Boc-Phenylglycine: The Reagent of Choice for the Assignment of the Absolute Configuration of α-Chiral Primary Amines by ^{1}H NMR Spectroscopy

José Manuel Seco, Emilio Quiñoá, and Ricardo Riguera*

Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain

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The absolute configuration of an α-substituted primary amine can be easily determined by direct comparison of the ^{1}H NMR spectra of the (*R*)- and the (*S*)-Boc-phenylglycine derivatives. A simplified model, based on extensive conformational analysis and NMR data, is presented that associates the spatial location of the substituents around the asymmetric carbon of the amine with the signs of $\Delta\delta^{R,S}$. The substituent with a negative $\Delta\delta^{R,S}$ occupies the position of L_1 in Figure 7 and that with a positive $\Delta\delta^{R,S}$ the position of L_2. From this model the absolute configuration (*R*/*S*) of the chiral center can be determined.The BPG amides give rise to much higher $\Delta\delta^{R,S}$ values than the classical reagents MTPA and MPA and offer a greater guarantee for the correct assignment of the absolute configuration.

Introduction

A very attractive method for the determination of the absolute configuration of organic compounds in solution is based on the NMR technique.[1] This consists of the derivatization of the substrate (B) of unknown configuration with the *R* and *S* enantiomers of a chiral auxiliary reagent (A) and subsequent comparison of the NMR spectra of the resulting diastereomeric compounds. The configuration of B is established by means of a model that correlates the configuration of the substrate B with the sign of the differences observed in the chemical shifts ($\Delta\delta^{R,S}$) of the substituents bonded directly to the chiral center (L_1/L_2). The general structure of the chiral auxiliary (A) is shown in Figure 1 along with that of the substrate B and the two diastereoisomers whose NMR spectra must be compared. The chiral auxiliary reagent must meet some criteria:[2] It must contain (a) a group (Z) to bond the auxiliary to the substrate (i.e., a carboxylate group); (b) a group (Y) with a marked anisotropic effect (aromatic ring, carbonyl group, etc.); and (c) a polar group (R_1 or R_2), which helps to fix a preferred conformation.

The preference for a particular conformation must be maintained in the two diastereoisomeric derivatives and give rise to group Y acting strongly and selectively on substituents L_1 or L_2.

The most widely experienced approach for the determination of the absolute configuration by NMR was introduced by Mosher[3] and uses MTPA (**1**) and MPA (**2**) (Figure 2) as the auxiliary reagents and secondary alcohols as substrates.

New reagents have been developed[2,4a] in this field (AMAAs, **3**−**5**, Figure 2) that are much more efficient than the commercial MTPA (**1**) and MPA (**2**). Other advances involved optimization of the experimental conditions,[4b] use of a single derivative instead of two,[4c] and evaluation of the esterification shifts.[4d]

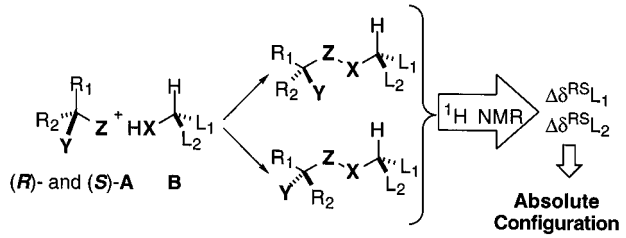

Figure 1.

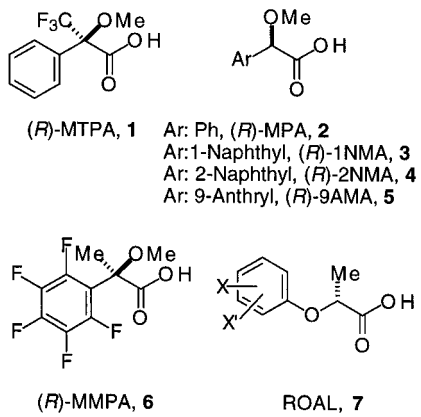

Figure 2. Common NMR reagents for primary amines.

In the case of amines, the results obtained have not been as good, and AMAAs that have given excellent results with secondary alcohols have not been of particular relevance for amines.[5] Some new reagents have

* To whom correspondence should be addressed. Fax: +34-81-591091.

(1) For a review, see: Uray, G. In *Houben-Weyl Methods in Organic Chemistry*; Helchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, New York, 1996; Vol. 1, p 253.

(2) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *Tetrahedron* **1997**, *53*, 8541−8567.

(3) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147.

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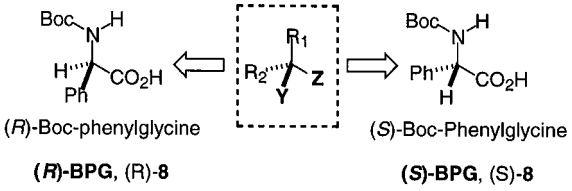

Figure 3.

developed for amines[6] [MMPA (**6**) and ROAL (**7**)], but the best results are still obtained with MTPA[7a] and MPA.[5,7b]

To predict the absolute configuration with guarantee, the $\Delta\delta^{R,S}$ absolute values must be sufficiently large and well greater than the experimental error. In the amides derived from both MTPA and MPA, these values are generally very small and are close to the limits of experimental error.[7a] For this reason, there is an inherent risk of assigning the configuration incorrectly. We therefore decided to investigate the use of alternative auxiliary reagents in an attempt to obtain improved results, in comparison with MTPA and MPA, for α-substituted primary amines.

Boc-phenylglycine possesses the structural prerequisites described above for a suitable reagent for amines (Figure 1); its structure incorporates a phenyl ring as anisotropic group (Y), NH−Boc acts as the polar group (R_1), and the carboxyl (Z) provides a linkage to the substrate. In addition, the two enantiomers (*R*)- and (*S*)-Boc-phenylglycine [(*R*)- and (*S*)-BPG, (*R*)-**8** and (*S*)-**8**, Figure 3] are cheap and commercially available in optically pure form.

In the work described here we undertook an investigation into the utility of Boc-phenylglycine as a chiral auxiliary reagent for α-substituted primary amines and compared its effectiveness with MTPA and MPA.

Calculations

Our study on the conformational preference of BPG amides began with Molecular Mechanics calculations (MM) on the BPG amide of methylamine (**9**). The main conformers were generated by rotation of bonds ω1 (Cα−CO), ω2 (Cα−Ph), ω3 (Cα−NH), and ω4 (NH−Boc) (Figure 4).

The most important process involves rotation around the Cα−CO (ω1) bond, and two main conformers were found for this rotation: the ap conformation, in which the Cα−H bond is anti-periplanar with respect to the C═O bond (Figure 4b), and the sp conformation, in which these two bonds are in a syn-periplanar disposition (Figure 4c).

When rotation about the Cα−Ph bond (ω2) is examined, the minimum energy conformation presents the phenyl ring coplanar with the Cα−H bond (Figure 4d). As far as rotation about the Cα−NH (ω3) and NH−Boc (ω4) bonds is concerned, the greatest stability is represented by conformers having the Cα−H, N−H, and C═O bonds coplanar, the Cα−H and N−H bonds anti, and the N−H anti with respect to the C═O bond (Figure 4e).

The Molecular Mechanics calculations (Table 1) indicate that the ap conformation is more stable than the sp conformation by 1.76 kcal/mol. To obtain more reliable data regarding the energy value, semiempirical calculations were performed

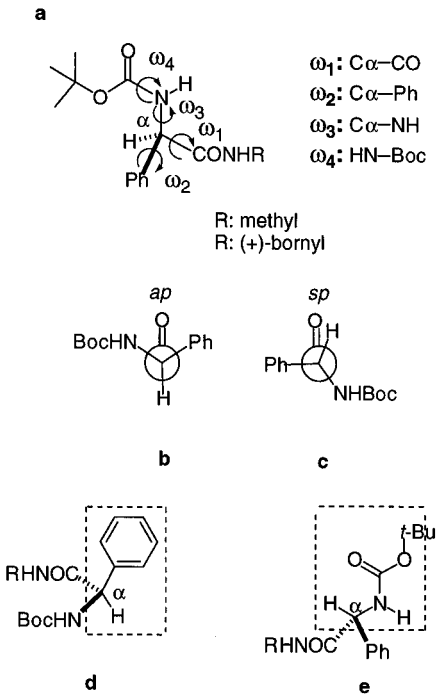

Figure 4. Dihedral angles in BPG amides (a); low-energy rotamers around the Cα−CO bond (b and c), Cα−Ph bond (d), and Cα-NH (e).

Table 1. MM and AM1 Relative Energies Calculated for the Lower Energy Conformers of (*R*)-BGP Methylamide [(*R*)-9] and (*R*)- and (*S*)-PBG (+)-Bornylamide (10a,b)

compd	conformer	MM (kcal/mol)	AM1 (kcal/mol)
(*R*)-**9**	ap	0.00	0.00
	sp	1.76	1.04
10a	ap	0.00	0.00
	sp	0.37	1.06
10b	ap	0.00	0.00
	sp	0.37	1.05

on the same system (AM1, Table 1), and the order of stability was found to remain identical with a difference of 1.04 kcal/mol.

The same type of calculations were also performed on a more complex system, namely the (*R*)- and (*S*)-BPG amides of (+)-bornylamine (**10a** and **10b**, respectively). Both the MM and semiempirical calculations (AM1) confirmed that ap is more stable than sp (Table 1).

The calculations also indicate that in the most stable conformer (ap) the phenyl ring is coplanar with the Cα−H bond, which permits effective transmission of the shielding effects to the substituents (L_1/L_2) of the amine.

According to these results, the L_1 substituent in the (*R*)-BPG amides should be shielded in the ap conformation, while the L_2 substituent will remain unaffected. In contrast, in the sp conformation it is L_2 that is slightly shielded, while L_1 remains unaffected (Figure 5a). In the case of the (*S*)-BPG amides, it is L_2 that is shielded in the ap conformer with L_1 remaining unaffected, and in the sp conformer L_1 is slightly shielded while L_2 is unaffected (Figure 5b).

Given that the population of the ap conformer is greater than that of the sp conformer, L_1 will be more shielded in the (*R*)-BPG amide than in the (*S*)-analogue, and conversely, L_2 will be more shielded in the (*S*)-BPG amides than in the (*R*)-analogue.

If we define the differences in the chemical shifts ($\Delta\delta^{R,S}$) as the difference between the chemical shift of a group (L_1/L_2) in the (*R*)-amide minus that in the (*S*)-amide, the following relationship $\Delta\delta^{R,S}L_1 < 0$ and $\Delta\delta^{R,S}L_2 > 0$ allows the assignment of the spatial position of L_1/L_2 by comparison of the ^{1}H NMR spectra of the two diastereoisomers.

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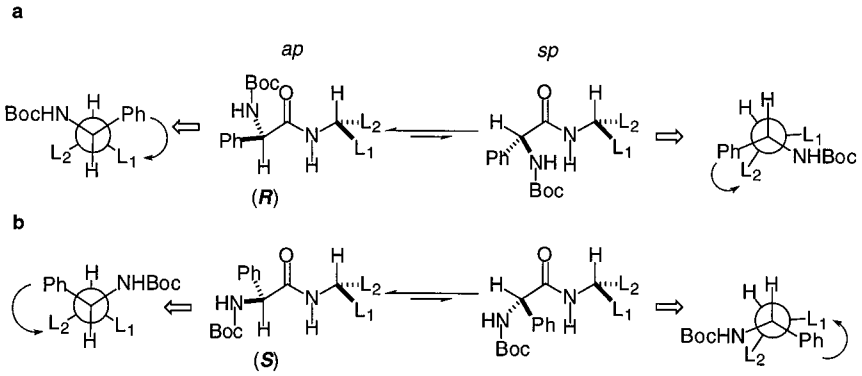

Figure 5. Equilibrium between the ap and sp conformers of the (*R*)- and (*S*)-BPG amides.

NMR Results

The next step in this study was to assess the validity of the theoretical predictions and the utility of (*R*)- and (*S*)-BPG as reagents for the determination of the absolute configuration of α-substituted primary amines. We therefore prepared the amides derived from the two enantiomers of BPG and a variety of α-substituted primary amines of known configuration and diverse structures (**10**−**19**, Figure 6).

The ^{1}H NMR spectra of the resulting compounds were recorded, and the same trend was observed in all cases. The substituent corresponding to L_1 in Figure 5 is more shielded in the (*R*)-BPG amides than in the (*S*)-BPG analogues, while the substituent corresponding to L_2 in Figure 5 is more shielded in the (*S*)-BPG amides than in those derived from (*R*)-BPG. This trend is the same as predicted in the theoretical study.

It can be seen in Figure 6 that the $\Delta\delta^{R,S}$ values for the substituents directly bonded to the chiral center (L_1/L_2) show the same distribution of signs in each case: i.e., $\Delta\delta^{R,S}L_1 < 0$ and $\Delta\delta^{R,S}L_2 > 0$.

The distribution of the shielding effects, and therefore the signs of the $\Delta\delta^{R,S}$ values, is in agreement with the conformational analysis discussed previously and is not affected by the presence of different functional groups (polar, aromatic, etc.) in the amine structure.

Simplified Model for the Determination of the Absolute Configuration of the Amides. To determine the absolute configuration of a primary amine it is necessary to prepare both the (*R*)- and (*S*)-BPG amides, record the ^{1}H NMR spectra of these two compounds, and calculate the $\Delta\delta^{R,S}$. The absolute configuration can be determined by applying the model represented in Figure 7. The model is relatively simple in that the conformational equilibrium is simplified to include only the most relevant conformers from the point of view of NMR. In this sense, the most highly populated conformers (ap) have the Cα−H, C═O, and C_1'−H bonds in a coplanar arrangement with the Cα−H and C═O bonds anti and the C═O and C_1'−H bonds in a syn arrangement. The phenyl ring selectively shields the substituent (L_1/L_2) located in the same side of the plane. For this reason, the substituent that has negative $\Delta\delta^{R,S}$ values will occupy the L_1 position, while the substituent giving rise to a positive $\Delta\delta^{R,S}$ value will occupy the L_2 position.

Thus, the configuration of any primary amine can be determined by NMR spectroscopy using this simplified model.

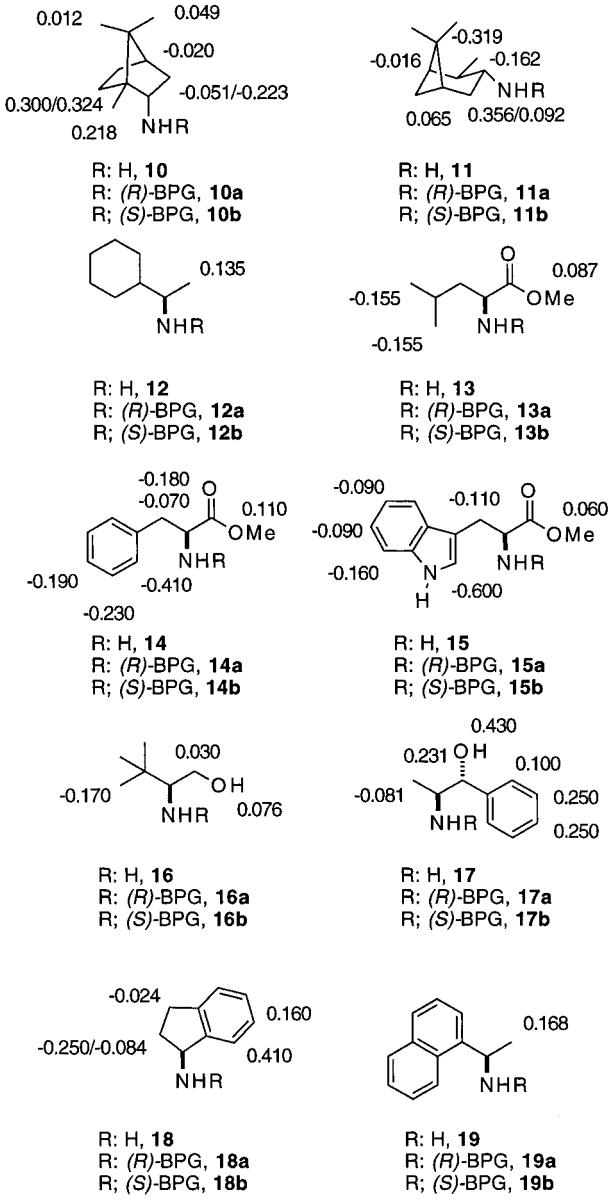

Figure 6. Selected $\Delta\delta^{R,S}$ values for (*R*)- and (*S*)-BPG amides.

BPG versus MPA and MTPA

Having demonstrated that the configuration of primary amines can be determined by ^{1}H NMR spectroscopy using BPG, we proceeded to compare the utility of the three reagents BPG, MTPA, and MPA.

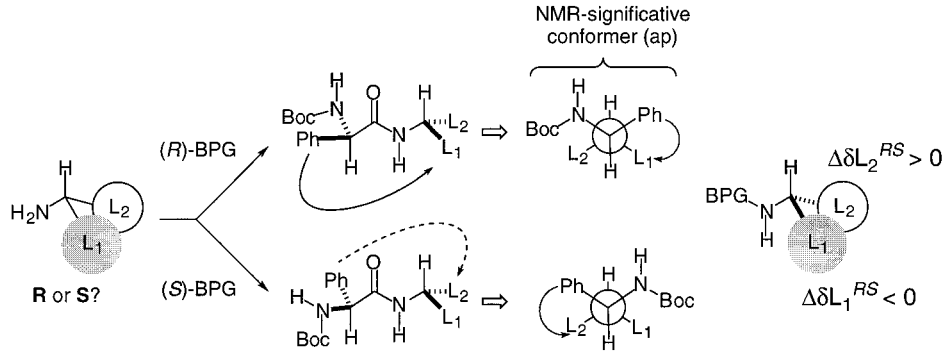

Figure 7. Simplified model for the determination of absolute configuration of BPG amides.

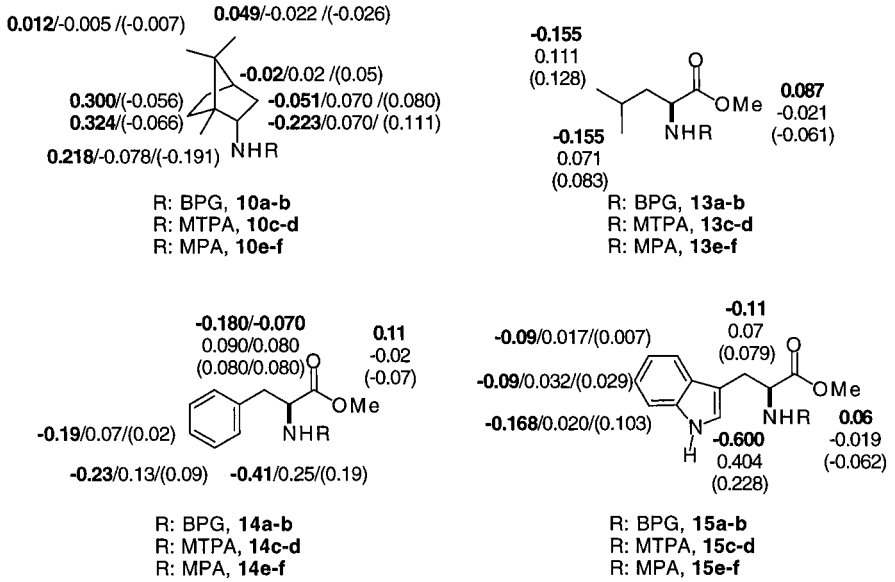

Figure 8. Comparison of $\Delta\delta^{R,S}$ values of BPG (bold), MTPA (plain), and MPA amides (parentheses).

The differences in chemical shifts ($\Delta\delta^{R,S}$) obtained with the different reagents for a selection of amines[8] are shown in Figure 8. Two points must be highlighted regarding this model: (a) the signs of the $\Delta\delta^{R,S}$ values obtained with BPG are opposite to those obtained with MTPA and MPA, and (b) in all cases the $\Delta\delta^{R,S}$ values obtained with BPG are larger than those obtained with MTPA and MPA (with the best value being three times greater).

The reason the signs of the $\Delta\delta^{R,S}$ values obtained with BPG are opposite to those for MTPA and MPA is that L_1 is shielded in the (*S*)-MTPA and MPA amides, whereas L_2 is shielded in the (*R*)-MTPA and MPA amides, meaning that $\Delta\delta^{R,S}L_1 > 0$ and $\Delta\delta^{R,S}L_2 < 0$ (Figure 9a,b). In contrast, in the case of the BPG amides the opposite is true: L_1 is shielded in the (*R*)-BPG amides and L_2 is shielded in the (*S*)-BPG derivatives, and therefore, the signs are opposite ($\Delta\delta^{R,S}L_1 > 0$ and $\Delta\delta^{R,S}L_2 > 0$, Figure 9c), as deduced by the conformational analysis.

As previously shown, the calculations suggest that the BPG amides exist in an equilibrium between two conformers. In the most stable conformer (ap) the aromatic ring is coplanar with the Cα−H bond (Figure 10a), placing L_1/L_2 in the direction of maximum shielding.[9] A combination of these two factors [i.e., (i) a simple equilibrium between the two conformers (ap and sp) and (ii) a suitable orientation of the phenyl ring] leads to the

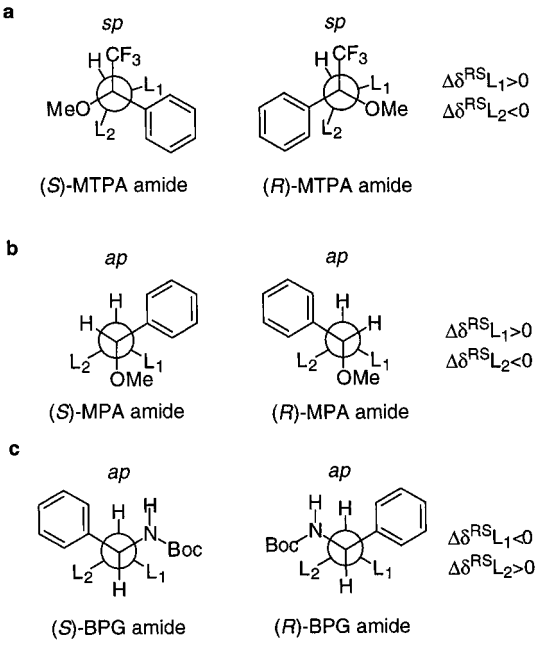

Figure 9. NMR-representative conformers of MTPA (a), MPA (b), and BPG amides (c).

(8) For NMR data of MTPA and MPA amides, see ref 7a and references therein.

(9) Haigh, C. W.; Mallion, R. B. *Progress in NMR Spectroscopy*; Pergamon Press: Ltd.: New York, 1980; Vol. 13, pp 303−344.

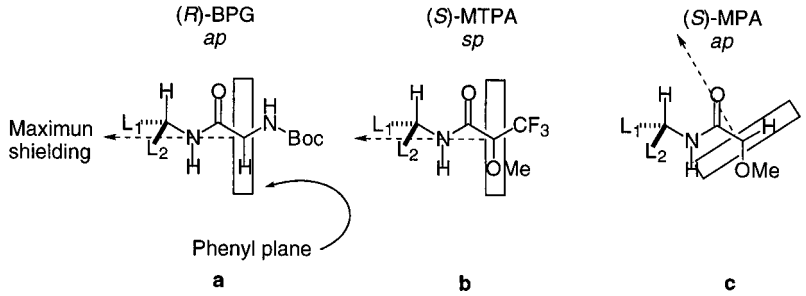

Figure 10. Main orientation of the phenyl ring and direction of maximum shielding in BPG (a), MTPA (b), and MPA amides (c).

$\Delta\delta^{R,S}$ values being larger than in the cases of the MTPA and MPA amides.

We must remember that in the case of the most stable conformer of the MTPA amides[10] (sp) the aromatic ring adopts a conformation that is equivalent to that in the BPG amides, with the ring coplanar with the Cα−OMe bond (Figure 10b), and for this reason the substituents L_1/L_2 are located in the direction of maximum shielding. However, this improved spatial arrangement is counteracted by a more complicated conformational situation[10] (three conformers in equilibrium), and thus, the $\Delta\delta^{R,S}$ values are small. In the case of the MPA amides there are only two conformers in equilibrium,[11] but this advantage is offset by the less favorable disposition of the phenyl ring, which is coplanar with the Cα−H bond. This means that L_1/L_2 are forced to a position further from the region of maximum shielding (Figure 10c). As a consequence, the $\Delta\delta^{R,S}$ values are small and are, in fact, comparable to those for the MTPA analogues.

The BPG amides combine both favorable situations: (i) a conformational equilibrium between only two conformers (as in MPA), meaning that a greater contribution is made by the representative conformer to the average chemical shift in the equilibrium, and (ii) a more favorable orientation of the aromatic ring (as in MTPA, Figure 10b) in a parallel disposition to the C=O bond, which permits the shielding effects[9] to be transmitted more effectively to the substituents. The combination of these two factors means that the $\Delta\delta^{R,S}$ values are larger than those obtained from MTPA and MPA (Figure 8), making this a better reagent for the assignment of the absolute configuration of the amines in question.

Conclusion

It has been demonstrated in this work that Boc-phenylglycine (BPG), a reagent commercially available in both pure enantiomeric forms, can be used in the determination of the absolute configuration of α-substituted primary amines using NMR spectroscopy. The BPG derivatives give rise to much higher $\Delta\delta^{R,S}$ values than the classical reagents MTPA and MPA, and this offers a greater guarantee in correctly determining the absolute configuration by NMR.

To determine the configuration of the primary amine, the amides with the two enantiomers of the auxiliary reagent (*R*)- and (*S*)-BPG must be prepared, their ^{1}H NMR recorded, and the differences in the chemical shifts ($\Delta\delta^{R,S}$) calculated. The substituent with a negative $\Delta\delta^{R,S}$ value occupies the position L_1 in Figure 7 and that with a positive $\Delta\delta^{R,S}$ value occupies the position L_2. From this model the absolute configuration (*R*/*S*) of the chiral center can be determined.

Experimental Section

NMR Spectroscopy and Computational Methods. ^{1}H and ^{13}C NMR spectra of samples in $CDCl_3$ (4 mg in 0.5 mL) were recorded at 250 MHz. Chemical shifts (ppm) are internally referenced to the TMS signal (0 ppm) in all cases. For 1D ^{1}H NMR spectra, size 32 K, pulse length 2.8 ms (30°), 16 acquisitions were used. The NMR spectra were repeated at concentrations from ca. 8 mg/mL up to ca. 1 mg/mL to establish the absence of concentration effects.

Molecular mechanics and semiempirical AM1 calculations were performed by the Insight II package. For additional information on NMR spectroscopy and computational methods, see ref 7a.

Optical rotations were measured in a JASCO Dip 360 polarimeter.

General Methods. Preparation of diastereomeric amides from the free amine and (*R*)- and (*S*)-Boc-phenylglycine was carried out with DCC in CH_2Cl_2. The reaction mixture was filtered to remove the dicyclohexylurea, and the amide was purified by flash chromatography on silica gel using hexanes−ethyl acetate as eluent. Further purification was accomplished by HPLC (Spherisorb S5W, 10 mm × 250 mm, hexanes−ethyl acetate).

(+)-Bornyl (*R*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (10a): $[\alpha]_D = -48.6$ ($c = 0.031$, $CHCl_3$); HPLC t_R = 17.96 min (hexane/ethyl acetate 80:20, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.56 (dd, J = 4.5, 8.4 Hz, 1H), 0.81 (s, 3H), 0.85 (s, 3H), 0.91 (s, 3H), 0.96−1.06 (m, 1H), 1.33−1.43 (m, 2H), 1.41 (s, 9H), 1.60 (m, 1H), 1.64−1.76 (m, 1H), 2.18−2.31 (m, 1H), 4.10−4.20 (m, 1H), 5.12 (br, 1H), 5.85−5.88 (m, 2H), 7.24−7.37 (m, 5H); ^{13}C NMR (62.97 MHz) δ 13.6, 18.5, 19.7, 27.8, 28.1, 28.2, 37.4, 44.7, 48.1, 49.4, 54.2, 80.0, 127.1, 128.2, 128.9, 138.4, 155.2, 170.1; MS (EI) *m*/*z* 386 (M^+).

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.47; H, 8.85; N, 7.23.

(+)-Bornyl (*S*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (10b): $[\alpha]_D = +52.8$ ($c = 0.035$, $CHCl_3$); HPLC t_R = 21.21 min (hexane/ethyl acetate 80:20, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.59 (s, 3H), 0.78 (dd, J = 4.5, 8.4 Hz, 1H), 0.80 (s, 3H), 0.89 (s, 3H), 0.97−1.27 (m, 3H), 1.40 (s, 9H), 1.59−1.80 (m, 1H), 2.23−2.36 (m, 1H), 4.13−4.22 (m, 1H), 5.15 (br, 1H), 5.93−5.97 (m, 2H), 7.21−7.37 (m, 5H); ^{13}C NMR (62.97 MHz) δ 13.4, 18.5, 19.6, 27.4, 28.1, 28.2, 37.1, 44.7, 47.9, 49.7, 53.8, 57.1, 79.8, 127.1, 128.1, 128.8, 128.9, 138.8, 155.2, 170.1; MS (EI) *m*/*z* 386 (M^+).

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.43; H, 8.88; N, 7.25.

(−)-Isopinocampheyl (*R*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (11a): $[\alpha]_D = -50.9$ ($c = 0.017$, $CHCl_3$); HPLC t_R = 19.08 min (hexane/ethyl acetate 80:20, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.70 (d, J = 9.8 Hz, 1H), 1.99 (s, 3H),

(10) Main conformers of MTPA amides: sp (CF_3 syn-periplanar to C=O bond, lowest in energy), ap3 (CF_3 anti-periplanar to C=O bond, phenyl ring coplanar to Cα−CF_3 bond), and ap1 (CF_3 anti-periplanar to C=O bond, phenyl ring coplanar to Cα−OMe bond). See ref 7a.

(11) Main conformers of MPA amides: ap (MeO anti-periplanar to C=O bond, lowest in energy) and sp (MeO syn-periplanar to C=O). See ref 5.

1.09 (d, J = 7.1 Hz, 3H), 1.18 (s, 3H), 1.21−1.32 (m, 1H), 1.40 (s, 9H), 1.69−1.89 (m, 3H), 2.82−2.52 (m, 2H), 4.16−4.29 (m, 1H), 5.10 (br, 1H), 5.68 (br, 1H), 5.84 (br, 1H), 7.28−7.82 (m, 5H); ^{13}C NMR (62.97 MHz) δ 20.6, 23.3, 24.9, 27.9, 8.2, 33.8, 35.2, 36.7, 38.3, 41.4, 46.1, 47.6, 48.2, 79.9, 127.1, 128.2, 128.8, 138.6, 155.2, 169.5; MS (EI) m/z 386 (M^+).

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.45; H, 8.85; N, 7.26.

(−)-Isopinocampheyl (*S*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (11b): $[\alpha]_D$ = +36.1 (c = 0.020, $CHCl_3$); HPLC t_R = 19.79 min (hexane/ethyl acetate 80:20, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.74 (d, J = 9.8 Hz, 1H), 0.92 (d, J = 7.2 Hz, 3H), 0.99 (s, 3H), 1.18 (s, 3H), 1.40 (s, 9H), 1.46−1.60 (m, 2H), 1.70−1.78 (m, 1H), 1.85−1.91 (m, 1H), 2.30−2.39 (m, 1H), 2.45−2.59 (m, 1H), 4.15−4.27 (m, 1H), 5.14 (br, 1H), 5.79−5.86 (m, 2H), 7.27−7.71 (m, 5H); ^{13}C NMR (62.97 MHz) δ 20.6, 23.3, 27.9, 28.3, 35.1, 36.6, 38.3, 41.3, 45.9, 47.6, 48.2, 79.9, 127.1, 128.2, 128.9, 138.5, 155.2, 169.4; MS (EI) m/z 386 (M^+).

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87; N, 7.25. Found: C, 71.45; H, 8.85; N, 7.26.

(*R*)-1-Cyclohexylethyl (*R*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (12a): $[\alpha]_D$ = −59.5 (c = 0.017, $CHCl_3$); HPLC t_R = 21.21 min (hexane/ethyl acetate 80:20, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.55−1.01 (m, 5H), 1.05 (d, J = 6.6 Hz, 3H), 1.09−1.22 (m, 4H), 1.40 (s, 9H), 1.44−1.57 (m, 2H), 3.74−3.89 (m, 1H), 5.04 (br, 1H), 5.46 (d, J = 9.0 Hz, 1H), 5.86 (br, 1H), 7.27−7.35 (m, 5H); ^{13}C NMR (62.97 MHz) δ 18.4, 26.4, 26.5, 26.7, 28.6, 28.7, 29.3, 43.4, 50.1, 80.4, 127.6, 128.7, 129.4, 139.4, 155.5, 169.5; MS (EI) m/z 360 (M^+).

Anal. Calcd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95; N, 7.77. Found: C, 69.90; H, 8.91; N, 7.75.

(*R*)-1-Cyclohexylethyl (*S*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (12b): $[\alpha]_D$ = +46.1 (c = 0.020, $CHCl_3$); HPLC t_R = 17.06 min (hexane/ethyl acetate 80:20, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.92 (d, J = 6.7 Hz, 3H), 0.97−1.33 (m, 7H), 1.40 (s, 9H), 1.66−1.75 (m, 4H), 3.79 (m, 1 H), 5.06 (br, 1H), 5.48 (d, J = 8.5 Hz, 1H), 5.82 (br, 1H), 7.27−7.35 (m, 5H); ^{13}C NMR (62.97 MHz) δ 18.0, 26.4, 26.7, 28.7, 29.4, 29.5, 43.3, 50.4, 80.4, 127.6, 128.6, 129.4, 130.1, 155.6, 169.7; MS (EI) m/z 360 (M^+).

Anal. Calcd for $C_{21}H_{32}N_2O_3$: C, 69.97; H, 8.95; N, 7.77. Found: C, 69.96; H, 8.93; N, 7.75.

(*S*)-*N*-((*R*)-2-Phenyl-*N*-(*tert*-butoxycarbonyl)glycinyl)-leucine methyl ester (13a): $[\alpha]_D$ = −48.1 (c = 0.035, $CHCl_3$); HPLC t_R = 19.17min (hexane/ethyl acetate 75:25, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.76 (d, J = 6.56 Hz, 6 H), 1.39 (s, 9H), 1.24−1.57 (m, 3H), 3.71 (s, 3H), 4.58 (m, 1H), 5.16 (br, 1H), 6.36 (d, J = 8.28 Hz, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR (62.97 MHz) δ 21.9, 23.1, 25.0, 28.6, 41.6, 51.2, 52.8, 80.5, 127.6, 128.7, 129.3, 138.7, 155.4, 170.3, 173.6; MS (EI) m/z 378 (M^+).

Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.50; H, 7.91; N, 7.45.

(*S*)-*N*-((*S*)-2-Phenyl-*N*-(*tert*-butoxycarbonyl)glycinyl)-leucine methyl ester (13b): $[\alpha]_D$ = +40.1 (c = 0.027, $CHCl_3$); HPLC t_R = 17.89 min (hexane/ethyl acetate 75:25, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.91 (d, J = 5.85 Hz, 6H), 1.41 (s, 9H), 1.46−1.58 (m, 3H), 3.63 (s, 3H), 4.59 (m, 1H), 5.15 (br, 1H), 5.73 (br, 1H), 6.15 (d, J = 8.16 Hz, 1H), 7.30−7.37 (m, 5 H); ^{13}C NMR (62.97 MHz) δ 22.3, 23.2, 25.2, 28.7, 41.8, 51.4, 52.6, 80.5, 127.4, 128.8, 129.4, 138.2, 155.7, 170.3, 173.2; MS (EI) m/z 378 (M^+).

Anal. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40. Found: C, 63.46; H, 7.95; N, 7.43.

(*S*)-*N*-((*R*)-2-Phenyl-*N*-(*tert*-butoxycarbonyl)glycinyl)-phenylalanine methyl ester (14a): $[\alpha]_D$ = +11.7 (c = 0.018, $CHCl_3$); HPLC t_R = 12.69 min (hexane/ethyl acetate 60:40, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 1.33 (s, 9H), 2.90 (d, J = 5.37 Hz, 2H), 3.64 (s, 3H), 4.84 (m, 1H), 5.02 (br, 1H), 5.74 (d, J = 4.61 Hz, 1H), 6.09 (d, J = 5.90 Hz, 1H), 6.56 (d, J = 6.97 Hz, 2H), 6.96−7.19 (m, 3H), 7.22−7.32 (m, 5H); ^{13}C NMR (62.97 MHz) δ 28.2, 37.5, 52.2, 52.3, 52.9, 53.4, 79.9, 126.9, 127.1, 127.2, 128.3, 128.4, 128.5, 128.9, 129.0, 129.2, 135.0, 135.5, 154.8, 169.3, 171.3; MS (EI) m/z 412 (M^+).

Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.90; H, 6.81; N, 6.75.

(*S*)-*N*-((*S*)-2-Phenyl-*N*-(*tert*-butoxycarbonyl)glycinyl)-phenylalanine methyl ester (14b): $[\alpha]_D$ = +61.5 (c = 0.025, $CHCl_3$); HPLC t_R = 12.20 min (hexane/ethyl acetate 60:40, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 1.37 (s, 3H), 3.00 (dd, J = 5.98, 13.86 Hz, 1H), 3.12 (dd, J = 5.56, 13.88 Hz, 1H), 3.59 (s, 3H), 4.76 (m, 1H), 5.08 (br, 1H), 5.63 (br, 1H), 6.26 (d, J = 7.47 Hz, 1H), 7.00 (d, J = 7.58 Hz, 2H), 7.10−7.31 (m, 8H); ^{13}C NMR (62.97 MHz) δ 28.2, 29.6, 37.6, 52.2, 52.3, 53.4, 80.1, 127.1, 127.2, 128.3, 128.4, 128.5, 128.8, 129.0, 129.2, 135.5, 137.6, 154.9, 169.7, 171.3; MS (EI) m/z 412 (M^+).

Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.98; H, 6.80; N, 6.75.

(*S*)-*N*-((*R*)-2-Phenyl-*N*-(*tert*-butoxycarbonyl)glycinyl)-tryptophan methyl ester (15a): $[\alpha]_D$ = +2.8 (c = 0.033, $CHCl_3$); HPLC t_R = 19.14 min (hexane/ethyl acetate 60:40, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 1.39 (s, 9H), 3.10 (dd, J = 5.04, 14.82 Hz, 1H), 3.26 (dd, J = 5.31, 14.83 Hz, 1H), 3.63 (s, 3H), 4.90 (m, 1H), 5.12 (br, 1H), 5.82 (br, 1H), 6.24 (d, J = 2.36 Hz, 1H), 6.36 (d, J = 7.63 Hz, 1H), 7.02 (dd, J = J' = 6.89 Hz,), 7.13 (dd, J = J' = 6.89 Hz), 7.23−7.33 (m, 7H), 8.02 (br, 1H); ^{13}C NMR (62.97 MHz) δ 27.2, 28.2, 52.3, 52.6, 80.0, 108.7, 111.2, 118.1, 119.4, 121.9, 123.1, 127.1, 127.3, 128.2, 128.9, 135.9, 138.4, 154.9, 169.6, 171.8; MS (EI) m/z 451 (M^+).

Anal. Calcd for $C_{25}H_{29}N_3O_5$: C, 66.50; H, 6.47; N, 9.31. Found: C, 66.54; H, 6.40; N, 9.28.

(*S*)-*N*-((*S*)-2-Phenyl-*N*-(*tert*-butoxycarbonyl)glycinyl)-tryptophan methyl ester (15b): $[\alpha]_D$ = +56.2 (c = 0.035, $CHCl_3$); HPLC t_R = 21.29 min (hexane/ethyl acetate 60:40, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 1.41 (s, 9H), 3.29 (m, 2H), 3.57 (s, 3H), 4.85 (m, 1H), 5.12 (br, 1H), 5.73 (br, 1H), 6.36 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 2.12 Hz, 1H), 7.02−7.25 (m, 7H), 7.33 (d, J = 7.49 Hz, 1H), 7.49 (d, J = 7.59 Hz, 1H), 8.31 (br, 1H); ^{13}C NMR (62.97 MHz) δ 27.3, 28.2, 52.2, 52.3, 53.2, 80.1, 109.3, 111.3, 118.3, 119.5, 122.1, 123.0, 127.1, 127.2, 127.4, 128.2, 128.8, 136.0, 155.1, 169.8, 171.6; MS (EI) m/z 451 (M^+).

Anal. Calcd for $C_{25}H_{29}N_3O_5$: C, 66.50; H, 6.47; N, 9.31. Found: C, 66.49; H, 6.40; N, 9.33.

(*S*)-1-*tert*-Leucinyl (*R*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (16a): $[\alpha]_D$ = +40.9 (c = 0.015, $CHCl_3$); HPLC t_R = 21.16 min (hexane/ethyl acetate 60:40, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.74 (s, 9H), 1.40 (s, 9H), 3.07 (br, 1H), 3.46−3.55 (m, 1H), 3.76−3.84 (m, 2H), 5.20 (d, J = 4.8 Hz, 1H), 5.89 (d, J = 6.5 Hz, 1H), 6.32 (d, J = 8.5 Hz, 1H), 7.28−7.41 (m, 5H); ^{13}C NMR (62.97 MHz) δ 26.6, 28.3, 29.6, 33.8, 59.6, 62.2, 80.27, 127.1, 128.3, 128.8, 138.2, 155.4, 171. 2; MS (EI) m/z 350 (M^+).

Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.09; H, 8.60; N, 7.96.

(*S*)-1-*tert*-Leucinyl (*S*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (16b): $[\alpha]_D$ = +22.8 (c = 0.009, $CHCl_3$); HPLC t_R = 20.53 min (hexane/ethyl acetate 60:40, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 0.91 (s, 9H), 1.42 (s, 9H), 2.31 (br, 1H), 3.44 (m, 1H), 3.77 (m, 2H), 5.12 (d, J = 5.5 Hz, 1H), 5.63 (d, J = 5.3 Hz, 1H), 6.01 (d, J = 8.8 Hz, 1H), 7.29−7.39 (m, 5H); ^{13}C NMR (62.97 MHz) δ 26.8, 28.2, 33.4, 59.9, 62.5, 80.6, 127.2, 128.6, 129.1, 155.56, 170.9; MS (EI) m/z 350 (M^+).

Anal. Calcd for $C_{19}H_{30}N_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 65.11; H, 8.66; N, 7.98.

(1*R*,2*S*)-2-*N*-((*R*)-2-Phenyl-*N*-(*tert*-butoxycarbonyl)glycinyl)-1-phenyl-1-propanol (17a): HPLC t_R = 12.17 min (hexane/ethyl acetate 50:50, 2 mL/min); $[\alpha]_D$ = −70.2 (c = 0.023, $CHCl_3$); ^{1}H NMR (250.13 MHz) δ 0.87 (d, J = 6.8 Hz, 3H), 1.41 (s, 9H), 3.68 (br, 1H), 4.12−4.31 (m, 1H), 4.90 (br, 1H), 5.15 (br 1H), 5.78 (d, J = 6.6 Hz, 1H), 6.32 (d, J = 8.3 Hz, 1H), 7.21−7.35 (m, 10H); ^{13}C NMR (62.97 MHz) δ 13.5, 28.2, 51.2, 75.3, 80.3, 126.1, 127.1, 127.4, 128.2, 128.3, 128.9, 137.7, 140.6, 155.3, 170.5; MS (EI) m/z 384 (M^+).

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.70; H, 7.30; N, 7.26.

(1*R*,2*S*)-2-*N*-((*S*)-2-Phenyl-*N*-(*tert*-butoxycarbonyl)glycinyl)-1-phenyl-1-propanol (17b): HPLC t_R = 13.99 min (hexane/ethyl acetate 50:50, 2 mL/min); $[\alpha]_D$ = +10.0 (c = 0.023, $CHCl_3$); ^{1}H NMR (250.13 MHz) δ 0.95 (d, J = 6.9 Hz,

3H), 1.38 (s, 9H), 3.25 (br 1H), 4.27−4.35 (m, 1H), 4.69 (br, 1H), 5.12 (br, 1H), 5.84 (d, J = 6.5 Hz, 1H), 6.09 (br, 1H), 7.01−7.05 (m, 2H), 7.17−7.19 (m, 3H), 7.36 (m, 5H); ^{13}C NMR (62.97 MHz) δ 14.6, 28.2, 50.8, 75.9, 80.2, 124.9, 126.2, 127.2, 127.3, 128.0, 128.3, 129.0, 138.1, 139.9, 155.2, 170.6; MS (EI) m/z 384 (M^+).

Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.71; H, 7.32; N, 7.28.

(*S*)-1-Indanyl (*R*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)-acetamide (18a): $[\alpha]_D$ = +25.3 (c = 0.008, $CHCl_3$); HPLC t_R = 28.46 min (hexane/ethyl acetate 80:20, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 1.40 (s, 9H), 1.70−1.85 (m, 1H), 2.53−2.66 (m, 1H), 2.81−3.01 (m, 2H), 5.13 (br, 1H), 5.45 (dd, J = 7.94, 16.04 Hz, 1H), 5.83 (br 1H), 5.92 (d, J = 8.52 Hz, 1H), 6.81 (d, J = 7.43 Hz, 1H), 7.03−7.11 (m, 1H), 7.17−7.21 (m, 2H), 7.29−7.38 (m, 5H); ^{13}C NMR (62.97 MHz) δ 28.2, 30.2, 34.0, 54.8, 80.1, 123.5, 124.7, 126.7, 127.2, 127.9, 128.4, 129.0, 138.5, 142.6, 143.2, 155.4, 169.9; MS (EI) m/z 366 (M^+).

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.10; H, 7.14; N, 7.65.

(*S*)-1-Indanyl (*S*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)-acetamide (18b): $[\alpha]_D$ = −42.6 (c = 0.006, $CHCl_3$); HPLC t_R = 22.37 min (hexane/ethyl acetate 80:20, 2 mL/min); ^{1}H NMR (250.13 MHz) δ 1.41 (s, 9H), 1.52−1.66 (m, 1H), 2.45−2.58 (m, 1H), 2.81−2.88 (m, 2H), 5.13 (br, 1H), 5.46 (dd, J = 8.00, 15.68 Hz, 1H), 5.80 (br, 1H), 5.89 (d, J = 8.37 Hz, 1H), 7.22−7.24 (m, 4H), 7.27−7.38 (m, 5H); ^{13}C NMR (62.97 MHz) δ 28.2, 30.1, 33.6, 54.9, 80.0, 123.9, 124.8, 126.8, 127.2, 128.1, 128.4, 129.0, 138.3, 142.4, 143.3, 155.3, 169.8; MS (EI) m/z 366 (M^+).

Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.14; H, 7.13; N, 7.65.

(*R*)-1-(1-Naphthylethyl) (*R*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (19a): $[\alpha]_D$ = −88.9 (c = 0.021, $CHCl_3$); ^{1}H NMR (250.13 MHz) δ 1.36 (s, 9H), 1.62 (d, J = 6.78 Hz, 3H), 5.22 (br, 1H), 5.82 (m, 2H), 6.29 (br, 1H), 7.15 (d, J = 7.12 Hz, 1H), 7.23−7.46 (m, 8H), 7.71 (d, J = 8.15 Hz, 1H), 7.79 (d, J = 7.46 Hz, 1H), 7.83 (d, J = 6.89 Hz, 1H); ^{13}C NMR (62.97 MHz) δ 20.8, 28.2, 45.3, 79.9, 122.1, 123.0, 124.9, 125.6, 126.2, 127.1, 128.1, 128.5, 128.7, 130.7, 133.7, 137.8, 137.9, 155.1, 169.1; MS (EI) m/z 404 (M^+).

Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.20; H, 6.99; N, 6.95.

(*R*)-1-(1-Naphthylethyl) (*S*)-2-phenyl-2-*N*-(*tert*-butoxycarbonyl)acetamide (19b): $[\alpha]_D$ = +38.5 (c = 0.028, $CHCl_3$); ^{1}H NMR (250.13 MHz) δ 1.34 (s, 9H), 1.46 (d, J = 6.76 Hz, 3H), 4.98 (br, 1H), 5.74−5.85 (m, 2H), 6.18 (d, J = 8.04 Hz, 1H), 7.21−7.48 (m, 9H), 7.72 (d, J = 7.70 Hz, 1H), 7.78 (d, J = 7.50 Hz, 1H), 7.98 (d, J = 6.75 Hz, 1H); ^{13}C NMR (62.97 MHz) δ 20.3, 28.2, 45.0, 79.9, 122.5, 123.2, 125.1, 125.7, 126.5, 127.2, 127.4, 128.2, 128.3, 128.7, 128.8, 128.9, 130.9, 133.8, 137.6, 138.2, 154.9, 169.0; MS (EI) m/z 404 (M^+).

Anal. Calcd for $C_{25}H_{28}N_2O_3$: C, 74.23; H, 6.98; N, 6.93. Found: C, 74.19; H, 6.99; N, 6.91.

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