An NMR Strategy for Determination of Configuration of Remote Stereogenic Centers: 3-Methylcarboxylic Acids

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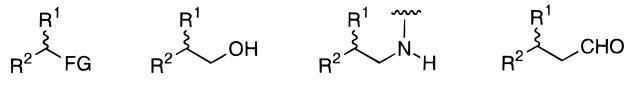
Abstract: A method has been developed for determining the absolute configuration of carboxylic acids bearing a methyl substituent at C(3). A series of 1-arylethylamide derivatives of such acids was prepared in which both the amine- and acid-derived portions were of known configuration. Diagnostic chemical shift differences ($\Delta\delta$'s) were identified for various proton resonances in each pair of diastereomeric amides and a new method was established based on the observed trends. A conformational model (supported by computational calculations) consistent with the observed differential shielding effects is offered. This approach represents a general strategy that can be adapted to other substructures.

NMR-based methods, utilizing various chiral auxiliaries, for establishing the absolute configuration of commonly encountered structural units are well-known.[1] Such methods are valuable in the context of natural product structure determination, especially in situations where the quantity of material is sufficiently limited to make degradation studies impractical. The functional group handle that is derivatized by the auxiliary is nearly always directly attached to the stereogenic center (i.e., α-branched) under examination (cf., **1a**). In a few cases, strategies have emerged for deducing the configuration of substrates in which the stereocenter is remote to the functional group handle. Strategies are available for β-branched primary alcohols [**1b**; Mosher esters/Eu(fod)$_3$],[2] amine derivatives (**1c**; Pirkle isocyanates),[3] and aldehydes (**1d**; ephedrine-derived oxazolidines).[4]

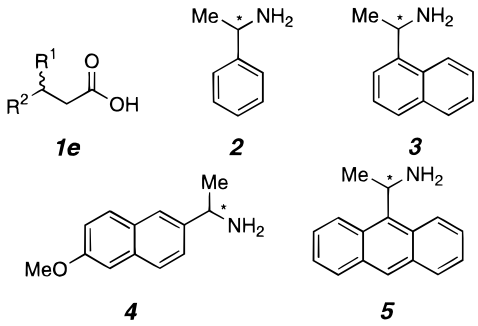


1a **1b** **1c** **1d**

Acyclic carboxylic acids containing remote stereocenters constitute another class of substrates for which a method of this type would be useful. β-Substituted acids **1e** represent a specific structural unit that is of interest to us in the context of several natural product structural questions. We describe here a solution to this problem and offer insight to the underlying conformational issues that are responsible for the success of the method. The approach also serves as a general strategy applicable to additional structural types.

α-Arylethylamides[5] (as well as -carbamates and -ureas) constitute the basis for NMR methods applicable to configurational determination of α-branched carboxylic acids (as well as secondary alcohols and amines) because of the well-recognized conformational properties of the XC(═O)NHCH(Me)(Ar) substructural unit.[6] The configurations of α-substituted acids have also been assigned from various phenylglycinamide derivatives.[7]

No NMR method is available for determination of configuration in remotely branched (i.e., β-, γ-, or δ-chiral) carboxylic acids. We have evaluated the potential of different 1-arylethylamines (**2**−**5**) as derivatizing agents for chiral carboxylic acids and conclude that those derived from 1-phenylethylamine (**2**) and 1-(1-naphthalenyl)ethylamine (**3**) are attractive for the assignment of configuration of chiral acids **1e**.



1e **2** **3** **4** **5**

To determine whether there would be sufficient anisotropic shielding to distinguish protons residing various distances from the carboxyl group, we first prepared the homologous series of *iso*amides derived from **2** through **5** and isobutyric (2-methylpropanoic), isovaleric (3-methylbutanoic), isocaproic (4-methylpentanoic), and 5-methylhexanoic acids. Amines **2** and **3** are commercially available in optically pure form, and compounds

(1) (a) Yamaguchi, S. In *Asymmetric Synthesis, Vol. 1, Analytical Methods*; Morrison, J. D., Ed.; Academic Press: New York, 1983; pp 125−152. (b) Parker, D. *Chem. Rev.* **1991**, *91*, 1441. It is important to distinguish between (the more numerous) methods that are suitable for determination of enantiomeric excess and those useful for the more demanding task of determination of configuration (e.g., Valentine, D., Jr.; Chan, K. K.; Scott, C. G.; Johnson, K. K.; Toth, K.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 62).

(2) Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* **1977**, 4085 and subsequent applications of that method.

(3) E.g.: (a) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520. (b) Pirkle, W. H.; Robertson, M. R.; Hyun, M. H. *J. Org. Chem.* **1984**, *49*, 2433.

(4) Agami, C.; Meynier, F.; Berlan, J.; Besace, Y.; Brochard, L. *J. Org. Chem.* **1986**, *51*, 73.

(5) E.g.: (a) Helmchen, G.; Völter, H.; Schühle, W. *Tetrahedron Lett.* **1977**, 1417 and references therein. (b) DeMunari, S.; Marazzi, G.; Forgione, A.; Longo, A.; Lombardi, P. *Tetrahedron Lett.* **1980**, *21*, 2273.

(6) Pirkle, W. H.; Finn, J. In *Asymmetric Synthesis, Vol. 1, Analytical Methods*; Morrison, J. D., Ed.; Academic Press: New York, 1983; pp 87−124 and references therein.

(7) Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853.

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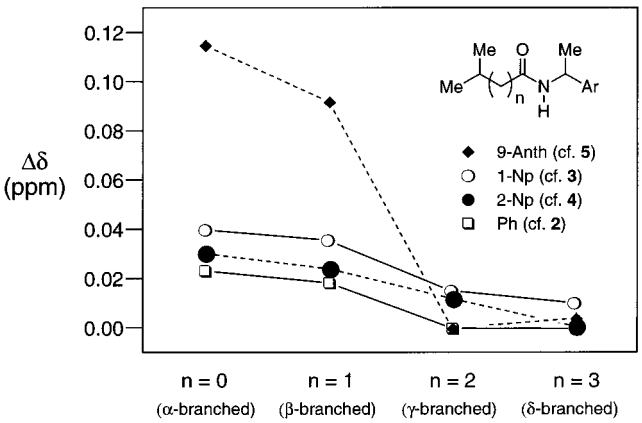
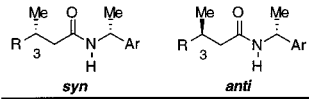


Figure 1. The magnitude of the anisotropic shielding effect ($\Delta\delta$) for diastereotopic Me groups in a series of α-, *β*-, *γ*-, and *δ*-branched carboxylic acid, *N*-1-arylethylamides.

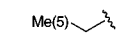
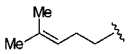
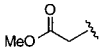
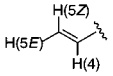
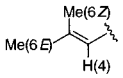
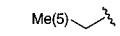
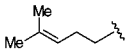
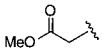
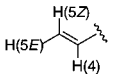
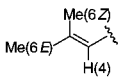
4 and **5** were prepared to perform the initial studies. The differences in ^{1}H NMR chemical shifts of the diastereotopic methyl groups are shown in Figure 1. As expected, the magnitude of the anisotropic effect for the anthracene-containing derivatives of **5** is generally larger than that for the other analogues. The second-strongest effect was observed for 1-naphthalenyl derivatives of **3**, and smaller $\Delta\delta$ values were observed for **4** and **2**.[8,9] Nevertheless, all of the amide derivatives provided sufficiently large differential anisotropic shielding to distinguish the diastereotopic methyl groups in the *β*-branched amides (cf. Figure 1, $n = 1$). This suggests that any of these amide derivatives could be used as chiral derivatizing agents for *β*-branched chiral acids. We used optically pure amines **2** and **3** for our further investigation because of the convenience of their ready availability.

It was first necessary to establish whether there would be a reliable trend in both the magnitude and, more importantly, sign of the chemical shift differences[10] across a series of amides derived from 3-substituted acids of known configuration. The data from amides **6**−**11** (from the phenyl-containing amine **2**) and **12**−**16** (from the 1-naphthalenyl-containing amine **3**) are summarized in Table 1. In entry 1 are the $\Delta\delta$ values for diagnostic resonances in the diastereomeric *syn*- and *anti*-(*R*)-*N*-1-phenylethylamides of *S*- and *R*-3-methylpentanoic acids (**6s** and **6*a***, respectively). We use *syn/anti* to define the relative orientation of the benzylic methyl group and the methyl substituent at C(3) when the main chains of the amides are oriented as shown in the structures at the top of Table 1. We define $\Delta\delta$ for any given resonance in a pair of diastereomeric amides as the value of the chemical shift in the syn diastereomer minus the value of the chemical shift of the anti diastereomer (i.e., $\Delta\delta = \delta_{syn} - \delta_{anti}$). The $\Delta\delta$ for the *β*-methyl group in the diastereomers **6a**/**6s** was positive (+0.032 ppm). The $\Delta\delta$ of the methyl protons of the ethyl group [i.e., C(5)] was both opposite in sign (−0.012 ppm) and smaller in magnitude.

Table 1. $\Delta\delta$ Values of the *β*-Methyl and Other Diagnostic Resonances in Diastereomeric *Syn* and *Anti* 1-Arylethylamides from 3-Methylcarboxylic Acids[a]

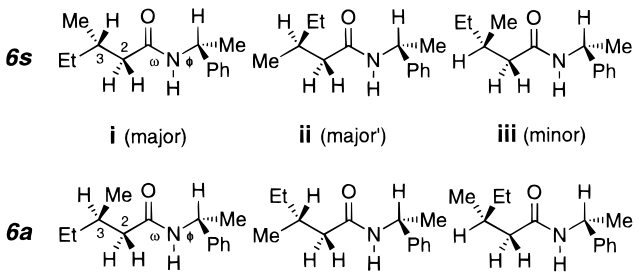


$\Delta\delta = \delta_{syn} - \delta_{anti}$

entry	*syn*	*anti*	R	Ar	$\Delta\delta_{C(3)\text{-}Me}$	$\Delta\delta_{other}$	
1	**6s**	**6a**		Ph	+0.032	-0.012	H(5)
2[b]	**7s**	**7a**		Ph	+0.03		
3	**8s**	**8a**		Ph	+0.033		
4	**9s**	**9a**		Ph	+0.013	-0.015	OMe
5	**10s**	**10a**		Ph	+0.030	-0.019 -0.021 -0.028	H(4) H(5*E*) H(5*Z*)
6	**11s**	**11a**		Ph	+0.013	-0.020 -0.048[c] -0.117[c]	H(4) Me(6*E*) Me(6*Z*)
7	**12s**	**12a**		1-Np	+0.050	-0.024	H(5)
8	**13s**	**13a**		1-Np	+0.050		
9	**14s**	**14a**		1-Np	+0.019	-0.032	OMe
10	**15s**	**15a**		1-Np	+0.041	-0.028 -0.050 -0.042	H(4) H(5*E*) H(5*Z*)
11	**16s**	**16a**		1-Np	+0.018	+0.020 -0.062[c] -0.154[c]	H(4) Me(6*E*) Me(6*Z*)

[a] In some cases the enantiomers of the compounds shown here were prepared. These are designated as ***ent*-##** in the Experimental Section. This, of course, does not affect the $\Delta\delta$ values reported here for the *diastereomeric* pairs. [b] Data from ref 11. The compounds were actually the enantiomers of those shown here. [c] See ref 18.

To account for the observed chemical shift differences, we created a conformational model based on the following considerations. The 1-arylethylamide derivatives used in our method have numerous degrees of rotational freedom. Detailed analysis of the conformational population is complex at best. However, we have devised a working model, perhaps only a mnemonic, to rationalize the observed shifts. The three staggered rotamers **i**−**iii** arise from rotation about C(2)−C(3) in the syn and anti 3-methylvaleramides **6s** and **6*a***. With respect to rotation about the N−$C_{benzylic}$ bond, we only consider those (presumably dominant) conformations having the benzylic C−H bond eclipsed with the amide carbonyl bond for the *s-trans* amide rotamer (i.e., $\omega = 180°$ and $\phi_{C-H} = 0°$). We assume



the conformational populations among rotamers **i**−**iii** to be similar for both diastereomers. Rotamers **i** and **ii** have the C(2)-to-carbonyl carbon bond anti to either the C(3) ethyl or C(3) methyl

(8) Jacobus, J.; Raban, M.; Mislow, K. *J. Org. Chem.* **1968**, *33*, 1142.

(9) It is interesting that there appears to be a stepwise rather than linear correlation between the rate of decease in the magnitude of the $\Delta\delta$ values and the number of methylenes in the isoamides. This suggests that an "even−odd" effect may be operative.

(10) Comparison of magnitude and sign of $\Delta\delta$ values between analogous pairs of resonances in two diasteromeric derivatives is a commonly used NMR strategy for deducing configuration and is most frequently encountered in the Mosher method: (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973,** *38*, 2143. (d) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

group. Rotamers **i** and **ii** should be similarly populated. In rotamer **iii** the C(2)-to-carbonyl carbon bond is anti to H(3) and bisects the larger methyl and ethyl groups. Thus, rotamer **iii** should be the least populated among **i**−**iii**. It follows that the methyl attached to C(3) in the syn diastereomer **6*s*** will be less highly shielded relative to the anti diastereomer **6*a***. Since the contribution of conformations **iii** is small, the relative shielding of the C(3) methyl group is most dependent upon conformations **i**, that of H(5) in the ethyl group upon conformation **ii**. Let us examine how the other entries in Table 1 are also consistent with this model.

Entry 2 shows data for the diastereomeric 1-phenylethylamides derived form 3-cyclohexylbutanoic acid (**7s** and **7a**), which were recently described by Sibi and Porter.[11] The C(3) methyl $\Delta\delta$ value is very similar in magnitude and identical in sign with that of **6**. Likewise, the $\Delta\delta$ for the C(3)-methyl group in the amides derived from (*R*)-citronellic acid **8*s***/**8*a*** was +0.033 (entry 3). The diastereomeric 3-methylglutarate derivatives **9*s***/**9*a***[12] gave two readily distinguishable resonances. The $\Delta\delta$ was positive for the C(3)-methyl group (+0.013, entry 4) and negative for the methoxy group (−0.015, entry 4). The 1-phenylethylamides of 3-methyl-4-pentenoic acids **10*s***/**10*a*** and of 3,5-dimethyl-4-hexenoic acids **11*s***/**11*a*** show positive $\Delta\delta$ values for the C(3) methyl group and negative values for all of the resonances associated with the olefin-containing substituents (entries 5 and 6).[13] The observed $\Delta\delta_{C(3)-Me}$ values for all of the diastereomeric pairs **6**−**11** are self-consistent and rationalizable by the proposed conformational model. Namely, the β-methyl groups appear farther downfield in the syn diastereomers than in the anti diastereomers. Where detectable, all resonances associated with the other substituent at C(3) are complementarily farther upfield in the syn isomers.

We have also prepared the analogous set of 1-(1-naphthalenyl)ethylamide derivatives **12**−**16**. As expected, the magnitude of the $\Delta\delta$ value was larger for these naphthalenes by a factor of ∼1.5−2 when compared with the phenyl-containing analogues (cf. entries 7 vs 1, 8 vs 3, 9 vs 4, 10 vs 5, and 11 vs 6 in Table 1). The assignments of relative configuration for **12** and **13** rest on the known absolute configurations of the precursor acid and amine (**3**). One of the diastereomers of **14** is known.[12b,c] The amides **15** were prepared from a racemic sample of the acid and separated (MPLC, silica gel). We then initially predicted the relative configuration of each isomer by analogy of the sign of the $\Delta\delta$'s for both the C(3)−Me and the vinyl resonances (entry 10) with the previous examples. Subsequent hydrogenation of the sample assigned structure **15*s*** produced **12s**, thereby proving its relative configuration and further validating the method. Finally, the configuration of the **16*s***/**16*a*** pair was assigned on the basis of analogous ^{1}H NMR spectral data and chromatographic behavior to those of **11*s***/**11*a***. Once again the β-methyl groups were always more highly deshielded in the syn series than in the anti. Protons in the other β-substituent were always relatively shielded in the syn isomers, with one exception: we observed that the vinylic H(4) in the **16s**/**16a** pair actually has a positive, rather than the expected negative, $\Delta\delta$ value (entry 11). This suggests a caveat for the application of this method; whenever possible, multiple proton resonances corresponding to multiple sites in the molecule should be analyzed.

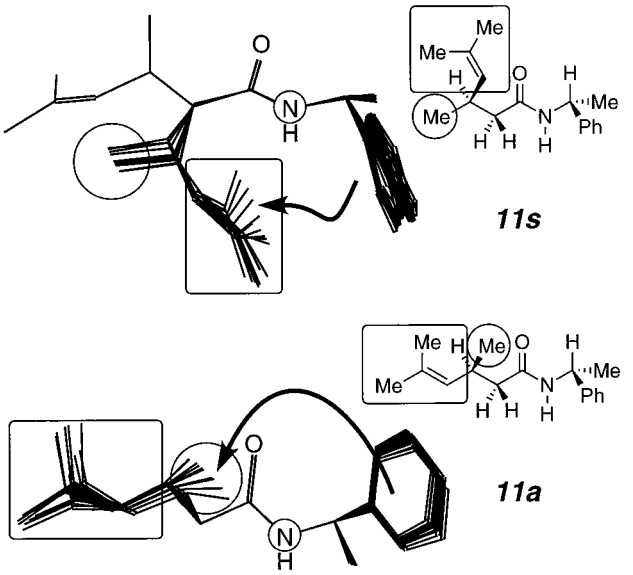


Figure 2. Arrays of the 10 lowest energy conformers representing the majority of the population of **11s** and **11a** diastereomers of 3,5-dimethyl-4-pentenoic acid (hydrogens removed for clarity) and their simplified ChemDraw models. The circle represents the position of the β-methyl substituent and the box that of the dimethylallyl moiety in **11**.

To provide an alternative perspective of the conformational issues in these amide derivatives, we have carried out a series of Monte Carlo searches of conformational space using the AMBER force field as implemented in the MacroModel[14] software package. Due to the flexible nature of these acyclic amides, dozens of conformations were found within 3 kcal/mol from the global minimum energy conformation for each of the 3-substituted amides that was searched. No one of the calculated low-energy conformations corresponds precisely to the rotamers **i**−**iii** shown above, although distinct similarities can be found. Instead of relying heavily on any single structure obtained from the calculations, we consider families of low-energy conformations that represent the majority of the population. Such analysis suggests those portions of the molecule that are likely to spend more time in the shielding region of the aromatic ring.

As an example, consider the arrays of superpositions of the 10 lowest energy conformations of **11s** and of **11a** that are shown in Figure 2. The C−(C═O)−NH−C sequence of atoms was superimposed in all 10 structures to generate these views. It is clear that in the family of low-energy conformers for **11s**, the phenyl ring is located quite near the 1-isobutenyl group in 9 out of the 10 lowest energy conformations. The opposite is observed for the anti isomer **11a**; the phenyl group is shielding the β-methyl substituent in all 10 conformations. This same trend is observed even when one examines families of, e.g., 20

(11) Sibi, M. P.; Ji J. G.; Wu, J. H.; Gurtler S.; Porter N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200.

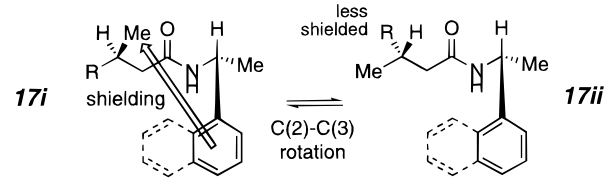
(12) (a) Assignment of the relative configuration in the major and minor products arising from opening of 3-methylglutaric anhydride with 1-phenylethylamine (**2**) (i.e., **9s** and **9a**, respectively) is based upon analogy with formation of the diastereomeric pair **14s** and **14a** by opening with 1-(1-naphthyl)ethylamine (**3**). Compound **14a** has been previously reported[12b,c] and its ^{1}H NMR data matched those of our minor diastereomer {δ = 3.638 (CO_2Me) and δ = 0.990 [C(3)Me]}. It is interesting that the sense of diastereoselectivity for this amide formation is opposite that observed for the reaction of 3-substituted glutaric anhydrides with 1-(1-naphthyl)-ethanol[12d] but the same as that observed with mandelate esters.[12b] (b) Konioke, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849. (c) Harusawa, S.; Takemura, S.; Yoneda, R.; Kurihara, T. *Tetrahedron* **1993**, *49*, 10577. (d) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142.

(13) The stereochemical assignments for the **10s** and **10a** were proven by hydrogenation of each separate diastereomer to authentic **6s** and **6a**, respectively. An analogous proof was performed for each of **15s** and **15a** to give **12s** and **12a**. The assignments for **11s**/**11a** and **16s**/**16a** rest on analogy of their ^{1}H NMR spectral data *vis*-à-vis those of the **10s**/**10a** and **15s**/**15a** pairs.

(14) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

or 30 of the calculated lowest energy conformations. For each of **11s** and **11a** the energy of the 30th conformer was ~1 kcal/mol above the global minimum. These analyses are consistent with the trends observed by ^{1}H NMR spectroscopy for compounds **11s**/**11a** (Table 1, entry 6). We have also carried out a similar force field conformational search with **6s**/**6a** and observed entirely analogous behavior. Thus, the computational results reinforce the theory and support the assignment of relative configuration in **11s** and **11a**. We recommend the use of this type of routinely accessible computational strategy when applying this methodology to new substrates.

In summary, we have developed a reliable method for determining the absolute configuration of carboxylic acids containing a stereogenic center at C(3). To apply this method (1) identify the resonance of the β-Me group as well as distinguishable ^{1}H NMR resonances for protons unique to the other substituent at C(3) (i.e., R in **17**) in the diastereomeric pair of 1-arylethylamides and (2) deduce the C(3)-configuration by comparing the sign of $\Delta\delta$ for one or more of these resonances (Table 1 can be used as a convenient guide). For example, in the anti isomer **17** of the *R*-amide of generic 3-methyl alkanoic acids, the methyl resonance will be observed at higher field than in the *syn*-diastereomer. Finally, complementarity exists; that is, the $\Delta\delta$'s of resonances within R and those of the methyl resonance will be of opposite sign. This approach to determining the configuration of a remote stereogenic center represents a general strategy that can be adapted to other substructures.



Experimental Section

General Procedures and Methods. (*S*)-6-Methoxy-α-methyl-2-naphthalenemethanamine (**4**) was prepared from commercial (+)-(*S*)-naproxen via the Curtius rearrangement route by a procedure analogous to one described in the literature for the Shioiri reaction using $(PhO)_2PON_3$.[15] The amides indicated in Figure 1 that were derived from isoacids (isobutyric through 5-methylhexanoic) and amines **2** through **5** were prepared via standard coupling procedures (DCC or the acid chloride) on a small scale for the practical purpose of obtaining ^{1}H NMR spectra. 9-Anthracenyl-derived amine **5** was obtained following the literature procedure.[16] 3-Methylpent-4-enoic acid (the precursor for **10s**/**10a** and **15s**/**15a**) and 3,5-dimethylhex-4-enoic acid (the precursor for **11s**/**11a** and **16s**/**16a**) were noncommercial samples available in our laboratory and prepared by Claisen rearrangement. All ^{1}H and ^{13}C NMR spectra were measured as $CDCl_3$ solutions.

[*S*-(*R,*S**)]-3-Methyl-*N*-[1-phenylethyl]pentanamide (6s).** In a 5 mL culture tube dicyclohexylcarbodiimide (DCC) (83 mg, 0.4 mmol) and (dimethylamino)pyridine (DMAP) (5 mg) were dissolved in 0.5 mL of dry CH_2Cl_2. (*S*)-3-Methylvaleric acid[17] (50 μL, 0.4 mmol) was added neat and a thick white precipitate formed instantaneously. After the mixture was stirred for 5 min (*R*)-α-methylbenzylamine (50 μL, 0.39 mmol) was added neat. The reaction mixture was stirred for 2 h and filtered through a layer of silica gel. The liquid was concentrated and purified by MPLC (3:1 hexanes/ethyl acetate) to give a colorless viscous oil (48.6 mg, 55%). ^{1}H NMR (300 MHz) δ 7.40−7.22 (m, 5H), 6.00 (br s, 1H), 5.12 (quintet, J = 7.0 Hz, 1H), 2.17 (nfom, 1H), 1.95−1.83 (m, 2H), 1.45 (d, J = 7.0 Hz, 3H), 1.34 (ddq, J = 14, 7, and 7 Hz, 1H), 1.17 (ddq, J = 14, 7, and 7.0 Hz, 1H), 0.91 (d, J = 6.0 Hz, 3H), and 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DEPT) (75 MHz) δ 171.9, 143.3, 128.6 (CH), 127.3 (CH), 126.2 (CH), 48.7 (CH), 44.1 (CH_2), 32.4 (CH), 29.4, (CH_2), 21.8 (CH_3), 19.1 (CH_3), and 11.3 (CH_3). IR ($CHCl_3$) 3282 (broad), 3063, 3030, 2962, 2929, 1639, 1545, 1495, and 1453 cm^{-1}. LRMS (EI) *m*/*z* 219 (M^+). Anal. Calcd: C, 76.66; H, 9.65. Found: C, 76.82; H, 9.44.

[*R*-(*R,*R**)]-3-Methyl-*N*-[1-phenylethyl]pentanamide (6a).** The same procedure as for **6s** was used to convert a racemic mixture of 3-methylvaleric acid into a mixture of diastereomeric amides **6s** and **6a** (91%). Spectral data for the mixture (methyl resonances for **6a** are italicized): ^{1}H NMR (300 MHz) δ 7.40−7.21 (m, 5H, Ph), 5.91 (br s, 1H), 5.13 (quintet, J = 7.0 Hz, 1H), 2.17 (nfom, 1H), 1.95−1.83 (m, 2H), 1.48 (d, J = 7.0 Hz, 3H), 1.41−1.14 (m, 2H), 0.91 (d, J = 6.0 Hz, 1.5H), *0.88* (d, J = 6.0 Hz, 1.5H), *0.87* (t, J = 7.2 Hz, 1.5H), and 0.86 (t, J = 7.2 Hz, 1.5H). ^{13}C NMR (75 MHz) δ 171.9, 143.4/143.3, 128.6, 127.3, 126.2, 48.6, 44.2$^+$/44.2$^-$, 32.4$^+$/32.4$^-$, 29.4, 21.7, 19.2/19.1, and 11.4/11.3. LRMS (EI) *m*/*z* 219 (M^+).

[*R*-(*R,*R**)]-3,7-Dimethyl-*N*-[1-phenylethyl]-6-octenamide (8a).** DCC coupling analogous to the one used for **6s** was used to prepare **8a** from commercially available *R*-citronellic acid and *R*-**2**. The crude amide was purified by MPLC (4:1 hexanes/ethyl acetate) to give **8a** as white crystals (75%). Mp 62−63 °C. ^{1}H NMR (500 MHz) δ 7.38−7.20 (m, 5H), 5.95 (br s, 1H), 5.14 (quintet, J = 7.0 Hz, 1H), 5.07 (t, J = 7.0 Hz, 1H), 2.19 (dd, J = 5.0 and 13.0 Hz, 1H), 2.04−1.90 (m, 4H), 1.67 (s, 3H), 1.59 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H), 1.35 (m, 1H), 1.19 (m, 1H), and 0.90 (d, J = 6.0 Hz, 3H). ^{13}C NMR (DEPT, HETCOR) (125 MHz) δ 171.6 (C, none), 143.4 (C, none), 131.4 (C, none), 128.6 (CH, 7.3), 127.28 (CH, 7.2), 126.22 (CH, 7.3), 124.4 (CH, 5.07), 48.5 (CH, 5.14), 44.5 (CH_2, 2.19, 1.92), 36.9 (CH_2, 1.47, 1.35), 30.5 (CH, 1.88), 25.7 (CH_3, 1.67), 25.4 (CH_2, 2.00), 21.7 (CH_3, 1.47), 19.5 (CH_3, 0.90), and 17.68 (CH_3, 1.59). Anal. Calcd: C, 79.07; H, 9.95. Found: C, 79.15; H, 9.81.

[*R*-(*R,*S**)]-3,7-Dimethyl-*N*-[1-phenylethyl]-6-octenamide (*ent*-8s).** DCC coupling analogous to the one used for **6s** was used to prepare ***ent*-8s** from commercially available *R*-citronellic acid and *S*-**2**. The crude amide was purified by MPLC (4:1 hexanes/ethyl acetate) to give ***ent*-8s** as a colorless oil (65%). ^{1}H NMR (500 MHz) δ 7.40−7.20 (m, 5H), 5.85 (br s, 1H), 5.14 (dq, J = 7.0 and 7.0 Hz, 1H), 5.07 (t septets, J = 7.0 and 1.5 Hz, 1H), 2.18 (dd, J = 4.5 and 13.0 Hz, 1H), 2.10−1.90 (m, 4H), 1.66 (s, 3H), 1.58 (s, 3H), 1.48 (d, J = 7.0 Hz, 3H), 1.31−1.39 (m, 1H), 1.17−1.21 (m, 1H), and 0.93 (d, J = 6.0 Hz, 3H). ^{13}C NMR (125 MHz) δ 171.61, 143.30, 131.45, 128.64, 127.32, 126.23, 124.37, 48.57, 44.57, 36.92, 30.55, 25.72, 25.44, 21.71, 19.51, and 17.66.

[*R*-(*R,*R**)]- and [*S*-(*R**,*S**)]-3-Methyl-5-[(1-phenylethyl)amino]-5-oxopentanoic Acid, Methyl Ester (9s and 9a).** 3-Methylglutaric anhydride (101.2 mg, 0.79 mmol), 1-(*R*)-phenylethylamine (101 μL, 0.79 mmol), and DMAP (100 mg, 0.82 mmol) were dissolved in 2 mL of dry CH_2Cl_2 and stirred for 1 h. DCC (163 mg, 0.79 mmol) was added as one portion. After several minutes 1 mL of dry MeOH was added. The reaction mixture was stirred for 24 h, then filtered through silica. The solution was washed with 5% HCl (2 × 2 mL) and concentrated $NaHCO_3$ (2 mL). Drying over $MgSO_4$ and concentration in vacuo yielded compounds **9s** and **9a** as a mixture with a 1.9:1 ratio (colorless oil) (191.6 mg, 92%). The crude material was of sufficient purity for spectroscopic analysis, with only a trace of 3-methylglutaric acid dimethyl ester as an impurity. The NMR resonances of **9s** vs **9a** were easy to distinguish because of the difference in relative intensity. **9s**: ^{1}H NMR (500 MHz) δ 7.38−7.21 (m, 5H), 5.90 (brs, 1H), 5.16

(15) (a) Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 3007. (b) Wolber, E. K. A.; Rüchardt, C. *Chem. Ber.* **1991**, *124*, 1667.

(16) Ciganek, E., U.S. Patent 4 076 830, 1978; *Chem. Abstr. 89*, 24136.

(17) An authentic sample of (*S*)-3-methylvaleric acid was prepared by the deamination of L-isoleucine: Doldouras, G. A.; Kollonitsch, J. *J. Am. Chem. Soc.* **1978**, *100*, 341.

(18) The assignment of resonances to the methyl groups (6*Z* and 6*E*) for the **11s**/**11a** and **16s**/**16a** pairs is based both on their relative chemical shifts [cf. other 1,1-dimethyl-substituted alkenes in which the *cis*-methyl group appears upfield from the *trans*-methyl group (e.g., the six *cis*-disposed methyl groups in squalene have a chemical shift of 1.60 ppm while the two *trans*-disposed methyls are at 1.68 ppm)]. Even if the differential anisotropic shielding effect of the aromatic ring in either of these pairs were sufficiently large to reverse that assignment for one or both of the diastereomers, the signs of the resulting $\Delta\delta$ values would remain negative.

(dq, J = 7.0 and 7.0 Hz, 1H), 3.66 (s, 3H), 2.45−2.20 (m, 4H), 2.10 (dd, 1H, J = 14.0 and 7.0 Hz), 1.44 (d, 3H, J = 7.0 Hz), and 1.02 (d, 7.0 Hz). The ^{1}H NMR spectrum of **9a** was virtually the same as that for **9s** with the following differences: δ 3.67 (s, 3H) and 1.01 (d, 7.0 Hz). ^{13}C NMR (DEPT) (**9a**/**9s** mixture) (75 MHz) δ 173.14 (C), 170.67 (C), 143.34 (C), 128.62 (CH), 127.28 (CH), 126.14 (CH), 51.49/51.29 (CH_3), 48.64 (CH), 43.03 (CH_2), 40.35/40.30 (CH_2), 28.25 (CH), 21.88/21.79 (CH_3), and 19.29 (CH_3). LRMS (EI) (**9a**/**9s** mixture) *m*/*z* 263 ($M^{\bullet+}$). FT-IR (**9a**/**9s** mixture) 3436, 1728, 1659 cm^{-1}. Anal. Calcd: C, 68.42; H, 8.04. Found: C, 68.23; H, 8.05.

[*R*-(*R,*R**)]-3-Methyl-*N*-[1-phenylethyl]-4-pentenamide (10s) and [*S*-(*R**,*S**)]-3-Methyl-*N*-[1-phenylethyl]-4-pentenamide (10a).** (±)-3-Methyl-4-pentenoic acid was coupled by using DCC (cf. preparation of **6s**) with *R*-**2** to give a mixture of diastereomers **10s**/**10a** that was separated by MPLC (4:1 hexanes/ethyl acetate) to give **10s** and **10a** as individual compounds (>95% de by NMR). **10s:** ^{1}H NMR (500 MHz) δ 7.40−7.20 (m, 5H), 5.76 (ddd, J = 6.9, 10.2, and 17.1 Hz, 1H), 5.70 (br s, 1H), 5.15 (dq, 1H, J = 7.5 and 7.5 Hz), 5.01 (dd, J = 1.5 and 17.4 Hz, 1H), 4.94 (dd, J = 1.2 and 10.2 Hz, 1H), 2.69 (septet, J = 6.9 Hz, 1H), 2.25−2.08 (m, 2H), 1.48 (d, J = 6.6 Hz, 3H), and 1.05 (d, J = 6.6 Hz, 3H). **10a:** ^{1}H NMR (500 MHz) δ 7.37−7.18 (m, 5H), 5.77 (ddd, J = 6.9, 10.2, and 17.1 Hz, 1H), 5.67 (br s, 1H), 5.15 (dq, 1H, J = 7.5 and 7.5 Hz), 5.03 (dd, J = 1.5 and 17.4 Hz, 1H), 4.97 (dd, J = 1.2 and 10.2 Hz, 1H), 2.70 (septet, J = 6.9 Hz, 1H), 2.24−2.08 (m, 2H), 1.47 (d, J = 6.6 Hz, 3H), and 1.03 (d, J = 6.6 Hz, 3H). **10s**/**10a** mixture: ^{13}C NMR (DEPT) (75 MHz) δ 170.81 (C), 143.24 (C), 142.80 (CH), 128.60/128.58 (CH), 127.28 (CH), 126.22/126.20 (CH), 113.52 (CH_2), 48.62/48.59 (CH), 43.83 (CH_2), 34.91/34.85 (CH), 21.73/21.69 (CH_3), 19.69/19.64 (CH_3). LRMS (EI): *m*/*z* 217 ($M^{\bullet+}$), 202, 188, 174, 162, 120, 106, 105 (100%), 98, 91, 77, 69 and 55. FT-IR 3437, 1658 cm^{-1}. Anal. Calcd: C, 77.38; H, 8.81. Found: C, 77.39; H, 8.83.

[*S*-(*R,*R**)]-3,5-Dimethyl-*N*-[1-phenylethyl]-4-hexenamide (*ent*-11s) and [*R*-(*R**,*S**)]-3,5-Dimethyl-*N*-[1-phenylethyl]-4-pentenamide (*ent*-11a).** (±)-3,5-Dimethyl-4-hexenoic acid was coupled by using DCC (cf. preparation of **6s**) with *S*-**2** to give a mixture of diastereomers ***ent*-11s**/***ent*-11a** that was separated by MPLC (4:1 hexanes/ethyl acetate) to give ***ent*-11s** and ***ent*-11a** as individual compounds (>95% de by NMR). The relative (syn or anti) configuration was assigned on the basis of a trend in chemical shift differences ($\delta\Delta$'s) observed for diastereomeric amides **6**−**10** and **12**−**15** and the results of computational studies (see text). ***ent*-11s**: ^{1}H NMR (500 MHz) δ 7.21−7.39 (m, 5H), 5.70 (br d, 1H, J = 7.4 Hz), 5.11 (dq, 1H, J = 7.1 and 7.1 Hz), 4.91 (d of septets, 1H, J = 9.7 and 1.3 Hz), 2.85 (dtq, 1H, J = 5.7, 9.2 and 6.8 Hz), 2.17 (dd, 1H, J = 5.5 and 13.8 Hz), 2.06 (dd, 1H, J = 9.0 and 14.1 Hz), 1.62 (d, 3H, J = 1.5 Hz), 1.52 (d, 3H, J = 1.5 Hz), 1.47 (d, 3H, J = 7.0 Hz), and 0.97 (d, 3H, J = 6.5 Hz). LRMS (EI) *m*/*z* 245 ($MI^{\bullet+}$), 230, 202, 174, 163, 148, 120, 105 (100%), 83, 59, 55. ***ent*-11a**: ^{1}H NMR (500 MHz) δ 7.21−7.39 (m, 5H), 5.71 (br d, 1H, J = 7.7 Hz), 5.11 (dq, 1H, J = 7.1 and 7.1 Hz), 4.93 (d of septets, 1H, J = 9.7 and 1.5 Hz), 2.86 (dtq, 1H, J = 5.8, 9.0 and 6.4 Hz), 2.16 (dd, 1H, J = 5.8 and 14.1 Hz), 2.07 (dd, 1H, J = 8.8 and 14.0 Hz), 1.67 (d, 3H, J = 1.0 Hz), 1.64 (d, 3H, J = 1.0 Hz), 1.44 (d, 3H, J = 7.0 Hz), and 0.96 (d, 3H, J = 6.5 Hz). LRMS (EI) identical with that of ***ent*-11s**.

[*S*-(*R,*R**)]-3-Methyl-*N*-[1-(1-naphthalenyl)ethyl]pentanamide (*ent*-12a).** By the method used to prepare **6s**, (*S*)-3-methylvaleric acid and *S*-**3** were coupled with DCC to prepare ***ent*-12a**. Gradient elution through a SiO_2 column with hexanes and ethyl acetate gave a white solid. ^{1}H NMR (300 MHz), δ 8.11 (d, 1H, J = 7.5 Hz), 7.87 (dd, 1H, J = 7.0 and 2.2 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.4−7.55 (m, 4H), 5.96 (dq, 1H, J = 6.9 and 6.9 Hz), 5.70 (br d, 1H, J = 7.0 Hz), 2.16 (m, 1H), 1.9−1.8 (m, 2H), 1.67 (d, 3H, J = 6.6 Hz), 1.35 (m, 1H), 1.17 (m, 1H), 0.87 (t, 3H, J = 7.3 Hz), and 0.87 (d, 3H, J = 6.3 Hz).

[*R*-(*R,*S**)]-3-Methyl-*N*-[1-(1-naphthalenyl)ethyl]pentanamide (*ent*-12s).** The same procedure as for ***ent*-12a** was used to convert a racemic mixture of 3-methylvaleric acid and *S*-**3** into a mixture of diastereomeric amides ***ent*-12s** and ***ent*-12a** (white solid, mp 120−126 °C) that gave no indication of separation, even in the leading and trailing peak edges, by MPLC on SiO_2 (9:1 hexanes:EtOAc). Spectral data for the mixture (the methyl resonances due to ***ent*-12s** are in italics): ^{1}H NMR (300 MHz) δ ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, 1H, J = 7.5 Hz), 7.86 (dd, 1H, J = 7.0 and 2.2 Hz), 7.79 (d, 1H, J = 8.0 Hz), 7.42−7.55 (m, 4H), 5.95 (dq, 1H, J = 6.9 and 6.9 Hz), 5.69 (br d, 1H, J = 7.0 Hz), 2.15 (m, 1H), 1.94−1.82 (m, 2H), 1.66 (d, 3H, J = 6.6 Hz), 1.34 (m, 1H), 1.16 (m, 1H), *0.92* (d, 1.5H, J = 6.0 Hz), 0.87 (t, 1.5H, J = 7.2 Hz), 0.87 (d, 1.5H, J = 6.0 Hz), and *0.84* (t, 1.5H, J = 7.2 Hz). ^{13}C NMR (DEPT) (75 MHz) δ 171.44 (C), 138.22 (C), 133.90 (C), 131.17 (C), 128.70 (CH), 128.37 (CH), 126.50 (CH), 125.89 (CH), 125.12 (CH), 123.61 (CH), 122.56 (CH), 44.37 (CH_3), 44.24 (CH_2), 32.40 (CH), 29.43 (CH_2), 20.55 (CH_3), 19.19 (CH_3), and 11.33 (CH_3). LRMS (EI) *m*/*z* 269 ($M^{\bullet+}$), 254, 213, 198, 170, 156 (100%), 142, 129, 115, 99, 85, 81, 71, and 57. FT-IR 3439, 1653 cm^{-1}. Anal. Calcd: C, 80.25; H, 8.61. Found: C, 80.12; H, 8.63.

[*R*-(*R,*S**)]-3,7-Dimethyl-*N*-[1-(1-naphthalenyl)ethyl]-6-octenamide (*ent*-13s) and [*R*-(*R**,*R**)]-3,7-Dimethyl-*N*-[1-(1-naphthalenyl)-ethyl]-6-octenamide (13a).** (*R*)-Citronellic acid was coupled by using DCC (cf. preparation of **6s**) with *R*-**3** and *S*-**3** to give diastereomers **13a** and ***ent*-13s** correspondingly. **13a:** ^{1}H NMR (500 MHz) δ 8.07 (d, 1H, J = 7.0 Hz), 7.85 (dd, 1H, J = 7.0 and 2.0 Hz), 7.79 (d, 1H, J = 7.0 Hz), 7.41−7.55 (m, 4H), 5.95 (dq, J = 7.0 and 7.0 Hz, 1H), 5.85 (br d, 1H, J = 7.0 Hz), 5.04 (t septets, J = 7.0 and 1.5 Hz, 1H), 2.15−1.90 (m, 5H), 1.66 (d, J = 6.3 Hz, 3H), 1.65 (s, 3H), 1.56 (s, 3H), 1.40−1.05 (m, 2H), and 0.87 (d, J = 6.3 Hz, 3H). The ^{1}H NMR spectrum of ***ent*-13s** was virtually identical with that of **13a** with the exception of the aliphatic methyl resonance: δ 0.92 (d, 3H, J = 6.3 Hz).

[*R*-(*R,*R**)]- and [*S*-(*R**,*S**)]-3-Methyl-5-[[1-(1-naphthalenyl)-ethyl]amino]-5-oxopentanoic Acid, Methyl Ester (14s and 14a).** The compounds **14s** and **14a** were obtained from 3-methylglutaric anhydride and *R*-**3** by a procedure similar to the one used for the preparation of compounds **9s**/**9a** as a mixture with a 1.65:1 ratio. The NMR resonances between these two were easy to distinguish by using the difference in relative intensity. **14s**: ^{1}H NMR (500 MHz) δ 8.09 (d, 1H, J = 7.8 Hz), 7.86 (dd, 1H, J = 7.1 and 2.0 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.54−7.41 (m, 4H), 5.97−5.80 (m, 2H), 3.61 (s, 3H), 2.47−2.01 (m, 5H), 1.65 (d, 3H, J = 6.5 Hz), and 1.01 (d, 7.0 Hz). The ^{1}H NMR spectrum of **14a** was virtually the same as for **14s**, with the following differences: δ 3.64 (s, 3H) and 0.99 (d, 7.0 Hz). Professor Harusawa confirmed for us (7-30-96) that his sample of **14a** had resonances at δ 3.64 and 0.99 ppm and his sample of **14s** had resonances at δ 3.61 and 1.01 for the methyl ester and C(3) methyl groups, respectively. In the original report these values were provided ambiguously.[12c]

[*S*-(*R,*R**)]-3-Methyl-*N*-[1-(1-naphthalenyl)ethyl]-4-pentenamide (*ent*-15s) and [*R*-(*R**,*S**)]-3-Methyl-*N*-[1-(1-naphthalenyl)-ethyl]-4-pentenamide (*ent*-15a).** (±)-3-Methyl-4-pentenoic acid was coupled by using DCC (cf. preparation of **6s**) with *S*-**3** to give a mixture of diastereomers ***ent*-15s**/***ent*-15a** that was separated by MPLC (4:1 hexanes/ethyl acetate) to give ***ent*-15s and *ent*-15a** as individual compounds (>95% de by NMR). ^{13}C NMR (***ent*-15s**/***ent*-15a** mixture) (75 MHz) δ 170.55, 142.72, 138.17, 133.90, 131.14, 128.71, 128.38, 126.52, 125.89, 125.12, 123.60, 122.57, 113.53, 44.51/44.47, 43.84/43.80, 34.88/34.83, 20.58, 19.68/19.64. LRMS (EI) (***ent*-15s**/***ent*-15a** mixture) *m*/*z* 267 ($M^{\bullet+}$). IR: 3438 and 1657 cm^{-1}. This mixture was fractionated (MPLC, silica gel, 4:1 hexanes/ethyl acetate) into enriched samples of ***ent*-15s** (92% de by NMR) and ***ent*-15a** (80% de by NMR). ***ent*-15s**: ^{1}H NMR (500 MHz) δ 8.10 (d, 1H, J = 8.5 Hz), 7.86 (dd, 1H, J = 8.0 and 1.5 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.44−7.55 (m, 4H), 5.95 (dq, 1H, J = 7.0 and 7.0 Hz), 5.75 (ddd, 1H, J = 7.0, 10.5, and 17.5 Hz), 5.66 (br d, 1H, J = 7.0 Hz), 5.02 (ddd, 1H, J = 1.5, 1.5, and 17.5 Hz), 4.95 (ddd, 1H, J = 1.5, 1.5, and 10.5 Hz), 2.72 (∼septet, 1H, J ∼ 6.5 Hz), 2.18 (dd, 1H, J = 6.5 and 14.0 Hz), 2.08 (dd, 1H, J = 6.0 and 14.0 Hz), 1.66 (d, 3H, J = 6.5 Hz), and 1.01 (d, 3H, J = 6.5 Hz). ***ent*-15a**: ^{1}H NMR (500 MHz) δ 8.09 (d, 1H, J = 8.0 Hz), 7.87 (dd, 1H, J = 7.5 and 2.0 Hz), 7.80 (d, 1H, J = 8.0 Hz), 7.43−7.55 (m, 4H), 5.95 (dq, 1H, J = 7.0 and 7.0 Hz), 5.72 (ddd, 1H, J = 7.0, 10.5, and 17.5 Hz), 5.66 (br d, 1H, J = 7.0 Hz), 4.97 (ddd, 1H, J = 1.5, 1.5, and 17.0 Hz), 4.90 (ddd, 1H, J = 1.5, 1.5, and 10.5 Hz), 2.68 (∼septet, 1H, J ∼ 7.0 Hz), 2.19 (dd, 1H, J = 7.5 and 14.0 Hz), 2.10 (dd, 1H, J = 7.0 and 14.0 Hz), 1.67 (d, 3H, J = 6.5 Hz), and 1.05 (d, 3H, J = 7.0 Hz). Anal. Calcd: C, 80.86; H, 7.92. Found: C, 80.44; H, 7.83.

[*S*-(*R,*R**)]-3,5-Dimethyl-*N*-[1-(1-naphthalenyl)ethyl]-4-hexenamide (*ent*-16s) and [*R*-(*R**,*S**)]-3,5-Dimethyl-*N*-[1-(1-naphthalenyl)-ethyl]-4-pentenamide (*ent*-16a).** (±)-3,5-Dimethyl-4-hexenoic acid was coupled by using DCC (cf. preparation of **6s**) with *S*-**3** to give a mixture of diastereomers ***ent*-16s**/***ent*-16a** that was separated by MPLC (4:1 hexanes/ethyl acetate) to give ***ent*-16s** and ***ent*-16a** as individual compounds (>95% de by NMR). The relative (syn or anti) configuration was assigned on the basis of a trend in chemical shift differences ($\delta\Delta$'s) observed for diastereomeric amides **6**−**10** and **12**−**15** and the results of computational studies (see text). ***ent*-16s**: ^{1}H NMR (300 MHz) δ 8.09 (d, 1H, J = 2.5 Hz), 7.87−7.78 (m, 2 Hz), 7.55−7.42 (m, 4H), 5.91 (dq, 1H, J = 7.8 and 7.8 Hz), 5.67 (br d, 1H, J = 7.5 Hz), 4.86 (d of septets, 1H, J = 9.6 and 1.2 Hz), 2.85−2.75 (m, 1H), 2.17−2.04 (m, 2H), 1.64 (d, 3H, J = 6.6 Hz), 1.53 (d, 3H, J = 1.5 Hz), 1.40 (d, 3H, J = 1.2 Hz), and 0.95 (d, 3H, J = 6.6 Hz). LRMS (EI) *m*/*z* 245 ($MI^{\bullet+}$), 230, 202, 174, 163, 148, 120, 105 (100%), 83, 59, 55. ***ent*-16a**: ^{1}H NMR (300 MHz) δ 8.11 (d, 1H, J = 2.5 Hz), 7.88−7.79 (m, 2 Hz), 7.56−7.42 (m, 4H), 5.91 (dq, 1H, J = 7.8 and 7.8 Hz), 5.70 (br d, 1H, J = 7.8 Hz), 4.84 (d of septets, 1H, J = 9.6 and 1.5 Hz), 2.92−2.82 (m, 1H), 2.17 (dd, 1H, J = 6.0 and 14.1 Hz), 2.06 (dd, 1H, J = 8.4 and 14.1 Hz), 1.62 (d, 3H, J = 6.6 Hz), 1.59 (d, 3H, J = 1.2 Hz), 1.55 (d, 3H, J = 1.5 Hz), and 0.93 (d, 3H, J = 6.9 Hz). LRMS (EI) identical with that for ***ent*-16s**.

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