$BrCH_2C{\equiv}CH$, 106-96-7; $BrCH_2C(CH_3){=}CH_2$, 1458-98-6; $BrCH_2CH{=}CHCH_3$, 4784-77-4; $Br(CH_2)_2CH{=}CH_2$, 5162-44-7; $Br(CH_2)_2CH_3$, 106-94-5; $BrCH_2C_6H_5$, 100-39-0; $BrCH_2CN$, 590-17-0; $BrCH(CH_3)CN$, 19481-82-4; $BrCH_2CO_2Me$, 96-32-2; $BrCH_2COCH_3$, 598-31-2; $BrCH_2COC_6H_5$, 70-11-1; $BrCH(CH_3)COCH_3$, 814-75-5; $BrCH_2COCH_2CH_3$, 816-40-0; $BrH(C_2H_5)COCH_3$, 815-48-5; $BrCH_2CO(CH_2)_2CH_3$, 817-71-0; $BrCH(COCH_3)CH_2CH{=}CH_2$, 114614-77-6; $BrCH(CH_3)COCH_2CH_3$, 815-52-1; $BrCH_2COCH(CH_3)_2$, 19967-55-6; $BrCH_2COCH_2C_6H_5$, 20772-12-7; $BrC(CH_3)_2COCH_3$, 2648-71-7; $Br(CH_2)_2OH$, 540-51-2; $BrCH_2CH(OH)CH_2C_6H_5$, 28988-98-9; $Br(CH_2)_2OCH_3$, 6482-24-2; $BrCH_2CH(OMe)_2$, 7252-83-7; $BrCH_2CH(OMe)CH_3$, 23465-33-0; $BrCH_2O(CH_2)_2OCH_3$, 100107-97-9; $Br(CH_2)_2O(CH_2)_2OMe$, 54149-17-6; $HO(CH_2)_2CH(OH)CH_3$, 107-88-0; $HO(CH_2)_2CH(OMe)CH_3$, 2517-43-3; $TsO(CH_2)_2Cl$, 80-41-1; $Cl_2(CH_2)_5$, 628-76-2; $Cl(CH_2)_2O(CH_2)_2Cl$, 111-44-4; (*R*)-2-[2-(methoxyethoxy)methoxy]propionic acid methyl ester, 114614-78-7; (*R*)-2-[2-(methoxyethoxy)methoxy]propanol, 114614-79-8; (*S*)-2-[2-(methoxyethoxy)methoxy]propionic acid methyl ester, 114614-80-1; (*S*)-2-[2-(methoxyethoxy)methoxy]propanol, 114614-81-2; 1,2-diaminoethane, 107-15-3; 3-(diethylamino)-1-chloropropane hydrochloride, 4535-85-7; *N*-[(1-allyl-2-pyrrolidinyl)methyl]-6-hydroxy-1-(*tert*-butyloxycarbonyl)benzotriazole-5-carboxamide, 114614-82-3; 3-chloro-2-butanone, 4091-39-8; 2-bromocyclohexanone, 822-85-5; 2-bromocyclopentanone, 21943-50-0; 2-(bromoacetyl)thiophene, 10531-41-6; *cis*-1-bromo-2-methoxycyclohexane, 51332-48-0; *trans*-1-bromo-2-methoxycyclohexane, 5927-93-5; 4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane, 36236-76-7; (bromomethyl)oxirane, 3132-64-7; 2-(bromomethyl)-2-methyloxirane, 49847-47-4; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; 2-(bromomethyl)tetrahydrofuran, 1192-30-9; 5-(bromomethyl)-3-methylisoxazole, 36958-61-9; 2-(bromomethyl)pyridine, 55401-97-3; 2-(bromomethyl)-1,3-dioxolane, 4360-63-8; dompiridone, 57808-66-9.

Stereoisomers of Allenic Amines as Inactivators of Monoamine Oxidase Type B. Stereochemical Probes of the Active Site[1]

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The kinetics of inactivation of mitochondrial monoamine oxidase type B (MAO-B) by a series of 18 stereoisomers of tertiary α-allenic amines have been investigated in detail. The chirality of the allene group in *N*-methyl-*N*-aralkylpenta-2,3-dienamines was found to have a profound effect on the inactivation rate, with the (*R*)-allenes being up to 200-fold more potent than their (*S*)-allenic counterparts. The ability of (*S*)-allenes to inactivate MAO was severely compromised by the presence of *N*-phenethyl or *N*-α-substituted-aralkyl substituents. The opposing chiralities in both the allene and aralkyl groups of (*R*,*R*)- and (*S*,*S*)-*N*-methyl-*N*-(1,2,3,4-tetrahydro-1-naphthyl)-penta-2,3-dienamine resulted in a difference of more than 3 orders of magnitude in inactivation rates. The stereoselectivity of MAO-B was examined further with a series of reversible aralkylamine inhibitors; thus (*R*)-1,2,3,4-tetrahydro-1-naphthylamine was determined to be 150-fold more potent than its enantiomer.

As a result of its important role in psychopharmacology, the enzyme monoamine oxidase [amine: oxygen oxidoreductase (deaminating, flavin-containing); EC 1.4.3.4; MAO] has been the subject of active research for the last three decades.[2] A number of inhibitors of MAO have proved useful in clinical psychiatry for the treatment of depression; however, their effectiveness has been complicated by the "cheese effect", a serious hypertensive response to the tyramine present in common foodstuffs.[2] An attractive strategy for the development of MAO inhibitors that are devoid of such side effects focusses on the selective inhibition of the multiple forms of MAO, termed types A and B,[3] as it is believed that inhibitors that are selective for the B form should not exhibit the cheese effect.[4] However, while MAO-B selective inhibitors have found application in the L-DOPA treatment of Parkinson's disease,[5] the role of MAO-B in depression remains controversial;[6] one point of view holds that antidepressant agents should be directed to the selective inhibition of MAO-A.[7] The most widely investigated selective inhibitors are *l*-deprenyl (an irreversible MAO-B inhibitor) and clorgyline (an irreversible MAO-A inhibitor);[2] most recently, selective inhibitors such as 3-fluoro-2-arylallylamines[8] and oxazolidinones[9] have been reported. The MAO substrate and inhibitory activity of MPTP, a tetrahydropyridine that induces irreversible Parkinsonism, is also of current interest.[10]

Both reversible and irreversible stereoselective inhibitors of monoamine oxidase have been developed.[3,11-14] The

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Table I. Physical Characteristics of α-Allenic Amines

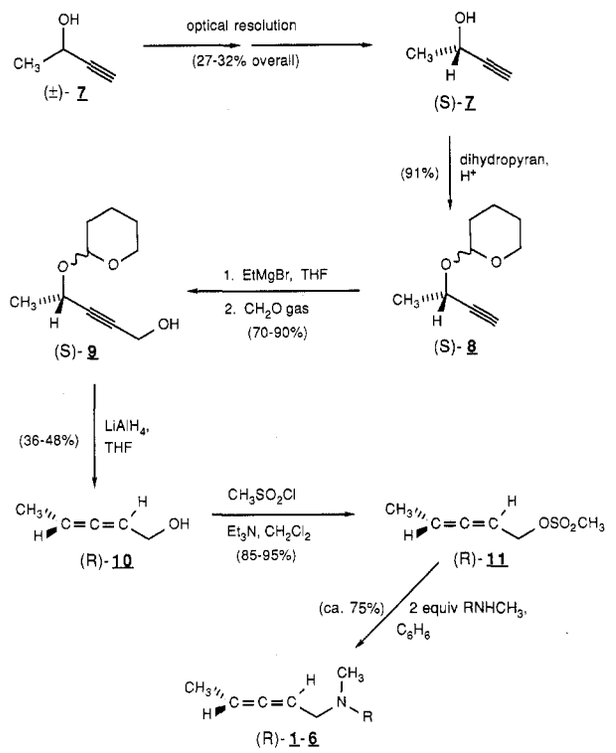
compd	R	$[\alpha]^{21}_D$	mp, °C	formula[a]
(*R*)-**1**	CH_3	−52.0 (*c* 1.15, water)	124–125.5	$C_7H_{13}N\cdot C_2H_2O_4$
(*S*)-**1**	CH_3	+50.1 (*c* 1.09, water)	123–124.5	$C_7H_{13}N\cdot C_2H_2O_4$
(*R*)-**2**[b]	$PhCH_2$	−46.8 (*c* 0.87, MeOH)	137–138	$C_{13}H_{17}N\cdot C_2H_2O_4$
(*S*)-**2**[b]	$PhCH_2$	+44.8 (*c* 0.91, MeOH)	137–138	$C_{13}H_{17}N\cdot C_2H_2O_4$
(*R,R*)-**3**[c]	(*R*)-$PhCH(CH_3)$	+56.8 (*c* 1.61, EtOH)	oil	$C_{14}H_{19}N$
(*S,S*)-**3**[c]	(*S*)-$PhCH(CH_3)$	−57.8 (*c* 2.58, EtOH)	oil	$C_{14}H_{19}N$
(*R,S*)-**3**[d]	(*S*)-$PhCH(CH_3)$	−125.6 (*c* 0.92, EtOH)	141–141.5	$C_{14}H_{19}N\cdot HCl$
(*S,R*)-**3**[d]	(*R*)-$PhCH(CH_3)$	+125.1 (*c* 1.40, EtOH)	141.5–142	$C_{14}H_{19}N\cdot HCl$
(*R*)-**4**	$PhCH_2CH_2$	−43.1 (*c* 1.04, water)	148–148.5	$C_{14}H_{19}N\cdot C_2H_2O_4$
(*S*)-**4**	$PhCH_2CH_2$	+44.7 (*c* 0.96, water)	148.5–149	$C_{14}H_{19}N\cdot C_2H_2O_4$
(*R,R*)-**5**	(*R*)-$PhCH_2CH(CH_3)$	−59.0 (*c* 1.55, water)	126–127	$C_{15}H_{21}N\cdot C_2H_2O_4$
(*S,S*)-**5**	(*S*)-$PhCH_2CH(CH_3)$	+59.1 (*c* 1.51, water)	126–126.5	$C_{15}H_{21}N\cdot C_2H_2O_4$
(*R,S*)-**5**	(*S*)-$PhCH_2CH(CH_3)$	−25.2 (*c* 1.07, water)	145–146	$C_{15}H_{21}N\cdot C_2H_2O_4$
(*S,R*)-**5**	(*R*)-$PhCH_2CH(CH_3)$	+29.4 (*c* 1.11, water)	145.5–146	$C_{15}H_{21}N\cdot C_2H_2O_4$
(*R,R*)-**6**	(*R*)-1,2,3,4-tetrahydro-1-naphthyl	−64.4 (*c* 1.04, water)	112–113.5	$C_{16}H_{21}N\cdot C_2H_2O_4$
(*S,S*)-**6**	(*S*)-1,2,3,4-tetrahydro-1-naphthyl	+65.3 (*c* 1.18, water)	109.5–111	$C_{16}H_{21}N\cdot C_2H_2O_4$
(*R,S*)-**6**	(*S*)-1,2,3,4-tetrahydro-1-naphthyl	−34.8 (*c* 0.99, water)	109–110 dec	$C_{16}H_{21}N\cdot C_2H_2O_4$
(*S,R*)-**6**	(*R*)-1,2,3,4-tetrahydro-1-naphthyl	+34.3 (*c* 1.08, water)	108–109 dec	$C_{16}H_{21}N\cdot C_2H_2O_4$

[a] All compounds gave correct C, H combustion analyses. All compounds are hydrogen oxalate salts, except as noted; recrystallization solvents were ethanol for compounds **1**, **4**, and **5** and ethanol–ether for **2** and **6**. [b] Samples of (*R*)- and (*S*)-**2** were provided by Prof. A. Claesson;[20] physical data for **2** are from ref 20. [c] Liquid free amine (no crystalline salt could be prepared). [d] Hydrochloride salt, recrystallized from benzene.

reversible inhibitors 2,3-dichloro-α-methylbenzylamine[11] and 4-(dimethylamino)-2,α-dimethylphenethylamine (Amiflamine)[12] are particularly interesting, as the enantiomers of each of these compounds exhibit opposite selectivity in the inhibition of MAO-A and MAO-B. In the case of various chiral oxazolidinones (e.g. Cimoxatone and Toloxatone), it has been shown that MAO-A is more sensitive to stereochemical changes in inhibitor structure than is the MAO-B active site.[13] An excellent compilation of the stereochemical aspects of various MAO substrates and inhibitors has recently been published.[14]

α-Allenic amines were first reported to be effective inhibitors of MAO by Halliday et al. in 1968.[15] Krantz and co-workers have since demonstrated that α-allenic amines are k_{cat} or "suicide" inhibitors of MAO-B: the inactivation is both time-dependent and irreversible, and 1 equiv of inhibitor suffices to abolish MAO activity with the formation of a covalent adduct.[16-19] This adduct is a reduced flavin, but not a flavocyanine as is afforded by inactivation of MAO by a propargyl amine such as pargyline. Inhibition of MAO by α-allenic amines was also shown to be general, with a variety of structural types including terminally substituted allenes (e.g. penta-2,3-dienamines) exhibiting varying degrees of effectiveness. As the penta-2,3-dienamine group is both chiral and capable of inactivating MAO, this system provides a unique opportunity for probing the effects of chirality within an inactivating functional group, rather than in an asymmetric aralkyl substituent (such as in deprenyl[14]). The in vivo and in vitro MAO inhibitory activities of a variety of allenic amines, including the enantiomers of *N*-methyl-*N*-benzylpenta-2,3-dienamine, were recently reported by Claesson and co-workers.[20] We have communicated the kinetics of inactivation of MAO-B by these same enantiomeric allenes, as well as kinetic data for a variety of diastereomeric allenic amines;[21] we now describe the complete details of our investigation.

Scheme I. Synthesis of Chiral Allenic Amines **1–6**



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Chemistry

Although a variety of methods are known for the synthesis of α-allenic amines[22] and many types of chiral allenic compounds,[23] the most viable route to penta-2,3-dien-1-amines of high enantiomeric purity appeared to be via elaboration of the corresponding chiral allenic alcohol. Olsson and Claesson[24] have defined the conditions necessary for the preparation of penta-2,3-dien-1-ol of high optical purity. Thus, the enantiomers of this α-allenic alcohol were synthesized and converted, through their mesylates, to the required tertiary allenic amines (Scheme I). Sahlberg et al.[20] have also used this route in their preparation of (*R*)- and (*S*)-*N*-methyl-*N*-benzylpenta-2,3-dienamine (**2**). The physical characteristics of **2** and the allenic amines synthesized in this work are collected in Table I.

The chiral specificity of our synthesis was established by analyses of intermediates and final allenic products. Complete resolution of 3-butyn-1-ol (**7**) was confirmed by NMR analyses of the diastereomeric α-methylbenzylamine hydrogen phthalate salts and by NMR analyses of *R* and *S* enantiomers of **7** and **10** in the presence of the chiral shift reagent Eu(dcm)$_3$[25,26] (see the Experimental Section). A variety of other chromatographic and spectroscopic analyses of **10**, diastereomeric derivatives of **10**, and allenic amines **1–6** proved to be ineffective.[27] Therefore, on the basis of optical rotations of enantiomeric pairs of **1–6** (which generally agreed within 4%) and NMR/Eu(dcm)$_3$ analyses of alcohol precursors **7** and **10**, we estimate the enantiomeric/diastereomeric purities of our allenic amines to be >95%. Indeed, the most sensitive assay for enantiomeric purity proved to be the MAO-B assay itself, and these experiments confirmed our estimate of purity (see below).

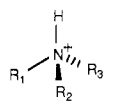
The secondary *N*-methyl amines required for the tertiary allenic amine syntheses were prepared by lithium aluminum hydride reduction of the appropriate N-formylated primary amine. When necessary, optical resolutions were accomplished by crystallizations of diastereomeric acid salts.

Table II. Reversible Inhibition of Bovine Liver MAO-B by Enantiomers of α-Substituted Aralkyl Amines (25 °C, pH 7.2)

compound	K_i,[a] μM *R*	*S*	$K_{i(S)}/K_{i(R)}$
13, $PhCH(CH_3)NH_2$	190	520	2.7
	100[b]	150[b]	1.5
14, $PhCH(CH_3)NHCH_3$	630	1600	2.5
15, $PhCH_2CH(CH_3)NH_2$ (amphetamine)	380	300	0.79
	180[c]	160[c]	0.89
	760[d]	580[d]	0.76
16, $PhCH_2CH(CH_3)NHCH_3$	800	550	0.69
	340[c]	270[c]	0.79
17, 1,2,3,4-tetrahydro-1-naphthylamine	0.72	110	150.
18, *N*-methyl-1,2,3,4-tetrahydro-1-naphthylamine	1.4	12	8.6

[a] Our K_i value have standard errors <16%. [b] Bovine or porcine liver MAO-B, 30 °C, pH 9.0 (ref 32). [c] Rat liver MAO-B, 37 °C, pH 7.4 (ref 33). [d] Rat liver MAO-B, 30 °C, pH 7.2 (ref 34).

The NMR characteristics of these chiral allenic amine salts are noteworthy. In $CDCl_3$ solution, each of the enantiomeric HCl salts of (*R*,*S*)-**3** and (*S*,*R*)-**3** is observed to exist as a cleanly resolved pair of diastereomers that arise from the newly generated asymmetric center at the protonated nitrogen atom (**12**). In these spectra, the signal



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for the *N*-methyl group appears as a pair of doublets. Upon addition of a drop of D_2O to the NMR sample, rapid proton–deuterium exchange occurs to provide a much simpler spectrum: the pair of *N*-methyl doublets collapses to one slightly broad singlet (i.e., loss of *N*-methyl–NH coupling and coalescence of the separate signals due to nitrogen asymmetry are observed). In the case of the hydrogen oxalate salt (*R*,*S*)-**5** in D_2O solution, the *N*-methyl signal appears as a pair of singlets at 30 °C, which completely coalesces to a single peak at 50 °C. Similar behavior is noted in the ^{13}C NMR spectra of (*R*,*S*)-**3**, (*R*,*S*)-**5**, (*S*,*R*)-**6**, and (*S*,*S*)-**6**; complete ^{13}C NMR data for compounds **1–6** are available as supplementary material. To our knowledge, the observation of asymmetry caused by protonation on nitrogen in NMR spectra has few precedents.[28]

Results and Discussion

As part of our study of the stereoselectivity of MAO-B, we considered it important to examine the reversible, competitive inhibition effected by the primary amines and secondary *N*-methyl amines derived from the allenic amine aralkyl substituents. The inhibition of bovine liver MAO-B[29,30] was determined spectrophotometrically[31] (pH

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(26) NMR/Eu(dcm)$_3$ analyses of the chiral allenic alcohols (*R*)- and (*S*)-**10** (with simultaneous decoupling by irradiation of the C*H*CH_2OH signal) revealed no enantiomeric impurities. However, simulations of these NMR spectra (Spencer, R. W., unpublished work) indicate that for comparable peak width and peak separation the detection limit is ca. 5% of enantiomeric impurity.

(27) Other analyses of the enantiomeric or diastereomeric purities of our samples were ineffective: diastereomeric α-methoxy-α-(trifluoromethyl)phenylacetyl esters (from Mosher's reagent) of **10** could not be cleanly resolved by ^{19}F NMR measurement; GC measurements utilizing a chiral column (5% SP-300 on 100/120 Supelcoport, *n*-lauryl-L-valine *tert*-butylamide stationary phase) did not provide any separation of enantiomers of allenic compounds (**10**, **1**), or of primary or secondary amines (the tertiary amines were completely retained on this column); reverse-phase HPLC (MeOH/aqueous $C_5H_{11}SO_3Na$), GC (5% OV-101) and capillary GC (15 m × 0.25 mm i.d. SE-30) analyses did not effect any separation of diastereomers of the tertiary allenic amines; GC analyses of diastereomeric camphanic acid esters of **10** were also ineffective.

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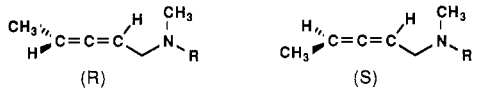
Table III. Kinetic Parameters for the Time-Dependent Inhibition of Bovine Liver MAO-B by Diastereomeric α-Allenic Amines (25 °C, pH 7.4)[a]



		(*R*)-allenes		(*S*)-allenes	
compd	R	K_i, mM	k_2, min^{-1}	K_i, mM	k_2,[b] min^{-1}
1	CH_3	0.059	0.22	0.10	0.29
2	$PhCH_2$	0.2	1.	0.82	0.16
3	(*R*)-$PhCH(CH_3)$	0.73	0.61	2.6[c]	0.012[d]
3	(*S*)-$PhCH(CH_3)$	1.8	0.44	1.1[c]	0.007[d]
4	$PhCH_2CH_2$	0.43	0.99	0.65	0.013
5	(*R*)-$PhCH_2CH(CH_3)$	1.3	0.15	0.69[c]	0.007[d]
5	(*S*)-$PhCH_2CH(CH_3)$	0.18	0.009	0.72[c]	0.015[d]
6	(*R*)-tetrahydro-1-naphthyl	0.2	0.8	0.15[c]	0.012[d]
6	(*S*)-tetrahydro-1-naphthyl	0.25	0.13	0.15[c]	0.0006[d]

[a] Kinetic parameters were calculated by the method of Kitz and Wilson,[41] except as noted. For details of determination methods and standard errors, see the Experimental Section. [b] All values of $k_2 < 0.02$ represent upper limits, as these very low values may be accounted for in whole or in part by a few percent (<4%) of diastereomeric (*R*)-allenic amine impurities. [c] Competitive K_i determined from initial rate measurements. [d] Calculated from measured rates of inactivation (k_{obsd}) at one inhibitor concentration and K_i.

7.2, 25 °C) with benzylamine as the enzyme substrate; competitive K_i values are summarized in Table II along with related literature data.[32-34] The variable enantioselectivity of MAO-B for these reversible inhibitors is intriguing. In the case of the α-methylbenzylamines **13** and **14**, the *R* enantiomers have more than twice the inhibitory activity of the *S* enantiomers, while in the case of the α-methylphenethyl analogues **15** and **16**, there is little (if any) enantioselectivity. The very slight preference for the *S* chirality observed by us and others[33,34] for inhibitors **15** and **16** is contrary to the significant *R* selectivity found for the related 4-(dimethylamino)-α,2-dimethylphenethylamine (Amiflamine). K_i values for Amiflamine have been given as 210 μM for the *S* isomer and 25 μM for the *R* isomer.[3,13] The derivatives **17** and **18** serve as conformationally restricted α-substituted benzylamines, and the better inhibitors are again the *R* enantiomers. The 1,2,3,4-tetrahydro-1-naphthylamines are not only the best reversible competitive inhibitors among this group of compounds but they also exhibit the highest degree of stereoselectivity toward MAO-B. The ratio of K_i's for (*S*)- and (*R*)-**17** is 150, which is, to our knowledge, the largest K_i ratio known for any pair of enantiomeric competitive MAO-B inhibitors.[3,13,14] Indeed, MAO-B has been found to be quite insensitive to the chirality of a variety of oxazolidinone derivatives including Cimoxatone and Toloxatone.[13] It is somewhat surprising that the inhibition constants for **17** and **18** have not been reported before, considering the potent irreversible MAO-B inhibition observed for the analogous propargylamines.[35-38] The corresponding indanamines are likewise of interest; we measured a K_i of 11 μM for (±)-1-indanamine, compared to 2.6 μM for (±)-**17**. We also determined the following K_i's: 2-indanamine, 41 μM; phenethylamine, 42 μM; and *N*-methylphenethylamine, 42 μM. The interesting effects of α-substitution of substrates and inhibitors on MAO A vs B selectivity have been addressed by Williams and Walker.[39]

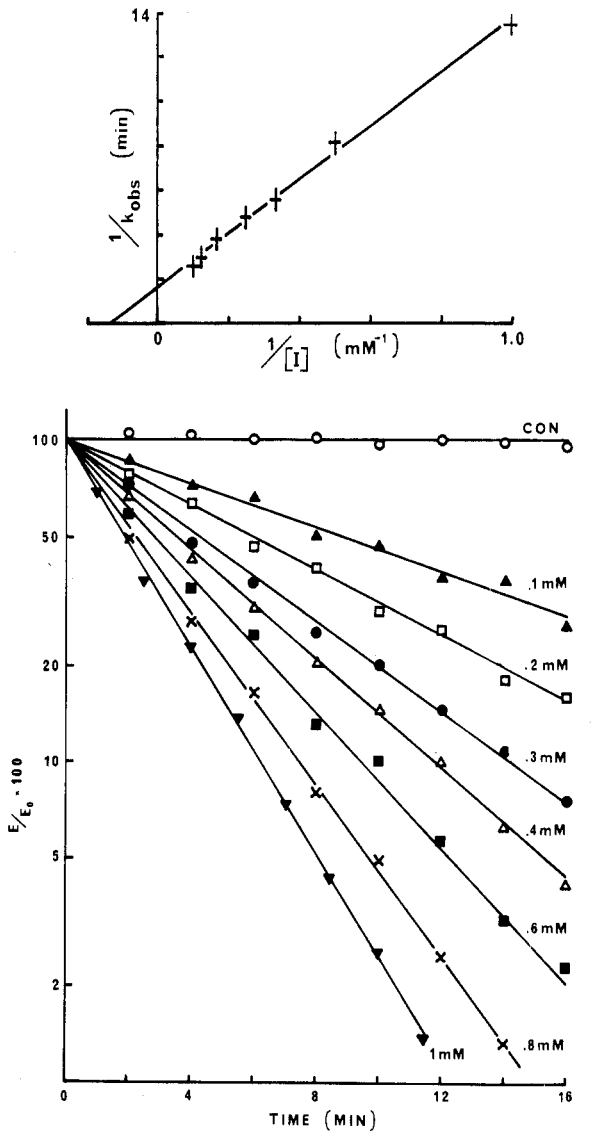


Figure 1. Time-dependent inactivation of MAO-B by (*R*,*R*)-**3** and double-reciprocal plot.

As discussed earlier, Krantz and co-workers have studied the time-dependent and irreversible inhibition of MAO-B by a variety of α-allenic amines in detail and found these compounds to behave as k_{cat} or "suicide" inhibitors,[16-19] as do the propargylamine MAO inhibitors such as *l*-deprenyl.[40] In the case of the chiral allenic amines **1-6**, time-dependent loss of MAO activity was again consistent with reversible binding of inhibitor to the enzyme followed by a first-order chemical process leading to inactive enzyme. This mechanism may be represented as in eq 1,

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(34) Mantle, T. J.; Tipton, K. F.; Garrett, N. J. *Biochem. Pharmacol.* **1976**, *25*, 2073.
(35) Huebner, C. F.; Donoghue, E. M.; Plummer, A. J.; Furness, P. A. *J. Med. Chem.* **1966**, *9*, 830.
(36) Magyar, K.; Ecseri, Z.; Bernath, G.; Satory, E.; Knoll, J. *Adv. Pharmacol. Res. Pract., Proc. Congr. Hung. Pharmacol. Soc., 3rd* **1979**, *4*, 11-21.
(37) Knoll, J.; Ecsery, Z.; Magyar, K.; Satory, E. *Biochem. Pharmacol.* **1978**, *27*, 1739.
(38) Tipton, K. F.; McCrodden, J. M.; Kalir, A. S.; Youdim, M. B. H. *Biochem. Pharmacol.* **1982**, *31*, 1251.
(39) (a) Williams, C. H. *J. Pharm. Pharmacol.* **1982**, *43*, 386. (b) Williams, C. H.; Walker, B., in ref 2e, pp 41-52.
(40) Fowler, C. J.; Mantle, T. J.; Tipton, K. F. *Biochem. Pharmacol.* **1982**, *31*, 3555.

where E and I represent the free enzyme and inhibitor, E·I is the noncovalent enzyme–inhibitor complex, E–I is the covalent inactive adduct, and with kinetics in accordance with eq 2.[41,42]

$$E + I \overset{K_i}{\rightleftharpoons} E{\cdot}I \overset{k_2}{\rightarrow} E{-}I \quad (1)$$

$$k_{obsd} = k_2/(1 + K_i/[I]) \quad (2)$$

Our kinetic parameters for allenic amines 1–6[21] are summarized in Table III, with a typical graphical analysis shown in Figure 1. In the case of *N*-methyl-*N*-(*S*)-α-phenethyl-(*R*)-penta-2,3-dienamine [(*R*,*S*)-**5**], the rate of inactivation was very slow, with K_i = 0.18 mM and k_2 = 0.009 min^{-1}. By treating this compound as a reversible competitive inhibitor, initial rate measurements upon addition of enzyme to substrate–inhibitor mixtures afforded a competitive K_i = 0.17 mM in agreement with the above K_i value. Therefore, for other allenic amines that exhibited very slow rates of inactivation, K_i values were obtained from experiments in which the amine was treated as a reversible competitive inhibitor, followed by calculation of k_2 from rates of inactivation (k_{obsd}) measured at one allenic amine concentration and K_i.[41]

The very slow rates of inactivation observed for most of the (*S*)-allenic amines prompted suspicions that these time-dependent phenomena might be due, possibly completely, to the presence of (*R*)-allenic amine impurities. In such a case the (*S*)-allenic amine would be acting simply as a reversible competitive inhibitor. Consideration of the kinetics for time-dependent inhibition of enzyme E by inhibitor I in the presence of a reversible competitive inhibitor J[41] (eq 3) allows for evaluation of the apparent equilibrium constant $K_{app} = K_iK_j/(xK_j + K_i)$, where "*x*" is the ratio [I]/[J]. Thus, if the relative amount of irreversible inhibitor I present is very small and K_j is not very much greater than K_i, K_{app} approximates K_j (i.e. *K* of the reversible inhibitor J). Further, the apparent rate constant k_{app} is evaluated as $k_{app} = k_2/[1 + (K_i/xK_j)]$, or alternatively the ratio "*x*" may be expressed as $x = K_ik_{app}/[K_j(k_2 - k_{app})]$. If the slow time-dependent inhibition observed for many of the (*S*)-allenic amines is considered to be due entirely to the presence of diastereomeric or enantiomeric (*R*)-allenic amine impurities, then a calculation of the maximum amount of such impurities is possible. For example, if the data for (*S*)-**4** are considered as K_j and k_{app} resulting from the presence of inhibitor (*R*)-**4** (with K_i and k_2), then the ratio "*x*" is determined as 0.0088; that is, the maximum amount of (*R*)-**4** that may be present is 0.9%. The synthetic route for these allenic amines dictates that, statistically, any significant impurities in compounds **3**, **5**, and **6** should be diastereomeric rather than enantiomeric. Calculations as above indicate that diastereomeric (*R*)-allenic amine impurities in the (*S*)-allenic amine samples **2**–**6** are less than 4.5%. Thus, the low values of k_2 determined for all (*S*)-allenic amines other than (*S*)-**1** represent upper limits, as these values may be accounted for in whole or in part by a few percent of diastereomeric (*R*)-allenic amine impurities. The sensitivity of MAO-B to allene chirality has therefore allowed a confirmation of our earlier estimates of diastereomeric purity.

$$E{\cdot}J \overset{K_j}{\rightleftharpoons} J + E + I \overset{K_i}{\rightleftharpoons} E{\cdot}I \overset{k_2}{\rightarrow} E{-}I \quad (3)$$

Our results (Table III) for inhibition by diastereomeric allenic amines clearly demonstrate the sensitivity of MAO-B to stereochemistry. In general, the rates of inactivation (k_2) by allenic amines having the *R* configuration are considerably greater than their (*S*)-allenic counterparts. This selectivity was most dramatic in the opposing allene chiralities of the (*S*)-tetrahydro-1-naphthyl derivatives (*R*,*S*)-**6** and (*S*,*S*)-**6** ($k_2(RS)/k_2(SS)$ = 220).

The relative importance of allene chirality on inactivation rate shows a strong dependence on the size of the *N*-alkyl or *N*-aralkyl group. When this group is methyl as in **1**, inactivation rates for *R* and *S* enantiomers are approximately equal, whereas differences in rates for enantiomers of the *N*-benzyl derivatives **2** are 7-fold, and for the *N*-phenethyl compounds **4** they are almost 80-fold. It is also noted that all (*S*)-allenic amines having *N*-aralkyl substituents bulkier than benzyl are very poor inactivators (k_2 < 0.015 min^{-1}), effectively acting only as competitive reversible inhibitors. As discussed above, the slow time-dependent behavior observed may in fact be due to the presence of very small amounts of diastereomeric (*R*)-allenic amines. In the case of (*R*)-allenic amines having *N*-aralkyl substituents larger than benzyl, inactivation rates are quite respectable (k_2 = 0.1–1.0 min^{-1}), with the notable exception of the (*S*)-α-methylphenethyl derivative (*R*,*S*)-**5**. For comparison, MAO-B inactivation rates for pargyline and *l*-deprenyl are 0.20 and >0.99 min^{-1}, respectively (30 °C).[3,40] The achiral allenic amine analogous to **2** lacking a terminal methyl group (*N*-methyl-*N*-benzylbuta-2,3-dienamine) is substantially more potent than either enantiomer of **2**, with kinetic parameters[19] at 2.5 °C of K_i = 0.066 mM and k_2 = 4.0 min^{-1}.

The influence of *N*-aralkyl group chirality on MAO-B inactivation rates was found to be significantly less than that of the allene chirality. For the (*S*)-allenic amines, the presence of an *N*-α-substituted-aralkyl group of either chirality severely compromised the time-dependent activity of these inhibitors. In the (*R*)-allene series, inactivation rates (k_2) were consistently better (1.4–17-fold) for those inhibitors having (*R*)- rather than (*S*)-aralkyl groups. The more potent enantiomer of deprenyl (*l*-deprenyl) is also that having the (*R*)-α-methylphenethyl group.[14] It is interesting that an allenic amine having an *N*-tetrahydronaphthyl group has potency comparable to that of the best inhibitor, (*R*)-**2**, if the chirality of both the allene and tetrahydro-1-naphthyl groups are chosen correctly as in (*R*,*R*)-**6**. In sharp contrast, the enantiomeric species (*S*,*S*)-**6** shows the poorest activity, with a rate constant (k_2) at least 1300-fold less than that of (*R*,*R*)-**6**.

Some measure of the "affinity" of an inactivator for the enzyme may be provided by K_i, although there appears to be no simple pattern to the K_i values presented in Table III except that generally lower values were obtained for all of the tetrahydronaphthyl derivatives. This is reasonable, as the amines **17** and **18** were much better competitive inhibitors than the corresponding benzyl and phenethylamines (Table II). However, the K_i values for pargyline (0.5 μM) and *l*-deprenyl (0.97 μM competitive K_i)[3,40] are 2–3 orders of magnitude lower than the K_i's of some of the best penta-2,3-dienamines (i.e., K_i = 0.2 mM). As the inactivation rates for these propargylamines are comparable to those of some of our allenic amines (see above), the large difference in K_i values renders the propargylamines the more potent inactivators. However, unlike the allenic amines, opportunities for selective inhibition that exploit stereochemistry are limited to the *N*-aralkyl groups of propargylamine inhibitors.

(41) (a) Kitz, R.; Wilson, I. B. *J. Biol. Chem.* **1962**, *237*, 3245. (b) Various other symbols have also been used in the literature to represent the inactivation kinetic parameters k_{obsd}, K_i, and k_2: e.g. k_{obsd} as k_{app}; K_i as K_I or K_{inact}; and k_2 as k_{inact}, k_{cat}, k_{inh}, or k_3.

(42) (a) Cleland, W. W. *Methods Enzymol.* **1979**, *63*, 103. (b) Cleland, W. W. *Adv. Enzymol.* **1967**, *29*, 1.

Samples of the enantiomeric primary allenic amines (*R*)-(−)- and (*S*)-(+)-penta-2,3-dienamine (provided by Sahlberg and Claesson[20,43]) allowed a further study of MAO selectivity. The inactivation of MAO-B by these primary amines did not exhibit saturation kinetics; however, the apparent second-order rate constants observed for the *R* and *S* isomers (255 and 72 mM^{-1} min^{-1}, respectively) once again indicate the (*R*)-allene to have the preferred chirality. As well, inhibition of plasma MAO by these primary amines revealed the *R* isomer (ca. 300 mM^{-1} min^{-1}) to be more potent than the *S* isomer (90 mM^{-1} min^{-1}).

Conclusions

Our investigation has clearly illustrated that a chiral allene group may serve as a selective probe of active-site geometry. Although we have demonstrated that inactivation of MAO-B is strongly dependent on the chirality of the allene group, it is as yet unknown whether this is a consequence of active-site geometric/steric constraints on the formation, or on the capture of the putative allenic iminium ion intermediate.[19] If one considers that the amine nitrogen electron lone pair and *pro-R*[14,39] α-allenic hydrogen must both occupy specific positions at the active site for enzyme chemistry (possibly leading to inactivation) to occur, then it follows that the orientation of the allene group will be somewhat restricted, and that one allene chirality might be sterically inappropriate to this arrangement. Apparently, when the chiral allenic amine lacks an *N*-aralkyl substituent as in **1**, there is sufficient conformational freedom at the active site to allow the enantiomers to be equally competent as inactivators ($k_2(R)/k_2(S) = 0.8$). Indeed, these enantiomers are both slightly more rapid inactivators than the analogous achiral compound *N,N*-dimethylbuta-2,3-dienamine (which lacks a terminal methyl) (K_i = 0.16 mM, k_2 = 0.16 min^{-1}, 30 °C[19]). The profound MAO-B stereoselectivity observed for allenic amines having *N*-aralkyl substituents (**3–6**) suggests the existence of a lipophilic subsite, which binds these *N*-aralkyl groups and is sufficiently restrictive so as to limit the conformational freedom of the allene substituent, and thereby define the (*R*)-allene selectivity. The effect of *N*-aralkyl group chirality on k_2 of the (*R*)-allenes, and the K_i data of Table II, suggest that this subsite is best able to accommodate (*R*)-α-substituted-aralkyl groups. It is interesting to note that while the reversible inhibitor (*R*)-**17** is 150-fold better than (*S*)-**17** in decreasing the rate of oxidation of the substrate benzylamine by MAO-B, its (*R*)-allene derivative (*R,R*)-**6** is 200-fold better (k_2) than (*R,S*)-**6** in the suicide inactivation of MAO-B. That is, amine (*R*)-**17** may bind to a subsite and thereby hinder enzyme chemistry on a substrate, yet facilitate enzyme chemistry on an (*R*)-allene group attached to itself (as in (*R,R*)-**6**). As all four derivatives **5** are rather poor inhibitors, a limit in the size/shape of the lipophilic subsite may have been reached and defined by the *N*-α-methylphenethyl group.

Finally, as further information regarding the mechanism and active-site structure of monoamine oxidase becomes available, we expect that our results will be valuable in understanding the stereochemical selectivities of MAO and as an aid in the design of more specific reversible and irreversible inhibitors.

Experimental Section

Chemistry. Unless stated otherwise, chemical reagents were obtained from commercial sources and were used directly. Reactions were routinely conducted under a dry argon atmosphere. Tetrahydrofuran and benzene were distilled from sodium/benzophenone, commercial anhydrous diethyl ether was used directly, and methylene chloride was distilled from P_2O_5. Melting points (Büchi 510 apparatus) and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 298 grating spectrophotometer. Nuclear magnetic resonance spectra were measured with a Bruker WP80 spectrometer at 80 MHz for proton spectra and at 20 MHz for carbon-13 spectra; ^{13}C NMR spectra were determined by a J-modulated spin echo technique to differentiate carbons with zero or two attached protons from those with an odd number of protons. Gas chromatographic analyses were obtained by using a Varian Model 3700 gas chromatograph equipped with a flame-ionization detector, and a Hewlett-Packard 3390A Reporting Integrator; a 2 m × 0.125 in. glass column of 5% OV-101 on Chromosorb W (A/W-DMCS, 80/100 mesh) was used except where stated otherwise. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. Column chromatography was accomplished with Whatman LPS-2 silica gel (37–53 μm). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

(*R*)-(+)-3-Butyn-2-ol [(*R*)-7].[44-46] (a) (±)-3-Butyn-2-ol Hydrogen Phthalate. To a mixture of 28.0 g (0.40 mol) of (±)-3-butyn-2-ol [(±)-**7**] (Farchan) and 88.9 g (0.60 mol) of phthalic anhydride was added 240 mL of ice-cold 10% aqueous NaOH in 3 portions, with swirling. The mixture was shaken for 5 min, rapidly filtered, and then acidified by gradual addition of ice-cold 5 N HCl. The mixture was extracted with chloroform (4 × 100 mL), and the combined organic phases were filtered, dried ($MgSO_4$), and evaporated to afford 63.7 g (73%) of a slightly yellow crystalline solid, mp 96.5–98 °C (lit.[46] mp 96–98 °C; lit.[45] mp 90 °C).

(b) (*R*)-3-Butyn-2-ol Hydrogen Phthalate (*R*)-α-Methylbenzylammonium salt. To 166.7 g (0.764 mol) of 3-butyn-2-ol hydrogen phthalate stirring in 1.0 L of acetone was added 92.6 g (0.764 mol) of (*R*)-(+)-α-methylbenzylamine ($[\alpha]_D$ +38° (neat), Aldrich) over a 5-min period. The resulting semicrystalline mass was mixed thoroughly by shaking, heated at gentle reflux for 30 min, and then left at room temperature overnight. Several (six to seven) recrystallizations of the precipitate and its mother liquors from acetone afforded 80.8 g (63%) of the (*R*)-3-butyn-2-ol hydrogen phthalate (*R*)-α-methylbenzylammonium salt diastereomer, mp 138.5–139 °C. Diastereomeric purity was confirmed by the clean acetylenic proton NMR ($CDCl_3$) signal (2.46 ppm, d, J = 2 Hz; the *S,R* diastereomer signal appeared at 2.50 ppm).

With (*S*)-(−)-α-methylbenzylamine ($[\alpha]_D$ −39° (neat)), the (*S*)-3-butyn-2-ol hydrogen phthalate (*S*)-α-methylbenzylammonium salt diastereomer, mp 138.5–139 °C, was similarly obtained.

Resolution via the brucine salt[46] was found, in our hands, to be extremely inefficient.

(c) (*R*)-(+)-3-Butyn-2-ol [(*R*)-7]. Aqueous HCl (185 mL, 4 N) was added portionwise with swirling to a slurry of 80.28 g (0.236 mol) of (*R*)-3-butyn-2-ol hydrogen phthalate (*R*)-α-methylbenzylammonium salt in 375 mL of water. The mixture was extracted with ether (3 × 300 mL), and the combined ether phases were washed twice with water, dried (Na_2SO_4), rotary evaporated, and dried at high vacuum. The crude (*R*)-phthalate ester (a viscous oil) was mixed with 80 mL of 10 N aqueous KOH at 0 °C and then stirred at 0 °C for 30 min and at room temperature for 2 h. Continuous extraction (Et_2O, 5–6 days) was followed by removal of most of the ether by careful distillation (1 atm). The residual concentrated ethereal solution of (*R*)-(+)-**7**[44-46] (65–70% yield by NMR analysis) was used without further purification.

(*S*)-(−)-3-Butyn-2-ol [(*S*)-**7**] in Et_2O was obtained in a likewise manner. By ^1H NMR analyses ($CDCl_3$) with the chiral shift reagent Eu(dcm)$_3$ (Alfa),[25] no enantiomeric impurities were detected in either (*R*)- or (*S*)-**7** samples. When shifted to ca. 4.0

(43) $[\alpha]^{22}_D$ for penta-2,3-dienamine oxalates: (*R*) −51.6° (*c* 1.89, MeOH); (*S*) +50.6° (*c* 2.13, MeOH). Sahlberg, C. Doctoral Thesis, Uppsala University, Uppsala, Sweden, 1982.

(44) Weidmann, R.; Schools, A.; Horeau, A. *Bull. Soc. Chim. Fr.* **1976**, 645.
(45) Baker, C. S. L.; Landor, P. D.; Landor, S. R.; Patel, A. N. *J. Chem. Soc.* **1965**, 4348.
(46) Schlossarczyk, H.; et al. *Helv. Chim. Acta* **1973**, *56*, 875.

ppm, the methyl signal (d, J = 6.6 Hz) for (*R*)-**7** appears ca. 0.2 ppm upfield of that of (*S*)-**7**.

(*R*)-3-(2-Tetrahydropyranyloxy)-1-butyne [(*R*)-8]. Concentrated HCl (1 mL) was added dropwise at 0 °C to a stirred solution of 0.17 mol of (*R*)-**7** in ether (as above) and 32.6 mL (0.36 mol) of dihydropyran. The mixture was stirred 15 min at 0 °C and then heated in a 70 °C bath for 2.5 h, allowing the small amount of ether present to be distilled off. After 1 h at room temperature, the solution was diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) and brine (25 mL), dried (Na_2SO_4), and distilled to afford 23.6 g (90%) of a colorless liquid, bp 72–114 °C (10 mm). Different fractions of the distillate contained varying ratios of the two diastereomers (new asymmetric center in the THP group) by ^1H NMR analysis; these ratios correlated well (r^2 = 0.997, 6 pts) with the optical rotations of the distillate fractions. Thus, calculated optical rotations for the two THP-protected (*R*)-3-butyn-2-ol diastereomers are $[\alpha]^{21}_D$ −92.7° and +229° (*c* 5, MeOH); actual rotations of distillate fractions were in the range of +30° to +125° [lit.[47] bp 44–49 °C (1.9 mm) for racemic **8**; lit.[24] $[\alpha]^{22}_D$ −122.3° (*c* 10.8, MeOH) for (*S*)-**8**].

(*S*)-**8** was obtained in a similar manner from (*S*)-**7**.

(*R*)-4-(2-Tetrahydropyranyloxy)-2-pentyn-1-ol [(*R*)-9]. Via the literature procedure[47] but with (*R*)-**8**, (*R*)-**9** was obtained (73–90% yield), bp 100–106 °C (0.2 mm); [lit.[47] bp 125 °C (1.0 mm) for racemic **9**]. (*S*)-**9** was obtained in a similar manner. Observed rotations were $[\alpha]^{21}_D$ +108.1° (*c* 3.16, MeOH) for (*R*)-**9**, and $[\alpha]^{21}_D$ −99.8° (*c* 4.66, MeOH) for (*S*)-**9** [lit.[24] $[\alpha]^{22}_D$ −118.7° (*c* 11.4, MeOH)]. However, each of these samples exists as a mixture of diastereomers due to the additional asymmetric center in the THP group.

(*S*)-Penta-2,3-dien-1-ol [(*S*)-10]. On the basis of the procedure described by Olsson and Claesson,[24] 23.7 g (0.128 mol) of (*R*)-**9** in 125 mL of THF was added dropwise during a 2-h period to a mixture of $LiAlH_4$ (7.2 g, 0.18 mol) in 200 mL of THF stirring at 0 °C. The mixture was then stirred at room temperature for 12 h, the reaction being monitored for optimal yield by GC analysis of quenched aliquots. The mixture was quenched at 0 °C by dropwise addition of saturated aqueous NH_4Cl (100 mL) and then diluted with 100 mL of Et_2O. The organic phase was separated and the aqueous phase was extracted with THF (4 × 100 mL). Combined organic phases were washed with saturated NH_4Cl, rotary evaporated, diluted with Et_2O, dried (Na_2SO_4), and distilled to afford a 36–48% yield of (*S*)-**10** as a colorless liquid, bp 66.5–71.5 °C (19–20 mm) [lit.[47] bp 56–58 °C (20 mm) for (±)-**10**]; IR (film) 1970 cm^{-1}. GC analysis (5% OV-101 or 5% Carbowax 20M) indicated ca. 85% chemical purity. ^1H NMR analysis ($CDCl_3$), using $Eu(dcm)_3$ and simultaneous decoupling of the $=CHCH_2OH$ signal, revealed no enantiomeric impurity. (With the CH_2OH signal shifted to ca. 8.9 ppm, and irradiation of the $=CHCH_2OH$ signal now at 7.65 ppm, the resulting pseudosinglet for CH_2OH of (*R*)-**10** is ca. 0.1 ppm downfield of that of (*S*)-**10**).

(*R*)-**10** was obtained similarly; again, no enantiomeric impurity could be detected by ^1H NMR/$Eu(dcm)_3$ analysis.

(*S*)-Penta-2,3-dien-1-yl Methanesulfonate [(*S*)-11]. The standard mesylation procedure[48] was followed. Distilled methanesulfonyl chloride (3.0 g, 26.2 mmol) was added dropwise during 20 min to a solution of 2.00 g (23.8 mmol) of (*S*)-**10** and 3.60 g (35.6 mmol) of triethylamine in 135 mL of methylene chloride stirring in a ca. −25 °C bath. The mixture was stirred for 1 h at 0 °C, then washed with the following ice-cold solutions: water, 10% HCl (2×), saturated aqueous $NaHCO_3$, and brine. The solution was dried (Na_2SO_4) and concentrated in vacuo to afford 3.61 g (94%) of (*S*)-**11**[20] as a slightly yellow liquid, which was used immediately without further purification.

(*R*)-**11** was prepared in a similar manner.

***N*-Methyl-*N*-aralkylpenta-2,3-dienamines (3-6). General Procedure.** A solution of 405 mg (2.5 mmol) of (*R*)-**11** or (*S*)-**11** in 10 mL of benzene was added dropwise at room temperature to a stirred solution of the appropriate secondary amine (5.0 mmol) in 30 mL of benzene. The solution was left at room temperature for 3–4 days, then rotary evaporated to give a yellow oil. Trituration with Et_2O effected crystallization, and the crude crystals ($RNHCH_3{\cdot}CH_3SO_3H$) were filtered and washed with Et_2O. The filtrate was rotary evaporated and passed through a small amount (ca. 2 g) of silica gel (10–50% Et_2O–hexane eluant) to afford the tertiary α-allenic amine as an oil in 80–90% yield; IR (film) 1965–1970 cm^{-1}.

The free amine (2.0 mmol) in 10 mL of Et_2O was added dropwise with stirring to a solution of anhydrous oxalic acid (189 mg, 2.1 mmol) in 15 mL of Et_2O. The resulting mixture was stirred at room temperature overnight and then filtered. Recrystallization afforded the tertiary α-allenic amine hydrogen oxalate in 50–80% yield (1–2 crops of crystals); IR (KBr) 1970–1975 cm^{-1} (see Table I).

In the case of (*R*,*S*)- and (*S*,*R*)-**3**, crystalline oxalate salts could not be obtained; these amines were converted to their hydrochloride salts (anhydrous HCl, Et_2O). In the case of (*R*,*R*)- and (*S*,*S*)-**3**, the acid salts (hydrochloride, hydrogen oxalate, sulfate, formate) could not be induced to crystallize; these free amines were purified by silica gel chromatography (10–50% Et_2O–hexane eluant) and stored in the freezer under argon.

Representative ^1H NMR spectral data follow:

(*R*,*R*)- or (*S*,*S*)-3 free amine: NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.3–4.9 (m, 2 H), 3.62 (q, J = 7 Hz, 1 H), 3.4–2.7 (m, 2 H), 2.22 (s, 3 H), 1.64 (m, 3 H), 1.36 (d, J = 7 Hz, 3 H).

(*R*,*S*)- or (*S*,*R*)-3·HCl salt: NMR ($CDCl_3$) δ 7.5 (m, 5 H), 5.7–5.1 (m, 2 H), 4.6–4.0 (m, 1 H), 4.0–3.0 (m, 2 H), 2.81 & 2.52 (2 d, each J = 5 Hz, 3 H total), 1.89 & 1.86 (2 d, each J = 7 Hz, 3 H total), 1.8–1.6 (m, 3 H); NMR ($CDCl_3$ + 1 drop D_2O) δ 7.5 (m, 5 H), 5.7–5.1 (m, 2 H), 4.35 (br q, J = 7 Hz, 1 H), 3.8–3.2 (br m, 2 H), 2.64 (br s, 3 H), 1.87 (d, J = 7 Hz, 3 H), 1.71 (m, 3 H).

(*R*,*R*)- or (*S*,*S*)-5 hydrogen oxalate: NMR ($CDCl_3$) δ 7.26 (m, 5 H), 5.6–5.1 (m, 2 H), 4.1–3.1 (m, 4 H), 2.80 (s, 3 H), 2.8–2.4 (m, 1 H), 1.8–1.6 (m, 3 H), 1.20 (d, J = 7 Hz, 3 H).

(*R*,*S*)- or (*S*,*R*)-5 hydrogen oxalate: NMR (D_2O, 30 °C) δ 7.41 (m, 5 H), 5.7–5.1 (m, 2 H), 4.75 (HDO), 4.2–3.4 (m, 2 H), 3.4–2.7 (m, 3 H), 2.88 & 2.84 (2 s, 3 H total), 1.70 (dd, J = 3 & 7 Hz, 3 H), 1.29 & 1.26 (2 d, each J = 7 Hz, 3 H total); at 50 °C the doubled signals have coalesced to δ 2.86 (s, 3 H) and 1.27 (d, J = 7 Hz, 3 H).

(*R*)-*N*,*N*-Dimethylpenta-2,3-dienamine Hydrogen Oxalate [(*R*)-1]. Anhydrous dimethylamine gas was bubbled through a stirred solution of (*R*)-**11** (421 mg, 2.60 mmol) in 75 mL of Et_2O for 15 min. The white mixture was stirred at room temperature overnight and filtered, and the filtrate was concentrated to half-volume by careful distillation (1 atm) of Et_2O/Me_2NH. Succinic anhydride (250 mg) was added to the residual solution, and this was then stirred overnight (formation of $Me_2NCOCH_2CH_2COOH$). The solution was stirred with 10 mL of 15% aqueous NaOH and then extracted twice with Et_2O. The combined ether phases were dried ($MgSO_4$) and then added dropwise to a solution of anhydrous oxalic acid (257 mg, 2.86 mmol) in 20 mL of Et_2O. The mixture was stirred overnight and then filtered. Recrystallization from hot absolute ethanol afforded 204 mg (39%) of (*R*)-**1** hydrogen oxalate as white crystals (see Table I); IR (KBr) 1970 cm^{-1}; NMR (D_2O) δ 5.7–5.1 (m, 2 H), 4.75 (HDO), 3.68 (dd, J = 7 & 2 Hz, 2 H), 2.88 (s, 6 H), 1.70 (dd, J = 7 & 3 Hz, 3 H).

(*S*)-**1** was obtained in a similar manner from (*S*)-**11**.

(*R*)- and (*S*)-*N*,α-Dimethylbenzylamines [(*R*)- and (*S*)-14]. These amines were prepared according to literature procedures.[35,49,50] Thus, by conversion of the chiral primary amines **13** (Aldrich) to their formamides (58–65% crude yield), followed by $LiAlH_4$ reduction (75–80% yield), were obtained (*R*)-(+)-**14**, bp 76–79 °C (14 mm) [lit.[50] bp 80 °C (12 mm)], $[\alpha]^{21}_D$ +62.3° (*c* 4.41, EtOH) [lit.[49] $[\alpha]^{22}_D$ +62.7 ± 0.5° (*c* 3.99, EtOH)], and (*S*)-(−)-**14**, bp 75–79 °C (14 mm), $[\alpha]^{21}_D$ −62.5° (*c* 3.85, EtOH).

(±)-α-Methylphenethylamine [(±)-15]. Benzaldehyde and nitroethane were condensed in the presence of butylamine to afford 2-nitro-1-phenylpropene as yellow crystals in 70% yield, mp 65–65.5 °C (EtOH) (lit.[51] mp 65 °C). This nitroalkene (0.2

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mol, 32.6 g) in 200 mL of anhydrous THF was added dropwise to a mixture of $LiAlH_4$ (0.88 mol, 35.2 g) in 500 mL of anhydrous Et_2O stirring at 0 °C. After complete addition, the mixture was heated at reflux for 2 h and then quenched at 0 °C by the dropwise addition of 35 mL of EtOH, 35 mL of H_2O, and 35 mL of 15% aqueous NaOH. The mixture was filtered, and the filtrate was extracted with 10% aqueous HCl (3×). The aqueous extracts were basified at 0 °C by the gradual addition of 15% aqueous NaOH and then extracted with CH_2Cl_2 (4×). The combined CH_2Cl_2 phases were dried ($MgSO_4$) and distilled to afford 20.9 g (77%) of (±)-**15** ((±)-amphetamine) as a colorless liquid, bp 81–86 °C (10–12 mm) [lit.[52] bp 82–85 °C (13 mm)].

Resolution of (±)-α-Methylphenethylamine [(±)-15]. (*R*)-15: (±)-**15** (20.3 g, 0.15 mol) was added to a hot ethanol solution of D-(−)-tartaric acid (22.5 g, 0.15 mol); $[\alpha]^{20}_D$ −12° (H_2O). The solution was allowed to cool to room temperature and the white crystals (24.9 g) were collected and recrystallized twice more from ethanol to give 9.9 g (46%) of the D-tartaric acid salt of (*R*)-**15** as white crystals, mp 182–183 °C; $[\alpha]^{20}_D$ −20.8° (*c* 2.0, MeOH). An authentic enantiomeric sample prepared from (*S*)-(+)-amphetamine (Sigma) and L-(+)-tartaric acid ($[\alpha]^{20}_D$ + 12° (H_2O)) had mp 181–181.5 °C; $[\alpha]^{20}_D$ +20.5° (*c* 2.1, MeOH).

(*R*)- and (*S*)-*N*,α-Dimethylphenethylamines [(*R*)- and (*S*)-16]. The D-tartaric acid salt of (*R*)-**15** obtained above (9.9 g) in 100 mL of H_2O was treated with 50 mL of 15% aqueous NaOH and extracted with Et_2O (4×). The ether extract was dried ($MgSO_4$) and rotary evaporated to afford 4.7 g of (*R*)-(−)-**15** as a colorless liquid, $[\alpha]^{21}_D$ −30.2° (*c* 2.55, MeOH). Similar treatment of (*S*)-**15** sulfate (D-amphetamine sulfate, Sigma) afforded (*S*)-(+)-**15** as a colorless liquid, $[\alpha]^{21}_D$ +29.2° (*c* 2.09, MeOH).

These chiral primary amines were then converted[35,50] to their formamides (80–87% crude yield) followed by $LiAlH_4$ reduction (71–89%) to afford (*R*)-(−)-**16**, $[\alpha]^{21}_D$ −10.9° (*c* 4.20, EtOH) (undistilled), and (*S*)-(+)-**16**, bp 89–90.5 °C (9-10 mm) [lit.[50] bp 56 °C (3 mm)], $[\alpha]^{21}_D$ +9.11° (*c* 3.90, EtOH).

Resolution of (±)-1,2,3,4-Tetrahydro-1-naphthylamine [(±)-17]. (*R*)-17: (±)-1,2,3,4-Tetrahydro-1-naphthylamine hydrochloride (4.0 g, 21.8 mmol) was treated with aqueous NaOH, extracted with ether, dried ($MgSO_4$), and evaporated to quantitatively provide the free amine as an oil. To a solution of this oil in 50 mL of 95% EtOH was added L-(+)-tartaric acid (3.27 g, 21.8 mmol), and the resulting mixture was warmed to effect complete solution. Rotary evaporation provided a solid (mp 147–166 °C, $[\alpha]^{20}_D$ +14.8° (*c* 2.40, MeOH)), which was recrystallized three times from 95% EtOH (to constant melting point and $[\alpha]_D$) to afford 1.76 g (54%) of the (*R*)-**17** hydrogen L-tartrate, mp 167.5–168.5 °C, $[\alpha]^{21}_D$ +17.7° (*c* 2.0, MeOH) (lit.[53] $[\alpha]_D$ +18.4° (*c* 4, MeOH)). Treatment with aqueous NaOH and extraction with ether gave the free amine (*R*)-(−)-**17** as a white solid, mp 116–119 °C, $[\alpha]^{21}_D$ −47.6° (*c* 0.47, C_6H_6) (lit.[54] calcd $[\alpha]^{22}_D$ −46° (*c* 5, C_6H_6)). Hydrogen oxalate salt: mp 197–199 °C (2-PrOH), $[\alpha]^{22}_D$ +3.9° (*c* 1.07, MeOH). HCl salt: mp 242–243 °C, $[\alpha]^{23}_D$ +2.7° (*c* 1.95, MeOH) (lit.[53] mp 243–245 °C, $[\alpha]^{22}_D$ +2.9° (*c* 4, MeOH)).

(*S*)-17: The mother liquors from the above resolution were treated with aqueous NaOH and extracted with ether to afford the free amine enriched in the *S* isomer. Treatment with 1 equiv of D-(−)-tartaric acid in 95% EtOH, followed by recrystallizations to constant melting point and $[\alpha]_D$, afforded 1.60 g (49%) of the (*S*)-**17** hydrogen D-tartrate, mp 169–170 °C, $[\alpha]^{22}_D$ −17.3° (*c* 1.97, MeOH). The free amine (*S*)-(+)-**17** was isolated as above and converted to its hydrogen oxalate salt, mp 197–199 °C (2-PrOH), $[\alpha]^{22}_D$ −3.3° (*c* 1.00, MeOH). HCl salt: mp 242–243 °C, $[\alpha]^{23}_D$ −2.2° (*c* 2.10, MeOH) (lit.[53] mp 244–246 °C, $[\alpha]^{22}_D$ −2.8° (*c* 4, MeOH)).

(±)-*N*-Methyl-1,2,3,4-tetrahydro-1-naphthylamine [(±)-18]. (±)-**17** hydrochloride was treated with aqueous NaOH and extracted to afford the free amine, which was then converted[35] to the formamide (97% yield, mp 81–83 °C) (lit.[55] mp 81–82 °C). This was followed by $LiAlH_4$ reduction to afford (±)-**18**[55] (an oil), which was purified by silica gel chromatography (50–100% Et_2O–hexane eluant; 85% yield).

Resolution of (±)-*N*-Methyl-1,2,3,4-tetrahydro-1-naphthylamine [(±)-18]. (*S*)-18: (−)-Dibenzoyltartrate (40.6 g, 0.018 mol; $[\alpha]^{22}_D$ −108.8° (*c* 1.1, EtOH)) was added to a hot solution of (±)-**18** (17.4 g, 0.108 mol) in methanol (300 mL). The hot solution was allowed to cool to room temperature, and the crystals collected (20 g) were recrystallized four times from methanol to give 5.5 g (ca. 20%) of the (−)-dibenzoyltartrate salt of (*S*)-**18** as pink crystals, mp 175–176 °C; $[\alpha]^{22}_D$ −86.0° (*c* 2.2, MeOH). The (*S*)-amine dibenzoyltartrate salt (5.18 g, 9.97 mmol) was treated with 15% aqueous NaOH (75 mL) and extracted with ether to afford 1.37 g (85%) of (*S*)-(+)-**18**[55] as an oil; $[\alpha]^{21}_D$ +10.7° (*c* 2.06, EtOH) (lit.[55] $[\alpha]^{20}_D$ +3.9° (*c* 4.6, EtOH) for a partial racemate).

(*R*)-18: (+)-Dibenzoyltartrate (25.7 g, 68 mmol; $[\alpha]^{24}_D$ +111.7° (*c* 9, EtOH)) was added to a hot methanol solution (200 mL) of **18** (11.0 g, 68 mmol) recovered from the residues of the above resolution (i.e. enriched in the *R* enantiomer). The crystals were collected and recrystallized four times (MeOH) to give 5.9 g (ca. 20%) of pink crystals, mp 173.5–174 °C; $[\alpha]^{21}_D$ +83.6° (*c* 1.8, MeOH). The free amine (*R*)-(−)-**18** was isolated as above in 94% yield as an oil, $[\alpha]^{21}_D$ −10.4° (*c* 1.98, EtOH).

The addition of $Eu(dcm)_3$ (23 mM) to a $CDCl_3$ solution of **18** shifted the *N*-methyl singlet from 2.5 to 6.6 ppm for the (*S*)-amine and 6.2 ppm for the (*R*)-amine, allowing estimates of enantiomeric purities of 96% for (*S*)-**18** and >99% for (*R*)-**18**.

Enzyme Purification and Assay. Beef liver mitochondrial MAO was purified according to the procedure of Salach.[29,30] Enzyme activity was assayed spectrophotometrically by a modification of the method of Tabor et al.[31] The enzyme was added to 1 mL of assay buffer (67 mM potassium phosphate, pH 7.2; 0.2% (w/v) Triton X-100) containing benzylamine hydrochloride (recrystallized twice from EtOH) (4 mM), at 25 °C. The production of benzaldehyde was followed at 250 nm (ε 12 080 M^{-1} cm^{-1}) with a Gilford 2600 spectrophotometer, with 1 unit of activity taken as the formation of 1.0 μmol of product/min. The K_m for benzylamine was found to be 360 ± 20 μM (lit.[32] 380 μM at 30 °C, pH 9.0).

Reversible Competitive Inhibition Experiments. Stock solutions of inhibitors were prepared in assay buffer. In a typical inhibition experiment, MAO (0.002 unit) was added to 1 mL of assay buffer (25 °C) containing benzylamine hydrochloride (100, 200, 300, or 400 μM) and inhibitor at various concentrations. Initial rates of benzaldehyde production were monitored at 250 nm, with four replicate measurements for each combination of substrate and inhibitor concentration. Competitive K_i values were calculated from the initial rate data by the program COMP.[42]

Time-Dependent Inhibition Experiments. In a typical experiment, MAO (0.02 unit) was incubated at 25 °C in 100 μL of potassium phosphate (50 mM, pH 7.4) containing allenic amine (1 μM–10 mM). Aliquots (10 μL) were removed at various times and immediately assayed (in duplicate) for residual MAO activity. The first-order rate constant (k_{obsd}) for the exponential decay of MAO activity with time was determined by nonlinear regression of the observed enzyme activity E to the expression $E = E_o \exp(-k_{obsd}t) + E_\infty$. The kinetic constants K_i and k_2[41] (Table III) were obtained by linear regression of $1/k_{obsd}$ vs. $1/[I]$ (Figure 1). Standard errors were generally 15–35% for K_i and 5–15% for k_{obsd} and k_2. Larger errors were observed for the more rapid inhibitors (*R*)-**2** and (*R*,*R*)-**6**, due to limitations of the assay method; in these cases, precise values are available only for $k_2/K_i = 5.3 \pm 0.2$ mM^{-1} min^{-1} and 3.5 ± 0.3 mM^{-1} min^{-1}, respectively. Rate data (k_{obsd} & [I]) were also fit to the equation $k_{obsd} = k_2[I]/(K_i + [I])$,[42] and the K_i and k_2 values so determined were found to agree well with those obtained from the secondary reciprocal plots (except for (*R*)-**2** and (*R*,*R*)-**6**, in which case values for k_2/K_i agreed within 30%).

For systems exhibiting very slow rates of inactivation as indicated in Table III, competitive K_i values were determined from

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initial rates, k_{obsd} was determined at one allenic amine concentration (2–4-fold greater than K_i), and k_2 was then calculated as $k_2 = k_{obsd}(1 + K_i/[I])$.[41] The value of k_2 for (*S,R*)-**5** was calculated with a forced zero-activity endpoint [i.e., fit to $E = E_0 \exp(-kt)$]. A rough estimate for the inactivation rate of (*S,S*)-**6** was made on the basis of ca. 90% enzyme activity remaining (relative to control) after 260 min of a 0.4 mM incubation.

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Registry No. (*R*)-**1**, 89290-07-3; (*R*)-**1**·$C_2H_2O_4$, 114351-89-2; (*S*)-**1**, 89290-08-4; (*S*)-**1**·$C_2H_2O_4$, 114351-90-5; (*R*)-**2**, 85506-93-0; (*R*)-**2**·$C_2H_2O_4$, 85506-94-1; (*S*)-**2**, 85506-95-2; (*S*)-**2**·$C_2H_2O_4$, 85506-96-3; (*R,R*)-**3**, 89290-09-5; (*S,S*)-**3**, 89362-15-2; (*R,S*)-**3**, 89362-14-1; (*R,S*)-**3**·HCl, 114351-91-6; (*S,R*)-**3**, 89362-13-0; (*S,R*)-**3**·HCl, 114351-92-7; (*R*)-**4**, 89290-10-8; (*R*)-**4**·$C_2H_2O_4$, 114351-93-8; (*S*)-**4**, 89290-11-9; (*S*)-**4**·$C_2H_2O_4$, 114351-94-9; (*R,R*)-**5**, 89290-12-0; (*R,R*)-**5**·$C_{H2}O_4$, 114351-95-0; (*S,S*)-**5**, 89362-18-5; (*S,S*)-**5**·$C_2H_2O_4$, 114351-96-1; (*R,S*)-**5**, 89362-17-4; (*R,S*)-**5**·$C_2H_2O_4$, 114351-97-2; (*S,R*)-**5**, 89362-16-3; (*S,R*)-**5**·$C_2H_2O_4$, 114377-11-6; (*R,R*)-**6**, 89290-13-1; (*R,R*)-**6**·$C_2H_2O_4$, 114377-12-7; (*S,S*)-**6**, 89362-21-0; (*S,S*)-**6**·$C_2H_2O_4$, 114351-98-3; (*R,S*)-**6**, 89362-20-9; (*R,S*)-**6**·$C_2H_2O_4$, 114351-99-4; (*S,R*)-**6**, 89362-19-6; (*S,R*)-**6**·$C_2H_2O_4$, 114352-00-0; (±)-**7**, 65337-13-5; (±)-**7** (hydrogen phthalate), 42969-62-0; (*R*)-**7**, 42969-65-3; (*R*)-**7** (hydrogen phthalate·(*R*)-PhCH(CH_3)NH_2), 114351-86-9; (*S*)-**7**, 2914-69-4; (*S*)-**7** (hydrogen phthalate·(*S*)-PhCH(CH_3)NH_2), 100837-08-9; (*R*)-**8** (*R*-THP), 114351-87-0; (*R*)-**8** (*S*-THP), 114352-04-4; (*S*)-**8** (*R*-THP), 114352-05-5; (*S*)-**8** (*S*-THP), 114351-88-1; (*R*)-**9** (*R*-THP), 114419-86-2; (*R*)-**9** (*S*-THP), 114419-90-8; (*S*)-**9** (*R*-THP), 114419-91-9; (*S*)-**9** (*S*-THP), 114419-87-3; (*R*)-**10**, 65032-23-7; (*S*)-**10**, 85507-21-7; (*R*)-**11**, 85507-16-0; (*S*)-**11**, 85507-17-1; (*R*)-**13**, 3886-69-9; (*S*)-**13**, 2627-86-3; (*R*)-**14**, 5933-40-4; (*S*)-**14**, 19131-99-8; (±)-**15**, 300-62-9; (*R*)-**15**, 156-34-3; (*R*)-**15**·L-tartrate, 114352-01-1; (*S*)-**15**, 51-64-9; (*S*)-**15**·$^1/_2H_2SO_4$, 51-63-8; (*R*)-**16**, 33817-09-3; (*S*)-**16**, 537-46-2; (±)-**17**, 32908-38-6; (±)-**17**·HCl, 49800-23-9; (*R*)-**17**, 23357-46-2; (*R*)-**17**·L-tartrate, 32908-39-7; (*S*)-**17**, 23357-52-0; (*S*)-**17**·D-tartrate, 114352-02-2; (±)-**18**, 42882-35-9; (*R*)-**18**, 114419-88-4; (*R*)-**18**·(+)-dibenzoyltartrate, 114419-89-5; (*S*)-**18**, 49681-43-8; (*S*)-**18**·(−)-dibenzoyltartrate, 114352-03-3; MAO, 9001-66-5; $(CH_3)_2NH$, 124-40-3; $Ph(CH_2)_2NHCH_3$, 589-08-2; PhCHO, 100-52-7; $C_2H_5NO_2$, 79-24-3; $PhCH{=}C(NO_2)CH_3$, 705-60-2.

Supplementary Material Available: Complete ^{13}C NMR spectral data with peak assignments for compounds **1–6** (3 pages). Ordering information is given on any current masthead page.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Analogues. Inactivation of Monoamine Oxidase by Conformationally Rigid Analogues of *N,N*-Dimethylcinnamylamine

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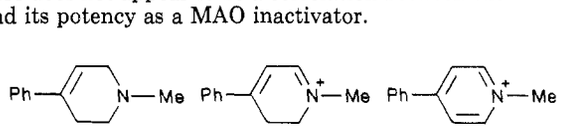
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a potent neurotoxin and also an inactivator of monoamine oxidase (MAO). Since MPTP is a conformationally rigid analogue of *N,N*-dimethylcinnamylamine, other conformationally rigid analogues of *N,N*-dimethylcinnamylamine were synthesized and tested as inhibitors and inactivators of MAO. (*E*)-2-(Phenylmethylene)cyclohexanamine (**5a**), (*E*)-*N,N*-dimethyl-2-(phenylmethylene)cyclohexanamine (**5b**), 3-phenyl-2-cyclohexen-1-amine (**6a**), *N,N*-dimethyl-3-phenyl-2-cyclohexen-1-amine (**6b**), and (*E*)- and (*Z*)-*N*-methyl-3-(phenylmethylene)piperidine (**7** and **8**) are all inhibitors and time-dependent inactivators of MAO B, but none is as potent as MPTP. α-Methylation and methylation of the amino group in all cases increases the K_i value relative to that for the parent compound. Compounds **5a**, **5b**, **6a**, and **6b** are highly cytotoxic, but cytotoxicity is not prevented by pretreatment of the cells with pargyline. There does not appear to be a correlation between the configuration of the *N,N*-dimethylcinnamylamine analogue and its potency as a MAO inactivator.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**1**, MPTP) is a potent neurotoxin that produces symptoms identical with those associated with Parkinson's disease.[1-3] The neurotoxicity of MPTP is blocked in animals by pretreatment with selective inactivators of monoamine oxidase (MAO), and, therefore, it was concluded that the neurotoxicity of MPTP is derived from a metabolite produced by a MAO-catalyzed oxidation of MPTP.[3,4] Chiba et al.[4] showed that MPTP was metabolized by MAO B to 1-methyl-4-phenyl-2,3-dihydropyridinium ion (**2**, $MPDP^+$) and to 1-methyl-4-phenylpyridinium ion (**3**, MPP^+). Not



1 **2** **3**

only is MPTP a substrate for MAO, but it also is a mechanism-based inactivator[5] of MAO.[6-9] Inactivation by [^{14}C]MPTP results in attachment of radioactivity to the enzyme, which remains bound, even after denatura-

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