Binding Orientation of Amphetamine and Norfenfluramine Analogues in the Benzonorbornene and Benzobicyclo[3.2.1]octane Ring Systems at the Active Site of Phenylethanolamine *N*-Methyltransferase (PNMT)[1a]

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In a continuation of studies directed at characterizing the conformational basis of binding β-phenylethylamines at the active site of phenylethanolamine *N*-methyltransferase (PNMT), *anti*-10-amino- (**12**) and *syn*-10-amino-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**13**) were prepared and evaluated as substrates and inhibitors for PNMT. These conformationally defined amphetamine analogues mimic a low energy half-chair form of 2-aminotetralin (2AT). Further, in order to determine the active site binding orientation of β-phenylethylamines bearing aryl lipophilic substituents, the aryl trifluoromethyl-substituted derivatives of **12** and **13** (**20–27**), as well as *anti*-9-amino-5-(trifluoromethyl)- (**18**) and *anti*-9-amino-6-(trifluoromethyl)benzonorbornene (**19**), were prepared and evaluated. The competitive inhibition displayed by the fully extended analogue **12** coupled with the uncompetitive kinetics exhibited by the folded isomer **13** supports previous findings that a fully extended side chain conformation is optimal for binding to the active site of PNMT. In addition, the fact that **12** displayed enhanced affinity as an inhibitor over its β-phenylethylamine counterparts in the benzonorbornene and 1,4-ethanonaphthalene ring systems suggests that a half-chair conformation is preferred when 2AT analogues interact at the active site of the enzyme. This would be consistent with previous results that PNMT preferentially binds molecules with a more coplanar relationship between the aromatic ring and the amino nitrogen. The lack of activity as a substrate in **12** indicates that the negative steric interactions of the ethano bridging unit prohibits it from binding in a manner consistent with the known PNMT substrates *exo*-2-amino- (**6**) and *anti*-9-aminobenzonorbornene (**8**). Given the emergence of activity as a substrate in **20** and **21** (the 1-trifluoromethyl- and the 2-trifluoromethyl-substituted derivatives of **12**), it appears that the positive interaction of the trifluoromethyl group orients these analogues in a manner in which the ethano bridge lies in regions of steric bulk tolerance. This would suggest that the region of steric intolerance has a degree of directionality. Finally, although the aromatic ring binding region of the active site of PNMT contains a large degree of lipophilic character, only specific spatial orientations between the trifluoromethyl group and the amino nitrogen of aryl trifluoromethyl-substituted β-phenylethylamines allow both to interact simultaneously in a manner that allows the amine to bind in a region of the active site in which methylation can occur.

While a number of reports have indicated that the neurotransmitter epinephrine (Epi) is involved in a variety of centrally mediated physiological functions including the regulation of blood pressure,[2-6] the release (and inhibition of release) of pituitary hormones,[7-9] and the regulation of α_2-adrenoreceptors,[10-12] its exact role within the central nervous system (CNS) remains poorly understood. For this reason, the design and synthesis of an agent that regulates epinephrine levels within the CNS has become of recent interest in drug design. The most common approach to this end has been through inhibition of the enzyme noradrenalin *N*-methyltransferase (also referred to as phenylethanolamine *N*-methyltransferase; PNMT; EC 2.1.1.28). This enzyme has been shown to exist within the mammalian CNS[13-16] and catalyzes the last step in epinephrine biosynthesis by the transfer of an active methyl group from *S*-adenosyl-L-methionine to the primary amine of norepinephrine (NE).[17] While a number of potent PNMT inhibitors are currently available,[18-21] all interact at other biologically relevant sites (i.e., α_2-adrenoreceptors[22-25]) and therefore suffer from a lack of selectivity. This drawback limits their use as pharmacological tools

(1) (a) Paper 10 in our series "Conformationally Defined Adrenergic Agents". For paper 9 see Grunewald, G. L.; Arrington, H. S.; Bartlett, W. J.; Reitz, T. J.; Sall, D. S. *J. Med. Chem.* **1986**, *29*, 1972. (b) Summer Undergraduate Research Participant, University of Kansas, Department of Medicinal Chemistry, 1985. (c) NIH Predoctoral Trainee (Grant GM 07775), and recipient of the 1986 Robert Irsdy–Norman Dahle Award in Medicinal Chemistry at the University of Kansas.

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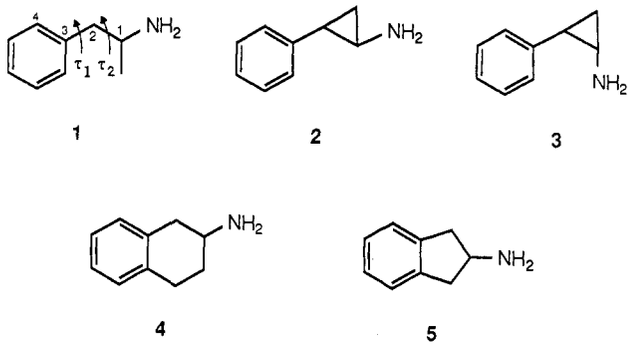

Figure 1. Structure of amphetamine (α-methyl-β-phenylethylamine; 1), which undergoes free rotation about the ethylamine side chain. The torsion angles τ_1 (defined by atoms C4, C3, C2, and C1) and τ_2 (defined by atoms C3, C2, C1, and N) refer to the angles of rotation about the two carbon–carbon bonds as depicted. Also shown are conformationally restricted amphetamine analogues *trans*-2-phenylcyclopropylamine (**2**), *cis*-2-phenylcyclopropylamine (**3**), 2-aminotetralin (2AT; 4), and 2-aminoindan (**5**).

in further elucidating the role of Epi within the CNS.

As part of an ongoing project directed at the design and synthesis of a potent yet selective inhibitor of PNMT, we have attempted to determine the overall topography of the active site of the enzyme by defining those interactions that occur when substrates and competitive inhibitors bind. Enhanced selectivity may then result through the design of inhibitors that take advantage of those binding interactions that are exclusively characteristic of the active site of PNMT.

While a wide variety of ligands have been found to interact at the active site of PNMT, most fall into one of three structural categories: (1) phenylethanolamines (substrates and thus alternate substrate inhibitors), (2) amphetamines (competitive inhibitors), and (3) benzylamines (also competitive inhibitors). Of these three, the amphetamine class has been the most widely studied in terms of conformation–activity relationships.[21,26-29]

Amphetamine (1; Figure 1), in which the ethylamine side chain undergoes free rotation as dictated by torsion angles τ_1 and τ_2, exists in an unlimited number of conformations, any of which may potentially interact at the active site of the enzyme. The fact that PNMT exhibits conformational biases when binding ligands of this class was first realized when it was found that the fully extended *trans*-2-phenylcyclopropylamine (**2**) was a considerably more potent inhibitor of the enzyme than its corresponding cis isomer **3**.[26] In addition, 2-aminotetralin (2AT; 4) and 2-aminoindan (2AI; **5**), which like **2** and **3** are conformationally restricted analogues of amphetamine, have been shown to exhibit a 50-fold enhancement in PNMT binding affinity over the flexible parent amphetamine (1) itself.[27,28] Molecular models, however, show that each of these amphetamine analogues retains a certain degree of conformational flexibility and therefore can only be used to define a range of conformations that are preferred for binding at the active site of PNMT. In an effort to determine the side chain conformation in β-phenylethylamines that leads to optimal interaction at the active site of the enzyme, conformationally defined amphetamine analogues **6**–**11** (Figure 2), in which the rigid carbocyclic framework fixes the ethylamine side chain in a single conformation, were studied. Analogues **6**, **8**, and **10** (in which the amine and aromatic ring are held in a trans antiperiplanar relationship with $\tau_2 \simeq 180°$) displayed enhanced competitive inhibition over amphetamine (1), while **7**, **9**, and **11** (which represent a gauche side chain conformation with $\tau_2 \simeq 60°$) exhibited only weak uncompetitive kinetics. This suggested that a fully extended side chain conformation ($\tau_2 \simeq 180°$) is optimal for active site binding.[28]

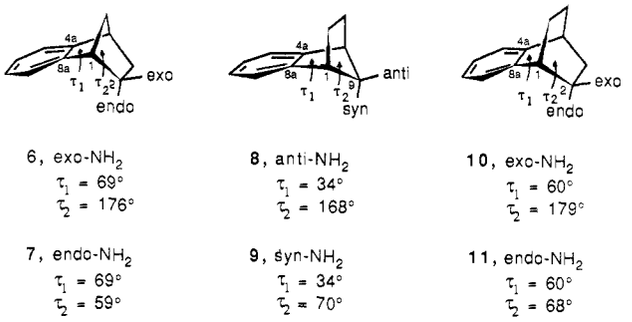

Figure 2. Structures of the conformationally defined amphetamine analogues **6**–**11** with the values for torsion angles τ_1 and τ_2. In the case of **6**,**7** and **10**,**11**, τ_1 refers to the dihedral angle between the planes defined by carbons 4a, 8a, and 1 and by carbons 8a, 1, and 2. For analogues **8**,**9**, the planes are defined by carbons 4a, 8a, and 1 and by carbons 8a, 1, and 9. In the case of the fully extended analogues **6**, **8**, and **10**, τ_2 refers to the dihedral angle between the planes defined by carbons 8a, 1, and 2 (8a, 1, and 9 in the case of **8**) and by carbons 1, 2, and *exo*-NH_2 (*anti*-NH_2 for **8**). For the folded stereoisomers **7**, **9**, and **11**, the planes are defined by carbons 8a, 1, and 2 (8a, 1, and 9 in the case of **8**) and by carbons 1, 2, and *endo*-NH_2 (*syn*-NH_2 for **8**). The values for the torsion angles τ_1 and τ_2 were taken from ref 30.

In addition, the enhanced affinity of **8** over **6** and **10** indicated that the enzyme preferentially binds molecules with a more coplanar relationship between the aromatic ring and the amino nitrogen. The greater coplanarity in **8** is a result of a lower torsion angle τ_1 (the angle that, when τ_2 approximates 180°, defines the position of the amino nitrogen with respect to the plane of the aromatic ring). Another important result from this study was the fact that **6** and **8** displayed marginal activity as substrates.[29] This was the first example of a β-phenylethylamine displaying activity as a substrate while lacking a β-hydroxyl group (or other heteroatom functionality) on the ethylamine side chain. We have proposed that locking the side chain of β-phenylethylamines in a fully extended conformation (as in **6** and **8**) serves the same purpose as the β-hydroxyl group of an ethanolamine substrate, so as to anchor the primary amine in a region of the active site in which methylation can occur.[29]

While the pairs **6**/**10** and **7**/**11** represent conformationally defined analogues of amphetamine, they can also be viewed as mimicking two boat forms of 2AT and therefore offer a certain amount of information concerning the PNMT binding conformation of the conformationally restricted yet still flexible 2AT ring system. The finding that **7** and **11** display only weak uncompetitive inhibition suggests that this boat conformation, which fixes the ethylamine side chain in a gauche conformation, is not preferred for bound 2ATs at the active site of PNMT. Analogues **6** and **10** on the other hand displayed competitive kinetics. This would suggest that the boat form of 2AT in which the ethylamine side chain is held in a fully extended conformation (as in **6** and **10**) is allowed for active site binding of this ring system. While the binding affinities of **6** and **10** are greater than that of amphetamine,

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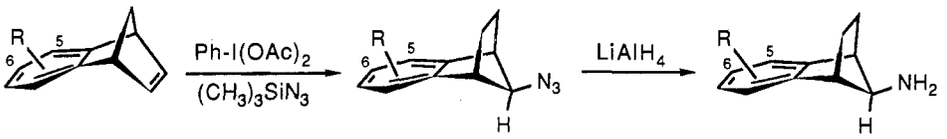
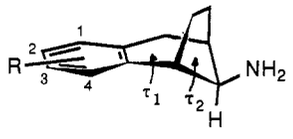
Scheme I



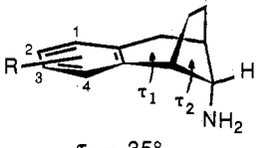
28, R = 5-CF_3 **29**, R = 5-CF_3 **18**, R = 5-CF_3
30, R = 6-CF_3 **31**, R = 6-CF_3 **19**, R = 6-CF_3

they are less than that of 2AT by factors of 30- and 85-fold, respectively.[28] This diminished activity could be accounted for by a number of reasons, one of which is a negative steric interaction resulting from the added bridging units. Consistent with this is the fact that the relative binding affinities of 2AT, **6**, and **10** decrease as the steric bulk above the alicyclic ring increases. Alternatively, the low affinities of **6** and **10** may be due to the fact that they are fixed in a less than optimal active site binding conformation. Since the 2AT ring system retains a certain degree of conformational flexibility, it may assume a number of conformations, including a low energy half-chair conformation.[31]

The pronounced PNMT binding affinity of β-phenylethylamines that are incorporated into the 2AT ring system warranted further studies regarding the active site binding conformation of this particular ring system. In this regard, we have prepared the 10-amino-5,8-methano-5,6,7,8-tetrahydro-9*H*-benzocycloheptene analogue **12** (τ_1 = 37° and τ_2 = 170°),[32] which represents a low energy, half-chair conformation of 2AT. Since the additional



τ_1 = 35°
τ_2 = 170°

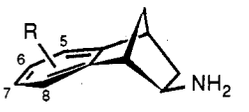


τ_1 = 35°
τ_2 = 50°

12, R = H **13**, R = H
20, R = 1-CF_3 **24**, R = 1-CF_3
21, R = 2-CF_3 **25**, R = 2-CF_3
22, R = 3-CF_3 **26**, R = 3-CF_3
23, R = 4-CF_3 **27**, R = 4-CF_3

steric bulk of the ethano bridge in **12** is comparable to that of **10**, any enhancement in binding affinity found for **12** (over **10**; τ_1 = 60°) should be reflective of whether the boat or half-chair conformation of 2AT is preferred for binding at the active site of the enzyme. In addition, analogue **13**, which contains a gauche side chain conformation (τ_2 = 47°),[32] was examined. Its activity, compared to that of **12** (τ_2 = 170°), should test our previous finding that a fully extended side chain conformation (τ_2 = 180°) of β-phenylethylamines is required for optimal binding at the active site of PNMT.

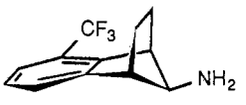
An additional feature of conformationally defined analogues of type **6–11** is that locking the aromatic ring in a fixed orientation produces two distinguishable aryl positions (carbons C5 and C7) that are meta to the ethylamine side chain. Following reports that electron-withdrawing, lipophilic substituents on the aromatic ring greatly enhance the PNMT binding affinity of phenylethanolamines (substrates)[29,33,34] and amphetamines (competitive inhibitors),[29,34,35] we prepared the conformationally defined norfenfluramine analogues **14–17** in order to study the



14, R = 5-CF_3
15, R = 6-CF_3
16, R = 7-CF_3
17, R = 8-CF_3

directionality of these lipophilic interactions with respect to the point of amine interaction of bound β-phenylethylamines of type **6**.[29] The finding that **14** and **15** displayed a pronounced enhancement in activity as substrates over parent unsubstituted analogue **6** suggested that the trifluoromethyl group interacts with a discrete lipophilic pocket which exists off of carbons C5 and C6 of bound β-phenylethylamines of type **6**. In addition, the fact that **16** and **17** act as competitive inhibitors of the enzyme (while **14** and **15** are substrates) indicates that the lipophilic interaction is very strong and exerts a profound influence on the qualitative mode of binding of these analogues. Finally, the finding that **14** displays activity as a substrate while **16** acts as a competitive inhibitor suggests that **14** better represents the active site binding orientation of bound substrates that possess lipophilic substituents at positions meta to the ethylamine side chain.

On the basis of the pronounced influence of the lipophilic substituent on the binding orientation of **14–17** and the fact that, at present, analogue **8** best represents the active site binding conformation of β-phenylethylamines, we have chosen to define the nature of the lipophilic interaction with respect to the point of amine interaction in analogues of structural type **8**. In this regard, norfenfluramine analogues **18** and **19** have been prepared and evaluated for activity as substrates and inhibitors of PNMT.



18

19

Finally, in order to probe the nature and importance of the lipophilic interaction with respect to the binding orientation of **12** and **13**, we prepared and evaluated the trifluoromethyl-substituted analogues **20–27**. The results

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(31) Gieseck, J. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1980**, *B36*, 110.
(32) The torsion angle τ_1 in both **12** and **13** were obtained from X-ray crystallographic studies on similar molecules in this rigid bicyclic system. The values for torsion angle τ_2 for each isomer were obtained by using the SYBYL molecular graphics package (see ref 55) using an energy minimized representation (MAXIMIN command) of each stereoisomer.
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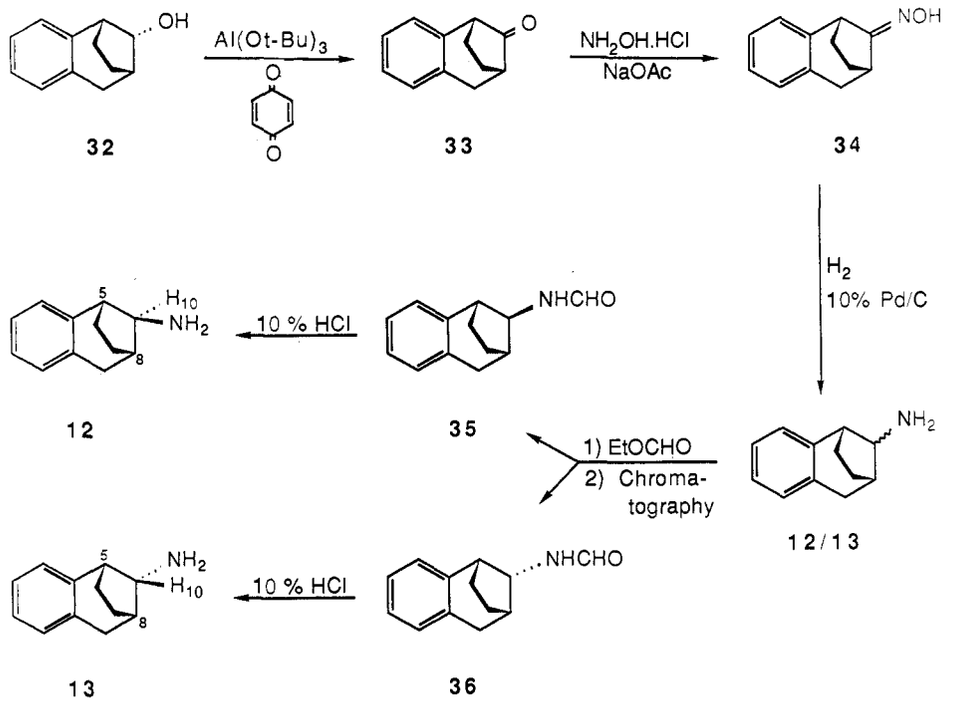
Scheme II



from these studies should further our understanding of the active site binding orientation of β-phenylethylamine substrates and inhibitors that possess lipophilic substituents on the aromatic ring.

Chemistry

The syntheses of *anti*-9-amino-5-(trifluoromethyl)- (**18**) and *anti*-9-amino-6-(trifluoromethyl)benzonorbornene (**19**) are shown in Scheme I. In the case of amine **18**, 5-(trifluoromethyl)benzonorbornadiene (**28**)[36] was treated with (diacetoxyiodo)benzene and azidotrimethylsilane according to the conditions of Ehrenfreund and Zbiral,[37] to afford the rearranged *anti*-9-azide **29**. Following chromatography, **29** was reduced by using $LiAlH_4$ to afford amine **18**. Employing analogous conditions, we synthesized the 6-trifluoromethyl-substituted regioisomer **19** from the known diene **30**.[38] Although amine **19** has been previously prepared by this route,[39] it was reported that the crude azide mixture (i.e., **31**) from the rearrangement step was resistant to purification. Subsequent reduction was reported to give the amine, which also proved difficult to purify. We have found that a shortened reaction time yields azide **31** in a form that is readily purified by flash chromatography so that, upon reduction, amine **19** is obtained in high purity.

Synthesis of the unsubstituted anti and syn amine analogues in the 5,8-methano-5,6,7,8-tetrahydro-9*H*-benzocycloheptene system (**12** and **13** respectively) begins with *syn*-10-hydroxy-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**32**; Scheme II),[40,41] which was prepared according to the method of Kitamogi and Takano.[41] Oppenauer oxidation of alcohol **32** afforded the known but not fully characterized ketone **33**.[40] Conversion of **33** to an *E*/*Z* mixture of oxime **34** was effected by using hydroxylamine hydrochloride and sodium acetate. The fact that **34** existed as an equilibrium mixture of geometrical isomers was evident by the duplicate signals in both the ^1H and ^{13}C NMR spectra. Originally, reduction of oxime **34** was carried out by using $LiAlH_4$. By this method, a 4:1 ratio of syn to anti amine was obtained. In an attempt to enhance the degree of formation of the anti stereoisomer **12**, reduction of oxime **34** was attempted by using the conditions of Woods,[42] who has previously reported that catalytic hydrogenation of 9-(hydroxyimino)benzonorbornene led exclusively to the *anti*-9-amino isomer. Under these conditions, a 2.5 to 1 mixture of *anti*-10-amino- (**12**) and *syn*-10-amino-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**13**) was realized. To effect separation, the amines were converted to the corresponding formamides, **35** and **36**, which were easily separated by chromatography. As is evident from the duplicate signals in the ^1H and ^{13}C NMR spectra, both **35** and **36** existed as an equilibrium mixture of conformers. Finally, acid hydrolysis of the separated formamides yielded anti amine **12** and syn amine **13**.

Stereochemical assignment (syn versus anti) was accomplished at the amine stage by using ^1H NMR and was based on the magnitude of vicinal coupling between hydrogen H10 and the bridgehead hydrogens H5 and H8. For stereoisomer **12**, hydrogen H10 occurs at 3.28 ppm while for isomer **13**, H10 occurs at 3.31 ppm. In the case of the anti isomer, **12**, the dihedral angles $\phi_{H10,H5}$ and $\phi_{H10,H8}$ are 76° and 81°, respectively. According to the equation derived by Karplus,[43] dihedral angles of this magnitude translate into coupling constants ($J_{H10,H5}$ and $J_{H10,H8}$) on the order of 0–1 Hz. Consistent with this, hydrogen H10 appears as a singlet in the 300-MHz ^1H NMR spectrum of **12**. For the syn isomer **13**, $\phi_{H10,H5}$ and

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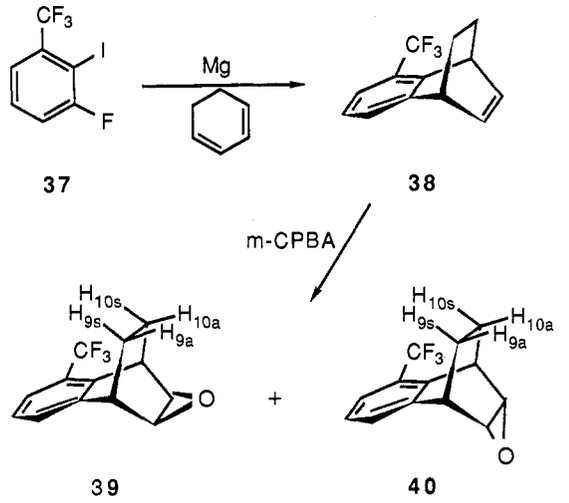
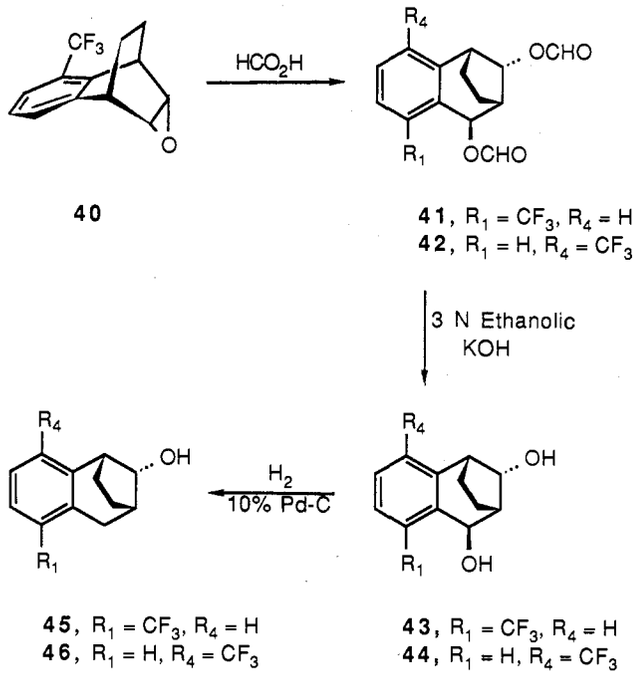
(42) Woods, L. Ph.D. Dissertation, University of Illinois at the Medical Center, Chicago, IL, 1979; *Diss. Abstr. Int, B* **1979**, *40*, 1730.
(43) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

Scheme III

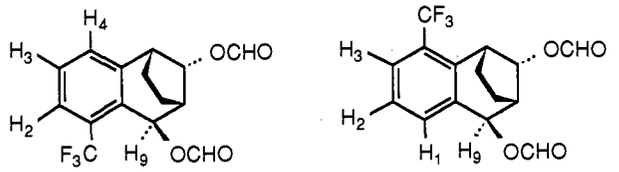


Scheme IV



$\phi_{H10,H8}$ are 47° and 44°, respectively. Consistent with the Karplus equation, hydrogen H10 appears as two overlapping doublets (J = 4.6 and 4.9 Hz) in the 300-MHz ^{1}H NMR spectrum of **13**. Finally, the stereochemical purity of **12** and **13** was estimated by ^{1}H and ^{13}C NMR spectrometry and ultimately determined by gas chromatography. Each isomer was found to be greater than 99.5% free of the other.

The syntheses of the aryl trifluoromethyl-substituted amines **20–27** were based in part on the methodology for preparation of the parent unsubstituted analogues **12** and **13**. With respect to amines **20**, **23**, **24**, and **27**, synthesis of the requisite *syn*-10-hydroxy-1-(trifluoromethyl)- (**45**) and *syn*-10-hydroxy-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**46**) is shown in Schemes III and IV. Under the general conditions of Tanida et al.,[44] entry into the bicyclic ring system begins with the Diels–Alder reaction between the CF_3-substituted benzyne generated from 2-iodo-3-fluorobenzotrifluoride



41 **42**

Figure 3. Structures of 9-*exo*,10-*syn*-bis(formyloxy)-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**41**) and 9-*exo*,10-*syn*-bis(formyloxy)-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**42**). In nuclear Overhauser studies, irradiation of the hydrogen H9 signal in **42** leads to an enhancement in the signal for hydrogen H1 in the ^{1}H NMR spectrum. Due to the lack of an H1 hydrogen in **41**, irradiation of the hydrogen H9 signal produces no effect on the aromatic region of the ^{1}H NMR spectrum for this regioisomer.

(**37**)[45] and cyclohexadiene, to afford 5-(trifluoromethyl)-1,4-dihydro-1,4-ethanonaphthalene (**38**; Scheme III). While diene **38** could not be fully purified by conventional means, partial purification was achieved by medium-pressure liquid chromatography (MPLC). The fraction containing the desired diene (as detected by ^{1}H NMR) was treated with 3-chloroperoxybenzoic acid (*m*-CPBA) to afford the exo (**39**) and endo (**40**) epoxides, which were separated by chromatography. Stereochemical assignment (exo vs. endo) was based on the previous work of Tori et al. in the corresponding unsubstituted system.[46] In the case of the exo isomer **39**, a deshielding effect caused by the presence of the exo oxirane ring shifts anti hydrogens H_{9a} and H_{10a} downfield (1.03 ppm) relative to the corresponding syn hydrogens H_{9s} and H_{10s}. In the case of endo epoxide **40**, however, the deshielding effect is minimal and hydrogens H_{9a} and H_{10a} are relatively unaffected. In this isomer, hydrogens H_{9a} and H_{10a} lie only 0.4 ppm downfield from hydrogens H_{9s} and H_{10s}.

Conversion of endo epoxide **40** to the requisite syn alcohols **45** (R_1 = CF_3) and **46** (R_4 = CF_3; Scheme IV) followed from the methodology of Kitamogi and Takano.[41] Treatment of **40** with 98% formic acid afforded a 3:1 mixture of 9-*exo*,10-*syn*-bis(formyloxy)-1-(trifluoromethyl)- (**41**) and 9-*exo*,10-*syn*-bis(formyloxy)-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**42**), respectively, which were readily separated by chromatography. Hydrolysis to the corresponding diols **43** (R_1 = CF_3) and **44** (R_4 = CF_3) was effected by using 1 N ethanolic KOH. Finally, for both **43** and **44**, reductive cleavage of the benzylic hydroxyl proceeded smoothly with 10% Pd/C in $CHCl_3$/AcOH (9:1) at 45 psi to afford the requisite alcohols **45** (R_1 = CF_3) and **46** (R_4 = CF_3), respectively.

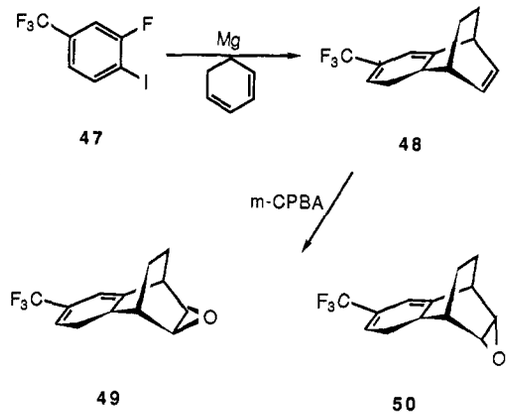
Regiochemical assignment (1-CF_3 versus 4-CF_3 substitution) was accomplished at the bis(formyloxy) stage (**41** and **42**) by using nuclear Overhauser experiments which were based on the long-range coupling between benzylic hydrogen H9 and the adjacent aromatic hydrogen H1 (Figure 3). Irradiation of the hydrogen H9 signal at 5.93 ppm in the 300-MHz ^{1}H NMR spectrum of **42** (R_4 = CF_3) led to an enhancement of the signal for aromatic hydrogen H1, which occurred as a doublet at 7.50 ppm. Due to the lack of an aromatic H1 hydrogen, irradiation of the hydrogen H9 signal (6.11 ppm) for **41** (R_1 = CF_3) had no

(44) Tanida, H.; Muneyuki, R.; Tsuji, T. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 40.

(45) Grunewald, G. L.; Palanki, M. S. S.; Reitz, T. J.; Sall, D. J., submitted for publication in *Org. Prep. Proced. Int.*

(46) Tori, K.; Kitahonoki, K.; Takano, Y.; Tanida, H.; Tsuji, T. *Tetrahedron Lett.* **1964**, 559.

Scheme V



effect on the aromatic region of the spectrum.

Synthesis of the syn alcohols **56** ($R_2 = CF_3$) and **57** ($R_3 = CF_3$), which were required for the preparation of amines **21**, **22**, **25**, and **26**, was modeled after the synthesis of **45** and **46** and is depicted in Schemes V and VI. Addition of the CF_3-substituted benzyne generated from 3-fluoro-4-iodobenzotrifluoride (**47**)[45] to cyclohexadiene afforded 6-(trifluoromethyl)-1,4-dihydro-1,4-ethanonaphthalene (**48**; Scheme V). As in the case of **38**, diene **48** could only be partially purified by MPLC. The semipure diene fraction was treated with 3-chloroperoxybenzoic acid (*m*-CPBA) to afford an exo/endo epoxide mixture, of which the endo isomer **50** was obtained in pure form by chromatography. Assignment of endo stereochemistry to **50** followed from ^1H NMR according to the work of Tori et al.[46] and as described for **39** and **40** (see above).

Acid-catalyzed rearrangement of endo epoxide **50** using 98% formic acid afforded an inseparable mixture of 2-(trifluoromethyl)- and 3-(trifluoromethyl)-9-*exo*,10-*syn*-bis(formyloxy)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**51**; Scheme VI). This mixture was directly hydrolyzed to the corresponding diol mixture **52**/**53**, which was ultimately separated by chromatography of the corresponding bis(3,5-dinitrobenzoate esters) **54** and **55**. The separated regioisomers **54** and **55** were hydrolyzed back to diols **52** ($R_2 = CF_3$) and **53** ($R_3 = CF_3$) by using 3 N aqueous KOH. Reductive cleavage of the benzylic hydroxyl in **52** ($R_2 = CF_3$) and **53** ($R_3 = CF_3$), to afford the requisite alcohols **56** and **57**, proved more difficult than in the previous cases. In regard to regioisomer **53** ($R_3 = CF_3$), catalytic hydrogenation according to the conditions used in the preparation of **45** and **46** resulted, at best, in only partial reduction. In view of the findings of Meschke and Hartung,[47] product formation is thought to retard further reduction of the starting diol. To circumvent this difficulty, reduction of **53** to **57** was carried out under more stringent conditions by using 10% Pd/C in AcOH at pressures of 50 psi. In this way, high yields of alcohol **57** were realized. Applying these harsh conditions to the reduction of **52**, however, only resulted in complex product mixtures. In order to effect high yields of **56** over moderate reaction times, it was necessary to reduce diol **52** at 30 psi in AcOH with a 2:1 w/w ratio of 10% Pd/C to diol.

Assignment of the regiochemistry (2-CF_3 versus 3-CF_3 substitution) for this pair of isomers was accomplished at the diol stage (**52** and **53**) again by using nuclear Overhauser experiments based on the long-range coupling between benzylic hydrogen H9 and the adjacent aromatic hydrogen H1 (Figure 4). Irradiation of the hydrogen H9 signal in **53** ($R_3 = CF_3$) led to an enhancement of the signal

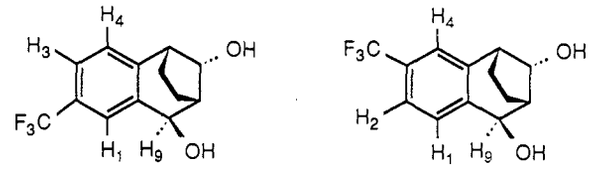


Figure 4. Structures of 9-*exo*,10-*syn*-dihydroxy-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**52**) and 9-*exo*,10-*syn*-dihydroxy-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**53**). In nuclear Overhauser experiments, irradiation of the hydrogen H9 signal in regioisomer **52** leads to enhancement of the signal for hydrogen H1, which appears as a singlet in the ^1H NMR spectrum due to the lack of ortho coupling. Irradiation of the hydrogen H9 signal in **53** leads to an enhancement for the hydrogen H1 signal, which for this regioisomer occurs as a doublet in the ^1H NMR spectrum due to ortho coupling with hydrogen H2.

for aromatic hydrogen H1, which occurred as a doublet, due to the ortho coupling with H2, at 7.57 ppm. While irradiation of the hydrogen H9 signal also enhanced the signal for aromatic hydrogen H1 in isomer **52** ($R_2 = CF_3$), the signal for hydrogen H1 occurred as a singlet (7.74 ppm), due to the lack of ortho coupling, and is therefore easily distinguished from hydrogen H1 in **53**.

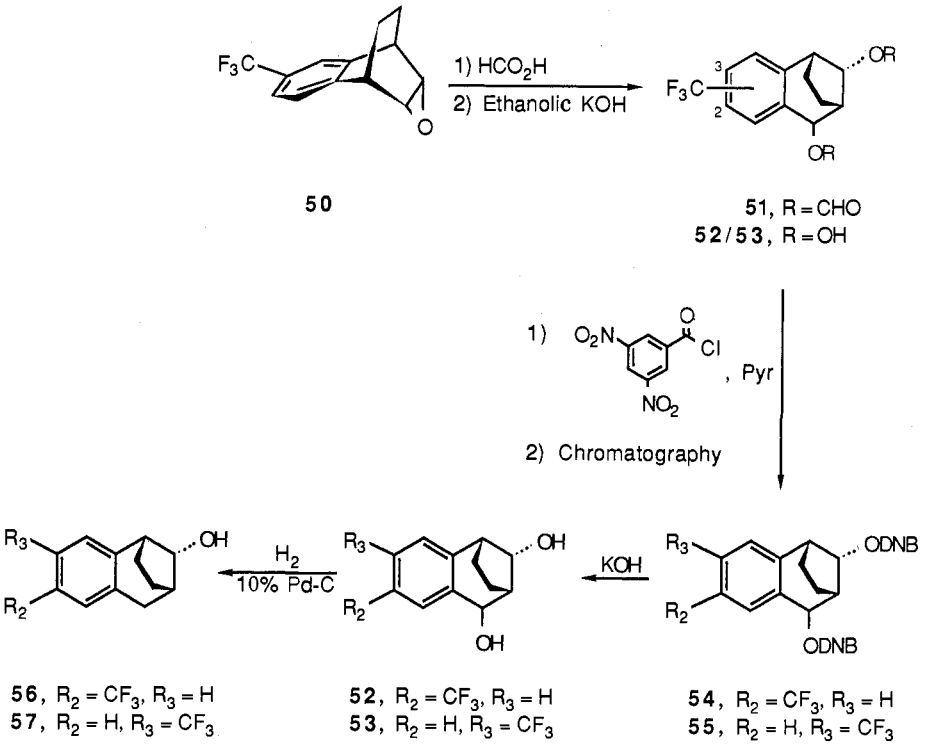
Conversion of the syn alcohols **45**, **46**, **56**, and **57** to amines **20–27** (Scheme VII) follows from the methodology used in the preparation of unsubstituted analogues **12** and **13**. Oppenauer oxidation of the syn alcohols afforded the corresponding ketones **58–61**, which in turn were transformed into oxime derivatives **62–65** by using hydroxylamine hydrochloride and sodium acetate. In each case, the oximes existed as an equilibrium mixture of the *E* and *Z* isomers as evidenced by the duplicate signals in both the ^1H and ^{13}C NMR spectra.

Modeled after the reduction of oxime **34**, hydrogenation of **65** was initially attempted over 10% Pd/C at 45 psi in MeOH saturated with HCl(g). The major product of the reaction (75% of the isolated material) was ketone **61**, which resulted from aqueous hydrolysis, during workup, of the corresponding imine, which is a known intermediate in the hydrogenation of oximes.[48] Extended reaction times did not alleviate this problem. In an attempt to increase the reactivity of the intermediary imine, hydrogenation was carried out in glacial acetic acid. Under these conditions, a 95% yield of a mixture of anti amine **23** and syn amine **27** was realized. The amine mixture was separated by chromatography of the corresponding formamides **72** and **73**. Subsequent hydrolysis afforded isomerically pure **23** and **27**. Catalytic hydrogenation, according to the conditions outlined above, also proved successful in reducing oximes **62–64** to the corresponding amine mixtures, which were readily separated by chromatography of the respective formamide derivatives. With respect to the reduction of oximes **63** and **64**, a higher degree of formation of the anti stereoisomer was realized when hydrogenation was carried out at lower pressure (30 psi) and longer reaction times (48 h). Finally, acid hydrolysis of the separated formamides (**66–71**) afforded the corresponding amines **20–22** and **24–26**. Assignment of the stereochemistry (syn versus anti) for amines **20–27** was based on the splitting pattern of hydrogen H10 as discussed in the stereochemical assignment of **12** and **13**. Stereochemical purity (syn versus anti) was established by ^1H and ^{13}C NMR spectrometry

(47) Meschke, R. W.; Hartung, W. H. *J. Org. Chem.* **1960**, *25*, 137.

(48) Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic: New York, 1967; Chapter 9.

Scheme VI



50

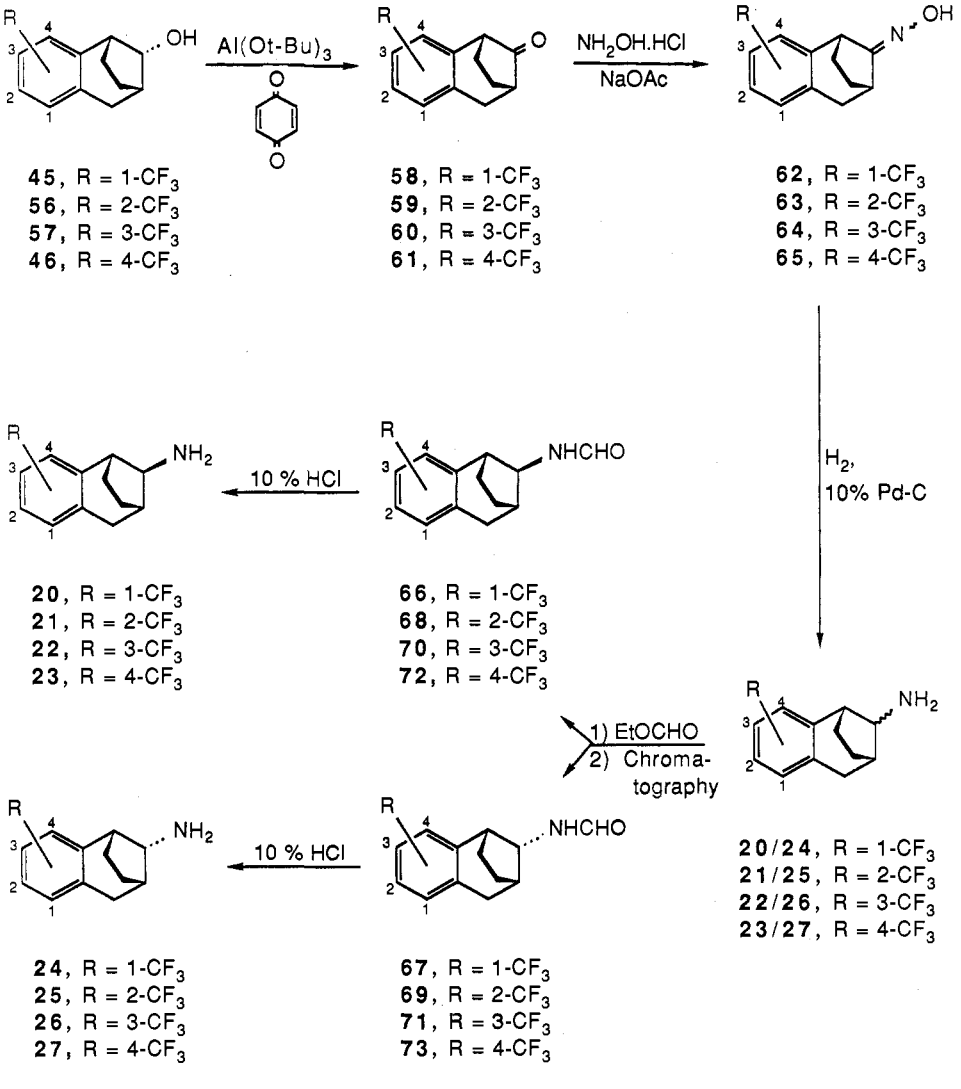
51, R = CHO
52/53, R = OH

56, $R_2 = CF_3$, $R_3 = H$
57, $R_2 = H$, $R_3 = CF_3$

52, $R_2 = CF_3$, $R_3 = H$
53, $R_2 = H$, $R_3 = CF_3$

54, $R_2 = CF_3$, $R_3 = H$
55, $R_2 = H$, $R_3 = CF_3$

Scheme VII



45, R = 1-CF_3
56, R = 2-CF_3
57, R = 3-CF_3
46, R = 4-CF_3

58, R = 1-CF_3
59, R = 2-CF_3
60, R = 3-CF_3
61, R = 4-CF_3

62, R = 1-CF_3
63, R = 2-CF_3
64, R = 3-CF_3
65, R = 4-CF_3

20, R = 1-CF_3
21, R = 2-CF_3
22, R = 3-CF_3
23, R = 4-CF_3

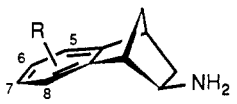
66, R = 1-CF_3
68, R = 2-CF_3
70, R = 3-CF_3
72, R = 4-CF_3

20/24, R = 1-CF_3
21/25, R = 2-CF_3
22/26, R = 3-CF_3
23/27, R = 4-CF_3

24, R = 1-CF_3
25, R = 2-CF_3
26, R = 3-CF_3
27, R = 4-CF_3

67, R = 1-CF_3
69, R = 2-CF_3
71, R = 3-CF_3
73, R = 4-CF_3

Table I. In Vitro Activity of Conformationally Defined β-Phenylethylamines in the Benzonorbornene System as Substrates and Inhibitors of PNMT



6, R = H
14, R = 5-CF_3
15, R = 6-CF_3
16, R = 7-CF_3
17, R = 8-CF_3

8, R = H
18, R = 5-CF_3
19, R = 6-CF_3

	K_i ± SEM, μM	K_m ± SEM, μM	V_{max}[a] ± SEM	(V_{max}/K_m) × 100 ± SEM
6	479 ± 27[b]	392 ± 127[c]	0.04 ± 0.003[c]	0.01 ± 0.002
8	258 ± 27[b]	151 ± 19[c]	0.17 ± 0.006[c]	0.12 ± 0.012
14		33 ± 4	0.49 ± 0.024	1.51 ± 0.011
15		52 ± 9	1.38 ± 0.086	2.67 ± 0.34
16	204 ± 65[c]			
17	350 ± 59[c]			
18	12.1 ± 0.6			
19		14.6 ± 2.2	0.57 ± 0.033	3.90 ± 0.38
4	15 ± 2[b]			
10	1296 ± 170[b]			

[a] Units of V_{max}: nanomoles of product formed per milligram of protein per minute. [b] Taken from ref 28. [c] Taken from ref 29.

and ultimately by gas chromatography. Each of the amines was at least 99.5% free of the other isomers.

Biochemistry

Amines **12**, **13**, and **18–27** were evaluated as their hydrochloride salts for activity as both substrates and inhibitors. Bovine adrenal PNMT,[49] which had been purified according to the method of Connett and Kirshner through the isoelectric precipitation step,[50] was used. In vitro activity as substrates and inhibitors of PNMT was assessed by use of a standard radiochemical assay that has been previously described for both substrates[51] and inhibitors.[28] For the determination of the kinetic constants for substrates, the assay was carried out by using at least six concentrations of the variable substrate. Inhibition constants in this investigation were determined by using at least three different concentrations of inhibitor, as previously described, with phenylethanolamine as the variable substrate.

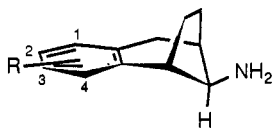
Results and Discussion

Conformationally defined analogues **12**, **13**, and **18–27** were evaluated in vitro for activity as both substrates and inhibitors of PNMT. With respect to the trifluoromethyl-substituted β-phenylethylamines in the benzonorbornene system (Table I), amine **19** (6-CF_3) was found to display enhanced activity as a substrate (K_m = 14.6 μM, (V_{max}/K_m) × 100 = 3.90) over **6**, **8**, **14**, and **15**. While regioisomer **18** (5-CF_3) does not exhibit activity as a substrate up to concentrations of 2 mM, it displays greater affinity as a competitive inhibitor (K_i = 12.1 μM) over **6**, **8**, **16**, and **17**. In regard to the β-phenylethylamines in the 5,8-methano-5,6,7,8-tetrahydro-9*H*-benzobicycloheptene system (Table II), neither of the unsubstituted analogues **12** and **13** displayed any detectable activity as a substrate up to concentrations of 2 mM. Rather, fully extended analogue **12** exhibited competitive inhibition (K_i = 106 μM) that was greater than that found for unsubstituted analogues **6** and **8** (Table I) and analogue **10** (Table II). Predictably, gauche analogue **13** displayed only weak uncompetitive kinetics. In regard to the trifluoromethyl-substituted derivatives **20–27**, fully extended analogues **20** (1-CF_3) and **21** (2-CF_3) displayed significant activity as substrates (K_m = 34.4 μM, (V_{max}/K_m) × 100 = 1.51, and K_m = 45.8 μM, (V_{max}/K_m) × 100 = 1.00, respectively). Regioisomers **22** (3-CF_3) and **23** (4-CF_3) and the gauche analogues **25** (2-CF_3) and **26** (3-CF_3), however, acted as competitive inhibitors (K_i = 31.8, 51.1, 1803, and 801 μM respectively). Isomers **24** (1-CF_3) and **27** (4-CF_3) exhibited uncompetitive inhibition. The fact that **12**, **18**, **22**, **23**, **25**, and **26** displayed competitive inhibition kinetics is consistent with binding to the same site within the enzyme to which phenylethanolamine binds.

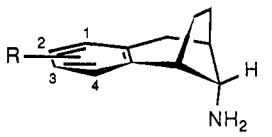
Trifluoromethyl-substituted amines **18** and **19** were prepared in order to study the nature of the lipophilic pocket with respect to amine interaction in bound β-phenylethylamines of type **8**. The enhanced affinity of **18** (5-CF_3) as an inhibitor, over parent unsubstituted analogue **8**, coupled with the fact that the 6-CF_3 regioisomer **19** proved to be a better substrate than **8**, indicates that the CF_3 group adds a positive contribution to binding in each of these regioisomers. The large degree of enhancement in activity found for both **18** and **19** would be suggestive of a very strong interaction of the CF_3 group at the lipophilic pocket within the aromatic ring binding region of the active site of PNMT. In addition, the finding that **18** and **19** displayed enhanced affinity over their respective inhibitor (**16**,**17**) and substrate (**14**,**15**) counterparts adds further support to our argument that PNMT prefers to bind molecules with a more planar relationship (τ_1 = 0°) between the aromatic ring and the amino nitrogen.

The fact that **18** does not display activity as a substrate, despite the positive contribution of the CF_3 group, is

Table II. In Vitro Activity of Conformationally Defined β-Phenylethylamines in the Benzobicyclo[3.2.1]octane System as Substrates and Inhibitors of PNMT



12, R = H
20, R = 1-CF_3
21, R = 2-CF_3
22, R = 3-CF_3
23, R = 4-CF_3



13, R = H
24, R = 1-CF_3
25, R = 2-CF_3
26, R = 3-CF_3
27, R = 4-CF_3

	K_i ± SEM, μM	K_m ± SEM, μM	V_{max}[a] ± SEM	(V_{max}/K_m) × 100 ± SEM
12	106 ± 4			
13	8900 ± 1050[b]			
20		34.4 ± 2.9	0.52 ± 0.016	1.51 ± 0.086
21		45.8 ± 9.3	0.46 ± 0.030	1.00 ± 0.15
22	31.8 ± 1.1			
23	51.1 ± 1.5			
24	1429 ± 240[b]			
25	1803 ± 82			
26	801 ± 24			
27	191 ± 54[b]			
4	15 ± 2[c]			
10	1296 ± 170[b]			

[a] Units of V_{max}: nanomoles of product formed per milligram of protein per minute. [b] Uncompetitive inhibition; all others are competitive. [c] Taken from ref 28.

(49) Adrenal PNMT has been found to be similar to the brain enzyme in terms of its susceptibility to inhibitors: Fuller, R. W. *Annu. Rev. Pharmacol. Toxicol.* **1982**, *22*, 31 and references therein.
(50) Connett, R. J.; Kirshner, N. *J. Biol. Chem.* **1970**, *245*, 329.
(51) Grunewald, G. L.; Grindel, J. M.; Vincek, W. C.; Borchardt, R. T. *Mol. Pharmacol.* **1975**, *11*, 694.

surprising in light of the fact that introduction of the CF_3 at carbon C5 in **6** (i.e., **14**), leads to a significant enhancement in activity as a substrate. Obviously, **18** is not binding in an orientation that allows the methyl donor, AdoMet, to approach close enough for methyl transfer to occur. Given the strength of the interaction of lipophilic substituents at the aromatic ring binding region of the active site, it is possible that the positive interaction of the 5-CF_3 group in **18** displaces the aromatic ring into a slightly different binding orientation. Since this system is conformationally fixed, this displacement would necessarily translate to the bicyclic portion of the molecule. In this way, the amino nitrogen, while still in a region in which it could interact and add a positive binding contribution, would be shifted out of the region of the active site where AdoMet approaches to transfer its methyl group. This finding, coupled with the fact that structurally similar **14**, **15**, and **19** act as substrates for the enzyme, suggests that only specific spatial orientations between the lipophilic substituent and the amino nitrogen allow both to interact simultaneously in a manner in which the amine lies in the methylation zone.

Conformationally defined amphetamine analogues **12** and **13** (Table II) were studied in order to gain better insight into the conformational basis of binding β-phenylethylamines, which are incorporated into the 2AT system, at the active site of PNMT. The fact that **12** (τ_2 = 170°) displays competitive inhibition while **13** (τ_2 = 47°) exhibits only weak uncompetitive kinetics supports our previous finding[29] that a fully extended side chain conformation (τ_2 = 180°) is preferred when β-phenylethylamines bind at the active site of PNMT. Further inspection of the data in Table II also reveals that **12** (K_i = 106 μM) is a better competitive inhibitor of PNMT than both **6** (K_i = 479 μM) and **10** (K_i = 1296 μM). In light of the fact that the additional steric bulk of the ethano bridge is the same in analogues **12** and **10**, the pronounced enhancement in binding affinity of **12** (over **10**) indicates that the lower energy, half-chair conformation mimicked by **12** (τ_1 = 35°) is preferred for active site binding over the boat form found in both **6** and **10** (τ_1 = 69° and 60° respectively). This result is consistent with our previous finding that molecules with a lower τ_1 torsion angle preferentially bind to the active site of PNMT.

Given that **6** and **8** exhibit marginal activity as substrates for PNMT, it might be expected that conformationally similar **10** and **12** would display similar activity. The fact that they do not may suggest that the negative steric interaction of the ethano bridge orients the molecules in a manner in which the amino nitrogen is shifted out of the region of the active site where AdoMet approaches to transfer its activated methyl group. This does not appear to be the case for analogues **20** (1-CF_3) and **21** (2-CF_3; Table II), however, in which introduction of the trifluoromethyl group results in good activity as substrates. One possible explanation for this result would be that interaction of the trifluoromethyl group in **20** and **21** displaces the aromatic ring into a slightly different binding orientation. Because of the rigidity of this system, this displacement would necessarily translate to the bicyclic portion of the molecule and, as a result, **20** and **21** would bind in an orientation in which the ethano bridge has shifted into a region of the active site that has fewer steric constraints. Through elimination of the negative steric interactions, the amino nitrogen could interact in a region of the active site in which methylation can take place. These findings would suggest that the region of steric intolerance above the alicyclic ring in the active site of the enzyme has a degree of directionality.

Evidence for the overall lipophilic nature of the aromatic ring binding region within the active site of PNMT is abundant. Fuller et al.[35] have previously shown that amphetamine analogues that possess electron-withdrawing, lipophilic substituents in the meta and/or para positions show enhanced activity as inhibitors with respect to amphetamine itself. Similar findings have also been reported for the benzylamine[34,52] and phenylethanolamine[33,34] classes of PNMT ligands. In this regard, the trifluoromethyl-substituted analogues **20–27** were prepared in order to study the nature of the lipophilic interaction with respect to bound β-phenylethylamines of type **12** and **13**. Similar to the previous results for **14–17**, introduction of a trifluoromethyl group at carbons C1 and C2 in **12** (i.e., **20** and **21**) results in good activity as substrates. Substitution of a trifluoromethyl group at carbons C3 and C4, on the other hand (i.e., **22** and **23**), resulted in competitive inhibition which was greater than that found for **12**. Both of these results indicate that substitution of a trifluoromethyl group at any point on the aromatic ring in **12** results in a positive binding contribution and would support previous findings that the aromatic ring binding region of the active site of PNMT contains a large degree of lipophilic character.

On the basis of the pronounced enhancement in activity found for **12** over **10**, the positive contribution to binding of the ethylamine side chain conformation in **20–23** should be large. Because of the additional steric bulk of the ethano bridge, however, it is difficult to estimate the degree to which the preferred side chain conformation in **20–23** enhances the binding affinity of these analogues. In this regard, the fact that **20** and **21** are only as good as or weaker than substrates such as **14** and **15** may indicate that the enhanced binding affinity that results from the preferred conformation in **20** and **21** is canceled out by the negative steric interaction of the carbocyclic skeleton needed to impose such a conformational constraint. Similar arguments may explain why **22** and **23** display enhanced competitive inhibition over **16** and **17** yet diminished affinity with respect to **18**, which holds the ethylamine side chain in a similar conformation.

Another very interesting result from this study is the fact that **25** and **26**, despite possessing a folded side chain conformation, display competitive inhibition kinetics. In view of our previous results that a fully extended side chain conformation is required for β-phenylethylamines to interact at the active site of PNMT, it would seem that **25** and **26** are not binding in a manner consistent with other β-phenylethylamine ligands. Given that the distance between the center of the aromatic ring and the amino nitrogen in **25** and **26** (3.65 Å) is the same as that (3.70 Å) in tetrahydroisoquinoline (a folded β-phenylethylamine that is thought to bind to PNMT as a benzylamine[53]), it may be that **25** and **26** are binding in a manner more consistent with the benzylamine class of PNMT inhibitors. In this regard, the poor activity of **25** and **26** is consistent with recent findings that indicate that steric bulk is not tolerated at the benzylamine binding region within the active site of PNMT.[54]

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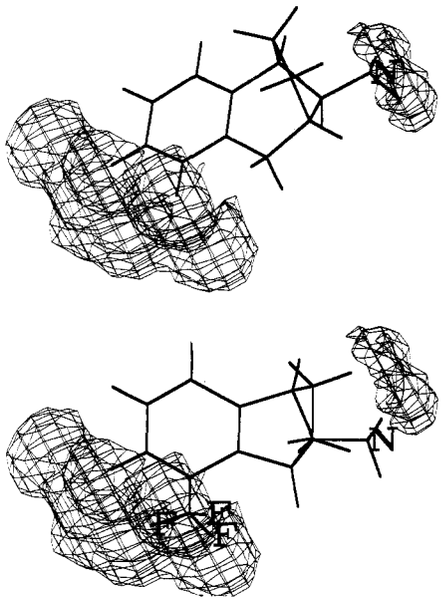

Figure 5. Representation of the lipophilic pocket with respect to the region in the PNMT active site at which methylation occurs. The SYBYL[55] molecular graphics system was used to generate these figures. The five trifluoromethyl-substituted conformationally defined amphetamines that displayed activity as a substrate (**14**, **15**, **19–21**) were overlayed by a least-squares fit of the center of the aromatic rings, the amino nitrogens, and the carbon to which the nitrogen is attached (using the FIT command of SYBYL). The top figure shows the union of volumes of the carbocyclic skeletons of **6**, **8**, and **12** subtracted from the union of volumes for the substrates **14**, **15**, **19–21** using the MVOLUME command and therefore represents the lipophilic pocket (webbed area at left) in relationship to the amine binding region in which methylation takes place (webbed area at right). To orient the reader, the structure of *anti*-10-amino-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**12**) is shown. Analogues **14**, **15**, and **19–21** allow simultaneous interaction at both these sites and therefore exhibit activity as substrates. The fact that structurally and conformationally similar **18** does not display activity as a substrate indicates that it does not contain the necessary spatial arrangement to allow for simultaneous interaction at both sites. For the two most active substrates, **15** and **19**, the distances between the carbon of the trifluoromethyl group and the amino nitrogen are 7.39 and 7.09 Å, respectively. The corresponding distance in analogue **18**, however, is only 5.48 Å. As depicted in the lower figure, this shorter distance does not allow simultaneous interaction at both the lipophilic pocket and the methylation zone. For this reason, despite being structurally and conformationally similar to analogues **14**, **15**, and **19–21**, **18** does not display activity as a substrate.

The finding that the trifluoromethyl group enhances the binding affinity in each of the analogues **20–23** yet only **20** and **21** display activity as substrates further suggests that only specific spatial orientations between the lipophilic trifluoromethyl substituent and the amino nitrogen allow both to interact simultaneously in a manner in which the amine lies in a region of the active site in which methylation can take place. A perfect example of this is the fact that analogues **14**, **15**, **19**, **20**, and **21** display good activity as substrates while structurally very similar **18** is completely inactive. In an effort to explain this result, the SYBYL molecular graphics package[55] was used to generate Figure 5, which represents the orientation of the methylation zone with respect to the lipophilic pocket within the active site of PNMT. In order for the trifluoromethyl-substituted, conformationally defined β-phenylethylamines in this study to display activity as substrates, simultaneous interaction at both binding regions must occur.

In summary, the findings from this study, coupled with previous results, indicate that β-phenylethylamines (substrates and inhibitors) bind at the active site of PNMT in a fully extended conformation ($\tau_2 = 180°$) with a more planar relationship between the aromatic ring and the amino nitrogen ($\tau_1 = 0°$). In addition, and consistent with these facts, it has been shown through the use of conformationally defined analogue **12** that PNMT preferentially binds 2AT analogues which exist in the half-chair conformation. The lack of activity as a substrate for **12** indicates that regions of steric bulk intolerance exist within the active site of PNMT and are situated above the alicyclic ring of bound **12**. Further, this region of intolerance appears to have a directionality.

We have also prepared and evaluated a number of conformationally defined norfenfluramine analogues in order to characterize the lipophilic interaction that occurs when β-phenylethylamines possessing aryl lipophilic substituents bind at the active site of PNMT. Consistent with previous results, the findings from this study indicate that the aromatic ring binding region of the active site of PNMT contains a large degree of lipophilic character. Interactions at these regions of lipophilic character appear to be very strong since they can alter the relative binding orientation of structurally and conformationally similar analogues. In this light, it has been shown that, in the case of the trifluoromethyl-substituted, conformationally defined analogues used in this study, only specific spatial orientations between the trifluoromethyl group and the amino nitrogen allow both to interact simultaneously in a manner that allows the amine to bind in a region in which methylation can occur.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus calibrated with known compounds and are corrected accordingly. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on either a Varian FT-80A or XL-300 spectrometer using deuteriated chloroform ($CDCl_3$) as the solvent, and chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS; 0.0 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on either a Varian FT-80A or XL-300 spectrometer using $CDCl_3$ as the solvent, and chemical shifts are reported in parts per million relative to $CDCl_3$ (77.0 ppm). Infrared spectra (IR) were recorded on either an IBM FT-IR 32 or a Perkin-Elmer IR-727 spectrometer. Electron-impact mass spectra (EIMS) were obtained on either a Varian Atlas CH-5 or Ribermag R 10-10 mass spectrometer. Gas chromatography was performed on a Hewlett-Packard Model 5880A equipped with a 10% KOH on Apiezon column ($^1/_4$ in. × 72 in.) and an FID detector. Combustion analyses were performed on a Hewlett-Packard Model 185B CHN analyzer at the University of Kansas or by Midwest Microlab, Ltd. (Indianapolis, IN) and were within 0.4% of the calculated values. Preparative centrifugal thin-layer chromatography (PC-TLC) was performed on a Harrison Model 7924 Chromatotron (Harrison Research, Palo Alto, CA) using Merck silica gel 60 PF254 containing $CaSO_4 \cdot 0.5H_2O$ binder on 1-, 2-, or 4-mm-thickness plates. Medium-pressure liquid chromatography (MPLC), using an adaptation of the apparatus of Meyers and co-workers,[56] and flash chromatography were performed by using

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Merck silica gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed by using silica gel with fluorescent indicator coated on 1 × 3 inch glass plates in 0.2-mm thickness. Bulb-to-bulb distillations were carried out by using a Kugelrohr distillation apparatus (Aldrich Chemical Co.).

S-Adenosyl-L-methionine was obtained from Sigma Chemical Co. (St. Louis, MO). [*methyl*-^{3}H]-*S*-Adenosyl-L-methionine, which was used in the radiochemical assays, was purchased from New England Nuclear Corp. (Boston, MA). Bovine adrenal glands, required for the purification of the enzyme used in this study, were obtained from Pel-Freez Biologicals (Rogers, AR). Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) and ether (Et_2O) were distilled from sodium/benzophenone ketyl; dry methylene chloride (CH_2Cl_2) was obtained by distillation over phosphorus pentoxide; dry benzene was obtained by distillation from calcium hydride; and anhydrous methanol (MeOH) and ethanol (EtOH) were obtained by distillation from magnesium. Unless otherwise stated, all MeOH and EtOH used was anhydrous. Where appropriate, amine hydrochloride salts were prepared by passing anhydrous HCl gas over a dried ethereal solution of the free base. All reactions requiring anhydrous conditions and/or an inert atmosphere were performed under a positive N_2 or Ar flow, and all glassware was oven-dried and/or flame-dried.

***anti*-9-Amino-6-(trifluoromethyl)benzonorbornene (19).** Amine **19** was synthesized by using a modified version of the procedure of Ehrenfreund and Zbiral.[37] To a solution of 6-(trifluoromethyl)benzonorbornadiene (**30**; 7.20 g; 34.3 mmol), prepared according to the method of Schubert,[38] and (diacetoxyiodo)benzene (22.5 g; 69.9 mmol) in 1600 mL of dry CH_2Cl_2 at −25 °C was slowly added 17.4 g (151 mmol) of azidotrimethylsilane in 200 mL of anhydrous CH_2Cl_2. The mixture was stirred at −25 °C for 5 h and was allowed to warm to room temperature over 7 h. The reaction mixture was washed with H_2O (6 × 500 mL), saturated aqueous $NaHCO_3$ (2 × 500 mL), and H_2O (2 × 500 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded 16.8 g of yellow oil, which was subjected to flash chromatography using hexanes as the eluent to afford 2.90 g (11.5 mmol; 33%) of azide **31** (IR 2120 cm^{-1}) as a clear oil.

Azide **31** (2.90 g; 11.5 mmol) in 70 mL of anhydrous Et_2O was dripped into a slurry of 14.1 g of $LiAlH_4$ in 400 mL of dry Et_2O at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was quenched by the successive addition of H_2O (55 mL), 3 N aqueous NaOH (150 mL), and H_2O (100 mL). The reaction mixture was filtered, and the residue was washed well with $(CH_3)_2CO$ (2 × 100 mL) and Et_2O (2 × 100 mL). The aqueous and organic layers were separated, and the latter was extracted with 3 N aqueous HCl (8 × 100 mL). The pooled acidic extracts were basified with solid KOH and were extracted with Et_2O (6 × 100 mL). The organic pool was washed with H_2O (2 × 150 mL) and brine (100 mL) and dried over K_2CO_3. Evaporation of the solvent in vacuo gave 2.38 g (10.5 mmol; 91% based on azide **31**) of **19** as a clear oil: ^{1}H NMR ($CDCl_3$; 80 MHz) 7.40–7.26 (m, 3 H, Ar H), 3.06 (m, 3 H, bridgeheads and H9), 2.13–2.02 (m, 2 H, exo H2 and exo H3), 1.70–1.01 (m, 4 H, 2 H exchangeable in D_2O, endo H2, endo H3, and NH_2); IR (film) 3400, 3310, 2988, 2899, 1640, 1468, 1352, 1321, 1283, 1148, 1110, 1051, 886, 832, 708 cm^{-1}; ^{13}C NMR ($CDCl_3$; 20 MHz) 151.0, 147.6, 131.6, 122.9, 121.2, 118.1, 68.1, 48.5, 32.8. **19**·HCl: mp 254.8–256.5 °C (recrystallized from EtOH/Et_2O); EIMS, *m/z* (relative intensity) 227 (M^+, 22.9), 210 (42.1), 196 (52.1), 184 (54.0), 177 (52.7), 164 (25.5), 151 (27.4), 141 (82.6), 128 (75.0), 115 (100). Anal. ($C_{12}H_{13}ClF_3N$) C, H, N.

***anti*-9-Amino-5-(trifluoromethyl)benzonorbornene (18).** Amine **18** was prepared according to the conditions outlined in the preparation of **19**. In this manner, 4.80 g (22.8 mmol) of 5-(trifluoromethyl)benzonorbornadiene (**28**), prepared according to the method of Grunewald et al.,[36] afforded, after bulb-to-bulb distillation (85 °C (0.15 mm)), 2.50 g (11.0 mmol; 48% based on diene **28**) of **18** as a clear oil: ^{1}H NMR ($CDCl_3$; 80 MHz) 7.43–7.10 (m, 3 H, Ar H), 3.47–3.20 (m, 1 H, bridgehead), 3.13–2.93 (m, 2 H, bridgehead and H9), 2.27–1.87 (m, 2 H, exo H2 and exo H3), 1.52 (s, 2 H, exchangeable in D_2O, NH_2), 1.32–0.93 (m, 2 H, endo H2 and endo H3); IR (film) 3410, 3338, 2989, 1660, 1599, 1439, 1347, 1325, 1222, 1169, 1117, 1056, 1002, 818, 763, 712 cm^{-1}; ^{13}C NMR ($CDCl_3$; 20 MHz) 148.4, 148.1, 144.5, 125.6, 124.3, 122.1, 67.4, 47.8, 47.2, 23.1, 22.5. **18**·HCl: mp >300 °C (recrystallized from MeOH/Et_2O); EIMS, *m/z* (relative intensity) 227 (M^+, 29.8), 210 (20.7), 196 (100), 177 (47.4), 172 (22.4), 151 (25.9), 141 (48.0), 128 (53.4), 115 (52.7). Anal. ($C_{12}H_{13}ClF_3N$) C, H, N.

***exo*- and *endo*-2,3-Epoxy-5-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene (39 and 40 respectively).** Intermediate 5-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene (**38**) was prepared according to the general procedure used by Tanida et al.[44] for the preparation of similar dienes in the benzonorbornadiene class. To 4.0 g (164 mmol) of Mg turnings in a flame-dried flask under Ar was added 10 mL of a solution of 30.0 g (103 mmol) of 2-iodo-3-fluorobenzotrifluoride (**37**)[45] and 25 mL (21.0 g; 262 mmol) of freshly distilled cyclohexadiene dissolved in 300 mL of anhydrous THF. The contents of the flask were heated gently to initiate reaction, and the remainder of the solution was added at such a rate as to maintain a slow reflux. The resulting mixture was heated at reflux for an additional 2 h, cooled to room temperature, and then treated with 100 mL of 10% aqueous NH_4Cl. The aqueous and organic layers were separated, and the latter was washed with 10% aqueous NH_4Cl (100 mL), H_2O (100 mL), and brine (100 mL). After drying over Na_2SO_4, the solvent was evaporated in vacuo to give 29.5 g of a dark brown oil, which was partially purified by MPLC with hexanes as the eluent. The presence of the desired diene **38** was detected by ^{1}H NMR in which the olefinic protons (H2 and H3) appear as a multiplet at 6.50–6.40 ppm and the bridgehead protons (H1 and H4) appear as multiplets at 4.45–4.25 and 4.12–3.75 ppm. The fraction containing the desired diene (21.1 g) was carried on to the next reaction.

To a solution of 30 g (174 mmol) of *m*-chloroperoxybenzoic acid in 400 mL of anhydrous CH_2Cl_2 was slowly added a solution of 18.3 g of the above crude diene mixture in 75 mL of dry CH_2Cl_2. The reaction mixture was stirred under Ar at room temperature for 72 h and was treated with saturated aqueous $NaHCO_3$ (100 mL), and the aqueous and organic layers were separated. The organic phase was washed with 5% aqueous $NaHCO_3$ (3 × 100 mL) and H_2O (100 mL). After drying over Na_2SO_4, evaporation of the solvent in vacuo gave 15.1 g of a yellow oil, which was subjected to MPLC using hexanes/ethyl acetate (5:1) as the eluent to afford 4.10 g of **40** and 6.95 g of crude **39** (TLC R_f values in the same solvent: **39**, 0.45; and **40**, 0.37).

***exo*-2,3-Epoxy-5-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene (39).** Subjecting 400 mg of the fraction containing **39** to PCTLC (4 mm) using hexanes as the eluent, followed by bulb-to-bulb distillation (68 °C (0.09 mm)), afforded 240 mg of pure **39** for spectral analysis: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.50 (d, 1 H, J = 8.3 Hz, Ar H), 7.40 (d, 1 H, J = 7.3 Hz, Ar H), 7.27 (t, 1 H, J = 7.8 Hz, Ar H), 3.87 (s, 1 H, bridgehead), 3.43 (s, 1 H, bridgehead), 3.29–3.23 (m, 2 H, H2 and H3), 2.10 (d, 2 H, J = 7.4 Hz, anti H9 and anti H10), 1.07 (d, 2 H, J = 7.2 Hz, syn H9 and syn H10); IR (film) 3070, 3002, 1605, 1475, 1458, 1420, 1355, 1340, 1325, 1252, 1170, 1140, 1080, 995, 957, 860, 810, 792, 760 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 145.39, 141.89, 128.73, 126.55 (q, J_{CF} = 32.0 Hz, C5), 126.00, 124.25 (q, J_{CF} = 272.6 Hz, CF_3), 123.06 (q, J_{CF} = 4.8 Hz), 57.49, 57.31, 38.06, 34.76, 23.00, 22.46; EIMS, *m/z* (relative intensity) 240 (M^+, 17.1), 222 (21.8), 196 (96.8), 191 (40.6), 177 (46.8), 141 (46.8), 128 (31.2), 115 (100). Anal. ($C_{13}H_{11}F_3O$) C, H.

***endo*-2,3-Epoxy-5-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene (40).** Compound **40** (4.10 g; 17.1 mmol; 17% from **37**) was obtained as a white solid: mp 72.1–72.6 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) 7.52 (d, 1 H, J = 5.5 Hz, Ar H), 7.32–7.22 (m, 2 H, Ar H), 3.95 (s, 1 H, bridgehead), 3.54 (s, 1 H, bridgehead), 3.48–3.38 (m, 2 H, H2 and H3), 1.80 (d, 2 H, J = 8.4 Hz, anti H9 and anti H10), 1.36 (d, 2 H, J = 7.2 Hz, syn H9 and syn H10); IR (film) 3017, 2951, 1473, 1350, 1317, 1180, 1157, 1116, 1068, 844 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 140.18, 136.34, 127.94, 126.30, 125.41 (q, J_{CF} = 30.5 Hz, C5), 124.36 (q, J_{CF} = 231.3 Hz, CF_3), 123.36 (q, J_{CF} = 4.8 Hz), 48.54, 48.37, 37.10, 33.17, 21.75, 21.59; EIMS, *m/z* (relative intensity) 240 (M^+, 50.6), 222 (42.1), 212 (48.1), 196 (63.6), 191 (55.1), 184 (36.0), 164 (16.9), 128 (40.3), 115 (100). A small sample was sublimed (75 °C (0.4 mm)) for elemental analysis. Anal. ($C_{13}H_{11}F_3O$) C, H.

9-*exo*,10-*syn*-Bis(formyloxy)-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (41) and 9-*exo*,10-*syn*-Bis(formyloxy)-4-(trifluoromethyl)-5,6,7,8-

tetrahydro-5,8-methano-9*H*-benzocycloheptene (42). According to the methodology of Kitamogi and Takano,[41] a solution of 7.20 g (30.0 mmol) of epoxide **40** and 72.0 mL of 98% formic acid in 55 mL of anhydrous Et_2O was heated under Ar at 33 °C for 24 h. The reaction mixture was diluted with 100 mL of Et_2O and carefully washed with 5% aqueous $NaHCO_3$ (3 × 100 mL), H_2O (100 mL), and brine (100 mL). After drying over Na_2SO_4, evaporation of the solvent in vacuo afforded 10.7 g of a mixture of **41** and **42**, which was separated by MPLC using hexanes/ethyl acetate (7:1) as the eluent (TLC R_f values in the same solvent: **42**, 0.21; and **41**, 0.16).

9-*exo*,10-*syn*-Bis(formyloxy)-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (41). Compound **41** (1.96 g; 6.24 mmol; 21%) was obtained as clear crystals: mp 117.8–119.3 °C (recrystallized from ethyl acetate/hexanes); ^1H NMR ($CDCl_3$; 300 MHz) 7.99 (s, 1 H, OCHO), 7.94 (s, 1 H, OCHO), 7.65 (d, 1 H, J = 7.8 Hz, Ar H), 7.46 (t, 1 H, J = 7.3 Hz, H3), 7.34 (d, 1 H, J = 7.3 Hz, Ar H), 6.11 (s, 1 H, H9), 5.08 (t, 1 H, J = 4.3 Hz, H10), 3.43 (t, 1 H, J = 4.9 Hz, H5), 3.18–3.05 (m, 1 H, H8), 2.23–1.96 (m, 2 H, exo and endo H6), 1.67–1.44 (m, 2 H, exo and endo H7); IR (KBr) 3021, 2936, 1727, 1310, 1227, 1194, 1174, 1152, 1125, 762 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 160.97, 159.81, 142.25, 132.38, 130.16 (q, J_{CF} = 30.5 Hz, C1), 129.48, 128.92, 126.24 (q, J_{CF} = 4.1 Hz), 124.19 (q, J_{CF} = 274.6, CF_3), 73.50, 70.76, 43.79, 37.68, 28.35, 22.29; EIMS, m/z (relative intensity) 314 (M^+, 6.0), 286 (18.5), 269 (21.8), 240 (77.5), 223 (62.1), 212 (97.7), 192 (100), 177 (38.4), 171 (19.3), 153 (22.7), 141 (24.4), 128 (22.0), 115 (38.0). Anal. ($C_{15}H_{13}F_3O_4$) C, H.

9-*exo*,10-*syn*-Bis(formyloxy)-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (42). Compound **42** (6.24 g; 19.8 mmol; 66%) was obtained as clear prisms: mp 62.0–63.5 °C (recrystallized from ethyl acetate/hexanes); ^1H NMR ($CDCl_3$; 300 MHz) 8.12 (s, 1 H, OCHO), 7.92 (s, 1 H, OCHO), 7.67 (d, 1 H, J = 7.8 Hz, H3), 7.50 (d, 1 H, J = 7.8 Hz, H1), 7.38 (t, 1 H, J = 7.8 Hz, H2), 5.93 (s, 1 H, H9), 5.16 (t, 1 H, J = 5.0 Hz, H10), 3.85–3.77 (m, 1 H, H5), 3.03–2.95 (m, 1 H, H8), 2.24–2.03 (m, 2 H, exo and endo H6), 1.72–1.61 (m, 1 H, exo or endo H7), 1.58–1.48 (m, 1 H, exo or endo H7); IR (film) 2947, 1722, 1462, 1367, 1334, 1317, 1172, 1153, 1122, 1076, 1045, 997, 810, 794 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 160.75, 160.28, 138.60, 133.63, 133.27, 127.91 (q, J_{CF} = 29.9 Hz, C4), 126.65, 126.41 (q, J_{CF} = 6.3 Hz), 124.08 (q, J_{CF} = 273.8 Hz, CF_3), 73.23, 72.49, 38.28, 37.73, 27.99, 22.78; EIMS, m/z (relative intensity) 314 (M^+, 3.1), 286 (3.6), 269 (7.2), 240 (41.9), 223 (16.7), 212 (100), 199 (17.7), 177 (14.1), 128 (7.9), 115 (13.7). Anal. ($C_{15}H_{13}F_3O_4$) C, H.

9-*exo*,10-*syn*-Dihydroxy-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (43). According to the conditions of Kitamogi and Takano,[41] bis(formyloxy) derivative **41** (1.60 g; 5.09 mmol) was stirred at room temperature in 50 mL of 1 N ethanolic KOH for 21 h. The reaction mixture was concentrated in vacuo to give an oily solid, which was dissolved in 50 mL of H_2O and 50 mL of Et_2O. The two layers were separated, and the aqueous phase was extracted with Et_2O (2 × 50 mL). The organic pool was washed with H_2O (20 mL) and brine (20 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave 1.38 g of a white solid, which was recrystallized from ethyl acetate to afford 1.26 g (4.88 mmol; 96%) of **43** as clear crystals: mp 125.9–127.0 °C; ^1H NMR ($CDCl_3$; 300 MHz) 7.60 (d, 1 H, J = 7.3 Hz, Ar H), 7.38 (t, 1 H, J = 8.0 Hz, H3), 7.29 (d, 1 H, J = 7.3 Hz, Ar H), 4.94–4.86 (m, 1 H, H9), 4.38–4.29 (m, 1 H, H10), 4.10 (s, 1 H, exchangeable in D_2O, OH), 3.99 (s, 1 H, exchangeable in D_2O, OH), 3.19 (t, 1 H, J = 3.9 Hz, H5), 2.72–2.61 (m, 1 H, H8), 2.04–1.83 (m, 2 H, exo and endo H6), 1.48–1.37 (m, 1 H, exo or endo H7), 1.31–1.20 (m, 1 H, exo or endo H7); IR (KBr) 3399, 2973, 1449, 1431, 1366, 1312, 1219, 1192, 1138, 1117, 1078, 1017, 978, 810, 771 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 141.29, 134.18, 132.94, 129.83 (q, J_{CF} = 31.0 Hz, C1), 128.57, 125.48 (q, J_{CF} = 6.3 Hz), 124.77 (q, J_{CF} = 274.8 Hz, CF_3), 74.44, 71.43, 46.83, 40.55, 29.00, 21.78; EIMS, m/z (relative intensity) 258 (M^+, 0.6), 240 (100), 222 (95.6), 209 (65.1), 196 (74.6), 191 (76.8), 177 (34.8), 151 (18.6), 142 (42.2), 128 (25.6), 115 (38.5). Anal. ($C_{13}H_{13}F_3O_2$) C, H.

9-*exo*,10-*syn*-Dihydroxy-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (44). Under conditions analogous to those used in the preparation of **43**, 5.86 g (18.6 mmol) of bis(formyloxy) derivative **42** afforded 4.75 g of a white solid, which was recrystallized from ethyl acetate to give 4.35 g (16.8 mmol, 91%) of **44** as white needles: mp 133.4–134.9 °C; ^1H NMR ($CDCl_3$; 300 MHz) 7.64 (d, 1 H, J = 7.8 Hz, Ar H), 7.60 (d, 1 H, J = 7.9 Hz, Ar H), 7.33 (t, 1 H, J = 7.9 Hz, H2), 4.49–4.15 (m, 2 H, H9 and H10), 4.33 (s, 1 H, exchangeable in D_2O, OH), 3.59–3.42 (m, 1 H, H5), 3.51 (s, 1 H, exchangeable in D_2O, OH), 2.63–2.51 (m, 1 H, H8), 2.01–1.84 (m, 2 H, exo and endo H6), 1.59–1.48 (m, 1 H, exo or endo H7), 1.27–1.13 (m, 1 H, exo or endo H7); IR (KBr) 3412, 3279, 3011, 2951, 1593, 1458, 1431, 1350, 1313, 1223, 1197, 1169, 1153, 1113, 1080, 1010, 980, 771 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 138.57, 137.25, 134.52, 127.92 (q, J_{CF} = 29.5 Hz, C4), 126.33, 125.75 (q, J_{CF} = 6.3 Hz), 124.26 (q, J_{CF} = 236.4 Hz, CF_3), 74.53, 74.36, 41.42, 40.95, 28.98, 22.47; EIMS, m/z (relative intensity) 258 (M^+, 2.7), 240 (100), 222 (60.2), 196 (68.9), 191 (80.5), 184 (49.4), 177 (38.3), 133 (32.4), 128 (21.6), 115 (44.5). Anal. ($C_{13}H_{13}F_3O_2$) C, H.

***exo*- and *endo*-2,3-Epoxy-6-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene (49 and 50 respectively).** According to the conditions employed in the preparation of **38**, 35.85 g (124 mmol) of 3-fluoro-4-iodobenzotrifluoride (**47**)[45] gave, after bulb-to-bulb distillation (55 °C (0.08 mm)) and MPLC using hexanes as the eluent, 12.46 g of crude 6-(trifluoromethyl)-1,4-dihydro-1,4-ethanonaphthalene (**48**; ^1H NMR showed the olefinic protons as a multiplet at 6.52–6.27 ppm and the bridgehead protons as a multiplet at 4.07–3.73 ppm).

The fraction containing diene **48** was treated with *m*-chloroperoxybenzoic acid according to the conditions outlined in the preparation of **39** and **40**. After workup, MPLC using hexanes/ethyl acetate (7:1) as the eluent afforded 5.15 g of **50** and 6.32 g of crude **49** (TLC R_f values in the same solvent: **49**, 0.44; and **50**, 0.21).

***exo*-2,3-Epoxy-6-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene (49).** A sample of crude **49** (1.0 g) was further purified for spectral analysis by recrystallization from hexanes. The mother liquor, which contained partially purified **49**, was concentrated in vacuo to give 740 mg of a white solid, which was subjected to PCTLC (4 mm) using hexanes as the eluent, to afford 360 mg of pure **49** as a white solid: mp 103.2–104.7 °C; ^1H NMR ($CDCl_3$; 300 MHz) 7.57–7.31 (m, 3 H, Ar H), 3.58–3.30 (m, 4 H, H2, H3, and bridgeheads), 2.10 (d, 2 H, J = 7.8 Hz, anti H9 and anti H10), 1.07 (d, 2 H, J = 8.4 Hz, syn H9 and syn H10); IR (KBr) 3031, 2975, 1348, 1329, 1306, 1175, 1154, 1117, 1063, 957, 841, 806 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 147.48, 144.21, 128.60 (q, J_{CF} = 32.4 Hz, C6), 125.29, 124.32 (q, J_{CF} = 271.9 Hz, CF_3), 123.47 (q, J_{CF} = 4.0 Hz), 121.87 (q, J_{CF} = 4.5 Hz), 57.59, 57.48, 38.09, 38.04, 23.04; EIMS, m/z (relative intensity) 240 (M^+, 21.4), 222 (13.6), 221 (13.8), 209 (30.3), 196 (100), 191 (37.5), 177 (26.2), 153 (15.3), 141 (32.2), 128 (23.0), 115 (37.3). A small sample was sublimed (72 °C (0.08 mm)) for elemental analysis. Anal. ($C_{13}H_{11}F_3O$) C, H.

***endo*-2,3-Epoxy-6-(trifluoromethyl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene (50).** Compound **50** (5.15 g; 21.4 mmol; 21% based on **47**) was obtained as white crystals: bp 85 °C (0.2 mm); ^1H NMR ($CDCl_3$; 300 MHz) 7.48 (d, 1 H, J = 6.3 Hz, Ar H), 7.35 (s, 1 H, H5), 7.16 (d, 1 H, J = 7.2 Hz, Ar H), 3.55–3.33 (m, 4 H, H2, H3, and bridgeheads), 1.76 (d, 2 H, J = 8.3 Hz, anti H9 and anti H10), 1.30 (d, 2 H, J = 8.6 Hz, syn H9 and syn H10); IR (film) 3017, 2951, 1466, 1443, 1337, 1321, 1240, 1163, 1120, 1066, 953, 852, 843 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 142.29, 138.92, 128.60 (q, J_{CF} = 31.8 Hz, C6), 124.45 (q, J_{CF} = 271.7 Hz, CF_3), 124.34, 123.51 (q, J_{CF} = 3.6 Hz), 120.87, 48.65, 36.78, 36.72, 21.89; EIMS, m/z (relative intensity) 240 (M^+, 57.0), 221 (27.1), 211 (67.4), 196 (100), 191 (63.6), 184 (35.3), 177 (38.9), 164 (18.8), 142 (44.1), 128 (25.2), 115 (74.0). Anal. ($C_{13}H_{11}F_3O$) C, H.

9-*exo*,10-*syn*-Dihydroxy-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene Bis(3,5-dinitrobenzoate ester) (54) and 9-*exo*,10-*syn*-Dihydroxy-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene Bis(3,5-dinitrobenzoate ester) (55). Under conditions similar to those described in the synthesis of **41** and **42**, treatment of 8.80 g (36.7 mmol) of **50** with 98% formic acid afforded 9.79 g (31.2 mmol; 85%) of a mixture of 2-(trifluoromethyl)- and 3-(trifluoromethyl)-9-*exo*,10-*syn*-bis(formyloxy)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**51**). This mixture could not be separated and therefore was hydrolyzed, by using 3 N ethanolic KOH, to give 8.70 g of a viscous yellow

oil. Purification by MPLC using hexane/ethyl acetate (2:1) as the eluent afforded 7.05 g (27.3 mmol; 95%) of a mixture of 2-(trifluoromethyl)- and 3-(trifluoromethyl)-9-*exo*,10-*syn*-dihydroxy-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**52/53**).

To effect separation of **52/53**, the mixture was converted to the bis(3,5-dinitrobenzoate esters). A solution of 7.00 g (27.1 mmol) of **52/53** and 25.0 g (108 mmol) of 3,5-dinitrobenzoyl chloride in 100 mL of anhydrous pyridine was stirred for 9 h at room temperature. The reaction mixture was poured into 500 mL of H_2O and the mixture was extracted with CH_2Cl_2 (6 × 100 mL). The organic phase was washed with 1 N aqueous HCl (3 × 250 mL) and 5% aqueous $NaHCO_3$ (2 × 250 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave 19.8 g of an orange solid, which was recrystallized from ethyl acetate to afford 16.6 g (25.7 mmol; 95%) of a mixture of the bis(3,5-dinitrobenzoate esters) **54** and **55**. Separation of the regioisomers was accomplished by MPLC using hexanes/ethyl acetate (3:1) as the eluent (TLC R_f values in the same solvent: **54**, 0.27, and **55**, 0.18).

9-*exo*,10-*syn*-Dihydroxy-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene Bis(3,5-dinitrobenzoate ester) (54). Compound **54** (7.22 g; 11.2 mmol; 41%) was obtained as light yellow crystals: mp 210.7–211.9 °C (recrystallized from ethyl acetate); ^{1}H NMR ($CDCl_3$; 80 MHz) 9.11 (q, 2 H, J = 2.2 Hz, Ar H), 8.84 (d, 2 H, J = 2.2 Hz, Ar H), 8.73 (d, 2 H, J = 2.3 Hz, Ar H), 7.70 (s, 1 H, Ar H), 7.60 (s, 1 H, Ar H), 7.34 (d, 1 H, J = 7.7 Hz, Ar H), 6.23 (s, 1 H, H9), 5.45 (t, 1 H, J = 4.7 Hz, H10), 3.74–3.54 (m, 1 H, H5), 3.35–3.10 (m, 1 H, H8), 2.49–1.60 (m, 4 H, exo H6, exo H7, endo H6, and endo H7); IR (KBr) 3098, 1732, 1630, 1547, 1346, 1282, 1169, 1076, 731 cm^{-1}; EIMS, m/z (relative intensity) 627 (M^+ – F, 1.0), 451 (1.3), 434 (19.0), 255 (4.7), 238 (26.2), 221 (20.4), 195 (100), 179 (12.9), 149 (32.8). Anal. ($C_{27}H_{17}F_3N_4O_{12}$) C, H, N.

9-*exo*,10-*syn*-Dihydroxy-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene Bis(3,5-dinitrobenzoate ester) (55). Compound **55** (6.85 g; 10.6 mmol; 39%) was obtained as light yellow crystals: mp 189.8–191.3 °C (recrystallized from ethyl acetate); ^{1}H NMR ($CDCl_3$; 80 MHz) 9.09 (q, 2 H, J = 1.9 Hz, Ar H), 8.84 (d, 2 H, J = 2.2 Hz, Ar H), 8.73 (d, 2 H, J = 2.2 Hz, Ar H), 7.60 (s, 2 H, Ar H), 7.48 (s, 1 H, Ar H), 6.23 (s, 1 H, H9), 5.47 (t, 1 H, J = 4.7 Hz, H10), 3.77–3.62 (m, 1 H, H5), 3.39–3.13 (m, 1 H, H8), 2.53–1.65 (m, 4 H, exo H6, exo H7, endo H6, and endo H7); IR (KBr) 3100, 1732, 1630, 1547, 1346, 1327, 1283, 1167, 1076, 922, 731 cm^{-1}; EIMS, m/z (relative intensity) 627 (M^+ – F, 1.0), 451 (1.1), 434 (11.4), 406 (3.6), 255 (4.2), 238 (19.7), 221 (17.9), 195 (100), 179 (12.5), 149 (38.4). Anal. ($C_{27}H_{17}F_3N_4O_{12}$) C, H, N.

General Procedure for Hydrolysis of Bis(3,5-dinitrobenzoate esters) 54 and 55 to the Corresponding Diols 52 and 53. A solution of the bis(3,5-dinitrobenzoate ester) in a 1:1 mixture of MeOH/THF (10 mL/mmol) was treated with 3 N aqueous KOH (6 mL/mmol) and the mixture stirred at room temperature for 3 h. The reaction mixture was evaporated to $^1/_3$ volume and extracted with Et_2O (5 × 75 mL). The organic pool was washed with H_2O (100 mL) and 5% aqueous Na_2CO_3 (100 mL) and dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded the desired diol.

9-*exo*,10-*syn*-Dihydroxy-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (52). Compound **54** (7.05 g; 10.9 mmol) afforded 2.60 g (10.1 mmol; 92%) of **52** as white needles: mp 127.7–128.9 °C (recrystallized from ethyl acetate); ^{1}H NMR ($CDCl_3$; 300 MHz) 7.74 (s, 1 H, H1), 7.50 (d, 1 H, J = 8.41 Hz, Ar H), 7.18 (d, 1 H, J = 7.71 Hz, Ar H), 4.48–4.40 (m, 2 H, H9 and H10), 4.16 (s, 1 H, exchangeable in D_2O, OH), 3.46 (s, 1 H, exchangeable in D_2O, OH), 3.18–2.92 (m, 1 H, H5), 2.63–2.51 (m, 1 H, H8), 2.10–1.76 (m, 2 H, exo and endo H6), 1.57–1.35 (m, 1 H, exo or endo H7), 1.25–1.10 (m, 1 H, exo or endo H7); IR (KBr) 3441, 2934, 1393, 1327, 1233, 1194, 1175, 1154, 1127, 1078, 980, 642 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 142.91, 137.25, 129.20 (q, J_{CF} = 32.3 Hz, C2), 128.71, 127.31 (q, J_{CF} = 4.0 Hz), 125.02 (q, J_{CF} = 3.6 Hz), 124.18 (q, J_{CF} = 272.4 Hz, CF_3), 74.70, 74.25, 45.75, 41.08, 29.04, 22.28; EIMS, m/z (relative intensity) 258 (M^+, 1.2), 240 (100), 222 (76.2), 209 (87.0), 196 (72.5), 191 (68.1), 177 (33.1), 142 (38.1), 128 (21.2), 115 (34.4). Anal. ($C_{13}H_{13}F_3O_2$) C, H.

9-*exo*,10-*syn*-Dihydroxy-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (53). Compound **55** (7.40 g; 11.46 mmol) afforded 2.85 g (11.0 mmol; 96%) of **53** as clear crystals: mp 91.2–93.2 °C (recrystallized from ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$; 300 MHz) 7.57 (d, 1 H, J = 7.8 Hz, H1), 7.51 (d, 1 H, J = 8.3 Hz, H2), 7.33 (s, 1 H, H4), 4.44–4.37 (m, 3 H, 1 H exchangeable in D_2O, H9, H10, and OH), 3.87 (s, 1 H, exchangeable in D_2O, OH), 3.18–3.07 (m, 1 H, H5), 2.65–2.57 (m, 1 H, H8), 2.02–1.83 (m, 2 H, exo and endo H6), 1.56–1.44 (m, 1 H, exo or endo H7), 1.25–1.15 (m, 1 H, exo or endo H7); IR (KBr) 3405, 3240, 2945, 1431, 1325, 1169, 1150, 1127, 1115, 1086, 1016, 976 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 140.28, 139.68, 130.82, 130.29 (q, J_{CF} = 31.5 Hz, C3), 125.01 (q, J_{CF} = 3.7 Hz), 124.07 (q, J_{CF} = 272.3 Hz, CF_3), 123.53 (q, J_{CF} = 3.6 Hz), 74.52, 74.15, 45.71, 40.93, 29.04, 22.13; EIMS, m/z (relative intensity) 240 ($M^+ - H_2O$, 100), 222 (84.1), 209 (90.3), 196 (75.7), 191 (84.5), 177 (34.9), 153 (23.5), 133 (40.3), 128 (29.2), 115 (56.0). Anal. ($C_{13}H_{13}F_3O_2$) C, H.

***syn*-10-Hydroxy-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (45).** A solution of 1.25 g (4.84 mmol) of diol **43** in 85 mL of chloroform/acetic acid (9:1) in a 500-mL Parr shaker bottle was treated with 750 mg of 10% Pd/C which had been prewetted with 5 mL of the same solvent. The mixture was hydrogenated for 16 h at an initial pressure of 45 psi. The catalyst was removed by filtration and the reaction mixture concentrated in vacuo to give 1.28 g of an oily white solid, which was recrystallized from hexanes to afford 1.10 g (4.54 mmol; 94%) of **45** as white needles: mp 143.0–144.0 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) 7.47 (d, 1 H, J = 6.6 Hz, Ar H), 7.27–7.16 (m, 2 H, Ar H), 4.31 (t, 1 H, J = 4.9 Hz, H10), 3.35 (dd, 1 H, J = 17.7 and 4.0 Hz, H9), 3.08–3.01 (m, 1 H, H5), 2.81 (d, 1 H, J = 17.4 Hz, H9), 2.47–2.36 (m, 1 H, H8), 2.08–1.94 (m, 2 H, exo H6 and exo H7), 1.75–1.50 (m, 2 H, endo H6 and endo H7), 1.69 (s, 1 H, exchangeable in D_2O, OH); IR (KBr) 3256, 3013, 2928, 1462, 1360, 1217, 1170, 1149, 1120, 1084, 808 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 142.25, 133.60, 132.77, 128.91 (q, J_{CF} = 29.1 Hz, C1), 126.21, 124.58 (q, J_{CF} = 274.1 Hz, CF_3), 124.26 (q, J_{CF} = 5.4 Hz), 73.21, 46.18, 35.85, 31.92, 30.85, 27.13; EIMS, m/z (relative intensity) 242 (M^+, 10.7), 224 (12.7), 209 (8.5), 196 (100), 177 (8.3), 128 (6.8), 115 (13.2). Anal. ($C_{13}H_{13}F_3O$) C, H.

***syn*-10-Hydroxy-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (56).** A solution of 700 mg (2.71 mmol) of diol **52** in 120 mL of glacial acetic acid in a 500-mL Parr shaker bottle was treated with 1.40 g of 10% Pd/C which had been prewetted with 20 mL of the same solvent. The mixture was hydrogenated for 20 h at an initial pressure of 30 psi. The catalyst was removed by filtration and the solvent evaporated in vacuo to afford 792 mg of a white solid, which was sublimed (100 °C (0.11 mm)) to give 650 mg (2.68 mmol; 99%) of **56**: mp 123.5–124.2 °C (recrystallized from hexanes); ^{1}H NMR ($CDCl_3$; 300 MHz) 7.39–7.34 (m, 2 H, Ar H), 7.11 (d, 1 H, J = 8.3 Hz, Ar H), 4.35 (t, 1 H, J = 4.3 Hz, H10), 3.30 (dd, 1 H, J = 17.1 and 3.9 Hz, H9), 3.09–2.98 (m, 1 H, H5), 2.63 (d, 1 H, J = 17.1 Hz, H9), 2.44–2.36 (m, 1 H, H8), 2.10–1.90 (m, 2 H, exo H6 and exo H7), 1.75–1.50 (m, 2 H, endo H6 and endo H7), 1.65 (s, 1 H, exchangeable in D_2O, OH); IR (KBr) 3299, 2935, 1429, 1352, 1327, 1166, 1145, 1125, 1081, 1073, 830 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 144.66, 135.56, 128.99, 128.50 (q, J_{CF} = 30.7 Hz, C2), 125.71 (q, J_{CF} = 2.25 Hz), 124.34 (q, J_{CF} = 272.0 Hz, CF_3), 122.84 (q, J_{CF} = 4.4 Hz), 73.51, 45.48, 35.87, 33.76, 31.84, 27.02; EIMS, m/z (relative intensity) 242 (M^+, 9.5), 224 (6.6), 209 (11.4), 196 (100), 177 (7.7), 155 (7.3), 128 (7.9), 115 (13.5). Anal. ($C_{13}H_{13}F_3O$) C, H.

***syn*-10-Hydroxy-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (57).** Under conditions analogous to those used in the preparation of **45**, 1.18 g (4.57 mmol) of diol **53** afforded 1.06 g (4.38 mmol; 96%) of **57** as a white solid: mp 87.7–88.9 °C (recrystallized from hexanes); ^{1}H NMR ($CDCl_3$; 300 MHz) 7.37 (d, 1 H, J = 7.81 Hz, Ar H), 7.26–7.17 (m, 3 H, Ar H), 4.28 (t, 1 H, J = 4.9 Hz, H10), 3.27 (dd, 1 H, J = 17.2 and 3.1 Hz, H9), 3.02–2.95 (m, 1 H, H5), 2.59 (d, 1 H, J = 17.5 Hz, H9), 2.37–2.32 (m, 1 H, H8), 2.03–1.90 (m, 3 H, 1 H exchangeable in D_2O, OH, exo H6, and exo H7), 1.73–1.45 (m, 2 H, endo H6 and endo H7); IR (KBr) 3384, 2949, 1620, 1437, 1327, 1266, 1227, 1167, 1117, 1073, 951, 820 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 141.18, 139.15, 129.34, 128.35 (q, J_{CF} = 32.5 Hz, C3), 125.46 (q, J_{CF} = 4.7

Hz), 124.35 (q, J_{CF} = 271.6 Hz, CF_3), 123.05 (q, J_{CF} = 3.7 Hz), 73.57, 45.62, 35.91, 33.91, 31.93, 27.12; EIMS, *m/z* (relative intensity) 242 (M^+, 13.9), 224 (8.4), 209 (10.1), 196 (100), 177 (7.0), 155 (5.9), 128 (6.7), 115 (12.0). Anal. ($C_{13}H_{13}F_3O$) C, H.

***syn*-10-Hydroxy-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (46).** Under conditions similar to those used in the preparation of **45**, 1.50 g (5.81 mmol) of diol **44** afforded, after MPLC using hexanes/ethyl acetate (3:1) as the eluent, 50 mg (0.21 mmol) of starting diol **44** and 1.30 g (5.37 mmol; 96% based on unrecovered starting material) of **46** as a white solid: mp 95.3–96.9 °C (recrystallized from hexanes); ^1H NMR ($CDCl_3$; 300 MHz) 7.45 (d, 1 H, *J* = 7.3 Hz, Ar H), 7.27 (d, 1 H, *J* = 7.8 Hz, Ar H), 7.19 (t, 1 H, *J* = 7.2 Hz, H2), 4.29 (t, 1 H, *J* = 4.8 Hz, H10), 3.45–3.36 (m, 1 H, H5), 3.30 (dd, 1 H, *J* = 17.6 and 4.5 Hz, H9), 2.61 (d, 1 H, *J* = 17.7 Hz, H9), 2.37–2.28 (m, 1 H, H8), 2.10–1.89 (m, 2 H, exo H6 and exo H7), 1.85 (s, 1 H, exchangeable in D_2O, OH), 1.79–1.68 (m, 1 H, endo H6 or endo H7), 1.58–1.46 (m, 1 H, endo H6 or endo H7); IR (KBr) 3348, 2953, 1462, 1356, 1315, 1223, 1169, 1145, 1113, 1084, 796 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 138.91, 136.62, 132.89, 128.42 (q, J_{CF} = 28.3 Hz, C4), 125.64, 124.60 (q, J_{CF} = 274.2 Hz, CF_3), 123.61 (q, J_{CF} = 6.3 Hz), 73.26, 41.06, 35.71, 34.33, 31.81, 27.29; EIMS, *m/z* (relative intensity) 242 (M^+, 11.0), 224 (12.3), 209 (7.5), 196 (100), 177 (7.2), 128 (7.5), 115 (13.6). Anal. ($C_{13}H_{13}F_3O$) C, H.

General Procedure for the Oxidation of Alcohols 32, 45, 46, 56, and 57 to Ketones 33 and 58–61 as Detailed for the Preparation of 5,6,7,8-Tetrahydro-5,8-methano-9*H*-benzocyclohepten-10-one (33). A solution of 2.60 g (14.9 mmol) of *syn*-10-hydroxy-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (**32**), conveniently prepared according to the method of Kitamogi and Takano,[41] 1.95 g (18.0 mmol) of benzoquinone, and 7.10 g (28.8 mmol) of aluminum tri-*tert*-butoxide in 100 mL of anhydrous benzene was heated at reflux for 5.5 h. The reaction mixture was allowed to cool and then was washed successively with 4 N H_2SO_4 (4 × 50 mL), 3 N NaOH (4 × 50 mL), H_2O (50 mL), and brine (50 mL). After drying over Na_2SO_4, evaporation of the solvent in vacuo afforded 2.60 g of a yellow oil, which was distilled bulb-to-bulb (87 °C (0.05 mm)) to afford 2.40 g (13.9 mmol; 94%) of **33** as a white solid: mp 59.4–60.8 °C (lit.[40] mp 59–60 °C); ^1H NMR ($CDCl_3$; 300 MHz) 7.20–6.93 (m, 4 H, Ar H), 3.55 (dd, 1 H, *J* = 16.2 and 4.5 Hz, H9), 3.20 (dd, 1 H, *J* = 16.6 and 2.6 Hz, H9), 3.05 (d, 1 H, *J* = 4.6 Hz, H5), 2.55–2.48 (m, 1 H, H8), 2.23–2.15 (m, 2 H, exo H6 and exo H7), 2.10–2.01 (m, 1 H, endo H6 or endo H7), 1.91–1.78 (m, 1 H, endo H6 or endo H7); IR (film) 3015, 2961, 2913, 1748, 1453, 1138, 774, 737, 668 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 216.67, 142.77, 132.40, 128.57, 127.46, 127.08, 126.71, 49.86, 43.35, 42.36, 30.61, 24.19; EIMS, *m/z* (relative intensity) 172 (M^+, 45.0), 154 (2.5), 141 (11.5), 129 (100), 116 (56.3). Anal. ($C_{12}H_{12}O$) C, H.

1-(Trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocyclohepten-10-one (58). Alcohol **45** (1.20 g; 4.95 mmol) afforded, after bulb-to-bulb distillation (85 °C (0.25 mm)), 1.16 g (4.83 mmol; 97%) of **58** as a clear oil: ^1H NMR ($CDCl_3$; 300 MHz) 7.55 (d, 1 H, *J* = 7.2 Hz, Ar H), 7.29 (t, 1 H, *J* = 7.1 Hz, H3), 7.17 (d, 1 H, *J* = 7.6 Hz, Ar H), 3.60 (dd, 1 H, *J* = 17.1 and 3.9 Hz, H9), 3.45 (d, 1 H, *J* = 17.2 Hz, H9), 3.21–3.16 (m, 1 H, H5), 2.61–2.52 (m, 1 H, H8), 2.29–1.80 (m, 4 H, exo H6, exo H7, endo H6, and endo H7); IR (film) 2967, 1759, 1458, 1352, 1321, 1248, 1207, 1167, 1146, 1118, 1080, 804, 733, 628 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 215.33, 145.33, 131.56, 127.16, 125.01 (q, J_{CF} = 5.2 Hz), 124.17 (q, J_{CF} = 274.1 Hz, CF_3), 50.29, 41.91, 40.75, 30.48, 24.20; EIMS, *m/z* (relative intensity) 240 (M^+, 50.3), 212 (14.0), 197 (64.1), 184 (100), 177 (57.0), 164 (11.4), 143 (19.4), 128 (35.4), 115 (46.2). Anal. ($C_{13}H_{11}F_3O$) C, H.

2-(Trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocyclohepten-10-one (59). Alcohol **56** (1.60 g; 6.60 mmol) afforded, after MPLC using hexanes/ethyl acetate (3:1) as the eluent, 401 mg (1.66 mmol) of starting alcohol **56** and 1.15 g (4.76 mmol; 96% based on unrecovered **56**) of **59** as a clear oil: bp 85 °C (0.09 mm); ^1H NMR ($CDCl_3$; 300 MHz) 7.53–7.34 (m, 2 H, Ar H), 7.09 (d, 1 H, *J* = 7.82 Hz, H1), 3.55 (dd, 1 H, *J* = 17.0 and 4.0 Hz, H9), 3.31–3.13 (m, 2 H, H9 and H5), 2.59–2.47 (m, 1 H, H8), 2.34–2.00 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.92–1.78 (m, 1 H, endo H6 or endo H7); IR (film) 2967, 1755, 1620, 1426, 1327, 1233, 1123, 1073, 1030, 907, 835 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 215.15, 146.70, 133.43, 129.50 (q, J_{CF} = 32.3 Hz, C2), 127.94, 125.57 (q, J_{CF} = 4.4 Hz), 123.97 (q, J_{CF} = 271.8 Hz, CF_3), 123.67 (q, J_{CF} = 4.6 Hz), 49.65, 42.93, 42.08, 30.47, 24.06; EIMS, *m/e* (relative intensity) 240 (M^+, 52.7), 221 (12.0), 212 (31.3), 197 (82.3), 184 (87.3), 177 (100), 164 (14.7), 143 (43.4), 128 (55.0), 115 (47.9). Anal. ($C_{13}H_{11}F_3O$) C, H.

3-(Trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocyclohepten-10-one (60). Alcohol **57** (1.65 g; 6.81 mmol) afforded, after PCTLC (4 mm) using hexanes/ethyl acetate (3:1) as the eluent, 0.280 g (1.16 mmol) of starting alcohol **57** and 1.32 g (5.49 mmol; 97% based on unrecovered **57**) of ketone **60** as a clear oil: bp 83.5 °C (0.1 mm); ^1H NMR ($CDCl_3$; 300 MHz) 7.43 (d, 1 H, *J* = 7.8 Hz, Ar H), 7.27–7.19 (m, 2 H, Ar H), 3.54 (d, 1 H, *J* = 17.1 Hz, H9), 3.24 (d, 1 H, *J* = 17.1 Hz, H9), 3.16 (d, 1 H, *J* = 4.5 Hz, H5), 2.58–2.49 (m, 1 H, H8), 2.30–2.17 (m, 2 H, exo H6 and exo H7), 2.13–2.03 (m, 1 H, endo H6 or endo H7), 1.90–1.75 (m, 1 H, endo H6 or endo H7); IR (film) 2969, 1757, 1424, 1333, 1300, 1190, 1123, 1075, 901, 826, cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 215.30, 143.46, 136.80, 129.18, 129.15 (q, J_{CF} = 33.5 Hz, C3), 124.36 (q, J_{CF} = 4.3 Hz), 123.98 (q, J_{CF} = 272.0 Hz, CF_3), 123.90 (q, J_{CF} = 4.5 Hz), 49.64, 43.05, 42.04, 30.49, 24.13; EIMS, *m/z* (relative intensity) 240 (M^+, 94.5), 222 (12.2), 221 (19.1), 212 (20.5), 197 (100), 184 (79.8), 177 (82.3), 143 (42.3), 128 (58.2), 115 (55.4). Anal. ($C_{13}H_{11}F_3O$) C, H.

4-(Trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocyclohepten-10-one (61). Alcohol **46** (2.75 g; 11.4 mmol) afforded, after MPLC using hexanes/ethyl acetate (5:1) as the eluent, 600 mg (2.48 mmol) of starting alcohol **46** and 2.11 g (8.78 mmol; 99% based on unrecovered **46**) of **61** as a clear oil: bp 65 °C (0.2 mm); ^1H NMR ($CDCl_3$; 300 MHz) 7.52 (d, 1 H, *J* = 7.3 Hz, Ar H), 7.33–7.24 (m, 2 H, Ar H), 3.62–3.47 (m, 2 H, H5 and H9), 3.26 (dd, 1 H, *J* = 16.5 and 2.4 Hz, H9), 2.73–2.61 (m, 1 H, H8), 2.32–2.09 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.92–1.79 (m, 1 H, endo H6 or endo H7); IR (film) 2970, 1759, 1460, 1351, 1319, 1221, 1182, 1161, 1118, 1082, 798, 744 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 215.50, 140.69, 134.88, 132.64, 127.12 (q, J_{CF} = 29.4 Hz, C4), 126.76, 124.31 (q, J_{CF} = 6.4 Hz), 123.98 (q, J_{CF} = 274.1 Hz, CF_3), 45.68, 45.65, 43.39, 42.30, 30.44, 24.26; EIMS, *m/z* (relative intensity) 240 (M^+, 81.0), 221 (8.0), 212 (16.0), 197 (77.1), 184 (100), 177 (70.6), 164 (14.0), 143 (30.8), 128 (41.2), 115 (49.5). Anal. ($C_{13}H_{11}F_3O$) C, H.

General Procedure for the Preparation of Oximes 34 and 62–65 as Detailed for the Synthesis of 10(*E*/*Z*)-(Hydroxyimino)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (34). A solution of 2.60 g (15.1 mmol) of 5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocyclohepten-10-one (**33**) in 30 mL of 95% EtOH was added to a solution of 1.70 g (24.5 mmol) of hydroxylamine hydrochloride and 4.35 g (31.9 mmol) of sodium acetate in 45 mL of H_2O. The resulting mixture was heated at 75 °C for 2 h. The reaction mixture was extracted with Et_2O (5 × 25 mL) and the organic pool washed with H_2O (50 mL) and brine (50 mL). After drying over $MgSO_4$, evaporation of the solvent in vacuo afforded 3.5 g of a yellow crystalline solid. Recrystallization from ethyl acetate/hexanes afforded 2.61 g (13.9 mmol; 92%) of **34**, which ^1H and ^{13}C NMR showed to be a mixture of *E* and *Z* isomers: mp 123.2–124.8 °C; ^1H NMR ($CDCl_3$; 300 MHz) 9.38 (br s, 1 H, NOH), 7.17–6.90 (m, 4 H, Ar H), 4.25–4.12 and 3.69–3.59 (2 m, 1 H, H9, *E* and *Z* isomers), 3.47–3.21 and 3.01–2.78 (2 m, 3 H, H5, H8, and H9, *E* and *Z* isomers), 2.20–1.78 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.72–1.53 (m, 1 H, endo H6 or endo H7); IR (film) 3252, 3149, 2957, 2907, 1701, 1485, 1453, 945, 915, 771, 674 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 166.92, 166.36 (CNOH, *E* and *Z* isomers); EIMS, *m/z* (relative intensity) 187 (M^+, 66.8), 170 (34.6), 159 (24.3), 141 (65.9), 128 (95.6), 115 (100). Anal. ($C_{12}H_{13}NO$) C, H, N.

10(*E*/*Z*)-(Hydroxyimino)-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (62). Ketone **58** (1.10 g; 4.58 mmol) afforded 1.10 g (4.31 mmol; 94%) of a mixture of *E* and *Z* isomers of **62** as a white solid: mp 135.1–137.5 °C; ^1H NMR ($CDCl_3$; 300 MHz) 8.66 and 8.62 (2 br s, 1 H, NOH, *E* and *Z* isomers), 7.53–7.45 (m, 1 H, Ar H), 7.28–7.16 (m, 2 H, Ar H), 4.28 (d, 0.5 H, *J* = 3.8 Hz), 4.71 (br s, 0.5 H), 3.54–3.36 (m, 1.5 H), 3.27–3.11 (m, 1 H), 2.96 (br s, 0.5 H), 2.17–1.88 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.75–1.63 (m, 1 H, endo H6 or endo H7); IR (film) 3274, 2955, 1460, 1325, 1314, 1209, 1182, 1157, 1118, 1107, 1080, 925, 723 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 165.92 and 165.22 (CNOH, *E* and *Z* isomers); EIMS,

m/z (relative intensity) 255 (M^+, 100), 238 (64.2), 227 (86.1), 210 (69.1), 209 (62.0), 196 (48.2), 191 (32.1), 183 (48.2), 177 (33.0), 164 (16.7), 158 (20.0), 140 (35.9), 133 (20.5), 128 (32.8), 115 (49.7). Anal. ($C_{13}H_{12}F_3NO$) C, H, N.

10(*E*/*Z*)-(Hydroxyimino)-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (63). Ketone **59** (1.37 g; 5.70 mmol) gave rise to 1.39 g (5.44 mmol; 96%) of a mixture of *E* and *Z* isomers of **63** as a white solid: mp 47–53 °C (recrystallized from hexanes/ethyl acetate); ^1H NMR ($CDCl_3$; 300 MHz) 9.18 and 9.14 (2 s, 1 H, NOH, *E* and *Z* isomers), 7.43–7.32 (m, 2 H, Ar H), 7.20–7.07 (m, 1 H, Ar H), 4.26 (br s, 0.5 H), 3.69 (br s, 0.5 H), 3.55–3.30 (m, 1.5 H), 3.10–2.85 (m, 1.5 H), 2.21–1.83 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.73–1.62 (m, 1 H, endo H6 or endo H7); IR (film) 3320, 2990, 1430, 1340, 1328, 1159, 1142, 1118, 1072, 920, 834 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 166.15 and 165.48 (CNOH, *E* and *Z* isomers); EIMS, m/z (relative intensity) 255 (M^+, 100), 238 (39.7), 236 (31.8), 227 (65.0), 210 (60.5), 209 (62.7), 196 (48.7), 191 (26.3), 183 (35.7), 177 (24.7), 164 (11.7), 158 (18.3), 140 (32.5), 128 (25.8), 115 (35.0). Anal. ($C_{13}H_{12}F_3NO$) C, H, N.

10(*E*/*Z*)-(Hydroxyimino)-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (64). Ketone **60** (1.50 g; 6.24 mmol) afforded, after PCTLC (4 mm) using hexanes/ethyl acetate (3:1) as the eluent, 1.58 g (6.19 mmol; 99%) of a mixture of *E* and *Z* isomers of oxime **64** as a gum, which resisted crystallization: ^1H NMR ($CDCl_3$; 300 MHz) 9.60 and 9.54 (2 s, 1 H, NOH, *E* and *Z* isomers), 7.41–7.33 (m, 1 H, H2), 7.27 (s, 1 H, H4), 7.16 (d, J = 7.8 Hz, H1), 4.27 (d, 0.5 H, J = 4.0 Hz), 3.67 (s, 0.5 H), 3.52 (d, 0.5 H, J = 3.3 Hz), 3.45–3.29 (m, 1 H), 3.02 (s, 0.5 H), 2.98–2.88 (m, 1 H), 2.20–1.85 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.70–1.58 (m, 1 H, endo H6 or endo H7); IR (film) 3260, 2945, 1620, 1424, 1331, 1300, 1163, 1120, 1074, 939, 823 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz), 166.18 and 165.55 (CNOH, *E* and *Z* isomers); EIMS, m/z (relative intensity) 255 (M^+, 100), 238 (45.1), 227 (63.0), 209 (65.4), 196 (32.0), 183 (37.9), 177 (23.4), 140 (36.3), 128 (27.5), 115 (34.1). Anal. ($C_{13}H_{12}F_3NO$) C, H, N.

10(*E*/*Z*)-(Hydroxyimino)-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (65). Ketone **61** (2.80 g; 11.7 mmol) afforded 2.95 g (11.5 mmol; 98%) of a mixture of *E* and *Z* isomers of **65** as a white solid: mp 152.0–154.5 °C (recrystallized from ethyl acetate/hexanes); ^1H NMR ($CDCl_3$; 300 MHz) 9.17 and 9.09 (2 br s, 1 H, NOH, *E* and *Z* isomers), 7.51–7.42 (m, 1 H, Ar H), 7.29–7.18 (m, 2 H, Ar H), 4.70 (s, 0.5 H), 3.90 (s, 0.25 H), 3.69 (s, 0.25 H), 3.49–3.31 (m, 1 H), 3.08–2.91 (m, 2 H), 2.20–1.95 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.77–1.61 (m, 1 H, endo H6 or endo H7); IR (film) 3273, 2974, 1458, 1446, 1319, 1152, 1120, 1105, 951, 799, 764 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 166.09 and 165.28 (CNOH, *E* and *Z* isomers); EIMS, m/z (relative intensity) 255 (M^+ 100), 238 (40.1), 227 (78.0), 210 (50.8), 209 (53.5), 196 (47.5), 191 (28.8), 183 (36.5), 177 (27.6), 158 (35.1), 140 (36.2), 128 (29.6), 115 (36.5). Anal. ($C_{13}H_{12}F_3NO$) C, H, N.

***anti*-10-Formamido-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (35) and *syn*-10-Formamido-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (36).** To a solution of 2.00 g (10.7 mmol) of oxime **34** in 50 mL of dry EtOH in a 500-mL Parr shaker bottle were added 3 mL of concentrated aqueous HCl and 400 mg of 10% Pd/C catalyst which had been prewetted with 2 mL of anhydrous EtOH. The mixture was hydrogenated for 9 h at an initial pressure of 50 psi. The catalyst was removed by filtration, and the reaction mixture was evaporated in vacuo to give a tan solid. The residue was taken up in 1 N aqueous HCl (50 mL) and washed with Et_2O (2 × 20 mL). The acidic phase was basified with solid KOH and extracted with Et_2O (4 × 30 mL). The organic pool was dried over K_2CO_3 and the solvent evaporated in vacuo to afford a yellow oil, which was distilled bulb-to-bulb (82–87 °C (0.15 mm)) to give 1.20 g (6.93 mmol; 65%) of a mixture of **12** and **13** as a clear oil. To effect separation, the amine mixture was converted to the corresponding formamides.

The amine mixture (**12**/**13**; 1.10 g; 6.35 mmol) and 35 mL of ethyl formate were heated in a 200-mL Wheaton pressure bottle at 100 °C for 17 h. After cooling, the reaction mixture was concentrated in vacuo to give 1.30 g of a mixture of formamides **35** and **36**, which were separated by using MPLC with $CHCl_3$/THF (20:1) as the eluent (TLC R_f values in the same solvent: **35**, 0.23; and **36**, 0.39).

***anti*-10-Formamido-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (35).** Compound **35** (750 mg; 3.73 mmol; 35% from **34**) was obtained as a white solid: mp 143.5–144.3 °C (recrystallized from ethyl acetate/hexanes); ^1H NMR ($CDCl_3$; 300 MHz) 8.12 (s, 1 H, CHO), 7.25–6.80 (m, 4 H, Ar H), 5.83 and 5.52 (2 br s, 1 H, NH, conformers), 4.98–4.22 and 3.91–3.86 (2 m, 1 H, CHN, conformers), 3.31–3.18 (m, 1 H), 3.09–2.95 (m, 1 H), 2.82–2.67 (m, 1 H), 2.53–2.42 (m, 1 H), 2.17–1.76 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.63–1.48 (m, 1 H, endo H6 or endo H7); IR (KBr) 3281, 3063, 2943, 1653, 1549, 1456, 1387, 1240, 1103, 1064, 748; ^{13}C NMR ($CDCl_3$; 75 MHz) 164.25 and 160.79 (NHCHO, conformers), 59.35 and 56.43 (CHNH, conformers); EIMS, m/z (relative intensity) 201 (M^+, 21.2), 173 (14.5), 156 (26.0), 141 (19.7), 128 (100), 115 (31.1). Anal. ($C_{13}H_{15}NO$) C, H, N.

***syn*-10-Formamido-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (36).** Compound **36** (400 mg; 1.99 mmol; 19% from **34**) was obtained as a white solid: mp 151.3–152.0 °C (recrystallized from ethyl acetate/hexanes); ^1H NMR ($CDCl_3$; 300 MHz) 7.99 (s, 1 H, CHO), 7.23–6.87 (m, 4 H, Ar H), 5.93–5.37 (br, 1 H, NH), 4.50–4.22 (m, 1 H, CHN), 3.14–2.95 (m, 2 H), 2.75–2.63 (m, 2 H), 2.17–1.94 (m, 2 H, exo H6 and exo H7), 1.83–1.70 (m, 1 H, endo H6 or endo H7), 1.64–1.48 (m, 1 H, endo H6 or endo H7); IR (KBr) 3220, 3025, 2950, 1673, 1645, 1539, 1487, 1381, 1356, 1232, 770, 737 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 163.94 and 161.21 (NHCHO, conformers), 55.54 and 51.37 (CHNH, conformers); EIMS, m/z (relative intensity) 201 (M^+, 21.1), 173 (13.5), 156 (22.3), 141 (17.2), 128 (100), 115 (27.0). Anal. ($C_{13}H_{15}NO$) C, H, N.

***anti*-10-Formamido-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (66) and *syn*-10-Formamido-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (67).** A solution of 800 mg (3.13 mmol) of oxime **62** in 155 mL of glacial acetic acid in a 500-mL Parr shaker bottle was treated with 800 mg of 10% Pd/C which had been prewetted with 5 mL of the same solvent. The mixture was hydrogenated for 18 h at an initial pressure of 45 psi. The catalyst was removed by filtration, and the reaction mixture was concentrated in vacuo to give a yellow oil, which was immediately dissolved in 50 mL of Et_2O. The ethereal phase was extracted with 1 N aqueous HCl (7 × 30 mL). The acidic pool was basified with solid KOH and was extracted with Et_2O (8 × 30 mL). The organic phase was dried over K_2CO_3 and the solvent evaporated in vacuo to give 652 mg of a yellow oil, which after bulb-to-bulb distillation (80–85 °C (0.2 mm)) afforded 565 mg (2.34 mmol; 75%) of a mixture of **20** and **24** as a clear oil. The amine mixture was converted directly to the corresponding formamides **66** and **67**, which were separated by PCTLC (4 mm) using $CHCl_3$/THF (20:1) as the eluent (TLC R_f values in the same solvent: **66**, 0.13; and **67**, 0.26).

***anti*-10-Formamido-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (66).** Compound **66** (368 mg; 1.37 mmol; 58% based on amine mixture **20**/**24**) was obtained as a white solid: mp 135.9–136.8 °C (recrystallized from hexanes/ethyl acetate (5:1)); ^1H NMR ($CDCl_3$; 300 MHz) 8.26 and 8.19 (2 s, 1 H, CHO, conformers), 7.52–7.41 (m, 1 H, Ar H), 7.26–7.11 (m, 2 H, Ar H), 6.75 and 6.17 (2 br s, 1 H, NH, conformers), 4.26 and 3.91 (2 d, 1 H, J = 6.83 and 7.81 Hz respectively, CHN, conformers), 3.35 (dd, 1 H, J = 17.8 and 3.5 Hz, H9), 3.18 and 3.06 (2 d, 1 H, J = 4.40 and 6.35 Hz respectively, H5, conformers), 2.95 (d, 1 H, J = 18.3 Hz, H9), 2.49–2.56 (m, 1 H, H8), 2.15–1.99 (m, 2 H, exo H6 and exo H7), 1.90–1.80 (m, 1 H, endo H6 or endo H7), 1.65–1.46 (m, 1 H, endo H6 or endo H7); IR (KBr) 3260, 3038, 2951, 1674, 1647, 1539, 1460, 1329, 1311, 1149, 1113, 1082, 810, 721 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 164.32 and 160.95 (NHCHO, conformers), 58.60 and 55.69 (CHNH, conformers); EIMS, m/z (relative intensity) 269 (M^+, 23.6), 249 (13.7), 224 (34.5), 209 (17.2), 196 (100), 183 (12.8), 177 (9.8), 155 (14.7), 128 (10.5), 115 (16.6). Anal. ($C_{14}H_{14}F_3NO$) C, H, N.

***syn*-10-Formamido-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (67).** Compound **67** (218 mg; 0.81 mmol; 34% based on amine mixture **20**/**24**) was obtained as a white solid: mp 152.8–153.8 °C (recrystallized from hexanes/ethyl acetate (5:1)); ^1H NMR ($CDCl_3$; 300 MHz) 8.14

and 8.03 (2 s, 1 H, CHO, conformers), 7.51 (d, 1 H, J = 7.5 Hz, Ar H), 7.32–7.17 (m, 2 H, Ar H), 5.78 and 5.58 (2 br s, 1 H, NH, conformers), 4.40–4.30 and 4.02–3.86 (2 m, 1 H, CHN, conformers), 3.22–3.05 (m, 2 H, H5 and H9), 2.87 (d, 1 H, J = 18.6 Hz, H9), 2.61 and 2.45 (2 br s, 1 H, H8, conformers), 2.21–2.02 (m, 2 H, exo H6 and exo H7), 1.83–1.52 (m, 2 H, endo H6 and endo H7); IR (KBr) 3245, 3038, 2947, 1672, 1653, 1537, 1462, 1379, 1313, 1157, 1145, 1128, 1118, 804, 719 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 163.71 and 161.32 (NHCHO, conformers), 54.41 and 50.75 (CHNH, conformers); EIMS, m/z (relative intensity) 269 (M^+, 22.2), 249 (12.9), 224 (23.2), 209 (13.0), 196 (100), 183 (10.1), 177 (9.3), 155 (10.3), 128 (9.2), 115 (12.8). Anal. ($C_{14}H_{14}F_3NO$) C, H, N.

***anti*-10-Formamido-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (68) and *syn*-10-Formamido-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (69).** Formamides **68** and **69** were prepared in a fashion analogous to the preparation of **66** and **67**. In this case, reduction of oxime **63** (700 mg; 2.74 mmol) was carried out over 48 h and at an initial pressure of 30 psi to afford, after bulb-to-bulb distillation (83–86 °C (0.2 mm)), 570 mg (2.36 mmol; 86%) of a mixture of **21** and **25** as a clear oil. The amine mixture was converted to the respective formamide derivatives **68** and **69**, which were separated by PCTLC (4 mm) using $CHCl_3$/THF (20:1) as the eluent (TLC R_f values in the same solvent: **68**, 0.09; and **69**, 0.23).

***anti*-10-Formamido-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (68).** Compound **68** (342 mg; 1.26 mmol; 53% based on amine mixture **21/25**) was obtained as a white solid: mp 183.0–183.5 °C (recrystallized from hexanes/ethyl acetate (5:1)); ^1H NMR ($CDCl_3$; 300 MHz) 8.26 and 8.20 (2 s, 1 H, CHO, conformers), 7.43–7.27 (m, 2 H, Ar H), 7.18–7.06 (m, 1 H, Ar H), 6.42 and 5.82 (2 br s, 1 H, NH, conformers), 4.27 and 3.90 (2 d, 1 H, J = 6.35 and 7.81 Hz respectively, CHN, conformers), 3.41–3.02 (m, 2 H, H9 and H5), 2.89–2.72 (m, 1 H, H9), 2.53 (br s, 1 H, H8), 2.23–1.98 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.71–1.54 (m, 1 H, endo H6 or endo H7); IR (KBr) 3290, 3091, 2997, 1655, 1548, 1384, 1337, 1244, 1172, 1157, 1122, 1078, 840 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 164.12 and 160.79 (CHO, conformers), 59.00 and 56.14 (CHN, conformers); EIMS, m/z (relative intensity) 269 (M^+, 22.0), 250 (7.4), 241 (6.6), 224 (32.1), 209 (17.8), 196 (100), 177 (10.9), 155 (11.2), 128 (10.4), 115 (14.7). Anal. ($C_{14}H_{14}F_3NO$) C, H, N.

***syn*-10-Formamido-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (69).** Compound **69** (292 mg; 1.08 mmol; 45% based on amine mixture **21/25**) was obtained as a white solid: mp 118.7–120.0 °C (recrystallized from hexanes/ethyl acetate (5:1)); ^1H NMR ($CDCl_3$; 300 MHz) 8.02 (s, 1 H, CHO), 7.43–7.37 (m, 2 H, Ar H), 7.14 (d, 1 H, J = 9.0 Hz, Ar H), 5.72 and 5.53 (2 br s, NH, conformers), 4.48–4.36 and 4.06–3.96 (2 m, 1 H, CHN, conformers), 3.20–3.05 (m, 2 H, H9 and H5), 2.78–2.57 (m, 2 H, H9 and H8), 2.19–2.02 (m, 2 H, exo H6 and exo H7), 1.84–1.53 (m, 2 H, endo H6 and endo H7); IR (KBr) 3320, 2994, 1687, 1662, 1540, 1337, 1158, 1123, 1078, 840 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 163.68 and 161.24 (CHO, conformers), 54.83 and 51.25 (CNH, conformers); EIMS, m/z (relative intensity) 269 (M^+, 20.4), 250 (6.4), 241 (5.9), 224 (25.8), 209 (14.3), 196 (100), 177 (9.8), 155 (9.8), 128 (9.6), 115 (12.6). Anal. ($C_{14}H_{14}F_3NO$) C, H, N.

***anti*-10-Formamido-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (70) and *syn*-10-Formamido-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (71).** Formamides **70** and **71** were prepared under conditions similar to those used in the preparation of **68** and **69**. In this manner 420 mg (1.65 mmol) of oxime **64** afforded, after bulb-to-bulb distillation (90–94 °C (0.12 mm)), 349 mg (1.45 mmol; 88%) of a mixture of amines **22** and **26**. The amine mixture was converted directly to the corresponding formamides **70** and 71, which were separated by using MPLC with $CHCl_3$/THF (20:1) as the eluent (TLC R_f values in the same solvent: **70**, 0.13; and **71**, 0.27).

***anti*-10-Formamido-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (70).** Compound **70** (211 mg; 0.780 mmol; 54% based on amine mixture **22/26**) was obtained as a clear oil, which solidified on standing: bp 105 °C (0.05 mm); ^1H NMR ($CDCl_3$; 300 MHz) 8.25 and 8.20 (2 s, 1 H, CHO, conformers), 7.39–7.32 (m, 1 H, Ar H), 7.27–7.15 (m, 2 H, Ar H), 6.54 and 5.94 (2 br s, 1 H, NH, conformers), 4.26 and 3.90 (2 d, 1 H, J = 6.84 and 7.81 Hz respectively, H10), 3.35–3.03 (m, 2 H, H9 and H5), 2.90–2.72 (m, 1 H, H9), 2.53 (br s, 1 H, H8), 2.28–1.81 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.64–1.53 (m, 1 H, endo H6 or endo H7); IR (film) 3274, 3047, 2947, 1661, 1537, 1427, 1385, 1333, 1263, 1117, 1076, 928, 823 cm^{-1}; ^{13}C NMR ($CDCl_3$) 164.18 and 160.81 (CHO, conformers), 59.10 and 56.23 (CHN, conformers); EIMS, m/z (relative intensity) 269 (M^+, 22.0), 250 (7.6), 241 (4.8), 224 (26.4), 209 (18.4), 196 (100), 177 (10.6), 155 (13.8), 128 (10.9), 115 (16.6). Anal. ($C_{14}H_{14}F_3NO$) C, H, N.

***syn*-10-Formamido-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (71).** Compound 71 (141 mg; 0.520 mmol; 36% based on amine mixture **22/26**) was obtained as a clear oil, which solidified on standing: bp 115 °C (0.05 mm); ^1H NMR ($CDCl_3$; 300 MHz) 8.03 and 7.97 (2 s, 1 H, CHO, conformers), 7.40 (d, 1 H, J = 6.83 Hz, Ar H), 7.28 (s, 1 H, H4), 7.23 (d, 1 H, J = 7.81 Hz, Ar H), 5.87 and 5.63 (2 s, 1 H, NH, conformers), 4.40–4.30 and 4.02–3.93 (2 m, 1 H, CHN, conformers), 3.21–2.96 (m, 2 H, H9 and H5), 2.77–2.42 (m, 2 H, H9 and H8), 2.18–2.01 (m, 2 H, exo H6 and exo H7), 1.83–1.71 (m, 1 H, endo H6 or endo H7), 1.64–1.51 (m, 1 H, endo H6 or endo H7); IR (film) 3274, 3040, 2947, 1661, 1533, 1433, 1383, 1360, 1341, 1323, 1265, 1240, 1165, 1118, 1072, 731 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 163.70 and 161.28 (CHO, conformers), 54.78 and 51.32 (CHN, conformers); EIMS, m/z (relative intensity) 269 (M^+, 17.5), 250 (4.4), 241 (4.1), 224 (17.5), 209 (13.5), 196 (100), 177 (11.2), 155 (10.9), 128 (9.2), 115 (12.8). Anal. ($C_{14}H_{14}F_3NO$) C, H, N.

***anti*-10-Formamido-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (72) and *syn*-10-Formamido-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (73).** Under conditions analogous to those employed in the preparation of **66** and **67**, hydrogenation of 350 mg (1.37 mmol) of oxime **65** afforded, after bulb-to-bulb distillation (81–84 °C (0.1 mm)), 321 mg (1.33 mmol; 97%) of a mixture of amines **23** and **27**. Separation of 800 mg (3.31 mmol) of the amine mixture, as the respective formamides, was effected by PCTLC (4 mm) using $CHCl_3$/THF (20:1) as the eluent (TLC R_f values in the same solvent: **72**, 0.22; and **73**, 0.35).

***anti*-10-Formamido-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (72).** Compound **72** (635 mg; 2.36 mmol; 71% based on amine mixture **23/27**) was obtained as a white solid: mp 146.0–147.5 °C (recrystallized from hexanes/ethyl acetate (5:1)); ^1H NMR ($CDCl_3$; 300 MHz) 8.25 and 8.19 (2 s, 1 H, CHO, conformers), 7.46–7.39 (m, 1 H, Ar H), 7.28–7.16 (m, 2 H, Ar H), 6.76 and 6.26 (2 br s, 1 H, NH, conformers), 4.29 and 3.91 (2 d, 1 H, J = 7.5 and 7.7 Hz respectively, CHN, conformers), 3.48–3.29 (m, 2 H, H5 and H9), 2.79 (d, 1 H, J = 17.6 Hz, H9), 2.60–2.47 (m, 1 H, H8), 2.26–1.83 (m, 3 H, exo H6, exo H7, and endo H6 or endo H7), 1.69–1.53 (m, 1 H, endo H6 or endo H7); IR (KBr) 3260, 3071, 2955, 1684, 1655, 1558, 1460, 1385, 1319, 1165, 1145, 1115, 1078, 808, 767 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 164.26 and 160.89 (NHCHO, conformers), 59.01 and 55.97 (CHNH, conformers); EIMS, m/z (relative intensity) 269 (M^+, 21.0), 249 (19.7), 224 (33.1), 209 (15.8), 196 (100), 183 (13.2), 177 (7.8), 155 (10.9), 128 (8.3), 115 (12.7). Anal. ($C_{14}H_{14}F_3N$) C, H, N.

***syn*-10-Formamido-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (73).** Compound **73** (201 mg; 0.750 mmol; 23% based on amine mixture **23/27**) was obtained as a white solid: mp 143.5–144.8 °C (recrystallized from hexanes/ethyl acetate (5:1)); ^1H NMR ($CDCl_3$; 300 MHz) 8.08 and 7.98 (2 s, 1 H, CHO, conformers), 7.47 (d, 1 H, J = 7.30 Hz, Ar H), 7.30 (d, 1 H, J = 7.70 Hz, Ar H), 7.23 (t, 1 H, J = 7.2 Hz, H2), 5.89 and 5.59 (2 br s, 1 H, NH, conformers), 4.42–4.33 and 4.05–3.95 (2 m, 1 H, CHN, conformers), 3.49 (br s, 1 H, H5), 3.14 (dd, 1 H, J = 17.9 and 3.9 Hz, H9), 2.78–2.42 (m, 2 H, H8 and H9), 2.20–1.96 (m, 2 H, exo H6 and exo H7), 1.87–1.53 (m, 2 H, endo H6 and endo H7); IR (KBr) 3233, 3032, 2957, 1678, 1649, 1537, 1462, 1381, 1317, 1155, 1142, 1124, 1113, 1076, 949, 841, 796 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 163.72 and 161.28 (NHCHO, conformers), 54.48 and 51.03 (CHNH, conformers); EIMS, m/z (relative intensity) 269 (M^+, 18.0), 249 (18.7), 224 (19.6), 209 (10.9), 196 (100), 183 (11.5), 177 (8.6), 155 (8.9), 128 (9.3), 115 (12.3). Anal. ($C_{14}H_{14}F_3NO$) C, H, N.

General Procedure for the Hydrolysis of Formamides 35, 36, and 66–73 To Produce Amines 12, 13, and 20–27. The respective formamide was stirred in 3 N aqueous HCl (10 mg/mL) which was heated at reflux under Ar, for 17 h. The mixture was cooled, basified with solid KOH, and extracted with Et_2O (6 × 30 mL). The organic pool was dried over K_2CO_3 and concentrated in vacuo to give an oil, which was distilled bulb-to-bulb to afford the desired amine. After spectral characterization, the amine was converted to its hydrochloride salt and recrystallized for elemental analysis.

***anti*-10-Amino-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (12).** Formamide **35** (170 mg; 0.85 mmol) afforded 143 mg (0.830 mmol; 98%) of **12** as a clear oil: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.15–6.88 (m, 4 H, Ar H), 3.28 (s, 1 H, H10), 3.12 (dd, 1 H, J = 16.9 and 3.83 Hz, H9), 2.74 (d, 1 H, J = 5.4 Hz, H5), 2.66 (d, 1 H, J = 16.2 Hz, H9), 2.28–1.97 (m, 3 H, H8, exo H6, and exo H7), 1.79–1.66 (m, 1 H, endo H6 or endo H7), 1.57–1.37 (m, 1 H, endo H6 or endo H7), 1.50 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3364, 3293, 3017, 2917, 1578, 1487, 1454, 953, 879, 774, 741, 629 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 144.64, 133.70, 129.06, 127.06, 126.07, 125.66, 59.00, 48.50, 41.40, 39.64, 33.10, 27.36. **12**·HCl (recrystallized from EtOH/Et_2O): mp >300 °C; EIMS, m/z (relative intensity) 173 (M^+, 30.7), 156 (8.4), 141 (15.8), 128 (100), 115 (33.5). Anal. ($C_{12}H_{16}ClN$) C, H, N.

***syn*-10-Amino-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (13).** Formamide **36** (700 mg; 3.48 mmol) afforded 549 mg (3.33 mmol; 96%) of **13** as a clear oil: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.12–6.92 (m, 4 H, Ar H), 3.31 (dd, 1 H, J = 4.64 and 4.88 Hz, H10), 3.16 (dd, 1 H, J = 17.2 and 4.5 Hz, H9), 2.83–2.75 (m, 1 H, H5), 2.54 (d, 1 H, J = 17.6 Hz, H9), 2.22–2.16 (m, 1 H, H8), 2.14–1.89 (m, 2 H, exo H6 and exo H7), 1.72–1.63 (m, 1 H, endo H6 or endo H7), 1.57–1.41 (m, 1 H, endo H6 or endo H7), 1.21 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3366, 3293, 3015, 2938, 1579, 1487, 1454, 1391, 772, 737 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 140.69, 133.76, 128.72, 128.68, 125.78, 55.18, 46.58, 36.79, 33.47, 33.39, 28.30. **13**·HCl (recrystallized form EtOH/Et_2O): mp >300 °C; EIMS, m/z (relative intensity) 173 (M^+, 56.9), 156 (14.4), 141 (21.3), 128 (100), 115 (28.5). Anal. ($C_{12}H_{16}ClN$) C, H, N.

***anti*-10-Amino-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (20).** Formamide **66** (310 mg; 1.15 mmol) afforded, after bulb-to-bulb distillation (88 °C (1.0 mm)), 270 mg (1.12 mmol; 97%) of **20** as a clear oil: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.46–7.41 (m, 1 H, Ar H), 7.17–7.11 (m, 2 H, Ar H), 3.33 (s, 1 H, H10), 3.23 (dd, 1 H, J = 18.2 and 3.3 Hz, H9), 2.92 (d, 1 H, J = 18.3 Hz, H9), 2.85 (d, 1 H, J = 6.0 Hz, H5), 2.34–2.03 (m, 3 H, H8, exo H6, and exo H7), 1.78–1.67 (m, 1 H, endo H6 or endo H7), 1.52–1.41 (m, 1 H, endo H6 or endo H7), 1.21 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3420, 3315, 2939, 1589, 1458, 1439, 1307, 1188, 1113, 1080, 933, 806, 721 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 146.55, 132.52, 130.91, 128.90 (q, J_{CF} = 29.2 Hz, C1), 125.65, 124.98 (q, J_{CF} = 275.6 Hz, CF_3), 123.84 (q, J_{CF} = 4.4 Hz), 58.01, 48.73, 40.76, 36.52, 32.72, 27.13. **20**·HCl (recrystallized from EtOH/Et_2O): mp >300 °C; EIMS, m/z (relative intensity) 241 (M^+, 58.1), 224 (9.5), 222 (7.0), 209 (12.3), 196 (100), 177 (11.4), 129 (16.0), 128 (11.3), 115 (20.4), 56 (100). Anal. ($C_{13}H_{15}ClF_3N$) C, H, N.

***syn*-10-Amino-1-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (24).** Formamide **67** (216 mg; 0.80 mmol) afforded, after bulb-to-bulb distillation (98 °C (1.5 mm)), 176 mg (0.73 mmol; 91%) of **24** as a clear oil: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.49–7.45 (m, 1 H, Ar H), 7.24–7.14 (m, 2 H, Ar H), 3.80 (t, 1 H, J = 4.3 Hz, H10), 3.28 (dd, 1 H, J = 18.3 and 4.5 Hz, H9), 2.94–2.87 (m, 1 H, H5), 2.80 (d, 1 H, J = 18.8 Hz, H9), 2.33–2.23 (m, 1 H, H8), 2.10–1.97 (m, 2 H, exo H6 and exo H7), 1.74–1.46 (m, 2 H, endo H6 and endo H7), 1.35 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3415, 3325, 2934, 1595, 1460, 1446, 1361, 1313, 1190, 1147, 1115, 806, 721 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 142.98, 133.17, 132.87, 128.86 (q, J_{CF} = 30.7 Hz, C1), 126.16, 124.57 (q, J_{CF} = 273.9, CF_3), 124.03 (q, J_{CF} = 6.0 Hz), 54.66, 47.32, 36.81, 33.61, 30.57, 28.53. **24**·HCl (recrystallized from EtOH/Et_2O): mp >300 °C; EIMS, m/z (relative intensity) 241 (M^+, 48.6), 224 (7.2), 222 (5.2), 209 (10.2), 196 (84.9), 177 (10.2), 129 (14.5), 128 (11.7), 115 (25.6), 56 (100). Anal. ($C_{13}H_{15}ClF_3N$) C, H, N.

***anti*-10-Amino-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (21).** Formamide **68** (510 mg; 1.89 mmol) afforded, after bulb-to-bulb distillation (84 °C (0.15 mm)), 371 mg (1.54 mmol; 81%) of **21** as a clear oil: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.34–7.27 (m, 2 H, Ar H), 7.06 (d, 1 H, J = 8.3 Hz, Ar H), 3.33 (br s, 1 H, H10), 3.16 (dd, 1 H, J = 17.1 and 4.2 Hz, H9), 2.83 (d, 1 H, J = 5.9 Hz, H5), 2.73 (d, 1 H, J = 17.1 Hz, H9), 2.34–2.04 (m, 3 H, H8, exo H6, and exo H7), 1.77–1.66 (m, 1 H, endo H6 or endo H7), 1.52–1.41 (m, 1 H, endo H6 or endo H7), 1.24 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3440, 3355, 2985, 1631, 1440, 1348, 1189, 1174, 1131, 1080, 900, 842 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 148.40, 134.43, 128.09 (q, J_{CF} = 32.5 Hz, C2), 127.14, 125.61 (q, J_{CF} = 2.4 Hz), 122.28 (q, J_{CF} = 4.2 Hz), 58.48, 48.21, 40.94, 39.20, 32.71, 27.10. **21**·HCl (recrystallized from EtOH/Et_2O): mp >300 °C; EIMS, m/z (relative intensity) 241 (M^+, 51.5), 224 (11.3), 222 (7.5), 209 (17.2), 196 (87.8), 177 (11.2), 155 (8.7), 129 (16.7), 128 (12.5), 115 (21.0), 56 (100). Anal. ($C_{13}H_{15}ClF_3N$) C, H, N.

***syn*-10-Amino-2-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (25).** Formamide **69** (474 mg; 1.76 mmol) afforded, after bulb-to-bulb distillation (92 °C (0.5 mm)), 368 mg (1.53 mmol; 87%) of **25** as a clear oil: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.38–7.32 (m, 2 H, Ar H), 7.09 (d, 1 H, J = 7.81 Hz, Ar H), 3.40 (t, 1 H, J = 4.88 Hz, H10), 3.22 (dd, 1 H, J = 17.3 and 4.5 Hz, H9), 2.92–2.86 (m, 1 H, H5), 2.60 (d, 1 H, J = 17.6 Hz, H9), 2.29–2.21 (m, 1 H, H8), 2.08–1.96 (m, 2 H, exo H6 and exo H7), 1.73–1.59 (m, 1 H, endo H6 or endo H7), 1.57–1.42 (m, 1 H, endo H6 or endo H7), 1.18 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3438, 3350, 2990, 1612, 1436, 1338, 1172, 1160, 1121, 1078, 908, 840 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 145.20, 134.99, 129.04, 128.16 (q, J_{CF} = 32.6 Hz, C2), 125.67 (q, J_{CF} = 4.2 Hz), 124.24 (q, J_{CF} = 271.9 Hz, CF_3), 122.73 (q, J_{CF} = 4.0 Hz), 55.04, 46.66, 36.79, 33.47, 28.38. **25**·HCl (recrystallized from EtOH/Et_2O): mp >300 °C; EIMS, m/z (relative intensity) 241 (M^+, 61.6), 224 (12.3), 222 (8.1), 209 (19.1), 196 (100), 177 (12.5), 155 (9.5), 129 (17.4), 128 (13.0), 115 (21.0). Anal. ($C_{13}H_{15}ClF_3N$) C, H, N.

***anti*-10-Amino-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (22).** Formamide **70** (411 mg; 1.53 mmol) afforded, after bulb-to-bulb distillation (78 °C (0.09 mm)), 293 mg (1.21 mmol; 79%) of **22** as a clear oil: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.31 (d, 1 H, J = 7.92 Hz, Ar H), 7.23 (s, 1 H, H4), 7.12 (d, 1 H, J = 7.81 Hz, Ar H), 3.31 (br s, 1 H, H10), 3.14 (d, 1 H, J = 16.5 Hz, H9), 2.88–2.64 (m, 2 H, H5 and H9), 2.36–2.03 (m, 3 H, H8, exo H6, and exo H7), 1.78–1.64 (m, 1 H, endo H6 or endo H7), 1.51–1.38 (m, 1 H, endo H6 or endo H7), 1.21 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3374, 3299, 2941, 1620, 1582, 1434, 1426, 1333, 1313, 1184, 1117, 1074, 822 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 145.11, 138.06, 129.19, 127.68 (q, J_{CF} = 32.3 Hz, C3), 124.24 (q, J_{CF} = 272.2 Hz, CF_3), 123.55 (q, J_{CF} = 4.9 Hz), 122.51 (q, J_{CF} = 2.6 Hz), 58.59, 48.28, 40.89, 39.31, 32.75, 27.14. **22**·HCl (recrystallized from EtOH): mp >300 °C; EIMS, m/z (relative intensity) 241 (M^+, 58.3), 224 (12.4), 222 (13.6), 212 (13.7), 209 (18.0), 196 (100), 177 (13.7), 155 (11.6), 129 (18.9), 128 (13.0), 115 (24.3). Anal. ($C_{13}H_{15}ClF_3N$) C, H, N.

***syn*-10-Amino-3-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (26).** Formamide **71** (307 mg; 1.14 mmol) afforded, after bulb-to-bulb distillation (85 °C (0.1 mm)), 237 mg (0.98 mmol; 86%) of **26** as a clear oil: ^{1}H NMR ($CDCl_3$; 300 MHz) 7.36 (d, 1 H, J = 7.81 Hz, Ar H), 7.26 (s, 1 H, H4), 7.19 (d, 1 H, J = 7.81 Hz, Ar H), 3.40 (t, 1 H, J = 4.4 Hz, H10), 3.22 (d, 1 H, J = 15.9 Hz, H9), 2.92–2.85 (m, 1 H, H5), 2.60 (d, 1 H, J = 18.2 Hz, H9), 2.29–2.20 (m, 1 H, H8), 2.11–1.94 (m, 2 H, exo H6 and exo H7), 1.77–1.65 (m, 1 H, endo H6 or endo H7), 1.58–1.41 (m, 1 H, endo H6 or endo H7), 1.21 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3376, 3283, 2941, 1620, 1433, 1321, 1265, 1163, 1116, 1072, 901, 821, 727 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 141.83, 138.65, 129.24, 128.21 (q, J_{CF} = 32.2 Hz, C3), 125.44 (q, J_{CF} = 4.5 Hz), 124.24 (q, J_{CF} = 272.1 H, CF_3), 122.64 (q, J_{CF} = 4.0 Hz), 55.02, 46.77, 36.77, 33.59, 33.52, 28.42. **26**·HCl (recrystallized from EtOH/Et_2O): mp 275 °C dec; EIMS, m/z (relative intensity) 241 (M^+, 66.8), 224 (12.7), 222 (9.5), 212 (13.6), 209 (19.0), 196 (100), 177 (14.3), 155 (11.3), 129 (19.3), 128 (12.8), 115 (20.5). Anal. ($C_{13}H_{15}ClF_3N$) C, H, N.

***anti*-10-Amino-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (23).** Formamide **72** (590 mg; 2.19 mmol) afforded, after bulb-to-bulb distillation (76 °C (0.15 mm)), 513 mg (2.12 mmol; 97%) of **23** as a clear oil: ^{1}H NMR

($CDCl_3$; 300 MHz) 7.39 (d, 1 H, J = 7.3 Hz, Ar H), 7.21 (d, 1 H, J = 7.3 Hz, Ar H), 7.13 (t, 1 H, J = 7.2 Hz, H2), 3.32 (s, 1 H, H10), 3.29–3.10 (m, 2 H, H9 and H5), 2.74 (d, 1 H, J = 17.1 Hz, H9), 2.40–2.04 (m, 3 H, H8, exo H6, and exo H7), 1.84–1.73 (m, 1 H, endo H6 or endo H7), 1.54–1.42 (m, 1 H, endo H6 or endo H7), 1.23 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3420, 3345, 2946, 1590, 1460, 1350, 1316, 1184, 1147, 1115, 1084, 829, 797, 766 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 142.71, 135.49, 132.79, 126.43 (q, J_{CF} = 31.1 Hz, C4), 125.31, 124.46 (q, J_{CF} = 274.0 Hz, CF_3), 122.95 (q, J_{CF} = 6.1 Hz), 58.37, 44.18, 40.63, 39.82, 32.66, 27.42. **23**·HCl (recrystallized from EtOH): mp >300 °C; EIMS, m/z (relative intensity) 241 (M^+, 24.8), 224 (5.9), 209 (7.7), 196 (100), 177 (10.0), 129 (16.8), 128 (13.7), 115 (25.6). Anal. ($C_{13}H_{15}ClF_3N$) C, H, N.

***syn*-10-Amino-4-(trifluoromethyl)-5,6,7,8-tetrahydro-5,8-methano-9*H*-benzocycloheptene (27).** Formamide **73** (187 mg; 0.69 mmol) afforded, after bulb-to-bulb distillation (74 °C (0.35 mm)), 160 mg (0.66 mmol; 95%) of **27** as a clear oil: ^1H NMR ($CDCl_3$; 300 MHz) 7.44 (d, 1 H, J = 7.2 Hz, Ar H), 7.26 (d, 1 H, J = 7.9 Hz, Ar H), 7.16 (t, 1 H, J = 7.9 Hz, H2), 3.42–3.20 (m, 3 H, H10, H9, and H5), 2.61 (d, 1 H, J = 17.6 Hz, H9), 2.26–2.19 (m, 1 H, H8), 2.16–1.92 (m, 2 H, exo H6 and exo H7), 1.80–1.68 (m, 1 H, endo H6 or endo H7), 1.56–1.42 (m, 1 H, endo H6 or endo H7), 1.22 (s, 2 H, exchangeable in D_2O, NH_2); IR (film) 3425, 3320, 2940, 1589, 1460, 1446, 1352, 1316, 1186; 1113, 1073, 903, 827, 796, 721 cm^{-1}; ^{13}C NMR ($CDCl_3$; 75 MHz) 139.57, 136.04, 132.74, 128.32 (q, J_{CF} = 29.5 Hz, C4), 125.25, 124.45 (q, J_{CF} = 273.8 Hz, CF_3), 123.39 (q, J_{CF} = 6.2 Hz), 54.65, 42.09, 36.49, 33.99, 33.29, 28.59. **27**·HCl (recrystallized from $EtOH/Et_2O$): mp >300 °C; EIMS, m/z (relative intensity) 241 (M^+, 30.4), 224 (7.7), 209 (9.9), 196 (100), 177 (7.6), 129 (11.0), 115 (11.8). Anal. ($C_{13}H_{15}ClF_3N$) C, H, N.

Radiochemical Assay for PNMT Activity. The assay employed in this study has been described elsewhere.[28,51] Briefly, a typical assay mixture consisted of 50 μL of 0.5 M phosphate buffer (pH 8.0), 25 μL of a 10 μM solution of unlabeled AdoMet, 5 μL of [*methyl*-^{3}H]AdoMet, containing approximately 2×10^6 dpm (specific activity approximately 15 mCi/mmol), 25 μL of substrate solution, 25 μL of inhibitor solution (if applicable), 25 μL of the enzyme preparation, and sufficient water to achieve a final volume of 250 μL. After incubation for 30 min at 37 °C, the reaction mixture was quenched by the addition of 250 μL of 0.5 M borate buffer (pH 10) and was extracted with toluene/isoamyl alcohol (7:3). The organic layer was removed and transferred to a scintillation vial and diluted with cocktail for counting. The mode of inhibition was ascertained by inspection of the $1/V$ vs $1/S$ plot of the data.

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Inhibition of Phenylethanolamine *N*-Methyltransferase (PNMT) by Aromatic Hydroxy-Substituted 1,2,3,4-Tetrahydroisoquinolines: Further Studies on the Hydrophilic Pocket of the Aromatic Ring Binding Region of the Active Site

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In a continuation of studies directed toward characterizing the hydrophilic pocket within the aromatic ring binding region of the active site of phenylethanolamine *N*-methyltransferase (PNMT), 5-, 6-, 7-, and 8-hydroxy-1,2,3,4-tetrahydroisoquinoline were prepared and evaluated as substrates and inhibitors of PNMT. In order to discern the necessity of an acidic hydrogen for interaction at this pocket the corresponding methyl ethers were also evaluated. The enhanced affinity of 7-hydroxy-1,2,3,4-tetrahydroisoquinoline (**16**) versus tetrahydroisoquinoline (**13**) itself indicates that a hydrophilic pocket exists off of carbon C7 in bound tetrahydroisoquinolines. The diminished affinity of the corresponding methyl ether is consistent with a requirement for the acidic hydrogen of **16** for interaction of the aromatic hydroxyl at this site. From the relative activities of the other regioisomeric aromatic hydroxyl-substituted tetrahydroisoquinolines, their corresponding methyl ethers, and 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, it appears that the hydrophilic pocket is spatially compact with respect to bound tetrahydroisoquinolines and is surrounded by larger areas of lipophilic character. To allow a comparison of the results of this study with previous data on bound β-phenylethylamines, the methyl ethers of 5-, 6-, 7-, and 8-hydroxy-*exo*-2-aminobenzonorbornene and of 5- and 6-hydroxy-*anti*-9-aminobenzonorbornene were also evaluated for their activity as substrates and inhibitors for PNMT. The results of this study are in agreement with previous findings for bound β-phenylethylamines and support the conclusion that the natural substrate for PNMT, norepinephrine, has a different active site binding orientation than most known substrates and competitive inhibitors of the enzyme.

In recent years, we have been engaged in the design of a potent yet selective inhibitor of phenylethanolamine *N*-methyltransferase (PNMT; EC 2.1.1.28). This enzyme is known to catalyze the transfer of an active methyl group from *S*-adenosyl-L-methionine (AdoMet) to the primary amine of norepinephrine (NE, **1**) to produce the hormone/neurotransmitter epinephrine (Epi, **2**; Figure 1).[2] Since initial reports that PNMT exists within the mammalian central nervous system (CNS),[3-6] Epi has been implicated in a multitude of physiological functions including the regulation of blood pressure,[7-11] the release

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