Synthesis of Lactam and Ketone Precursors of 2,7-Substituted Octahydropyrrolo[1,2-*a*]pyrazines and Octahydro-2*H*-pyrido[1,2-*a*]pyrazines

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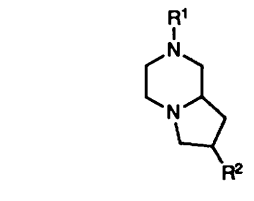
This report describes the synthesis of the hexahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-ones **6**, the hexahydropyrrolo[1,2-*a*]pyrazin-7(6*H*)-ones **7**, and the hexahydro-2*H*-pyrido[1,2-*a*]pyrazin-7-(6*H*)-ones **8**, precursors of 2,7-substituted octahydropyrrolo- and octahydro-2*H*-pyrido[1,2-*a*]pyrazines. The synthetic sequence leading to the ketones **7** and **8** starts with the construction of the piperazine ring through intramolecular 1,4-addition of the unsaturated amino ester **18** or reductive cyclization of the amino keto ester **11**. The resulting piperazin-2-yl-acetates **19** and -propanoates **12** are then subjected to alkylation with methyl bromoacetate, Dieckmann cyclization and acidic demethoxycarbonylation. Depending on the reaction conditions, ring closure of the piperazin-2-ylpropanoates **12** afforded the lactams **6** or the 8a-methoxy lactam **14**.

The octahydropyrrolo[1,2-*a*]pyrazine and the octahydro-2*H*-pyrido[1,2-*a*]pyrazine structures **1** and **2**, (R^2 = H) form the basis of various compounds of pharmacological interest.[1] The 2,7-substituted analogues **1** and **2** (R^1 and R^2 = appropriate pharmacophoric substituents) can be regarded as conformationally restricted forms of piperazine drugs such as flunarizine **3**, fluanisone **4** and lidoflazine **5**. Provided this restriction conforms to the 'active conformation' of the monocyclic drug compounds, it results in greater specificity of interaction with the complementary receptor site and hence more selectivity in its pharmacological activity.



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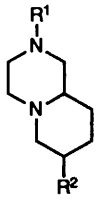

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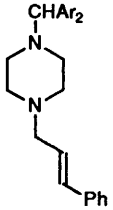

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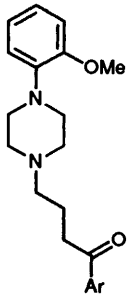

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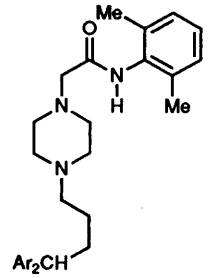
Ar = C_6H_4F-*p*



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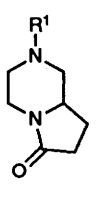
Until now, few 7-substituted pyrrolo- and pyrido-pyrazines **1** and **2** have been reported.[2,3] Recently we prepared the ketone precursors **8a,b** of the 2,7-substituted pyridopyrazines **2**.[4,5] Starting from 1-benzyl-3,3-ethylenedioxypiperidine, the synthetic route to **8a,b** involved Hg^{2+}-oxidation and trapping of the resulting 6-iminium ion with cyanide, then further elaboration to the bicyclic ketone. Here we describe an alternative approach to the lactam and ketone synthons **6**, **7** and **8**, proceeding through initial formation of the piperazine ring. In these synthons, position 7 can be substituted by reaction with either nucleophiles (ketones **7**, **8**) or electrophiles (lactam enolate of **6**). The N-2 substituents are introduced at the start of the synthetic sequence, *e.g.* aryl groups, or following *N*-debenzylation. The unsubstituted lactam structure **6** (R^1 = H) was mentioned in a recent patent.[6]



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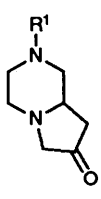

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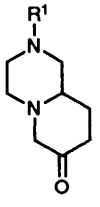

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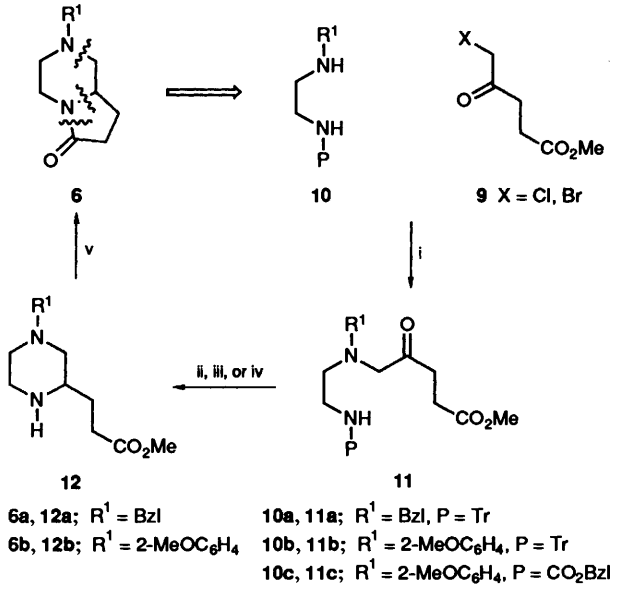
6a, 7a, 8a; R^1 = Bzl
6b, 7b, 8b; R^1 = 2-$MeOC_6H_4$

Results and Discussion

Bond fission analysis of the lactam **6** (Scheme 1) indicates a synthetic route consisting of a threefold substitution of a *N*-aryl- or *N*-benzyl-ethylenediamine with a five-carbon electrophilic reagent. In this respect, the α-chloro keto ester **9**[7] seems most appropriate since the differential reactivity of the three electrophilic centres permits the desired sequential order of substitution. In the nucleophilic diamine partner **10**, this order of reactivity is matched by initial blocking of the primary amine as the *N*-trityl derivatives **10a,b** or the carbamate **10c**.

The *N'*-protected diamine reagents **10a,b** were prepared by tritylation of *N*-benzyl- and *N*-(2-methoxyphenyl)-ethylenediamine. The latter precursor of **10b** was derived from the HBr salt of bromoethylamine through chemoselective substitution with *o*-anisidine. As an alternative to salt formation, the amino group of bromoethylamine was blocked as the carbamate which, in turn, underwent ready substitution with *o*-anisidine to afford **10c**. As expected, attack of the free amino group of the diamine reagents **10a–c** occurred regioselectively at the α-chloro position of **9** to give the keto esters **11a–c**. The carbonyl absorptions in the IR spectra of **11a–c** show them to be uniformly present as non cyclic ketones (as opposed to the cyclic hemiaminal forms of **11a,b**).

Acid-promoted detritylation of **11a**, then reductive cyclization with $NaCNBH_3$ afforded the secondary amine **12a**; this could

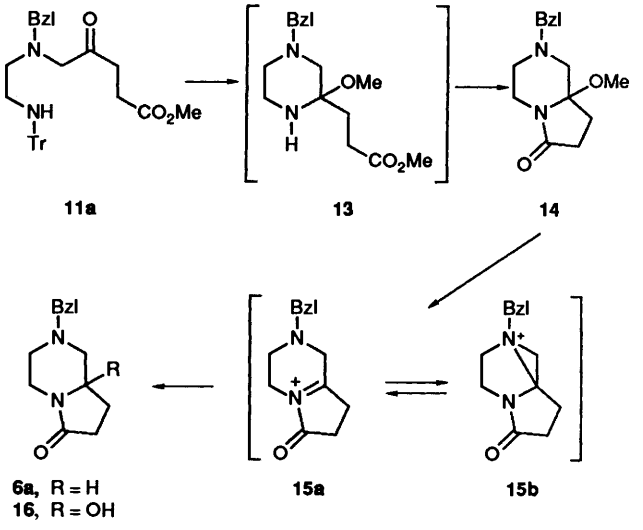


Scheme 1 *Reagents and conditions:* i, acetone, K_2CO_3, KI; ii, MeOH–HCl, reflux; iii, $NaCNBH_3$, MeOH, pH 5; iv, MeOH–HOAc, H_2–Pd/C; v, MeOH, K_2CO_3, reflux

be isolated as the free base or cyclized to the lactam **6a** by further heating in basic medium. Under the same conditions (reflux with HCl in methanol), compound **11b** underwent acidic cleavage of both the trityl group and the 2-oxomethyl group. Probably, this result can be attributed to the good leaving group properties of the protonated aromatic amine. These properties are enhanced further by formation of a stable H-bond with the *o*-methoxy group and the relief of steric hindrance. Catalytic hydrogenation of the *N*-trityl compound **11b** and the carbamate **11c** effected both the desired deprotection and the reductive cyclization to give first the amino ester **12b** and then, by further heating of the free base, lactam **6b**.

TLC analysis of the crude amino ester **12a** revealed the presence of a less-polar side product, to which the bicyclic structure **14** with an angular 8a-methoxy group was attributed. Indeed, when after acid deprotection of **11a** addition of $NaCNBH_3$ was omitted, the neutralized reaction mixture afforded **14** as the only reaction product (Scheme 2). Apparently, the amino ether **13** formed by solvent trapping of the intermediate iminium ion, cyclizes more readily than the reduced amine **12a**. Reduction of the lactam **14** to **6a** required prolonged heating with $NaCNBH_3$ in slightly acidic medium (pH 5–6). The ability to transform **14** into the bicyclic acyliminium ion **15a** or the tricyclic aziridinium ion **15b**, and hence to introduce other angular substituents, was demonstrated by conversion of **14** into the 8a-hydroxy compound **16** on treatment with trifluoroacetic acid and alkaline work-up. The structure of **16** was confirmed by the great similarity of the ^1H and ^{13}C NMR spectra to those of the 8a-methoxy lactam **14**. An attempt to introduce the 8a-cyano group with KCN in trifluoroacetic acid–dichloromethane led to a mixture of products. Besides the 8a-hydroxy compound **16**, a small amount of a dehydrogenated cyano adduct (M^+ 253) was isolated.

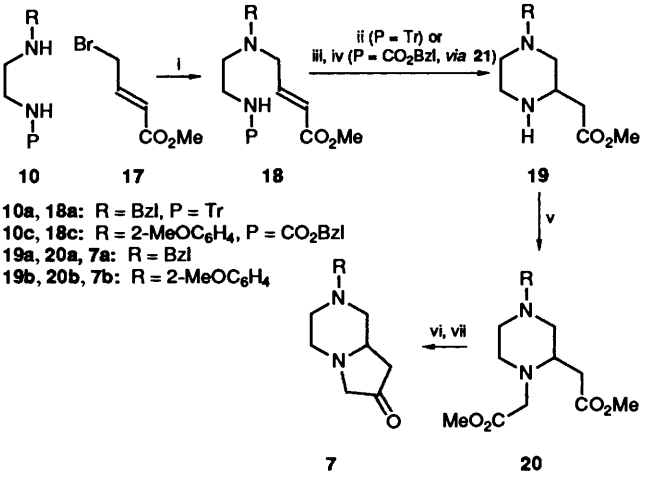
The synthetic route to the ketone synthons **7** (Scheme 3) starts with an allylic substitution of methyl 4-bromobut-2-enoate **17** by the secondary amino group of the monoprotected ethylenediamines **10a,c**. Subsequent 1,4-addition of the other amino group on the α,β-unsaturated ester then proceeds either *via* acidic deprotection (**18a** ⟶ **19a** for P = Tr) or *via* generation of the carbamate anion (**18c** ⟶ **21** ⟶ **19b** for P = CO_2Bzl). *N*-Alkylation of the resulting piperazin-2-ylacetates **19** leads to



Scheme 2

the diacetates **20** which eventually give the desired ketones **7** through Dieckmann cyclization and demethoxycarbonylation.

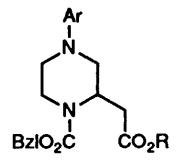
Reaction of amines **10a,c** with **17** to form **18a,c** proceeded without difficulty. Acid deprotection of **18a** and neutralization afforded piperazin-2-ylacetate **19a** in 85% yield. For the preparation of the analogous compound **19b**, 1,4-addition producing the cyclic carbamate **21** had to precede hydrogenolytic deprotection. Brief treatment of the carbamate **18c** with KOBu^t in toluene afforded **21** in good yield (85%). However, a more prolonged reaction with KOBu^t led to the corresponding piperazin-2-ylacetic acid **22**.



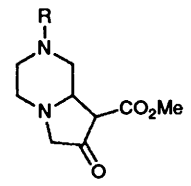
Scheme 3 i, acetone, K_2CO_3, KI; ii, MeOH–HCl, reflux, then aq. K_2CO_3; iii, toluene, KOBu^t; iv, CH_3CO_2H, H_2–Pd/C; v, acetone, $BrCH_2CO_2Me$, K_2CO_3, KI; vi, toluene, KOBu^t, 0 °C; vii, aq. HCl, reflux

Dieckmann cyclization of the diesters **20a,b**, obtained from **19a,b** by alkylation with methyl bromoacetate, could produce the regioisomeric ketoesters **23a,b** and **24a,b**. However, only the more stable keto esters **23a,b** were detected and isolated (**23a**: 49%, **23b**: 35%). If formed, the regioisomeric keto esters **24a,b** presumably decompose *via* the enol–enamine tautomer. The total yield of the conversion **20a,b** ⟶ **7a,b** was increased (57% for **7a** and 55% for **7b**) when acidic hydrolysis of the keto esters was performed directly on the crude reaction product.

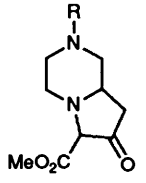
The 2-benzyl- and 2-(2-methoxyphenyl)-hexahydro-2*H*-pyrido[1,2-*a*]pyrazin-7(6*H*)-ones **8a,b** have been described previously.[5] An alternative synthesis (Scheme 4) takes advantage of the slow cyclization of the amino esters **12a,b**. *N*-Alkylation of



21 : Ar = 2-MeOC$_6$H$_4$, R = Me
22 : Ar = 2-MeOC$_6$H$_4$, R = H

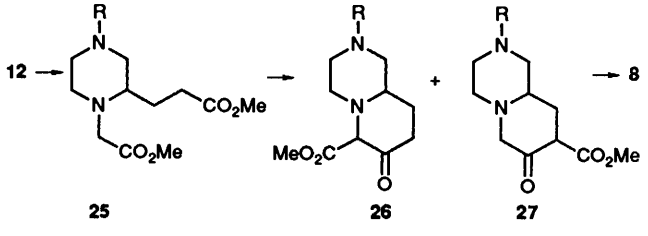


23a : R = Bzl
23b : R = 2-MeOC$_6$H$_4$



24a : R = Bzl
24b : R = 2-MeOC$_6$H$_4$

12a,b with methyl bromoacetate cleanly produced diesters **25a,b** (**25a**: 72%, **25b**: 76%). However, Dieckmann cyclization of **25a,b** required the use of strong bases (LDA or KH in THF). Probably this result is due to the decreased basicity of the α-protons of the 2-propanoate ester side-chain compared to the 2-acetate ester group of **17a,b**. TLC analysis of the crude keto ester mixture obtained from **12a** indicated the existence of a labile and a more stable keto ester (**26a** and **27a**). Column chromatography of the keto esters gave rise to isolation of only the keto ester **27a** in low yield. Acid hydrolysis was carried out on the crude keto ester mixture, affording the desired ketones **8a,b** identical with the compounds described previously[5] (yield **8a**: 43%, **8b**: 33%).

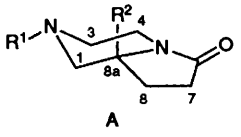


12a, 25a, 26a, 27a, 8a : R = Bzl
12b, 25b, 26b, 27b, 8b : R = 2-MeOC$_6$H$_4$

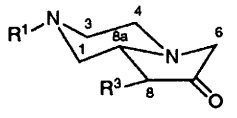
Scheme 4

The important features of the ^{1}H NMR spectra of lactams **6a,b**, 8a-methoxylactam **14**, ketones **7a,b** and keto ester **23a** are assembled in Table 1. For the ketone compounds **7a,b** which have a tetrahedral sp^3 N, the coupling patterns are consistent with a *trans*-fused conformation **B**, in which all protons of the bicyclic system occupy either an axial or an equatorial position. Conformation **B** is supported by the values of the vicinal coupling constants $^3J_{8ax,8a}$ 11 Hz, $^3J_{8eq,8a}$ 5.5 Hz and $^3J_{1ax,8a}$ 10 (9.5) Hz for **7a,b** and the value $^3J_{1eq,8a}$ 2 Hz for **7b**. In contrast, due to the trigonal geometry of the sp^2 N, lactams **6a,b** adopt conformation **A**, in which the piperazine ring forms a chair and the pyrrolidinone ring is nearly planar. The chair form of the piperazine ring is shown by the coupling constant values $^3J_{1ax,8a}$ 11 Hz and $^3J_{1eq,8a}$ 3 (2) Hz. The intermediate and similar values found for protons 7-H, 8-H and 8a-H ($^3J_{7,8}$ 9, 9, 7, 5 Hz; $^3J_{8,8a}$ 7, 6 Hz) confirm the nearly planar geometry of the lactam ring that is suggested by inspection of molecular models. In compound **14**, C-8 is pushed slightly down this plane by interaction with the 8a-methoxy group, resulting in a shift of the coupling constants to both higher and lower values ($^3J_{7,8}$ 10, 8.5, 10, 3.5 Hz).

The bicyclic structure of lactams **6a,b**, **14** and **16**, ketones **7a,b** and the keto ester **23a** is confirmed by the ^{13}C NMR spectra (see Experimental section). In addition, the chemical shift values reveal the location of the 8a-methoxy group in **14** and of the ester group at C-8 in the keto ester **25a**.



A



B

R^1 = Bzl or 2-MeOC$_6$H$_4$
R^2 = H or MeO

R^1 = Bzl or 2-MeOC$_6$H$_4$
R^3 = H or CO_2Me

The lactam and ketone precursors described in the present work provide a general route to the 2,7-substituted target compounds **1** and **2**, the bicyclic analogues of 1,4-substituted piperazine drugs. The enolate anions of lactams **6a,b** can be substituted with either the final group or with an auxiliary group X (X = Cl, Br, CO_2R, SPh) which, in turn, can be transformed to the final substituent. The introduction of the auxiliary group allows for radical reactions (SPh), reactions with electrophiles (CO_2R) or reactions with nucleophilic reagents analogous to those used for the 7-ketones **7a,b** and **8a,b** (Cl, Br, CO_2R). Finally, generation of the acyliminium or aziridinium ion from the α-methoxy lactam **14** could serve as a tool for introduction of angular 8a-substituents.

Experimental

All m.p.s are uncorrected. IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM 250 instrument operating at 250 MHz for ^{1}H and 63 MHz for ^{13}C measurements. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. *J* values are recorded in Hz. Mass spectra were run on a Kratos MS50 instrument and DS90 data system; the ion source temperature was 150–250 °C as required. Exact mass measurements were performed at a resolution of 10 000. Analytical and preparative thin layer chromatography was performed using Merck silica gel 60 PF-224 or neutral aluminum oxide 60 F-254. Column chromatography was carried out using 70–230 mesh silica gel 60 (E.M. Merck) or 100–125 mesh neutral aluminum oxide (Brockmann activity 4) (Fluka).

N-(2-*Methoxyphenyl*)*ethane*-1,2-*diamine*.—A stirred mixture of 2-methoxybenzenamine (18 cm^3, 0.16 mol) and bromoethylammonium bromide (32.70 g, 0.16 mol) in toluene (200 cm^3) was refuxed for 5 h under an atmosphere of nitrogen. The toluene layer was separated and discarded. The salt phase was dissolved in water (160 cm^3), made alkaline with saturated aqueous KOH (50 cm^3) and extracted with CH_2Cl_2 (3 × 1 dm^3). The combined CH_2Cl_2 layers were evaporated and the residue was purified by vacuum distillation (150 °C/6 mm Hg) to give the title compound (19 g, 71%); ν_{max}(KBr)/cm^{-1} 3420 (NH); δ_H(250 MHz; $CDCl_3$) 1.47 (2 H, br s, NH_2), 2.73 (1 H, m, NH), 2.98 (2 H, m, CH_2NH), 3.19 (2 H, m, CH_2NH_2), 3.83 (3 H, s, CH_3O) and 6.52–7.11 (4 H, m, Ph).

N-*Benzyl*-N′(*triphenylmethyl*)*ethane*-1,2-*diamine* **10a**.—To a cooled (0 °C) and stirred solution of N-benzylethane-1,2-diamine[8] (32 g, 0.213 mol) and Et_3N (16 g, 0.158 mol) in dry CH_2Cl_2 (30 cm^3) was added dropwise a solution of triphenylmethyl chloride (60 g, 0.214 mol) in dry CH_2Cl_2 (300 cm^3). The mixture then was allowed to come to room temp. for 1 h. The $Et_3N^+HCl^-$ was filtered off, the filtrate was evaporated and the residue was chromatographed on a silica column (EtOAc) to

Table 1 ^{1}H NMR spectra of the lactams **6a** and **6b**, the methoxy lactam **14**, ketones **7a** and **7b**, and the keto ester **23a**[a–g]

	6a	6b	14	7a	7b	23a
1_{ax}-H	1.71 (t) 11[b,c]	2.35 (t) 11[b,c]	1.95 (d) 11.5[b]	2.04 (t) 10[b,c]	2.68 (dd) 10.5,[b] 9.5[c]	2.18 (dd) 10.5,[b] 9.5[c]
1_{eq}-H	2.92 (m)	3.59 (dt) 11,[b] 2,[d] 2[f]	3.17 (dd) 11.5,[b] 1.5[f]	2.99 (m)	3.60 (dt) 10.5,[b] 2,[d] 2[f]	2.82 (m)
3_{ax}-H	1.96 (td) 11,[b,c] 3[d]	2.58 (td) 11,[b,c] 3[d]	2.05 (td) 11.5,[b,c] 4[d]	2.37 (td) 11,[b,c] 2.5[d]	2.97 (td) 11,[b,c] 3[d]	2.34 (ddd) 11,[c] 10.5,[b] 2.5[d]
3_{eq}-H	2.85 (m)	3.42 (dm) 11[b]	2.89 (dm) 11.5[b]	2.87 (dm) 11[b]	3.48 (dm) 11[b]	2.97 (dt) 10.5,[b] 2[d,e]
4_{ax}-H	2.84 (m)	3.11 (td) 12.5,[b,c] 3[d]	3.03 (dddd) 13,[b] 11.5,[c] 3.5,[d] 1.5[g]	2.50 (td) 11,[b,c] 2.5[d]	2.74 (td) 11,[b,c] 2,5[d]	2.51 (td) 11,[b,c] 2[d]
4_{eq}-H	3.96 (dm) 12.5[b]	4.11 (ddd) 10.5,[b] 3,[d] 2[e]	3.92 (ddd) 13,[b] 4,[d] 1.5[e]	2.99 (dm) 11[b]	3.09 (ddd) 11,[b] 3,[d] 2[e]	3.07 (dm) 11[b]
6_{ax}-H				2.69 (d) 16.5[b]	2.78 (d) 16[b]	2.88 (d) 16.5[b]
6_{eq}-H				3.41 (d) 16.5[b]	3.43 (d) 16[b]	3.47 (d) 16.5[b]
7-H	2.34 (m)	2.44 (m)	2.36 (ddd) 17,[b] 10, 3.5			
7-H	2.34 (m)	2.44 (m)	2.53 (dddd) 17,[b] 10, 8.5, 1.5[g]			
8_{ax}-H[h]	1.52 (dtd) 12,[b] 9, 9, 6	1.65 (dtd) 12,[b] 9, 9, 6	1.82 (ddd) 14.5,[b] 10, 8.5	2.09 (dd) 17,[b] 11[c]	2.18 (dd) 17,[b] 11[c]	3.14 (m)
8_{eq}-H[h]	2.02 (dtd) 12,[b] 7, 7, 5	2.22 (dtd) 12,[b] 7, 7, 5	2.13 (ddd) 14.5,[b] 10, 3.5	2.27 (dd) 17,[b] 5.5[d]	2.37 (dd) 17,[b] 5.5[d]	
8_a-H	3.60 (dddd) 11,[c] 7, 6, 3[d]	3.87 (m)		2.72 (m)	2.97 (m)	3.14 (m)

[a] 250 MHz spectra in $CDCl_3$; δ values in ppm; J values in Hz. These J values are indicated as follows: [b] $^2J_{AB}$, [c] $^3J_{ax,ax}$, [d] $^3J_{ax,eq}$ or $^3J_{eq,ax}$, [e] $^3J_{eq,eq}$, [f] ^4J; [g] ^5J; [h] The denomination 8_{ax}-H and 8_{eq}-H does not apply to lactams **6a**, **6b** and **14**.

give **10a** as a solid (69 g, 83%), m.p. 85 °C (EtOAc); ν_{max}(KBr)/cm^{-1} 3280 (NH); δ_H(250 MHz; $CDCl_3$) 1.7 (2 H, br s, NH), 2.4–2.9 (4 H, 2 × t, J 5, CH_2CH_2), 3.7 (2 H, s, CH_2Ph) and 7.0–7.7 (20 H, m, Ph); m/z 393 $(MH)^+$, 392 $(M)^+$, 315 $(M - Ph)^+$, 243 $(Tr)^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 392.2190. $C_{28}H_{28}N_2$ requires M, 392.2251).

N-(2-*Methoxyphenyl*)-N′-(*triphenylmethyl*)*ethane*-1,2-*diamine* **10b**.—To a stirred solution of *N*-(2-methoxyphenyl)-ethane-1,2-diamine (11.60 g, 70 mmol) and Et_3N (7.06 g, 70 mmol) in dry CH_2Cl_2 (500 cm^3) was added dropwise a solution of triphenylmethyl chloride (21.5 g, 77 mmol) in dry CH_2Cl_2 under an atmosphere of nitrogen. The mixture was stirred for 16 h at room temp. and then worked up as described for **10a**. Chromatography of the residue on silica ($CHCl_3$) afforded **10b** (24.85 g, 87%) as a solid, m.p. 119 °C (EtOAc); ν_{max}(KBr)/cm^{-1} 3460 and 3310 (NH) and 1450 and 1360 (OCH_3); δ_H(250 MHz; $CDCl_3$) 1.75 (1 H, br s, NH), 2.44 (2 H, t, J 6, CH_2NHTr), 3.24 (2 H, t, J 6, CH_2NHPh), 3.82 (3 H, s, CH_3O), 4.53 (1 H, br s, NH), 6.59 (1 H, dd, J 7.5, 1.5, 6′-H of Ph), 6.65 (1 H, td, J 7.5, 1.5, 4′-H of Ph), 6.76 (1 H, dd, J 7.5, 1.5, 3′-H of Ph), 6.84 (1 H, td, J 7.5, 1.5, 5′-H of Ph), 7.15 (3 H, tt, J 7, 1.5, *p*-H Tr), 7.22 (6 H, td, J 7, 1.5, *m*-H Tr) and 7.47 (6 H, dt, J 7, 1.5, *o*-H Tr); m/z 408 $(M)^+$, 243 $(Tr)^+$ (Found: M^+, 408.2200. $C_{28}H_{28}N_2O$ requires M, 408.2208).

N-(*Benzyloxycarbonyl*)-N′-(2-*methoxyphenyl*)*ethane*-1,2-*diamine* **10c**.—A mixture of *N*-(benzyloxycarbonyl)-2-bromoethanamine[9] (15.0 g, 0.06 mol) and 2-methoxyaniline (28.7 g, 0.30 mol) in toluene (250 cm^3) was refluxed for 6 h under N_2. It was then washed with HCl (1 mol dm^{-3}; 100 cm^3) and made alkaline with aq. K_2CO_3. Extraction with CH_2Cl_2, drying over $MgSO_4$ and evaporation gave a residue which was purified by column chromatography (silica, 6:94 EtOAc–$CHCl_3$) to give **10c** (14.9 g, 75%); ν_{max}(NaCl)/cm^{-1} 3320 (NH), 2820 (NCH_2) and 1700 (NCO_2); δ_H(250 MHz; $CDCl_3$) 1.7 (1 H, s, NH), 3.4 (4 H, m, CH_2CH_2), 3.8 (3 H, s, CH_3O), 4.3 (1 H, s, NH), 5.3 (2 H, s, CO_2CH_2), 6.8 (4 H, $MeOC_6H_4$ and 7.5 (5 H, s, CH_2Ph); m/z 300 $(M)^+$ and 136 $(MeOC_6H_4NH{=}CH_2)^+$ (Found: M^+, 300.1462. $C_{17}H_{20}N_2O_3$ requires M, 300.1474).

Methyl 5-{N-*Benzyl*-N-[2-(*triphenylmethylamino*)*ethyl*]-*amino*}-4-*oxopentanoate* **11a**.—To a stirred mixture of **10a** (9.5 g, 24 mmol), K_2CO_3 (7.0 g, 51 mmol) and KI (4.0 g, 24 mmol) in acetone (200 cm^3) was added **9** (5.0 g, 30 mmol). After 3 h the mixture was worked up by addition of water and extraction with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure and the residue was purified over silica gel (5:95 EtOAc–$CHCl_3$) to give **11a** as pale yellow crystals (12 g, 95%), m.p. 82 °C (Et_2O); ν_{max}(KBr)/cm^{-1} 3320 (NH), 1745 (CO_2) and 1715 (CO); δ_H(250 MHz; $CDCl_3$) 2.20–2.35 (1 H, br s, NH), 2.20–2.35 (2 H, t, J 5, CH_2CO_2), 2.52 (2 H, t, J 5, $COCH_2$), 2.72 (4 H, m, NCH_2CH_2N), 3.08 (2 H, s, NCH_2CO), 3.49 (2 H, s, CH_2Ph), 3.64 (3 H, s, CH_3O) and 7.05–7.55 (20 H, m, Tr); m/z 520 $(M)^+$, 443 $(M - Ph)^+$, 277 $(M - Tr)^+$, 248 $(M - TrNHCH_2)^+$, 243 $(Tr)^+$, 134 [Bzl(Me)-N=CH_2]$^+$, 91 $[C_7H_7]^+$ (Found: M^+, 520.2737. $C_{34}H_{36}N_2O_3$ requires M, 520.2725).

Methyl 5-{N-(2-*methoxyphenyl*)-N-[2-(*triphenylmethyl-amino*)*ethyl*]*amino*}-4-*oxopentanoate* **11b**.—To a stirred mixture of **10b** (4.43 g, 10.8 mmol), K_2CO_3 (3.00 g, 21.7 mmol) and KI (1.80 g, 10.8 mmol) in acetone (65 cm^3), **9** (1.97 g, 12.0 mmol) was added dropwise. After being stirred under N_2 for 2 days, the mixture was worked up as described for **11a** and the resulting product was chromatographed over silica gel (gradient elution, 1:9 to 3:7 EtOAc–$CHCl_3$) to give **11b** as crystals (4.35 g, 78%), m.p. 82–83 °C (EtOAc–hexane); ν_{max}(KBr)/cm^{-1} 3340 (NH), 1740 (CO_2) and 1705 (CO); δ_H(250 MHz; $CDCl_3$) 1.23 (1 H, m, NH), 2.09–2.36 (2 H, m, CH_2NHTr), 2.41–2.65 (2 H, m, CH_2CO_2), 2.65–2.89 (2 H, m, $COCH_2$), 3.32 (2 H, t, NCH_2), 3.60 (3 H, s, CH_3O), 3.69 (3 H, s, CH_3O), 3.74 (2 H, s, NCH_2CO), 6.69–6.72 (4 H, m, $MeOC_6H_4$) and 7.10–7.49 (15 H, m, Tr); m/z 536 $(M)^+$, 459 $(M - Ph)^+$, 293 $(M - Tr)^+$, 264 $(CH_2{=}NHTr)^+$ and 243 $(Tr)^+$ (Found: M^+, 536.2663. $C_{34}H_{36}N_2O_4$ requires M, 536.2673).

Methyl 5-{N-(2-*methoxyphenyl*)-N-[2-(*benzyloxycarbonylamino*)*ethyl*]*amino*}-4-*oxopentanoate* **11c**.—To a mixture of **10c** (2.00 g, 7 mmol), K_2CO_3 (0.92 g, 7 mmol) and KI (1.11 g, 7 mmol) in acetone (50 cm^3), **9** (2.19 g, 13 mmol) was added dropwise. After the mixture had been stirred at room temp. under N_2 for 7 days, the solvent was evaporated and the residue dissolved in CH_2Cl_2. The organic phase was washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography of the residue on a silica column (15:85 EtOAc–$CHCl_3$) afforded **11c** as an oil (2.22 g, 78%); ν_{max}(NaCl)/cm^{-1} 3320 (NH), 2820 (NCH_2) and 1720 (CO, CO_2, NCO_2); δ_H(250 MHz; $CDCl_3$) 2.4 (4 H, m, $COCH_2CH_2CO_2$), 3.1 (4 H, m, NCH_2CH_2N), 3.4 (3 H, s, CH_3O), 3.6 (3 H, s, CH_3O), 3.7 (2 H, s, NCH_2CO), 4.9 (2 H, s, CH_2Ph), 6.1 (1 H, s, NH), 6.8 (4 H, m, $MeOC_6H_4$) and 7.2 (5 H, s, CH_2Ph); *m*/*z* 428 $(M)^+$, 410 $(M - H_2O)^+$, 397 $(M - OMe)^+$, 313 $(M - COCH_2CH_2CO_2Me)^+$, 264 $(M - CH_2NHCO_2Bzl)^+$, 205 (313 – BzlOH) and 91 $(C_7H_7)^+$ (Found: M^+, 428.1963. $C_{23}H_{28}N_2O_6$ requires *M*, 428.1947).

Methyl 4-*Benzylpiperazin*-2-*ylpropionate* **12a**.—Compound **11a** (5.35 g, 10 mmol) was dissolved in HCl–MeOH (2 mol dm^{-3}; 30 cm^3). After being heated under reflux for 1 h the reaction mixture was evaporated and the residue was treated with methanol (50 cm^3). $NaCNBH_3$ (1.29 g, 21 mmol) was added to the filtered solution (removal of TrOMe) after which the mixture was brought to pH 6 with HCl–MeOH and refluxed for 1 h. After neutralization with aq. K_2CO_3 the mixture was extracted with CH_2Cl_2, and the extract was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude polar amine **12a** (TLC, alumina, 6:94 MeOH–$CHCl_3$, R_f 0.15); ν_{max}(NaCl)/cm^{-1} 3600–3000 (NH), 3090, 3060 and 3030 (ArH), 2950 (CH_2), 2810 (NCH_2), 1740 (CO_2) and 750 and 700 (ArH); δ_H(90 MHz; $CDCl_3$) 1.40–3.00 (12 H, m, NH, CH_2), 3.47 (2 H, s, NCH_2Ph), 3.67 (3 H, s, CO_2CH_3) and 7.33 (5 H, s, Ph); *m*/*z* 262 $(M)^+$, 231 $(M - OMe)^+$, 230 $(M - MeOH)^+$, 171 $(M - Bzl)^+$, 146 $[Bzl(CH_2{=}CH)N{=}CH_2]^+$, 139 (171 – MeOH), 134 $[Bzl(Me)N{=}CH_2]^+$ and 91 $(C_7H_7)^+$.

Methyl 4-(2-*Methoxyphenyl*)*piperazin*-2-*ylpropionate* **12b**.—(a) A solution of **11c** (3.2 g, 7.5 mmol) in methanol–acetic acid (1:1; 35 cm^3) was hydrogenated over 10% Pd/C (0.6 g) under a hydrogen pressure of 3 atm (Parr apparatus) for 16 h. The catalyst was filtered off and washed with methanol. The solvent was partially evaporated and the resulting solution (*ca.* 5 cm^3) was diluted with CH_2Cl_2 (25 cm^3). The CH_2Cl_2 solution was washed with aq. K_2CO_3, dried ($MgSO_4$) and evaporated to afford crude **12b**, which was used directly in the next step (TLC silica, 1:4 MeOH–EtOAc, R_f = 0.17).

(b) A solution of **11b** (3.08 g, 5.74 mmol) was hydrogenated in the same way and equally gave **12b**.

2-*Benzylhexahydro*-8a-*methoxypyrrolo*[1,2-a]*pyrazin*-6(2H)-*one* **14**.—A solution of **11a** (4.38 g, 8 mmol) in HCl–MeOH (2 mol dm^{-3}; 25 cm^3) was refluxed for 1 h. The mixture was evaporated and the residue dissolved in methanol (25 cm^3). The solid material ($TrOCH_3$) was filtered off and the filtrate was brought to pH 6 with K_2CO_3. After being refluxed for 30 min. and stirred at room temp. for 16 h, the solution was made alkaline with aq. K_2CO_3 and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated and the residue was purified over silica gel (2:98, MeOH–$CHCl_3$) to afford **14** (1.44 g, 65%) as an oil; ν_{max}(NaCl)/cm^{-1} 3090, 3070 and 3030 (ArH), 2940 (CH_2), 2820, 2770 (NCH_2, OCH_3), 1690 (NCO), 1600, 1585 and 1495 (ArH) and 730 and 700 (ArH); δ_H(250 MHz; $CDCl_3$) 3.15 (3 H, s, CH_3O), 3.57, 3.77 (2 H, d, *J* 13.5, NCH_2Ph), 7.30 (5 H, m, Ph) (for the other values, see Table 1); δ_C(63 MHz; $CDCl_3$) 28.1 (C-8), 29.4 (C-7), 36.3 (C-4), 49.0 (CH_3O), 51.1 (C-3), 61.5 (C-1), 62.2 (NCH_2Ph), 90.3 (C-8a), 127.0 (C-*p*), 128.0 (C-*o*), 128.9 (C-*m*), 136.4 (C-*i*) and 172.6 (NCO); *m*/*z* 260 $(M)^+$, 245 $(M - Me)^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 260.1518. $C_{15}H_{20}N_2O_2$ requires *M*, 260.1525).

2-*Benzylhexahydro*-8a-*hydroxypyrrolo*[1,2-a]*pyrazin*-6(2H)-*one* **16**.—The methoxy lactam **14** (200 mg, 0.8 mmol) was dissolved in trifluoroacetic acid (5 cm^3) and the solution stirred for 15 min at room temp. It was then evaporated and the residue dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with aq. K_2CO_3, dried ($MgSO_4$) and evaporated and the residue was purified over silica gel (6:94, MeOH–$CHCl_3$) to give **16** as an oil (157 mg, 83%; ν_{max}(NaCl)/cm^{-1} 3600–3300 (OH), 3090, 3070 and 3040 (ArH), 2950 (CH_2), 2820 (NCH_2), 1680 (NCO) and 730 and 700 (ArH); δ(250 MHz; $CDCl_3$) 1.90 (1 H, ddd, *J* 18, 10, 8, 8_{ax}-H), 2.09 (1 H, d, *J* 11, 1_{ax}-H), 2.02–2.17 (2 H, m, 3_{ax}-H, 8_{eq}-H), 2.30 (1 H, ddd, *J* 16.5, 10, 3.5, 7_{ax}-H), 2.58 (1 H, ddd, *J* 16.5, 8, 7, 7_{eq}-H), 2.88 (1 H, d, *J* 11.5, 3_{eq}-H), 2.97 (1 H, dd, *J* 11, 1.5, 1_{eq}-H), 3.07 (1 H, td, *J* 13, 4, 4_{ax}-H), 3.56, 3.62 (2 H, d, *J* 14, NCH_2Ph), 3.83 (1 H, dd, *J* 13, 2, 4_{eq}-H), 4.38 (1 H, br s, OH) and 7.30 (5 H, s, Ph); δ_C(63 MHz; $CDCl_3$) 28.9 (C-8), 29.2 (C-7), 36.1 (C-4), 51.4 (C-3), 62.0, 63.0 (NCH_2Ph, C-1), 86.2 (8a-C), 127.3 (C-*p*), 128.2 (C-*o*), 128.7 (C-*m*), 136.7 (C-*i*), and 172.6 (NCO); *m*/*z* 246 $(M)^+$, 228 $(M - H_2O)^+$, 155 $(M - Bzl)^+$, 137 (155 – H_2O), 134 $[Bzl(Me)N{=}CH_2]^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 246.1354. $C_{14}H_{18}N_2O_2$ requires *M*, 246.1368).

2-*Benzylhexahydropyrrolo*[1,2-a]*pyrazin*-6(2H)-*one* **6a**.—A solution of crude **12a**, prepared from **11a** (5.35 g, 10 mmol), in saturated K_2CO_3–methanol was refluxed for 30 min and then evaporated under reduced pressure. The residue was partitioned between water and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica, 3:97, MeOH–$CHCl_3$) to give **6a** as an oil (1.44 g, 61% from **11a**); ν_{max}(NaCl)/cm^{-1} 3090, 3070 and 3040 (ArH), 2940 (CH_2), 2820 (NCH_2), 1690 (NCO) and 730 and 700 (ArH); δ_H(250 MHz; $CDCl_3$) 3.49 and 3.57 (2 H, d, *J* 14, NCH_2Ph) and 7.30 (5 H, s, Ph) (for the other values, see Table 1); δ_C(63 MHz; $CDCl_3$) 21.5 (C-8), 29.6 (C-7), 38.9 (C-4), 51.3 (C-3), 55.0 (C-8a), 59.1 (C-1), 62.0 (NCH_2Ph), 126.6 (C-*p*), 127.7 (C-*o*), 128.3 (C-*m*), 137.0 (C-*i*) and 172.3 (NCO); *m*/*z* 230 $(M)^+$, 215 $(M - Me]^+$, 211 $(M - CO - H)^+$, 197 (215 – H_2O), 187 (215 – CO), 153 $(M - Ph)^+$, 146 $[Bzl(CH_2{=}CH)N{=}CH_2]^+$, 139 $(M - Bzl)^+$ and 134 $[Bzl(Me)N{=}CH_2]^+$ (Found: M^+, 230.1412. $C_{14}H_{18}N_2O$ requires *M*, 230.1419).

Hexahydro-2-(2-*methoxyphenyl*)*pyrrolo*[1,2-a]*pyrazin*-6(2H)-*one* **6b**.—Crude **12b**, prepared from **11c** (3.2 g, 7.5 mmol), was treated in the same manner as described for the conversion of **12a** into **6a**. Purification over silica gel (3:97, MeOH–$CHCl_3$) afforded **6b** as an oil (1.75 g, 95% from **11c**); ν_{max}(NaCl)/cm^{-1} 2960 (CH_2), 2840 (NCH_2), 1680 (CON), 1590 and 1500 (ArH) and 750 (ArH); δ_H(250 MHz; $CDCl_3$) 3.88 (3 H, s, CH_3O) and 6.18–7.10 (4 H, m, Ph) (for the other values, see Table 1); δ_C(63 MHz; $CDCl_3$) 22.0 (C-8), 30.1 (C-7), 39.8 (C-4), 49.8 (C-3), 55.4, 55.6 (C-8a, CH_3O), 57.8 (C-1), 111.3, 118.6, 120.9, 123.5 (CH of Ph), 140.6 (C-1′ of Ph), 152.1 (C-2′ of Ph) and 173.1 (NCO); *m*/*z* 246 $(M)^+$, 203 $(M - CO - Me)^+$, 162 $[MeOC_6H_4(CH_2{=}CH)N{=}CH_2]^+$, 149 $[MeOC_6H_4(CH_2)N{=}CH_2]^+$, 135 $(MeOC_6H_4N{=}CH_2)^+$ and 120 (135 – Me) (Found: M^+, 246.1359. $C_{14}H_{18}N_2O_2$ requires *M*, 246.1368).

Methyl 4-{N-*Benzyl*-N-[2-(*triphenylmethylamino*)*ethyl*]*amino*}*but*-2-*enoate* **18a**.—To a mixture of **10a** (1.79 g, 4.6 mmol) and K_2CO_3 (1.26 g, 9.2 mmol) in acetone (30 cm^3) was added methyl 4-bromobut-2-enoate **17** (90% purity; 0.91 g, 4.6 mmol) dissolved in acetone (30 cm^3). After being stirred at room temp. under N_2 for 16 h, the solution was filtered and the solvent

removed under reduced pressure. The residue was purified by column chromatography (silica, 1:9 EtOAc–hexane) to give **18a** as an oil (1.61 g, 72%); ν_{max}(NaCl)/cm^{-1} 3700–3100 (NH), 3080, 3060 and 3030 (ArH), 2950 (CH_2), 2820 (NCH_2) and 1725 (CO_2); δ_H(250 MHz; $CDCl_3$) 1.97 (1 H, s, NH), 2.25 and 2.57 (4 H, m, NCH_2CH_2N), 2.93 (2 H, d, *J* 4, NCH_2CH), 3.40 (2 H, s, NCH_2Ph), 3.70 (3 H, s, CH_3O), 5.93 (1 H, d, *J* 11, $CH{=}CHCO_2$), 6.90 (1 H, dd, *J* 11, 4, $CH{=}CHCO_2$) and 7.10–7.60 (20 H, m, Tr, Ph); *m/z* 490 $(M)^+$, 247 $(M - Tr)^+$, 243 $(Tr)^+$, 218 $(M - TrNHCH_2)^+$, 128 $(M - TrN{=}CH_2 - Bzl)^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 490.2639. $C_{33}H_{34}N_2O_2$ requires *M*, 490.2620).

Methyl 4-{N-(2-*Methoxyphenyl*)-N-[2-(*phenylmethoxycarbonylamino*)*ethyl*]*amino*}*but*-2-*enoate* **18c**.—To a stirred mixture of **10c** (2.00 g, 6 mmol), K_2CO_3 (0.95 g, 6 mmol) and KI (1.14 g, 6 mmol) in acetone (50 cm^3) was added dropwise methyl 4-bromobut-2-enoate **17** (2.45 g, 12 mmol) in acetone (50 cm^3). The solution was stirred at room temp. under N_2 for 2 days and was then worked up as described for the preparation of **18a**. Purification by column chromatography (silica, 35:65 EtOAc–hexane) afforded **18c** as an oil (2.22 g, 84%); ν_{max}(NaCl)/cm^{-1} 3380 (NH), 2820 (NCH_2), 1720 (CO_2, NCO_2), 1660 (C=C) and 750 (ArH); δ_H(250 MHz; $CDCl_3$) 3.2 (4 H, m, NCH_2CH_2N), 3.6 (3 H, s, CH_3O), 3.8 (3 H, s, CH_3O), 3.9 (2 H, s, $NCH_2CH{=}C$), 5.1 (2 H, s, CO_2CH_2), 5.6 (1 H, s, NH), 5.9 (1 H, d, *J* 16, $CH{=}CHCO_2$), 6.9 (5 H, m, $MeOC_6H_4$, $CH{=}CHCO_2$) and 7.3 (5 H, s, Ph); *m/z* 398 $(M)^+$, 365 $(M - MeOH)^+$, 307 $(M - Bzl)^+$, 234 $(M - CH_2NHCO_2Bzl)^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 398.1832. $C_{22}H_{26}N_2O_5$ requires *M*, 398.1842).

Methyl 4-(2-*Methoxyphenyl*)-1-(*phenylmethoxycarbonyl*)-*piperazin*-2-*ylacetate* **21**.—A mixture of **18c** (1.08 g, 2.7 mmol) and KOBu^t (0.61 g, 5.4 mmol) in dry toluene (100 cm^3) was stirred at room temp. under an atmosphere of nitrogen. After 3 min acetic acid–methanol (1:9; 25 cm^3) was added. The solution was washed with water and evaporated. The residue was dissolved in CH_2Cl_2 and the solution washed with aq. K_2CO_3, dried ($MgSO_4$) and evaporated. The product was purified by column chromatography on silica gel (5:95, EtOAc–$CHCl_3$) to afford **21** as an oil (0.91 g, 85%); ν_{max}(NaCl)/cm^{-1} 1740 (CO_2) and 1700 (NCO_2); δ_H(250 MHz; $CDCl_3$) 2.5 (3 H, m, 5_{ax}-H, CH_2CO_2), 3.3 (4 H, m, 3_{ax}-H, 3_{eq}-H, 5_{eq}-H, 6_{ax}-H), 3.7 (3 H, s, CH_3O), 3.8 (3 H, s, CH_3O), 4.0 (1 H, m, 6_{eq}-H), 4.7 (1 H, m, 2_{ax}-H), 5.2 (2 H, s, CH_2Ph), 6.9 (4 H, m, $MeOC_6H_4$) and 7.4 (5 H, m, CH_2Ph); δ_C (63 MHz; $CDCl_3$) 34.47 (CH_2CO_2), 40.43 (C-6), 48.98 (C-2), 49.83 (C-5), 51.56 (CH_3OCO), 54.16 (C-3), 55.22 ($CH_3OC_6H_4$), 67.26 (CH_2Ph), 111.07, 118.18, 120.67, 122.95 (CH of $MeOC_6H_4$), 127.51, 127.67, 128.15 (CH of CO_2Ph), 136.36 (C-1′ of CO_2Ph), 140.71 (C-1′ of $MeOC_6H_4$), 152.04 (C-2′ of $MeOC_6H_4$), 154.75 (NCO_2) and 171.66 (CO_2); *m/z* 398 $(M)^+$, 367 $(M - OMe)^+$, 339 $(M - CO_2Me)^+$, 325 $(M - CH_2CO_2Me)^+$, 263 $(M - Bzl - CO_2)^+$, 234 (325 – Bzl) and 162 $[MeOC_6H_4(CH_2{=}CH)N{=}CH_2]^+$ (Found: M^+, 398.1829. $C_{22}H_{26}N_2O_5$ requires *M*, 398.1842).

Methyl 4-*Benzylpiperazin*-2-*ylacetate* **19a**.—Compound **18a** (0.60 g. 1.2 mmol) was dissolved in HCl–MeOH (2 mol dm^{-3}; 10 cm^3) and the solution refluxed for 10 min. After neutralization with saturated aq. K_2CO_3 and extraction with $CHCl_3$, the organic phase was dried ($MgSO_4$) and evaporated. The residue was purified over a silica column (6:94, MeOH–$CHCl_3$) to give **19a** as an oil (0.26 g, 85%); ν_{max}(NaCl)/cm^{-1} 3700–3100 (NH), 3080, 3060 and 3030 (ArH), 2950 (CH_2), 2810 (NCH_2), 1735 (CO_2) and 740 and 700 (ArH); δ_H(250 MHz; $CDCl_3$) 1.84 (1 H, dd, *J* 11, 9, 3_{ax}-H), 2.05–2.16 (1 H, ddd, *J* 11, 9, 5, 5_{ax}-H), 2.36–2.39 (3 H, d, s, NH, CH_2CO_2), 2.68–2.75 (2 H, m, 3_{eq}-H, 5_{eq}-H), 2.91–2.95 (2 H, m, 6_{ax}-H, 6_{eq}-H), 3.14–3.25 (1 H, m, 2_{ax}-H), 3.50 (2 H, s, NCH_2Ph), 3.67 (3 H, s, CH_3O) and 7.30 (5 H, s, Ph); δ_C(63 MHz; $CDCl_3$) 37.97 (CH_2CO_2), 50.96, 51.03 (C-2, CH_3O), 44.80, 52.98, 58.38 (CH_2), 62.66 (NCH_2Ph), 126.45 (C-*p*), 127.64 (C-*o*), 128.43 (C-*m*), 137.59 (C-*i*) and 171.69 (CO_2); *m/z* 248 $(M)^+$, 217 $(M - OMe)^+$, 175 $(M - CH_2CO_2Me)^+$, 146 $[Bzl(CH_2{=}CH)N{=}CH_2]^+$, 134 $[Bzl(Me)N{=}CH_2]^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 248.1523. $C_{14}H_{20}N_2O_2$ requires *M*, 248.1525).

Methyl 4-(2-*Methoxyphenyl*)*piperazin*-2-*ylacetate* **19b**.—A solution of **21** (1.17 g, 2.9 mmol) in acetic acid (50 cm^3) was hydrogenated over 10% Pd/C (0.23 g) at room temp. under a hydrogen pressure of 3 atm (Parr apparatus) for 16 h. The catalyst was filtered off and the solvent removed under reduced pressure. The residue was dissolved in water and the solution neutralized with K_2CO_3 and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to give crude compound **19b**, which was used directly in the next step.

Dimethyl 4-*Benzylpiperazine*-1,2-*diyldiacetate* **20a**.—To a stirred mixture of **19a** (1.72 g, 6.9 mmol) and K_2CO_3 (1.90 g, 13.8 mmol) in acetone (100 cm^3) was added dropwise methyl bromoacetate (1.16 g, 7.6 mmol) in acetone (50 cm^3). The reaction was allowed to proceed at room temp. under N_2 for 16 h. The solution was filtered and evaporated. The residue was purified over a silica column (1:3, EtOAc–$CHCl_3$) to give **20a** as an oil (1.60 g, 72%); ν_{max}(NaCl)/cm^{-1} 3090, 3070, 3030 (ArH), 2960 (CH_2), 2820 (NCH_2), 1755–1740 (CO_2) and 740 and 700 (ArH); δ_H(250 MHz; $CDCl_3$) 2.27–2.78 (8 H, m, CH_2CO_2, 3-H, 5-H, 6-H), 3.22 (1 H, m, 2-H), 3.34 (2 H, s, NCH_2CO_2), 3.43, 3.53 (2 H, d, *J* 13, NCH_2Ph), 3.60 (3 H, s, CH_3O), 3.69 (3 H, s, CH_3O) and 7.30 (5 H, m, Ph); δ_C(63 MHz; $CDCl_3$) 33.54 ($CHCH_2CO_2$), 51.40 (2 × CH_3O), 49.99, 52.41, 55.23 (CH_2), 55.44 (C-2), 57.20 (NCH_2CO_2), 62.44 (NCH_2Ph), 126.80 (C-*p*), 127.95 (C-*o*), 128.74 (C-*m*), 137.81 (C-*i*), 170.74 (CO_2) and 172.31 (CO_2); *m/z* 320 $(M)^+$, 261 $(M - CO_2Me)^+$, 247 $(M - CH_2CO_2Me)^+$, 156 (247 – Bzl), 146 $[Bzl(CH_2{=}CH)N{=}CH_2]^+$, 134 $[Bzl(Me)N{=}CH_2]^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 320.1740. $C_{17}H_{24}N_2O_4$ requires *M*, 320.1736).

Dimethyl 4-(2-*Methoxyphenyl*)*piperazine*-1,2-*diyldiacetate* **20b**.—To a stirred mixture of crude **19b** (2.9 mmol), K_2CO_3 (0.60 g, 2.9 mmol) and KI (0.73 g, 2.9 mmol) in acetone (25 cm^3) was added dropwise methyl bromoacetate (0.67 g, 3.2 mmol) in acetone (25 cm^3). The reaction was allowed to proceed at room temp. for 6 h, after which the acetone was evaporated and the residue was distributed between CH_2Cl_2 and water. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica, 1:4 EtOAc–$CHCl_3$) to yield **20b** as an oil (0.73 g, 76%); ν_{max}(NaCl)/cm^{-1} 2840 (NCH_2) and 1760 and 1730 (CO_2); δ_H(250 MHz; $CDCl_3$) 2.63 (1 H, dd, *J* 15.5, 4, $CHCH_2CO_2$), 2.82 (1 H, dd, *J* 15.5, 7.5, $CHCH_2CO_2$), 2.84–2.92 (2 H, m, 5_{ax}-H, 6_{ax}-H), 2.93–3.01 (1 H, m, 5_{eq}-H), 3.02 (1 H, dd, *J* 11.5, 6.5, 3_{ax}-H), 3.14–3.22 (1 H, dd, *J* 11.5, 4.5, 3_{eq}-H), 3.21–3.27 (1 H, m, 2-H), 3.41 (2 H, s, NCH_2CO_2), 3.70 (3 H, s, CH_3O), 3.74 (3 H, s, CH_3O), 3.89 (3 H, s, CH_3O) and 6.81–7.00 (4 H, m, Ph); δ_C(63 MHz, $CDCl_3$) 32.81 ($CHCH_2CO_2$), 49.87, 50.22, 51.52, 55.30, 55.56 (CH_2), 51.59, 55.17 (CH_3O), 55.71 (C-2), 111.27, 118.26, 120.89, 122.82 (CH of Ph), 141.07 (C-1′ of Ph) and 152.21 (C-2′ of Ph); *m/z* 336 $(M)^+$, 277 $(M - CO_2Me)^+$, 263 $(M - CH_2CO_2Me)^+$ and 150 $[MeOC_6H_4(Me)N{=}CH_2]^+$ (Found: M^+, 336.1672. $C_{17}H_{24}N_2O_5$ requires *M*, 336.1685).

Methyl 2-*Benzyloctahydro*-7-*oxopyrrolo*[1,2-a]*pyrazine*-8-*carboxylate* **23a**.—To a suspension of KOBu^t (0.72 g, 6.4 mmol) in dry toluene (25 cm^3) was added slowly a mixture of **20a** (1.03 g, 3.2 mmol) in dry toluene (75 cm^3). After being stirred at 0 °C under N_2 for 3 h, the mixture was poured into cold pH 7

phosphate buffer and extracted with CH_2Cl_2. The solvent was evaporated and the residue chromatographed (silica, 1:1 EtOAc–$CHCl_3$) to give **23a** (0.454 g, 49%); ν_{max}(NaCl)/cm^{-1} 2820 (NCH_2), 1770 (CO), 1735 (CO_2) and 755 and 700 (ArH); δ_H(250 MHz; $CDCl_3$) 3.44 and 3.54 (2 H, d, *J* 13, NCH_2Ph), 3.75 (3 H, s, CH_3O) and 7.30 (5 H, s, Ph) (for the other values, see Table 1); δ_H(63 MHz; $CDCl_3$) 50.7 (C-3), 51.8 (C-4), 52.9 (CH_3O), 56.3 (C-1), 57.7 (C-8), 61.1 (C-6), 62.5 (C-8a, NCH_2Ph), 127.1 (C-*p*), 128.2 (C-*o*), 129.0 (C-*m*), 137.0 (C-*i*), 167.1 (CO_2) and 205.4 (C-7); *m/z* 288 $(M)^+$, 229 $(M - CO_2Me)^+$, 197 $(M - Bzl)^+$, 169 (197 – CO), 151 (197 – MeOH), 146 $[Bzl(CH_2{=}CH)N{=}CH_2]^+$, 134 $[Bzl(Me)N{=}CH_2]^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 288.1470. $C_{16}H_{20}N_2O_3$ requires *M*, 288.1474).

Methyl Octahydro-2-(2-methoxyphenyl)-7-oxopyrrolo[1,2-a]*pyrazine-8-carboxylate* **23b**.—Compound **20b** was treated in the same way as described for the preparation of **23a** to give the β-keto ester **23b** (35%); ν_{max}(NaCl)/cm^{-1} 2960 (CH_2), 2820 (NCH_2), 1770 (CO), 1730 (COO) and 750 (ArH); δ_H(250 MHz; $CDCl_3$) 2.75 (1 H, td, *J* 10.5, 2.5, 4_{ax}-H), 2.87 (1 H, dd, *J* 10.5, 8, 1_{ax}-H), 2.98 (1 H, td, *J* 10.5, 2.5, 3_{ax}-H), 2.99 (1 H, d, *J* 17, 6_{ax}-H), 3.09 (1 H, dt, *J* 10.5, 2.5, 4_{eq}-H), 3.32 (1 H, d, *J* 11, 8_{ax}-H), 3.38 (1 H, ddd, *J* 11, 8, 2, 8_a-H), 3.55 (1 H, d, *J* 17, 6_{eq}-H), 3.49–3.58 (1 H, m, 3_{eq}-H), 3.58–3.64 (1 H, dt, *J* 10.5, 2, 1_{eq}-H), 3.78 (3 H, s, CH_3O), 3.88 (3 H, s, CH_3O) and 6.90 (4 H, m, Ph); δ_C(63 MHz; $CDCl_3$) 50.19 (C-3), 51.23 (C-4), 52.40 (CH_3O), 53.60 (C-1), 55.34 (CH_3O), 57.07 (C-8), 61.56 (C-6), 63.06 (C-8a), 111.45, 118.64, 120.93, 123.30 (CH of Ph), 140.56 (C-1′ of Ph), 152.18 (C-2′ of Ph), 167.16 (CO_2) and 204.92 (C-7); *m/z* 304 $(M)^+$, 273 $(M - OMe)^+$ and 245 $(M - CO_2Me)^+$ (Found: M^+, 304.1418. $C_{16}H_{20}N_2O_4$ requires *M*, 304.1423).

2-Benzylhexahydropyrrolo[1,2-a]*pyrazin-7(6H)-one* **7a**.—To a stirred and cooled (0 °C) suspension of KOBu^t (2.05 g, 18.3 mmol) in dry toluene (50 cm^3) was added slowly a solution of **20a** (2.93 g, 9.2 mmol) in dry toluene (100 cm^3). The mixture was stirred at 0 °C under N_2 for 3 h and then extracted with HCl (6 mol dm^{-3}; 2 × 25 cm^3). The water layer was refluxed for 2 h, cooled, made alkaline with Na_2CO_3 and extracted with CH_2Cl_2. The organic phase was evaporated and the residue chromatographed over alumina (1:1, EtOAc–hexane) to afford **7a** as an oil (1.19 g, 57%); ν_{max}(NaCl)/cm^{-1} 3015 (ArH), 2940 (CH_2), 2810 (NCH_2), 1765 (CO), 1600, 1580 and 1495 (ArH) and 745 and 700 (ArH); δ_H(250 MHz; $CDCl_3$) 3.53 and 3.61 (2 H, d, *J* 8.5, NCH_2Ph) and 7.35 (5 H, m, Ph) (for the other values, see Table 1); δ_C(63 MHz; $CDCl_3$) 41.7 (C-8), 51.1 (C-3), 52.2 (C-4), 56.9 (C-1), 60.4 (C-8a), 61.6 (C-6), 62.8 (NCH_2Ph), 127.1 (C-*p*), 128.2 (C-*o*), 129.0 (C-*m*), 137.8 (C-*i*) and 212.2 (C-7); *m/z* 230 $(M)^+$, 202 (M – CO), 146 $[Bzl(CH_2{=}CH)N{=}CH_2]^+$, 139 $(M - Bzl)^+$, 134 $[Bzl(Me)N{=}CH_2]^+$ and 111 (139 – CO) (Found: M^+, 230.1418. $C_{14}H_{18}N_2O$ requires *M*, 230.1419).

Hexahydro-2-(2-methoxyphenyl)pyrrolo[1,2-a]*pyrazin-7(6H)-one* **7b**.—To a stirred and cooled (0 °C) solution of **20b** (1 g, 3 mmol) in dry toluene (75 cm^3) was added KOBu^t (0.67 g, 6 mmol). After reaction at 0 °C under N_2 for 1 h, the mixture was extracted with HCl (6 mol dm^{-3}; 2 × 25 cm^3). The water layer was refluxed for 3 h, cooled, made alkaline with K_2CO_3 and extracted with CH_2Cl_2. The organic phase was evaporated and the residue purified over silica gel (EtOAc) to give **7b** (0.50 g, 55%) as an oil; ν_{max}(NaCl)/cm^{-1} 2940 (CH_2), 2820 (NCH_2), 1760 (CO), 1500 (ArH) and 750 (ArH); δ_H(250 MHz; $CDCl_3$) 3.85 (3 H, s, CH_3O) and 6.83–7.05 (4 H, m, Ph) (for the other values, see Table 1); δ_C(63 MHz; $CDCl_3$) 41.1 (C-8), 49.8 (C-3), 51.0 (C-4), 54.3 (C-1), 60.2 (C-8a), 61.3 (C-6), 111.2, 118.4, 120.8, 123.0 (CH of Ph), 140.7 (C-1′ of Ph), 152.0 (C-2′ of Ph) and 211.5 (C-7); *m/z* 246 $(M)^+$, 218 $(M - CO)^+$, 217 (218 – H), 215 $(M - OMe)^+$, 203 (218 – CH_3), 162 $[MeOC_6H_4(CH_2{=}CH)N{=}CH_2]^+$ and 150 $[MeOC_6H_4(Me)N{=}CH_2]^+$ (Found: M^+, 246.1376. $C_{14}H_{18}N_2O_2$ requires *M*, 246.1368).

Methyl 4-Benzyl-2-methoxycarbonylethylpiperazin-1-ylacetate **25a**.—The crude product **12a**, prepared from **11a** (2.5 g, 41 mmol). was dissolved in acetone (100 cm^3) and to this solution was added K_2CO_3 (1.5 g, 10.9 mmol), KI (1 g, 6.0 mmol) and methyl bromoacetate (3.5 g, 24.6 mmol). The mixture was stirred under N_2 for 16 h, diluted with water and extracted with CH_2Cl_2 (2 × 300 cm^3). The combined extracts were evaporated and the residual oil chromatographed on silica gel (1:1, EtOAc–$CHCl_3$) to give **25a** (8.1 g, 59% from **11a**) as an oil; ν_{max}(CCl_4)/cm^{-1} 1740 (CO_2); δ_H(250 MHz; $CDCl_3$) 1.84 (2 H, m, $CH_2CH_2CO_2$), 2.06 (1 H, dd, *J* 11, 9, 3_{ax}-H), 2.22 (1 H, dd, *J* 11, 2, 3_{eq}-H), 2.30 (2 H, q, *J* 7, $CH_2CH_2CO_2$), 2.65 (4 H, tt, 5-H, 6-H), 2.80–2.90 (1 H, m, 2-H), 3.30, 3.50 (2 H, dd, *J* 16, NCH_2CO_2), 3.43 (2 H, d, *J* 13, NCH_2Ph) and 7.30 (5 H, m, Ph); *m/z* 334 $(M)^+$, 303 $(M - OMe)^+$, 275 $(M - CO_2Me)^+$, 247 $(M - CH_2CH_2CO_2Me)^+$, 188 $(MeO_2CCH_2NH{=}CHCH_2CH_2CO_2Me)^+$, 156 (247 – Bzl), 134 $[Bzl(Me)N{=}CH_2]^+$ and 91 $(C_7H_7)^+$ (Found: M^+, 334.1904. $C_{18}H_{26}N_2O_4$ requires *M*, 334.1892).

Methyl 2-Methoxycarbonylethyl-4-(2-methoxyphenyl)piperazin-1-ylacetate **25b**.—To a stirred mixture of the crude product **12b**, prepared from **11b** (3.08 g, 5.7 mmol) and K_2CO_3 (1.59 g, 11.5 mmol) in acetone (90 cm^3), was added dropwise methyl bromoacetate (0.68 cm^3, 7.2 mmol). The reaction mixture was stirred at room temp. under N_2 for 16 h. Work-up as described for **25a** and chromatography of the residue on silica (gradient elution 1:10 to 1:2, EtOAc–$CHCl_3$) afforded **25b** (1.39 g, 69% from **11b**) as an oil; ν_{max}(CCl_4)/cm^{-1} 1750 (CO_2); δ_H(250 MHz; $CDCl_3$) 1.86–2.01 (2 H, m, $CH_2CH_2CO_2$), 2.24–2.57 (2 H, m, $CH_2CH_2CO_2$), 2.66–3.31 (7 H, m, 2-H, 3-H, 5-H, 6-H), 3.31, 3.59 (2 H, d, *J* 16.5, NCH_2CO_2), 3,67 (3 H, s, CH_3O), 2.73 (3 H, s, CH_3O), 3.85 (3 H, s, CH_3O) and 6.80–7.10 (4 H, m, Ph); *m/z* 350 $(M)^+$, 319 $(M - OMe)^+$, 263 $(M - CO_2Me)^+$, 219 $(M - CH_2CH_2CO_2Me)^+$ and 150 $[MeOC_6H_4(Me)N{=}CH_2]^+$ (Found: M^+, 350.1834. $C_{18}H_{26}N_2O_5$ requires *M*, 350.1841).

Methyl 2-Benzyloctahydro-7-oxo-2H-pyrido[1,2-a]*pyrazine-8-carboxylate* **27a**.—To a stirred and cooled (0 °C) solution of diisopropylamine (2.14 cm^3, 15.2 mmol) in dry THF (2 cm^3) was added BuLi (1.6 mol dm^{-3} in hexane; 9 cm^3, 14.5 mmol). After 20 min the solution was cooled to −60 °C, followed by dropwise addition of **12a** (2.43 g, 7.3 mmol) dissolved in dry THF (10 cm^3). After being stirred at −30 °C for 30 min, the reaction mixture was quenched with water, brought to pH 7 by addition of phosphate buffer and extracted with CH_2Cl_2. The extract was evaporated and the residue purified by flash chromatography (silica, 5:95 MeOH–$CHCl_3$) to yield a mixture of **26a** and **27a** (1.5 g, 68%). Rechromatography on a slower column (silica, 1:1, EtOAc–hexane) gave **27a** as crystals (200 mg), m.p. 57–67 °C; ν_{max}(NaCl)/cm^{-1} 3400 (OH), 2810, 2760 (NCH_2), 1740 (CO), 1730 (CO_2) and 1670 and 1630 (C=C-OH); δ_H(250 MHz; $CDCl_3$) 1.92 (1 H, t, *J* 10, 1_{ax}-H), 2.05 (1 H, m, 9_a-H), 2.13–2.45 (4 H, m, 3_{ax}-H, 4_{ax}-H, 9-H), 2.83 (1 H, d, *J* 17, 6_{ax}-H), 2.70–2.98 (3 H, m, 3_{eq}-H, 4_{eq}-H, 1_{eq}-H), 3.37 (1 H, d, *J* 17, 6_{eq}-H), 3.51 (2 H, s, NCH_2Ph), 3.74 (3 H, s, CH_3O) and 7.30 (5 H, s, Ph); *m/z* 302 $(M)^+$, 271 $(M - OMe)^+$, 270 $(M - MeOH)^+$, 243 $(M - CO_2Me)^+$, 211 $(M - Bzl)^+$, 179 (211 – MeOH), 146 $[Bzl(CH_2{=}CH)N{=}CH_2]^+$, 134 $[Bzl(Me)N{=}CH_2]^+$, 91 $(C_7H_7)^+$ (Found: M^+, 302.1628. $C_{17}H_{22}N_2O_3$ requires *M*, 302.1628).

Methyl Octahydro-2-(2-methoxyphenyl)-7-oxo-2H-pyrido[1,2-a]*pyrazine-8-carboxylate* **27b**.—To a stirred and cooled

(0 °C) solution of **12b** (95 mg, 0.28 mmol) in dry THF (10 cm^3) was added KH (35% in mineral oil; 71 mg, 0.62 mmol). After the mixture had been stirred at 0 °C for 5 h the excess hydride was destroyed by dropwise addition of MeOH. The mixture was distributed between cold phosphate buffer (pH 7) and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to give a product consisting mainly of **27b** (TLC, silica, 1:1 EtOAc–$CHCl_3$, R_f 0.5); δ_H(250 MHz; $CDCl_3$) 3.37 (1 H, d, *J* 16, 6_{ax}-H) and 3.52 (1 H, d, *J* 16, 6_{eq}-H); *m/z* 318 $[M]^+$, 286 $(M - MeOH)^+$, 259 $(M - CO_2Me)^+$, 162 $[MeOC_6H_4(CH_2{=}CH)N{=}CH_2]^+$ and 150 $[MeOC_6H_4(Me)N{=}CH_2]^+$ (Found: M^+, 318.1567. $C_{17}H_{22}N_2O_4$ requires *M*, 318.1579).

2-*Benzylhexahydro*-2H-*pyrido*[1,2-a]*pyrazin*-7(6H)-*one* **8a**. —To a cooled (−50 °C) solution of LDA, prepared at 0 °C from diisopropylamine (2.5 cm^3, 17.8 mmol) in dry THF (10 cm^3) and BuLi (1.6 mol dm^{-3} in hexane; 10 cm^3, 16.2 mmol), was added dropwise a solution of **25a** (3 g, 9.0 mmol) in dry THF (10 cm^3) under an atmosphere of N_2. After being allowed to react at 50 °C for 30 min, the mixture was acidified with HCl (2 mol dm^{-3}; 30 cm^3). The solution was concentrated under reduced pressure and the residue refluxed with HCl (6 mol dm^{-3}; 50 cm^3) for 4 h. After evaporation, the resulting product was dissolved in water (20 cm^3), and the solution was made alkaline with K_2CO_3 and extracted with CH_2Cl_2 (2 × 200 cm^3). The combined CH_2Cl_2 layers were dried and evaporated. Column chromatography (silica, 5:95 MeOH–EtOAc) of the residue gave **8a** (935 mg, 43%) as an oil, identical (R_f value, spectral data) to the product described previously.[5]

Hexahydro-2-(2-*methoxyphenyl*)-2H-*pyrido*[1,2-a]*pyrazin*-7(6H)-*one* **8b**.—Reaction of **25b** (95 mg, 0.28 mmol) and KH was carried out as described for the preparation of **27b**. After quenching with methanol, the reaction mixture was treated with HCl (6 mol dm^{-3}) and the THF removed by extraction with ether. The aqueous phase was refluxed for 2 h. The solvent was evaporated and the residue partitioned between aq. K_2CO_3 and CH_2Cl_2. The CH_2Cl_2 layer was evaporated and the residue was purified by preparative TLC (silica, EtOAc) to give **8b** (23 mg, 33%) as an oil, identical (R_f value, spectral data) with the product described previously.[5]

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