Synthesis and 2,7-Functionalization of the Bicyclic Lactam 2-Benzyloctahydropyrido[1,2-a]pyrazin-6-one

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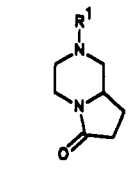
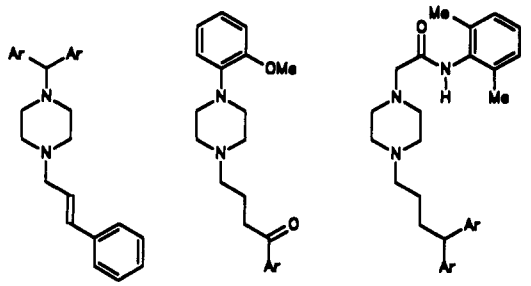
This report describes the synthesis of the title compound **7** and its conversion into 2,7-substituted octahydro-2*H*-pyrido[1,2-*a*]pyrazines, i.e., bicyclic analogues of the monocyclic piperazine drug lidoflazine. The synthesis of **7** is based on a 3-fold amino substitution of methyl 6-chloro-5-oxohexanoate (**12**), initiated by displacement of chlorine with *N*-benzyl-*N'*-trityl-1,2-ethanediamine. The required trielectrophile **12** was prepared readily from commercially available diethyl 2-acetylglutarate. The 7-position of compound **7** was functionalized through reaction of the lactam anion with benzophenone electrophiles. Further elaboration into the target compounds **8–10** involved dehydration, reduction of the lactam group, and different modes of *N*-debenzylation. Conformational aspects for lactam compounds **17** and **18** and the modes of ring fusion for the diastereomeric amines **9** and **10** were examined by using proton NMR and infrared spectroscopy.

Recently, we reported[1,2] the synthesis of bicyclic lactam **1** and ketones **2** and **3** which can serve as precursors of 2,7-substituted octahydropyrrolo[1,2-*a*]pyrazines and octahydro-2*H*-pyrido[1,2-*a*]pyrazines.[3] When fitted with appropiate pharmacophoric substituents, these bicyclic compounds can be regarded as conformationally restricted analogues of piperazine drugs such as flunarizine **4**, fluanisone **5**, and lidoflazine **6**.[4]



1 **2** **3**

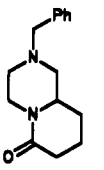
R^1 = benzyl, *o*-methoxyphenyl



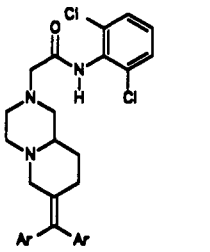
4 **5** **6**

Ar = *p*-fluorophenyl

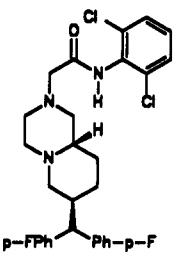
As another example of bicyclic modeling, we now wish to report an efficient and large-scale preparation of the previously unknown bicyclic lactam **7** and its use in the synthesis of analogues **8–10** of the coronary vasodilator lidoflazine **6**. Generation of the lactam anion provides a suitable alternative for ketone **3** with regard to functionalization of the 7-position of octahydro-2*H*-pyrido[1,2-*a*]pyrazines since it allows for reaction with halide and carbonyl electrophiles.



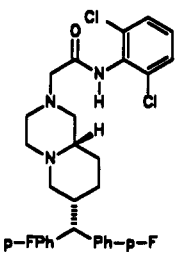
7



8a : Ar = *p*-fluorophenyl
8b : Ar = phenyl



9 : trans isomer



10 : cis isomer

Bond fission analysis of key compound **7** indicates a synthetic route consisting of a 3-fold substitution of *N*-benzylethanediamine with the α-chloro keto ester **12** as a six-carbon electrophilic reagent. The differential reactivity of the three electrophilic centers of **12** can be matched in the diamine partner by initial blocking of the primary amino group as the *N'*-trityl derivative **11**.

The required methyl 6-chloro-5-oxohexanoate (**12**)[5] was prepared from the commercially available diethyl 2-acetylglutarate by using a sequence analogous to that described[1,6] for the preparation of methyl 5-chloro-4-oxopentanoate from diethyl acetylsuccinate (Scheme II).

† Research Assistant of the National Fund for Scientific Research (NFWO).

(1) Van den Branden, S.; Compernolle, F.; Hoornaert, G. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1035.

(2) Compernolle, F.; Saleh, M. A.; Toppet, S.; Hoornaert, G. *J. Org. Chem.* **1991**, *56*, 5192.

(3) For a recent synthesis of 2,7-substituted octahydro-2*H*-pyrido[1,2-*a*]pyrazines, see: Bright, G. M.; Desai, K. A. (Pfizer Inc.) PCT Int. Appl. WO 90 08,148, 1990; *Chem. Abstr.* **1991**, *114*, 81886r.

(4) Budavari, S. *The Merck Index*, 11th ed.; Budavari, S., Ed.; Merck and Co.: Rahway, 1989; and references cited therein.

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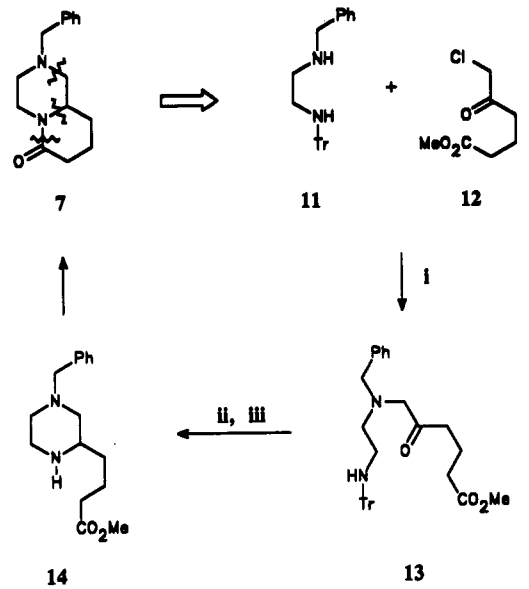
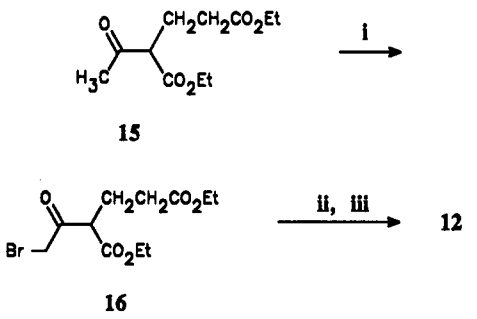
Scheme I[a]



[a] (i) K_2CO_3, KI, acetone (ii) HCl–MeOH; (iii) $NaCNBH_3$, MeOH, pH 5.

Scheme II[a]

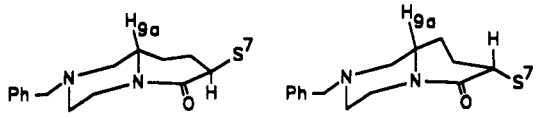


[a] (i) Br_2 (HBr); (ii) HCl–H_2O–AcOH; (iii) MeOH, H_2SO_4.

Initial bromination at the 2-position of **15** can be reversed in the presence of HBr: regenerated bromine then attacks on the more slowly enolizing methyl position. The resulting α-bromo keto diester **16** was decarboxylated by heating with a mixture of aqueous HCl and acetic acid. Final esterification of the intermediate keto acid afforded the α-chloro keto ester **12** admixed with a minor amount of the analogous α-bromo compound.

The three electrophilic centers of the α-chloro keto ester **12** show a marked difference in reactivity, which was developed in a matched sequence of amination steps (Scheme I). In the first step the acyclic amino keto ester **13** was generated by displacement of the more reactive α-chloro group with the *N*-benzylamino group of the *N'*-trityl-protected diamine **11**. Without isolation of further intermediates compound **13** was transformed into bicyclic lactam **7** in an overall yield of 80%. This was effected via consecutive acid-promoted detritylation, internal reductive amination with $NaCNBH_3$ in MeOH at pH 5, and further cyclization of the transient piperazinebutanoic ester **14**.

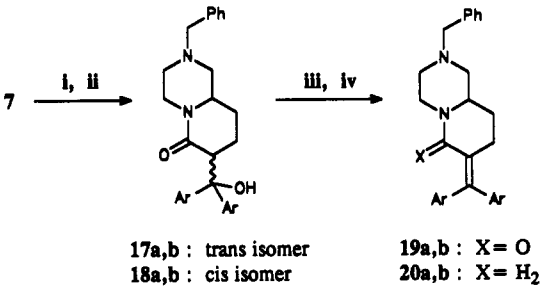
The application of lactam synthon **7** in the synthesis of 2,7-substituted octahydro-2*H*-pyrido[1,2-*a*]pyrazines **9** and **10** and the corresponding 7-diarylmethylene compounds **8** is depicted in Scheme III.



S^7 = C(OH)Ar_2 (Ar = phenyl, *p*-fluorophenyl)

Figure 1.

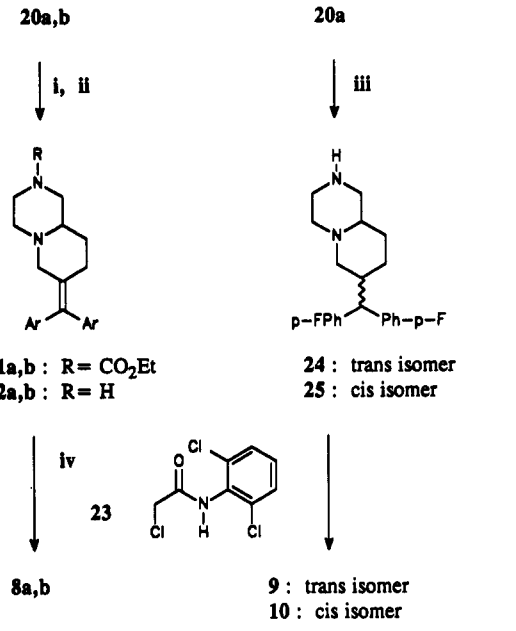
Scheme III



17a,b : trans isomer
18a,b : cis isomer

19a,b : X = O
20a,b : X = H_2

i: LDA; ii: Ar_2CO; iii: 48% HBr; iv: $LiAlH_4$.



21a,b : R = CO_2Et
22a,b : R = H

24 : trans isomer
25 : cis isomer

9 : trans isomer
10 : cis isomer

i: $ClCO_2Et$; ii: KOH, i-PrOH; iii: H_2, Pd/C, AcOH, 70 °C; iv: K_2CO_3, KI, acetone.

a : Ar = *p*-fluorophenyl
b : Ar = phenyl

Treatment of the enolate anion of lactam **7**, generated with LDA in THF,[7] at −10 °C with 4,4'-difluorobenzophenone (or benzophenone) led to the diastereomeric tertiary alcohols **17** and **18** in an overall yield of 65%. Due to its steric requirements, the 7-diarylhydroxymethyl substituent is oriented equatorially for both the trans compound **17** and the cis compound **18** giving rise to the two alternate half-chair conformations shown in Figure 1.

In the proton NMR spectra of both isomers, the axial proton H-7 displays an axial–axial and an axial–equatorial

(5) This reagent has been prepared previously via a less effective route (ca. 40%) involving reaction of diazomethane with methyl 4-chloroformylbutyrate: (a) Lartillot, S.; Baron, C. *Bull. Soc. Chim. Fr.* **1964**, 783. (b) Summerton, J.; Bartlett, P. A. *J. Mol. Biol.* **1978**, *122*, 145.
(6) (a) Julia, M.; Bagot, J. *Bull. Soc. Chim. Fr.* **1964**, 1924. (b) Lartillot, S.; Baron, C. *Bull. Soc. Chim. Fr.* **1966**, *12*, 3798.

(7) Bradley, G.; Cavalla, J. F.; Edington, T.; Shepherd, R. G.; White, A. C.; Bushell, B. J.; Johnson, J. R.; Weston, G. O. *Eur. J. Med. Chem.* **1980**, *15*, 375.

coupling with protons H-8 (17: ^3J = 12.5 and 5.5 Hz; 18: ^3J = 12 and 5.5 Hz). For the trans isomer 17 the proton H-9a has an axial orientation relative to both the piperidinone and the piperazine ring resulting in the observation of two axial–axial and two axial–equatorial couplings (^3J = 10, 11 and 4, 4 Hz) with protons H-1 and H-9. However, for the cis isomer 18 proton H-9a is quasiequatorial relative to the piperidinone ring and axial relative to the piperazine ring. This orientation results in an axial–axial and an axial–equatorial coupling with protons H-1ax and H-1eq (^3J = 11 and 3 Hz). The vicinal coupling constant values observed for the coupling with the cis-disposed axial proton H-9ax and the trans-disposed equatorial proton H-9eq (^3J = 7 and < 3 Hz) are in agreement with the dihedral angles of about 30° and 90° estimated from inspection of a molecular model.

Dehydration of the tertiary alcohols **17a,b** and **18a,b** was effected with 48% aqueous HBr affording the single 7-diarylmethylene compounds **19a,b** which were reduced to the diamines **20a,b** on treatment with $LiAlH_4$. The subsequent conversion of these bicyclic diamines to the final products **8a,b** and **9, 10** involved two different ways of deprotection of the *N*-benzyl group followed by alkylation with 2-chloro-*N*-(2,6-dichlorophenyl)acetamide (**23**) (Scheme III).

On reaction with ethyl chloroformate compounds **20a,b** were converted to the corresponding carbamates **21a,b** which were saponified by reflux with KOH in isopropyl alcohol yielding the secondary amines **22a,b**.[8] Final alkylation with the α-chloroacetamide **23** gave the crystalline target compounds **8a,b**. The overall yield for the six-step sequence starting from lactam **7** was 40% for **8a** and 34% for **8b**.

For the preparation of target molecules **9** and **10** we subjected diamine **20a** to hydrogenation (Pd/C, ethyl acetate, 50 °C) in order to effect both deprotection of the *N*-benzyl group and reduction of the double bond at the 7-position. However, under these circumstances only debenzylation occurred to give secondary amine **22a** (suggesting a possible shortcut in the sequence leading to **8**). When the hydrogenation was carried out in acetic acid at 70 °C, reduction of the double bond also was attained.[9] The resulting crude mixture of the diastereomeric secondary amines **24** and **25** was alkylated with the α-chloro acetamide **23** affording the target compounds **9** and **10**. The stereoisomers were easily separated by column chromatography in respective yields of 32 and 12% (overall 44%) starting from lactam **7**.

Assignment of the stereoisomers **9** and **10** was based on analysis of the infrared and proton NMR spectra. For both isomers trans fusion of the piperidine–piperazine ring system was indicated by the Bohlmann bands[10] observed at 2780 and 2760 cm^{-1}. The anti orientation of the angular proton H-9a relative to the lone pair on N-5 was confirmed by the high-field absorptions[11] at δ 1.94 (^3J = 10, 10, 3 and 3 Hz) for **9** and δ ca 2.02 (unresolved multiplet) for **10**. On the basis of this trans mode of ring fusion (Figure 2), structure **9** was assigned to the isomer with axial proton H-7 (on irradiation of C*H*Ar_2: tt, $^3J_{7ax-6ax} = {}^3J_{7ax-8ax}$ = 11 Hz, $^3J_{7ax-6eq} = {}^3J_{7ax-8eq}$ = 3 Hz). The assignment of H-7ax was confirmed by the COSY spectrum which showed cross peaks with $CH(ArF)_2$ (d, δ 3.34), H-6eq (m, δ 2.60) and H-6ax (t, δ 1.65). In the 500-MHz spectrum of cis isomer **10** the equatorial position of proton H-7 (Figure 2, form **A**) was shown by the small coupling constant (^3J = 3.1 Hz) with the high-field proton H-6ax (δ 2.03, anti to the lone pair on N-5). In the COSY spectrum cross peaks were observed with $CH(ArF)_2$ (d, δ 4.45), H-6eq (m, δ 2.30), and H-6ax (dd, δ 2.03). Apparently, for cis isomer **10** a trans-fused form **A** with axial diphenylmethyl group is preferred over the alternative form **B** involving an equatorial orientation of this group and concomittant cis fusion of the bicyclic ring system.[12] For the trans-fused form **A** the single H-atom on the axially disposed diphenylmethyl group allows one to avoid the more severe nonbonded interactions.

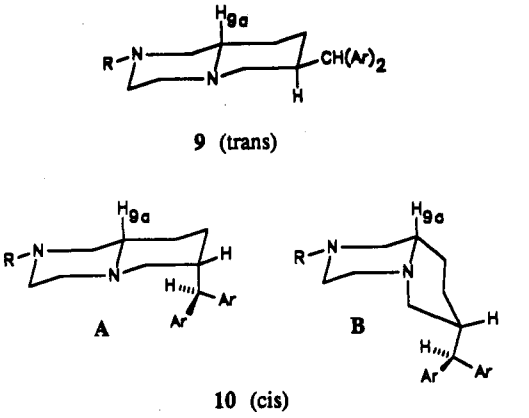


Figure 2.

In summary, an efficient synthesis has been developed for the bicyclic lactam synthon **7**. Functionalization of the 7- and 2-positions, required for bicyclic modeling of 1,4-substituted piperazine drugs, is accomplished via generation of the lactam enolate anion and by using different modes of *N*-debenzylation.

Experimental Section

IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer. ^1H NMR spectra and ^{13}C NMR spectra were recorded on Bruker WM 250, AM 400 (for **9**), and AM 500 (for **10**) instruments operating at 250, 400, and 500 MHz for ^1H and 62.9, 100, and 125 MHz for ^{13}C measurements. The ^1H and ^{13}C chemical shifts are reported in ppm relative to TMS as an internal standard. Mass spectra were run on a Kratos MS50 instrument and DS90 data system; the ion source temperature was 150–200 °C as required. Exact mass measurements were performed at a resolution of 10 000. Besides the spectral and analytical data mentioned below, the purity of all compounds was checked by TLC.

Methyl 6-Halo-5-oxohexanoate 12 (X = Cl, Br). To a stirred solution of diethyl 2-acetylglutarate (50 g, 0.22 mol), in 300 mL of anhyd ether was added bromine (11.1 mL, 0.22 mol) dropwise at 0 °C. After the reaction flask was closed the mixture was kept at rt for 20 h. Then it was concentrated by rotary evaporation at 20 °C to give the crude diethyl 2-(bromoacetyl)glutarate. This was treated with 200 mL of 12 N HCl–HOAc (1:1), and the mixture was stirred at rt for 4 h and then it was heated at 80 °C for 3.5 h. After concentration by rotary evaporation the residue was

(8) Ziegler, F. E.; Bennett, G. B. *J. Am. Chem. Soc.*, **1973**, *95*, 7458.
(9) (a) Rylander, P. N. In *Best Synthetic Methods: Hydrogenation Methods*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: London, 1985; Chapters 2 and 13. (b) Ito, Y.; Saegusa, T. *J. Org. Chem.* **1982**, *47*, 741.
(10) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
(11) Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109.
(12) For the tetracyclic system piperidino[1′,2′:4,5]piperazino[1,2-*a*]-benzimidazol-3-one a conformational equilibrium between the trans- and the cis-fused form was observed: Compernolle, F.; Saleh, M. A.; Toppet, S.; De Buysser, W.; Hoornaert, G. *J. Heterocycl. Chem.* **1991**, *28*, 1965.

treated with MeOH (17.5 mL, 0.43 mol) and a few drops of concentrated H_2SO_4, and the solution was refluxed for 3 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), and the CH_2Cl_2 solution was washed successively with water and $NaHCO_3$ solution. The organic layer was evaporated, and the residue was distilled under reduced pressure (bp 90–100 °C/2–2.5 mmHg) to give the mixture **12** (X = Cl, Br) in a ratio Cl:Br = 2:1 according to both ^1H NMR and MS (32.9 g, 78%): IR (NaCl) ν 1750–1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (s, $ClCH_2$), 3.91 (s, $BrCH_2$), 3.70 (s, 3 H, OCH_3), 2.70 (m, 2 H, H-4), 2.36 (m, 2 H, H-2), 1.92 (q, 2 H, ^3J = 7 Hz, H-3); MS *m/z* (X = Cl) 165 and 163, 149 and 147, 143, 129 (100), 101, 87; (X = Br) 209 and 207, 193 and 191, 143, 129 (100), 101, 87.

Methyl 6-[*N*-Benzyl-*N*-[2-(tritylamino)ethyl]amino]-5-oxohexanoate (13). To a stirred mixture of **11**[1] (15.0 g, 38 mmol), K_2CO_3 (12.0 g, 87 mmol), and KI (3.0 g, 18 mmol) in 300 mL of acetone was added compound **12** (8.2 g, 42 mmol). After 4 h the solvent was evaporated and the residue was distributed between 600 mL of CH_2Cl_2 and 60 mL of water. The organic layer was separated and evaporated. Column chromatography of the residue on silica using first $CHCl_3$ and then 10% EtOAc–$CHCl_3$ afforded **13** (18.9 g, 92.5%) as an oil: IR (NaCL) ν 3320, 1745, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.10 (m, 20 H, 4Ph), 3.62 (s, 3 H, OCH_3), 3.47 (s, 2 H, NCH_2Ph), 3.02 (s, 2 H, H-6), 2.68 (t, 2 H, ^3J = 7 Hz, NCH_2CH_2NH), 2.38 (t, 2 H, ^3J = 7 Hz, H-4), 2.28 (br s, 1 H, NH), 2.28 (t, 2 H, ^3J = 7 Hz, NCH_2CH_2NH), 2.28 (t, 2 H, ^3J = 7 Hz, H-2), 1.82 (q, 2 H, ^3J = 7 Hz, H-3); MS *m/z* 534 (M^+), 503, 457, 403, 291, 262, 243 (100); exact mass calcd for $C_{35}H_{38}N_2O_3$ 534.2881, found 534.2869.

2-Benzyloctahydropyrido[1,2-*a*]pyrazin-6-one (7). A mixture of **13** (21 g, 39 mmol) and 30 mL of 2 N HCl in MeOH was refluxed for 1 h. After concentration by rotary evaporation, the residue was dissolved in 150 mL of MeOH. To the stirred solution was added portionwise $NaCNBH_3$ (5.2 g, 83 mmol), and the solution was adjusted to pH 6 by dropwise addition of 2 N HCl in MeOH. The stirred reaction mixture was refluxed under nitrogen for 2.5 h. The excess $NaCNBH_3$ was decomposed by addition of 10 mL of 2 N HCl to the cooled mixture. After addition of 500 mL of CH_2Cl_2 and aqueous K_2CO_3, the layers were separated and the aqueous phase was further extracted with 200 mL of CH_2Cl_2. The combined extracts were evaporated to one-fourth its volume to give a mixture of the crude products **14** and **7**. This was allowed to stand at rt for 3 h to complete the cyclization of **14** to **7**. After complete evaporation, the crude product was purified by column chromatography on silica gel with 5% MeOH–EtOAc to afford pure **7** (8.1 g, 85% from **13**) as an oil: IR (CCl_4) ν 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5 H, Ph), 4.60 (ddd, 1 H, ^2J = 13 Hz, $^3J_{4e,3ax}$ = 3 Hz, $^3J_{4e,3e}$ = 2 Hz, H-4e), 3.53 and 3.47 (AB q, 2 H, ^2J = 13 Hz, NCH_2Ph), 3.43 (m, 1 H, H-(9a)ax), 2.89–2.78 (m, 2 H, H-3e, 1e), 2.72 (ddd, 1 H, ^2J = 13 Hz, $^3J_{4ax,3ax}$ = 12 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.50–2.20 (m, 2 H, H-7), 2.02 (td, 1 H, $^2J = {}^3J_{3ax,4ax}$ = 12 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 1.95–1.55 (m, 3 H, H-8, 9e), 1.80 (t, 1 H, $^2J = {}^3J_{1ax,(9a)ax}$ = 11 Hz, H-1ax), 1.40 (m, 1 H, H-9ax); ^{13}C NMR ($CDCl_3$) δ 168.9 (C=O), 137.6 (C-ipso), 128.9 (C-m), 128.2 (C-o), 127.1 (C-p), 62.6 (CH_2Ph), 59.8 (C-1), 55.4 (C-9a), 52.7 (C-3), 41.1 (C-4), 32.7 (C-7), 27.3 (C-9), 19.4 (C-8); MS *m/z* 244 (M^+), 229, 187, 167, 153, 146, 134, 91; exact mass calcd for $C_{15}H_{20}N_2O$ 244.1575; found 244.1578.

***trans*- and *cis*-2-Benzyl-7-[bis(*p*-fluorophenyl)hydroxymethyl]octahydropyrido[1,2-*a*]pyrazin-6-one (17a) and (18a).** To a stirred solution of diisopropylamine (2.9 mL, 21 mmol) in 15 mL of anhyd THF was added *n*-BuLi, 1.6 M in hexane (12.8 mL, 20.5 mmol), at 0 °C under nitrogen. After 20 min the bath temperature was lowered to −15 °C, and a solution of **7** (4.15 g, 17.0 mmol) in 25 mL of anhyd THF was added dropwise. Anion formation was allowed to proceed for 20 min, and then a solution of 4,4′-difluorobenzophenone (4.10 g, 18.8 mmol) in 15 mL of anhyd THF was added dropwise. The reaction mixture was stirred at −15 °C for 15 min and then was quenched with water and extracted with CH_2Cl_2 (2 × 300 mL). The organic layer was evaporated, and the residue was purified by column chromatography on silica gel using 30% EtOAc–$CHCl_3$ as eluent to give the less polar trans isomer **17a** (3.52 g, 45%) and the more polar cis isomer **18a** (1.90 g, 24%) as solids (total yield 69%).

Trans isomer **17a**: mp 146–147 °C (EtOAc): IR (KBr) ν 3490, 2810, 2790, 1615 cm^{-1}; (CCl_4) ν 3510, 3350, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.10 (m, 9 H, H-o Ar, Ph), 6.95 (m, 4 H, H-m Ar), 6.55 (s, 1 H, OH), 4.55 (ddd, 1 H, ^2J = 13 Hz, $^3J_{4e,3ax}$ = 3 Hz, $^3J_{4e,3e}$ = 2 Hz, H-4e), 3.55 (m, 1 H, H-(9a)ax) (in C_6D_6: 3.0, ddt, $^3J_{(9a)ax,9ax}$ = 11 Hz, $^3J_{(9a)ax,1ax}$ = 10 Hz, $^3J_{(9a)ax,1e} = {}^3J_{(9a)ax,9e}$ = 4 Hz), 3.53, 3.47 (AB q, 2 H, ^2J = 13 Hz, CH_2Ph), 3.0 (dd, 1 H, $^3J_{7ax,8ax}$ = 12.5 Hz, $^3J_{7ax,8e}$ = 5.5 Hz, H-7ax), 2.94–2.82 (m, 2 H, H-3e, 1e), 2.77 (ddd, 1 H, ^2J = 13 Hz, $^3J_{4ax,3ax}$ = 12 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.03 (td, $^2J = {}^3J_{3ax,4ax}$ = 12 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 1.84 (dm, 1 H, H-9e), 1.77 (t, 1 H, $^2J = {}^3J_{1ax,(9a)ax}$ = 11 Hz, H-1ax) (in C_6D_6: 1.33, dd, ^2J = 11 Hz, $^3J_{1ax,(9a)ax}$ = 10 Hz), 1.70 (td, 1 H, $^2J = {}^3J_{8ax,7ax}$ = 12.5 Hz, $^3J_{8ax,9e}$ = 3 Hz, H-8ax), 1.40 (m, 1 H, H-9ax), 1.30 (m, 1 H, H-8e); MS *m/z* 462 (M^+), 444, 353, 316, 244, 218, 153, 134, 91 (100); exact mass calcd for $C_{28}H_{28}F_2N_2O_2$ 462.2117, found 462.2112. Anal. Calcd for $C_{28}H_{28}F_2N_2O_2$: C, 72.71; H, 6.10; N, 6.06. Found: C, 72.58; H, 6.11; N, 5.98.

Cis isomer **18a**: mp 108–110 °C (EtOAc): IR (KBr) ν 3320, 1615 cm^{-1}; (CCl_4) ν 3400, 3320, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.20 (m, 9 H, H-o Ar, Ph), 6.95 (m, 4 H, H-m Ar), 6.45 (s, 1 H, OH), 4.58 (dm, 1 H, H-4e), 3.61, 3.52 (AB q, 2 H, ^2J = 13 Hz, CH_2Ph), 3.60 (m, 1 H, H(9a)ax) (in C_6D_6: 3.04, ddm, $^3J_{(9a)ax,1ax}$ = 11 Hz, $^3J_{(9a)ax,9ax}$ = 7 Hz), 3.03 (dd, $^3J_{7ax,8ax}$ = 11 Hz, $^3J_{7ax,8e}$ = 5.5 Hz, H-7ax), 2.84 (dm, 1 H, H-3e), 2.75 (td, 2 H, $^2J = {}^3J_{4ax,3ax}$ = 12 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.66 (dm, 1 H, H-1e), 2.06 (t, 1 H, $^2J = {}^3J_{1ax,(9a)ax}$ = 11 Hz, H-1ax), 1.98 (td, 1 H, $^2J = {}^3J_{3ax,4ax}$ = 12 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 1.84 (m, 1 H, H-9ax), 1.80 (m, 1 H, H-8ax) (in C_6D_6: 1.48, qd, $^2J = {}^3J_{8ax,7ax} = {}^3J_{8ax,9ax}$ = 12 Hz, $^3J_{8ax,9e}$ = 3 Hz), 1.48 (m, 1 H, H-9e), 1.35 (m, 1 H, H-8e); MS similar to that of **17a**; exact mass calcd for $C_{28}H_{28}F_2N_2O_2$ 462.2117, found 462.2104. Anal. Calcd for $C_{28}H_{28}F_2N_2O_2$: C, 72.71; H, 6.10; N, 6.06. Found: C, 72.83; H, 6.18; N, 6.06.

***trans*- and *cis*-2-Benzyl-7-(diphenylhydroxymethyl)octahydropyrido[1,2-*a*]pyrazin-6-one (17b) and (18b).** In a procedure similar to that described for **17a** and **18a**, a solution of LDA in THF (15 mL) was prepared from *n*-BuLi, 1.6 M in hexane (8.2 mL, 13.1 mmol), and diisopropylamine (1.90 mL, 13.5 mmol). To this solution was added first a solution of **7** (3.17 g, 13.0 mmol) in 20 mL of THF and then a solution of benzophenone (2.40 g, 13.2 mmol) in 15 mL of THF. Workup as described for **17a** and **18a** and chromatography over silica with 30% EtOAc–$CHCl_3$ afforded the less polar trans isomer **17b** (2.45 g, 44%) and the more polar cis isomer **18b** (1.0 g, 18%) as solids (total yield 62%).

Trans isomer **17b**: mp 135–136 °C (EtOAc); IR similar to that of **17a**; ^1H NMR similar to that of **17a**; MS *m/z* 426 (M^+), 408, 244, 182, 105; exact mass calcd for $C_{28}H_{30}N_2O_2$ 426.2305, found 426.2320. Anal. Calcd for $C_{28}H_{30}N_2O_2$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.52; H, 7.14; N, 6.44.

Cis isomer **18b**: mp 133–134 °C (EtOAc); IR similar to that of **18a**; ^1H NMR similar to that of **18a**; MS similar to that of **17b**; exact mass calcd for $C_{28}H_{30}N_2O_2$ 426.2305, found 426.2333. Anal. Calcd for $C_{28}H_{30}N_2O_2$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.54; H, 7.14; N, 6.43.

2-Benzyl-7-[bis(*p*-fluorophenyl)methylene]octahydropyrido[1,2-*a*]pyrazin-6-one (19a). A stirred solution of the two diastereoisomers **17a** and **18a** (9.53 g, 20.6 mmol) in 3 mL of CH_2Cl_2 was treated with 15 mL of 48% aqueous HBr. After 40 min the solution was poured into a mixture of ice (50 g) and CH_2Cl_2 (200 mL). The aqueous phase was made alkaline with K_2CO_3 and was further extracted with CH_2Cl_2 (100 mL). The combined extracts were evaporated, and the residue was chromatographed on a silica column using 5% MeOH–EtOAc as the eluent to give **19a** (8.83 g, 96%) as white crystals, mp 60–61 °C (EtOAc): IR (KBr) ν 2810, 2770, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–6.90 (m, 13 H, Ph, Ar), 4.57 (dt, 1 H, ^2J = 13 Hz, $^3J_{4e,3ax}$ = 3.5 Hz, $^3J_{4e,3e}$ = 2 Hz, H-4e), 3.56, 3.50 (AB q, 2 H, ^2J = 12.5 Hz, CH_2Ph), 3.52 (m, 1 H, H-(9a)ax), 2.85 (m, 2 H, H-3e, 1e), 2.74 (td, 1 H, ^2J = 13 Hz, $^3J_{4ax,3ax}$ = 12 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.60 (ddd, 1 H, ^2J = 13 Hz, $^3J_{8e,9ax}$ = 5 Hz, $^3J_{8e,9e}$ = 3.5 Hz, H-8e), 2.40 (ddd, 1 H, ^2J = 13 Hz, $^3J_{8ax,9ax}$ = 12 Hz, $^3J_{8ax,9e}$ = 3.5 Hz, H-8ax), 2.05 (td, 1 H, $^2J = {}^3J_{3ax,4ax}$ = 12 Hz, $^3J_{3ax,4e}$ = 3.5 Hz, H-3ax), 1.95 (m, 1 H, H-9e), 1.88 (t, 1 H, ^2J = 11 Hz, $^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 1.52 (tdd, 1 H, $^2J = {}^3J_{9ax,8ax}$ = 12 Hz, $^3J_{9ax,(9a)ax}$ = 10 Hz, $^3J_{9ax,8e}$ = 5 Hz, H-9ax); MS *m/z* 444 (M^+), 429, 353, 311, 255, 227, 187, 161, 146, 133, 91; exact mass calcd for $C_{28}H_{26}F_2N_2O$ 444.2012, found 444.2009. Anal. Calcd for $C_{28}H_{26}F_2N_2O$: C, 75.66; H, 5.90; N, 6.30. Found: C, 75.53; H, 5.89, N, 5.95.

2-Benzyl-7-(diphenylmethylene)octahydropyrido[1,2-*a*]-pyrazin-6-one (19b). A solution of the two diastereoisomers **17b** and **18b** (2.00 g, 4.7 mmol) in 2 mL of CH_2Cl_2 was treated with 10 mL of 48% aqueous HBr, and the mixture was stirred for 30 min. Workup as described for **19a** and chromatography over silica with EtOAc afforded **19b** (1.80 g, 94%) as white crystals, mp 125.4 °C (EtOAc): IR similar to that of **19a**; ^{1}H NMR similar to that of **19a**; MS *m/z* 408 (M^+), 317, 275, 262, 229, 219, 201, 146; exact mass calcd for $C_{28}H_{28}N_2O$ 408.2200, found 408.2200. Anal. Calcd for $C_{28}H_{28}N_2O$: C, 82.32; H, 6.91; N, 6.86. Found: C, 82.08; H, 6.97; N, 6.74.

2-Benzyl-7-[bis(*p*-fluorophenyl)methylene]octahydro-2*H*-pyrido[1,2-*a*]pyrazine (20a). To a stirred solution of **19a** (8.20 g, 18.4 mmol) in 300 mL of anhyd THF was added $LiAlH_4$ (2.09 g, 55.2 mmol) portionwise. After 30 min the excess hydride was decomposed by dropwise addition of MeOH. Then CH_2Cl_2 (400 mL), K_2CO_3 (3.75 g), and water (25 mL) were added successively. The organic layer was separated and evaporated. The crude product was purified through a silica column with 50% EtOAc–$CHCl_3$ to give **20a** (7.15 g, 90%) as white crystals, mp 143.5 °C (EtOAc): IR (KBr) ν 2800, 2760, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H, Ph), 7.15–7.0 (m, 4 H, H-o, Ar), 6.96 (td, 4 H, H-m Ar), 3.65 (dd, 1 H, ^2J = 12 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 3.50 (s, 2 H, CH_2Ph), 2.90–2.70 (m, 4 H, H-8e, 4e, 3e, 1e), 2.65 (d, 1 H, ^2J = 12 Hz, H-6ax), 2.40–2.30 (m, 2 H, H-3ax, 4ax), 2.25 (tt, 1 H, $^3J_{(9a)ax,1ax}$ = $^3J_{(9a)ax,9ax}$ = 10 Hz, $^3J_{(9a)ax,1e}$ = $^3J_{(9a)ax,9e}$ = 4 Hz, H-(9a)ax), 1.96 (td, 1 H, ^2J = $^3J_{8ax,9ax}$ = 12 Hz, $^3J_{8ax,9e}$ = 4 Hz, H-8ax), 1.95 (t, 1 H, ^2J = $^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 1.56 (dqd, 1 H, ^2J = 12 Hz, $^3J_{9e,8ax}$ = $^3J_{9e,(9a)ax}$ = $^3J_{9e,8e}$ = 4 Hz, $^4J_{9e,1e}$ = 2 Hz, H-9e), 1.35 (tdd, 1 H, ^2J = $^3J_{9ax,8ax}$ = 12 Hz, $^3J_{9ax,(9a)ax}$ = 10 Hz, $^3J_{9ax,8e}$ = 4 Hz, H-9ax); MS *m/z* 430, 339, 298, 241, 220, 201, 125 (100), 109, 95; exact mass calcd for $C_{28}H_{28}F_2N_2$ 430.2219, found 430.2217. Anal. Calcd for $C_{28}H_{28}F_2N_2$: C, 78.11; H, 6.55; N, 6.51. Found: C, 77.73; H, 6.61; N, 6.52.

2-Benzyl-7-(diphenylmethylene)octahydro-2*H*-pyrido-[1,2-*a*]pyrazine (20b). In a procedure similar to that for **20a** a stirred solution of **19b** (2.00 g, 4.9 mmol) in 100 mL of anhyd THF was treated with $LiAlH_4$ (0.50 g, 13 mmol) to give after workup and column purification **20b** (1.75 g, 91%) as white crystals, mp 133–134 °C (EtOAc): IR similar to that of **20a**; ^{1}H NMR ($CDCl_3$) δ 7.40–7.05 (m, 15 H, 3Ph), 3.65 (dd, 1 H, ^2J = 12 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 3.50 (s, 2 H, CH_2Ph), 2.85–2.65 (m, 4 H, H-1e, 3e, 4e, 8e), 2.65 (d, 1 H, ^2J = 12 Hz, H-6ax), 2.35–2.25 (m, 2 H, H-3ax, 4ax), 2.20 (tt, 1 H, $^3J_{(9a)ax,1ax}$ = $^3J_{(9a)ax,9ax}$ = 10 Hz, $^3J_{(9a)ax,1e}$ = $^3J_{(9a)ax,9e}$ = 4 Hz, H-(9a)ax), 1.97 (td, 1 H, ^2J = $^3J_{8ax,9ax}$ = 12 Hz, $^3J_{8ax,9e}$ = 4 Hz, H-8ax), 1.93 (t, 1 H, ^2J = $^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 1.56 (dqd, 1 H, ^2J = 12 Hz, $^3J_{9e,8ax}$ = $^3J_{9e,(9a)ax}$ = $^3J_{9e,8e}$ = 4 Hz, $^4J_{9e,1e}$ = 2 Hz, H-9e), 1.36 (tdd, 1 H, ^2J = $^3J_{9ax,8ax}$ = 12 Hz, $^3J_{9ax,(9a)ax}$ = 10 Hz, $^3J_{9ax,8e}$ = 4 Hz, H-9ax); ^{13}C NMR ($CDCl_3$) δ 142.5 and 142.0 (C-ipso CPh_2), 138.2 (C-ipso CH_2Ph), 137.0 (CPh_2), 133.5 (C-7), 129.8 and 129.5 (C-m CPh_2), 129.2 (C-m CH_2Ph), 128.2 (C-o CH_2Ph), 127.9 and 127.8 (C-o CPh_2), 127.0 (C-p CH_2Ph), 126.6 and 126.5 (C-p CPh_2), 63.1 (CH_2Ph), 61.2 (C-9a), 59.0 (C-1), 58.8 (C-6), 55.1 (C-4), 52.9 (C-3), 30.8 (C-9), 29.8 (C-8); MS *m/z* 394 (M^+), 303 (100), 262, 205, 115, 91; exact mass calcd for $C_{28}H_{30}N_2$ 394.2407, found 394.2413. Anal. Calcd for $C_{28}H_{30}N_2$: C, 85.24; H, 7.66; N, 7.10. Found: C, 84.92; H, 7.60; N, 6.99.

2-(Ethoxycarbonyl)-7-[bis(*p*-fluorophenyl)methylene]-octahydro-2*H*-pyrido[1,2-*a*]pyrazine (21a). To a stirred solution of **20a** (2.50 g, 5.8 mmol) in 50 mL of CH_2Cl_2 was added ethyl chloroformate (0.61 mL, 6.4 mmol) dropwise at 0 °C. The reaction mixture was kept at 0 °C under nitrogen for 2 h and then at rt for 1 h. The solution was made alkaline with aqueous K_2CO_3 and extracted with CH_2Cl_2 (2 × 150 mL). The combined extracts were evaporated and chromatographed on a silica column using 40% EtOAc–$CHCl_3$ as the eluent to afford **21a** (2.25 g, 94%) as white crystals, mp 144–145 °C (EtOAc): IR (KBr) ν 2820, 2760, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 55 °C) δ 7.0 (m, 8 H, 2Ar), 4.14 (q, 2 H, ^3J = 7 Hz, OCH_2CH$_3$), 4.02 (m, 1 H, H-3e), 3.97 (m, 1 H, H-1e), 3.51 (dd, 1 H, ^2J = 12 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 3.02 (td, 1 H, ^2J = $^3J_{3ax,4ax}$ = 12 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.70–2.50 (m, 3 H, H-8e, 4e, 1ax), 2.62 (d, 1 H, ^2J = 12 Hz, 1 H, H-6ax), 2.13 (td, 1 H, ^2J = $^3J_{4ax,3ax}$ = 12 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.05 (m, 1 H, H-(9a)ax), 2.0 (td, 1 H, ^2J = $^3J_{8ax,9ax}$ = 14 Hz, $^3J_{8ax,9e}$ = 5 Hz, H-8ax), 1.67 (dxm, 1 H, H-9e), 1.32 (tdd, 1 H, ^2J = $^3J_{9ax,8ax}$ = 14 Hz, $^3J_{9ax,(9a)ax}$ = 10.5 Hz, $^3J_{9ax,8e}$ = 5 Hz, H-9ax), 1.25 (t, 3 H, ^3J = 7 Hz, OCH$_2$CH_3); MS *m/z* 412 (M^+) (100), 384, 339, 317, 241, 227, 209, 157, 130, 109, 83; exact mass calcd for $C_{24}H_{26}F_2N_2O_2$ 412.1958, found 412.1960. Anal. Calcd for $C_{24}H_{26}F_2N_2O_2$: C, 69.89; H, 6.35; N, 6.79. Found: C, 69.85; H, 6.47; N, 6.68.

2-(Ethoxycarbonyl)-7-(diphenylmethylene)octahydro-2*H*-pyrido[1,2-*a*]pyrazine (21b). In a procedure similar to that described for **21a**, a stirred solution of **20b** (1.60 g, 4.0 mmol) in 30 mL of CH_2Cl_2, was treated with ethyl chloroformate (0.40 mL, 4.2 mmol) to furnish after column purification **21b** (1.40 g, 92%) as an oil: IR (NaCl) ν 2820, 2760, 1695, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.12 (m, 10 H, 3Ph), 4.22 (q, 2 H, ^3J = 7 Hz, OCH_2CH$_3$), 4.02 (m, 1 H, H-3e), 3.97 (m, 1 H, H-1e), 3.51 (dd, 1 H, ^2J = 12 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 3.02 (td, 1 H, ^2J = $^3J_{3ax,4ax}$ = 12 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.70–2.50 (m, 3 H, H-8e, 4e, 1ax), 2.62 (d, 1 H, ^2J = 12 Hz, 1 H, H-6ax), 2.12 (td, 1 H, ^2J = $^3J_{4ax,3ax}$ = 12 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.05 (m, 1 H, H-(9a)ax), 2.0 (td, 1 H, ^2J = $^3J_{8ax,9ax}$ = 14 Hz, $^3J_{8ax,9e}$ = 5 Hz, H-8ax), 1.65 (m, 1 H, H-9e), 1.38 (tdd, 1 H, ^2J = $^3J_{9ax,8ax}$ = 14 Hz, $^3J_{9ax,(9a)ax}$ = 10.5 Hz, $^3J_{9ax,8e}$ = 5 Hz, H-9ax), 1.25 (t, 3 H, ^3J = 7 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 155.0 (C=O), 142.1 and 141.7 (C-ipso), 137.0 (CPh_2), 132.7 (C-7), 129.8 and 129.5 (C-m), 127.9 and 127.8 (C-o), 126.5 and 126.4 (C-p), 61.2 (OCH$_2$CH$_3$), 60.9 (C-9a), 58.6 (C-6), 54.5 (C-4), 48.6 (C-1), 43.3 (C-3), 30.0 (C-9), 29.5 (C-8), 14.6 (OCH$_2$CH$_3$); MS *m/z* 376 (M^+) (100), 347, 303, 299, 246, 209, 130, 91; exact mass calcd for $C_{24}H_{28}N_2O_2$ 376.2148, found 376.2153.

7-[Bis(*p*-fluorophenyl)methylene]octahydro-2*H*-pyrido-[1,2-*a*]pyrazine (22a). A stirred mixture of **21a** (1.95 g, 4.73 mmol), isopropyl alcohol (17 mL), and KOH (11 g) was refluxed for 1 h under nitrogen. The solvent was evaporated, the residue was treated with CH_2Cl_2 (4 × 200 mL), and the solids were filtered off. The combined filtrates were evaporated, and the residual product was chromatographed on a short silica column with 1% Et_2NH–5% MeOH–94% EtOAc as eluent to yield **22a** (1.50 g, 93%) as a semisolid product: IR (NaCl) ν 3300, 2810, 2750, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.12–7.02 (m, 4 H, H-o), 6.97 (td, 4 H, H-m), 3.49 (dd, ^2J = 12 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 3.15 (br s, 1 H, NH), 3.0–2.85 (m, 3 H, H-3e, 1e, 4e), 2.70–2.50 (m, 3 H, H-1ax, 3ax, 8e), 2.65 (d, 1 H, ^2J = 12 Hz, H-6ax), 2.25 (m, 1 H, H-4ax), 2.14 (m, 1 H, H-(9a)ax), 2.0 (td, ^2J = $^3J_{8ax,9ax}$ = 13.5 Hz, $^3J_{8ax,9e}$ = 5 Hz, H-8ax), 1.60 (dxm, 1 H, H-9e), 1.34 (tdd, 1 H, ^2J = $^3J_{9ax,8ax}$ = 13.5 Hz, $^3J_{9ax,(9a)ax}$ = 10.5 Hz, $^3J_{9ax,8e}$ = 5 Hz, H-9ax); ^{13}C NMR ($CDCl_3$) δ 161.5 (C-F), 134.7 (CAr_2), 137.9 and 137.5 (C-ipso), 133.4 (C-7), 131.3 and 131.0 (C-o), 114.9 and 114.7 (C-m), 62.6 (C-9a), 59.2 (C-1), 55.8 (C-6), 51.6 (C-4), 45.7 (C-3), 30.6 (C-9), 30.0 (C-8); MS *m/z* 340 (M^+) (100), 311, 298, 284, 241, 227, 201, 109; exact mass calcd for $C_{21}H_{22}F_2N_2$ 340.1750, found 340.1746.

7-(Diphenylmethylene)octahydro-2*H*-pyrido[1,2-*a*]pyrazine (22b). A stirred mixture of **21b** (1.30 g, 3.45 mmol), isopropyl alcohol (15 mL), and KOH (8.0 g) was refluxed under nitrogen for 1 h. Workup as for **22a** and chromatography on a short silica column with 1% Et_2NH–5% MeOH–94% EtOAc afforded **22b** (0.82 g, 78%) as an oil: IR similar to that of **22a**; ^{1}H NMR ($CDCl_3$, 55 °C) δ 7.40–7.10 (m, 10 H, 3Ph), 3.53 (dd, 1 H, ^2J = 12 Hz, $^3J_{6e,8e}$ = 2 Hz, H-6e), 3.0–2.85 (tm, 3 H, H-4e, 3e, 1e), 2.83 (br s, 1 H, NH), 2.70–2.57 (m, 2 H, H-8e, 3ax), 2.65 (d, 1 H, ^2J = 12 Hz, H-6ax), 2.53 (dd, ^2J = 12 Hz, $^3J_{1ax,(9a)ax}$ = 10.5 Hz, H-1ax), 2.30–2.10 (m, 1 H, H-4ax), 2.08 (m, 1 H, H-(9a)ax), 2.0 (td, 1 H, ^2J = $^3J_{8ax,9ax}$ = 13.5 Hz, $^3J_{8ax,9e}$ = 5 Hz, H-8ax), 1.58 (dm, 1 H, H-9e), 1.34 (tdd, ^2J = $^3J_{9ax,8ax}$ = 13.5 Hz, $^3J_{9ax,(9a)ax}$ = 10.5 Hz, $^3J_{9ax,8e}$ = 5 Hz, H-9ax); ^{13}C NMR ($CDCl_3$) δ 142.5 and 142.1 (C-ipso), 133.0 (C-7), 129.9 and 129.6 (C-m), 128.0 and 127.8 (C-o), 126.4 (C-p), 62.6 (C-9a), 59.2 (C-1), 55.8 (C-6), 51.6 (C-4), 45.7 (C-3), 30.6 (C-9), 30.0 (C-8); MS *m/z* 304 (M^+) (100), 262, 227, 137; exact mass calcd for $C_{21}H_{24}N_2$ 304.1938, found 304.1934.

***N*-(2,6-Dichlorophenyl)-7-[bis(*p*-fluorophenyl)methylene]octahydro-2*H*-pyrido[1,2-*a*]pyrazine-2-acetamide (8a).** A mixture of **22a** (1.30 g, 3.8 mmol), K_2CO_3 (2.0 g, 14 mmol), KI (0.90 g, 5.4 mmol), and 2-chloro-*N*-(2,6-dichlorophenyl)acetamide (1.00 g, 4.2 mmol) in 200 mL of acetone was stirred overnight under nitrogen. The solvent then was evaporated, and the residue was distributed between CH_2Cl_2 (2 × 200 mL) and water (50 mL). The combined extracts were evaporated, and the crude product was chromatographed on a silica column using 50% EtOAc–$CHCl_3$ as the eluent to give **8a** (1.60 g, 77%) as crystals, mp 94.6 °C (MeOH): IR (KBr) ν 3300, 2750, 1710, 1570, 1220

cm^{-1}; (CCl_4) ν 3330, 1712, 1570, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.0 (s, 1 H, NH), 7.30 (2 × d, 2 H, H-m $ArCl_2$), 7.16 (dd, H-p $ArCl_2$), 7.13–7.02 (m, 4 H, H-o ArF), 7.02–6.92 (m, 4 H, H-m ArF) 3.55 (dd, 1 H, ^2J = 12 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 3.22 (s, 2 H, NCH_2CO), 3.0–2.90 (m, 2 H, H-3e, 1e), 2.75–2.60 (m, 2 H, H-8e, 4e), 2.65 (d, 1 H, ^2J = 12 Hz, H-6ax), 2.59 (td, 1 H, $^2J = {}^3J_{3ax,4ax}$ = 11 Hz, $^3J_{3a,4e}$ = 3 Hz, H-3ax), 2.37 (td, 1 H, $^2J = {}^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.25 (m, 1 H, H-(9a)ax), 2.25 (t, 1 H, $^2J = {}^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 2.02 (td, 1 H, $^2J = {}^3J_{8ax,9ax}$ = 14 Hz, $^3J_{8ax,9e}$ = 5 Hz, H-8ax), 1.64 (dm, 1 H, H-9e), 1.40 (tdd, 1 H, $^2J = {}^3J_{9ax,8ax}$ = 14 Hz, $^3J_{9ax,(9a)ax}$ = 10.5 Hz, $^3J_{9ax,8e}$ = 5 Hz, H-9ax); ^{13}C NMR ($CDCl_3$) δ 168.4 (C=O), 161.6 (*C*-F ArF), 138.0 and 137.6 (C-ipso ArF), 134.9 ($C(ArF)_2$), 133.7 (C-7), 133.3 (C-Cl $ArCl_2$), 132.0 (C-ipso $ArCl_2$), 131.4 and 131.1 (C-o ArF), 128.5 (C-m $ArCl_2$), 128.3 (C-p $ArCl_2$), 115.0 and 114.8 (C-m ArF), 61.5 (CH_2CO), 61.3 (C-9a), 59.9 (C-1), 58.4 (C-6), 54.9 (C-4), 53.3 (C-3), 30.4 (C-9), 29.9 (C-8); MS *m/z* 542 (M$^+$), 353 (100), 339, 298, 241, 176, 109, 70; exact mass calcd for $C_{29}H_{27}Cl_2F_2N_3O$ 541.1499, found 541.1480. Anal. Calcd for $C_{29}H_{27}Cl_2F_2N_3O$: C, 64.21; H, 5.02; N, 7.75; F, 7.01; Cl, 13.07. Found: C, 63.70; H, 5.10; N, 7.55; F, 7.07; Cl, 13.07.

***N*-(2,6-Dichlorophenyl)-7-(diphenylmethylene)octahydro-2*H*-pyrido[1,2-*a*]pyrazine-2-acetamide (8b).** A mixture of **22b** (0.77 g, 2.53 mmol), K_2CO_3 (1.70 g, 12.3 mmol), KI (0.60 g, 3.6 mmol), and 2-chloro-*N*-(2,6-dichlorophenyl)acetamide (0.91 g, 3.8 mmol), in 150 mL of acetone was stirred overnight under nitrogen. Following workup in the manner described for **8a**, chromatography on a silica column using 50% EtOAc–$CHCl_3$ afforded **8b** (1.15 g, 90%) as crystals, mp 107.6 °C (MeOH): IR (KBr) ν 3240, 2810, 2750, 1690, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.0 (s, 1 H, NH), 7.36 (2 × d, 2 H, H-m Ar), 7.30–7.10 (m, 10 H, 2Ph), 7.15 (dd, 2 H, H-p Ar), 3.62 (dd, 1 H, ^2J = 12 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 3.21 (s, 2 H, NCH_2CO), 3.20–2.90 (m, 2 H, H-3e, 1e), 2.78–2.60 (m, 2 H, H-8e, 4e), 2.70 (d, 1 H, ^2J = 12 Hz, H-6ax), 2.60 (td, 1 H, $^2J = {}^3J_{3ax,4ax}$ = 11 Hz, $^3J_{3a,4e}$ = 3 Hz, H-3ax), 2.36 (td, 1 H, $^2J = {}^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.28 (m, 1 H, H-(9a)ax), 2.25 (t, 1 H, $^2J = {}^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 2.02 (td, 1 H, $^2J = {}^3J_{8ax,9ax}$ = 14 Hz, $^3J_{8ax,9e}$ = 5 Hz, H-8ax), 1.64 (dm, 1 H, H-9e), 1.42 (m, 1 H, H-9ax); ^{13}C NMR ($CDCl_3$) δ 61.4 (CH_2CO), 61.1 (C-9a), 59.1 (C-1), 58.3 (C-6), 54.8 (C-4), 53.3 (C-3), 30.5 (C-9), 29.8 (C-8); MS *m/z* 506 (M$^+$), 317 (100), 303, 291, 274, 262, 165, 129, 115; exact mass calcd for $C_{29}H_{29}Cl_2N_3O$ 505.1687, found 505.1687. Anal. Calcd for $C_{29}H_{29}Cl_2N_3O{\cdot}CH_3OH$: C, 66.91; H, 6.18; N, 7.80; Cl, 13.17. Found: C, 67.15; H, 6.14; N, 7.87; Cl, 13.07.

***trans*- and *cis*-*N*-(2,6-Dichlorophenyl)-7-[bis(*p*-fluorophenyl)methyl]octahydro-2*H*-pyrido[1,2-*a*]pyrazine-2-acetamide (9) and (10).** To a solution of **20a** (2.00 g, 4.6 mmol) in 50 mL of acetic acid was added 10% palladized carbon (3.0 g). The mixture was stirred under hydrogen (balloon) at 70 °C for 5 h. The cooled mixture then was filtered, the catalyst washed with MeOH, and the filtrates were evaporated. The resulting residue was distributed between aqueous K_2CO_3 (50 mL) and CH_2Cl_2 (2 × 200 mL). The combined extracts were evaporated to dryness to obtain a mixture of the crude amines **24** and **25** (1.44 g) as a solid, which was used directly in the next step: MS for benzoyl derivatives of **24** and **25** *m/z* EI 446 (M$^+$), 341, 312, 300, 243, 203, 133; CI 447 (MH$^+$).

The mixture of crude products **24** and **25**, K_2CO_3 (2.0 g, 14 mmol), KI (1.2 g, 7 mmol), and 2-chloro-*N*-(2,6-dichlorophenyl)-acetamide (1.50 g, 6.3 mmol) in 200 mL of acetone was stirred overnight under nitrogen. Subsequent workup as described for **8** and chromatography on silica gel with 20% EtOAc–$CHCl_3$ afforded the less polar cis isomer **10** (0.50 g, 20%) and the more polar trans isomer **9** (1.38 g, 54%) as white crystals. The overall yield thus was 74% from **20a**.

Trans isomer **9**: mp 80–81 °C (EtOAc): IR (KBr) ν 3300, 2780, 2760, 1710, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1 H, NH), 7.34 (2 × d, 2 H, H-m $ArCl_2$), 7.20 (m, 4 H, H-o ArF), 7.15 (dd, 1 H, H-p $ArCl_2$), 6.95 (m, 4 H, H-m ArF), 3.39 (d, 1 H, $^3J_{CH(ArF)2,7ax}$ = 11 Hz, $CH(ArF)_2$), 3.12 (s, 2 H, CH_2CONH), 2.92–2.82 (m, 2 H, H-3e, 1e), 2.62–2.56 (m, 2 H, H-4e, 6e), 2.44 (td, 1 H, $^2J = {}^3J_{3ax,4ax}$ = 11 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.35 (tt, 1 H, $^3J_{7ax,6ax} = {}^3J_{7ax,8ax} = {}^3J_{7ax,CH(ArF)2}$ = 11 Hz, $^3J_{7ax,6e} = {}^3J_{7ax,8e}$ = 3 Hz, H-7ax), 2.21 (td, 1 H, $^2J = {}^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.08 (dd, 1 H, ^2J = 11 Hz, $^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 1.94 (tt, 1 H, $^3J_{(9a)ax,1ax} = {}^3J_{(9a)ax,9ax}$ = 10 Hz, $^3J_{(9a)ax,9e} = {}^3J_{(9a)ax,1e}$ = 3 Hz, H-(9a)ax), 1.65 (t, 1 H, $^2J = {}^3J_{6ax,7ax}$ = 11 Hz, H-6ax), 1.57 (m, 1 H, H-8e), 1.47 (m, 1 H, H-9e), 1.20 (tdd, 1 H, $^2J = {}^3J_{9ax,8ax}$ = 13 Hz, $^3J_{9ax,(9a)ax}$ = 10 Hz, $^3J_{9ax,8e}$ = 4 Hz, H-9ax), 0.86 (tdd, 1 H, $^2J = {}^3J_{8ax,9ax}$ = 13 Hz, $^3J_{8ax,7ax}$ = 11 Hz, $^3J_{8ax,9e}$ = 4 Hz, H-8ax); ^{13}C NNR ($CDCl_3$) δ 168.5 (C=O), 163.3 and 159.4 (C-F ArF), 138.8 (C-ipso ArF), 133.3 (C-Cl $ArCl_2$), 132.0 (C-ipso $ArCl_2$), 129.0 (C-o ArF), 128.4 (C-m $ArCl_2$), 128.2 (C-p $ArCl_2$), 115.6 and 115.2 (C-m ArF), 61.4 (CH_2CO), 61.0 (C-9a), 60.3 (C-6), 59.3 (C-1), 55.6 ($CH(ArF)_2$), 54.9 (C-4), 53.4 (C-3), 39.9 (C-7), 29.5 (C-8), 29.4 (C-9); MS *m/z* 544, 509, 355, 341, 300, 229, 203 (100), 183, 153, 91; exact mass calcd for $C_{29}H_{29}Cl_2F_2N_3O$ 543.1655, found 543.1654. Anal. Calcd for $C_{29}H_{29}Cl_2F_2N_3O$: C, 63.97; H, 5.37; N, 7.72, F, 6.98; Cl, 13.02. Found: C, 63.40; H, 5.47; N, 7.41; F, 6.47; Cl, 13.20.

Cis isomer **10**: mp 90–91 °C (EtOAc): IR (KBr) similar to that of **9**; ^{1}H NMR ($CDCl_3$) δ 9.0 (s, 1 H, NH), 7.40 (2 × d, 2 H, H-m $ArCl_2$), 7.29 (m, 4 H, H-o ArF), 7.18 (dd, 1 H, H-p $ArCl_2$), 6.98 (m, 4 H, H-m ArF), 4.45 (d, 1 H, ^3J = 11.5 Hz, $CH(ArF)_2$), 3.15 (s, 2 H, CH_2CONH), 2.89 (ddd, 1 H, ^2J = 11 Hz, $^3J_{3e,4ax}$ = 3 Hz, $^3J_{3e,4e}$ = 2.5 Hz, H-3e), 2.82 (ddd, 1 H, ^2J = 10.5 Hz, $^3J_{1e,(9a)ax}$ = 3 Hz, $^3J_{1e,3e}$ = 2 Hz, H-1e), 2.49 (td, 1 H, $^2J = {}^3J_{3ax,4ax}$ = 11 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.36 (ddd, 1 H, ^2J = 11 Hz, $^3J_{4e,3ax}$ = 3 Hz, $^3J_{4e,3e}$ = 2.5 Hz, H-4e), 2.34–2.28 (m, 2 H, H-6e, 7e), 2.18 (t, 1 H, $^2J = {}^3J_{1ax,(9a)ax}$ = 10.5 Hz, H-1ax), 2.14 (td, 1 H, $^2J = {}^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.03 (dd, ^2J = 11.7 Hz, ^3J = 3.1 Hz, H-6ax), 2.01 (m, 1 H, H-(9a)ax), 1.55–1.15 (m, 4 H, H-8, 9); ^{13}C NMR ($CDCl_3$) δ 168.5 (C=O), 163.2 and 159.3 (C-F ArF), 139.4 (C-ipso ArF), 133.3 (C-Cl $ArCl_2$), 132.0 (C-ipso $ArCl_2$), 129.0 (C-o ArF), 128.4 (C-m $ArCl_2$), 128.2 (C-p $ArCl_2$), 115.6 and 115.2 (C-m ArF), 61.5 (CH_2CO), 61.3 (C-9a), 59.7 (C-1), 56.7 (C-6), 54.8 (C-4), 53.8 (C-3), 49.3 ($CH(ArF)_2$), 37.9 (C-7), 25.6 (C-8), 24.7 (C-9); MS *m/z* similar to that of **9**; exact mass calcd for $C_{29}H_{29}Cl_2F_2N_3O$ 543.1655, found 543.1637. Anal. Calcd for $C_{29}H_{29}Cl_2F_2N_3O$: C, 63.97; H, 5.37; N, 7.72; F, 6.98; Cl, 13.02. Found: C, 63.96; H, 5.50; N, 7.49; F, 6.58; Cl, 12.69.

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