Intramolecular Cyclizations via Arylnitrenium Ions. Formation of a Six-Membered Ring Rather than a Macrocycle

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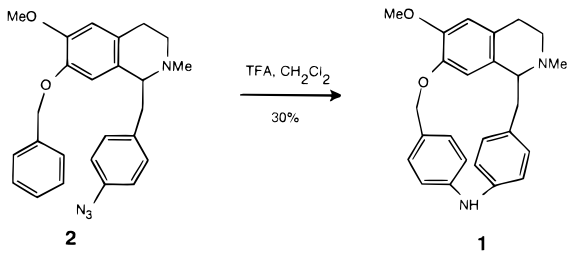
The stereochemistry of 1-(3-benzyloxyphenyl)-2-(4-nitrophenyl)ethane has been studied. MMX calculations predicted, and 2D NOESY confirmed, that the bent conformation (global energy minimum) was such that six-membered ring formation, and not macrocyclization, would occur using the corresponding nitrenium ion, and this was found to be the case. Acid-catalyzed decomposition of 1-(3-benzyloxyphenyl)-2-(4-azidophenyl)ethane followed by treatment with $(CF_3CO)_2O$ gave 48% of 2-benzyloxy-6-trifluoroacetamido-9,10-dihydrophenanthrene and 18% of 1-(3-benzyloxyphenyl)-2-(4-trifluoroacetamidophenyl)ethane. Blocking the original point of attack with a bromine atom led to the prediction (MMX, 2D NOESY) that, once again, small ring formation would take place, with macrocyclization possible but less likely. Again, this was found to be so. It is suggested that simple MMX calculations may provide a very rapid, empirical indicator of which precursors would have a readily accessible conformation that could result in intramolcular cyclization leading to macrocycles being preferred over intermolecular reactions.

Introduction

The synthesis of macrocyclic compounds has attracted extensive attention from synthetic chemists owing to the existence of a number of macrocyclic natural products that exhibit useful biological activities.[1] Many effective methods for macrocycle synthesis have been developed in recent years. An example of intramolecular electrophilic substitution is the formation of macrocycles via the Friedel−Crafts acylation.[2] Free-radical macrocyclization,[3] macrolactonization,[4] intramolecular Ullmann,[5] oxidative coupling,[6] metal-induced cyclization,[7] Diels−Alder,[8] Heck,[9] ring expansion,[10] Horner−Emmons,[11] and ring-closing metathesis reactions[12] have also been used. Since it might be expected that the stretched out conformation with the two ends as far away from each other as possible would be favored for the immediate precursor, high dilution techniques have often been used in order to avoid competition from intermolecular processes.

We previously reported the formation (in reasonable isolated yield) of a 16-membered highly strained ring (**1**) resulting from an intramolecular electrophilic aromatic amination by an arylnitrenium ion under normal concentration conditions.[13]



2 **1**

Of the various possible explanations considered, the preferred one was that there existed an attractive interaction between the highly electron-deficient arylnitrenium ion (or its protonated azide precursor) and the electron-rich benzyloxy group, such that the two rings were preoriented favorably, resulting in a lower activation energy and favorable entropy for intramolecular cyclization compared with other possible intermolecular pathways (thus satisfying the Curtin−Hammett hypothesis). If this were the case, and this phenomenon of intramolecular recognition was general, it might be used as the basis for designing novel approaches to desirable macrocycles, thus avoiding the need for high dilution.

Two applications of this idea were reported recently from this laboratory, which resulted in the successful synthesis of an 18-membered ring and a much less successful synthesis (also predicted by the method) of a

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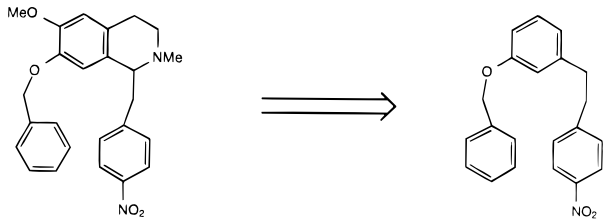
16-membered ring.[14] 1-(4-Nitrophenyl)-9-phenylnonane (the precursor of the corresponding nitrenium ion) having an electron-acceptor group ($C_6H_4NO_2$) and an electron-donor (Ph) group joined by a long, flexible tether was designed as a model compound. Its global minimum energy conformation was first predicted by MMX calculation and then confirmed by 2D NOESY, UV−vis, and fluorescence spectroscopy and was found to be such that the aryl rings were within easy bonding distance. The MMX calculation also suggested that the two aromatic rings were oriented partially edge-to-face to each other. The corresponding arylnitrenium ion was generated and cyclized to give mainly the 18-membered ring, 4,4′-nonamethylenediphenylamine. The corresponding 1-(4-nitrophenyl)-7-phenylheptane was predicted by MMX to also have a bent conformation in the global energy minimum form, but the two aryl rings were much further apart from each other than in the corresponding nonane owing to the shorter tether chain length: this also was confirmed by 2D-NOESY studies. The corresponding nitrenium ion cyclized to give only a very low yield of the 16-membered ring.[14] This supported the suggestion that when electron-deficient and electron-rich aryl rings were joined by a long, flexible chain intramolecular face-to-edge aromatic ring attractive interaction preorients them favorably for cyclization compared with intermolecular processes.

In this paper, we report some results of our continuing effort aimed at determining the scope of this possible intramolecular recognition to effect macrocylization via arylnitrenium ions. To this end, we revisited the original work[12] to see whether a stripped-down version of compound **3**, namely **4**, would also lead to a macrocycle via the corresponding nitrenium ion.

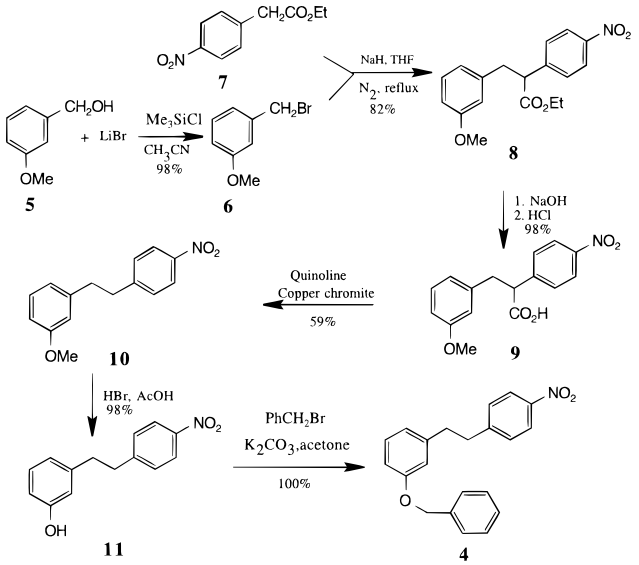


3 **4**

Results and Discussion

We started first by carrying out MMX calculations[15] on **3** as the model, since no MMX parameters are available for the nitrenium function. MMX predicted that **3** had a bent conformation as its global energy minimum ground state conformation (Figure 1; see the Supporting Information). The distance between the para position in the phenyl ring of the benzyloxy group and the nitrogen atom of nitrophenyl group is 3.465 Å as calculated by the MMX force field. While the energy difference between the bent and more open structure is predicted to be very small (as expected for an edge-to-face intramolecular attraction), it clearly indicates that the bent conformation should be readily accessible in the appropriate solvent.

Scheme 1



Surprisingly, MMX calculations on model compound **4** gave a different outcome: the calculations indicated that the linear conformation (**4a**) was the global energy minimum, preferred over the bent conformation (**4b**) (Figure 2; see the Supporting Information). The distance between the para position in ring **C** and the nitrogen atom of the nitrophenyl group is 14.329 Å. Ring A is, however, quite close to ring **B**. The distance between the position para to the nitro group and the position para to the oxygen atom in ring **B** is 4.608 Å and that between the position para to the nitro group and the position ortho to the ether oxygen in ring **B** is 4.742 Å, as calculated by the MMX force field.

On the basis of this result, we would expect that no macrocyclization would occur using the arylnitrenium corresponding to model compound **4** if our hypothesis of intramolecular recognition has generality as a predictive tool and if MMX calculations are empirically useful in predicting macrocycle formation. We continued with the synthesis of **4** to test whether, indeed, this is the case.

The synthesis of **4** is shown in Scheme 1. Bromide **6** was obtained in excellent yield from 3-methoxybenzyl alcohol (**5**) using LiBr/Me_3SiCl.[16] The use of trimethylsilyl chloride instead of trimethylsilyl bromide was successful, although there was a very small amount of 3-methoxybenzyl chloride formed [GC/MS: *m/e* 156 ($M^{\bullet+}$]. Alkylation of **7** with **6** using THF as the solvent under a nitrogen atmosphere with NaH as the base[17] afforded **8** as a yellow oil in a very good yield (82%). Hydrolysis and decarboxylation[18] led to **10** (58%), demethylation of which (HBr/AcOH)[19] gave **11.** Finally, O-benzylation to **4** was achieved in quantitative yield.[20]

The conformation of **4** in $CDCl_3$ (0.05 M) was then studied using 2D NOESY. In a properly executed NOESY

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(15) Using PC Model for Windows from Serena Software. To ensure that a global minimum energy had been reached, the various local minimum structures were altered repeatedly until the lowest energy conformation was reached consistently. Though these computations do not take into account the influence of solvent they do allow changes in the dielectric constant. The latter has been changed from 1.5 to 30.0 D without much change resulting in the global energy minimum conformations.

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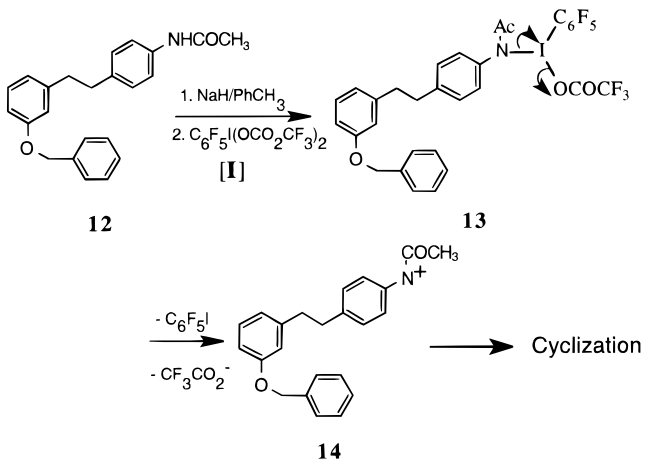
experiment, cross-peaks between two hydrogen atoms can be observed only if these protons are separated by a distance shorter than approximately 5.0 Å.[21] The sample was deoxygenated by freeze−thaw cycles in order to get optimum intensities of the enhancements. The assignments are given in the Experimental Section. No NOE signals between protons on rings **A** and **C** were observed. Instead, a weak NOE between the protons of rings **A** and **B** is seen (cross-peaks for the protons meta to the nitro group at δ 7.26 and the protons of the middle phenyl ring at δ 6.78−6.71). This suggests that the two end phenyl rings are not within easy bonding distance but that the nitrophenyl ring is reasonably close to ring **B** in the conformation of the molecule in **4**, in complete accord with the prediction based on our MMX calculations.

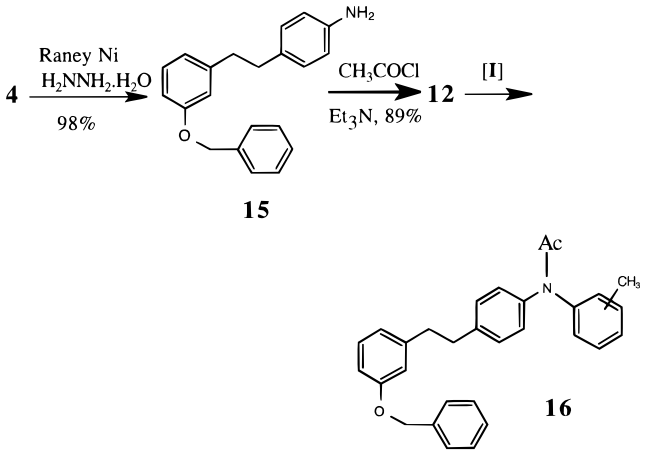
To see whether the synthetic chemistry would then follow these computational and physical measurements, we generated the corresponding nitrenium ion. We first attempted to do so by using a new route involving hypervalent iodine reagents[22] that have been used successfuly for the oxidation of phenols[23] and intramolecular oxidative aryl−aryl coupling.[24] A novel intramolecular cyclization reaction via diaryliodonium salts was also reported by Kita and co-workers.[25] Rodrigues, Abramovitch, and co-workers[26] reported intramolecular cyclizations via an aryloxenium ion from the oxidation of a phenol with $C_6F_5I(OCOCF_3)_2$, chosen because $C_6F_5I^+$-$(OCOCF_3)$ is an excellent leaving group and $CF_3CO_2^-$ a poor nucleophile, but also because C_6F_5 is not likely to undergo intramolecular C−C bond formation with an electron-deficient species. Finally, Stang and co-workers[27] reported a general approach to unsymmetrical tricoordinated iodinanes $PhI(X)OSO_2R$ by the reaction of PhIO with the appropriate derivatives of trimethylsilanes. The authors indicated that while the acetates, nitrile, and isocyanates were stable isolable compounds, adducts with X = $N(CH_3)_2$, ONH_2, N_3, and CH_2CN groups were unstable and rapidly decomposed between −30 and 0 °C with the formation of iodobenzene and uncharacterized polymeric material.

On the basis of these considerations, we attempted to generate the nitrenium ion **14** from the corresponding primary amide **12**, which would lead to intramolcular cyclization. Substrate **4** was converted to amine **15** without loss of the benzyloxy group using Raney Ni and hydrazine hydrate[28] in excellent yield, and this was acetylated to **12** (Scheme 2). Following N-deprotonation, it was treated with $C_6F_5I(OCOCF_3)_2$ in toluene solution.

Scheme 2



Scheme 3



GC/MS indicated that a complex mixtures was obtained. One of the major products appeared to be the N-arylated product **16** (Scheme 3), presumably formed by the attack of solvent toluene by the *N*-acylnitrenium ion or its precursor (see the Experimental Section). No attempt was made to isolate the individual components of this mixture owing to its complexity. The use of carbon tetrachloride as the solvent led to the recovery of mainly starting amide and a small amount of a complex mixture.

The desired nitrenium ion was then generated conventionally from azide **17,** obtained as usual[29] from the amine **15** (Scheme 4). Acid-catalyzed decomposition of **17** was first carried out in acetonitrile solution (32 mM) in the presence of trifluoroacetic acid (TFA) at 0 °C under a nitrogen atmosphere. The only product obtained in this reaction was the N-trifluoroacetylated hydrogen-abstraction product **18** (74%). The reaction was repeated using CCl_4 as the solvent, resulting in the formation of four products (Scheme 5), as indicated by GC/MS. The mass fragmentation patterns indicated that the four compounds could be divided into two pairs. In each pair, one product was the trifluoroacetylated derivative of the other. Also, there was a small peak for what could be a macrocycle. To simplify workup, the reaction mixture was treated with trifluoroacetic anhydride, which resulted in the formation of two main products: one was an intramolecular cyclization product and the other the hy-

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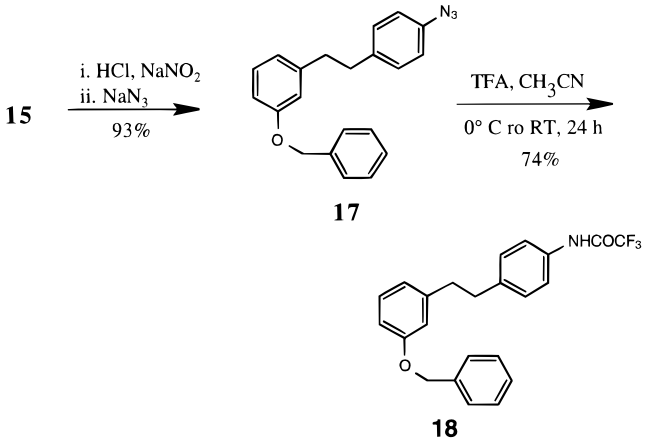
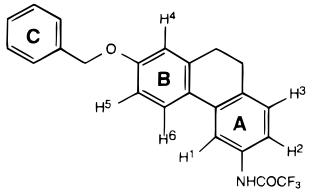
Scheme 4



drogen abstraction product (both trifluoroacetylated). The mixture was resolved by column chromatography.

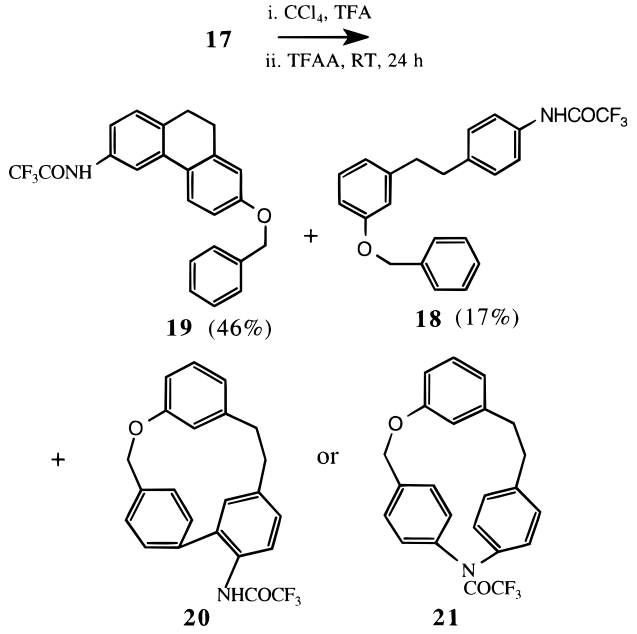
The major fraction (*m*/*z* 397) was assigned the phenanthrene structure **19** based mainly on its spectral properties [IR 3278 (NH), 1705 cm^{-1} (C═O)]; the presence of a CF_3CO group was confirmed by the ^{19}F NMR spectrum, which showed a single peak at −79.8 ppm,[30] and the mass spectral base peak at *m*/*e* 91 suggested the presence of the benzyloxy group unchanged. NMR spectroscopy further confirmed the assignments. The presence of a 1,2,4-trisubstituted phenyl was indicated by the peaks at δ 7.88 (d, J = 2.1 Hz, 1H), 7.34 (dd, J = 8.2 Hz, 2.1 Hz, 1H), and 7.22 (d, J = 8.2 Hz, 1H) and decoupling experiments. The δ 7.34 peak overlapped a multiplet in a range from 7.47 to 7.34 ppm, which was derived from the phenyl protons of the benzyloxy group. In the same way, another group of peaks [δ 7.66 (d, J = 8.5 Hz, 1H), 6.93 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H)] was assigned to a second 1,2,4-trisubstituted phenyl, this one bearing a more electron-donating substitutent ($PhCH_2O$). Structure **19** also accounts nicely for the somewhat downfield position of the "bay" ring protons H_1 and H_6 owing to the mutual deshielding by the two phenyl rings.



19

Two additional products were detected by GC/MS and are tentatively assigned structures **18** and **20** or **21**. Although, as for **19**, the parent ion peak for **20** or **21** is at *m*/*z* 397, which indicates that the cyclization has taken place, the base peaks are at *m*/*z* 89 and 90 [instead of 91 (benzyl) in **19**]. This strongly suggests that the benzyloxy group has been substituted and is involved in ring formation in this case. Unfortunately, product **20** (**21**) was formed in trace amounts (<1%), and it was not possible to isolate it. Product **18** gave a parent ion peak at *m*/*z* 399 with a base peak at *m*/*z* 91. No attempt was made to isolate this compound, and the yield was determined by the integration of its GC peak (compared

Scheme 5



with that of **19**). A likely mechanism for the formation of **19** (via the rearrangement of an initially formed ipso substitution product[31]) is shown in Scheme 6. Formation of **19** as the main product is in accord with the prediction based on the ground-state conformation of **4** (MMX and 2D NOESY).

The next step was to introduce a bromine substituent para to the benzyloxy group of the middle phenyl ring to prevent intramolecular cyclization at that position, decreasing the electron density in that ring as well, and perhaps force the formation of a macrocycle.

Bromination of **10** was effected with NBS in acetonitrile.[32] Careful control of the reaction temperature and time gave a single brominated compound (Scheme 7). Higher temperatures and longer reaction times led to the formation of a second monobrominated and some dibrominated products. The position of bromination was determined to be the position para to the methoxy group by a 1D NOE experiment; an NOE signal was observed between the methoxyl group protons and two aromatic protons instead of only one as expected in the case of ortho substitution. Attempted demethylation with HBr/AcOH gave a mixture of the debrominated, demethylated product, as well as several demethylated products in which bromine migration had occurred. Boron tribromide in methylene chloride[33] led cleanly to the desired phenol (**27**) in 87% yield. This was O-benzylated to **28** in 90% yield.

The results of MMX calculations on **28** (Figure 3; Supporting Information) show that the bent conformation is the global energy minimum, although the energy difference between the stretched out and bent conformations is smaller than that for **4**. The nitrophenyl group **A** is closer to ring **B** than to ring **C**. The distance between the para position of the benzyloxy group and nitrogen

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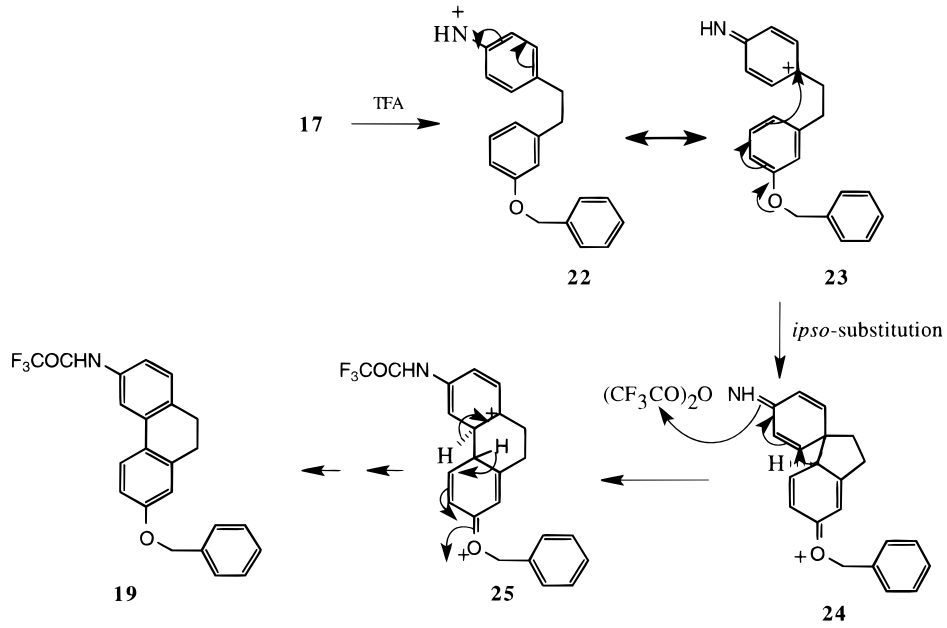
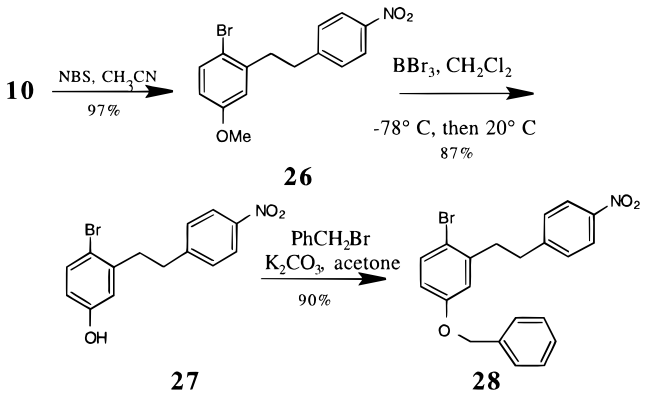
Scheme 6



Scheme 7



atom of the nitrophenyl ring is calculated to be 5.244 Å, and distances between the carbons of the benzyloxy phenyl and the position ortho to the nitro group of the nitrophenyl ring ranged from 4.529 to 7.672 Å; the distance between the position para to the nitro group and the position between the carbon side chain and the oxygen atom in ring **B** is 3.139 Å and between it and the bromine-bearing carbon is 4.168 Å. Thus, the MMX calculations suggested that cyclization onto ring **B** would be somewhat favored compared with macrocyclization.

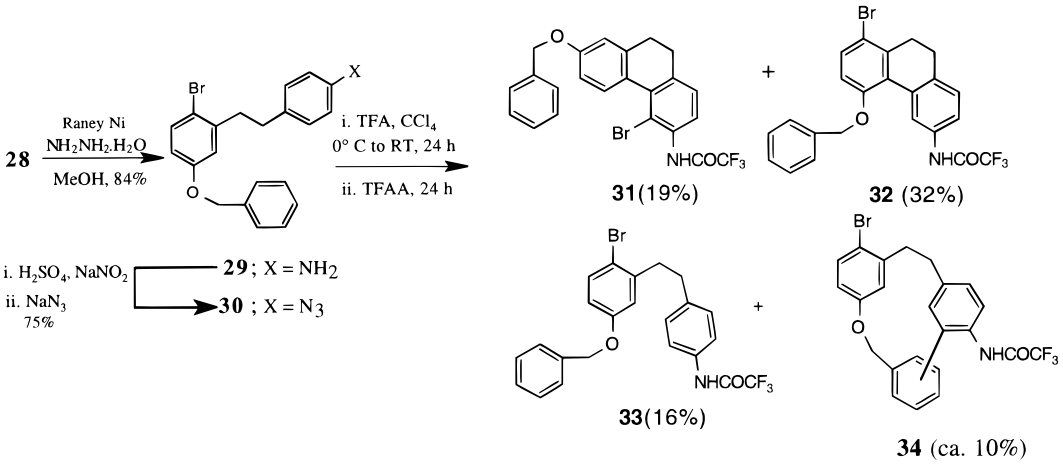
The 2D NOESY spectrum of **28** in deuteriochloroform exhibited no NOE between the protons of rings **A** and **C**, but neither is one observed between the nitrophenyl ring and ring **B**. The doublet at δ 8.14 is assigned to the protons ortho and the doublet at δ 7.32 to the protons meta to the nitro group (decoupling). The peaks at δ 7.25−7.39 (partial overlap with the protons meta to the nitro group) are owing to ring **C**. The doublet at δ 7.43 and multiplet at δ 6.70−6.74 are assigned to ring **B**. Thus, if MMX calculations have predictive value as discussed above, one would expect intramolecular cyclization to occur mainly onto ring **B**, with the possibility of some macrocycle formation. This prediction is borne out.

The nitro compound was converted as usual to the azide **30** via **29.** Trifluoroacetic acid-catalyzed decomposed **30** (25mM solution in CCl_4) at 0 °C under a nitrogen atmosphere, and the solution was then allowed to reach room temperature. After 24 h, it was treated with trifluoroacetic anhydride and stirred for another 24 h. Neutralization and workup gave a mixture whose GC/MS indicated that four products were formed (Scheme 8). Among them, one is the N-trifluoroacetylated hydrogen-abstraction product **33** (16%). A second is probably a macrocyclic product [parent ion at *m*/*z* 475(477)] based on the presence of a peak at *m*/*z* 89 instead of 91, indicating that the benzyloxy group had been substituted. The other two products had the same molecular weight as the macrocyclic product [*m*/*z* 475(477)] but had a base peak at *m*/*z* 91 (unsusbtituted benzyl), strongly suggesting the cyclization had occurred on ring **B**.

The reaction mixture was separated by preparative TLC into three zones. The bottom one (nearest to the origin) contained mainly the macrocyclic product (5.1 mg). The middle zone was a mixture of hydrogen-abstraction product and one of the small-ring cyclization products (23 mg). The top zone consisted of a pure small-ring product (9.1 mg, 19% yield). The latter was assigned structure **31** based on its mass and NMR spectrum. The former indicated a cyclized product and the presence of an unchanged benzyloxy group (*m*/*z* 91). The doublet in the NMR at δ 7.78 is owing to the proton ortho to CF_3-CONH− coupled with another doublet at δ 7.33, suggesting that this ring is 1,2,3,4-tetrasubstituted. A 1,2,4-trisubstituted benzene ring is also present [δ 7.45 (d,1H, J = 8.8 Hz); 6.79 (d,1H, J = 2.9 Hz); 6.73 (dd, 1H, J = 8.8, 2.9 Hz)]. This compared well with the proton spectrum for ring **B** in **19**.

The two components from the middle zone were resolved by preparative TLC, developed using 5% EtOAc in hexane. The pure cyclized product (32% yield) to which we assign structure **32** [parent ion *m*/*z* 475(477), base peak *m*/*z* 91] was obtained. Its ^{1}H NMR spectrum showed a doublet at δ 8.25 (J = 2.2 Hz) assigned to the bay proton ortho to the trifluoroacetamido group, coupled to the other ortho proton (decoupling). The latter gives rise to a doublet of doublets at δ 7.65 (J = 2.2 Hz, 8.1 Hz) [coupled with the meta proton; δ 7.25 (J = 8.1 Hz)],

Scheme 8



proving that the terminal ring is 1,2,4-trisubstituted. The doublets at δ 7.46 (J = 8.8 Hz) and 6.89 (J = 8.8 Hz) indicate the substitution pattern in the middle ring, which is in accord with structure **32**, as are the microanalytical data. The other compound in this mixture was not isolated in a pure state, but it was assigned structure **33** (ca. 16% yield) on the basis of its NMR and mass spectra (see the Experimental Section).

The bottom zone contained almost pure macrocyclization products [*m*/*z* 475(477)]. This was purified by preparative TLC (1.8 mg, 5% yield) (single peak in the GC/MS spectrum). That attack had taken place on the benzyloxy group was clear from the presence of a fragment ion at *m*/*z* 89, and the absence of one at *m*/*z* 91. Its ^{1}H NMR spectrum gave a complicated pattern that indicated that it was a mixture of two products possibly arising from C−N−C and C−C intramolecular bond formation or both from C−C bond formation. The presence of an NH stretching vibration in the IR spectrum (3309 cm^{-1}) confirmed the formation of a C−C bond. In all the previous compounds we discussed above, the methylene protons of the benzyloxy group gave rise to a sharp singlet and the ethylene group exhibited a broad singlet in the NMR. The benzyloxy CH_2 in the present case was a somewhat asymmetric doublet (δ 4.97−5.01), while the protons of ethylene group gave three symmetrical peaks [δ 3.13(1H), 2.91(2H), 2.72(1H)]. A further indication that the product is a mixture of two macrocycles comes from the fact that some of the aromatic protons inetgrate to 0.5 protons each (total or 10 aromatic and six aliphatic protons, as expected). It seems, therefore that neither GC nor preparative TLC resolved these two macrocycles, but further work on their separation was precluded by the very small amount of material available. The yields for products **32** and **33** are based on the proton ratios in the NMR spectra.

The formation of product **31** is unusual, and a possible mechanism that accounts for its formation is shown in Scheme 9. One of the macrocycles formed is readily accounted for by attack of the (delocalized) ortho cation on either the ortho or the para position of the benzyloxy group. It is also conceivable that the para cation could attack the ortho position of the benzyloxy group (ipso substitution; see Scheme 6), followed by a 1,2-shift in the cyclohexadienone imine to rearomatize the ring.

Conclusions

We started with the assumption that compound **4** (a stripped-down version of **2**) would behave like the latter such that the corresponding nitrenium ion would cyclize to give a macrocycle. To our surprise, MMX calculations indicated (and 2D NOESY confirmed) that the global minimum energy conformation in solution under normal concentration conditions was such that cyclization would lead to a six-membered ring, provided that the energy of activation of cyclization from that conformation was lower than that of other possible inter- and intramolecular processes. This prediction was confirmed experimentally with the observed formation of **19** as the main product. It is interesting to note that the MMX results predict a dihedral angle of 89° between the nitrophenyl group and the middle ring of **4**, suggesting that edge-to-face aromatic interactions[34] stabilize this conformation. Similarly, MMX calculations and 2D NOESY of **28** (under normal concentration conditions) suggested similar behavior, except that in this case, one computed internuclear C−C distance between the terminal aryl groups (4.529 Å) hinted at the possibility that macrocyclization could compete to some extent. Again, the results were in complete agreement with the predictions.

The MMX force field in PCModel includes parameters for stretching, bending, torsion, van der Waals, and charge charge electrostatic interactions, as well as the VESCF π routines from MMPI and the concept of generalized parameters from Still. It is a very low level computational method compared with ab initio calculations, but it does seem to predict reasonably well a variety of ground-state conformations. In our case, we have been able to confirm these approximate conformations by physical methods. Up to now, the conformations predicted by MMX in the systems we have examined have served very well as indicators of what to expect in the intramolecular cyclizations we have studied. If this can be generalized, then we suggest that MMX calculations could provide a very rapid *empirical* predictor of which molecules may be expected to lead to macrocycles and which may not, provided that the Curtin−Hammett hypothesis is met; i.e., the energy of activation for the

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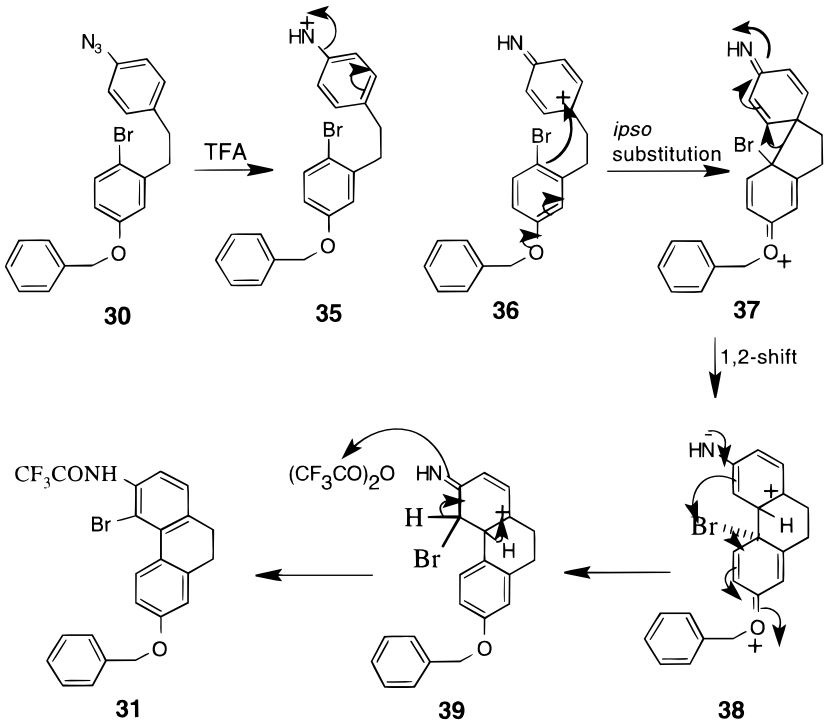
Scheme 9



macrocyclization from the predicted conformation is lower than those of other possible inter- and intramolecular reactions. We have tested this in a number of cases in which macrocyclizations have been reported in the literature by using MMX to predict the global minimum energy conformation of plausible models for the precursors, and in all the examples we have computed so far, MMX has predicted the bent conformation expected. For example, Marshall and co-workers[35] synthesized 12- to 16-membered propargylic alcohols through Lewis acid-promoted electrophilic ring-closure of diene ynals using $EtAlCl_2$ at −78 °C. MMX calculation of the corresponding O-protonated formyl precursor predicted that the global minimum energy conformation was that in which the protonated formyl was just above the penultimate alkene function, as required for macrocycle formation.[36]

Experimental Section

THF was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. Super-dry ethanol was prepared according to the procedure described in *Vogel's Textbook of Practical Organic Chemistry*.[37] Benzene, toluene, and diethyl ether were dried with sodium wire. All other solvents and reagents were used directly without further purification, unless otherwise noted. Column chromatography was carried out with Aldrich silica gel (70−230 mesh) or Fisher Scientific basic alumina (80−200 mesh). Thin-layer chromatography was carried out using commercial available aluminum plates coated with a 0.25 mm layer of silica gel containing a 254 nm fluorescent indicator. Preparative TLC was carried out on glass plates (20 × 20 cm) coated with a 1 mm layer of Aldrich silica gel, Merck, TLC grade 7749, with gypsum binder and fluorescent indicator. ^{19}F NMR was recorded using a Bruker AC-200 spectrometer. Melting points are uncorrected. MMX force field calculations were carried out by using PCMODEL for Windows from Serena Software, Bloomington, IN.

3-Methoxybenzyl Bromide (6). Chlorotrimethylsilane (33 mL) was added to a solution of lithium bromide (18.1 g) in dry acetonitrile (210 mL) with stirring under a nitrogen atmosphere. 3-Methoxybenzyl alcohol (15 g, 0.11 mol) was then added, and the resulting mixture was boiled under reflux for 22 h. Diethyl ether (850 mL) was added, and the solution was washed with water, with saturated aqueous $NaHCO_3$, and once again with water and dried ($MgSO_4$). Filtration and evaporation of the solvent afforded the product **6** as a colorless liquid (98%): GCn-MS (70 eV) *m/z* 200 (202) ($M^{\bullet+}$).

Ethyl 1-(3-Methoxyphenyl)-2-(4-nitrophenyl)propanoate (8). A suspension of sodium hydride (1.553 g, 60% in mineral oil, 0.039 mol) in anhydrous THF (70 mL) was cooled to 0 °C (N_2), ethyl 4-nitrophenyl acetate **7** (8.147 g, 0.039 mol) in THF (70 mL) was added dropwise through a dropping funnel over a period of 2 h, and the resulting mixture was stirred at 0 °C for 2 h. **6** (5.270 g, 0.026 mol) in THF (70 mL) was then added dropwise over a period of 2 h, and the resulting mixture was allowed to come to room temperature and was then stirred overnight. After filtration, the solvent was evaporated, and the residue was dissolved in ethyl acetate (80 mL). The organic layer was washed with H_2O and dried ($MgSO_4$), and the solvent was removed *in vacuo*. Silica gel column chromatography (hexane/EtOAc 7:1, v/v) of the crude product followed by bulb-to-bulb distillation (0.1 mmHg, 130−135 °C) gave **8** (7.07 g, 82%) as a pale yellow solid: mp 57−58 °C; IR (KBr) 1730 (s) (CO), 1515 (NO_2) (s), 1340 (NO_2) cm^{-1} (s); GC−MS (70 eV) *m/z* 329 ($M^{\bullet+}$). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.63, H, 5.83. Found: C, 65.42; H, 5.81.

1-(3-Methoxyphenyl)-2-(4-nitrophenyl)propanoic Acid (9). Ester **8** (7.0 g, 0.021 mol) was mixed with of 5% NaOH solution (64 mL) and boiled under reflux for 1.5 h. The mixture was then stirred at room temperature for 4 h, and 10% HCl solution (51 mL) was added to precipitate the carboxylic acid. The product was filtered, washed with water, and dried at 70 °C to give **9** (6.28 g, 98%) as a yellow-red solid: mp 133−134 °C; IR (KBr) 1700 (s) (CO_2H), 1515 (NO_2) (s), 1338 (NO_2) cm^{-1} (s). Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.77; H, 5.03. Found: C, 63.88; H, 5.08.

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(36) Abramovitch, R. A. Unpublished result (1993).

(37) *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; revised by Furniss, B. S., Hannaford, A. J., Smith, P. W. G., Tatchell, A. R.; Longman Scientific & Technical: Essex, 1989.

1-(3-Methoxyphenyl)-2-(4-nitrophenyl)ethane (10). Acid **9** (4.06 g, 0.013 mol) was dissolved in quinoline (19 mL), and copper chromite (0.359 g) was added. The mixture was heated under reflux in an oil bath kept at 210−220 °C for 1.5 h. The mixture was cooled, treated with 10% HCl (63 mL), and stirred for 1 h. The aqueous solution was extracted with diethyl ether and the combined organic layers were washed with 10% HCl (20 mL) and water and dried ($MgSO_4$). Silica gel (40−140 mesh) column chromatography of the crude product (petroleum ether/EtOAc 95:5, v/v) gave **10** (2.05 g, 59%) as a pale yellow solid: mp 48−49 °C; GC−MS (70 eV) *m/z* 257 ($M^{\bullet+}$). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.01; H, 5.89. Found: C, 69.93; H, 5.89.

1-(3-Hydroxyphenyl)-2-(4-nitrophenyl)ethane (11). Methyl ether **10** (0.79 g, 3.07 mmol) was dissolved in a mixture of glacial acetic acid (33 mL) and 48% aqueous HBr (33 mL). The resulting solution was boiled under reflux for 3.5 h. The solvent was removed in vacuo, and the residue was dissolved in diethyl ether (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution and then with water and then dried ($MgSO_4$). The ether solution was filtered, and the solvent was removed in vacuo to give **11** (0.73 g, 98%) as a pale yellow solid: mp 123−124 °C; IR (KBr) 3460 (bs) (OH), 1518 (NO_2) (s), 1345 (NO_2) cm^{-1} (s); GC−MS (70 eV) *m/z* 243 ($M^{\bullet+}$). Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.11; H, 5.40. Found: C, 68.92; H, 5.42.

1-(3-Benzyloxyphenyl)-2-(4-nitrophenyl)ethane (4). Compound **11** (0.60 g, 2.47 mmol) was added to a mixture of acetone (10 mL) and anhydrous K_2CO_3 (1.69 g). Benzyl bromide (0.52 mL) was added to the suspension, and the resulting mixture was boiled under reflux for 24 h. The mixture was filtered, and the solvent was removed in vacuo. The crude product was subjected to bulb-to-bulb distillation (0.6 mmHg, 100 °C) to remove excess benzyl bromide, giving **4** (0.83 g, 100%) as a pale yellow solid: mp 72−73 °C; IR (KBr) 1512 (NO_2) (s), 1342 (NO_2) (s), 745 (m) (Ph), 695 cm^{-1} (m) (Ph); ^1H NMR ($CDCl_3$) δ 8.14 (d, 2H, $J = 8.6$ Hz) (2H ortho to NO_2), 7.43−7.30 (m, 5H) (2H ortho to OCH_2), 7.26 (d, 2H, $J = 8.6$ Hz) (2H meta to NO_2), 7.21−7.16 (t, 1H) (H meta to CH_2O), 6.84−6.71 (m, 3H) (3H ortho and para to CH_2O), 5.03 (s, 2H) (OCH_2), 3.03−2.99 (m, 2H), 2.94−2.89 (m, 2H); GC−MS (70 eV) *m/z* 333 ($M^{\bullet+}$). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.65; H, 5.76. Found: C, 75.61; H, 5.82.

1-(3-Benzyloxyphenyl)-2-(4-aminophenyl)ethane (15). Nitro compound **4** (0.79 g, 2.37 mmol) was dissolved in methanol (39 mL) containing hydrazine hydrate (1.55 mL). A suspension of Raney Ni (ethanol) (0.4 mL) was added dropwise, and the suspension was stirred and boiled under reflux for 1.5 h. After filtration, the solvent was removed in vacuo, and the residue was dissolved in diethyl ether. The organic layer was washed with water and dried ($MgSO_4$). Filtration and evaporation gave the crude product, which was recrystallized from diethyl ether to give **15** (0.75 g, 99%) as a white solid: mp 73−74 °C; IR (KBr) 3435 (NH_2) (w), 3330 (NH_2) cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 7.43−7.34 (m, 5H), 7.22−7.17 (t, 1H), 6.98 (d, 2H, $J = 8.3$ Hz), 6.82−6.80 (m, 3H), 6.63 (d, 2H, $J = 8.3$ Hz), 5.04 (s, 2H), 3.56 (bs, 2H), 2.82 (s, 4H); GC−MS (70 eV) *m/z* 303 ($M^{\bullet+}$). Anal. Calcd for $C_{21}H_{21}NO$: C, 83.12; H, 6.99. Found: C, 82.88; H, 7.03.

1-(3-Benzyloxyphenyl)-2-(4-acetamidophenyl)ethane (12). Triethylamine (0.4 mL) and acetyl chloride (0.15 g, 2.36 mmol) were added to **15** (0.21 g, 0.69 mmol) in methylene chloride (4 mL) and the solution stirred at room temperature for 4 h, transferred to a separating funnel, washed with 5% aqueous $NaHCO_3$ and then water, and dried ($MgSO_4$). The solvent was evaporated, and the crude product was recrystallized (ethanol) giving pure **12** as a white solid (89%): mp 90−91.5 °C; IR (Nujol) 3345 (NH) (w), 1658 (CO) cm^{-1} (s); GC−MS (70 eV) *m/z* 345 ($M^{\bullet+}$). Anal. Calcd for $C_{23}H_{23}NO_2$: C, 79.96; H, 6.72. Found: C, 79.72; H, 6.76.

Attempted N-Oxidation of 12. To the solution of **12** (23 mg, 0.067 mmol) in toluene (5.6 mL) under N_2 was added sodium hydride (3 mg) at 0 °C. The mixture was cooled to −10 °C and stirred for 30 min. Pentafluorophenyliodine(III) bis-(trifluoroacetate) (39 mg) was then added and stirring continued at −10 °C for 2 h. The temperature was gradually raised to 0 °C and kept there for 3 h. The solution was then transferred to a separating funnel with the help of toluene, washed with water, and dried ($MgSO_4$). Filtration and evaporation of the solvent gave a crude product (39 mg). GC/MS suggested that the main product could be **16**: *m/z* 435 ($M^{\bullet+}$), 344, 328, 286, 238, 196, 132, 91 (see the Results and Discussion).

If the reaction was carried out in carbon tetrachloride solution, unchanged **12** was recovered, even after the reaction time at 0 °C was extended to 7 h.

1-(3-Benzyloxyphenyl)-2-(4-azidophenyl)ethane (17). Amine **15** (74 mg, 0.24 mmol) was dissolved in warm dilute HCl (0.5 mL concentrated HCl and 2.5 mL of H_2O) with heating. The mixture was cooled in ice and treated with $NaNO_2$ (28 mg) in H_2O (1.8 mL). After being stirred for 1 h, NaN_3 (28 mg) in H_2O (1.8 mL) was added to the mixture and the solution was stirred for 4 h. Extraction with ethyl acetate, washing the combined extracts with water, drying ($MgSO_4$), filtration, and evaporation yielded **17** (74.5 mg, 93%) as a white solid: mp 74−75 °C; IR (NaCl) 2100 (N_3) (s), 1285 (N_3); GC−MS (70 eV) *m/z* 329 ($M^{\bullet+}$). Anal. Calcd for $C_{21}H_{19}N_3O$: C, 76.56; H, 5.83. Found: C, 76.33; H, 5.79.

2-Benzyloxy-6-trifluoroacetamido-9,10-dihydrophenanthrene (19). Azide **17** (106 mg, 0.32 mmol) was dissolved in carbon tetrachloride (10 mL) at 0 °C under a nitrogen atmosphere. Trifluoroacetic acid (2 mL) was then added dropwise to the solution, which was stirred at 0 °C for 1 h and then at room temperature for 24 h. Trifluoroacetic anhydride (2 mL) was added, and stirring was continued for another 24 h. The solution was then washed with water and dried (Na_2SO_4). Column chromatography of the crude product on neutral alumina (20 g, column length 10") (hexane/EtOAc 9:1, v/v), followed by recrystallization from EtOH gave **19** (59.2 mg, 46.3%) as white solid: mp 164−165 °C; IR (KBr) 3278 (NH) (m), 1705 (CO) cm^{-1} (s); ^{19}F NMR ($CDCl_3$) δ −79.8; ^1H NMR ($CDCl_3$) δ 7.94 (bs, 1H), 7.89 (d, 1H, $J = 2.1$ Hz), 7.66 (d, 1H, $J = 8.5$ Hz), 7.47−7.33 (m, 6H), 7.23 (d, 1H, $J = 8.1$ Hz), 6.95−6.91 (m, 1H), 6.88 (d, 1H, $J = 2.6$ Hz), 5.10 (s, 2H), 2.85 (s, 4H); GC−MS (70 eV) *m/z* 397 ($M^{\bullet+}$). Anal. Calcd for $C_{23}H_{18}F_3NO$: C, 69.50; H, 4.57. Found: C, 69.36; H, 4.64. Two additional products were detected by GC−MS: the trifluoroacetylated hydrogen-abstraction product **18** (17%), GC−MS (70 eV) *m/z* 399 ($M^{\bullet+}$), and a product to which structure **20** or **21** is assigned (<1%), GC−MS (70 eV) *m/z* 397 ($M^{\bullet+}$), 210, 182, 165, 89.

1-(2-Bromo-5-methoxy)phenyl-2-(4-nitrophenyl)-ethane (26). Methyl ether **10** (0.75 g, 0.29 mmol) was dissolved in acetonitrile (15 mL). *N*-Bromosuccinimide (0.54 g) was then added. The solution was stirred at room temperature and monitored by TLC until the starting material had disappeared (6 h). The solvent was then evaporated under vacuum, and the crude product was repeatedly extracted with small amounts of diethyl ether to afford pure **26** as a pale yellow solid (97%): mp 80−81 °C; IR (KBr) 1508 (NO_2) (s), 1335 (NO_2) cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 8.15 (d, 2H, $J = 8.65$ Hz), 7.44 (d, 1H, $J = 9.49$ Hz), 7.35 (d, 2H, $J = 8.64$ Hz), 6.64−6.68 (m, 2H), 3.74 (s, 3H), 3.01 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 158.94, 149.04, 146.52, 140.68, 133.47, 129.37, 123.66, 116.28, 114.72, 113.54, 55.41, 37.94, 35.92, 29.56; $^1H-^{13}C$ DEPT five quaternary C's (δ 158.94, 149.04, 146.52, 140.68, 114.72); five tertiary C's (δ 133.47, 129.37, 123.66, 116.28, 113.54); two secondary C's (δ 37.94, 35.92); one primary C (δ 55.41); 1D NOE NOE (5%) between the peak at δ 3.74 and the peaks at δ 6.64−6.68; GC−MS (70 eV) *m/z* 335 (337) ($M^{\bullet+}$), 256, 199 (201). Anal. Calcd for $C_{15}H_{14}BrNO_3$: C, 53.58; H, 4.21. Found: C, 53.45; H, 4.18.

1-(2-Bromo-5-hydroxy)phenyl-2-(4-nitrophenyl)-ethane (27). A 50 mL three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, a rubber stopper, and a pressure-equalizing dropping funnel was charged with a solution of methyl ether **26** (0.86 g, 2.56 mmol) in methylene

chloride (16 mL). The solution was cooled to −80 °C, and a solution of boron tribromide (3.8 mL, 1.0 M in CH_2Cl_2) was added dropwise. The reaction mixture was allowed to warm to 20 °C over the course of 7 h and then kept at rt for 14.5 h. Addition of water (32 mL) resulted in the precipitation of a white solid that was extracted with diethyl ether (100 mL). The ether was washed with water (2 × 30 mL), dried (Na_2SO_4), filtered, and evaporated to give a crude product (0.74 g). Pure **27** (87%), mp 133−134 °C, was obtained after silica gel column chromatography using hexane/EtOAc (9:1, v/v) as eluant: IR (KBr) 3380 (bs) (OH), 1508 (NO_2) (s), 1338 (NO_2) cm^{-1} (s); GC−MS (70 eV) *m*/*z* 321(323) ($M^{\bullet+}$). Anal. Calcd for $C_{14}H_{12}BrNO_3$: C, 52.19; H, 3.76. Found: C, 52.15; H, 3.75.

1-(2-Bromo-5-benzyloxy)phenyl-2-(4-nitrophenyl)-ethane (28). Phenol **27** (0.72 g, 2.24 mmol) was dissolved in acetone (15 mL) and treated with anhydrous K_2CO_3 (2.1 g). Benzyl bromide (0.6 mL) was added, and the resulting mixture was stirred and boiled under reflux for 24 h. It was filtered and the solvent evaporated. The crude product was subjected to bulb-to-bulb distillation (0.6 mmHg, 100 °C) to remove excess benzyl bromide, giving **28** (0.83 g, 90%) as a pale yellow solid: mp 91−92 °C; IR (KBr) 1500 (NO_2) (s), 1332 (NO_2) (s), 740 (m) (Ph), 690 cm^{-1} (m) (Ph); GC−MS (70 eV) *m*/*z* 411 (413) ($M^{\bullet+}$). Anal. Calcd for $C_{21}H_{18}BrNO_3$: C, 61.17; H, 4.41. Found: C, 61.12; H, 4.39.

1-(2-Bromo-5-benzyloxy)phenyl-2-(4-aminophenyl)-ethane (29). Compound **28** (105 mg, 0.25 mmol) was reduced in the same way as **15** to give a crude product that was purified by silica gel column chromatography (hexane/EtOAc 8/2, v/v) to give **29** (80 mg, 82%) as a white solid: mp 63−64 °C; IR (KBr) 3430 (NH_2) (m), 3360 (NH_2) cm^{-1} (m); GC−MS (70 eV) *m*/*z* 381 (383) ($M^{\bullet+}$). Anal. Calcd for $C_{21}H_{20}BrNO$: C, 65.97; H, 5.28. Found: C, 65.85; H, 5.37.

1-(2-Bromo-5-benzyloxyphenyl)-2-(4-azidophenyl)-ethane (30). Amine **29** (70 mg, 0.18 mmol) was dissolved in warm dilute H_2SO_4 (0.8 mL of concentrated H_2SO_4, 4 mL of H_2O). The mixture was cooled to <5 °C in an ice bath and treated with $NaNO_2$ (23 mg) in H_2O (1.2 mL). After the mixture was stirred for 1 h, NaN_3 (23 mg) in H_2O (1.2 mL) was added, and the solution was stirred in an ice bath for 0.5 h and then at room temperature for 3.5 h. Extraction with ethyl acetate, washing with water, drying ($MgSO_4$), filtration, and purification by silica gel column chromatography (hexane/EtOAc 199:1, v/v) gave **30** (63 mg, 84%) as a white solid: mp 65.5−66.5 °C; IR (KBr) 2105 (s) (N_3), 1285 (N_3) cm^{-1} (m); GC−MS (70 eV) *m*/*z* 381 (383) 302, 210, 165, 106, 91 (no parent ion peak). Anal. Calcd for $C_{21}H_{18}BrN_3O$: C, 61.78; H, 4.44. Found: C, 61.75; H, 4.51.

1-Bromo-4-benzyloxy-6-trifluoroacetamido-9,10-dihydrophenanthrene (32). 1-(2-Bromo-5-benzyloxyphenyl)-2-(4-azidophenyl)ethane (**30**) (41 mg, 0.1 mmol) was dissolved in carbon tetrachloride (4 mL) at 0 °C under a nitrogen atmosphere. Trifluoroacetic acid (0.8 mL) was then added dropwise to the solution, which was then stirred at 0 °C for 1 h and then at room temperature for 24 h. Trifluoroacetic anhydride (0.8 mL) was added, and stirring was continued for another 24 h. The solution was then washed with water and dried (Na_2SO_4). Filtration and evaporation of the solvent afforded a crude product (41 mg), which was resolved by preparative TLC using hexane/EtOAc (9:1, v/v) as eluant. Three zones were resolved. The first zone (R_f = 0.26) afforded mainly a mixture of macrocycles **34** (5.1 mg, ca. 10%) that was resubjected to preparative TLC giving what appeared to be a pure product (GC−MS) but was a mixture of macrocycles as indicated by ^1H NMR: mp 62−74.5 °C; IR (neat) 3309 (NH) cm^{-1} (m); GC−MS (70 eV) *m*/*z* 475 (477) (90), 371 (369), 352 (354), 290 (100), 194 (89), 165 (167). The second zone (R_f = 0.48) gave a mixture (23 mg) of 1-(2-bromo-5-benzyloxyphenyl)-2-(4-trifluoroacetamidophenyl)ethane (**33**), GCN-MS (70 eV) *m*/*z* 477(479), and 1-bromo-4-benzyloxy-6-trifluoroacetamido-9,10-dihydrophenanthrene (**32**), GC−MS (70 eV) *m*/*z* 475(477). This zone was resolved again by preparative TLC, developed with hexane/EtOAc (95:5, v/v), to afford pure **32**, mp 145−146 °C. Anal. Calcd for $C_{23}H_{17}BrF_3NO_2$: C, 57.99; H, 3.60. Found: C, 58.24; H, 3.55. The third zone (R_f = 0.71) gave pure 2-benzyloxy-5-bromo-6-trifluoroacetamido-9,10-dihydrophenanthrene (**31**) (9.1 mg, 19%): GC−MS (70 eV) *m*/*z* 475(477).

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Supporting Information Available: Minimum energy conformations of model compounds **3**, **4**, and **28** as calculated be the MMX force field. This material is available free of charge via the Internet at http://pubs.acs.org.

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