spectroscopy. A strong anisotropic effect of the amide carbonyl group in **13** shifts H-5 downfield to $\delta = 3.40$ ppm, whereas in **14** this signal appears at $\delta = 2.68$ ppm. Additionally a NOE effect[33] is observed between CH_3-1 and the vinylic proton H-2′. According to the IR and NMR spectra the equilibrium between **15** and **16** is shifted entirely to the cyclic urea derivative. As there is no NOE between CH_3-7 and the vinylic proton H-2 we



Scheme 2



Scheme 3

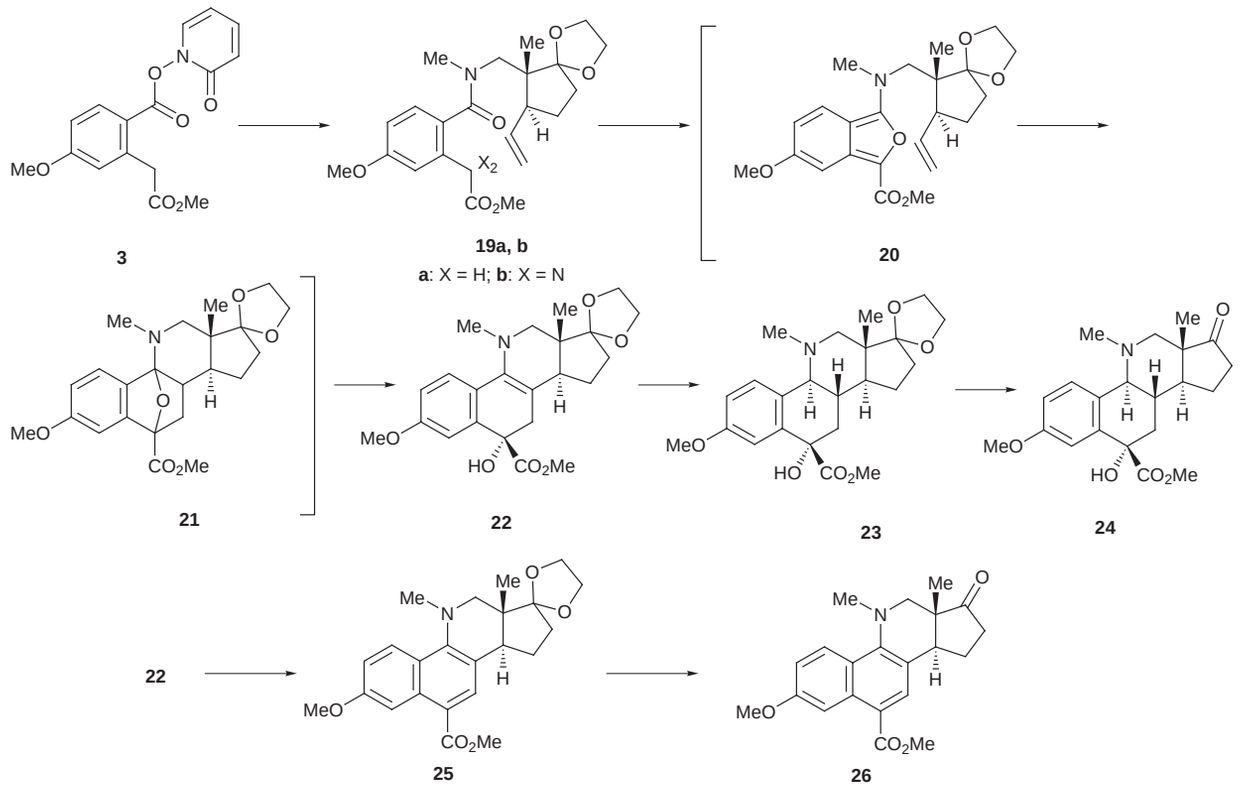
believe that the stereochemistry of **16** is as depicted in Scheme 3. Protection of the carbonyl group in **13** to give **17** and subsequent reduction of **17** with lithium aluminium hydride gave amine **18** in 83% yield. Treatment of the activated ester **3** with **18** yielded **19a** (Scheme 4) as a colourless, viscous oil which again was transformed to diazoester **19b**. Transition metal catalyzed decomposition of **19b** yielded **22** (52%) and the dehydration product **25** (14%). Deprotection of **25** was accomplished with silica–oxalic acid–water[34] to give compound **26** in 89% yield. Preliminary experiments revealed that catalyzed hydrogenation of **22** yields **23**. The course of reaction (*trans*) is unusual, but not without precendents.[35] Subsequent deprotection yielded ketone **24**. Overall, cycloadditions with 1-aminoisobenzofurans generated *in situ* from the corresponding diazoesters offer a convenient route to azapolycyclic compounds.

Theoretical investigations

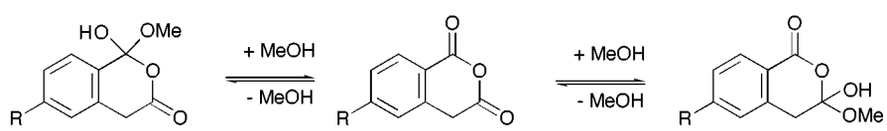
(a) As has already been discussed, the regioselective ring opening of anhydride **1** yields **2** exclusively. This result is not unexpected. If one *assumes* that in the first—fast and reversible—reaction step acidic ortho-esters of type **27a** and **29a** (Scheme 5) are formed, than the product ratio depends on the thermodynamic stability of **27a** and **29a**. Both semi-empirical (AM1)[36,37] as well as *ab initio*[39,40] (density functional theory, DFT)[42,43] calculations show that—at least for the gas phase—compound **29a** is more stable. This result also holds for the unsubstituted derivatives (**27b**, **29b**).

(b) ^{1}H NMR spectra reveal that the equilibrium between **15** and **16** is entirely shifted to the cyclic urea derivative **16**. AM1 calculations for the *gas phase* are in accord with this observation (Scheme 6), but a solvent effect may shift the tautomeric equilibrium considerably.[45,46,47] Therefore we have extended these calculations; DFT studies with the inclusion of the self consistent reaction field (SCRF) model of Onsager[48] using a dielectric constant of $\varepsilon = 4.55$ results in only minor changes of the equilibrium values (Scheme 6), although other SCRF models may alter these values.[39c]

(c) *Qualitative* observations suggest that 1-amino-3-alkoxycarbonylisobenzofurans are less reactive in Diels–Alder reactions than the parent compound itself. In order to get some insight into the reactivity of variously substituted isobenzofurans (and heteroanalogues thereof) the model reactions shown in Scheme 7 have been investigated in some detail using again DFT methods. Recent studies in this field revealed[49] that DFT methods using the B-LYP nonlocal functional, or hybrid methods,[50] yield energy barriers in good agreement with experimental data. Although quantitative data (heats of reaction, transition state energies) are still lack-



Scheme 4



27a, b
a: R = OMe, **b**: R = H

1: R = OMe
28: R = H

29a, b
a: R = OMe, **b**: R = H

	27a		**29a**
AM1 (ΔH_f^o)	−193.43 kcal mol^{-1}	$\Delta\Delta H$ = 4.11 kcal mol^{-1} [a]	−197.54 kcal mol^{-1}
DFT (E)	−802.50599 a.u. [c]	ΔE = 5.72 kcal mol^{-1} [b]	−802.51511 a.u.
	27b		**29b**
AM1 (ΔH_f^o)	−155.37 kcal mol^{-1}	$\Delta\Delta H$ = 3.7 kcal mol^{-1} [a]	−159.07 kcal mol^{-1}
DFT (E)	−687.98264 a.u.	ΔE = 4.78 kcal mol^{-1} [b]	−687.99025 a.u.

[a] $\Delta\Delta H = \Delta H_f^o$ (**27**) − ΔH_f^o (**29**). [b] $\Delta E = E$ (**27**) − E (**29**). [c] a.u. in hartrees (E_h).

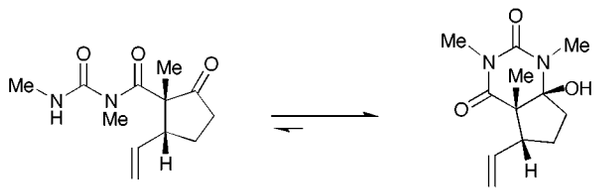
Scheme 5 Results of semi-empirical (AM1) and *ab initio* calculations (DFT; B3LYP/6-31G*).

ing,[51,53] it would be of interest to compare reactivities[54] of differently substituted isobenzofurans with different model olefins (alkynes) both for *inter*- and *intra*molecular cycloaddition reactions.[56] Preliminary studies indicated that for both isobenzofurans as well as for heteroanalogues[4l,n,o,p] the DFT methodology gives *geometrical* data which are in excellent agreement with experimental observations. The results of a crystal structure determination for 4,7-dimethoxyisobenzofuran[57] are given in Table 1. The agreement between these two sets of data is impressive.

Transition state calculations for the model reactions[58] (**1**)–(**7**) (Scheme 7) reveal, that—in line with expectations—the introduction of a methoxy group into the isobenzofuran nucleus *lowers* ΔE(ts), whereas the introduction of an ester group *raises* ΔE(ts). According to these calculations 1-methoxy-3-methoxycarbonylisobenzofuran **37** should be *less reactive* than **35**. The transition state energy for an *intra*molecular Diels–Alder reaction (reaction 7) is higher than the corresponding value for an *inter*molecular reaction (reaction 3). Steric and entropic reasons may be responsible for this difference. The transition state geometries (selected examples: Fig. 1 to Fig. 4, Tables 2–4) are in good agreement with other calculations.[12b,60]

Experimental

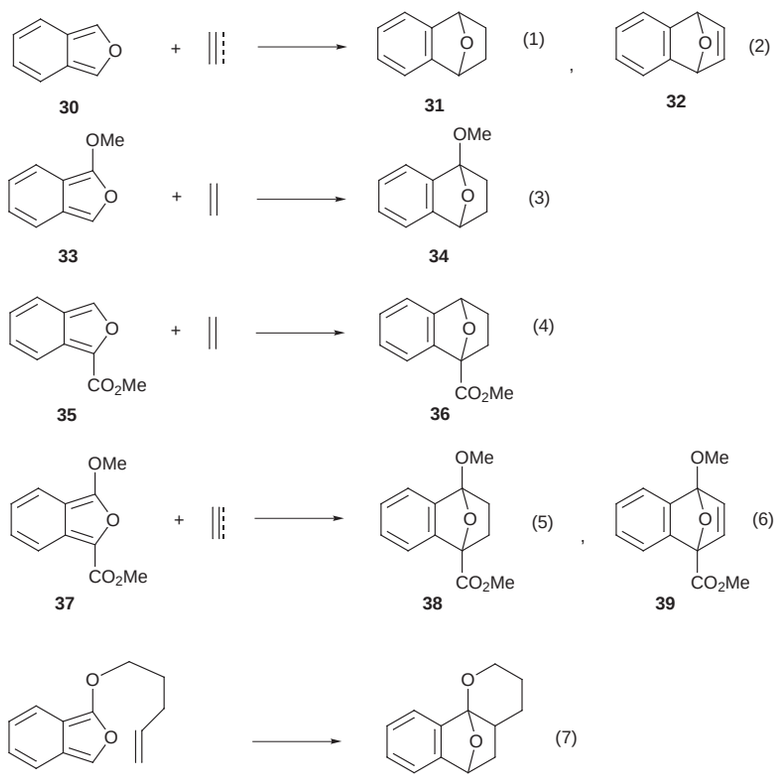
All mps were determined on a Dr Tottoli melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1600 spectrophotometer. NMR spectra: Bruker AM 300 (300 MHz: FT ^{1}H NMR; 75 MHz: ^{13}C NMR); Bruker AC 200 (200 MHz: FT ^{1}H NMR; 50 MHz: ^{13}C NMR); Varian EM 360 (60 MHz, ^{1}H NMR), internally referenced on Me_4Si ($CDCl_3$) or DMSO ([$^2H_6$]DMSO). *J* Values are given in Hz. UV spectra: Zeiss DMR 10 spectrophotometer; mass spectra: Finnigan MAT 8230 mass spectrometer at 70 eV ionisation potential (EI) or the chemical ionisation (CI) (isobutane) method. Radial chromatography was carried out with a



15 16

	15		16
AM1 (ΔH_f^o)	−79.38 kcal mol^{-1}	$\Delta\Delta H$ = 5.95 kcal mol^{-1}	−85.33 kcal mol^{-1}
DFT (E)	−803.27724 a.u.	ΔE = 12.69 kcal mol^{-1}	−803.29746 a.u.
DFT (SCRF = dipole)	−803.28014 a.u.	ΔE = 11.56 kcal mol^{-1}	−803.29856 a.u.

Scheme 6 Results of semi-empirical (AM1) and *ab initio* calculations (DFT; B3LYP/6-31G* and inclusion of a self-consistent reaction field model).



Scheme 7

Harrison-Research Chromatotron on silica gel PF_{245} (Merck, Darmstadt). If assignments of spectral data are ambiguous, this is marked with asterisks (*, **).

Materials

All solvents were dried or purified using standard procedures.[61] Dichloromethane "ultra dry" was distilled over lithium aluminium hydride.[62] Triethylamine was distilled over potassium hydroxide and sodium–benzophenone. 6-Methoxyhomophthalic acid[63] was obtained from anisic acid.[18]

Crystal data of compound 9 †

$C_{17}H_{23}NO_4$, M 305.36. Monoclinic, a 9.413(7), b 16.01(2), c 10.856(a) Å, β 104.33(6)°, V 1585(2) Å^3, space group $P2_1/a$, Z 4, D_{calc} 1.279 g cm^{-3}.

Data collection and processing

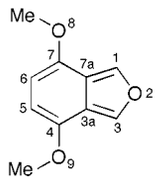
Graphite-monochromated Mo-K_a radiation; τ range for data collection: $1.94 \leqslant \tau \leqslant 22.5°$, index range: $-10 \leqslant h \leqslant 9, 0 \leqslant k \leqslant 17, 0 \leqslant l \leqslant 11$, reflections collected: 2064, independent reflections: 2064, refinement method: full-matrix least-squares on F^2, final R ($I > 2\sigma(I)$) 0.0381.

6-Methoxyisochromane-1,3-dione 1

1.35 g (6.4 mmol) of 6-methoxyhomophthalic acid in 7 ml (0.1 mol) acetyl chloride was refluxed for 2 h. After evaporation the residue was recrystallized from benzene to provide 1.1 g (89%) of colourless crystals, mp 168 °C (lit.,[16] 171 °C); ν_{max}/cm^{-1} 1785, 1740 (s, CO–O–CO); δ_H (300 MHz; D_3CCOCD_3; 20 °C) 3.95 (s, 3H, OCH_3), 4.23 (s, 2H, CH_2-CO), 6.98–7.17 (m, 2H, Ar-H), 8.05 (d, J 8.1, 1H, Ar-H); m/z 192 (M, 37%), 164 (6), 148 (100), 120 (38).

† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/280.

Table 1 Experimental[57] and calculated[a] geometric data for 4,7-dimethoxyisobenzofuran



Bond length/Å	Exp.[b]	Calc.	Bond angle (°)	Exp.[b]	Calc.
1–2	1.363	1.359	1–2–3	107.8	108.6
1–7a	1.359	1.372	1–7a–3a	106.3	106.1
3a–4	1.432	1.434	1–7a–7	134.0	133.8
3a–7a	1.441	1.448	2–3–3a	109.8	109.6
4–5	1.350	1.370	3a–4–5	118.8	118.1
5–6	1.445	1.443	3a–4–9	114.3	115.0
7–8	1.374	1.366	4–5–6	121.6	121.8

[a] DFT (Becke3LYP/6-31G*, C_{2v}). [b] Mean values.

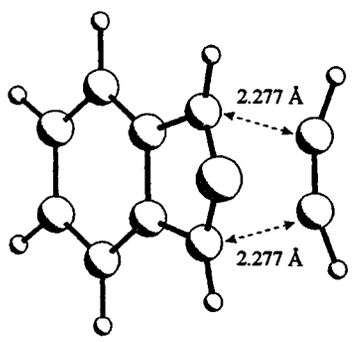


Fig. 1 Transition state of reaction (2) (B3LYP/6-31G*).

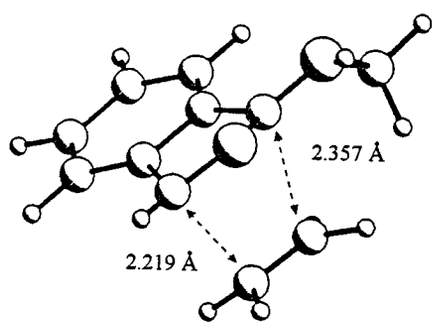


Fig. 2 Transition state of reaction (3) (B3LYP/6-31G*).

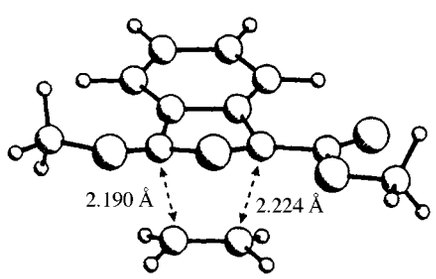


Fig. 3 Transition state of reaction (5) (B3LYP/6-31G*).

4-Methoxy-2-methoxycarbonylmethylbenzoic acid 2

A mixture of 10.0 g (0.048 ml) 6-methoxyhomophthalic acid and 52 ml (0.73 mol) of acetyl chloride was refluxed for 2 h. After evaporation the residue was taken up with 100 ml methanol, 1 drop conc. sulfuric acid was added and the mixture was heated to 60 °C for 3 h. On cooling 9.9 g (93%) of **2** separated as colourless rods, mp 154 °C (lit.,[19] 157–158 °C); ν_{max}/cm^{-1} 3350–2200 (s, br, OH), 1735 (s, C=O), 1680 (s, C=O), 1250, 1210 (s, C–O); δ_H (300 MHz; D_3CCOCD_3; 20 °C) 3.59 (s, 3H, $COOCH_3$), 3.86 (s, 3H, OCH_3), 4.03 (s, 2H, CH_2COOCH_3), 6.83–7.03 (m, 2H, Ar-H), 8.05 (d, *J* 9.0, 1H, Ar-H), 7.00–10.00 (br s, 1H, exchangeable with D_2O).

Table 2 DFT energies[a,b] for **30**–**41** and the transition states of reactions (1)–(7)[c] (in a.u.)

Compound	E	Reaction	E
30	−383.65037	(1)	−462.21329
31	−462.28524	(2)	−460.94769
32	−461.03090	(3)	−576.73721
33	−498.17186	(4)	−690.09456
34	−576.80992	(5)	−804.61496
35	−611.53457	(6)	−803.35623
36	−690.15690	(7)	−654.16053
37	−726.06082		
38	−804.67445		
39	−803.42787		
40	−654.19586		
41	−654.23060		

[a] B3LYP/6-31G*. [b] Ethylene: −78.58746 a.u., acetylene: −77.32565 a.u. [c] The Hesse matrix of the transition states showed one negative eigenvalue.

Table 3 Reaction energies (ΔE) and transition state energies [E(ts)] for reactions (1)–(7) (DFT results[a] in kcal mol^{-1})

Reaction	ΔE[b]	E(ts)[c]
(1)	−29.8	+15.4
(2)	−34.4	+17.8
(3)	−31.8	+13.9
(4)	−21.9	+17.2
(5)	−16.4	+20.9
(6)	−26.0	+19.0
(7)	−21.8	+22.2

[a] B3LYP/6-31G*. [b] ΔE = E(product) − E(reactant). [c] Energy difference between the initial state and the transition state.

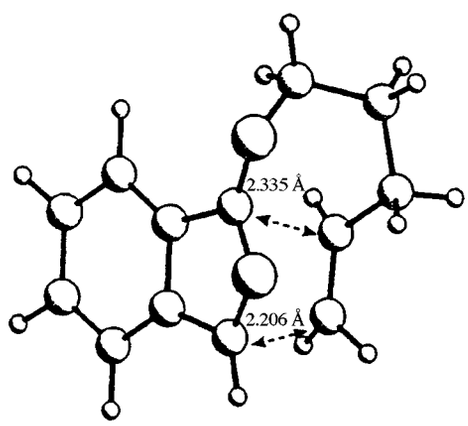


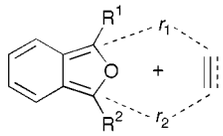
Fig. 4 Transition state of reaction (7) (B3LYP/6-31G*).

4-Methoxy-2-methoxycarbonylmethylbenzoic acid 2-oxo-1,2-dihydropyridin-1-yl ester 3

To a solution of 3.70 g (33 mmol) *N*-hydroxy-2-pyridone and 6.18 g (30 mmol) dicyclohexylcarbodiimide in 100 ml dichloromethane a solution of 6.72 g (30 mmol) monoester **2** in 800 ml dichloromethane was added during 8 h. After further standing for 3 h at room temperature the solution was filtered, evaporated and the oily residue recrystallized from acetic ester to yield 8.49 g (89%) of **3**, mp 128–129 °C; ν_{max}/cm^{-1} 3080 (m), 3005 (m), 2955 (m, CH_2), 2842 (m, OCH_3), 1755 (s, C=O), 1735 (s, C=O), 1665 (s, C=O), 1335 (s), 1240 (s, C–O); δ_H (300 MHz; $CDCl_3$; 20 °C)‡ 3.64 (s, 3H, $COOCH_3$), 3.85 (s, 3H, OCH_3), 4.03 (s, 2H, 6-H), 6.07–6.27 (m, 2H, Ar-H), 6.63–6.97 (m, 3H,

‡ In the NMR data for compounds **3**, **4a**, **7**–**9**, **19a** and **19b** steroid numbering has been used to assign the signals.

Table 4 Transition state geometries for reactions (1)–(7)



Reaction	R^1	R^2	r_1[a]	r_2[a]
(1)	H	H	2.260	2.260
(2)	H	H	2.277	2.277
(3)	MeO	H	2.357	2.219
(4)	H	CO_2Me	2.153	2.310
(5)	MeO	CO_2Me	2.190	2.224
(6)	MeO	CO_2Me	2.213	2.271
(7)	$O(CH_2)_3CH{=}CH_2$	H	2.335	2.206

[a] Values in Å.

Ar-H), 7.25–7.47 (m, 2H, Ar-H), 8.25 (d, *J* 8.4, 1H, 1-H); δ_C (75 MHz; $CDCl_3$; 20 °C) 40.12 (C-6), 51.98 (COO*C*H_3), 55.55 (OCH_3), 104.87 (C-11), 112.51 (C-2), 117.38 (C-9), 118.35 (C-4), 122.81 (C-13), 133.9 (C-1), 135.94 (C-14), 139.17 (C-12), 139.86 (C-5), 157.25 (C-10), 162.76 (C-8), 163.86 (C- 3), 171.20 (*C*OOCH$_3$); *m*/*z* 317 (M, 0.36%), 286 (0.58), 207 (87), 179 (100); $C_{16}H_{15}NO_6$ requires: 317.0899 found: 317.0900 (MS).

[5-Methoxy-2-(*N*-methyl-*N*-pent-4-enylaminocarbonyl)phenyl]-acetic acid methyl ester 4a

To a solution of 512 mg (2.0 mmol) dicyclohexylcarbodimide and 222 mg (2.0 mmol) *N*-hydroxy-2-pyridone in 30 ml of dichloromethane, a solution of 448 mg (2.0 mmol) **2** in 30 ml of dichloromethane was added over a period of 4 h. After stirring for 16 h at room temperature the urea was filtered off and the clear filtrate was treated with 110 mg (2.2 mmol) of *N*-methyl-pent-4-enylamine. The solution was stirred for a further 2 h at room temperature and for 1 h at 40 °C. After evaporation of the solvent the residue was treated with diethyl ether. The *N*-hydroxy-2-pyridone was filtered off, the ethereal solution evaporated, the oily residue taken up with acetone and purified by radial chromatography on silica gel with cyclohexane–acetone (3 : 1) to provide 518 mg (85%) of a colorless oil, which solidified on standing at −20 °C; ν_{max}/cm^{-1} 3030 (w, C=CH), 2930 (m, C–H), 2840 (m, OCH_3), 1735 (s, ester, -C=O), 1625 (s, C=O), 1570 (m, C=C), 1480 (s, CH_2, CH_3), 1430 (s, CH_2, CH_3), 1400 (m), 1305 (m), 1250 (s, br, Ar–O–C), 1160 (s, br, C–O), 1030 (m), 910 (CH=CH_2), 825 (m, *o*-disubst. aromat); λ_{max} (CH_3CN)/nm (log ε) 200 (4.785), 226 (4.194), 274 (3.417), 284 (sh, 3.334); δ_H (300 MHz; CD_2Cl_2; 20 °C) 1.42–1.75 (m, 2H, H-13), 1.85–1.92 and 2.08–2.13 (m, 2H, H-14), 2.82 and 3.00 (s, 3H, NCH_3), 3.08–3.13 and 3.44–3.49 (m, 2H, H-12), 3.63 (s, 3H, CO_2CH_3), 3.66 and 3.68 (s, 2H, H-6), 3.81 (s, 3H, Ar-OCH_3), 4.88–5.10 (m, 2H, H-7), 5.61–5.75 and 5.81–5.95 (m, 1H, H-8), 6.79–6.83 (m, 2H, H-2 and H-4), 7.11–7.14 (m, 1H, H-1); δ_H (300 MHz; $C_2D_2Cl_4$; 80 °C) 1.66–1.76 (m, 2H, H-13), 2.00–2.13 (m, 2H, H-14), 2.91 (s, br, 3H, NCH_3), 3.28–3.39 (t, br, H-12), 3.67 (s, 3H, CO_2CH_3), 3.69 (s, 2H, H-6), 3.83 (s, 3H, Ar-OCH_3), 4.97–5.08 (m, 2H, H-7), 5.75–5.89 (m, 1H, H-8), 6.82 (dd, 2H, *J* 2.4, *J* 8.4, 1H, H-2), 6.88 (d, *J* 2.4, 1H, H-4), 7.12 (d, *J* 8.4, 1H, H-1); δ_C (75 MHz; CD_2Cl_2; 30 °C) 25.92 and 27.21 (C-13), 30.43 and 30.88 (C-6), 32.29 and 33.58 (C-14), 37.00 and 38.10 (N-*C*H_3), 46.57 and 50.46 (C-12), 51.90 (CO_2-*C*H_3), 55.27 (Ar-O*C*H_3), 111.97 (C-2), 114.95 and 115.05 (C-7), 116.38 (C-4), 127.51 and 127.70 (C-5)*, 128.93 and 129.25 (C-10)*, 133.06 (C-1), 137.07 and 137.73 (C-8), 159.43 (C-3), 170.06 and 170.38 (C-9), 171.22 (*C*O_2CH_3); δ_C (75 MHz; $C_2D_2Cl_4$; 90 °C) 26.74 (C-13), 30.65 (C-6), 34.88 (C-14), 38.07 (N-*C*H_3), 48.15 (C-12), 51.35 (CO_2*C*H_3), 55.26 (Ar-O*C*H_3), 112.31 (C-2), 114.68 (C-7), 116.49 (C-4), 127.52 (C-5)*, 129.77 (C-10)*, 133.13 (C-1), 137.40 (C-8), 159.81 (C-3), 170.23 (C-9), 170.79 (*C*O_2CH_3); *m*/*z* 305 (M, 29%), 250 (19), 207 (63), 179 (100), 149 (15); $C_{17}H_{23}N_1O_4$ requires: 305.1634 found: 305.1641 (MS).

2-[5-Methoxy-2-(*N*-methyl-*N*-pent-4-enylaminocarbonyl)-phenyl]-2-diazoacetic acid methyl ester 4b

A solution of 0.86 g (2.82 mmol) amide **4a** in 10 ml dry acetonitrile under argon was treated with 0.90 ml (6.03 mmol) 1,8-diazabicyclo[5.4.0]undec-7-ene. After 10 min, 1.30 g (6.60 mmol) toluene-*p*-sulfonyl azide was added, the mixture stirred for 24 h in the dark, 0.42 g (2.13 mmol) toluene-*p*-sulfonyl azide added and stirred for a further 48 h. The solvent was evaporated and the residue purified by column chromatography on silica gel with cyclohexane–ethyl acetate (1 : 2) providing 0.92 g (99%) of **4b** as a yellow oil. ν_{max}/cm^{-1} 3070, 2085 (s, CN_2), 1705 (s, CO), 1630 (s, CO).

6-Hydroxy-8-methoxy-1-methyl-1,2,3,4,5,6-hexahydrobenzo-[*h*]quinoline-6-carboxylic acid methyl ester 7

A solution of 665 mg (2.01 mmol) diazo amide **4b** in 60 ml toluene was added under argon during 4.5 h to a boiling solution of 50 mg (0.11 mmol) copper(II) hexafluoroacetyl-acetonate in 100 ml toluene. After evaporation of the solvent the residue was filtered with ethyl acetate through a short column of silica gel (deactivated with triethylamine). Purification of the residue by radial chromatography on silica gel with pentane–diethyl ether–triethylamine (2 : 2 : 1) provided 266 mg (44%) of **7** as colorless crystals with mp 113–114 °C (ethyl acetate–pentane); ν_{max}/cm^{-1} 3488 (s, OH), 1715 (s, C=O), 1635 (m), 1610 (m, C=C); δ_H (300 MHz; $CDCl_3$) 1.62–1.80 (m, 2H, 16-H), 2.07 (tt, J_1 1.4, J_2 6.6, 2H, 14-H), 2.48 (s, 3H, NCH_3), 2.50 (td, J_1 1.4, J_2 16.1, 1H, 7-H), 2.68 (td, J_1 1.4, J_2 16.1, 1H, 7-H), 2.98 (ddd, J_1 1.1, J_2 4.2, J_3 6.2, 2H, 12-H), 3.20–3.50 (s, 1H, OH), 3.69 (s, 3H, CO_2CH_3), 3.73 (s, 3H, $ArOCH_3$), 6.74 (d, *J* 2.6, 1H, 4-H), 6.78 (dd, J_1 2.6, J_2 8.5, 1H, 2-H), 7.36 (d, *J* 8.5, 1H, 1-H); δ_C (50 MHz; $CDCl_3$) 16.71 (C-13), 28.60 (C-14), 40.93 (C-7), 40.93 (NCH_3), 51.41 (C-12), 52.87 (CO_2CH_3), 55.30 ($ArOCH_3$), 74.76 (C-6), 109.06 (C-2)*, 112.97 (C-8), 113.14 (C-4)*, 124.94 (C-1), 125.68 (C-10), 137.17 (C-5)**, 138.78 (C-9)**, 158.45 (C-3), 175.95 (*C*O_2CH_3); *m*/*z* 303 (M, 19%), 285 (100), 254 (31), 243 (20), 226 (20), 214 (29); $C_{17}H_{21}NO_4$ requires: 303.1471 found: 303.1468 (MS).

8-Methoxy-1-methyl-1,2,3,4-tetrahydrobenzo[*h*]quinoline-6-carboxylic acid methyl ester 8

A solution of 19 mg (0.06 mmol) enamine **7** and 90 mg (0.52 mmol) toluene-*p*-sulfonic acid in 5 ml dioxane was refluxed for 61 h. The solvent was continuously dried with molecular sieves (3 Å). After cooling to room temperature 1 ml triethylamine was added and the solution filtered with diethyl ether through a short column of silica gel. After purification by radial chromatography (pentane–diethyl ether, 9 : 1) 11 mg (62%) of a colorless oil was obtained. δ_H (300 MHz; $CDCl_3$) 1.89–1.97 (m, 2H, 13-H), 2.88 (br t, *J* 6.5, 2H, 14-H), 3.01 (s, 3H, NCH_3), 3.24–3.28 (m, 2H, 12-H), 3.94 (s, 3H, CO_2CH_3)*, 3.96 (s, 3H, $ArOCH_3$)*, 7.10 (dd, J_1 2.7, J_2 9.0, 1H, 2-H), 7.96 (t, *J* 0.8, 1H, 7-H), 8.03 (d, *J* 9.0, 1H, 1-H), 8.53 (d, *J* 2.7, 1H, 4-H); δ_C (75 MHz; $CDCl_3$) 17.85 (C-13), 27.77 (C-14), 45.45 (NCH_3), 51.50 (CO_2CH_3), 51.98 (C-12), 55.23 ($ArOCH_3$), 105.00 (C-2), 116.88 (C-4), 117.20 (C-10), 120.79 (C-8), 123.22 (C-6), 126.01 (C-1), 134.00 (C-5), 134.08 (C-7), 150.63 (C-9), 158.49 (C-3), 167.97 (*C*O_2CH_3); *m*/*z* 285 (M, 100%), 254 (32), 226 (20), 210 (11), 183 (11); $C_{17}H_{19}NO_3$ requires: 285.1365 found: 285.1364 (MS).

6α-Hydroxy-8-methoxy-1-methyl-1,2,3,4,4a,5,6,10b-octa-hydrobenzo[*h*]quinoline-6β-carboxylic acid methyl ester 9

A solution of 154 mg (0.51 mmol) enamine **7** in 10 ml dry methanol was hydrogenated with Pd–C (32 mg, 24 h, room

temperature). After evaporation of the solvent and purification of the residue by radial chromatography on aluminium oxide with cyclohexane–ethyl acetate (1 : 1) 55 mg (35%) of **9** as colorless needles with mp 116.5–118.5 °C (ethyl acetate–pentane) were obtained; ν_{max}/cm^{-1} 3403 (s, OH), 2987 (m, C=CH), 2934 (m, C–H), 2838 (w, ArOCH$_3$), 1707 (s, C=O), 1608 (m, C=C); δ_H (300 MHz; CDCl$_3$) 1.47–1.53 (m, 1H, 13β-H), 1.56 (ddd, J_1 1.1, J_2 2.8, J_3 13.0, 1H, 7β-H), 1.66–1.91 (m, 3H, 14α-H, 14β-H and 13α-H), 2.09–2.18 (m, 1H, 12β-H), 2.14 (s, 3H, NCH$_3$), 2.28 (ddddd, J_1 1.0, J_2 2.8, J_3 2.8, J_4 6.7, J_5 13.0, 1H, 8-H), 2.85 (br d, J 2.8, 1H, 9-H), 2.90–2.96 (m, 1H, 12α-H), 3.19 (dd, J_1 13.0, J_2 13.0, 1H, 7α-H), 3.75 (s, 1H, OH), 3.76 (s, 3H, CO$_2$CH$_3$)*, 3.78 (s, 3H, ArOCH$_3$)*, 6.66 (d, J 2.7, 1H, 4-H), 6.79 (dd, J_1 2.7, J_2 8.5, 1H, 2-H), 7.08 (d, J 8.5, 1H, 1-H); δ_C (50 MHz; CDCl$_3$) 21.52 (C-13), 29.98 (C-14), 31.07 (C-8), 35.81 (C-7), 44.09 (NCH$_3$), 53.29 (CO$_2$-*C*H$_3$), 55.23 (ArOCH$_3$), 57.94 (C-12), 65.57 (C-9), 75.72 (C-6), 111.85 (C-2)*, 113.34 (C-4)*, 129.44 (C-10), 133.56 (C-1), 138.58 (C-5), 159.32 (C-3), 177.50 (*C*O$_2$-CH$_3$); *m*/*z* 305 (M, 26%), 246 (100), 228 (17), 215 (12), 187 (11), 175 (14); $C_{17}H_{23}NO_4$ requires: 305.1627 found: 303.1626 (MS).

(*trans*)-*N*,1-Dimethyl-2-oxo-5-vinylcyclopentane-1-carboxamide 13, (*cis*)-*N*,1-dimethyl-2-oxo-5-vinylcyclopentane-1-carboxamide 14, 1-methyl-1-(2,4-diaza-1,3-dioxopentan-1-yl)-5-vinylcyclopentanone 15 and (±)-2,4-dimethyl-3,5-dioxo-1α-hydroxy-6α-methyl-7β-vinyl-2,4-diazabicyclo[4.3.0]nonane 16

A solution of 10.0 g (51 mmol) of silyl ether **11** in 160 ml dry diethyl ether was treated at −19 °C with 33 ml (52.8 mmol) of a 1.6 M solution of methyllithium in diethyl ether under an argon atmosphere. After stirring at room temperature for 15 h the mixture was cooled down to −100 °C (ethanol–liquid nitrogen) and a pre-cooled (−78 °C) solution of 5.0 ml (82 mmol) methyl isocyanate in 15 ml dry diethyl ether was added during 20 min. After 2 h at −100 °C and 2 h at room temperature 2 M hydrochloric acid was added until pH = 1. The organic phase was separated and the aqueous phase extracted six times with 200 ml diethyl ether. The combined organic phases were dried with potassium carbonate, evaporated and the residue subjected to column chromatography on silica gel with cyclohexane–ethyl acetate (1 : 1).

The first fraction gave 3.91 g (41%) of compound **13** as colorless rods, mp 64 °C; ν_{max}/cm^{-1} 3350 (s, N–H), 3080 (w, C=CH), 2960 (m, C–H), 2880 (m, C–H), 1735 (s, C=O), 1645 (s, C=O), 1540 (s, N–H), 1410 (m, CH$_2$), 1270 (m, C–O), 1145 (m, C–O), 915 (s, CH=CH$_2$); λ_{max} (CH$_3$CN)/nm (log ε) 200 (3.767), 278 (1.392); δ_H (300 MHz; CDCl$_3$) 1.15 (s, 3H, CH$_3$), 1.77 (dddd, J_1 8.3, J_2 10.7, J_3 11.5, J_4 12.5, 1H, 4β-H), 2.10 (dddd, J_1 2.6, J_2 6.2, J_3 8.4, J_4 12.5, 1H, 4α-H), 2.37 (ddd, J_1 8.4, J_2 10.7, J_3 19.0, 1H, 3α-H), 2.48 (ddd, J_1 2.6, J_2 8.3, J_3 19.0, 1H, 3β-H), 2.80 (d, J 4.9, 3H, N-CH$_3$), 3.40 (ddddd, J_1 1.6, J_2 1.6, J_3 6.2, J_4 6.2, J_5 11.5, 1H, 5-H), 5.18 (ddd, J_1 1.6, J_2 1.6, J_3 10.2, 1H, H-2′a),), 5.19 (ddd, J_1 1.6, J_2 1.6, J_3 17.9, 1H, H-2′b), 6.10 (ddd, J_1 6.2, J_2 10.2, J_3 17.9, 1H, H-1′); δ_C (75 MHz; CDCl$_3$) 18.39 (CH$_3$), 22.91 (C-4), 26.23 (NHCH$_3$), 37.50 (C-3), 46.03 (C-5), 58.17 (C-1), 116.18 (CH=C*H*$_2$), 137.14 (C*H*=CH$_2$), 171.62 (CO), 219.41 (C-2); *m*/*z* 181 (M, 3.5%), 126 (23), 123 (13), 119 (12), 117 (13), 99 (63), 97 (100); $C_{10}H_{15}NO_2$ requires: 181.1102 found: 181.1101 (MS).

The second fraction gave 50 mg (0.5%) of compound **14** as a colorless oil; ν_{max}/cm^{-1} 2944 (m, C–H), 1743 (s, C=O), 1633 (s, C=O), 1537 (m), 1454 (m, CH$_2$/CH$_3$), 1410 (m, CH$_2$/CH$_3$), 1259 (w), 1056 (w), 921 (w, RCH=CH$_2$); δ_H (300 MHz; CDCl$_3$) 1.32 (s, 3H, CH$_3$), 2.12 (dddd, J_1 5.6, J_2 6.9, J_3 9.1, J_4 12.8, 1H, 4-βH), 2.17 (dddd, J_1 7.3, J_2 8.0, J_3 8.8, J_4 12.8, 1H, 4α-H), 2.35 (ddd, J_1 7.3, J_2 9.1, J_3 19.5, 1H, 3β-H), 2.57 (dddd, J_1 0.6, J_2 5.6, J_3 8.8, J_4 19.5, 1H, 3α-H), 2.68 (dddddd, J_1 0.6, J_2 0.9, J_3 1.0, J_4 6.9, J_5 8.0, J_6 8.0, 1H, 5-H), 2.77 (br d, J 4.8, 3H, NCH$_3$), 5.11 (ddd, J_1 0.9, J_2 1.6, J_3 10.3, 1H, 2′-Ha), 5.14 (ddd, J_1 1.0, J_2 1.6, J_3 17.2, 1H, 2′-Hb), 5.87 (ddd, J_1 8.0, J_2 10.3, J_3 17.2, 1H, 1′-H), 6.26 (br s, 1H, NH); δ_C (75 MHz; CDCl$_3$) 19.99 (CH$_3$), 24.78 (C-4), 26.00 (NCH$_3$), 36.64 (C-3), 52.00 (C-5), 59.65 (C-1), 116.75 (C-2′), 137.13 (C-1′), 170.74 (*C*ONHCH$_3$), 218.62 (C-2).

The third fraction gave 32 mg (0.3%) of compound **16** as colorless crystals, mp 158–160 °C; ν_{max}/cm^{-1} 3357 (s, br, O–H), 3080 (w, C=C–H), 2991 (m, C–H), 1699 (s, C=O), 1651 (s, C=O), 1472, 1417 (s, CH$_2$/CH$_3$), 1380 (s), 1338 (s), 1208 (m), 1130 (m), 1091 (s), 1051 (s), 1009 (m), 962 (w), 924 (s), 754 (s); λ_{max} (CH$_3$CN)/nm (log ε) 200 (4.038), 214 (3.803), 308 (2.394), 323 (sh, 2.339); δ_H (200 MHz; CDCl$_3$) 1.23 (s, 3H, 12-H), 1.74 (dddd, J_1 5.2, J_2 8.8, J_3 11.1, J_4 13.2, 1H, 4β-H), 1.89 (dddd, J_1 6.0, J_2 8.0, J_3 9.0, J_4 13.2, 1H, 4α-H), 2.05 (ddd, J_1 6.0, J_2 11.1, J_3 14.1, 1H, 5α-H), 2.37 (ddd, J_1 5.2, J_2 9.0, J_3 14.1, 1H, 5β-H), 2.76 (s, 1H, OH, exchanges with D$_2$O), 2.90 (ddddd, J_1 1.3, J_2 1.4, J_3 7.6, J_4 8.8, J_5 8.9, 1H, 3-H), 3.12 (s, 3H, 11-H), 3.19 (s, 3H, 9-H), 4.99 (ddd, J_1 1.4, J_2 1.4, J_3 17.0, 1H, 1α-H), 5.11 (ddd, J_1 1.3, J_2 1.4, J_3 10.3, 1H, 1β-H), 5.76 (ddd, J_1 7.6, J_2 10.3, J_3 17.0, 1H, 2-H); δ_C (75 MHz; CDCl$_3$) 13.16 (C-12), 24.61 (C-4), 28.36 (C-11), 29.70 (C-9), 34.20 (C-5), 50.06 (C-3), 54.80 (C-7), 93.81 (C-6), 117.27 (C-1), 136.29 (C-2), 152.39 (C-10), 172.77 (C-8); *m*/*z* 238 (M, 5%), 223 (13), 220 (30), 205 (18), 195 (34), 170 (100), 148 (13, 123 (49); $C_{12}H_{18}N_2O_3$ requires: 238.1317 found: 238.1325 (MS).

N,6-Methyl-7-vinyl-1,4-dioxaspiro[4,4]nonane-6-carboxamide 17

A mixture of 916 mg (5.1 mmol) **13**, 1.5 ml (25.3 mmol) ethane-1,2-diol, 2.8 ml (25.3 mmol) trimethyl orthoformate and 32 mg (0.16 mol) toluene-*p*-sulfonic acid hydrate was stirred at room temperature for 48 h. After adding 20 mg sodium hydrogen carbonate and stirring for a further 5 h the mixture was filtered over silica gel with ethyl acetate and evaporated. The residue was purified by column chromatography on silica gel with cyclohexane–ethyl acetate (1 : 5) to yield 1.055 g (93%) of **17** as colorless needles with mp 119 °C (ethyl acetate–pentane); ν_{max}/cm^{-1} 3350 (s, N–H), 3080 (w, C=CH), 2960 (m, C–H), 2940 (m, C–H), 2880 (m, C–H), 1645 (s, C=O), 1530 (s, N–H), 1405 (m, CH$_2$), 1380 (m, CH$_2$), 1145 (m, br, C–O), 905 (s, CH=CH$_2$); λ_{max} (CH$_3$CN)/nm (log ε) 200 (3.796); δ_H (300 MHz; CDCl$_3$) 1.13 (s, CH$_3$), 1.55–1.67 (m, 1H, H-8), 1.69–1.94 (m, 3H, 8α-H, 9α-H, 9β-H), 2.79 (d, J 4.9, 3H, NCH$_3$), 3.30 (dddddd, J_1 1.3, J_2 1.4, J_3 1.4, J_4 6.9, J_5 8.0, J_6 9.5, 1H, H-7), 3.86–4.00 (m, 4H, O-CH$_2$CH$_2$-O), 5.08 (ddd, J_1 1.4, J_2 1.9, J_3 10.4, 1H, H-2′), 5.12 (ddd, J_1 1.4, J_2 1.9, J_3 17.3, 1H, H-2′), 5.94 (ddd, J_1 6.9, J_2 10.4, J_3 17.3, 1H, H-1′); δ_C (75 MHz; CDCl$_3$) 15.53 (CH$_3$), 23.20 (C-8), 26.16 (NHCH$_3$), 32.81 (C-9), 45.93 (C-7), 55.84 (C-6), 64.21, 65.02 (O-CH$_2$CH$_2$-O), 115.51 (CH=*C*H$_2$), 118.59 (C-5), 138.62 (*C*H=CH$_2$), 174.12 (s, *C*ONHCH$_3$); *m*/*z* 225 (M, 4%), 167 (15), 139 (23), 126 (81), 123(22), 109 (9), 100 (100), 99 (70); $C_{12}H_{19}NO_3$ requires: 225.1364 found: 225.1363 (MS) (Found: C, 64.07; H, 8.43; N, 6.23. $C_{12}H_{19}NO_3$ requires C, 63.98; H, 8.50; N, 6.22%).

N-(6-Methyl-7-vinyl-1,4-dioxaspiro[4,4]nonan-6-ylmethyl)-methylamine 18

A solution of 960 mg (4.35 mmol) **17** in 80 ml diethyl ether was added during 3.5 h under an argon atmosphere to 420 mg (11.05 mmol) lithium aluminium hydride in 30 ml diethyl ether. The mixture was stirred for 65 h at room temperature and refluxed for 10 h. Working up by the Miçoviç–Mihailoviç[64] procedure and column chromatography on silica gel with ethyl acetate gave 226 mg (28%) of starting material **17**. Subsequent elution with ethyl acetate–triethylamine (5 : 1) yielded 576 mg (60%, 83% on consumed starting material) of compound **18** as a colorless oil; ν_{max}/cm^{-1} 3350 (w, N–H), 3070 (w, C=CH), 2970 (s, C–H), 2880 (s, C–H), 2780 (m, NCH$_3$), 1640 (m, C=C), 1465 (m, CH$_2$CH$_3$), 1375 (m, CH$_3$), 1135 (s, br, C–O), 1000, 915 (CH=CH$_2$); λ_{max} (CH$_3$CN)/nm (log ε) 200 (3.781); δ_H (300 MHz;

$CDCl_3$) 0.97 (s, 3H, CH_3), 1.54–1.90 (m, 5H), 2.37 (s, 3H, NCH_3), 2.48 (d, *J* 11.5, 1H, -C*H*$_2$NHCH$_3$), 2.53 (1H, NH), 2.58 (d, *J* 11.5, 1H, -C*H*$_2$NHCH$_3$), 3.83–3.96 (m, 4H, O-CH_2CH_2O), 5.02 (ddd, J_1 0.8, J_2 2.2, J_3 9.5, 1H, H-2′), 5.03 (ddd, J_1 1.1, J_2 2.2, J_3 17.8, 1H, H-2′), 5.80 (ddd, J_1 8.3, J_2 9.5, J_3 17.8, 1H, H-1′); δ_C (75 MHz; $CDCl_3$) 15.24 (CH_3), 25.08 (C-8), 33.20 (C-9), 37.12 (NCH_3), 48.66 (C-7), 48.77 (C-6), 57.42 (CH_2-$NHCH_3$), 64.06, 64.58 (O-CH_2CH_2-O), 115.45 (CH=*C*H$_2$), 119.79 (C-5), 139.52 (*C*H=CH$_2$); *m*/*z* (CI, isobutane) 212 (M + 1, 100%), 169 (24), 99 (5).

{5-Methoxy-2-[*N*-methyl-(6-methyl-7-vinyl-1,4-dioxaspiro[4,4]-nonan-6-ylmethylaminocarbonyl]phenyl}acetic acid methyl ester 19a

To a solution of 900 mg (2.79 mmol) **3** in 25 ml dichloromethane was added 536 mg (2.54 mmol) amine **18** in 25 ml dichloromethane. After 9 h at room temperature 25 ml of dichloromethane was distilled off, 1 ml triethylamine was added and the mixture refluxed for 30 h. After evaporation of the solvent the amide **19a** was separated by radial chromatography on silica gel with cyclohexane–ethyl acetate (2:1) to yield 742 mg (70%) of **19a** as a colorless, viscous oil; ν_{max}/cm^{-1} 3072 (w, C=C–H), 2950 (m, C–H), 1738 (s, C=O), 1668 (w), 1631 (s, C=O), 1608 (s, C=C), 1576 (w), 1534 (w), 1435, 1409 (m, CH_2/CH_3), 1304 (m), 1247 (s, Ar–O–C), 1159 (s), 919 (w), 828 (w); λ_{max} (CH_3CN)/nm (log ε) 200 (4.691), 226 (4.127), 243 (sh, 3.930), 278 (3.428), 284 (sh, 3.373), 300 (3.021); δ_H (300 MHz; $CDCl_3$; selected data) 0.82 and 1.05 (2s, 3H, 18-H), 1.59–1.95 (m, 4H, 15α-H, 15β-H, 16α-H, 16β-H), 2.57–2.66 (m, 1H, 14-H), 2.88 and 3.05 (2s, 3H, NCH_3), 3.17–3.47 (m, br, 1H), 3.58–3.86 (m, br, 2H), 3.66 (s, 3H, CO_2CH_3), 3.81 (s, 3H, $ArOCH_3$), 3.90–4.02 (m, 5H), 5.04–5.11 (m, 2H, 7α-H, 7β-H), 5.85–5.97 (m, 1H, 8-H), 6.77–6.86 (m, 2H, Ar-H), 7.14–7.17 (m, 1H, Ar-H); δ_C (50 MHz; $CDCl_3$; selected data) 13.20 and 14.31 (C-18), 25.13 (C-15), 31.86 (C-16), 38.24 (C-6), 40.69 (NCH_3), 49.00 (C-14), 50.00 (C-12), 50.68 (C-13), 51.90 (CO_2CH_3), 55.26 ($ArOCH_3$), 63.42 (OCH_2CH_2O), 64.35 (OCH_2CH_2O), 112.32 (C-2), 116.19 (C-4), 116.27 (C-7), 118.78 (C-17), 128.17 (C-1), 130.14 (C-5), 133.28 (C-10), 138.89 (C-8), 159.70 (C-3), 171.75 (*C*O$_2$CH$_3$)*, 172.03 (C-9)*; *m*/*z* 417 (M, 10%), 386 (5), 250 (9), 207 (88), 179 (69), 167 (34), 149 (12), 139 (9), 99 (100); $C_{23}H_{31}NO_6$ requires: 417.2151 found: 417.2149 (MS).

2-{5-Methoxy-2-[*N*-methyl-(6-methyl-7-vinyl-1,4-dioxaspiro[4,4]-nonan-6-ylmethylaminocarbonyl]phenyl}-2-diazoacetic acid methyl ester 19b

750 mg (3.81 mmol) of toluene-*p*-sulfonyl azide and 0.50 ml (3.35 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene were added to a solution of 429 mg (1.03 mmol) amide **19a** in 10 ml dry acetonitrile. After standing for 41 h in the dark under an argon atmosphere a further 200 mg (1.02 mmol) of toluene-*p*-sulfonyl azide was added. After 21 h the mixture was concentrated to a few ml, taken up with ethyl acetate, filtered through a short silica gel column, and purified by radial chromatography on silica gel with pentane–diethyl ether (1:1) to yield 406 mg (89%) of **19b** as a yellow viscous oil; ν_{max}/cm^{-1} 2951 (m, C–H), 2090 (s, CN_2), 1706 (s, C=O), 1635 (s, C=O), 1601 (s, C=C), 1436 (m, CH_2/CH_3), 1399 (m), 1292 (m), 1234 (m), 1154 (m), 1033 (m), 914 (w), 822 (w); λ_{max} (CH_3CN)/nm (log ε) 200 (4.456), 221 (4.463), 247 (sh, 4.252), 325 (sh, 2.497), 390 (2.155); δ_H (300 MHz; $CDCl_3$; selected data) 0.78 and 1.05 (2s, 3H, 18-H), 1.58–1.90 (m, 15α-H, 15β-H, 16α-H, 16β-H), 2.55–2.68 (m, 14-H), 2.89 and 3.03 (2s, 3H, NCH_3), 3.79 (s, 3H, CO_2CH_3), 3.82 (s, 3H, $ArOCH_3$), 3.87–4.09 (m, OCH_2CH_2O), 5.04–5.11 (m, 7α-H, 7β-H), 5.85–5.96 (m, 8-H), 6.81–6.89 (m, Ar-H, 2-H), 7.00–7.10 (m, Ar-H, 4-H), 7.20–7.31 (m, Ar-H, 1-H); δ_C (50 MHz; $CDCl_3$; selected data) 13.24 and 14.33 (C-18), 25.22 (C-15), 31.96 (C-16), 40.58 (NCH_3), 48.93 (C-14), 49.50 (C-6), 50.24 (C-12), 50.71 (C-13), 51.98 (CO_2CH_3), 55.43 ($ArOCH_3$), 63.49 (OCH_2CH_2O), 64.37 (OCH_2CH_2O), 113.56 (C-2)*, 115.02 (C-10)*, 116.01 (C -7), 118.87 (C-17), 124.73 (C-5), 128.89 (C-4)**, 130.64 (C-1)**, 138.89 (C-8), 159.98 (C-3), 165.84 (*C*O$_2$CH$_3$), 172.03 (C-9); *m*/*z* 415 (M − N_2, 93%), 397 (59), 356 (88), 340 (12), 326 (18), 248 (20), 206 (45), 181 (26), 99 (100); $C_{23}H_{29}NO_6$ (M − N_2) requires: 415.1995 found: 415.1992 (MS).

Spiro[6-hydroxy-3-methoxy-6-methoxycarbonyl-11-methyl-11-azaestra-1,3,5(10),8-tetraene-17,2′-dioxolane] 22 and spiro[3-methoxy-6-methoxycarbonyl-11-methyl-11-azaestra-1,3,5(10),6,8(9)-pentaene-17,2′-dioxolane] 25

A solution of 493 mg (1.11 mmol) of diazo amide **19b** in 100 ml dry toluene was added during 12 h under argon to a boiling solution of 17 mg (0.02 mmol) copper(II) hexafluoroacetylacetonate, cooled and evaporated. The residue was purified by flash chromatography using silica gel and pentane–diethyl ether–diethylamine (8:4:1).

The first fraction gave 61 mg (14%) of compound **25** as colorless crystals, mp 145–148 °C (diethyl ether); ν_{max}/cm^{-1} 2943 (m, C–H), 1694 (s, C=O), 1618 (s, C=C), 1559 (m), 1435, 1408 (m, CH_2/CH_3), 1322 (m), 1258 (s), 1222 (s), 1041 (m); λ_{max} (CH_3CN)/nm (log ε) 205 (4.481), 210 (sh, 4.475), 225 (sh, 4.243), 247 (4.382), 278 (4.311), 287 (sh, 4.239), 306 (sh, 3.460), 325 (sh, 3.644), 338 (3.838), 376 (4.207); δ_H (300 MHz; $CDCl_3$) 0.74 (d, *J* 0.8, 3H, 18-H), 1.77 (dddd, J_1 6.5, J_2 11.5, J_3 11. 8, J_4 12.1, 1 H, 15β-H), 2.11 (ddd, J_1 6.5, J_2 9.6, J_3 14.5, 1H, 16α-H), 2.23 (ddd, J_1 3.4, J_2 11.5, J_3 14.5, 1H, 16β-H), 2.27 (dddd, J_1 3.4, J_2 7.4, J_3 9.6, J_4 12.1, 1H, 15α-H), 3.15 (dddd, J_1 1.2, J_2 1.2, J_3 7.4, J_4 11.8, 1H, 14-H), 3.25 (dd, J_1 1.2, J_2 10.6, 1H, 12α-H), 3.31 (s, 3H, NCH_3), 3.44 (qd, J_1 0.8, J_2 10.6, 1H, 12β-H), 3.79–4.09 (m, 4H, OCH_2CH_2O), 3.92 (s, 3H, CO_2CH_3)*, 3.96 (s, 3H, $ArOCH_3$)*, 7.01 (dd, J_1 2.7, J_2 9.3, 1H, 2-H), 7.87 (d, *J* 9.3, 1H, 1-H), 7.89 (d, *J* 1.2, 1H, 7-H), 8.64 (d, *J* 2.7, 1H, 4-H); δ_C (75 MHz; $CDCl_3$) 14.23 (C-18), 22.33 (C-15), 35.28 (C16), 43.70 (C-14), 46.33 (C-13), 46.73 (NCH_3), 51.31 (CO_2CH_3), 55.21 ($ArOCH_3$), 60.00 (C-12), 64.63 (OCH_2CH_2O), 65.19 (OCH_2CH_2O), 104.67 (C-2), 113.70 (C-10)*, 115.73 (C-4), 118.45 (C-17), 120.13 (C-8)*, 121.45 (C-6), 126.97 (C-1), 130.01 (C-7), 135.60 (C-5), 148.80 (C-9), 158.37 (C-3), 167.97 (CO_2R); *m*/*z* 397 (M, 100%), 366 (7), 296 (25), 264 (8), 125 (11), 111 (19); $C_{23}H_{27}NO_5$ requires: 397.1889 found: 397.1887 (MS).

The second fraction gave 240 mg (52%) of compound **22** as a colorless oil; ν_{max}/cm^{-1} 3700–3100 (s, br, O–H), 2948 (m, C–H), 2882 (m, C–H), 2834 (w, OCH_3), 1734 (s, C=O), 1608 (s, C=C), 1566 (w), 1492 (s, CH_2/CH_3), 1466, 1432 (m, CH_2/CH_3), 1380 (w), 1298 (s), 1264 (s), 1238 (s), 1156 (m), 1128 (m), 1100 (m), 1034 (m), 948 (m), 828 (w); λ_{max} (CH_3CN)/nm (log ε) 207 (4.509), 249 (4.147), 295 (3.895), 362 (sh, 3.095); δ_H (300 MHz; $CDCl_3$) 0.89 (d, J_1 0.6, 3H, 18-H), 1.33 (dddd, J_1 6.8, J_2 11.4, J_3 12.0, J_4 12.3, 1H, 15β-H), 1.80 (dddd, J_1 2.9, J_2 7.1, J_3 9.3, J_4 12.0, 1H, 15α-H), 1.96 (ddd, J_1 6.8, J_2 9.3, J_3 14.4, 1H, 16α-H), 2.14 (ddd, J_1 2.9, J_2 11.4, J_3 14.4, 1H, 16β-H), 2.51 (d, *J* 18.8, 1H, 7β-H), 2.77 (s, 3H, NCH_3), 2.88 (dd, br, J_1 3.0, J_2 18.8, 1H, 7α-H), 2.85–2.94 (m, br, 1H, 14-H), 3.05 (dd, J_1 1.2, J_2 10.7, 1H, 12α-H), 3.16 (d, br, *J* 10.7, 1H, 12β-H), 3.25–3.42 (m, br, 1H, OH), 3.79 (s, 3H, CO_2CH_3)*, 3.84 (s, 3H, $ArOCH_3$)*, 3.84–4.00 (m, 4H, OCH_2CH_2O), 6.64 (d, *J* 2.7, 1H, 4-H), 6.85 (dd, J_1 2.7, J_2 8.6, 1H, 2-H), 7.33 (d, *J* 8.6 Hz, 1H, 1-H); δ_C (75 MHz; $CDCl_3$) 14.06 (C-18), 21.39 (C-15), 35.62 (C-7), 36.84 (C-16), 43.41 (C-14), 44.29 (NCH_3), 45.85 (C-13), 52.90 (CO_2CH_3), 55.39 ($ArOCH_3$), 59.28 (C-12), 64.62 (OCH_2-CH_2O), 65.21 (OCH_2CH_2O), 74.87 (C-6), 109.27 (C-8), 111.18 (C-4)*, 112.89 (C-2)*, 118.44 (C-17), 125.18 (C-10), 125.89 (C-1), 136.58 (C-5)**, 137.10 (C-9)**, 158.01 (C-3), 175.91 (*C*O$_2$CH$_3$); *m*/*z* 415 (M, 100%), 397 (46), 370 (8), 355 (25), 340 (22), 326 (22), 314 (18), 296 (12), 282 (11), 254 (21), 240 (9), 208

(6), 99 (15); $C_{23}H_{29}NO_6$ requires: 415.1995 found: 415.1992 (MS).

Spiro[6-hydroxy-3-methoxy-6-methoxycarbonyl-11-methyl-11-azaestra-1,3,5(10)-triene-17,2′-dioxolane] 23

Palladium on charcoal (6 mg, 5% Pd) was added to a solution of 60 mg (0.14 mmol) of **22** in 2 ml methanol, hydrogenated until one equivalent of hydrogen was taken up, filtered and evaporated. The residue was purified by radial chromatography (silica gel, pentane–diethyl ether–diethylamine (8 : 4 : 1)). Yield: 46 mg (76%) colorless oil; ν_{max}/cm^{-1} 3700–3100 (s, br, O–H), 2948 (s, C–H), 2884 (m, C–H), 2802 (w, N–CH_3), 1734 (s, C=O), 1612 (m, C=C), 1582 (w), 1498 (m, CH_2/CH_3), 1464 (m, CH_2/CH_3), 1382 (w), 1254 (s), 1240 (s), 1214 (m), 1172 (m), 1098 (m), 1032 (m), 950 (w), 890 (w), 749 (w); λ_{max} (CH_3CN)/nm (log ε) 199 (4.839), 222 (sh, 4.222), 266 (sh, 3.372), 277 (3.536), 286 (sh, 3.483); δ_H (200 MHz; $CDCl_3$) 0.97 (d, *J* 0.6, 3H, 18-H), 1.17–1.32 (m, 1H, 15-H), 1.60–1.85 (m, 3H, 14α-H, 15-H, 16-H), 1.69 (dd, J_1 12.1, J_2 13.4, 1H, 7α-H), 1.86–2.06 (m, 2H, 8-H, 16-H), 2.34 (dd, J_1 4.2, J_2 13.4, 1H, 7β-H), 2.42 (s, 3H, NCH_3), 2.90 (d, *J* 12.1, 1H, 12β-H), 2.99 (qd, J_1 0.6, J_2 12.1, 1H, 12α-H), 3.35 (dd, J_1 1.1, J_2 9.9, 1H, 9-H), 3.70–3.89 (s, br, 1H, OH), 3.71 (s, 3H, CO_2CH_3)*, 3.73 (s, 3H, $ArOCH_3$)*, 3.76–3.89 (m, 4H, OCH_2CH_2O), 6.72 (d, *J* 2.7, 1H, 4-H), 6.86 (dd, J_1 2.7, J_2 8.6, 1H, 2-H), 7.42 (dd, J_1 8.6, J_2 1.1, 1H, 1-H); δ_C (75 MHz; $CDCl_3$) 16.19 (C-18), 22.31 (C-15), 34.31 (C16), 35.24 (C-8), 39.37 (C-7), 42.23 (NCH_3), 46.69 (C-13), 49.58 (C-14), 53.14 (CO_2CH_3), 55.30 ($ArOCH_3$), 61.41 (C-12), 64.53 (OCH_2-CH_2O), 65.18 (OCH_2CH_2O), 65.70 (C-9), 74.92 (C-6), 111.34 (C-4), 113.83 (C-2), 119.10 (C-17), 127.73 (C-1), 131.98 (C-10), 138.30 (C-5), 158.07 (C-3), 176.51 (CO_2CH_3); *m*/*z* 417 (M, 48%), 399 (60), 372 (6), 358 (11), 340 (41), 315 (32), 298 (7), 251 (13), 234 (13), 216 (66), 191 (18), 175 (100), 162 (10), 99 (17); $C_{23}H_{31}NO_6$ requires: 417.2152 found: 417.2124 (MS).

Methyl 6-hydroxy-3-methoxy-11-methyl-17-oxo-11-azaestra-1,3,5(10)-triene-6-carboxylate 24

13.0 mg (0.075 mmol) toluene-*p*-sulfonic acid monohydrate was added to a solution of 28.3 mg (0.068 mmol) dioxolane **23** in 10 ml acetone. After standing in the dark for 7 d, 15 mg (0.18 mmol) sodium hydrogen carbonate was added, the mixture stirred for 5 h at room temperature, filtered through a short column of sodium sulfate with diethyl ether–diethylamine (1 : 1), the solution evaporated and the residue purified by radial chromatography (silica gel, pentane–diethyl ether–diethylamine (8 : 4 : 1). Yield: 21.0 mg (83%) colorless foam. δ_H (300 MHz; $CDCl_3$) 1.05–1.26 (m, 1H), 1.08 (s, 3H), 1.53–1.68 (m, 1H), 1.83 (dd, 1H, J_1 13.5, J_2 11.8, H-7), 1.95–2.30 (m, 4H, H-16, H-8), 2.45 (s, 3H, NCH_3), 2.50 (dd, 1H, J_1 13.5, J_2 4.8, H-7), 2.58 (dd, 1H, J_1 12.3, J_2 1.0, H-12), 3.22 (d, 1H, *J* 12.3, H-12), 3.30 (dd, 1H, J_1 10.0, J_2 1.1, H-9), 3.78 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.67 (d, 1H, *J* 2.7, H-4), 6.88 (dd, 1H, J_1 8.6, J_2 2.7, H-2), 7.45 (dd, 1H, J_1 8.6, J_2 1.1, H-1); δ_C (75 MHz; $CDCl_3$) 15.19 (C-18), 21.55 (C-15), 35.57 (C-16), 35.81 (C-8), 38.84 (C-7), 42.91 (NCH_3), 48.18 (C-13), 50.40 (C-14), 53.35 (CO_2CH_3), 55.33 ($ArOCH_3$), 61.48 (C-12), 65.69 (C-9), 74.90 (C-6), 111.51 (C-4), 113.54 (C-2), 127.32 (C-1), 131.84 (C-10), 138.08 (C-5), 158.10 (C-3), 176.29 (CO_2CH_3), 217.97 (C-17).

Methyl 3-methoxy-11-methyl-17-oxo-11-azaestra-1,3,5(10),6,8-pentaene-6-carboxylate 26

22.0 mg (0.06 mmol) of ketal **25** was added to a mixture of 1.25 g silica gel (0.04–0.063 mm), 2.3 ml dichloromethane and 0.12 ml of an aqueous solution of oxalic acid (10%), stirred for 14 d, washed with cyclohexane–ethyl acetate (2 : 1), dried and purified by radial chromatography on aluminium oxide with pentane–ethyl acetate (6 : 1). Yield 17.5 mg (89%) colorless needles, mp 148–150 °C (diethyl ether); ν_{max}/cm^{-1} 2942 cm (m, C–H), 1736 (s, C=O), 1702 (s, C=O), 1618 (s, C=C), 1557 (m), 1508 (w), 1476, 1436, 1410 (m, CH_2/CH_3), 1318 (m), 1284 (m), 1257 (s, Ar–O–C), 1213 (s), 1152 (s), 1032 (m), 1000 (m), 924 (w), 896 (w), 871 (w), 821 (w), 784 (w), 718 (w), 700 (w); λ_{max} (CH_3CN)/nm (log ε) 205 (4.588), 210 (sh, 4.583), 227 (4.354), 247 (4.543), 278 (4.423), 286 (sh, 4.361), 309 (sh, 3.481), 325 (sh, 3.793), 339 (3.993), 374 (4.324); δ_H (300 MHz; $CDCl_3$) 0.81 (d, *J* 0.5, 3H, 18-H), 2.01 (dddd, J_1 8.8, J_2 9.3, J_3 11.8, J_4 12.4, 1H, 15β-H), 2.43 (ddd, J_1 8.7, J_2 8.8, J_3 19.3, 1H, 16α-H), 2.66 (dddd, J_1 1.2, J_2 6.0, J_3 8.7, J_4 11.8, 1H, 15α-H), 2.71 (ddd, J_1 1.2, J_2 9.3, J_3 19.1, 1H, 16β-H), 3.14 (dddd, J_1 1.1, J_2 1.5, J_3 6.0, J_4 12.4, 1H, 14-H), 3.23 (dd, J_1 0.5, J_2 11.2, 1H, 12β-H), 3.33 (s, 3H, NCH_3), 3.55 (dd, J_1 1.5, J_2 11.2, 1H, 12α-H), 3.95 (s, 3H, CO_2CH_3)*, 3.97 (s, 3H, $ArOCH_3$)*, 7.05 (dd, J_1 2.7, J_2 9.4, 1H, 2-H), 7.88 (d, *J* 9.4, 1H, 1-H), 7.94 (d, *J* 1.1, 1H, 7-H), 8.64 (d, *J* 2.7, 1H, 4-H); δ_C (75 MHz; $CDCl_3$) 14.22 (C-18), 21.37 (C-15), 36.55 (C-16), 44.31 (C-14), 46.49 (NCH_3), 48.93 (C-13), 51.49 (CO_2CH_3), 55.27 ($ArOCH_3$), 60.57 (C-12), 104.80 (C-2), 114.76 (C-10)*, 116.32 (C-4), 119.55 (C-8)*, 120.43 (C-6), 126.85 (C-1), 129.22 (C-7), 135.90 (C-5), 148.87 (C-9), 158.67 (C-3), 167.83 (CO_2CH_3), 217.37 (C-17); *m*/*z* 353 (M, 100%), 338 (7), 322 (13), 310 (9), 296 (25), 282 (14), 278 (8); $C_{21}H_{23}NO_4$ requires: 353.1627 found: 353.1626 (MS).

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