Determination of the Absolute Configuration of Amines and α-Amino Acids by ^{1}H NMR of (*R*)-*O*-Aryllactic Acid Amides†

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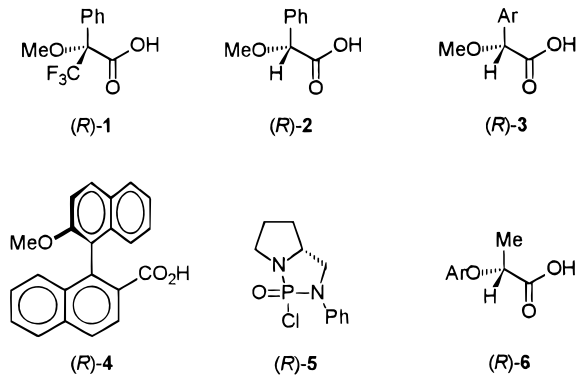
(*R*)-*O*-Aryllactic acid (ROAL) amides derived from α-chiral primary amines and α-amino acid esters show different chemical shifts in ^{1}H NMR spectroscopy (300 MHz) depending on their configuration. Molecular mechanics, semiempirical calculations, and ^{1}H NMR studies suggest that, in solution, these amides prefer an *ap*-*Z* conformation with the C_αOAr and C═O groups close to *anti*-periplanar as in the case of mandelic acid amides. The proposed conformational preference is different from that of the ROAL esters (C_αH and C═O groups in a *syn*-periplanar conformation). The conformational model for ROAL amides allows the absolute configuration assignment of primary amines and α-amino acid esters according to the relative position of the aryl group and the substituents on the amine moiety, and also their enantiomeric composition.

Introduction

One of the most classical and widely used methods to determine the absolute configuration of organic molecules is based on NMR studies of the different chemical shifts of diastereomers prepared from chiral derivatizing agents. This method is based on the anisotropy of aromatic rings in chiral auxiliaries (Scheme 1) derived from: (a) mandelic acid, such as (*R*)- or (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, **1**),[1] α-methoxy-α-phenylacetic acid (MPA, **2**),[2] or α-methoxy-α-arylacetic acids (AMAAs, **3**),[3] (b) axially chiral compounds such as 2′-methoxy-1,1′-binaphthyl-2′-carboxylic acid (MBNC, **4**),[4] (c) diazaphosphamidic chlorides such as **5**, derived from (*R*)-2-(anilinomethyl)pyrrolidine,[5] and (d) (*R*)-*O*-aryllactic acids (ROAL, **6**).[6] These reagents have been used for the configurational determination of alcohols and amines *via* their esters[1a,b,d,2a,3a,b,d,4−6] and amides,[1b,c,e,2b,3a,c,5] respectively, using ^{1}H or ^{19}F NMR spectroscopy.

(*R*)-*O*-Aryllactic acids (ROAL, **6**) are especially convenient chiral auxiliaries because of their easy preparation and the low cost of the starting lactic esters. They are obtained by reaction of ethyl (*S*)-lactate with phenols under Mitsunobu conditions followed by hydrolysis of the ester functionality.[7] These reagents have been used previously as (a) chiral derivatizing agents in the determination of enantiomeric purity of alcohols and amines by ^{19}F NMR analysis of their esters and amides respectively,[8] (b) in the determination of the absolute configuration of alcohols as ester derivatives,[6a] and (c) in the kinetic resolution of alcohols using esterification reagents.[9] We have recently used these ROAL acids as chiral solvating agents for the direct ^{1}H NMR determination of the enantiomeric purity of amines and amino alcohols.[10] The magnitude of the nonequivalent chemical shifts for the diastereomeric ROAL salts of racemic chiral amines and amino alcohols has, in general, a higher value than with the use of other acids such as MTPA[11] or (*R*)-*O*-acetylmandelic (ROAM) acids.[12] We report here the determination of the absolute configuration of amines

Scheme 1



† This paper is dedicated to Prof. Antonino Fava on his 73rd birthday.

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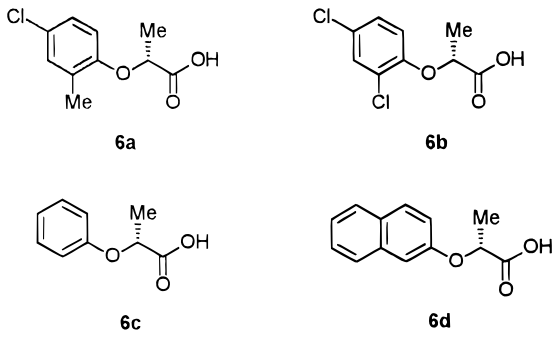
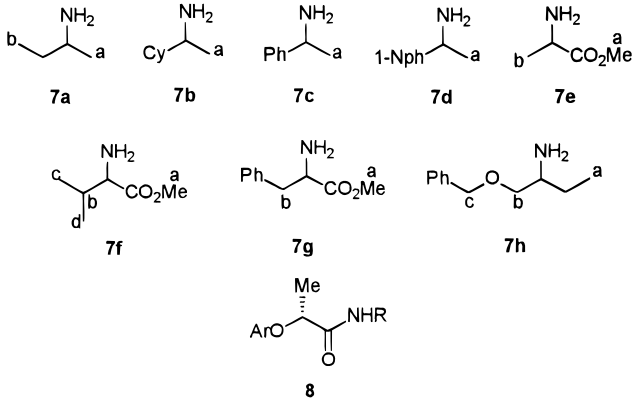
Scheme 2



Scheme 3



and α-amino acid esters by ^{1}H NMR spectroscopy using ROAL acids as chiral derivatizing agents.

Results and Discussion

In the present study, four representative ROAL acids (**6a**−**d**, Scheme 2) were employed for the preparation of a series of diastereomeric amides by combination with α-chiral primary amines (**7a**−**d**), α-amino acid esters (**7e**−**g**), and even an *O*-benzyl-protected *β*-amino alcohol[13] (**7h**) (Scheme 3). The oxalyl chloride method was used for the amidation reactions because it proved to afford higher yield of amides and also cleaner and faster reactions compared to the DCC methodology.[2b] Under these reaction conditions, no kinetic resolution was observed when the amidation was carried out with racemic amines, yielding 1:1 mixtures of diastereomeric amides.

In Table 1 the ^{1}H NMR chemical shifts for each set of the prepared amides **8** (Scheme 3) are summarized. Once the two diastereomeric amides were obtained from a ROAL acid **6** and a racemic amine **7**, their chemical shifts were assigned to a particular starting (*R*)- or (*S*)-amine by comparison with the corresponding shifts in the single-diastereomer amide prepared from an enantiomerically pure amine of known configuration. A series of consistent results can be observed in the chemical shifts given in Table 1. For example, for amides derived from (*S*)-amines **7a**−**d** the signal corresponding to the methyl group at C_α on the amine moiety always appears at a higher field (shielding effect) than that for amides from the corresponding (*R*)-amines (Table 1, entries 1−18). On the other hand, for amides derived from (*R*)-α-amino acid methyl esters **7e**−**g**, a shielding effect is observed on the methoxy group (Table 1, entries 19−26). All these results must agree with a preferred conformation for these ROAL amides, which would explain the differences obtained and give us an adequate model for predicting the absolute configuration of any α-chiral primary amine using ROAL acids.

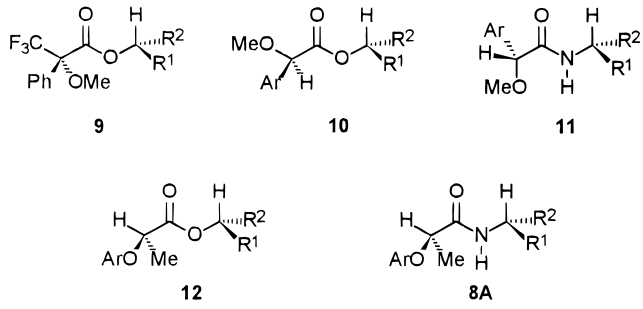
(13) Prepared by deprotonation of (*R*/*S*)- and (*S*)-2-aminobutanol with sodium hydride in refluxing THF and subsequent reaction with benzyl bromide.

Table 1. Selected Chemical Shifts of ROAL Amides[a] (300 MHz, $CDCl_3$)

			amide[b]				
entry	acid no.	amine no.	no.	H_a	H_b	H_c	H_d
1	**6a**	(*R*)-**7a**	(*R*,*R*)-**8aa**	1.15	0.77		
2	**6a**	(*S*)-**7a**	(*R*,*S*)-**8aa**	1.06	0.92		
3	**6c**	(*R*)-**7a**	(*R*,*R*)-**8ca**	1.13	0.70		
4	**6c**	(*S*)-**7a**	(*R*,*S*)-**8ca**	1.02	0.91		
5	**6d**	(*R*)-**7a**	(*R*,*R*)-**8da**	1.13	0.66		
6	**6d**	(*S*)-**7a**	(*R*,*S*)-**8da**	0.99	0.91		
7	**6a**	(*R*)-**7b**	(*R*,*R*)-**8ab**	1.09			
8	**6a**	(*S*)-**7b**	(*R*,*S*)-**8ab**	1.01			
9	**6a**	(*R*)-**7c**	(*R*,*R*)-**8ac**	1.51			
10	**6a**	(*S*)-**7c**	(*R*,*S*)-**8ac**	1.43			
11	**6b**	(*R*)-**7c**	(*R*,*R*)-**8bc**	1.52			
12	**6b**	(*S*)-**7c**	(*R*,*S*)-**8bc**	1.45			
13	**6c**	(*R*)-**7c**	(*R*,*R*)-**8cc**	1.48			
14	**6c**	(*S*)-**7c**	(*R*,*S*)-**8cc**	1.38			
15	**6d**	(*R*)-**7c**	(*R*,*R*)-**8dc**	1.47			
16	**6d**	(*S*)-**7c**	(*R*,*S*)-**8dc**	1.36			
17	**6a**	(*R*)-**7d**	(*R*,*R*)-**8ad**	1.61			
18	**6a**	(*S*)-**7d**	(*R*,*S*)-**8ad**	1.51			
19	**6a**	(*R*)-**7e**	(*R*,*R*)-**8ae**	3.72	1.46		
20	**6a**	(*S*)-**7e**	(*R*,*S*)-**8ae**	3.77	1.38		
21	**6a**	(*R*)-**7f**	(*R*,*R*)-**8af**	3.68	2.23	0.93	0.97
22	**6a**	(*S*)-**7f**	(*R*,*S*)-**8af**	3.76	2.14	0.75	0.80
23	**6c**	(*R*)-**7f**	(*R*,*R*)-**8cf**	3.62	2.20	0.92	0.96
24	**6c**	(*S*)-**7f**	(*R*,*S*)-**8cf**	3.73	2.10	0.68	0.74
25	**6a**	(*R*)-**7g**	(*R*,*R*)-**8ag**	3.68	3.11, 3.22		
26	**6a**	(*S*)-**7g**	(*R*,*S*)-**8ag**	3.74	3.05		
27	**6a**	(*R*)-**7h**	(*R*,*R*)-**8ah**	0.92	3.29, 3.45	4.26, 4.32	
28	**6a**	(*S*)-**7h**	(*R*,*S*)-**8ah**	0.79	3.47, 3.52	4.51	

[a] From the diastereomeric mixture. [b] Assignments referred to notation in Scheme 3.

Scheme 4



The proposed conformational models for MTPA,[1a] MPA,[2a] or AMAAs[3d] esters show that the methine proton, O−CO, and CF_3 (for MTPA) or OMe moieties (for MPA or AMAAs) lie roughly in a common plane and that the $C_\alpha CF_3$ or C_αOMe groups remain *syn*-periplanar to the C=O group (**9** and **10**, Scheme 4). In the case of the corresponding amides the conformational model differs because all the recent experimental[2b,3c] and theoretical[3c] studies on the conformation of MPA and AMAA amides in solution indicate a conformational preference for C_α-OMe and C=O groups in an *anti*-periplanar position (*ap*-*Z* conformation, **11**, Scheme 4). An intramolecular hydrogen bond[2b,14] between the amide hydrogen and the methoxy substituent and the lower dipole moment[3d] have been suggested as conformational stabilization factors.

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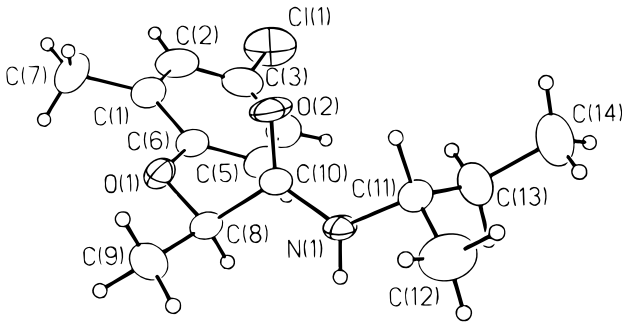
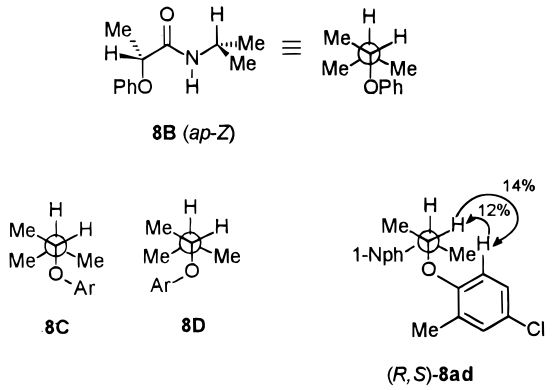


Figure 1. Thermal ellipsoid plot of one molecule of (*R,S*)-**8aa** showing the atom naming scheme. Non-hydrogen atoms are represented by their 50% probability ellipsoids.

X-ray analysis has supported the notion that the more stable conformation of ROAL esters is that with the C_αH and C=O groups occupying *syn*-periplanar positions[5] (**12**, Scheme 4). Apparently, an extension of the ROAL-ester conformational model to amides **8** would explain the different observed chemical shifts for amides from (*R*)- or (*S*)-amines as represented in conformer **8A** (Scheme 4). The stereodifferentiation of R^1 and R^2 would depend on the relative position of the aryl ring anisotropically inducing high-field shifts for protons in the R^1 group facing the aromatic system. With this background in mind, and in order to check if the conformational preference for ROAL amides in the solid state would also be accommodated in solution, suitable crystals of amide (*R,S*)-**8aa** were subjected to X-ray analysis. The structure, shown in Figure 1, revealed a conformation with C_αOAr and C=O groups close to a *syn*-periplanar arrangement (*sp-Z*) with a torsion angle O(1)−O(2) = 27°, and with the aromatic ring facing the ethyl group on the (*S*)-amine moiety. A conformer like this in solution would produce a shielding effect on the ethyl group in question, and therefore the ^{1}H NMR would show a displacement of the signals toward higher fields compared to those corresponding to the amide from the (*R*)-amine. This is totally opposite to the results obtained for (*R,R*)- and (*R,S*)-**8aa** in $CDCl_3$ solution (Table 1, entries 1 and 2) which reveal that the aromatic ring is shielding the *methyl* group on the amine moiety of (*R,S*)-**8aa**. This result shows that in this case it is not possible to extend conformational assignments from the solid state to compounds in solution in a reliable way. In the case of amide (*R,S*)-**8aa**, the X-ray studies revealed favorable crystal packing through intermolecular hydrogen bonds between N(1)−H(1) from one molecule and O(2) from another one, thus forcing the observed solid state conformation.

Due to the change in the conformational preference for MPA and AMAAs amides compared with the corresponding esters (see above), it seemed logical that an *ap-Z* conformation could also be the most stable one in solution for the case of ROAL amides. The *anti* conformation between the amide proton and the methine proton of the amine moiety in the ROAL amides can be established because of the coupling constant of ∼7−9 Hz in the ^{1}H NMR spectra, a characteristic that is general to amides from primary amines.[2b,3c] These facts prompted us to study the relative energies for the different rotamers of an example amide, created from the simplest ROAL acid **6c** and isopropylamine, using molecular mechanics[15] and semiempirical[16] calculations. From the former calculations we obtained a conformation *ap-Z* for ROAL amides, as represented in Scheme 5 by **8B** (together with its extended Newman projection), which shows a lower conformational energy by more than 2 kcal/mol compared to any of the other possible conformers created by rotation of the single C_α−C=O bond. Using the AM1 semiempirical method we obtained similar and, in some cases, larger energy differences. For example, the *ap-Z* conformer shows a conformational energy 5 kcal/mol lower than the *sp-Z* conformer (C_αOPh and C=O groups in a *syn*-periplanar position), the latter closely related to the conformer obtained by X-ray analysis for (*R,S*)-**8aa**. From the molecular mechanics modeling it was easy to see how the *ap-Z* conformer was also stabilized by the formation of an intramolecular hydrogen bond between the amide hydrogen and the phenoxy substituent, something similar to what has been previously suggested for the case of MPA amides.[2b] Moreover, this fact was supported by the absence of displacement of the ^{1}H NMR signal corresponding to the amide proton for samples of different concentration, and also by the presence of a sharp band at 3420 cm^{-1} in the IR spectrum of amide **8ad** (2% solution in CCl_4).[14]

Scheme 5



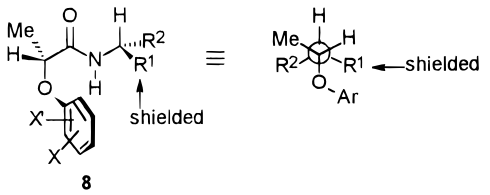
Once this conformational preference for ROAL amides was established, it was necessary to determine the orientation of the aryl group in the *ap-Z* rotamer, that is, the relative stability of the two possible *ap-Z* conformers **8C** and **8D** (Scheme 5), which would shield one group or the other (R^1 or R^2) in the amine fragment. This was investigated for ROAL amides from isopropylamine and acids **6a**−**d**, again using molecular mechanics calculations, with the result that conformer **8C** was 1.1 kcal/mol lower in energy than **8D** for amides from all of the ROAL acid used. The same energy difference was obtained using the AM1 semiempirical calculation method[16] for the case of the ROAL amide from isopropylamine and **6c**. It was also shown that the aromatic ring was preferentially located close to coplanarity with the C_α−H bond. Moreover, differential NOE experiments on amide (*R,S*)-**8ad** (Table 1, entry 18) showed increments only in the signals of protons C_αH (12%) and H_{ortho} (14%) after irradiation on H_{ortho} and C_αH respectively, whereas after irradiation on the aromatic methyl group no enhancement was observed at the methyl on C_α (Scheme 5).

All these results suggest that the preferred conformer of ROAL amides **8** should be close to the one represented

(15) PCMODEL for Windows from Serena Software was used for these calculations (MMX force field).

(16) AM1 as implemented in MOPAC 6.00; J. P. S. James, Franck J. Seiler Research Laboratory, United States Air Force Academy, CO 80840.

Scheme 6



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in Scheme 6 (together with its extended Newman projection), in which is shown the position of the aryl group shielding the R^1 group in the amine fragment, which suffers downfield chemical shifts compared to the unshielded R^2 group. With this proposed model it would be possible to predict the absolute configuration of any α-chiral primary amine, as confirmed by the results shown in Table 1.

With regard to the chemical shift values presented in Table 1, some points are worth noting. First, it can be deduced from the analysis of the conformational model for **8**, shown in Scheme 6, that the shielding effect should be more noticeable if the affected group is far from the chiral center in the amine moiety. That is shown, for example, in amides (*R,R*)- and (*R,S*)-**8aa** (Table 1, entries 1 and 2) derived from *sec*-butylamine **7a** where the difference in chemical shifts is 0.09 ppm for the methyl group (protons a) bonded directly to the chiral center whereas the difference is 0.15 ppm for the methyl in the ethyl substituent. The same effect can be observed in amides (*R,R*)- and (*R,S*)-**8af**, derived from (*R*)- and (*S*)-valine methyl ester respectively, where $\Delta\delta = 0.09$ ppm for the methine protons, whereas $\Delta\delta = 0.18$ and $\Delta\delta = 0.17$ ppm for the isopropyl methyls. Another fact is the observed loss of stereodifferentiation when the aryl system in the ROAL acid bears electron-withdrawing groups, thus decreasing the intensity of the induced ring current and therefore the anisotropic aromatic shielding effect. Thus, when two chlorine groups are present in the aromatic ring of the acid moiety (**6b**) as in amides (*R,R*)- and (*R,S*)-**8bc** (Table 1, entries 11 and 12), the difference in chemical shifts is 0.07 ppm for the methyl groups in the amine fragment, whereas in amides (*R,R*)- and (*R,S*)-**8cc** (Table 1, entries 13 and 14) from ROAL acid **6c** the difference is 0.10 ppm and for amides (*R,R*)- and (*R,S*)-**8dc** from acid **6d** the difference is 0.11 ppm (Table 1, entries 15 and 16). In general, the difference in ^{1}H NMR chemical shifts is larger for ROAL amides than for MTPA amides and, at least, their values are similar in magnitude to those of MPA or AMAA amides.

In all cases it was possible to determine the enantiomeric purity of the amines by integration of the signal corresponding to the residual diastereomer in the reaction crude. Thus, for amide (*R,S*)-**8ac** (Table 1, entry 10) from (*S*)-1-phenylethylamine (Aldrich 96%), 2% of the (*R,R*)-**8ac** amide was detected.

It is worthy of note that, since both enantiomers of lactate esters are commercially available, it is possible to prepare the corresponding enantiomeric (*S*)-*O*-aryllactic (SOAL) acids and therefore to obtain two diastereomeric amides by combination of a single amine of unknown configuration with ROAL and SOAL acids. That would allow the absolute configuration of α-chiral primary amines to be established when just one of the enantiomers is available, because the amide from the SOAL acid and the available amine will be enantiomeric to the amide from the ROAL acid with the nonavailable one. Comparison of the chemical shifts of both ROAL and SOAL amides from the same amine and application of the described above conformational model would allow the determination of the absolute configuration of the available amine.

Conclusions

In summary, we report that cheap and easily prepared (*R*)-*O*-aryllactic (ROAL) acids can be used for the determination of the absolute configuration of α-chiral primary amines and α-amino acid esters *via* the differences in the ^{1}H NMR shifts of their corresponding diastereomeric amides. The *ap-Z* conformational model proposed for these ROAL amides is consistent with those recently proposed for MPA and AMAA amides and different from that previously suggested for ROAL esters. As the difference in ^{1}H NMR chemical shifts is larger for ROAL amides than for MTPA amides and, at least, of a similar magnitude to that for MPA or AMAA amides, these acids turn out to be an interesting alternative to the use of other chiral derivatizing agents.

Experimental Section

General. Melting points are uncorrected. Optical rotations were measured in CH_2Cl_2. FT-IR spectra were obtained from KBr pellets unless otherwise stated. NMR spectra were determined at 300 MHz for ^{1}H and 75 MHz for ^{13}C using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra (EI) were obtained at 70 eV. Elemental analyses were performed by the Microanalyses Service of the University of Alicante. High resolution mass spectra (EI) were determined by the corresponding Service at the University of Zaragoza. X-ray data were collected using Mo Kα radiation (graphite crystal monochromator, $\lambda = 0.71073$ Å), $\mu = 0.72$ cm^{-1}, $T = 22-25 \pm 1$ °C. The atomic coordinates and other data for compound (*R,S*)-**8aa** were deposited in the Cambridge Crystallographic Data Centre. Benzene and toluene were dried over sodium wire. All starting materials were commercially available of the best grade and were used without further purification.

Preparation of Amides. General Procedure. The corresponding ROAL acid (0.5 mmol) was dissolved in benzene or toluene (3 mL) under an argon atmosphere, and then oxalyl chloride (0.84 mmol, 80 μL) was added at 0 °C followed by DMF (*ca.* 2 μL). The reaction mixture was stirred for 30 min at 0 °C and 2 h at room temperature, with the solvent then being evaporated (15 Torr), and benzene or toluene was added (3 mL). To this mixture was added dropwise a solution of amine (0.5 mmol) and pyridine (1 mmol, 80 μL) in benzene or toluene (2 mL). The resulting suspension was stirred for 2 h at room temperature, and then 2 N HCl was added (10 mL) and the mixture was extracted with ether (2 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), dried over anhydrous Na_2SO_4, and evaporated *in vacuo* (15 Torr) affording crude amides **7** with yields ranging between 80−90%. The crude amides were pure enough for ^{1}H NMR analysis (>90% by GC), but those obtained from enantiomerically pure amines were purified by crystallization or column chromatography on silica gel for analytical purposes.

(*S*)-*N*-*sec*-Butyl-(*R*)-2-(4-chloro-2-methylphenoxy)propionamide ((*R,S*)-8aa). Yield: 79%. Mp 126−127 °C (hexane/ether); $[\alpha]^{27}_D$ +13.6° (*c* = 1.0); IR ν 3272, 3088, 1655, 1560, 1244, 873, 800 cm^{-1}; ^{1}H NMR δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 1.43−1.54 (m, 2H), 1.57 (d, *J* = 6.7 Hz, 3H), 2.25 (s, 3H), 3.94 (m, 1H), 4.57 (q, *J* = 6.7 Hz, 1H), 6.16 (br d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 1H), 7.07−7.15 (m, 2H); ^{13}C NMR δ 10.21, 16.29, 18.93, 20.30, 29.62, 46.15, 75.92, 114.00, 126.50, 126.69, 129.00, 130.84, 153.77, 171.24; MS *m/z* 269 (M^+, 31), 169 (45), 128 (44), 100 (61), 72 (46), 57 (82), 44 (100). Anal. Calcd for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19. Found: C, 62.33; H, 7.52; N, 4.87.

(*S*)-*N*-*sec*-Butyl-(*R*)-2-phenoxypropionamide ((*R,S*)-8ca). Yield: 80%. Mp 69−70 °C (hexane); $[\alpha]^{25}_D$ +35.6° (*c* =

1.1); IR ν 3309, 3072, 1647, 1530, 1232, 695, 756 cm^{-1}; ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H), 1.47 (m, 2H), 1.57 (d, J = 6.7 Hz, 3H), 3.93 (m, 1H), 4.66 (q, J = 6.7 Hz, 1H), 6.22 (br d, J = 7.2 Hz, 1H), 6.88−7.03 (m, 3H), 7.30 (m, 2H); ^{13}C NMR δ 10.26, 18.95, 20.23, 29.58, 46.19, 75.12, 115.49, 122.00, 129.69, 156.88, 171.75; MS m/z 221 (M$^+$, 17), 121 (100), 77 (39), 57 (45). HRMS m/z calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1414.

(*S*)-*N*-*sec*-Butyl-(*R*)-2-(2-naphthyloxy)propionamide ((*R,S*)-8da). Yield: 78%. Mp 107−108 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +66.9° (c = 1.6); IR ν 3363, 3055, 1655, 1521, 1521, 1509, 1216, 843 cm^{-1}; ^{1}H NMR δ 0.92 (t, J = 7.3 Hz, 3H), 0.99 (d, J = 6.4 Hz, 3H), 1.47 (m, 2H), 1.64 (d, J = 6.7 Hz, 3H), 3.95 (m, 1H), 4.79 (q, J = 6.7 Hz, 1H), 6.20 (br d, J = 7.6, 1H), 7.16 (m, 1H), 7.41 (m, 3H), 7.76 (m, 3H); ^{13}C NMR δ 10.30, 19.06, 20.30, 29.62, 46.20, 75.37, 108.84, 118.49, 124.27, 126.65, 126.95, 127.58, 129.43, 129.80, 134.31, 154.75, 171.49; MS m/z 271 (M$^+$, 59), 171 (80), 144 (79), 128 (52), 127 (54), 72 (53), 57 (52), 44 (100). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.66; H, 7.87; N, 4.95.

(*S*)-*N*-(1-Cyclohexylethyl)-(*R*)-2-(4-chloro-2-methylphenoxy)propionamide ((*R,S*)-8ab). Yield: 79%. Mp 135−136 °C (hexane/ether); $[\alpha]^{25}_D$ +17.4° (c = 1.4); IR ν 3256, 3088, 1654, 1563, 1247, 870, 799 cm^{-1}; ^{1}H NMR δ 0.94−1.25 (m, 6H), 1.01 (d, J = 6.7 Hz, 3H), 1.58 (d, J = 6.7 Hz, 3H), 1.65−1.74 (m, 5H), 2.25 (2, 3H), 3.87 (m, 1H), 4.58 (q, J = 6.7 Hz), 1H), 6.22 (br d, J = 8.2 Hz, 1H), 6.69 (d, J = 8.5 Hz, 1H), 7.07−7.15 (m, 2H); ^{13}C NMR δ 16.33, 17.90, 18.97, 26.10, 26.36, 28.77, 29.18, 43.07, 48.89, 75.88, 113.93, 126.47, 126.69, 128.95, 130.85, 153.72, 171.06; MS m/z 323 (M$^+$, 7), 169 (24), 69 (20), 55 (27), 44 (100). Anal. Calcd for $C_{18}H_{26}ClNO_2$: C, 66.76; H, 8.09; N, 4.32. Found: C, 66.79; H, 8.14; N, 3.97.

(*S*)-*N*-(1-Phenylethyl)-(*R*)-2-(4-chloro-2-methylphenoxy)propionamide ((*R,S*)-8ac). Yield: 83%. Mp 127−128 °C (hexane/ether); $[\alpha]^{25}_D$ +6.7° (c = 2.0); IR ν 3262, 3082, 1652, 1558, 1243, 1252, 804, 696 cm^{-1}; ^{1}H NMR δ 1.43 (d, J = 7.0 Hz, 3H), 1.55 (d, J = 6.7 Hz, 3H), 2.23 (s, 3H), 4.62 (q, J = 6.7 Hz, 1H), 5.15 (quintet, J = 7.0 Hz, 1H), 6.62 (br d, J = 7.5 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 7.10−7.36 (m, 7H); ^{13}C NMR δ 16.31, 18.68, 21.75, 48.26, 75.86, 113.98, 125.91, 126.60, 126.72, 127.47, 128.77, 129.05, 130.91, 142.73, 153.73, 170.96; MS m/z 317 (M$^+$, 3), 105 (47), 44 (100). Anal. Calcd for $C_{18}H_{20}ClNO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 68.33; H, 6.41; N, 4.41.

(*S*)-*N*-(1-Phenylethyl)-(*R*)-2-(2,4-dichlorophenoxy)propionamide ((*R,S*)-8bc). Yield: 84%. Mp 127−128 °C (hexane/EtOAc); $[\alpha]^{22}_D$ −16.9° (c = 1.7); IR ν 3268, 3094, 1663, 1563, 1288, 807, 697 cm^{-1}; ^{1}H NMR δ 1.46 (d, J = 7.0 Hz, 3H), 1.59 (d, J = 6.7 Hz, 3H), 4.70 (q, J = 6.7 Hz, 1H), 5.13 (quintet, J = 7.0 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 7.03 (br d, J = 7.3 Hz, 1H), 7.19−7.42 (m, 7H); ^{13}C NMR δ 18.33, 22.04, 48.47, 76.80, 116.07, 124.43, 125.85, 127.41, 127.95, 128.72, 130.22, 142.75, 151.32, 169.96; MS m/z 337 (M$^+$, 1), 176 (49), 105 (100). Anal. Calcd for $C_{17}H_{17}Cl_2NO_2$: C, 60.37; H, 5.07; N, 4.14. Found: C, 60.48; H, 5.07; N, 3.80.

(*S*)-*N*-(1-Phenylethyl)-(*R*)-2-phenoxypropionamide ((*R,S*)-8cc). Yield: 81%. Mp 151−152 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +1.2° (c = 1.9); IR ν 3343, 3062, 3042, 1653, 1525, 1230, 755, 704 cm^{-1}; ^{1}H NMR δ 1.39 (d, J = 7.0 Hz, 3H), 1.55 (d, J = 6.7 Hz, 3H), 4.70 (q, J = 6.7 Hz, 1H), 5.15 (quintet, J = 7.0 Hz, 1H), 6.65 (br d, J = 7.0 Hz, 1H), 6.90−7.05 (m, 3H), 7.30 (m, 5H); ^{13}C NMR δ 18.70, 21.60, 48.16, 75.12, 115.52, 122.08, 125.99, 127.40, 128.70, 129.75, 142.77, 156.88, 171.23; MS m/z 269 (M$^+$, 12), 176 (42), 121 (100), 105 (69), 77 (57). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.76; H, 7.27; N, 4.79.

(*S*)-*N*-(1-Phenylethyl)-(*R*)-2-(2-naphthyloxy)propionamide ((*R,S*)-8dc). Yield: 80%. Mp 161−162 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +81.1° (c = 1.3); IR ν 3373, 3061, 3030, 1658, 1507, 1216, 844, 699 cm^{-1}; ^{1}H NMR δ 1.36 (d, J = 7.0 Hz, 3H), 1.62 (d, J = 6.7 Hz, 3H), 4.85 (q, J = 6.7 Hz, 1H), 5.16 (quintet, J = 7.0 Hz, 1H), 6.67 (br d, J = 7.5 Hz, 1H), 7.16−7.47 (m, 9H), 7.76 (m, 3H); ^{13}C NMR δ 18.78, 21.59, 48.22, 75.22, 108.82, 118.50, 124.33, 126.01, 126.69, 126.96, 127.43, 127.61, 128.72, 129.46, 129.87, 134.30, 142.74, 154.67, 171.20; MS m/z 319 (M$^+$, 44), 171 (65), 144 (63), (45), 105 (100). Anal. Calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: 78.66; H, 6.63; N, 4.01.

(*S*)-*N*-(1-Naphthylethyl)-(*R*)-2-(4-chloro-2-methylphenoxy)propionamide ((*R,S*)-8ad). Yield: 82%. Mp 174−175 °C (hexane/EtOAc); $[\alpha]^{25}_D$ +65.7° (c = 1.0); IR ν 3253, 3075, 3047, 1648, 1558, 1491, 1243, 1191, 1144, 875, 746 cm^{-1}; ^{1}H NMR δ 1.52 (d, J = 6.7 Hz, 3H), 1.60 (d, J = 6.7 Hz, 3H), 2.13 (s, 3H), 4.62 (q, J = 6.7 Hz, 1H), 5.94 (quintet, J = 6.7 Hz, 1H), 6.59 (br d, J = 7.2 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 7.13 (m, 2H), 7.47 (m, 4H), 7.85 (m, 2H), 8.05 (m, 1H); ^{13}C NMR δ 16.26, 18.83, 20.62, 44.47, 76.03, 113.92, 122.56, 123.27, 125.19, 125.94, 126.54, 126.59, 126.68, 128.53, 128.86, 129.06, 130.89, 131.05, 133.96, 137.74, 153.80, 170.89; MS m/z 367 (M$^+$, 12), 226 (56), 155 (100). Anal. Calcd for $C_{22}H_{22}ClNO_2$: C, 71.83; H, 6.03; N, 3.81. Found: C, 71.92; H, 6.05; N, 3.45.

(*S*)-*N*-[(*R*)-2-(4-Chloro-2-methylphenoxy)propanoyl]alanine Methyl Ester ((*R,S*)-8ae). Yield: 68%. Mp 107−108 °C (hexane); $[\alpha]^{25}_D$ +5.1° (c = 1.0); IR ν 3420, 3279, 1740, 1662, 1247, 802, 660 cm^{-1}; ^{1}H NMR δ 1.37 (d, J = 7.0 Hz, 3H), 1.58 (d, J = 6.7 Hz, 3H), 2.29 (s, 3H), 3.77 (s, 3H), 4.61 (quintet, J = 7.0 Hz, 1H), 4.64 (q, J = 6.7 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 7.02 (br d, J = 7.2 Hz, 1H), 7.15 (m, 2H); ^{13}C NMR δ 13.33, 18.30, 18.45, 47.67, 52.56, 75.32, 113.56, 126.49, 126.60, 129.20, 130.94, 153.60, 171.41, 173.07; MS m/z 299 (M$^+$, 26), 169 (50), 130 (38), 70 (32), 55 (38), 44 (100). HRMS m/z calcd for $C_{14}H_{18}ClNO_4$ 299.0924, found 299.0919.

(*S*)-*N*-[(*R*)-2-(4-Chloro-2-methylphenoxy)propanoyl]valine Methyl Ester ((*R,S*)-8af). Yield: 79%. $[\alpha]^{25}_D$ +10.0° (c = 1.4); IR (film) ν 3283, 3086, 1748, 1666, 1242, 873, 803, 660 cm^{-1}; ^{1}H NMR δ 0.75 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 1.60 (d, J = 6.7 Hz, 3H), 2.14 (m, 1H), 2.29 (s, 3H), 3.76 (s, 3H), 4.55 (dd, J = 9.1, 4.6 Hz, 1H), 4.69 (q, J = 6.7 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.86 (br d, J = 9.0 Hz, 1H), 7.16 (m, 2H); ^{13}C NMR δ 16.24, 17.32, 18.48, 18.77, 31.09, 52.16, 56.47, 75.08, 113.32, 126.40, 126.54, 128.89, 130.90, 153.53, 171.62, 171.95; MS m/z 327 (M$^+$, 30), 169 (53), 158 (44), 72 (100), 55 (50); HRMS m/z calcd for $C_{16}H_{22}ClNO_4$ 327.1237, found 327.1229.

(*S*)-*N*-[(*R*)-2-Phenoxypropanoyl]valine Methyl Ester ((*R,S*)-8cf). Yield: 77%. $[\alpha]^{25}_D$ +19.5° (c = 1.5); IR (film) ν 3426, 3064, 1743, 1687, 1226, 755, 692 cm^{-1}; ^{1}H NMR δ 0.68 (d, J = 6.7 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H), 1.59 (d, J = 6.7 Hz, 3H), 2.10 (m, 1H), 3.74 (s, 3H), 4.54 (dd, J = 9.0, 4.9 Hz, 1H), 4.75 (q, J = 6.7 Hz, 1H), 6.82 (br d, J = 8.9 Hz, 1H), 6.92 (m, 3H), 7.30 (m, 2H); ^{13}C NMR δ 17.26, 18.70, 18.75, 31.04, 52.12, 56.49, 74.68, 115.25, 122.02, 129.72, 156.88, 171.96, 172.13; MS m/z 279 (M$^+$, 6), 165 (30), 121 (100), 77 (41), 72 (51), 55 (32); HRMS m/z calcd for $C_{15}H_{21}NO_4$ 279.1471, found 279.1467.

(*S*)-*N*-[(*R*)-2-(4-Chloro-2-methylphenoxy)propanoyl]phenylalanine Methyl Ester ((*R,S*)-8ag). Yield: 76%. $[\alpha]^{27}_D$ +37.7° (c = 2.1); IR (film) ν 3416, 3064, 3030, 1745, 1672, 1242, 874, 806, 702 cm^{-1}; ^{1}H NMR δ 1.55 (d, J = 6.7 Hz, 3H), 2.13 (s, 3H), 3.05 (d, J = 5.8 Hz, 2H), 3.75 (s, 3H), 4.59 (q, J = 6.7 Hz, 1H), 4.90 (dt, J = 8.2 Hz, 5.8 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 6.74 (br d, J = 8.2 Hz, 1H), 6.82 (m, 1H), 7.02−7.14 (m, 6H); ^{13}C NMR δ 16.19, 18.69, 37.71, 52.33, 52.39, 75.09, 113.18, 126.38, 126.61, 127.11, 128.56, 128.92, 130.85, 135.20, 153.60, 171.53, 171.64; MS m/z 375 (M$^+$, 30), 213 (85), 169 (100), 146 (55), 120 (60), 91 (55), 55 (43), 44 (68); HRMS m/z calcd for $C_{20}H_{22}ClNO_4$ 375.1237, found 375.1227.

(*S*)-*N*-2-[1-(Benzyloxy)butyl]-(*R*)-2-(4-chloro-2-methylphenoxy)propionamide ((*R,S*)-8ah). Yield: 82%. Mp 98−99 °C (hexane/ether); $[\alpha]^{25}_D$ −10.2° (c = 1.7); IR ν 3267, 3091, 1657, 1559, 1249, 1191, 696, 661 cm^{-1}; ^{1}H NMR δ 0.79 (t, J = 7.3 Hz, 3H), 1.40−1.62 (m, 2H), 1.55 (d, J = 6.7 Hz, 3H), 2.20 (s, 3H), 3.47 (dd, J = 9.5, 4.0 Hz, 1H), 3.52 (dd, J = 9.5, 3.7 Hz, 1H), 4.01 (m, 1H), 4.52 (s, 2H), 4.61 (q, J = 6.7 Hz, 1H), 6.60 (br d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 7.08 (m, 2H), 7.31 (m, 5H); ^{13}C NMR δ 10.36, 16.24, 18.83, 24.70, 50.05, 70.90, 73.14, 75.57, 113.66, 126.37, 126.60, 127.51, 127.71, 128.39, 128.98, 130.84, 138.03, 153.75, 171.50; MS m/z 375 (M$^+$, 1), 91 (100), 58 (65). Anal. Calcd for $C_{21}H_{26}ClNO_3$: C, 67.10; H, 6.97; N, 3.73. Found: C, 66.92; H, 6.99; N, 3.35.

X-ray Structure Determination. Samples suitable for use in X-ray diffraction analysis were obtained by crystallization of (*R,S*)-**8aa** in hexane/EtOAc. Crystal data and a summary of data collection parameters and refinement results have been deposited with the Cambridge Crystallographic Data Centre.[17] A colorless crystal was mounted on a glass fiber and covered with a thin layer of epoxy. The unit-cell parameters were refined[18] to the zero-corrected positions of 25 reflections in the 2θ range 20.2−28.7°. The crystal is monoclinic, space group $P2_1$, with $a = 10.075(1)$, $b = 4.7537(4)$, $c = 15.860(2)$ Å, $\beta = 106.78(1)°$, $V = 727.2(2)$ Å^3, $Z = 2$. A hemisphere of data was collected, from 4.0 to 48.0° in 2θ. During data collection, three monitor reflections were remeasured after each hour of X-ray exposure, and three reflections were used to check crystal orientation after every 400 measurements. An empirical absorption correction[19] was based on the presence of two symmetry-equivalent quadrants of data and gave maximum and minimum correction factors of 0.93 and 0.84. The structure was solved by direct methods and refined to F_0^2 by full-matrix least-squares, using all unique data.[20] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in difference Fourier maps. The hydrogen atom attached to C(8) and one of the hydrogen atoms (H(14C)) attached to C(14) had their isotropic displacement parameters set to 1.2 times the equivalent isotropic displacement parameters of their respective parent carbon atoms, and a similarity restraint was used for the three C−H distances of the methyl group at C(14); otherwise, all hydrogens were refined freely, each with its own isotropic displacement parameter. In all, 242 parameters were refined to 2304 data and 4 restraints. The latter included an origin-fixing restraint[21] for the polar axis. The enantiomorph, established by the value of the Flack parameter,[22] −0.12(12), is in agreement with the absolute configuration established spectroscopically. The refinement converged (max, mean shift/esd = 0.199, 0.024) with $wR2 = 0.1080$, $R1 = 0.0455$, GOF = 1.060 and restrained GOF = 1.059. The final difference map had maximum and minimum densities of 0.14 and −0.14 e/Å^3.

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Supporting Information Available: Crystal packing diagram for compound (*R,S*)-**8aa** (1 page). 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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(17) The author has deposited atomic coordinates for (*R,S*)-**8aa** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(18) Diffractometer control program: CAD4-PC Version 1.5c, 1994, Delft Instruments X-ray Diffraction bv, Delft, The Netherlands.

(19) Data were processed on a Local Area VAXcluster (VMS V5.5-2), with the program XCAD4B (K. Harms, Philipps Universität Marburg) and with the commercial package SHELXTL-PLUS Release 4.21/V: 1990, Siemens Analytical X-ray Instruments, Inc., Madison, WI.

(20) (a) Least-squares calculations were done on a Hewlett-Packard 9000 715/50 (HP-UX V9.01), with the program Shelxl-93. (b) G. M. Sheldrick, Shelxl-93: FORTRAN-77 program for the refinement of crystal structures from diffraction data. University of Göttingen, 1993. (c) Sheldrick, G. M. Manuscript in preparation.

(21) Flack, H. D.; Schwarzenbach, D. *Acta Crystallogr. Sect. A* **1988**, *A44*, 499−506.

(22) (a) Flack, H. D. *Acta Crystallogr. Sect. A* **1983**, *A39*, 876−881. (b) Bernardinelli, G.; Flack, H. D. *Acta Crystallogr. Sect. A* **1985**, *A41*, 500−511.