Stereospecific Syntheses of the Four Diastereomeric 2-Amino-5-phenoxycyclopentanols

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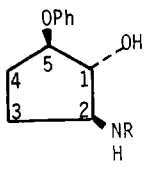
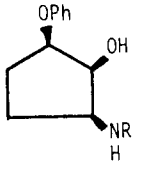
Stereospecific synthetic routes are described for the formation of the three contiguous chiral centers in the four diastereomeric 2-amino-5-phenoxycyclopentanols **1a–4a**. All four stereoisomers (**1a–4a**) were prepared, starting from 3-chlorocyclopentene (**6**). Among the key steps in the syntheses was the development of a mild method for the formation of the aromatic ether linkage in *cis*-2-phenoxy-6-oxabicyclo[3.1.0]hexane (**9**) while maintaining the stereochemistry at the three adjacent centers on the cyclopentane ring. The nucleophilic displacement of the aromatic halogen on π-(chloro- or π-(fluorobenzene)chromium tricarbonyl (**19a** or **19b**) with the anion of the *cis*-epoxy alcohol **10** proceeded to completion and essentially instantaneously at 45 °C. The presence of an adjacent heteroatom in epoxides **8**, **9**, **21**, and **24** provided high regiospecificity for the opening of these epoxides by oxygen and nitrogen nucleophiles. X-ray crystallographic analysis of *cis*-2-amino-*trans*-5-(4-bromophenoxy)cyclopentanol (**27**) was used in conjunction with proton NMR spectral data to confirm the structural assignments of the title compounds. The rationale for the synthesis of **1–4** is briefly discussed.

(Aryloxy)propanolamines **5** are an important class of compounds from which many clinically active agents have been developed for the treatment of a number of disease states including hypertension and heart disease.[1] The major action of these agents is to block β-adrenergic receptors and this is best accomplished with a bulky amino group such as isopropylamine (e.g., **5**, R = *i*-Pr).[1,2] We



1



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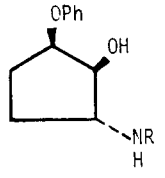

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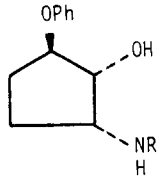

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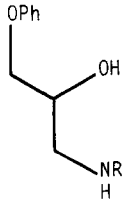

5

a, R=H
b, R=H (·HCl)
c, R=*i*-Pr
d, R=*i*-Pr(·HCl)

were interested in determining the conformational requirements for **5** to interact with β-adrenergic receptors, since this has important implications in understanding the biological activity of this class of compounds. There has been considerable discussion on this subject, but few definitive conclusions.[3-6] In order to accomplish our objective, the cyclopentane ring was chosen as a semirigid "backbone" for **5**, to provide the four diastereomeric (aryloxy)propanolamines **1–4**. Thus if a specific orientation of the three functional groups on **5** is needed for β-adrenergic receptor interaction, one of the four diastereomers **1–4** should exhibit much stronger β-blocking activity as shown by standard pharmacologic techniques.

We have developed stereospecific syntheses for all four diastereomeric 2-amino-5-phenoxycyclopentanols **1a–4a** from a common intermediate, 3-chlorocyclopentene (**6**).[7] Our strategy for the establishment of the three contiguous functionalized chiral centers in the four stereoisomers was to utilize the extremely reactive electrophile **6**[8] to introduce the appropriate oxygen or nitrogen functionality that would in turn direct an epoxidizing agent either cis or trans to itself. Regiospecific opening of the desired epoxide with the appropriate nucleophiles was a key part in the synthetic strategy.[9]

Results and Discussion

The initial route chosen for obtaining diastereomer **1** utilized the steric effects of the 3-phenoxy group on **7**, which was derived from **6**, for a stereoselective epoxidation of the cyclopentene ring from the α face (see Scheme I). A regioselective opening of the resulting epoxide **8** with sodium azide followed by catalytic hydrogenation was

(1) For a review of (aryloxy)propanolamines as β-adrenergic blocking agents, see: Evans, D. B.; Fox, R.; Hauck, F. P. *Annu. Rep. Med. Chem.* **1979**, *14*, p 81–90.
(2) Scriabine, A. *Annu. Rev. Pharmacol. Toxicol.* **1979**, *19*, 269.
(3) Jen, T.; Kaiser, C. *J. Med. Chem.* **1977**, *20*, 693.
(4) Zaagsma, J. *J. Med. Chem.* **1979**, *22*, 441.
(5) (a) Zatz, M. M. *Khim. Farm. Zh.* **1983**, *17*, 278. (b) Ammon, H. L.; Balsamo, A.; Macchia, B.; Macchia, F.; Howe, D. B.; Keefe, W. E. *Experientia* **1975**, *31*, 644. (c) Leger, J. M.; Gadret, M.; Carpy, A. *Mol. Pharmacol.* **1980**, *17*, 339.
(6) Patil, P. N.; Miller, D. D.; Trendelenburg, U. *Pharmacol. Rev.* **1974**, *26*, 323.
(7) Moffett, R. B. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 238.
(8) Brown, H. C.; Rao, C. G.; Ravindranathan, M. *J. Org. Chem.* **1978**, *43*, 4939.
(9) Parker, R. E.; Isaac, N. S. *Chem. Rev.* **1959**, *59*, 737.

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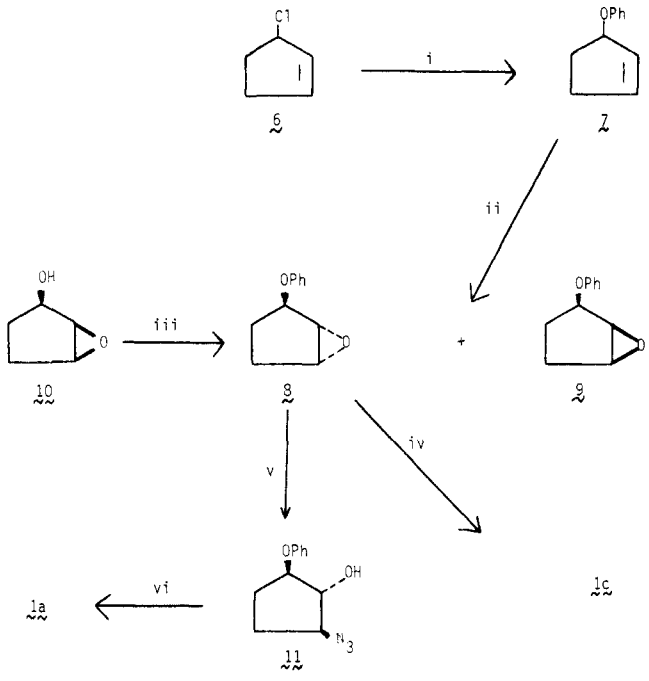
Scheme I[a]

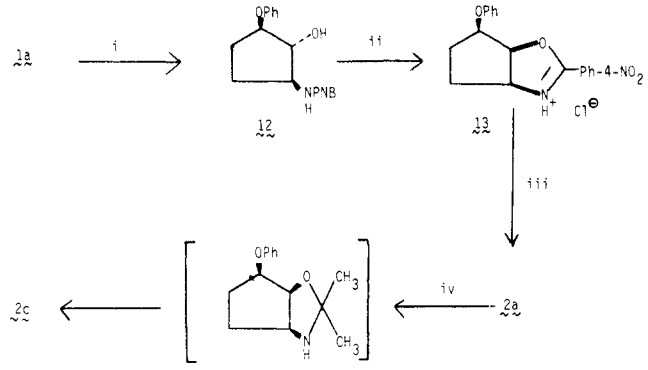


[a] (i) PhO^-Na^+, DMF, 100 °C; (ii) MCPBA; (iii) PhOH, Ph_3P, diisopropylazodicarboxylate, THF; (iv) *i*-PrOH, H_2, EtOH; (v) NaN_3, NH_4Cl, EtOH; (vi) H_2, Pd/C.

envisioned to give the targeted stereoisomer **1**.

Reaction of 3-chlorocyclopentene (**6**)[7] with sodium phenoxide under homogeneous reaction conditions in dimethylformamide[10] provided the O-alkylated starting material **7** in 73% yield. However, epoxidation of **7** with 3-chloroperbenzoic acid (MCPBA) under a variety of reaction conditions provided approximately a three to one mixture of the *trans*- and *cis*-epoxides **8** and **9**, respectively. Even though these epoxides were separable by HPLC, the method was unsatisfactory as a general route to *trans*-2-(aryloxy)-6-oxabicyclo[3.1.0]hexanes, since definitive structural assignments were not possible by ^1H NMR. Consequently, an unambiguous synthesis of **8** was developed, starting with *cis*-6-oxabicyclo[3.1.0]cyclohexan-2-ol (**10**). The starting material, epoxide **10**, was synthesized from 3-chlorocyclopentene (**6**) by reported methods. The allylic halide **6** was treated with aqueous sodium bicarbonate to provide 2-cyclopenten-1-ol,[11] which was epoxidized by the method of Sharpless.[12,13] A one-step photochemical synthesis of this material from cyclopentene has recently been published.[14] Treatment of the *cis*-epoxy alcohol **10** with phenol under Mitsunobu conditions[15] gave the desired *trans*-phenoxy epoxide **8**, exclusively, in 80% yield. The C1 and C5 hydrogens on the epoxide carbons in the ^1H NMR spectra of **8** and **9** were now diagnostic for the cis and trans configurations of the products, a distinction which proved valuable in the structural assignment of analogues (see below). These two hydrogens in the *trans*-epoxide **8** appear as a singlet at δ 3.55 ($CDCl_3$) whereas these hydrogens appear as a doublet (C5–H) and as a doublet of doublets (C1–H) in the *cis*-epoxide **9**.

Scheme II[a]



[a] (i) 4-NO_2PhCOCl, NEt_3, THF; (ii) $SOCl_2$, 40 °C; (iii) 5 N HCl, glyme; (iv) acetone, $PhCH_3$, then $NaCNBH_3$.

The *trans*-epoxide **8** was readily opened regiospecifically, as shown by HPLC and NMR, with isopropylamine to give the desired *trans*-2-(isopropylamino)-*trans*-5-phenoxycyclopentanol (**1c**). The preparation of the primary amine **1a** was accomplished by opening the epoxide with sodium azide followed by catalytic reduction of the resulting azide **11**.

The inversion of the hydroxyl group in **1** was envisaged as the pathway to the all-cis isomer **2**.[16] The required transformation was satisfactorily achieved by the treatment of the (4-nitrobenzoyl)amide **12** with thionyl chloride at 40 °C for 2 h (see Scheme II). The progress of oxazoline ring formation was monitored by ^1H NMR. The position and splitting pattern of the methine hydrogen on the carbon bearing the hydroxyl group was diagnostic of the extent of reaction. The crystalline oxazoline **13** was readily isolated in 80–93% yield. Subsequent hydrolysis of the oxazoline group gave the desired amine **2a**.

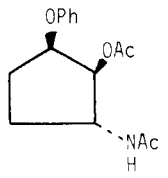
This material, **2a**, was converted to the isopropylamine **2c** by utilizing the procedure of Borch.[17] On treatment of **2a** with excess acetone in DMF a crystalline intermediate was isolated which was assigned the oxazolidine structure (see Scheme II) on the basis of the ^1H NMR spectrum. The isopropylidine methyl groups appeared at δ 1.28 and 1.45. This intermediate was readily reduced to the desired product **2c** with sodium cyanoborohydride.

An unequivocal synthesis of diastereomer **3** proved to be the most challenging. Only after extensive investigation was a satisfactory route developed. In the first approach, an S_N2 inversion of the hydroxyl group with an activated form of the trans-cis cyclopentyl amide **22** was envisaged as a convenient route. To examine this approach, **22** was treated with *p*-toluenesulfonyl chloride in pyridine.

Attempts to invert the hydroxyl group of the tosylate of **22** by the procedures of Corey[18] utilizing excess tetrabutylammonium formate in acetone–HMPA, even at 65 °C,[19] or of Liotta[20] or Durst[21] utilizing potassium acetate in the presence of 18-crown-6 [CH_3CN–Me_2SO (4:3), 95 °C] did not lead to any detectable amounts of the desired product **14**.

Stereospecific methods were then sought to prepare the *cis*-epoxide **9** since it was predicted that regiospecific attack of the epoxide group in **9** by amine nucleophiles would

(10) House, H. D. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972, pp 520–521.
(11) Alder, K.; Flock, F. *Chem. Ber.* **1956**, *89*, 1732.
(12) Itoh, T.; Jitsukowa, K.; Kaneda, K.; Terarishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.
(13) Sharpless, B. *Aldrichchimica Acta* **1979**, *12*, 63.
(14) Mihelich, E. D. U.S. Patent 4 345 894, 1979; private communication.
(15) Mitsunobu, O. *Synthesis* **1981**, 1.
(16) See, for example; Horton, D. In "The Amino Sugars 1a"; Jeanloz, R., Ed.; Academic Press: New York, 1976.
(17) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(18) Corey, E. J.; Terashima, S. *Tetrahedron Lett.* **1972**, 111.
(19) White, J. D.; Fukuyama, Y. *J. Am. Chem. Soc.* **1979**, *101*, 226.
(20) Liotta, C. L.; Harris, H. P.; McDermott, M.; Gonzalez, T.; Smith, K. *Tetrahedron Lett.* **1974**, 2417.
(21) Durst, H. D. *Tetrahedron Lett.* **1974**, 2421.



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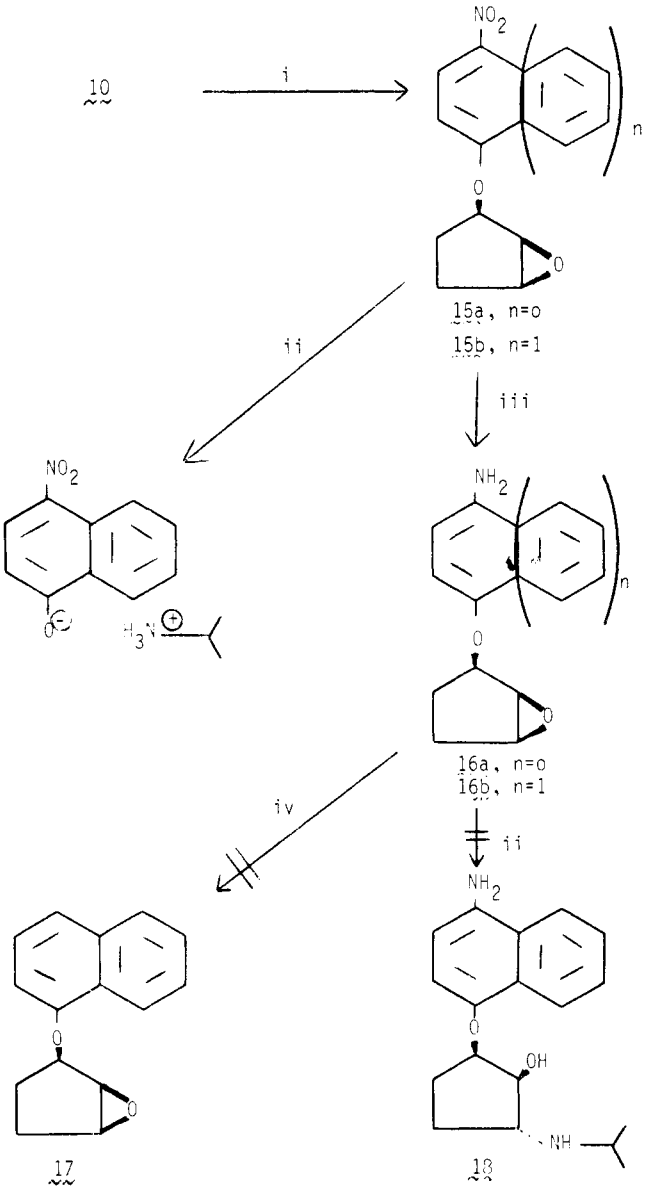
occur to give the desired isomer **3**. It should be noted that **9** was subsequently isolated as the minor component from the epoxidation of 3-phenoxycyclopentene (**7**), albeit by a cumbersome procedure. Since MCPBA gave predominant trans epoxidation of the phenoxy olefin **7**, the reaction of bromine–water[22] or variations thereof with **7** followed by base treatment of the intermediate bromohydrin was predicted to give the desired *cis*-epoxide **9**. However, this sequence gave as the major product the *trans*-epoxide **8** (see Scheme I). Similar results have been noted with 3-methoxycyclohexene,[23] and it was proposed that the ether oxygen was complexing with the bromonium ion, directing the electrophile to the same side of the ring as oxygen, leading to the trans-epoxide on treatment with base.

In an attempt to circumvent this difficulty, the aromatic moiety was introduced after the stereochemistry at the three adjacent centers was established and the epoxide was in place. The premise for this approach was that the anion of the resulting cis epoxy alcohol **10** could be used as a stable nucleophile to attack an activated haloaromatic system and provide the *cis*-epoxide **9**. The halogen of 4-nitro-1-fluorobenzene or 1-fluoro-4-nitronaphthalene (see Scheme III) was readily displaced by the anion of **10**, which was generated with potassium hydride. A solution of the anion in THF was added to a solution of the activated halogenated aromatic compound in either THF or Me_2SO at 40–50 °C. The reactions were essentially instantaneous as judged by TLC analysis and the resulting *cis*-(aryloxy)cyclopentene epoxides, **15a** and **15b**, were isolated in good yields. It should be noted that the ^1H NMR spectra were similar to that recorded for **9**.

Attempts to open the epoxide of the [(4-nitronaphthyl)oxy] epoxide **15b** with isopropylamine in ethanol at reflux resulted in the loss of the aryl group.[24] The only product isolated was the isopropylammonium salt of 4-nitro-1-naphthol. The aromatic nitro groups on epoxides **15a** and **15b** were selectively reduced to the amines **16a** and **16b**, respectively. However, attempts to open the epoxide of the naphthylamine **16b** with isopropylamine with the aim of producing **18** gave a multicomponent mixture as judged by TLC. Similar results were observed when the procedure of Doyle[25] (*t*-BuON=O in DMF) was used with the objective of forming **17** by replacing the aromatic amine on **16b** with hydrogen.

Therefore, attention was centered on activating the phenyl ring for nucleophilic attack in a different manner. The method of Semmelhack,[26] using (π-chlorobenzene)-

Scheme III[a]



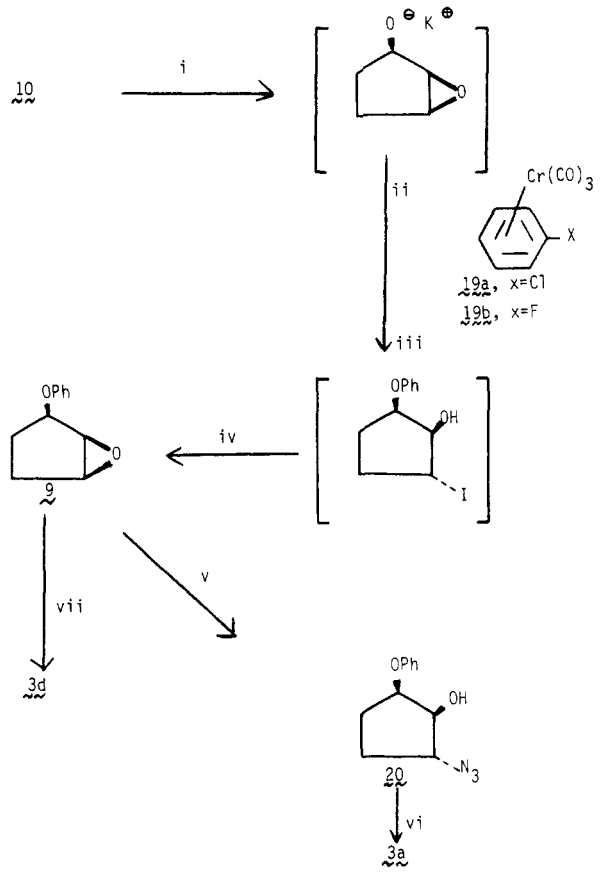
[a] (i) KH, THF, then 1-F-4-NO_2Ph for **15a** or 1-F-4-NO_2-naphthalene for **15b**; (ii) *i*-$PrNH_2$, EtOH; (iii) PtO_2, H_2, EtOAc; (iv) *n*-BuON=O, DMF.

chromium tricarbonyl (**19a**) or the corresponding fluorobenzene complex **19b** to activate the aromatic ring for the phenylation of anions has been reported with both amine and oxygen nucleophiles.[27,28] This route provided a facile method for the preparation of the desired ether **9**. The anion of **10** in THF was added to a THF solution of the chromium carbonyl complex **19a** or **19b** at 45 °C (Scheme IV). The nucleophilic displacement of the halogen was essentially instantaneous in both cases. The chromium carbonyl complex of the product was decomposed with iodine which caused concomitant opening of the epoxide to an iodohydrin. Treatment of the iodohydrin with ethanolic potassium hydroxide regenerated the epoxide in an overall yield of 85% from **19b**.

The important synthetic step of opening the epoxide **9** with amines proved to be less facile than in the case of the *trans*-epoxide **8**. A marked difference in the rate of re-

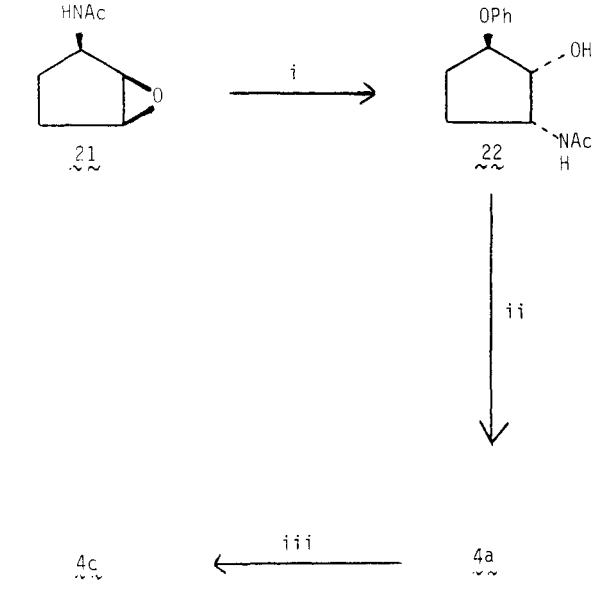
(22) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; pp 432–436.
(23) Cambie, R. C.; Rutledge, P. S.; Smith-Palmer, T.; Woodgate P. D. *J. Chem. Soc., Perkin Trans. 1* **1978**, *99*, 7.
(24) A referee suggested the use of the excellent procedure of: Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208. We have found the method of Overman (Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195) very useful for opening epoxides with amines for analogues of compounds reported herein (unpublished results). However, on treatment of an analogous electron-poor aromatic epoxide with NaN_3/NH_4Cl in warm EtOH, we observed the loss of the aryloxy group (i.e., 3-cyano-2-pyridyloxy).
(25) Doyle, M. P.; Dellaria, J. F., Jr.; Siegfried, B.; Bishop, S. W. *J. Org. Chem.* **1977**, *42*, 3494.
(26) Semmelhack, M. F.; Hall, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7091.
(27) Nicholls, B.; Whiting, M. C. *J. Chem. Soc.* **1959**, 551.
(28) Bunnett, J. F.; Hermann, H. *J. Org. Chem.* **1971**, *36*, 4081.

Scheme IV[a]



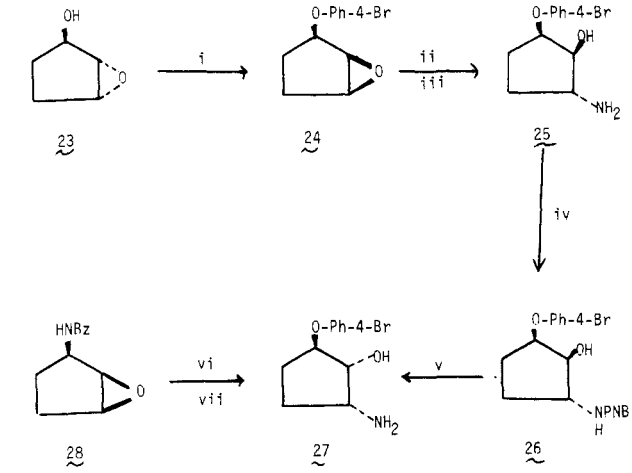
[a] (i) KH, THF; (iii) I_2, THF; (iv) KOH, EtOH, H_2O; (v) NaN_3, NH_4Cl, EtOH; (vi) Pd/C, H_2; (vii) *i*-$PrNH_2$, 1 equiv of HCl, EtOH.

Scheme V[a]



[a] (i) PhO^-Na^+, DMF, 100 °C; (ii) 3 N HCl; (iii) acetone, $NaCNBH_3$.

Scheme VI[a]



[a] (i) 4-BrPhOH, Ph_3P, diisopropylazodicarboxylate; (ii) NaN_3, NH_4Cl; (iii) Ph_3P, pyridine, then NH_4OH; (iv) 4-$NO_2PhCOCl$ (PNBCl), Et_3N; (v) $SOCl_2$, then 5 N HCl, glyme; (vi) 4-BrPhOH, $PhCH_3$, aqueous KOH, $PhCH_2NEt_3^+Cl$; (vii) $HOCH_2CH_2OH$, KOH, H_2O.

action was observed using 1 equiv of tryptamine as the nucleophile in ethanol at reflux. The reaction with the *trans*-epoxide **8** was complete, in 24 h, as judged by TLC, and the product **1e** (R = tryptamino) was isolated in 80% yield. However, in the case of the *cis*-epoxide **9**, the reaction was still not complete after 72 h, and the product (**3e**, R = tryptamino) was isolated in only 53% yield. The addition of an acid catalyst facilitated the opening of the epoxide **9**. Thus the reaction of **9** with isopropylamine in ethanol with 1 equiv of hydrogen chloride provided **3d** in 48% isolated yield after 40 h at reflux. Without the acid catalyst, the reaction with isopropylamine was extremely slow. It should be noted that the opening of the trans-phenoxy epoxide **8** with isopropylamine provided an 88% isolated yield of **1c** after 20 h reaction time without an acid catalyst. The primary amine **3a** was readily obtained by opening the epoxide with sodium azide (with NH_4Cl) followed by catalytic reduction (Scheme IV).

The route chosen for the preparation of diastereomer **4** required the phenoxide anion to act as a nucleophile for the opening of the *cis*-acetamide epoxide **21** (prepared from 3-chlorocyclopentene by the procedure of Vince and Daluge[29]). The poor nucleophilicity of the phenoxide anion caused some initial concern as to the success of this approach. However, treatment of this epoxide with phenol in DMF at 100 °C gave the desired product **22** in satisfactory yield (see Scheme V). The removal of the amide blocking group was readily accomplished with refluxing 3 N hydrochloric acid–methanol providing **4a**. The isopropylamino derivative **4c** was obtained by treatment of **4a** with Borch's reagent[17] in the presence of excess acetone.

The X-ray structure of the 4-bromophenoxy analogue of **4a**, *cis*-2-amino-*trans*-5-(4-bromophenoxy)cyclopentanol (**27**) was obtained (see ORTEP drawing in Figure 1, supplementary material). This compound was prepared by two alternative methods (see Scheme VI). The *cis*-benzamide epoxide **28**[29] was treated with 4-bromophenol at 80 °C in an aqueous caustic toluene two-phase system with a phase-transfer catalyst, to provide **27** after the removal of the benzamide blocking group. Alternatively, Mitsunobu inversion[15] of the hydroxyl group in **23** with 4-bromophenol provided *cis*-4-bromophenoxy epoxide **24**. Regiospecific opening of the epoxide with sodium azide was accomplished as with **9**. The azide was reduced to the amine **25** by the Staudinger reaction[30,31] using triphenyl-

(29) Vince, R.; Daluge, S. *J. Med. Chem.* **1974**, *17*, 578.

(30) Lin, T.; Prusoff, W. H. *J. Med. Chem.* **1978**, *21*, 106.

(31) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763.

Table I. ^{1}H NMR Data[a] for the 2-Amino-5-phenoxycyclopentanols 1a–4a

	δ			couplings, Hz	
isomer	H_5	H_1	H_2	$J_{1,5}$	$J_{1,2}$
1a	4.49	3.86	3.10	5.3	7.4
2a	4.62	4.00	3.28	4.4	4.6
3a	4.66	3.70	3.38	5.2	7.5
4a	4.62	3.91	3.53	<1	4.9

[a] In $CDCl_3$ solution, obtained on a Varian Model XL-300 spectrometer.

Table II. Dihedral Angles (Φ) for *cis*-2-Amino-*trans*-5-(4-bromophenoxy)cyclopentanol (27) Calculated from the X-ray Structure and Obtained from a Karplus Plot of the ^{1}H NMR ($CDCl_3$, 300 MHz) Coupling Constants

	Φ calcd from	
bonds	NMR	X-ray
H5–C5–C1–H1	−110°	−108°
H5–C5–C4–H4	35°	22°
H5–C5–C4–H4′	150°	142°
H3–C3–C2–H2	50°	52°
H3′–C3–C2–H2	155°	173°
H2–C2–C1–H1	−40°	−34°

phosphine/ammonium hydroxide. This route precluded concomitant hydrogenolysis of the aromatic bromine that resulted when catalytic hydrogenation (PtO_2) of the azide was attempted. Transformation of **25** to the 4-nitrobenzamide **26** and inversion of the hydroxyl group with thionyl chloride followed by removal of the oxazoline ring was accomplished as in the synthesis of **2a**. It should be noted that the 4-bromo amine **27** was converted to **4a** by hydrogenolysis of the bromine.

The 300-MHZ ^{1}H NMR chemical shift and coupling data for the three methine protons of the four isomeric 2-amino-5-phenoxycyclopentanols appear in Table I. The methine hydrogens on the hydroxyl-bearing carbon appear as a doublet of doublets for **1a–4a** which simplifies on irradiation of the methine on the phenoxy carbon. The coupling constant for this hydrogen is diagnostic for stereoisomers **2** and **4**. In the case of stereoisomers **1** and **3**, the coupling constants are very similar and it is assumed that the dihedral angles between the phenoxy methine hydrogen and the hydroxyl methine hydrogen are equal but opposite in direction. It should be noted that in the two isomers in which the isopropylamino group and the hydroxy group are cis (**2c** and **4c**), the isopropyl methyl groups appear as two sets of doublets in $CDCl_3$ (see Experimental Section). Intramolecular hydrogen bonding could hold the isopropylamino group in at least two distinct conformations. Addition of D_2O or CD_3OD causes the isopropyl methyl absorption to collapse to a doublet.

It is interesting to note that the solution conformation of **27** appears to be essentially identical with the crystal structure conformation (see Table II). The solution conformation was determined from the ^{1}H NMR (300 MHz) coupling constants, using the Karplus equation[32] to calculate the dihedral angles. The specific proton coupling constants were determined with the aid of homonuclear proton decoupling at the absorption frequency of each proton. The dihedral angles were taken from a Karplus plot of coupling constants vs. dihedral angles. These values were compared with the dihedral angles calculated from the single-crystal X-ray determination and the two sets of values are similar.

In conclusion, methods have been developed to introduce three contiguous hetero-substituted chiral centers stereospecifically in all four possible configurations on a cyclopentane ring. These methods provided stereospecific synthetic routes to the four diastereomeric 2-amino-5-phenoxycyclopentanols 1–4. The methodology developed has been shown to be applicable to a wide range of analogues of **1a–4a** and will be reported separately. In addition, the β-adrenergic receptor interaction of 1–4 is of interest and will be reported elsewhere.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 727B spectrophotometer and band positions were calibrated using polystyrene. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian EM-360 (60 MHz), Perkin-Elmer R-32 (90 MHz), and Varian XL-300 (300 MHz) spectrometers. All chemical shifts were reported in parts per million (δ units) from tetramethylsilane as an internal standard. Coupling constants were reported in hertz (Hz). For the 300-MHz ^{1}H NMR spectra of compounds **1a–4a**, the aromatic carbons were assigned as C6–C8 for the ortho, meta, and para positions. Thin layer chromatography (TLC) was performed on glass plates (5 × 10 cm) precoated with Silica Gel 60 F-254. Solvent systems (SS) used were SS1, $CHCl_3/CH_3OH$ (9:1), SS2, CH_2Cl_2, SS3, DMF/*i*-PrOH/NH_4OH (5:13:2), SS4, upper phase of EtOAc/*n*-PrOH/H_2O (4:1:2), SS5, $CHCl_3$/acetone (3:2), SS6, EtOAc/hexane (1:3), and SS7, EtOAc/MeOH (19:1). Components were observed under ultraviolet light or after staining with iodine vapor. Mass spectra were obtained on a Finnigan 4000 gas chromatograph–mass spectrometer. Elemental analyses were done by Steve Konopnicki, The Dow Chemical Co., Midland, MI. Gas chromatographic determinations were carried out on a Hewlett-Packard 5750 instrument equipped with a thermal conductivity detector and using a 8 ft × 0.125 in. column packed with 10% SE-52 on Chromasorb.

3-Phenoxycyclopentene (7). To a mixture of reagent grade DMF (3 L) and NaH (23.4 g, 0.975 mol) was added a solution of phenol (91.8 g, 0.975 mol) in DMF (40 mL) dropwise. After evolution of H_2 was complete, 3-chlorocyclopentene[7] (**6**) (96 g, 96 mL, 0.93 mol) was added to the reaction mixture over 30 min. The reaction was mildly exothermic and was kept below 25 °C with an ice bath. After stirring overnight at room temperature, the mixture was diluted with ethyl acetate (3 L) and water (3 L). The organic layer was washed with ice cold 1 N NaOH (6 × 1 L) and brine (500 mL) and dried (Na_2SO_4). The solvent was removed in vacuo yielding a light yellow oil, **7** (109 g, 73%), that could be used in the next experiment without further purification. Distillation of a portion of the product yielded a colorless oil: bp 77–80 °C (2.2 mm) [lit.[33] bp 78–88 °C (3 mm)]; ^{1}H NMR ($CDCl_3$) δ 1.5–2.9 (m, 4, CH_2CH_2), 5.27 (br d, 1, J = 5.5 Hz, C3–H), 5.97 (m, 2, olefin), 6.7–7.4 (m, 5, Ar).

***trans*-2-Phenoxy-6-oxabicyclo[3.1.0]hexane (8). Method A.** To a solution of the *cis*-epoxy alcohol **10** (3.0 g, 0.03 mol), phenol (4.2 g, 0.045 mol), and triphenylphosphine (9.4 g, 0.36 mol) in dry THF (60 mL) cooled in an ice bath under a nitrogen atmosphere was added isopropyl azocarboxylate (7.2 g, 0.036 mol) dropwise. The reaction temperature was kept below 20 °C during the addition and was then stirred at room temperature for 24 h. The light yellow solution was treated with 30% H_2O_2 (1.5 mL), diluted with ether, and washed with 20% aqueous $NaHSO_3$ (50 mL), 0.5 N NaOH (2 × 75 mL, ice cold), and brine (2 × 50 mL). The organic solution was dried ($MgSO_4$) and evaporated to an oil. The oil was diluted with ether (ca. 100 mL) and a few milliliters of hexane. Scratching induced crystallization of triphenylphosphine oxide. The filtrate was evaporated to an oil and purified by flash chromatography on silica gel (450 mL, 35 × 4 cm) using $CHCl_3$ as the solvent. The product 8 was obtained as

(32) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 281.

(33) British Patent 844312 (8110160) to Union Carbide; *Chem. Abstr.* **1961**, *55*, 17649g.

an analytically pure colorless oil (4.2 g, 79.5%) whose NMR spectra and TLC properties are identical with those of the product obtained in method B. The product can be distilled by Kugelrohr distillation: bp 90–100 °C (0.1 mm).

Method B. In a three-neck 2-L flask with overhead stirrer and thermometer was added 3-phenoxycyclopentene (7) (40 g, 0.25 mol) and CH_2Cl_2 (250 mL). The solution was cooled to 4 °C and a solution of ca. 85% 3-chloroperbenzoic acid (86 g) in CH_2Cl_2 (750 mL) was added dropwise. The reaction was stirred for 15 h, slowly warming to room temperature. The mixture was cooled in an ice bath and the precipitate was collected by filtration and washed with cold CH_2Cl_2 (75 mL). The light yellow filtrate was washed with an aqueous solution (500 mL) of Na_2SO_3 (60 g), ice cold 1 N NaOH (2 × 250 mL), and brine (100 mL). The colorless organic layer was dried (Na_2SO_4) and evaporated to ar. oil (41.8 g). The light yellow oil was dissolved in 150 mL of CH_2Cl_2/hexane (1:1) and purified on a Waters Prep LC/system 500 using two Prep PAK 500/silica cartridges. Integration of the peaks indicated a 74:26 ratio of two epoxides. The first fraction yielded 25 g (56%) of colorless epoxide 8: ^1H NMR ($CDCl_3$) δ 1.5–2.2 (m, 4, CH_2CH_2), 3.55 (s, 2, Cl–H, C5–H), 4.75 (d, 1, J = 3 Hz, C2-H), 6.65–7.4 (m, 5, Ar).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 75.0; H, 6.85.

***cis*-2-Phenoxy-6-oxabicyclo[3.1.0]hexane (9). Method A.** The second fraction obtained in the above procedure yielded 7.8 g (17.7%) of epoxide **9** as white crystals, mp 58–60 °C, identical with the product prepared by method B.

Method B. To a dry 500-mL three-neck flask with septum, Firestone valve, and football stirrer, which had been flushed with N_2, was added 17.7 g (0.1 mol) of 22.5% KH (oil dispersion). The KH was washed with pentane (3 × 50 mL) and anhydrous THF (200 mL, O_2 free) was added via syringe. The mixture was cooled in an ice bath and the epoxy alcohol **10** (10 g, 0.1 mol) dissolved in dry O_2-free THF (25 mL) was added dropwise (<10 °C). The light brown solution was immediately added via a Flex-needle to a second three-neck 500-mL flask under N_2 containing a solution of the chromium tricarbonyl complex of fluorobenzene **19b** (23.2 g, 0.1 mol) and THF (100 mL) preheated to 45 °C. The reaction temperature was maintained at 45 °C by the addition of the anion. The reaction was monitored by TLC (SS1) and was found to be instantaneous. The reaction was transferred to an Erlenmeyer flask and cooled in an ice bath and the chromoum complex was decomposed with excess I_2 (ca. 30 g) dissolved in THF. After gas evolution ceased, I_2 addition was stopped and the greenish solution was diluted with ether (100 mL) and extracted with an aqueous solution (700 mL) of Na_2SO_3 (100 g). The aqueous layer was extracted with ether (3 × 500 mL). The combined ether layers were washed with brine (200 mL), dried with Na_2SO_4 and Celite overnight, and evaporated to a light yellow oil (17.5 g). The oil was treated with a water–ethanol–KOH solution (75 mL, 450 mL, 15 g) at room temperature for 15 h. The solution was diluted with brine and extracted with $CHCl_3$ (3 × 300 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to a light yellow oil. Kugelrohr distillation gave **9**: bp 120–140 °C (0.1 mm) (7.2 g, 85%) as white crystals; mp 55–58 °C; ^1H NMR ($CDCl_3$) δ 1.1–2.3 (m, 4, CH_2CH_2), 3.42 (d, 1, $J_{5,1}$ = 3 Hz, C5–H), 3.6 (dd, 1, $J_{1,5}$ = 3, $J_{1,2}$ = 1.5 Hz, C1–H), 4.7 (ddd, $J_{2,1}$ = 1.5, J = 7, J = 7 Hz, C2–H), 6.65–7.35 (m, 5, Ar), irradiation at 4.7 simplified the dd at 3.6 to a d, $J_{1,5}$ = 3 Hz.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.87. Found: C, 74.9; H, 7.19. The reaction was run by the same procedure using the chromium carbonyl complex of chlorobenzene **19a**. The epoxide **9** was isolated in 60% yield.

***cis*-6-Oxabicyclo[3.1.0]cyclohexan-2-ol (10).** A 5.1 M solution of *tert*-butyl hydroperoxide in benzene was prepared by the procedure of Sharpless[13] substituting benzene for 1,2-dichloroethane. The reagent was titrated by the procedure in footnote 58 of ref 13. In a dry four-neck 100-mL flask with football stirrer, 50-mL dropping funnel, thermometer, septum, and N_2 inlet Firestone valve was added 2-cyclopenten-1-ol[11] (8.4 g, 0.1 mol), dry benzene (10 mL), and vanadyl acetylacetonate (150 mg, 0.57 mmol). The 5.1 M *tert*-butyl hydroperoxide (30 mL, 0.153 mol) was placed in the dropping funnel and the system was flushed with nitrogen. The reaction flask was placed in a 40 °C oil bath and the *tert*-butyl hydroperoxide was added over 15 min. The reaction warmed to 80 °C and refluxed briefly (cooled with a water bath). After 15 min, the reaction was cooled to 40 °C and was reheated in the 40 °C oil bath until GC analysis indicated an essentially complete reaction (5 h). The workup procedure of Dehnel[34] was used. The reaction mixture was cooled and extracted with water (4 × 25 mL). The combined water layers were saturated with NaCl and extracted with $CHCl_3$ (10 × 50 mL). The combined $CHCl_3$ layers were dried (Na_2SO_4) and evaporated in vacuo to an oil (16 g). Distillation provided 5.7 g (57%) of **10**: bp 43–48 °C (0.05 mm) [lit.[12] bp 38 °C (1.0 mm)]; ^1H NMR ($CDCl_3$) δ 1.0–2.3 (m, 4, CH_2CH_2), 3.3 (s, 1, OH, D_2O exchangeable), 3.47 (s, 2, epoxide), 4.23 (t, 2, J = 7 Hz, C2–H), identical with the reported spectrum.[34]

***trans*-2-Azido-*trans*-5-phenoxycyclopentanol (11).** *trans*-2-Phenoxy-6-oxabicyclo[3.1.0]hexane (8, 10 g, 0.057 mol) was dissolved in ethanol (100 mL). Sodium azide (10 g, 0.154 mol) and ammonium chloride (1.37 g, 0.025 mol) were dissolved in warm water (25 mL) and this solution was added to the ethanol solution. The reaction was refluxed under N_2 and was monitored by TLC (SS2). After it was refluxed for 16 h, the reaction was diluted with brine and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and evaporated to a yellow oil (12.4 g, 100%). TLC showed one spot with a lower R_f than 8. The oil was dissolved in a small volume of CH_2Cl_2 and filtered through a column of silica gel (75 g) using the same solvent. The fraction (ca. 600 mL) containing product was evaporated to a colorless oil (10.8 g, 87%): IR (thin film) 3375 (br), 2100 (s) cm^{-1}. The azide **11** was used immediately for the preparation of the amines **1a** and **1b**.

***trans*-2-Amino-*trans*-5-phenoxycyclopentanol (1a).** The hydroxy azide **11** was hydrogenated as in the preparation of **1b** with the exclusion of HCl yielding the amine **1a** which crystallizes from water: mp 99–100 °C; ^1H NMR ($CDCl_3$, 300 MHz), δ 1.54 (m, C3–H), 1.78 (m, 1, C4–H), 2.01 (m, 1, C3′–H), 2.20 (m, 1, C4′–H), 2.3 (br s, 3, OH and NH_2, exchange with D_2O), 3.10 (ddd, 1, C2–H), 3.86 (dd, 1, $J_{1,5}$ = 5.3, $J_{1,2}$ = 7.4 Hz, C1–H), 4.49 (ddd, 1, C5–H), 6.90 (d, 2, C6–H), 6.93 (dd, 1, C8–H), 7.27 (dd, 2 $J_{7,6}$ = 7.7, $J_{7,8}$ = 7.9 Hz, C7–H).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.12; H, 7.63; N, 7.34.

***trans*-2-Amino-*trans*-5-phenoxycyclopentanol Hydrochloride (1b).** The hydroxy azide **11** (10.8 g 0.049 mol) was dissolved in ethanol (150 mL) and 5% Pd/C (1 g) and concentrated hydrochloric acid (10 mL) were added. The mixture was hydrogenated at 55 psi for 16 h. The catalyst was removed by filtration and the filtrate was evaporated to a white solid. The solid was recrystallized from isopropyl alcohol yielding analytically pure **1b** (7.55 g, 67%): mp 213–5 °C; ^1H NMR (Me_2SO-d_6) δ 1.45–2.45 (m, 4, CH_2CH_2), 3.3 (m, 1, C2–H), 4.15 (m, 1, C1–H), 4.5 (m, 1, C5–H), 5.9 (m, 1, OH, exchangeable), 6.7–7.45 (m, 5, Ar), 8.5 (br s, 3, NH_3^+).

Anal. Calcd for $C_{11}H_{15}NO_2HCl$: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.6; H, 6.90; N, 6.10.

***trans*-2-[(1-Methylethyl)amino]-*trans*-5-phenoxycyclopentanol (1c).** The *trans*-epoxide 8 (12.0 g, 0.068 mol) was treated with a mixture of ethanol (100 mL) and isopropylamine (29 mL, 0.34 mol) at reflux. The progress of the reaction was monitored by TLC (SS1). After 20 h, the reaction was evaporated in vacuo yielding a colorless oil that crystallized on standing (14.0 g, 88%), mp 90–96 °C. A sample was recrystallized from $CHCl_3$/hexane (2:1) to give analytically pure **1c**: mp 98.5–99 °C; ^1H NMR ($CDCl_3$) δ 1.05 (d, 6, J = 6.5 Hz, $(CH_3)_2CH$), 1.4–2.3 (m, 4, CH_2CH_2), 2.6–3.6 (m, 4, OH, NH, C2–H and $CH(CH_3)_2$, 3.95 (dd, 1, $J_{1,5}$ = 5, $J_{1,2}$ = 7 Hz, C1–H), 4.47 (ddd, 1, $J_{5,1}$ = 5, J = 4, J = 4 Hz, C5–H), 6.65–7.35 (m, 5, Ar); irradiation at 4.47 caused the dd at 3.95 to collapse to a d, J = 7 Hz.

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 9.00; N, 5.95. Found: C, 71.58; H, 8.95; N, 6.05.

***trans*-2-[(1-Methylethyl)amino]-*trans*-5-phenoxycyclopentanol Hydrochloride (1d).** A 3-g portion of **1c** was dissolved in isopropyl alcohol (25 mL) and treated with HCl gas yielding

(34) Dehnel, R. B.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 953.

white crystals of **1d** (2.5 g): mp 243–244.5 °C; ^{1}H NMR (Me_2SO-d_6–D_2O) δ 1.3 (d, 6, J = 6 Hz, $CH(CH_3)_2$), 1.5–2.45 (m, 4, CH_2CH_2), (C_2 proton buried under solvent), 4.27 (dd, 1, J = 5, J = 6.5 Hz, C1–H), 4.55 (m, 1, C5–H), 6.7–7.5 (m, 5, Ar).

Anal. Calcd for $C_{14}H_{21}NO_2$·HCl: C, 61.9; H, 8.16; N, 5.15. Found: C, 62.02; H, 8.20; N, 5.20.

***N*-(*trans*-2-Hydroxy-*cis*-3-phenoxycyclopentyl)-4-nitrobenzamide (12).** To a solution of cyclopentylamine **1a** (3.86 g, 0.02 mol) in THF (75 mL), triethylamine (2.02 g, 0.02 mol), and ether (75 mL) was added a solution of *p*-nitrobenzoyl chloride (3.72 g, 0.02 mol) in THF/ether (1:1) (25 mL) all at once. After 10 min, the white precipitate (5.6 g) containing **12** and Et_3N·HCl was removed by filtration and washed with ether. The filtrate was evaporated to dryness in vacuo and the resulting solid was triturated with ether and collected by filtration (3.5 g). The original 5.6 g of material was added to water (100 mL), stirred for 15 min, collected by filtration, and combined with the second 3.5-g crop of product. Recrystallization of the combined product from ethanol gave analytically pure **12** (5.15 g, 75%): mp 204–206 °C; IR (Nujol) 3310, 1640, 1600, 1550, 1520 cm^{-1}; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6), 1.6–2.5 (m, 4, CH_2CH_2), 4.2 (m, 2, C1–H and C2–H), 4.58 (m, 1, C3–H), 5.25 (d, 1, J = 3 Hz, OH), 6.7–7.5 (m, 5, Ar), 8.22 (2 AB doublets, 4, J = 9.5 Hz, 4-NO_2 Ar).

Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30 N, 8.18. Found: C, 63.00; H, 5.15; N, 7.92.

***cis*-3-(4-Nitrophenyl)-8-phenoxy-2-oxa-4-azabicyclo[3.3.0]oct-3-ene Hydrochloride (13).** To a dry two-neck 15-mL round bottom with stirring bar, N_2 bubbler, and thermometer was added the (*p*-nitrobenzoyl)amide **12** (1.0 g, 2.9 mmol) and $SOCl_2$ (10 mL) (freshly distilled from $P(OPh)_3$). The light yellow solution was heated at 40 °C and the progress of the reaction was monitored by ^{1}H NMR. Me_4Si was added to a small aliquot of the reaction solution and the position and coupling of the cyclopentyl hydrogen on the phenoxy carbon was monitored. This hydrogen at 5 min reaction time was observed as a clean d of d at δ 5.6 which became a multiplet at δ 5.8 after 2 h. The reaction was poured into anhydrous ether (125 mL) under N_2 with overhead stirring. After 30 min, the fine light yellow precipitate of **13** was collected on a sintered glass funnel and washed with ether (0.85 g, 80%): mp 138–140 °C; IR (Nujol) 2350 (br), 1655, 1600, 1590, 1535, 1460, 1390 cm^{-1}; MS (CI/CH_4), m/e 325 (MH^+). On a larger scale, starting with 25 g (0.073 mol) of **12**, the yield of **13** was 93%, mp 135–140 °C.

***cis*-2-Amino-*cis*-5-phenoxycyclopentanol (2a) and the Hydrochloride 2b.** The oxazoline **13** (3.9 g, 10.8 mmol) was treated at reflux with glyme/5 N HCl (25:75 mL) for 24 h. The reaction was cooled in an ice bath and the white solid, mp 235–238 °C (*p*-nitrobenzoic acid, as determined by TLC) (1.7 g, 95%), was removed by filtration and washed with a small volume of water. The filtrate was evaporated in vacuo to a light pink crystalline solid. The crystals of **2b** were triturated with ether and collected by filtration (2.1 g, 85%), mp 214–216 °C. Recrystallization from isopropyl alcohol (ca. 75 mL) gave analytically pure **2b** (1.70 g): mp 216–217 °C; IR (Nujol) 3325, 3250 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.9 (br, s, 4, CH_2CH_2), 3.5 (m, 1, C_2–H), 4.23 (m, 1, C1–H), 5.68 (m, 1, OH), 6.7–7.4 (m, 5, Ar), 8.2 (br, s, 3, NH_3^+), (Me_2SO-d_6–D_2O) δ 4.25 (t, J = 4 Hz, C1–H); MS (CI/CH_4), m/e 194 (MH^+, base peak).

Anal. Calcd for $C_{11}H_{15}NO_2$·HCl: C, 57.51; H, 7.02, N, 6.10. Found: C, 57.62; H, 6.85; N, 5.97.

The free base **2a** crystallized from basic aqueous solution: mp 94–96 °C (toluene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69 (m, 1, C3–H), 1.92–2.16 (m, 3, C4,4'– and 3'–H), 2.29 (br s, 3, OH and NH_2), 3.28 (m, 1, C2–H), 4.00 (dd, 1, $J_{1,5}$ = 4.4, $J_{1,2}$ = 4.6 Hz, C1–H), 4.62 (ddd, 1, C5–H), 6.29 (d, 2, C6–H), 6.94 (dd, 1, C8–H, 7.27 (dd, 2, $J_{7,8}$ = 7.5, $J_{7,6}$ = 7.6 Hz, C7–H).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.2; H, 7.75; N, 7.12.

***cis*-2-[(1-Methylethyl)amino]-*cis*-5-phenoxycyclopentanol (2c) and the Hydrochloride 2d.** A mixture of the all cis amine **2a** (2.3 g, 10 mmol), acetone (10 mL), dry DMF (50 mL), and 4-Å molecular sieves (ca. 5 mL) was stirred at room temperature under a N_2 atmosphere for 3 days. TLC (SS2) indicated that no starting material was present. The colorless mixture was filtered through a Celite pad and the sieves were washed with toluene. The filtrate was evaporated in vacuo (oil pump) to a light yellow oil that crystallized on standing (2.6 g): ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3, CH_3), 1.45 (s, 3, CH_3), 1.6–2.2 (m, 4, CH_2CH_2), 3.85 (m, 1, C2–H), 4.35 (m, 2, C5–H, C1–H), 4.35 (m, 2, C5–H, C1–H), 6.7–7.3 (m, 5, Ar). The crystals were dissolved in methanol (100 mL) and $NaCNBH_3$ (1.0 g, 16 mmol) was added. The reaction was stirred at room temp for 15 h, concentrated in vacuo, and dissolved in methanol/water (1:1) (20 mL) and ice cold 5 N NaOH was added (20 mL). The mixture was extracted with EtOAc (4×75 mL) and the combined EtOAc layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to a white solid. Recrystallization from cyclohexane resulted in shiny white crystals of **2c** (1.0 g, 42%): mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (two sets of d of equal intensity separated by 4 Hz, 6, J = 6 Hz, $CH(CH_3)_2$), 1.4–2.2 (m, 4, CH_2CH_2), 2.5 (br, s, 2, exchangeable), 2.87 (septet, 1, J = 6 Hz, $CH(CH_3)_2$), 3.13 (ddd, 1, $J_{2,1}$ = 5, J = 1, J = 11 Hz, C2–H), 4.05 (dd, 1, $J_{1,2}$ = 5 Hz, C1–H), 4.58 (ddd, 1, $J_{5,1}$ = 4, J = 6, J = 6 Hz, C5–H), irradiation at 4.05 simplifies this ddd to a dd, J = 6 Hz), 6.8–7.4 (m, 5, Ar); ^{1}H NMR ($CDCl_3$–CD_3OD) δ 1.07 (d, 6, J = 6 Hz, *i*-Pr), 4.1 (t, 1, J = 4 Hz, C1–H).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.48; H, 9.00; N, 5.96. Found: C, 71.6; H, 8.99; N, 5.93.

The free base **2c** (500 mg) was converted into the hydrochloride salt **2d** (570 mg) by treatment with excess THF–HCl: mp 224–225 °C; ^{1}H NMR (Me_2SO-d_6) δ 4.37 (t, 1, J = 4 Hz, C1–H).

Anal. Calcd for $C_{14}H_{21}NO_2$·HCl: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.6; H, 8.10; N, 5.31.

***cis*-2-(4-Nitrophenoxy)-6-oxabicyclo[3.1.0]hexane (15a).** In a 100-mL 3-neck flask with rubber septum, thermometer, and Firestone valve was added KH (4.5 g of a 20% oil dispersion, 0.02 mol) (washed 3× with pentane) and dry THF (50 mL, via syringe). The mixture was cooled in an ice bath and the epoxide **10** (3.2 g, 0.02 mol) was added via syringe at a rate such that the temperature did not rise above 25 °C. After H_2 evolution had ceased (5 min), the solution of the resulting anion was added via cannula to a solution of 1-fluoro-4-nitrobenzene (2.82 g, 0.02 mol) in dry Me_2SO (25 mL) that had been heated to 50 °C under N_2. The dark solution was stirred overnight at room temperature, diluted with brine (100 mL), and extracted with ether (3 × 75 mL). The combined light yellow organic layer was washed with brine (75 mL), dried (Na_2SO_4), and evaporated leaving a light yellow crystalline solid (4.7 g). The product was recrystallized from ethanol (40 mL) giving analytically pure **15a** (3.0 g, 68%): mp 128.5–130 °C; ^{1}H NMR ($CDCl_3$) δ 1.2–2.5 (m, 4, CH_2CH_2), 3.55 (d, 1, $J_{5,1}$ = 3 Hz, C5–H), 3.7 (d with fine splitting, 1, $J_{1,5}$ = 3 Hz, C1–H), 4.9 (t with fine splitting, 1, J = 7 Hz, C2–H), 6.97 (d, 2, J = 9.5 Hz, Ar), 8.15 (d, 2, J = 9.5 Hz, Ar).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.3; H, 5.00; N, 5.15.

***cis*-4-[(6-Oxabicyclo[3.1.0]hex-2-yl)oxy]benzenamine (16a).** A 3.0 g (0.0135 mol) quantity of the nitro epoxide **15a** was dissolved in EtOAc. Platinum oxide (300 mg) was added and the mixture was shaken with H_2 at 25 psi. Within 5 min, the reaction had adsorbed 118% theoretical amount. TLC (SS1) showed a single slow moving spot (R_f 0.1) that stained dark brown with I_2 vapor. The catalyst was filtered and the filtrate was evaporated in vacuo to a light tan oil **16a** (3 g): ^{1}H NMR ($CDCl_3$) δ 1.2–2.4 (m, 4, CH_2CH_2), 3.4 (d, 1, $J_{5,1}$ = 3 Hz, C5–H), 3.6 (br s, 3, NH_2 and C1–H, addition of D_2O causes exchange of the NH_2 leaving a d with fine splitting, 1, $J_{1,5}$ = 3 Hz, C1–H), 4.52 (t, 1, J = 7 Hz, C2–H),6.55 (d, 2, J = 9 Hz, Ar), 6.8 (d, 2, J = 9 Hz, Ar).

***cis*-4-[(6-Oxabicyclo[3.1.0]hex-2-yl)oxy]naphthenamine (16b).** A 1.0 g (0.0037 mol) quantity of the nitro epoxide **15b** was dissolved in EtOAc (25 mL) and hydrogenated with PtO_2 (25 mg) as in the preparation of **16a**, providing a light tan oil (1.0 g): ^{1}H NMR ($CDCl_3$) δ 1.4–2.4 (m, 4, CH_2CH_2), 3.38 (d, 1, $J_{5,1}$ = 3 Hz, C5–H) 3.56 (d, with fine splitting, 1, $J_{1,5}$ = 3 Hz, C1–H), 3.85 (s, 2, NH_2), 4.6 (t, 1, J = 7 Hz, C2–H), 6.4–8.3 (m, 7, Ar).

(π-Chlorobenzene)chromium Tricarbonyl (19a). The procedure of Semmelhack[36] was followed. The reaction was heated at reflux using a rotating steel wire to prevent clogging of the condenser. TLC (SS2 and SS5) showed essentially complete reaction of the $Cr(CO)_6$ after 4 days. The product, **19a**, was

(35) Steyn, R.; Sable, H. Z. *Tetrahedron* **1971**, *27*, 4429.
(36) Semmelhack, M. F.; Seufert, W.; Keller, L. *J. Am. Chem. Soc.* **1980**, *102*, 6584, ref 7 and 8.

isolated in 99% yield and was stored under nitrogen, mp 98–100 °C (lit.[27] mp 102–103 °C).

(π-Fluorobenzene)chromium Tricarbonyl (19b). This compound was prepared by the above procedure. The reaction was heated at reflux for 3 weeks providing 72% yield of yellow crystalline **19b**, mp 112–113 °C. A small sample was recrystallized from pentane yielding yellow needles, mp 115–117 °C (lit.[27] mp 122.5–124 °C).

***trans*-2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-*trans*-5-phenoxycyclopentanol (1e).** A solution of the *trans*-epoxide **8** (3.52 g, 0.02 mol), tryptamine (3.2 g, 0.02 mol), and EtOH (20 mL) was heated at reflux under N_2 and the progress of the reaction was monitored by TLC (SS1). After 24 h, the yellow solution was evaporated to dryness in vacuo and the resulting light yellow solid was crystallized from EtOH (5.4 g, 80%). Recrystallization from EtOH gave shiny white crystals of **1e** (4.3 g): mp 152–155 °C; ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 1.4–2.3 (m, 4, cyclopentyl CH_2CH_2), 2.93 (s, 4, CH_2CH_2), 3.0–3.1 (m, 1, partially covered, C2–H), 3.92 (dd, 1, $J_{1,5}$ = 4.7, $J_{1,2}$ = 6 Hz, C1–H), 4.45 (m, 1, C5–H), 6.75 (m, 10, Ar), 9.97 (br s, 1, NH), irradiation at 4.45 causes the dd at 3.92 to collapse to a d, J = 6 Hz.

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.8; H, 7.06; N, 8.33.

***trans*-2-[[2-(1*H*-Indol-3-yl)ethyl]amino]-*cis*-5-phenoxycyclopentanol (3e).** A solution of the *cis*-phenoxy epoxide **9** (1.76 g, 0.01 mol), tryptamine (1.6 g, 0.01 mol), and EtOH (15 mL) was heated at reflux under N_2. The progress of the reaction was monitored by TLC (SS1). After 3 days, TLC still indicated the presence of some unreacted starting materials; however, the light brown solution was evaporated to dryness in vacuo and dissolved in a small volume of $CHCl_3/CH_3OH$ (9:1). The solution was applied to a silica gel column (100 g) and eluted with the same solvent pair. The product was obtained as a light tan solid (1.8 g, 53.5%). Recrystallization from CH_3CN (ca. 15 mL) gave white crystals of **3e** (1.25 g): mp 111–113 °C, ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 1.2–2.3 (m, 4, cyclopentyl CH_2CH_2) 3.0 (s, 4, CH_2CH_2) 3.2 (q, 1, J = 7 Hz, C2–H), 3.9 (dd, 1, J = 5.7 Hz, C1–H), 4.6 (m, 1, C5–H), 6.8–7.7 (m, 10, Ar), 9.7 (br s, 1, NH).

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: (after drying at 100 °C for 3 h): C, 74.66; H, 7.26; N, 8.27.

***trans*-2-Azido-*cis*-5-phenoxycyclopentanol (20).** The *cis*-epoxide **9** (3.5 g, 0.02 mol) was treated with NaN_3 (3.5 g, 0.054 mol) and NH_4Cl (0.48, 0.009 mol) in EtOH (50 mL)–H_2O (8 mL) as in the preparation of **11**, affording 3.7 g (85%) of **20** as a clear yellow oil, homogeneous by TLC, which was used in the next experiment without further purification: IR (thin film) 3575, 3470, 2100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2–2.5 (m, 4), 2.7 (m, 1), 4.0 (m, 2), 4.6 (m, 1), 6.5–7.5 (m, 5).

***trans*-2-Amino-*cis*-5-phenoxycyclopentanol (3a) and the Hydrochloride Salt 3b.** The azide **20** (9.3 g, 0.042 mol), 5% Pd/C (900 mg), and EtOH (150 mL) were combined in a Parr bottle and hydrogenated at 50 psi. After 6 h, TLC (SS2) indicated complete reduction and the reaction mixture was filtered through a Celite pad. The filtrate was evaporated in vacuo to a white solid that was recrystallized from water (ca. 80 mL). The resulting white needles (5.6 g, 68%) of **3a** were collected by filtration: mp 123–125 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (m, 1, C3–H), 1.85 (m, 1, C4–H), 1.9 (br, s, 3, OH and NH_2), 2.02–2.23 (m, 2, C3′- and 4′-H), 3.38 (dd, 1, C2–H), 3.70 (dd, 1, $J_{1,5}$ = 5.2, $J_{1,2}$ = 7.5 Hz, C1–H), 4.66 (m, 1, C5-H), 6.90 (d, 2, C6–H), 7 (dd, 1, C8–H), 7.29 (dd, 2, $J_{7,6}$ = 7.3, $J_{7,8}$ = 7.9 Hz, 6.97.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.22; H, 7.60; N, 7.23.

The hydrogenation of the azide **20** was repeated as above with concentrated HCl added to the mixture, providing **3b** in 65% yield (from EtOH): mp 233–234.5 °C; ^{1}H NMR (Me_2SO-d_6–D_2O) δ 1.4–2.3 (m, 4, CH_2CH_2), 3.5 (m, 1, partially obscured by HDO, C2–H), 4.2 (dd, $J_{1,5}$ = 4.5, $J_{1,2}$ = 7.5 Hz, C1–H), 4.7 (m, 1, C5–H), 6.8–7.5 (m, 5, Ar), irradiation at 1.8 simplifies the m at 4.7 to a doublet, J = 4.5 Hz.

Anal. Calcd for $C_{11}H_{15}NO_2$·HCl: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.6; H, 7.04; N, 6.12.

***trans*-2-[(1-Methylethyl)amino]-*cis*-5-phenoxycyclopentanol Hydrochloride (3d).** To a solution of the *cis*-epoxide **9** (3.0 g, 0.017 mol) in EtOH (75 mL) and isopropylamine (75 mL) was added 1 N HCl (17 mL, 0.017 mol). The reaction was heated at reflux for 40 h and evaporated in vacuo. The resulting light yellow oil was triturated with CH_3CN and the white crystals that formed were collected by filtration and recrystallized from isopropyl alcohol to yield analytically pure **3d** (2.2 g, 47.5%): mp 205–206.5 °C; ^{1}H NMR (Me_2SO-d_6–D_2O) δ 4.25 (dd, 1, $J_{1,5}$ = 4.5, $J_{1,2}$ = 7.5 Hz, C1–H); ^{1}H NMR (DMeSO-d_6) δ 1.28 (d, 6, J = 6 Hz, $CH(CH_3)_2$), 1.5–2.4 (m, 4, CH_2CH_2), 3.2–3.8 (m, 2), 4.32 (br dd, 1, C1–H), 4.68 (m, 1, C5–H), 5.45 (d, 1, J = 6 Hz, exchangeable OH), 6.7–7.4 (m, 5, Ar), 9.25 (br s, 2, exchangeable NH_2), irradiation at 1.9 simplifies the m at 4.68 to a doublet, J = 4.5 Hz.

Anal. Calcd for $C_{14}H_{21}NO_2$·HCl: C, 61.68; H, 8.16; N, 5.15. Found: C, 61.8; H, 8.23; N, 5.06.

(*cis*-2-Hydroxy-*trans*-3-phenoxycyclopentyl)acetamide (22). In a 250-mL three-neck round-bottom flask fitted with a N_2 inlet valve, condenser, and additional funnel was placed NaH (1.7 g, 0.071 mol) and dry DMF (30 mL). To this suspension was added a solution of phenol (13.0 g, 0.138 mol) in DMF (50 mL) dropwise. After the reaction subsided, a solution of *cis*-*N*-(6-oxabicyclo[3.1.0]hex-2-yl)acetamide[29] (**21**) (10 g, 0.071 mol) in DMF (45 mL) was added and the reaction was heated at 100 °C. The reaction was followed by GC (200 °C, DE-52 column) or ^{1}H NMR. After 16 h, the reaction was added to ice water (ca. 400 mL) and the mixture was extracted with EtOAc (5 × 150 mL). The combined extracts were washed thoroughly with brine, dried (Na_2SO_4), and evaporated to an oil. The oil was triturated with ether to induce crystallization and cyclohexane was added to complete crystallization. The crystalline product was collected by filtration and air dried to give 9.6 g (58%) of **22**, mp 123–125.5 °C. Recrystallization from acetonitrile gave analytically pure material: mp 126–128 °C; IR (KBr) 3340 and 1640 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.3–2.4 (m, 4, CH_2CH_2), 1.8 (s, 3, $COCH_3$), 3.95 (m, 1, C1–H), 4.05–4.4 (m, 1, C2–H), 4.55 (m, 1, C3–H), 5.2 (br s, 1, OH), 6.8–7.4 (m, 5, Ar) and 7.6 (d, 1, NH).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.35; H, 7.33; N, 5.83.

***cis*-2-Amino-*trans*-5-phenoxycyclopentanol (4a) and the Hydrochloride Salt 4b.** A 9.5-g (0.04 mol) quantity of the acetamide **22**, MeOH (125 mL), and 3 N HCl (125 mL) was heated at reflux for 15 h under a N_2 atmosphere. The solution was concentrated in vacuo to afford a slurry of crystalline product. The crystals were collected by filtration, washed with a small volume of EtOH, and dried in vacuo to give 7.5 g (81%) of the amine hydrochloride salt **4b**, mp 215–217 °C. A small sample was recrystallized from *i*-PrOH for analysis: mp 215–217 °C; ^{1}H NMR (Me_2SO-d_6) δ 1.3–2.5 (m, 4, CH_2CH_2), 3.45 (m, 1, C2–H), 4.13 (m, 1, C1–H), 4.65 (m, 1, C5–H), 6.0 (1 H, exchangeable), 6.7–7.4 (m, 5, Ar), 8.2 (3 H, exchangeable); (DMe_2SO-d_6–D_2O) δ 3.55 (dd, 1, $J_{2,1}$ = 5, J = 14 Hz, C2–H), 4.2 (dd, 1, J = 2, J = 5 Hz, C1–H), 4.72 (ddd, 1, $J_{5,1}$ = 2, J = 5, 2 Hz, C5–H), irradiation at 4.7 simplifies the dd at 4.2 to a d, $J_{1,2}$ = 5 Hz.

Anal. Calcd for $C_{11}H_{15}NO_2$·HCl: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.63; H, 6.90; N, 6.19.

From 1 g of the amide **22**, 0.7 g (85%) of the free base **4a** was isolated from the hydrolysis by partitioning the hydrochloride salt **4b** between ether (150 mL) and 1 M K_2CO_3 (75 mL) and evaporating the ether layer to obtain white crystals: mp 90–91 °C (from H_2O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69 (m, 1, C3–H), 1.92–2.16 (m, 3, C4,4′- and 3′-H), 2.29 (br s, 3, OH and NH_2), 3.28 (m, 1, C2–H), 4.00 (dd, 1, $J_{1,5}$ = 4.4, $J_{1,2}$ = 4.6 Hz, C1–H), 4.62 (ddd, 1, C5–H), 6.92 (d, 2, C6–H), 6.94 (dd, 1, C8–H), 7.27 (dd, 2, $J_{7,8}$ = 7.5, $J_{7,6}$ = 7.6 Hz, C7–H).

***cis*-2-[(1-Methylethyl)amino]-*trans*-5-phenoxycyclopentanol (4c) and the Hydrochloride Salt 4d.** A solution of amine **4a** (3.86 g, 0.02 mol) in acetone (25 mL) and $CHCl_3$ (25 mL) was concentrated to ca. 25 mL at reflux. TLC (SS7) indicated the formation of desired imine and the solution was evaporated to an oil in vacuo. The oil was dissolved in MeOH (25 mL) and $NaCNBH_3$ (1.26 g, 0.02 mol) and bromocresol green (ca. 2 mg) were added. The reaction was cooled in an ice bath and the dark blue solution was treated dropwise with EtOH–HCl to obtain a yellow solution. After 20 min, the yellow color persisted, and TLC indicated complete reaction. The solution was diluted with MeOH (25 mL) and H_2O (50 mL), made strongly basic with 1N NaOH, and extracted with ether (3 × 100 mL). The combined organic layer was washed with ice cold 0.5 N NaOH, dried ($MgSO_4$), and evaporated to a white crystalline solid **4c** (4.1 g, 87%), mp 89–90

°C, which can be recrystallized from ether or cyclohexane: ^{1}H NMR ($CDCl_3$) δ 1.07 (two sets of d of equal intensity separated by 4 Hz, 6, J = 6 Hz, $CH(CH_3)_2$), 1.2–2.4 (m, 4, CH_2CH_2), 2.82 (septet, 1, J = 6 Hz, $CH(CH_3)_2$, 3.28 (ddd, 1, $J_{2,1}$ = 5, J = 6 Hz, 10, C2–H), 3.85 (d, 1, $J_{1,2}$ = 5 Hz C1–H), 4.62 (br dd, 1, J = 3.5 Hz, 6.5, C5–H), 6.8–7.4 (m, 5, Ar); ^{1}H NMR ($CDCl_3$–D_2O) 1.07 δ (d, 6, J = 6 Hz, *i*-Pr); IR (KBr) 3300, 3100 (br), 2970, 2940, 2880, 2740 (br) cm^{-1}.

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00, N, 5.95. Found: C 71.6; H, 9.04; N, 5.91.

The hydrochloride salt **4d** was obtained (HCl–THF/hexane): mp 200–202 °C; ^{1}H NMR (Me_2SO-d_6–D_2O) δ 1.27 (d, 6, J = 6 Hz, *i*-Pr), 1.5–2.6 (m, 4, CH_2CH_2), 3.33 (septet, 1, J = 6 Hz, *i*-Pr), 4.23, (d, 1, J = 5 Hz, C1–H), 4.65 (m, 1, C5–H), 6.9–7.45 (m, 3, Ar); ^{1}H NMR (Me_2SO-d_6) 3.52 (m, 1, C2–H).

Anal. Calcd for $C_{14}H_{21}NO_2$·HCl: C, 61.89; H, 8.16; N, 5.16. Found: C, 62.0; H, 8.09; N, 5.17.

***cis*-2-(4-Bromophenoxy)-6-oxabicyclo[3.1.0]hexane (24).** A solution of the *trans*-epoxy alcohol **23**[35] (15 g, 0.15 mol), 4-bromophenol (39 g, 0.225 mol), and triphenylphosphine (47 g, 0.18 mol) in benzene (300 mL) was treated with diisopropylazodicarboxylate (36 g, 0.18 mol) in similar manner as that for **8** providing **24** as a white crystalline solid (32 g, 83%): mp 67–68 °C (hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (m, 1, $J_{3\alpha,4\beta}$ = 8.0, $J_{3\alpha,3\beta}$ = 12.6 Hz, C3α–H), 1.74 (ddt, 1, $J_{4\alpha,4\beta}$ = 13.9, $J_{4\alpha,3\beta}$ = 7.9 Hz, C4α–H), 2.05 (dt, 1, $J_{3\beta,2}$ = 7.8, $J_{3\beta,4\alpha}$ = 7.9, $J_{3\beta,3\alpha}$ = 12.6 Hz, C3β–H), 2.19 (dd, 1, $J_{4\beta,4\alpha}$ = 13.9, $J_{4\beta,3\alpha}$ = 8.0 Hz, C4β–H), 3.51 (d, 1, $J_{5,6}$ = 2.6 Hz, C5–H), 3.64 (dd, 1, $J_{1,5}$ = 2.6, $J_{1,2}$ < 1 Hz, C1–H), 4.72 (dt, 1, $J_{2,1}$ < 1, $J_{2,3\alpha}$ = $J_{2,3\beta}$ = 7.8 Hz, C2–H), 6.7 (d, 2, Ar), 7.26 (d, 2, Ar).

Anal. Calcd for $C_{11}H_{11}BrO_2$: C, 51.78; H, 4.35. Found: C, 51.83; H, 4.36.

***trans*-2-Amino-*cis*-5-(4-bromophenoxy)cyclopentanol (25).** The bromo epoxide **24** (30 g, 0.117 mol) was treated with sodium azide (20 g, 0.3 mol) and ammonium chloride (2.7 g) in water (50 mL)–ethanol (500 mL) as in the preparation of **11** provided a light yellow oil (35 g, 100%) of azido alcohol, IR (thin film) 2100 cm^{-1}. The azido alcohol (29.8 g, 0.1 mol) was dissolved in pyridine (500 mL) (drying tube) and treated with triphenylphosphine (42 g, 0.16 mol) for 3 h at room temperature. Ammonium hydroxide (100 mL) was added to the reaction, which was stirred for 16 h at room temperature. The solvents were removed in vacuo providing a light yellow oil that solidified. The solid was dissolved in a small volume of CH_2Cl_2/methanol (9:1) and applied to a column of silica gel (500 mL, 21 × 8 cm) packed with the same solvent pair. The Ph_3P and Ph_3PO eluted off the column immediately. The column was then eluted with CH_2Cl_2/MeOH/NH_4OH (450:60:10), and after a small forerun, product was collected. These fractions were combined and evaporated to a white crystalline solid. Recrystallization from benzene/cyclohexane (1:1) gave **25** analytically pure (15.4 g, 57%): mp 128–129 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (m, 1, C3–H), 1.81 (m, 1, C4-H, after D_2O exchange), 1.81 (br s, 3, OH and NH_2, D_2O exchangeable), 2.13 (m, 2, C3′– and C4′–H), 3.36 (dd, 1, $J_{2,1}$ = 7.8 Hz, C2–H), 3.70 (dd, 1, $J_{1,5}$ = 5.3, $J_{1,2}$ = 7.8 Hz, C1–H), 4.62 (ddd, 1, $J_{5,1}$ = 5.3 Hz, C5–H), 6.78 (d, 2, $J_{6,7}$ = 8.8, C6–H), 7.38 (d, 2, $J_{7,6}$ = 8.8 Hz, C7–H).

Anal. Calcd for $C_{11}H_{14}NO_2Br$:C, 48.54; H, 5.18; N, 5.15. Found: C, 48.41; H, 5.27; N, 4.98.

***N*-[*trans*-2-Hydroxy-*trans*-3-(4-bromophenoxy)cyclopentyl]-4-nitrobenzamide (26).** Prepared in a similar manner as **12** to provide analytically pure **26** in 93% yield: mp 203–204 °C (EtOH); IR (Nujol) 1625, 1595 cm^{-1}.

Anal. Calcd for $C_{18}H_{17}N_2O_5Br$: C, 51.32; H, 4.07; N, 6.65. Found: C, 51.36; H, 4.18; N, 6.71.

***cis*-2-Amino-*trans*-5-(4-bromophenoxy)cyclopentanol (27). Method A.** The amide **26** (7.8 g, 0.185 mol) was converted to **27** as **2a**. Flash chromatography [$CHCl_3$/MeOH/NH_4OH (40:10:1)] gave **27** (1.7 g, 34%). Recrystallization from cyclohexane gave analytically pure **27** (1.4 g): mp 110–111.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (m, 1, $J_{3,2}$ = 6.8 Hz, C3–H), 1.71 (m, 1, $J_{4',5}$ = 7.1 Hz, C4′–H), 2.04 (m, 1, $J_{3',2}$ = 8.0 Hz, C3′–H), 2.27 (m, 1, $J_{4,5}$ = 7.5 Hz), 3.52 (m, 1, $J_{2,1}$ = 5.2, $J_{2,3}$ = 5.8, $J_{2,3'}$ = 8.0 Hz), 3.86 (dd, 1, $J_{1,2}$ = 5.2, $J_{1,5}$ < 1 Hz, C1–H), 4.54 (ddd, 1, $J_{5,1}$ < 1, $J_{5,4}$ = 7.5, $J_{5,4}$ = 7.1 Hz C5–H), 6.81 (d, 2, J = 9.1 Hz, Ar H), 7.35 (d, 2, J = 9.1 Hz, Ar H).

Anal. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.54;, H, 5.18; N, 5.15. Found: C, 48.53; H, 5.08; N, 5.07.

Method B. In a 250-mL three-neck flask with overhead stirrer, thermometer, and nitrogen bubbler containing water (40 mL) was added 85% KOH pellets (33 g) slowly. To the resulting warm solution was added a solution of 4-bromophenol (52 g, 0.3 mol) in toluene (40 mL). Tetrabutylammonium hydrogen sulfate (6.9 g) and the benzamide epoxide **28**[29] (20 g, 0.1 mol) were added to the reaction. The mixture was heated at 65 °C with stirring under a nitrogen atmosphere for 16 h and was cooled in an ice bath. The resulting white crystals were collected by filtration and were washed with water. The benzamido alcohol was recrystallized from acetonitrile providing shiny white crystals (16.2 g, 43%), mp 147–149 °C.

The benzamide (15 g, 0.04 mol) was added to a solution of ethylene glycol (50 mL) and 85% potassium hydroxide pellets (15 g) dissolved in water (20 mL) and heated at reflux (120 °C). The starting material gradually went into solution. After 2 h, the reaction was diluted with water (100 mL) and cooled to 0 °C overnight. The resulting white crystals were collected by filtration and dried (7.8 g, 72%), mp 111–113.5 °C. Recrystallization from benzene gave analytically pure needles of **27**, mp 111.5–113 °C, identical by ^{1}H NMR and HPLC with the product obtained by method A.

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Registry No. **1a**, 97133-63-6; **1b**, 97168-74-6; **1c**, 97072-03-2; **1d**, 97133-64-7; **1e**, 97072-04-3; **2a**, 97133-65-8; **2b**, 97168-75-7; **2c**, 97133-66-9; **2d**, 97168-76-8; **3a**, 97133-67-0; **3b**, 97168-77-9; **3d**, 97134-59-3; **3e**, 97133-68-1; **4a**, 97133-69-2; **4a** (imine), 97072-18-9; **4b**, 97168-78-0; **4c**, 97133-70-5; **4d**, 97168-79-1; **6**, 96-40-2; **7**, 95526-36-6; **8**, 97133-71-6; **9**, 97133-72-7; **10**, 29782-88-5; **10** (iodohydrin), 97072-16-7; **11**, 97133-73-8; **12**, 97133-74-9; **13**, 97133-75-0; **14**, 97072-05-4; **15a**, 97072-06-5; **15b**, 97072-07-6; **16a**, 97072-08-7; **16b**, 97072-09-8; **17**, 97072-10-1; **18**, 97072-11-2; **19a**, 12082-03-0; **19b**, 12082-05-2; **20**, 97133-76-1; **21**, 97133-77-2; **22**, 97133-78-3; **22** (tosylate), 97072-20-3; **23**, 34310-95-7; **24**, 97102-05-1; **25**, 97072-12-3; **25** (azide), 97072-21-4; **26**, 97072-13-4; **27**, 97133-79-4; **27** (benzamido alcohol), 97072-19-0; **28**, 97072-14-5; 2-cyclopenten-1-01, 3212-60-0; 1-fluoro-4-nitrobenzene, 350-46-9; tryptamine, 61-54-1; *cis*-3,3-dimethyl-8-phenoxy-2-oxa-4-azabicyclo[3.3.0]octane, 97072-15-6; 1-hydroxy-4-nitronaphthalene isopropylamine salt, 97072-17-8; 1-fluoro-4-nitronaphthalene, 341-92-4.

Supplementary Material Available: Crystallography methods discussion, Figure 1, ORTEP drawing of **27**, Table III, crystal data summary for **27**, line drawing of **27** showing numbering scheme, Table IV listing fractional coordinates for atoms in **27** and isotropic thermal parameters for **27**, Table V listing angles in degrees for **27**, Table VI listing bond distances in Angstroms for **27**, and Table VII listing anisotropic thermal parameters (bij form) (8 pages). Ordering information is given on any current masthead page.