Determination of the Absolute Stereochemistry of Chiral Amines by ^{1}H NMR of Arylmethoxyacetic Acid Amides: The Conformational Model

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Molecular Mechanics, semiempirical, and *ab initio* calculations and DNMR experiments indicate that arylmethoxyacetic acid amides exist in solution as essentially two conformers in equilibrium. Of these conformers, the major one (denominated *ap*) has the C_αOMe and C=O groups antiperiplanar and the minor one (*sp*) synperiplanar; the aryl ring is approximately coplanar with the C_α–H bond in both conformers. This conformational preference of amides of MPA and other AMAAs is opposite to that of the esters (these prefer the *sp* conformation) and allows the correlation of the ^{1}H NMR chemical shifts with the absolute stereochemistry of the amine. On the basis of calculations and experimental results, low polar solvents are recommended for configurational assignment and ee measurement of amines by ^{1}H NMR of AMAA derivatives.

Introduction

In recent years widespread use has been made of chiral reagents for derivatization of optically active alcohols and amines and subsequent determination of their enantiomeric purity or absolute configuration by NMR.[1] The nature of these chiral reagents is such that atoms or groups around the chiral center of the amine or alcohol substrate become nonequivalent in the corresponding derivative.[2] For reagents with an aromatic ring at the chiral center, a model[2] accounting for the conformational compositions of the (*R*)- and (*S*)-derivatives and, in particular, the relative orientations of the aromatic ring and substrate group, has allowed correlation of the absolute configuration of the alcohol or amine with their chemical shifts in the corresponding derivative.

In a recent paper,[3] we showed that the time-averaged chemical shifts of the esters of chiral secondary alcohols with (*R*)- and (*S*)-arylmethoxyacetic acids (AMAAs) derive from several conformers in which anisotropic shielding effects are acting to differing degrees, that these shifts thus depend on the geometries of the low energy conformations and their relative populations, and also that the chemical shift in the (*R*)-derivative minus that in the (*S*)-derivative ($\Delta\delta^{RS}$) is increased by increasing the effective area of the shielding cone of the aromatic ring or the population of the conformer in which the shielding effect is greatest. The latter observations led to the development of several new AMAA reagents with aryl rings larger than benzene (α-methoxy-α-(2-naphthyl)acetic, α-methoxy-α-(1-naphthyl)acetic, and α-methoxy-α-(9-anthryl)acetic acids), and whose esters had $\Delta\delta^{RS}$ values two or three times higher than those of the corresponding esters of α-methoxy-α-phenylacetic acid (MPA).[4]

Results similar to those found for secondary alcohols would also be expected for amines. However, we have observed very small $\Delta\delta^{RS}$ values for derivatives of amines with several AMAAs and no improvement of signal separation, even with ordinarily highly effective AMAA reagents such as α-methoxy-α-(9-anthryl)acetic acid.[4] These observations suggest that AMAA amides either have a lower energy conformation in which aromatic shielding effects are much reduced or similarly populated shielded and nonshielded conformations (in equilibrium), and so produce small $\Delta\delta^{RS}$ values.

Data in the literature on the conformational preferences of amide and ester functional groups do in fact show clear differences[5]: the COC=O skeletal fragment shows a preference for the *Z* conformation, while the conformational distribution of CNHC=O is much more complex, with *Z*/*E* ratios ranging from 90/10 to 50/50 known.[5] The mobility about the CO–C_α bond, and lack of any strong conformational preference about the NH–CO bond of amides, may well explain the comparatively small values of $\Delta\delta^{RS}$ observed in the NMR spectra of AMAA derivatives of amines.

Shortly before this paper was ready for submission, we became aware of a recent communication by Trost *et al.*[6] which reports ^{1}H NMR data for amides of several α-chiral primary amines with (*R*)- and (*S*)-MPA and proposes an empirical conformational model explaining the chemical shifts observed and how they relate to absolute configuration. In this paper we present theoretical (MM, semiempirical, and *ab initio* calculations) and experimental evidence (DNMR) of the conformational geom-

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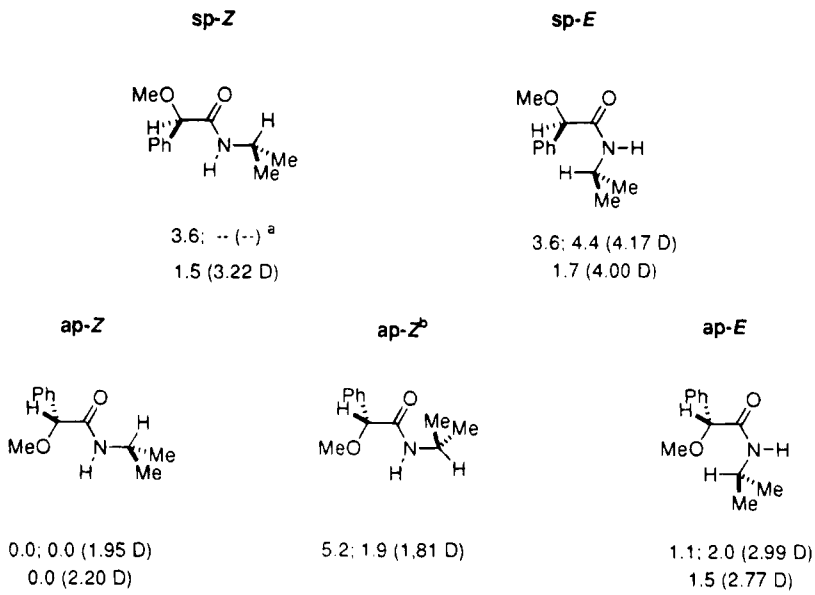

Figure 1. Low energy conformations and corresponding energies (in kcal/mol) and electric dipole moments (in D) of the MPA amide of isopropylamine (**1**). Data: first row gives conformational energy by MM (CVff); energy and dipole moment (in parentheses), both by AM1; second row gives energy and dipole moment (in parentheses), both by PM3. Key: (a) in the course of energy minimization by AM1, *sp-Z* was converted to *ap-Z*; (b) conformer *ap-Z*^{b} is the *ap-Z* with the NH *syn* to C(1′)-H.

etries and corresponding relative populations of amides of MPA and other AMAAs and also describe the use of AMAAs for determination of the absolute configuration of α-chiral primary amines by ^{1}H NMR.

Results and Discussion

Calculations. Our study of the conformational preferences of amides began with Molecular Mechanics (MM) calculations on the MPA derivatives of isopropylamine (**1**): the energies of the rotamers around the C_α–CO, CO–NH, MeO–C_α, and NH–C_α bonds were minimized; the conformations corresponding to energy minima were further refined; and conformers with energies within 5 kcal/mol of the lowest-energy conformer were selected. These calculations revealed that it is the rotamers about the C_α–CO and CO–NH bonds which most influence the conformational energy and that there are two preferred relative orientations—*syn*-periplanar (*sp*) and *anti*-periplanar (*ap*)[7] —of the C_α–OMe and C=O bonds in the low energy conformers, but that two more energy minima are obtained if both *Z* and *E* conformations of the amide fragment are considered (CO–NH *cis* and *trans*). Of these four low energy conformers (shown in Figure 1), all have the O–Me bond *gauche* to C_α–C=O and *anti* to C_α–Ph, the N–H and the C1′–H bonds *anti* (the *gauche* orientation seen in *ap-Z*^{b} is 5.2 kcal/mol higher in energy), and the aryl ring coplanar with the C_α–H bond. MM thus predicts conformational equilibria between four conformers (*sp-Z*, *sp-E*, *ap-Z*, and *ap-E*) for amides, which is double that found for esters.[3] Moreover, the conformational energies calculated by MM indicate that *sp* conformers (both *Z* and *E*) of AMAA amides are higher in energy than *ap* conformers (by ca. 3 kcal/mol); this is the opposite case to AMAA esters, for which the latter conformers are the minor ones.

AM1 semiempirical calculations for **1** supported the MM results and confirmed that the *ap-Z* conformer is lower in energy than the others in Figure 1; the preference for the *Z* conformation about the amide bond (CO–NH *cis*) is also well reproduced (cf. the AM1 value of ca. 2 kcal/mol and MM value of ca. 1.1 kcal/mol). AM1 failed to find an energy minimum corresponding to the *sp-Z* conformer, which was converted to the *ap-Z* conformer in the course of energy minimization; this again suggests that *ap-Z* is the lower energy conformer. Similarly, semiempirical PM3 calculations indicated *ap-Z* to be 1.57 kcal/mol lower in energy than *sp-Z*. The fact that the force-constant matrix had no negative eigenvalues confirmed these four structures to represent energy minima.

Table 1. Conformational Preference of the MPA Amide of Methylamine 2

method	parameter	ap-Z	ap-E	sp-Z	sp-E
MM (CVff)	Δ*E* (kcal/mol)	0.00	1.80	3.65	3.00
AM1	Δ*E* (kcal/mol)	0.00	1.83		4.22
	μ (D)	2.01	2.80		3.43
PM3	Δ*E* (kcal/mol)	0.00	1.52	1.39	1.81
	μ (D)	2.15	2.61	2.76	3.15
ab initio[a]	Δ*E* (kcal/mol)	0.00	6.83	6.48	11.72
ab initio[b]	Δ*E* (kcal/mol)	0.00	5.90	4.65	8.38

[a] RHF/3-21G//RHF/3-21G. [b] RHF/6-31G*//RHF/3-21G; for energy.

To confirm that the above results were not simply due to limitations of the empirical methods, we also performed *ab initio* calculations. Optimization of the geometry of the simplest model system, the amide of methylamine with MPA (**2**), was carried out at RHF level using the 3-21G basis set. Single point calculation of the corresponding conformational energies at RHF level by means of the larger 6-31G* basis set, confirmed that the lowest energy conformation corresponded to the *ap-Z* conformer (the conformational energies obtained by MM, semi-empirical and *ab initio* calculations are collated in Table 1). It is important to note that the semiempirical and *ab initio* calculations predict the same order of relative stabilities for the rotamers (*ap-Z* > *sp-Z* > *ap-E* > *sp-E*).

In summary, all three theoretical approaches predict conformational equilibria between four low energy con-

(7) These conformers are denominated *sp* and *ap* for the sake of convenience. In fact, the MeO and C=O groups form angles of ca. 30° in *sp* conformers and 150° in *ap* conformers.

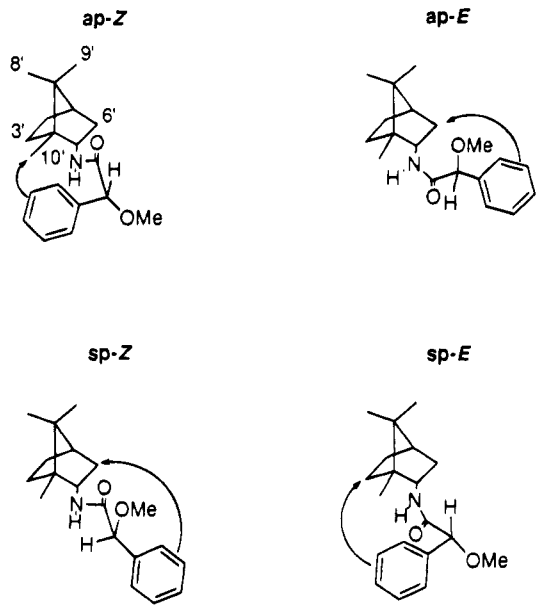

Figure 2. Low energy conformations of the (*R*)-MPA amide of (+)-bornylamine ((*R*)-**3**), with expected aromatic shielding effects shown by arrows.

formers of MPA amides and in every case indicate that these equilibria are biased toward the *ap* conformer, unlike those of esters of MPA and other AMAAs, which favor the *sp* conformation. Thus, if these different conformational preferences of ester and amide derivatives are supported experimentally, the NMR spectra of (*R*)- and (*S*)-MPA derivatives of chiral amines will show the opposite behavior to those of the corresponding chiral alcohols; i.e., the substituent at the chiral center which is shielded by the aromatic ring in the (*R*)-MPA ester will be nonshielded in the (*R*)-MPA amide, and similarly for the (*S*)-derivatives.

Furthermore, analysis of the conformational energy profiles for rotation about the C_α–C(O) and CO–NH bonds showed that the calculated energy barrier to *sp*–*ap* exchange in the former (3.9–5.7 kcal/mol) is much lower than that for *E*–*Z* interconversion in the latter (15.2–17.1 kcal/mol); it is therefore likely that rotation about the CO–NH will be slow on the NMR time scale at low temperatures.

The (*R*)- and (*S*)-MPA amides of (+)-bornylamine (**3**) were selected for ^{1}H NMR studies. According to calculations,[8] the conformational characteristics of (*R*)- and (*S*)-**3**[9] are similar to those of **1** and **2**, but they have the additional advantage that each of the four low energy conformations presents protons (shown for (*R*)-**3** in Figure 2) which are suitably oriented for use as probes of anisotropic aromatic shielding effects,[10] and thus conformational geometries and energy distributions of MPA amides in solution. Calculated shielding increments for

(8) Calculations on other MPA amides indicate that the conformational energy distribution for the amide group is little affected by changes in the amine moiety; it can therefore be expected that the conformational composition of all MPA amides is mainly determined by *ap-Z*, *sp-Z*, and *ap-Z* conformers, as was found for **1** and **2**.

(9) For simplification purposes and to keep coherence with the description of MPA derivatives in our previous papers (refs 3, 4, and 12), from now on we will refer to these compounds by **(R/S)-*n***, where **(R/S)** indicates the configuration at the variable center (i.e., MPA) and ***n*** the digit that corresponds to the parent amine in Figure 4; thus, (*R*)-**3** represents the (*R*)-MPA derivative of amine **3**.

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Table 2. Energies,[a] Electric Dipole Moments[b] (in Parentheses), and Calculated Shielding Increments[c] for the Principal Conformers of the (*R*)- and (*S*)-MPA Amides of (+)-bornylamine (3)

	config	MM[d]	AM1	H(3a′)	H(3e′)	H(6a′)	H(6e′)	Me(10′)
R	ap-Z	0.00	0.00 (2.23)	0.2	0.2			0.35
	ap-E	1.15	2.36 (2.8)			0.5	0.7	
	sp-Z	4.44				0.1	<0.2	
	sp-E	3.36	4.52 (4.3)	0.3	0.2			0.9
S	ap-Z	0.00	0.00 (2.3)			0.35	<0.2	
	ap-E	0.18	2.93 (2.8)					0.75
	sp-Z	2.82		0.75	0.4			0.35
	sp-E	3.42	4.39 (4.2)			0.6	1.5	

[a] In kcal/mol. [b] In D. [c] In ppm, according to semiclassical theory.[10] [d] CV force field.[15]

Table 3. Selected NMR Data and $\Delta\delta^{RS}$ Values (ppm) for Amides of (+)-Bornylamine with (*R*)- and (*S*)-Arylmethoxyacetic Acids (Ar is Phenyl (3), 1-Naphthyl (1-N; 4), or 9-Anthryl (9-A; 5)) in 4:1 CS_2/CD_2Cl_2

Ar	config	H(3a′)	H(3e′)	H(6a′)	H(6e′)	Me(8′)	Me(9′)	Me(10′)
	(*R*)-**3**	1.314	1.464	0.821	2.310	0.912	0.847	0.574
Ph	(*S*)-**3**	1.370	1.530	0.689	2.221	0.919	0.873	0.786
	$\Delta\delta^{RS}$	−0.056	−0.066	0.132	0.089	−0.007	−0.024	−0.212
	(*R*)-**4**			0.864	2.342	0.908	0.860	0.602
1-N	(*S*)-**4**			0.751	2.231	0.911	0.882	0.813
	$\Delta\delta^{RS}$			0.112	0.110	−0.003	−0.022	−0.211
	(*R*)-**5**	1.501	1.789	0.871	2.372	0.926	0.896	0.698
9-A	(*S*)-**5**	1.443	1.609	0.843	2.310	0.925	0.908	0.839
	$\Delta\delta^{RS}$	0.062	0.180	0.031	0.059	0.001	−0.012	−0.141

amides (*R*)-**3** and (*S*)-**3**, and other pertinent data, are given in Table 2.

^{1}H NMR Studies. Selected room-temperature ^{1}H NMR data for the MPA derivatives (*R*)-**3** and (*S*)-**3** are listed in Table 3. Among these data, the greater aromatic shielding observed for Me(10′) of (*R*)-**3** compared to that for Me(10′) in (*S*)-**3** suggests that *ap-Z* is the major conformer (Figure 2); the high field shifts observed for H(6′) in (*S*)-**3** compared to (*R*)-**3** also support this conclusion.

In order to further study the conformational equilibria, geometries, and energies of the amide derivatives, DNMR experiments were performed: by decreasing the temperature of the NMR probe, the rates of chemical exchange and relative populations of conformers in equilibrium were modified and consequently the observed NMR signals and their chemical shifts.

At ca. 233 K, the broad NH signals seen in the room-temperature spectrum of both (*R*)-**3** and (*S*)-**3** collapsed, and two sets of doublets were observed instead (integral ratios were 23:1 for (*R*)-**3** and 14:1 for (*S*)-**3**). At 156 K, the Me(10′) signal shifted to higher field (by 0.026 ppm in (*R*)-**3** and 0.058 ppm in (*S*)-**3**); the H(6a′) signal shifted to lower field (by 0.035 ppm in (*R*)-**3** and 0.067 ppm in (*S*)-**3**), and H(6e′) shifted to higher field (by 0.021 ppm) in (*S*)-**3** only.

Bearing in mind the high barrier to rotation about the CO–NH bond calculated above, we deduce that the collapse of signals observed at ca. 233 K, and the eventual appearance of two sets of signals of unequal intensities at 156 K, are due to slow exchange between *E* and *Z* forms of the major conformer. Precise assignment of each set of signals was based on our calculations (Table 1) and analysis of the experimental data,[5] which indicated that the major peaks were due to the *Z* form and the minor peaks to the *E* form. Line shape evolution of the major signals is indicative of chemical exchange between *ap-Z* and *sp-Z* forms; comparison of the aromatic shielding effects in the (*R*)- and (*S*)-derivatives, particularly the

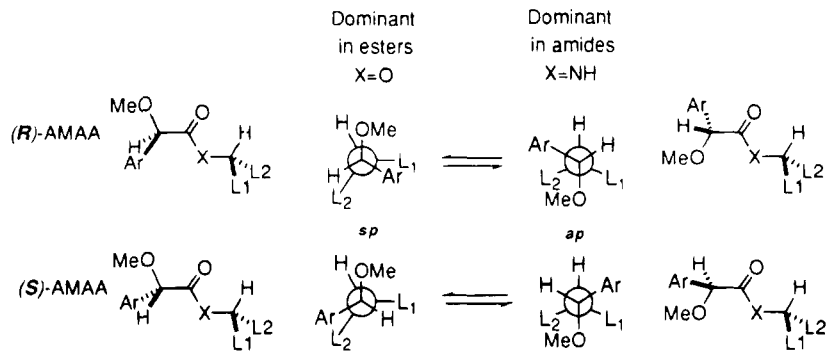

Figure 3. Conformational models for determination of the absolute configuration of MPA derivatives of alcohols and amines: Newman projections showing the orientation of the affected substrate groups (L_1 and L_2) relative to the aromatic ring (Ar).

high shifts of the signals due to Me(10′) in (*R*)-**3** and H-(6′) in (*S*)-**3** compared to those in the corresponding diastereoisomers, confirmed that *ap-Z* is the major conformer present (Figure 2).

Evidence for the proposed conformational geometry of the low energy conformers was also obtained from low-temperature NOESY experiments. For the major component, there were cross-relaxation peaks between OMe and NH protons and between Me(10′) and aryl ring protons: such cross peaks are consistent with a *syn*-periplanar arrangement of the N−H and C_α−OMe bonds and Me(10′) and aryl ring protons in close proximity to each other and thus confirm that the *ap-Z* conformer is the dominant one. In addition, nuclear Overhauser enhancements observed between N*H* and H(3a′) and H(6a′) protons are consistent with the *anti* orientation of the N−H and C(1′)−H bonds which was predicted by calculation.

Because of the very low population of the minor conformer, only the C_αH proton could be assigned with any confidence: C_αH in the minor conformer resonates at higher field (δ = 3.7 ppm) than in the major conformer (δ = 4.4 ppm) due to the stronger shielding effect of the carbonyl group in the *ap-E* conformer compared to the exchange averaged shielding effects due to this group in *ap-Z* and *sp-Z*.

Having established the main conformers present in solution, the room-temperature ^{1}H NMR spectrum of (*R*)-**3** and (*S*)-**3** can be interpreted as being predominantly due to *ap-Z*, with a significant contribution from *sp-Z*, and very small contributions from *ap-E* and *sp-E*. This interpretation is in agreement with the relative energies obtained for these conformers by comparison of calculated (semiclassical model, Table 2) and experimental aromatic shielding increments for Me(10′) of (*R*)- and (*S*)-**3**:[11] these indicate that *ap-Z* is more stable than *sp-Z* by ca. 0.4 kcal/mol, for both (*S*)- and (*R*)-MPA amides, and more stable than *ap-E* by ca. 1.1 and 1.3 kcal/mol, for (*S*)- and (*R*)-MPA amides, respectively. Furthermore, the latter differences are in reasonable agreement with the calculated energy data (Table 1).

DNMR experiments similar to those above were carried out on amides of AMAAs having larger aryl rings (α-methoxy-α-(2-naphthyl)acetic acid, α-methoxy-α-(1-naphthyl)acetic acid, and α-methoxy-α-(9-anthryl)acetic acid). In all cases, the shielding effects observed are similar to those of MPA amides (Table 3), and there are no remarkable changes in the spectra upon decreasing the probe temperature. Analysis of the evolution of line shape with temperature led us to conclude that these amides exist in solution as similar populations of *sp* and *ap* conformers in equilibrium and that *E* conformers contribute significantly to the observed ^{1}H NMR spectra.

The Prediction of the Absolute Stereochemistry of α-Chiral Primary Amines. The method for determination of the absolute configuration of alcohols and amines by NMR is based on two main factors: (a) the conformational preference of the functional group (ester or amide) and (b) the selective influence of the aromatic system on certain groups of the substrate. In the case of AMAA derivatives of alcohols,[3] an appreciation of the conformational equilibria of the ester group leads to a model comprising *sp* and *ap* conformers, of which the former is dominant in solution, and thus determines the appearance of the NMR spectra of ester derivatives (Figure 3).[12]

In the case of the MPA and other AMAA derivatives of secondary amines, the distribution of conformational energies is different from that of esters, and the *ap-Z* rather than the *sp-Z* conformer is the more abundant one. Interpretation of the chemical shifts of amide derivatives of MPA therefore requires a different conformational model to that for esters. Figure 3 illustrates both situations: the *sp* conformer is the major one in MPA and AMAA esters, and therefore L_1 in (*R*)- and L_2 in (*S*)-MPA esters are shifted to high field by the aromatic shielding effect; in MPA and AMAA amides, the *ap-Z* conformer is now more populated than the *sp* conformer, and L_2 in (*R*)- and L_1 in (*S*)-MPA amides experience the aromatic shielding effects and thus resonate at higher field. The different shifts of the L_1 and L_2 groups in NMR spectra allow determination of their relative orientations, and thus the absolute configuration at the asymmetric center of the alcohol or amine substrate.

As to why $\Delta\delta^{RS}$ values for amides derived from AMAAs with larger aryl rings are no better than those obtained for MPA derivatives (Table 3), we suggest that, as occurred for the corresponding esters,[3] steric and electrostatic interactions between the larger aryl ring and the α-carbonyl group destabilize the *ap* arrangement. This would increase the abundance of the *sp* form, resulting in closer populations of *sp* and *ap* conformers.

(11) $\Delta\delta^R$ = 0.24 ppm and $\Delta\delta^S$ = 0.03 ppm. These experimental shielding increments are the difference between the chemical shifts of Me(10′) in (*R*)-**3**, and (*S*)-**3**, respectively, with those of the same protons in the (*S*)-MPA ester of (*R*)-(+)-borneol at *T* = 153 K (δ = 0.817 ppm); at this temperature the ester is almost exclusively in the *sp* form and aromatic shielding effects do not contribute appreciable to the chemical shift.

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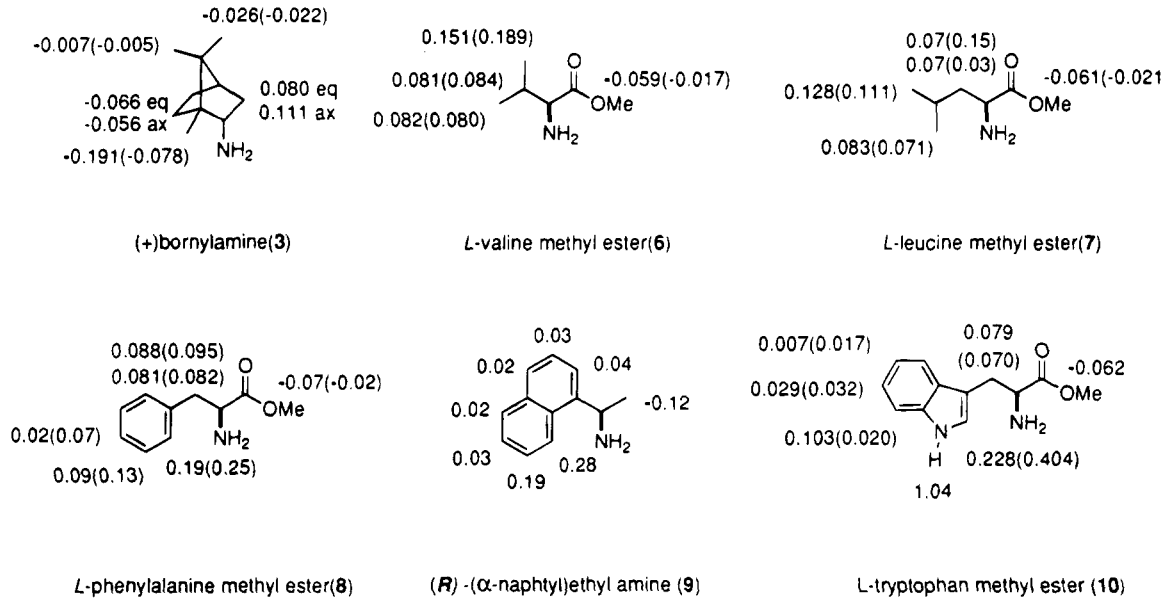

Figure 4. Selected $\Delta\delta^{RS}$ values (ppm) obtained from ^{1}H NMR spectra of the amides of the illustrated amines with (*R*)- and (*S*)-MPA (in $CDCl_3$). For comparison, values obtained with MTPA are shown in parentheses.[13]

In addition, since the conformational flexibility around the NH–CO bond of amides is greater than that of esters, the conformational equilibria of the former derivatives will be more complex, and interpretation of the NMR spectra less straightforward than for ester derivatives.

The general applicability of this model to determination of the absolute configuration of amines was confirmed by testing a series of chiral amines having a wide variety of substituents at the chiral center, and therefore an equally wide variety of possible steric and polar effects on the conformational equilibria of the amide array. In addition to (+)-bornylamine, the substrates chosen were L-valine methyl ester (**6**), L-leucine methyl ester (**7**), L-phenylalanine methyl ester (**8**), (*R*)-(α-naphthyl)ethyl amine (**9**), and L-tryptophan methyl ester (**10**). A selection of the $\Delta\delta^{RS}$ values obtained for various protons of these amines is shown in Figure 4.

These experimental results and those recently reported[6] prove that the configuration deduced using the model presented in this paper is coincident in all cases with the absolute stereochemistry of the starting amine and that different substituents at the amine part of the molecule do not affect the reliability of the conformational model. This applies too to compounds **6**, **7**, **8**, and **10**, bearing a polar unit such as the methoxycarbonyl group. The lack of, or very small, influence of this group on the conformational equilibrium around the AMAA have been observed before in the cases of the MTPA derivatives of α-amino esters and the MPA derivatives of α-hydroxy esters. Therefore, the conformational composition of MPA and the other AMAA amides seems to be essentially unaffected by the nature of the amine, and so, the chirality at the stereogenic center of an α-chiral primary amine can be obtained by interpretation of the chemical shifts of the (*R*)- and (*S*)-MPA derivatives according to the model depicted in Figure 3.

The Effect of the Polarity of the Solvent on the $\Delta\delta^{RS}$ Values. We have shown that the ability of NMR to differentiate between corresponding groups of the alcohol or amine moiety of (*R*)- and (*S*)-MPA derivatives is related to the equilibrium between *ap* and *sp* conformers. According to AM1, the various low energy conformations of these derivatives also present quite different dipole moments (Figure 1): the major conformer (*ap-Z*) has a smaller dipole moment than all the other principal conformers. If experimental dipole moments were in agreement with the AM1 predicted values, this could open up a way of fine tuning the conformational equilibria of these derivatives in solution: since the more polar, minor conformers would be less stabilized in nonpolar solvents,[14] recording the NMR spectrum in such solvents should bias the conformational equilibrium in favour of the *ap-Z* conformer and cause the value of $\Delta\delta^{RS}$ to increase.

NMR experiments on several (*R*), and (*S*)-MPA amides were found to be in full agreement with the prediction, and $\Delta\delta^{RS}$ showed a remarkable variation with the polarity of the solvent: Smaller values were obtained when the spectra were recorded in polar solvents and larger values in nonpolar ones. Experimental data showing that dependence for selected protons of compounds **3**, **6**, and **10** are presented in Figure 5.

Those spectra were taken in dilute solutions (ca. 8 mg/mL in chloroform), and so no great influence of concentration on the chemical shifts in nonpolar solvents could be expected. Nevertheless, the NMR spectra of compounds (*R*)-**7** and (*S*)-**7** were taken in CS_2 in a wide range of concentrations and found to produce practically constant chemical shifts and $\Delta\delta^{RS}$ values at 1.56, 9.36, and 15.60 mg/mL, respectively: $\Delta\delta^{RS}$ OMe, 0.006; $\Delta\delta^{RS}$ Me_a, 0.108; $\Delta\delta^{RS}$ Me_b, 0.154.

This definitively proves that the larger $\Delta\delta^{RS}$ values obtained in non polar solvents are not due to a concentration effect but the result of a selective stabilization of the less polar conformer (*ap-Z*).

Thus, nonpolar solvents must be recommended with preference to polar ones when this method is to be used to determine the absolute configuration, enantiomeric excess, or purity of chiral amines. Furthermore, these

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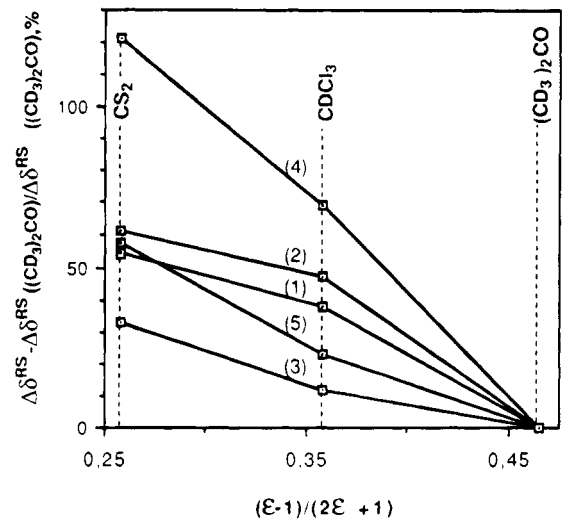

Figure 5. Plots showing the dependence of the $\Delta\delta^{RS}$ (expressed as percentage of $\Delta\delta^{RS}$ in $(CD_3)_2CO$) *versus* the polarity of the solvent (as $(\epsilon - 1)/(2\epsilon + 1)$, where ϵ is dielectric constant): line 1 corresponds to Me(10′) of **3**; lines 2 and 3 correspond to H(3′) and H(4′) of **6**, respectively; and lines 4 and 5 correspond to H(2′) and H(7′) of **10**, respectively.

results constitute an additional proof of the validity of the conformational analysis presented in this paper.

Conclusions

Summing up, amides of MPA and other AMAAs exist in solution in a conformational equilibrium principally involving two conformers. The most populated conformer (*ap-Z*) has its C_αOMe and C=O groups *anti*-periplanar, and the second most highly populated conformer (*sp-Z*) has these groups *syn*-periplanar; in both these conformers, the aryl ring is approximately coplanar with the C_α–H bond, and the CONH fragment is predominantly in the *Z* conformation. In keeping with previous studies on AMAA esters, the *ap*–*sp* exchange is the principal process in the equilibrium, but in amides the distribution of conformational energies is different to that of esters and the *ap* conformation is more stable than the *sp* conformation. As a consequence of this, the use of AMAA derivatives of amines for determination of their absolute configuration by ^{1}H NMR requires reversal of the rules established for AMAA esters. The validity of the conformational model described in this work, and the general applicability and accuracy of the NMR method proposed for determination of the absolute configuration of α-chiral primary amines have been established. Our results illustrate the usefulness of the conformationally-mobile model recently proposed for esters,[3,12] show that it is the relative populations of certain conformers that determine the appearance of the NMR spectra of AMAA amides, and provide theoretical and additional experimental evidence in support of the empirical results recently described by Trost *et al.*[6]

Experimental Section

Computational Methods. Molecular mechanics, AM1 (PM3), and *ab initio* molecular orbital calculations were performed by the Insight II package on a Silicon Graphics Iris computer.[15] Initial molecular geometries originated from the Builder Module of Insight II; 3D coordinates were then generated from the bond lengths, bond angles, and dihedral angles by the DG-II package.[16] The conformational space of each compound was scanned by MM (CV force field[17]) optimization of the sterically allowed conformations around key single bonds. Analysis of conformational transitions, identification of the low energy conformers, and calculation of the energy barriers between these conformers were all carried out by MM with an additional harmonic term of the form $k(1 + \cos(n\theta - \theta_0)$ included in the force field. The energies of conformations were minimized in Cartesian coordinate space by the block-diagonal Newton–Raphson method; minima corresponded to root mean square (rms) energy gradients <0.001 kcal/mol Å. The ground state energies of the geometries were then calculated by AM1[18a] and PM3[18b,c] using the MOPAC 6.0 program. For all compounds, full geometry optimization used the Broyden–Fletcher–Goldfarb–Shanno (BFGS) method and the PRECISE and MMOK options.[18a,b] All low energy conformers were characterized by calculating the full Hessian matrix, diagonalizing it and establishing that there was no negative eigenvalue [18d]. *Ab initio* electronic structure calculations (at the restricted Hartree–Fock level of theory) were performed using GAUSSIAN 92.[19] During the *ab initio* calculations all internal coordinates were optimized by Berny algorithm, and convergence was tested against criteria for the maximum force component, rms force, maximum step component, and rms step. No symmetry options were implemented.

NMR Spectroscopy. ^{1}H and ^{13}C NMR spectra of samples in 4:1 CS_2/CD_2Cl_2 (4 mg in 0.5 mL) were recorded at 500 and 250 MHz.

1D ^{1}H NMR spectra. Size 32 K, pulse length 2.8 μs (30°), 16 acquisitions.

1D ^{13}C NMR spectra. Size 64 K, pulse length 3.5 μs (30°), 1024 acquisitions.

2D COSY spectra. Sequence: D1-90-*t*1-90-t2; relaxation delay *D*1 = 0.5 s; 90° pulse 8.5 μs.

2D NOESY spectrum. Sequence: D1-90-*t*1-90-τ_{mix}-90-*t*2; relaxation delay *D*1 = 0.5 s; mixing time (τ_{mix}) 0.5 s; 90° pulse 8.5 μs; TPPI-mode, NS = 64.

General Procedure. Preparation of diastereomeric amides from either the free amine or the amine salt and *O*-methylmandelic, α-methoxy-α-(1-naphthyl)acetic, and α-methoxy-α-(9-anthryl)acetic acid was carried out with DCC (free amine) or DCC and DMAP (amine salt).[20] The reaction mixture was filtered to remove the dicyclohexylurea and the amide purified by flash chromatography on silica gel eluting with dichloromethane.

(+)-Bornyl-(*R*)-2-methoxy-2-phenyl acetamide ((*R*)-3): [α] = −47.61 (*c* = 0.015, EtOH); mp 65 °C (EtOH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 7.30–7.20 (m, 5H), 6.57 (db, *J* = 6.6 Hz, 1H), 4.43 (s, 1H), 4.10 (dddd, *J* = 2.3, 4.5, 9.4, 11.3 Hz, 1H), 3.30 (s, 3H), 2.31 (dddd, *J* = 3.4, 4.6, 11.0, 16.1 Hz, 1H), 1.77 (tq, *J* = 12.2, 4.3 Hz, 1H), 1.65 (t, *J* = 4.7 Hz, 1H), 1.49 (ddd, *J* = 4.5, 9.5, 13.8 Hz, 1H), 1.33 (dddd, *J* = 2.3, 4.7, 12.0, 14.4 Hz, 1H), 1.21 (ddd, 4.7, 9.5, 12.5 Hz, 1H), 0.91 (s, 3H), 0.85 (s, 3H), 0.82 (dd, *J* = 4.7, 13.4 Hz, 1H), 0.60(s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.79, 137.52, 128.50, 128.32, 126.98, 84.06, 57.01, 52.88 49.58, 48.04, 44.89, 37.39, 28.29, 27.89, 19.67, 18.50, 13.41; IR (NaCl) 3421, 3324, 3065,

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2945, 2886, 1667, 1523, 1460, 1379, 1312, 1245, 1197, 1101, 989, 727, 692 cm^{-1}; MS (EI) m/z 301 (M^+).

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 76.64; H, 9.02; N, 4.64; O, 9.70. Found: C, 76.61; H, 9.03; N, 4.65; O, 9.71.

(+)-Bornyl-*(S)*-2-methoxy-2-phenyl acetamide (***(S)*-3**): [α] = +63.66 (c = 0.006, EtOH); mp 115 °C (Cl_3CH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 7.30−7.20 (m, 5H), 6.4 (br, 1H), 4.43 (s, 1H), 4.10 (dddd, J = 2.3, 4.5, 9.4, 11.3 Hz, 1H), 3.34 (s, 3H), 2.22 (dddd, J = 3.4, 4.6, 11.0, 16.1 Hz, 1H), 1.76 (tq, J = 12.2, 4.3 Hz, 1H), 1.61 (t, J = 4.7 Hz, 1H), 1.52 (ddd, J = 4.5, 9.5, 13.8 Hz, 1H), 1.37 (dddd, J = 2.3, 4.7, 12.0, 14.4 Hz, 1H), 1.18 (ddd, 4.7, 9.5, 12.5 Hz, 1H), 0.92 (s, 3H), 0.87 (s, 3H), 0.69 (dd, J = 4.5, 13.2 Hz, 1H), 0.77 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.46, 137.34, 128.49, 128.30, 126.87, 83.93, 57.40, 53.18, 49.54, 48.15, 44.86, 37.47, 28.31, 19.74, 18.52, 13.65; IR (NaCl) 3420,3306, 3069, 2947, 2884, 2826, 1663, 1525, 1458, 1379, 1312, 1246, 1196, 104, 989, 790, 731, 696 cm^{-1}; MS (EI) m/z 301 (M^+).

Anal. Calcd for $C_{19}H_{27}NO_2$: C, 76.64; H, 9.02; N, 4.64; O, 9.70. Found: C, 76.61; H, 9.04; N, 4.67; O, 9.68.

(+)-Bornyl-*(R)*-2-methoxy-2-(1-napthyl)acetamide (***(R)*-4**): [α] = −71.47 (c = 0.0115); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 8.17−8.12 (m, 1H), 7.79−7.72 (m, 2H), 7.43−7.35 (m, 4H), 6.78 (db, J = 7.7 Hz, 1H), 5.04 (s, 1H), 4.14 (dddd, J = 2.3, 4.5, 9.2, 11.3 Hz, 1H), 3.30 (s, 3H), 2.34 (dddd, J = 3.4, 4.6, 11.0, 16.1 Hz, 1H), 1.80 (tq, J = 12.2, 4.3 Hz, 1H), 1.66 (t, J = 4.7 Hz, 1H), 1.60 (ddd, J = 4.5, 9.5, 13.8 Hz, 1H), 1.40 (dddd, J = 2.3, 4.7, 12.0, 14.4 Hz, 1H), 1.25 (ddd, 4.7, 9.5, 12.5 Hz, 1H), 0.91 (s, 3H), 0.86 (s, 3H), 0.86 (dd, J = 4.5, 13.2 Hz, 1H), 0.60 (s, 3H); ^{13}C NMR (62.9 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 169.74, 134.76, 134.00, 132.25, 129.92, 129.45, 127.62, 126.85, 126.69, 125.84, 125.44, 83.86, 57.51, 50.49, 48.91, 46.23, 38.55, 29.73, 29.15, 20.75, 19.48, 14.49; IR (NaCl) 3425, 3330, 3050, 2941, 1885, 1675, 1518, 1467, 1378, 1314, 1239, 1182, 1098, 985, 784 cm^{-1}; MS (EI) m/z 351 (M^+).

Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.48; H, 8.30; N, 3.98; O, 9.23. Found: C, 78.45; H, 8.30; N, 3.96; O, 9.29.

(+)-Bornyl-*(S)*-2-methoxy-2-(1-napthyl)acetamide (***(S)*-4**): [α] = +76.86 (c = 0.0115, EtOH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 8.11−8.06 (m, 1H), 7.76−7.69 (m, 2H), 7.41−7.35 (m, 4H), 6.65 (db, J = 7.7 Hz, 1H), 5.08 (s, 1H), 4.08 (dddd, J = 2.3, 4.5, 9.2, 11.3 Hz, 1H), 3.34 (s, 3H), 2.23 (dddd, J = 3.4, 4.6, 11.0, 16.1 Hz, 1H), 1.79 (tq, J = 12.2, 4.3 Hz, 1H), 1.63 (t, J = 4.7 Hz, 1H), 1.56 (ddd, J = 4.5, 9.5, 13.8 Hz, 1H), 1.40 (dddd, J = 2.3, 4.7, 12.0, 14.4 Hz, 1H), 1.22 (ddd, 4.7, 9.5, 12.5 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 3H), 0.75 (dd, J = 4.5, 13.2 Hz, 1H), 0.81 (s, 3H); ^{13}C NMR (62.9 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 169.60, 134.61, 133. 93, 132.27, 129.74, 129.30, 126.75, 126.74, 126.55, 125.76, 125.26, 83.16, 57.65, 50.15, 48.80, 46.07, 38.43, 29.57, 29.12, 28.17, 20.66, 19.38, 14.57; IR (NaCl) 3420, 3334, 3055, 2944, 2880, 1673, 1521, 1467, 1379, 1315, 1240, 1101, 989 cm^{-1}; MS (EI) m/z 351 (M^+).

Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.48; H, 8.30; N, 3.98; O, 9.23. Found: C, 78.50; H, 8.27; N, 3.98; O, 9.25.

(+)-Bornyl-*(R)*-2-methoxy-2-(9-anthryl)acetamide (***(R)*-5**): [α] = −48.88 (c = 0.0045, EtOH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 8.39−8.29 (m, 3H), 7.98−7.90 (m, 2H), 7.45−7.33 (m, 4H), 7.04 (b, 1H), 6.01(s, 1H), 4.21 (dddd, J = 2.3, 4.5, 9.2, 11.3 Hz, 1H), 3.19 (s, 3H), 2.37 (dddd, J = 3.4, 4.6, 11.0, 16.1 Hz, 1H), 1.86 (tq, J = 12.2, 4.3 Hz, 1H), 1.79 (ddd, J = 4.5, 9.5, 13.8 Hz, 1H), 1.69 (t, J = 4.7 Hz, 1H), 1.50 (dddd, J = 2.3, 4.7, 12.0, 14.4 Hz, 1H), 1.32 (ddd, 4.7, 9.5, 12.5 Hz, 1H), 0.93 (s, 3H), 0.90 (s, 3H), 0.87 (dd, J = 4.5, 13.2 Hz, 1H), 0.70 (s, 3H); ^{13}C NMR (62.9 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 169.96, 134.44, 132.05, 131.83, 129.98, 129.64, 128.67, 127.79, 126.73, 125.69, 125.07, 123.77, 78.64, 57.10, 50.44, 48.85, 46.13, 38.49, 29.70, 29.16, 20.67, 19.38, 14.50; IR (NaCl) 3505, 3416, 3049, 2944, 2879, 1670, 1520, 1455, 1379, 1314, 1100, 1020, 888, 749, 637 cm^{-1}; MS (EI) m/z 401 (M^+).

Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.77; N, 3.48; O, 7.99. Found: C, 80.74; H, 7.75; N, 3.49; O, 8.02.

(+)-Bornyl-*(S)*-2-methoxy-2-(9-anthryl)acetamide (***(S)*-5**): [α] = +34 (c = 0.003, EtOH); ^{1}H NMR (500.13 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 8.38−8.26 (m, 3H), 7.96−7.91 (m, 2H), 7.43−7.35 (m, 4H), 6.99 (b, 1H), 6.04 (s, 1H), 4.15 (dddd, J = 2.3, 4.5, 9.2, 11.3 Hz, 1H), 3.21 (s, 3H), 2.31 (dddd, J = 3.4, 4.6, 11.0, 16.1 Hz, 1H), 1.84 (tq, J = 12.2, 4.3 Hz, 1H), 1.68 (t, J = 4.7 Hz, 1H), 1.61 (ddd, J = 4.5, 9.5, 13.8 Hz, 1H), 1.45 (dddd, J = 2.3, 4.7, 12.0, 14.4 Hz, 1H), 1.30 (ddd, 4.7, 9.5, 12.5 Hz, 1H), 0.93 (s, 3H), 0.91 (s, 3H), 0.84 (dd, J = 4.5, 13.2 Hz, 1H), 0.84 (s, 3H); ^{13}C NMR (62.9 MHz, CS_2 + Cl_2CD_2 (4:1)) δ 169.95, 134.68, 132.05, 131.86, 129.99, 129.65, 128.75, 127.80, 126.77, 125.67, 124.97, 78.57, 57.20, 49.97, 48.75, 46.10, 38.51, 29.63, 29.21, 20.66, 19.39, 14.54; IR (NaCl) 3396, 3314, 3054, 2997, 2940, 2829, 1666, 1516, 1443, 1346, 1206, 1100, 1001, 912, 738, 700 cm^{-1}; MS (EI) m/z 401 (M^+).

Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.77; N, 3.48; O, 7.99. Found: C, 80.77; H, 7.78; N, 3.46; O, 7.99.

(S)*-*N*-(*(R)*-2-Methoxy-2-phenylacetyl)valine methyl ester** ((R)*-6**): [α] = −24.38 (c = 0.029, EtOH); mp 70 °C (EtOH); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.43−7.28 (m, 3H), 7.22 (br, 1H), 4.66 (s, 1H), 4.54 (dd, J = 4.4, 9.4 Hz, 1H), 3.70 (s, 3H), 3.39 (s, 3H), 2.24 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.12, 170.53, 136.91, 128.57, 127.32, 83.85, 57.18, 56.63, 52.01, 31.21, 19.00, 17.74; IR (NaCl) 3420, 3319, 3070, 3027, 2961, 2930, 2832, 1741, 1683, 1516, 1451, 1313, 1265, 1205, 1151, 1099, 993, 855, 735, 697 cm^{-1}; MS (EI) m/z 279 (M^+).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.57; N, 5.01; O, 22.92. Found: C, 64.48; H, 7.58; N, 5.01; O, 22.93.

(S)*-*N*-(*(S)*-2-Methoxy-2-phenylacetyl)valine methyl ester** ((S)*-6**): [α] = +49.79 (c = 0.0245, EtOH); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.43−7.28 (m, 5H), 7.23 (br, 1H), 4.63 (s, 1H), 4.55 (dd, J = 4.4, 9.4, 1H), 3.76 (s, 3H), 3.41 (s, 3H), 2.16 (m, 1H), 0.87 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.44, 170.74, 137.20, 128.59, 128.46, 126.87, 83.99, 57.36, 56.37, 52.09, 31.37, 18.85, 17.58; IR (NaCl) 3411, 3327, 3068, 3037, 2958, 2828, 1738, 1681, 1512, 1448, 1347, 1312, 1264, 1202, 1150,1098, 994, 731, 695 cm^{-1}; MS (EI) m/z 279 (M^+).

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.57; N, 5.01; O, 22.92. Found: C, 64.48; H, 7.55; N, 5.03; O, 22.94.

(S)*-*N*-(*(R)*-2-Methoxy-2-phenylacetyl)leucine methyl ester** ((R)*-7**): [α] = −57.11 (c = 0.021, EtOH); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.47−7.23 (m, 5H), 7.11 (db, J = 8.6 Hz, 1H), 4.63 (s, 1H), 4.63 (dd, J = 5.0, 8.6, 1H), 3.67 (s, 3H), 3.36 (s, 3H), 1.68 (m, 3H), 0.96 (d, J = 6.0 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.09, 170.37, 136.83, 128.54, 127.36, 83.72, 57.00, 52.09, 50.21, 41.61, 24.84, 22.74, 21.76; IR (NaCl) 3402, 3306, 3070, 3033, 2948, 2875, 1741, 1675, 1520, 1449, 1354, 1265, 1204,1160, 1101, 985, 742, 691 cm^{-1}; MS (EI) m/z 293 (M^+).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.89; N, 4.77; O, 21.82. Found: C, 65.53; H, 7.90; N, 4.74; O, 21.83.

(S)*-*N*-(*(S)*-2-Methoxy-2-phenylacetyl)leucine methyl ester** ((S)*-7**): [α] = +8 (c = 0.023, EtOH); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.42−7.27 (m, 5H), 7.09 (db, J = 8.6 Hz, 1H), 4.62 (s, 1H), 4.61 (dd, J = 5.0, 8.6, 1H), 3.74 (s, 3H), 3.40 (s, 3H), 1.74−1.45 (m, 3H), 0.88 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.0 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.38, 170.51, 136.99, 128.52, 128.43, 126.87, 83.78, 57.32, 52.17, 50.11, 41.44, 24.76, 22.63, 21.74; IR (NaCl) 3410, 3315, 3070, 3027, 2954, 2948, 2875, 2839, 1741, 1675, 1518, 1448, 1352, 1263, 1205, 1161, 1100, 998, 730, 699 cm^{-1}; MS (EI) m/z 293 (M^+).

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.89; N, 4.77; O, 21.82. Found: C, 65.52; H, 7.89; N, 4.75; O, 21.84.

(S)*-*N*-(*(R)*-2-Methoxy-2-phenylacetyl)phenylalanine methyl ester** ((R)*-8**): [α] = −46.26 (c = 0.013, EtOH); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.43−7.10 (m, 11H), 4.86 (dt, J = 8.5, 6.5 Hz, 1H), 4.58 (s, 1H), 3.68 (s, 3H), 3.28 (s, 3H), 3.17 (dq, J = 6.5, 14.1 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.69, 170.27, 136.79, 135.96, 129.24, 128.51, 127.22, 127.13, 83.74, 57.20, 52.68, 52.15, 37.90; IR (NaCl) 3403, 314, 3021, 2930, 2863, 1741,1676, 1512, 1446, 1355, 1205, 1096, 821, 741, 700 cm^{-1}; MS (EI) m/z 327 (M^+).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.45; N, 4.27; O, 19.56. Found: C, 69.70; H, 6.43; N, 4.28; O, 19.59.

(S)*-*N*-(*(S)*-2-Methoxy-2-phenylacetyl)phenylalanine methyl ester** ((S)*-8**): [α] = +24.66 (c = 0.0075, EtOH); mp 119 °C (EtOH); ^{1}H NMR (250.13 MHz, $CDCl_3$) δ 7.37−6.91 (m, 11H), 4.90 (dt, J = 8.5, 6.5 Hz, 1H), 4.61 (s, 1H), 3.75 (s, 3H), 3.36 (s, 3H), 3.09 (dq, J = 6.5, 13.9 Hz, 2H); ^{13}C NMR

(62.9 MHz, $CDCl_3$) δ 171.87, 170.28, 136.78, 135.64, 129.26, 128.46, 128.35, 126.98, 126.94, 83.72, 57.24, 52.38, 52.21, 37.68; IR (NaCl) 3580, 3345, 3033, 2960, 2918, 1741, 1652, 1503, 1441, 1374, 1273, 1175, 1079, 770, 742, 698 cm^{-1}; MS (EI) m/z 327 (M^+).

Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.45; N, 4.27; O, 19.56. Found: C, 69.73; H, 6.44; N, 4.25; O, 19.58.

(R)*-(+)-1-(1-Naphthylethyl)-*(R)*-2-methoxy-2-phenylacetamide** ((R)*-9**)SPCLN [α] = −24.40 (c = 0.029, EtOH); mp 131 °C (EtOH); ^1H NMR (250.13 MHz, $CDCl_3$) δ 8.18 (d, J = 8.1 Hz, 1H), 7.92−7.80 (m, 2H), 7.61−7.31 (m, 9H), 7.04 (db, J = 7.8 Hz, 1H), 5.96 (dq, J = 7.8, 6.8 Hz, 1H), 4.62 (s, 1H), 3.24 (s, 3H), 1.64 (d, J = 6.8 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.54, 138.34, 137.23, 133.95, 131.19, 128.81, 128.61, 128.46, 127.05, 126.55, 125.90, 125.26, 123.55, 122.69, 83.72, 57.16, 44.06, 20.75; IR (NaCl) 3402, 3326, 3064, 2979, 2931, 662, 1513, 1444, 189, 1100, 1024, 788, 706 cm^{-1}; MS (EI) m/z 319 (M^+).

Anal. Calcd for $C_{21}H_{21}NO_2$: C,78.97; H, 6.62; N, 4.38; O, 10.02. Found: C, 78.97; H, 6.60; N, 4.37; O, 10.06.

(R)*-(+)-1-(1-Naphthylethyl)-*(S)*-2-methoxy-2-phenylacetamide** ((S)*-9**): [α] = +53.46 (c = 0.0315, EtOH); mp 98 °C (EtOH); ^1H NMR (250.13 MHz, $CDCl_3$) δ 7.93−7.77 (m, 3H), 7.57−7.27 (m, 9H), 7.04(db, J = 7.8 Hz, 1H), 5.92 (dq, J = 7.8, 6.8 Hz, 1H), 4.68 (s, 1H), 3.30 (s, 3H), 1.76(d, J = 6.8 Hz, 3H): ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.32, 137.90, 136.91, 133.90, 131.18, 128.60, 128.42, 127.26, 126.38, 125.78, 125.06, 123.60, 122.54, 83.82, 56.77, 44.10, 20.39; IR (NaCl) 3401, 3299, 3050, 2977, 2933, 1664, 1510, 1447, 1328, 1248, 1189, 1100,997, 863, 788, 739, 706 cm^{-1}; MS (EI) m/z 319 (M^+).

Anal. Calcd for $C_{21}H_{21}NO_2$: C,78.97; H, 6.62; N, 4.38; O, 10.02. Found: C, 78.94; H, 6.62; N, 4.39; O, 10.05.

(S)*-*N*-((*R*)-2-Methoxy-2-phenylacetyl)tryptophan methyl ester** ((R)*-10**): [α] = −39.83 (c = 0.024, EtOH); ^1H NMR (250.13 MHz, $CDCl_3$) δ 8.4 (br, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.42−7.28 (m, 7H), 7.24−7.09 (m, 2H), 6.95 (d, J = 1.8 Hz, 1H), 4.95 (dt, J = 8.3, 5.8 Hz, 1H), 4.57 (s, 1H), 3.64 (s, 3H), 3.37 (d, J = 5.8 Hz, 2H), 3.19 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.12, 170,47, 136.83, 136.21, 128.54, 127.60, 127.41, 122.84, 122.14, 119.52, 118.64, 111.30, 109.95, 83.69, 56.97, 52.55, 52.21, 27.70; IR (NaCl) 3386, 3298, 3057, 2991, 2922, 2817, 1735, 1661, 1514, 1438, 1344, 1204, 1098, 1029, 911, 794, 738, 700 cm^{-1}; MS (EI) m/z 366 (M^+).

Anal. Calcd for $C_{21}H_{22}N_2O_4$: C,68.84; H, 6.04; N, 7.64; O, 17.48. Found: C, 68.82; H, 6.05; N, 7.63; O, 17.50.

(S)*-*N*-((*S*)-2-Methoxy-2-phenylacetyl)tryptophan methyl ester** ((S)*-10**): [α] = +56.85 (c = 0.035, EtOH); ^1H NMR (250.13 MHz, $CDCl_3$) δ 7.4 (b, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.34−7.23 (m, 7H), 7.23−7.7.06 (m, 2H), 6.71 (d, J = 2.5 Hz, 1H), 4.96 (dt, J = 8.3, 5.8 Hz, 1H), 4.62 (s, 1H), 3.70 (s, 3H), 3.31 (s, 3H), 3.29 (d, J = 5.8 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.34, 170.60, 136.80, 136.10, 128.46, 128.33, 127.43, 126.90, 122.95, 121.98, 119.45, 118.45, 111.23, 109.46, 83.59, 57.17, 52.28, 27.59; IR (NaCl) 396,3314, 3054, 2997, 2940, 2829, 1738, 1666, 1516, 1443, 1346, 1206, 1100, 1001, 912, 738, 700 cm^{-1}; MS (EI) m/z 366 (M^+).

Anal. Calcd for $C_{21}H_{22}N_2O_4$: C,68.84; H, 6.04; N, 7.64; O, 17.48. Found: C, 68.81; H, 6.03; N, 7.63; O, 17.53.

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Supplementary Material Available: ^1H NMR spectra for compounds (*R*)- and (*S*)-**3**, (*R*)- and (*S*)-**6**, (*R*)- and (*S*)-**7**, (*R*)- and (*S*)-**8**, (*R*)- and (*S*)-**9** and (*R*)- and (*S*)-**10**, COSY spectra for (*R*)- and (*S*)-**3**, and ^1H NMR spectra of (*R*)- and (*S*)-**7** at different concentrations (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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