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# Monoamine Oxidase-Catalyzed Oxidation of *endo,endo*-2-Amino-6-[(*Z*)-2′-phenyl]ethenylbicyclo[2.2.1]heptane, a Potential Probe for a Radical Cation Intermediate

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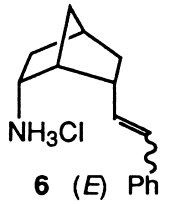
**Abstract**—An 11-step synthesis of *endo,endo*-2-amino-6-[(*E*)-2′-phenyl]ethenylbicyclo[2.2.1]heptane (**6**) and the corresponding (*Z*)-isomer (**7**) was carried out in an attempt to make a compound that could trap the purported amine radical cation intermediate during monoamine oxidase (MAO)-catalyzed oxidation of amines. The *E*-isomer was not a substrate for MAO, and the *Z*-isomer was a very poor substrate. No trapping product was observed. Possible explanations for the inability of these compounds to trap a potential radical cation intermediate are discussed. 

## Introduction

Monoamine oxidase (MAO, EC 1.4.3.4), a flavoenzyme in the outer mitochondrial membrane, catalyzes the oxidative deamination of a wide variety of biogenic and xenobiotic amines[1] to the corresponding imines, which are nonenzymatically hydrolyzed to aldehydes.[2] The mechanism of this enzyme-catalyzed reaction has long been debated; there are three principal pathways that have been proposed. Scheme 1 depicts a single-electron transfer mechanism, via the amine radical cation (**1**) to the α-radical (**2**), followed by either second electron transfer to the imine or radical combination with a group on the enzyme to **3** and then to the imine. The amine radical cation intermediate is supported by a variety of substrate analogue and inactivator studies.[3] The second mechanism (Scheme 2) bypasses the initial electron transfer in favor of direct hydrogen atom abstraction.[4] The support for this appears to come mainly from the inability to detect an initial amine radical cation intermediate spectroscopically. Scheme 3 shows the group transfer mechanism, in which the amine undergoes nucleophilic attack of the flavin to give a covalent adduct (**4**), which transfers electrons by elimination. This mechanism is supported by chemical model studies[5] and Hammett studies.[6]

Earlier we had synthesized (*E*)- and (*Z*)-2-(iodoethenyl)benzyl amine (**5**) as a potential probe for the formation of a radical cation;[7] it was hoped that the rate of cyclization of the double bond to the purported radical cation intermediate (Scheme 4) would be sufficient to trap it. Unfortunately, only amine oxidation of the *Z*-isomer was observed without cyclization. To enhance the chance for intramolecular cyclization, we synthesized (*E*)- and (*Z*)-*endo,endo*-2-amino-6-[2′-phenyl]ethenylbicyclo[2.2.1]heptane (**6** and **7**, respectively). Unfortunately, we again were unable to detect the formation of any cyclized products.




## Results and Discussion

### Syntheses of *endo,endo*-2-amino-6-[(*E*)-2′-phenyl]-ethenylbicyclo[2.2.1]heptane (6) and *endo,endo*-2-amino-6-[(*Z*)-2′phenyl]ethenylbicyclo[2.2.1]heptane (7)

Amines **6** and **7** were synthesized as shown in Scheme 5. Ketal ester **12** was prepared from cyclopentadiene in 5 steps.[8] Reduction of **12** with DIBAL did not stop at the

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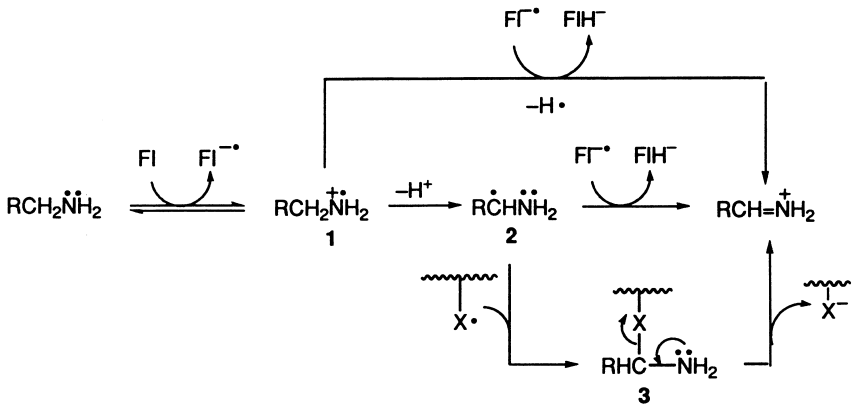


Scheme 1.

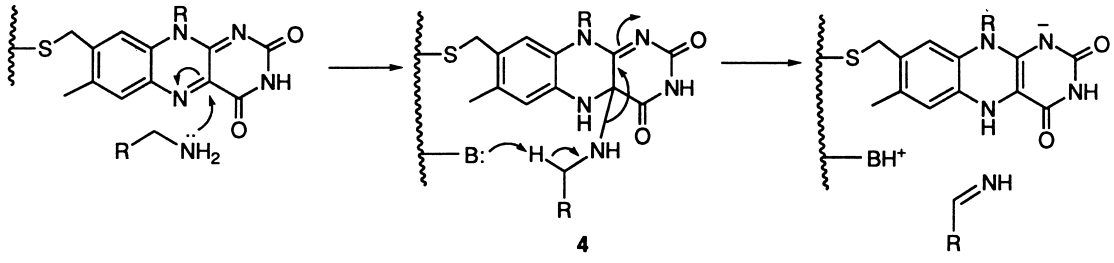
Scheme 2.

desired aldehyde but was reduced to alcohol **13**, whose structure was confirmed by X-ray diffraction analysis of the corresponding carboxylic acid (data not shown). A Wittig reaction with **14** afforded a mixture of both *E*- and *Z*-isomers (**15**) in a 1:1.3 ratio, which were inseparable by column chromatography. After deprotection, however, the corresponding (*E*)-**16** and (*Z*)-**17** ketones were isolated cleanly by preparative thin layer chromatography. Direct reductive amination of **16** and **17** with $NH_4OAc/NaCNBH_3$ did not yield any of the desired product. The corresponding oximes were synthesized, and various reducing reagents were tried to reduce the oximes. Among them, $TiCl_3/NaCNBH_3$ was the most successful.[9] Both the amino group and the phenylethenyl group were shown to be in the *endo* positions as confirmed by X-ray diffraction analysis of **7** (Fig. 1).

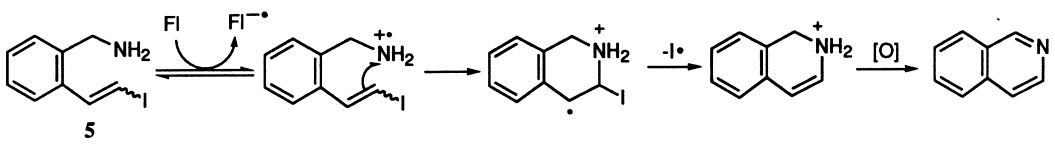
## Enzymatic studies of 6 and 7

Both **6** and **7** were found to be competitive inhibitors of beef liver MAO B as determined by Dixon[10] and Cornish-Bowden plots,[11] although **6** is slightly more potent than **7**. Compound **6** has a $K_i$ of 70 μM, and the $K_i$ for **7** is 180 μM. No time-dependent inactivation was observed. Prolonged incubation of both did not reveal any cyclized products by GC–MS detection. However, after five days of incubation, **7** was found to be converted to the normal turnover product, ketone **17**, as confirmed by comparison with an authentic sample.

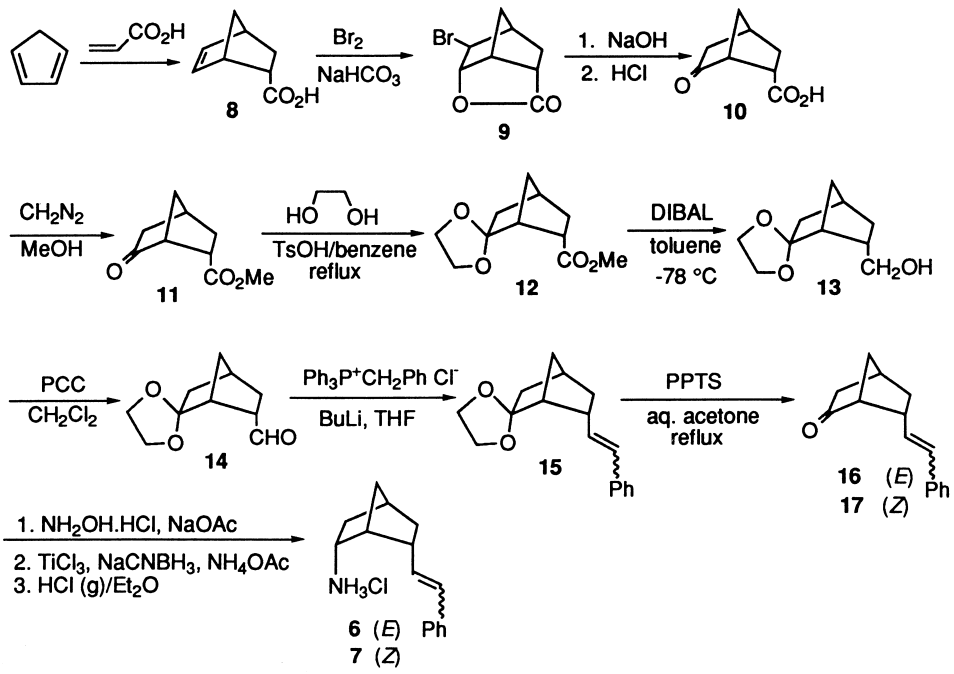
It is not clear why cyclization did not occur, but there are several possible explanations. The fact that both **6** and **7** are competitive inhibitors (with $K_i$ values lower than the $K_m$ value for good substrates) indicates that both compounds bind to the enzyme active site well. However, the fact that both are poor substrates (no turnover for **6** and very slow turnover for **7**) may suggest misorientation of the amino group or α-hydrogen with the flavin at the enzyme active site. This may result in a slow enzyme-catalyzed process, or possibly a slower than usual initial electron transfer, giving a shorter lived amine radical cation. The misorientation may be responsible for the slower rate of cyclization.



Scheme 3.



Scheme 4.




**Scheme 5.**

Alternatively, it is estimated that the amine radical cation intermediate **1** in Scheme 1 has a lifetime no longer than $10^{-6}$ s.[4c] Although the ring cyclizations for aminium radical cations have estimated rate constants of the order of $10^7$–$10^9$ $s^{-1}$,[12] the corresponding aminyl radicals (the neutral form) react at rates $10^3$–$10^5$ times slower than the corresponding aminium radical cations.[13] Given that the pH optimum for MAO is 9 and the p$K_a$ of an aminium radical cation is about 7,[13b] it is likely that the intermediate in the MAO-catalyzed reaction is the neutral, less reactive, amine radical form, which would have a much slower cyclization rate relative to α-deprotonation. Another possible explanation comes from the work of Zelechonok and Silverman,[14] who found that, in a chemical model study, formation of an α-radical cyclopropylamine led to cyclopropyl ring opening, but MAO-catalyzed oxidation of the corresponding parent cyclopropylamine gave the imine (isolated as the aldehyde) without cyclopropyl ring opening. It was suggested that when the intermediate cyclopropylamine radical is enzyme bound, it does not have the appropriate geometry for the cyclopropane orbitals to overlap with the α-radical, and ring cleavage becomes slow relative to α-proton removal. Support for that hypothesis came from the reaction of MAO with (aminomethyl)cubane,[15] which gives fragmentation of the cubane, indicating the formation of the α-radical; in this case there are more orientations of orbitals to overlap with the α-radical, so ring cleavage is favored. If the alkene *p*-orbitals of **7** are not aligned for addition by the amine radical (cation), cyclization will not occur or will occur at a much reduced rate.

Consistent with the last explanation, the X-ray crystal structure of **7** (Fig. 1) shows that the torsional angle of C6–C5–C8–C9 is −99.7°, but an optimal torsional angle for cyclization is 120°, as predicted from the chair-like transition state of the cyclization in hex-5-enyl systems.[16] Therefore, in the solid state, the amino group and the double bond are not in a favorable orientation for cyclization. If this occurs in the active site of the enzyme, the orientation of the amine radical orbital and the *p*-orbital of the double bond will be less than optimal, and the rate of cyclization will be slow relative to deprotonation and second electron transfer (Scheme 6).

## Conclusion

*endo,endo*-2-Amino-6-[(*E*)-2′-phenyl]ethenylbicyclo[2.2.1]-heptane (**6**) and the corresponding (*Z*)-isomer (**7**) were synthesized in an attempt to make a compound that could trap the purported amine radical cation intermediate during monoamine oxidase (MAO)-catalyzed oxidation of amines. The *E*-isomer was not a substrate for MAO, and the *Z*-isomer was a very poor substrate. No trapping product was observed. Although these specific compounds were not successful for the study of monoamine oxidase, this general approach has the potential to be applied to trapping of radical intermediates in other enzyme-catalyzed reactions.

## Experimental

### General methods

Optical spectra and MAO assays were recorded on a Perkin–Elmer Lambda 1, a Perkin–Elmer Lambda 10, or a Beckman DU-40 DU-40 UV/Vis spectrophotometer. NMR spectra were recorded on a Varian Gemini 300 MHz, a Varian VXR 300 MHz, or a Varian

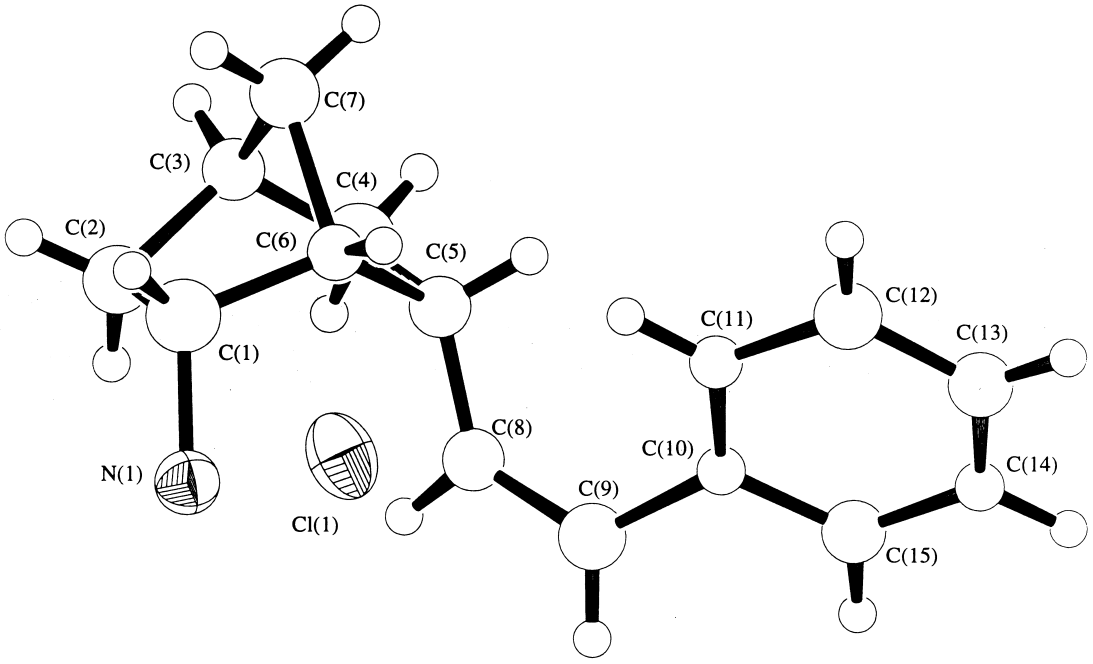
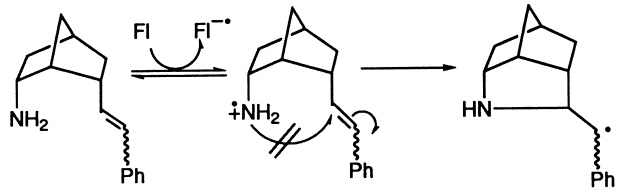



**Figure 1.** ORTEP drawing of the X-ray crystal structure of **7**.

Unity plus 400 spectrometer. Chemical shifts are reported as δ values in parts per million downfield from $Me_4Si$ as the internal standard in $CDCl_3$. An Orion Research Model 701 pH meter with a general combination electrode was used for pH measurements. Mass spectra were obtained on a VG Instrument VG70-250SE high resolution spectrometer with Maspec Data System. Elemental analyses were performed by either Oneida Research Service Inc. (Whiteboro, NY) or the Department of Geological Sciences at Northwestern University. Melting points were taken on a Fisher–Johns melting point apparatus. Small amounts of samples were centrifuged in a Beckman Microfuge B. The flash column chromatography was carried out with Merck silica gel 60 (230–400 mesh ASTM). TLC was run with EM Science silica gel 60 $F_{254}$ precoated glass plates. Lyophilization was carried out on a Heto CT60e lyophilizer. X-ray structure determinations were carried out on a Bruker SMART-1000 diffractometer. GC–MS studies were performed on a Hewlett Packard (HP) 6890 GC–MSD with an HP-5 MS phenyl methyl siloxane column (30 m× 250 μm×0.25 μm film thickness).

## Reagents

Deuterium oxide, chloroform-*d*, dimethyl sulfoxide-$d_6$, and methanol-$d_4$ were purchased either from Aldrich or Cambridge Isotope Laboratories. Other reagents and solvents were purchased from Aldrich or Fisher and were used without further purification unless otherwise stated. Dichloromethane, triethylamine, and toluene were freshly distilled from $CaH_2$. THF and ether were freshly distilled from sodium metal. Glassware was oven dried. Acetone was dried over 3 Å molecular sieves. All of the reactions were carried out in an atmosphere of inert gas.




**Scheme 6.**

## Crystal structure data for Figure 1

The nitrogen and chlorine atoms were refined anisotropically and the rest isotropically.

Cell parameters
$a = 33.157$ (6) Å
$b = 11.214$ (2) Å
$c = 16.633$ (3) Å
$\beta = 104.557$ (3)°
$V = 5985.8$ (15) Å$^3$

Space group
C2/c (#15)

$Z$ value
16 (2 independent molecules in an asymmetric unit)

No. of reflections
54,180 (14,833 unique)

No. of observations
1573

No. of variables
175

Residuals: R1; wR2
0.142; 0.292

Goodness of fit
4.62

***endo*-6-Carboxybicyclo[2.2.1]hept-2-ene (8).** The procedure of Alder and Stein[17] was followed. To acrylic acid (6.05 g, 84 mmol) was added freshly cracked cyclopentadiene (7.2 mL, 90 mmol) at 0 °C. The reaction was stirred for two days and distilled at 75–80 °C/0.1 mm Hg. Compound **8** was obtained as a colorless liquid (10.0 g, 85%). As reported,[18] it contained 10% of the *exo* isomer.

***endo*-2-Carboxy-*exo*-5-bromo-*endo*-6-hydroxynorbornane lactone (9).** Compound **9** was prepared according to a procedure reported by Roberts et al.[18] To a solution of **8** (4.0 g, 29 mmol) in aqueous sodium bicarbonate (6%, 80 mL) at 0 °C was added bromine (1.5 mL, 29 mmol) dropwise. After 0.5 h the yellow organic layer was extracted with ether (3×20 mL). The organic layers were combined, washed with 10% $Na_2S_2O_3$ (15 mL), brine and dried over $Na_2SO_4$. The solvent was evaporated in vacuo, recrystallized from EtOAc and hexane, and 3.6 g of solid was obtained (57%); mp 62–65 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 4.84–4.86 (d, 1H), 3.79–3.80 (d, 1H), 3.17–3.20 (t, 1H), 2.60–2.61 (m, 1H), 2.47–2.52 (dd, 1H), 2.22–2.26 (m, 1H), 2.05–2.12 (m, 1H), 1.66–1.74 (m, 2H); MS (EI) *m*/*z* 216 ($M^+$), 109, 93, 79; HRMS (EI) *m*/*z* calcd for $C_8H_7{}^{79}BrO_2$ ($M-H^+$): 215.9786, found 215.9794.

***endo*-6-Carboxybicyclo[2.2.1]heptan-2-one (10).** Preparation of **10** was carried out following the procedure of Iles and Worrall.[8] Lactone **9** (3 g, 14 mmol) was added to a solution of sodium hydroxide (2.24 g, 56 mmol) in water (40 mL) at 25 °C for 1 h. Concentrated HCl (3.52 mL) was added slowly. A trace of coagulated insoluble gum was removed by filtration. The filtrate was concentrated in vacuo without external heating and extracted with $CHCl_3$ (3×30 mL). The organic layers were combined, washed with brine, and dried over $Na_2SO_4$. The solvent was removed in vacuo, and the crude acid was purified by column chromatography (2.5% MeOH:97.5% $CH_2Cl_2$) to afford **10** as a white solid (1.4 g, 64%); mp 99–103 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.00–3.02 (m, 1H), 2.96–2.97 (m, 1H), 2.64–2.65 (m, 1H), 2.06–2.14 (m, 3H), 1.68–1.79 (m, 3H); MS (EI) *m*/*z* 154 ($M^+$), 126, 108, 81; HRMS (EI) *m*/*z* calcd for $C_8H_{10}O_3$ 154.0630 ($M^+$), found 154.0629.

***endo*-6-Carbomethoxybicyclo[2.2.1]heptan-2-one (11).** To a solution of **10** (9.2 g, 6.0 mmol) in methanol (100 mL) was added a solution of diazomethane in ether (100 mL, ca. 10 mmol) until the yellow color persisted. The reaction mixture was stirred for an additional 2 h. The solvent was removed in vacuo, and the crude ester was purified by column chromatography (17% EtOAc:83% hexanes) to afford **11** (9.4 g, 94%) as a white solid; mp 46–48 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 1H), 3.02–3.10 (m, 1H), 2.86–2.87 (m, 1H), 2.73 (m, 1H), 1.98–2.13 (m, 3H), 1.70–1.90 (m, 3H); MS (EI) *m*/*z* 168 ($M^+$), 140, 108, 81; HRMS (EI) *m*/*z* calcd for $C_9H_{12}O_3$ 168.0786 ($M^+$), found 168.0774.

***endo*-6-Carbomethoxyspiro[1,3-dioxolane-2,2′-bicyclo-[2.2.1]heptane] (12).** A solution containing keto ester **11** (7.0 g, 4.16 mmol), ethane-1,2-diol (6.0 mL, 107 mmol), and *p*-toluenesulfonic acid (100 mg) in benzene (40 mL) was heated to reflux for 6 h in a flask equipped with a Dean–Stark trap. After removal of the solvent under reduced pressure, saturated $NaHCO_3$ (30 mL) was added, and the mixture was extracted with ether (3×30 mL). The organic extracts were combined, washed with brine, dried over $Na_2SO_4$, concentrated, and chromatographed (15% EtOAc:85% hexanes) to afford **12** (7.4 g, 85%) as a colorless liquid; $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.88–3.98 (m, 3H) 3.74–3.79 (m, 1H), 3.71 (s, 3H), 2.66–2.77 (m, 2H), 2.31 (m, 1H), 1.80–1.97 (m, 3H), 1.65–1.74 (m, 2H), 1.42–1.46 (m, 1H); HRMS (EI) *m*/*z* calcd for $C_{11}H_{16}O_4$ 212.1048 ($M^+$), found 212.1054.

***endo*-6-(Hydroxymethyl)spiro[1,3-dioxolane-2,2′-bicyclo-[2.2.1]heptane] (13).** To a solution of **12** (5.5 g, 2.6 mmol) in toluene at −78 °C was added DIBAL (1.5 M in toluene, 45 mL) dropwise. After being stirred for 1 h the reaction was quenched with KOH solution (30%, 10 mL), and the temperature was slowly brought up to room temperature. More KOH solution was added (30%, 40 mL), and the reaction mixture was extracted with ether (3×50 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give **13** (4.6 g, 90%) as a colorless liquid; $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.82–3.98 (m, 4H), 3.66–3.80 (m, 2H), 2.91 (m, 1H), 2.16–2.30 (m, 3H), 1.70–1.90 (m, 3H), 1.35–1.45 (m, 2H), 1.05–1.10 (m, 1H); MS (EI) *m*/*z* 184 ($M^+$), 153, 99, 73; HRMS (EI) *m*/*z* calcd for $C_{10}H_{16}O_3$ 184.1099 ($M^+$), found 184.1101.

***endo*-6-Formylspiro[1,3-dioxolane-2,2′-bicyclo[2.2.1]heptane] (14).** To a vigorously stirred suspension of PCC (6.4 g, 3.0 mmol) and powdered molecular sieves in anhydrous dichloromethane (40 mL) was added alcohol **13** (3.0 g, 1.65 mmol). The reaction mixture was stirred for 2 h before ether (60 mL) was added. The solution was filtered through a pad of silica gel, concentrated and chromatographed (17% EtOAc:83% hexanes) to give **14** as a white solid; mp 92–94 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 9.76 (s, 1H), 3.76–3.99 (m, 4H), 2.75–2.76 (m, 1H), 2.55–2.61 (m, 1H), 2.38 (m, 1H), 1.70–1.95 (m, 4H), 1.56–1.61 (m, 1H), 1.44–1.48 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 204.3, 116.4, 65.4, 65.3, 51.5, 49.2, 44.8, 40.1, 36.3, 29.3; MS (EI) *m*/*z* 182 ($M^+$), 153, 73; HRMS (EI) *m*/*z* calcd for $C_{10}H_{14}O_3$ 182.0942 ($M^+$), found 182.0952; anal. calcd for $C_{10}H_{14}O_3{\cdot}0.6H_2O$: C, 62.22; H, 7.72; found: C, 62.19; H, 7.32.

***endo*-6-(2′-Phenyl)ethenylspiro[1,3-dioxolane-2,2′-bicyclo-[2.2.1]heptane] (15).** To a stirred suspension of benzyl triphenylphosphonium chloride (1.56 g, 4.0 mmol) in anhydrous THF (20 mL) was added *n*-butyl lithium (2.5 M in ether, 1.6 mL) dropwise. The above orange solution was transferred slowly via cannula to a solution of

aldehyde **14** (720 mg, 4.0 mmol) in THF (10 mL). The solution was stirred for another 30 min before saturated $NH_4Cl$ solution was added (20 mL) and extracted with ether (3×30 mL). The organic extracts were combined, washed with brine, evaporated in vacuo, and purified by chromatography (8% EtOAc/92% hexanes) to afford **15** (900 mg, 90%) as a mixture of the *E*- and *Z*-isomers in a 1.6:1 ratio.

***endo*-6-[(*E*)-2′-Phenyl]ethenylbicyclo[2.2.1]heptan-2-one (16) and *endo*-6-[(*Z*)-2′-phenyl]ethenylbicyclo[2.2.1]heptan-2-one (17).** A solution of **15** (660 mg, 2.6 mmol) in wet acetone (20 mL) containing pyridinium tosylate (50 mg, 0.2 mmol) was heated to reflux for 4 h. The solvent was removed in vacuo, ether (30 mL) was added, and the mixture was washed with $NaHCO_3$ solution and brine. The organic phase was dried over $Na_2SO_4$ and evaporated in vacuo to give a mixture of ketone **16** and **17**. The mixture was purified as follows. Flash chromatography gave **17** (180 mg) as a colorless oil. Preparative TLC of the concentrated uncollected fractions afforded additional pure **17** (120 mg) and **16** (180 mg) as a colorless oil with an overall yield of 90%.

Compound **16**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.34 (m, 5H), 6.40–6.45 (d, 1H), 5.92–6.00 (dd, 1H), 2.95–3.05 (m, 1H), 2.66–2.74 (m, 1H), 2.12–2.26 (m, 2H), 1.78–1.91 (m, 3H), 1.28–1.36 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 217.3, 138.1, 132.3, 132.0, 129.5, 128.3, 127.3, 57.2, 47.2, 42.5, 39.7, 36.6, 35.7; MS (EI) *m*/*z* 212 ($M^+$), 168, 128, 115, 91; HRMS (EI) *m*/*z* calcd for $C_{15}H_{17}O$ ($M+H^+$) 213.1279, found 213.1270.

Compound **17**: $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.19–7.34 (m, 5H), 6.44–6.47 (d, 1H), 5.34–5.39 (t, 1H), 3.19–3.28 (m, 1H), 2.65 (m, 1H), 2.56 (m, 1H), 2.10–2.21 (m, 2H), 1.64–1.89 (m, 3H), 1.17–1.23 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 217.6, 138.1, 134.2, 131.3, 129.6, 129.3, 127.9, 57.1, 47.2, 39.8, 37.4, 36.7, 32.0; MS (EI) *m*/*z* 212 ($M^+$), 168, 128, 115, 91; HRMS (EI) *m*/*z* calcd for $C_{15}H_{17}O$ ($M+H^+$) 213.1279, found 213.1280.

***endo,endo*-2-Amino-6-[(*E*)-2′-phenyl]ethenylbicyclo[2.2.1]heptane (6).** To a solution of hydroxylamine hydrochloride (71 mg, 1.0 mmol) and sodium acetate (115 mg, 1.25 mmol) in water were added ketone **16** (105 mg, 0.5 mmol) and sufficient ethanol to effect dissolution. This mixture was heated in an oil bath (50 °C) for 2 h, and the solution was concentrated. The remaining solution was extracted with $CHCl_3$ (3×10 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, and evaporated in vacuo to give the oxime (115 mg, 98%) as a colorless oil. This was used without further purification. Titanium trichloride (20% aqueous solution, 1.5 mL, 2.0 mmol) was added to a solution of the above oxime (115 mg, 0.5 mmol), sodium cyanoborohydride (135 mg, 2.2 mmol), and ammonium acetate (385 mg, 5 mmol) in methanol (10 mL) over a 14 h period. The mixture was diluted with water, made basic (pH > 10) with dilute 1 N NaOH solution (2×20 mL), and extracted with $CH_2Cl_2$. After evaporation of the solvent in vacuo, the product was purified by chromatography (17% MeOH:83% $CH_2Cl_2$). To a solution of the product in ether (5 mL) at 0 °C a solution of HCl gas in ether (3 N, 10 mL) was added dropwise. The solvent was removed and the solid was recrystallized from $CHCl_3$ and hexane (1:1) to obtain white needles (50 mg, 40%); mp 224–226 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.98 (b, 3H), 7.17–7.49 (m, 5H), 6.78–6.83 (d, 1H), 6.49–6.54 (d, 1H), 3.62 (m, 1H), 3.00 (m, 1H), 2.86 (m, 1H), 2.38 (m, 1H), 1.87–2.16 (m, 3H), 1.51–1.58 (m, 1H), 1.38–1.42 (m, 1H), 1.20–1.24 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 136.6, 131.9, 131.5, 128.9, 127.9, 127.0, 53.9, 44.2, 42.2, 39.7, 37.2, 36.3, 33.3; MS (EI) *m*/*z* 213 ($M^+$), 170, 115, 91; HRMS (EI) calcd for $C_{15}H_{19}N$ ($M^+$) 213.1517, found 213.1517; anal. calcd for $C_{15}H_{20}NCl{\cdot}0.2CHCl_3$: C, 66.22; H, 7.38; N, 5.12; found: C, 66.11; H, 7.50; N, 5.08.

***endo,endo*-2-Amino-6-[(*Z*)-2′-phenyl]ethenylbicyclo[2.2.1]heptane (7).** Compound **7** was prepared starting from **17** as described previously for **6** (55 mg, 45%); mp 217–219 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 8.419 (b, 3H), 7.22–7.34 (m, 5H), 6.61–6.65 (d, 1H), 6.09–6.16 (t, 1H), 3.59 (m, 1H), 3.09 (m, 1H), 2.71 (m, 1H), 2.23–2.24 (m, 1H), 2.17 (m, 1H), 1.91–1.98 (m, 1H), 1.83 (m, 1H), 1.30–1.43 (m, 2H), 1.14–1.22 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 137.4, 134.7, 133.0, 129.0, 128.4, 127.1, 53.6, 46.5, 40.3, 38.9, 38.3, 37.6, 35.1; MS (EI) *m*/*z* 213 ($M^+$), 170, 115, 91; HRMS (EI) calcd for $C_{15}H_{19}N$ ($M^+$) 213.1517, found 213.1517; anal. calcd for $C_{15}H_{20}NCl{\cdot}0.1CHCl_3$: C, 69.29; H, 7.70; N, 5.35; found: C, 68.90; H, 7.87; N, 5.58.

**Enzyme and assay.** Beef liver MAO B was isolated as described previously[19] and stored as a concentrated solution (15–25 mg/mL) in sodium phosphate buffer (50 mM, pH 7.2) at 4 °C. The specific activity varied among preparations, ranging from 3.5 to 7 units per mg, where a unit of activity is the conversion of 1 μmol of benzylamine to benzaldehyde per min at pH 9.0 and 30 °C.

**General procedure for inhibition of the MAO-catalyzed oxidation of cinnamylamine.** An MAO B solution was prepared by diluting 15 μL of the stock MAO B solution with 285 μL of Tris–HCl buffer (100 mM, pH 9.0). The amount of inhibition of the oxidation of various concentrations of cinnamylamine (0.2, 0.5, 0.67 and 0.8 mM in Tris–HCl buffer, 100 mM, pH 9.0) by various concentrations of inhibitor (0, 0.2, 0.4, 0.6, 0.8 mM in Tris–HCl buffer, 100 mM, pH 9.0) was determined by adding 10 μL of the above MAO solution to 490 μL of an inhibitor/substrate solution at 25 °C, followed by monitoring the increase in UV absorbance at 290 nm. The $K_i$ value was determined using a Dixon plot.[10] Cornish-Bowden plots[11] were used to determine the type of inhibition.

**General procedure for the isolation and detection of metabolites.** To a solution of **6** (10.0 mM) in Tris–HCl buffer (270 μL) was added MAO B (30 μL). Aliquots of 20 μL were periodically withdrawn, extracted with 40 μL of $CH_2Cl_2$ by spinning in a centrifuge, and analyzed by gas chromatography.

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