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Diastereoselective formation of α-aminoamides from carbamoylsilanes and aldehyde imines

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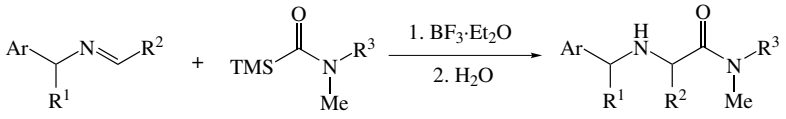
Abstract—Diastereoselectivities were determined for the reaction of a series of aldehyde imines with carbamoylsilanes, each containing chiral auxiliaries at nitrogen. A maximum de of 88% was achieved via a matched double differentiation.

1. Introduction

We recently reported a novel approach to the synthesis of α-aminoamides in which aldehyde imines **1a–c** were shown to add a carbamoylsilane **4a** promoted by equimolar amounts of $BF_3{\cdot}Et_2O$ to form **5**.[1] This provides a simple entry into compounds, which represent the building blocks of peptides and proteins, and have important pharmacological applications.[2] However for efficient application within these areas, enantioenriched substrates are required. We thus explored the potential of both single and double stereodifferentiation[3] in these addition reactions by incorporating chiral *N*-auxiliaries into the imine and/or carbamoylsilane components, thereby affording the possibility of separation and eventual *N*-deprotection of the resultant diastereomers to provide enantioenriched α-aminoamides.[4]

2. Results and discussion

Initially obtained product mixtures exhibited complex NMR spectra, as a total of four superimposed spectra resulted from the two newly formed diastereomers, each existing as a *syn*/*anti* mixture of amides (the *syn* and *anti* isomers for a given diastereomer derived from **4a** only differed by separate *N*-methyl resonances). However, the ^1H NMR region between δ 2.3 and 6.5, containing the *N*-methyl, the newly stereogenic C–H and the tertiary ethyl C–H protons of both chiral



1a Ar = Ph, R^1 = H, R^2 = Et
1b Ar = Ph, R^1 = H, R^2 = iPr
1c Ar = Ph, R^1 = H, R^2 = Ph

2a Ar = Ph, R^1 = Me, R^2 = Et
2b Ar = Ph, R^1 = Me, R^2 = iPr
2c Ar = Ph, R^1 = Me, R^2 = Ph

3a Ar = 1-Nph, R^1 = Me, R^2 = Et
3b Ar = 1-Nph, R^1 = Me, R^2 = iPr
3c Ar = 1-Nph, R^1 = Me, R^2 = Ph

4a R^3 = Me
4b R^3 = 1-phenylethyl

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auxiliaries was amenable to quantification. Diastereomeric ratios were determined on crude reaction mixtures, and the assignments of other NMR data were often possible after chromatographic separation or concentration.

Table 1 summarizes our results. Achiral imines **1a**–**c** were used first with carbamoylsilane (*S*)-**4b**. This combination afforded negligible diastereoselectivity, either in THF or benzene as solvent. In contrast, placing the (*S*)-1-phenylethyl group on the imine nitrogen instead of the amide nitrogen led to an immediate improvement in stereoselectivity when reactions of (*S*)-**2a**–**c** with achiral **4a** were examined (runs 5–12), affording de values between 33% and 67%. At this point, several experimental parameters were briefly examined to assess their influence on yield and de. In runs 12, 15 and 16, BCl_3 was used in place of BF_3. Although run 12 afforded an increased yield of adduct under these conditions relative to the use of BF_3, the dr was unimpressive, and results in runs 15 and 16 (compared to BF_3 run 14) were disappointing. There were also indications at this point (runs 3–4, 5–9) that of the solvents listed, benzene afforded the best yields with little or no negative effect on the dr, and benzene therefore became the solvent of choice for later runs.

Table 1. Yields and diastereomeric ratios of **5** obtained from **1** to **3** and **4**

Run	Imine	Carbamoylsilane	Solvent	Time[a] (h)	Yield[b] (%)	Dr
1	**1a**	(*S*)-**4b**	THF	13.5	[c]	—
2	**1b**	(*S*)-**4b**	THF	20.5	53	1:1
3	**1c**	(*S*)-**4b**	THF	12.5	56	1:1
4	**1c**	(*S*)-**4b**	PhH	17	76	1:1
5	(*S*)-**2a**	**4a**	THF	11.5	54	1:5
6	(*S*)-**2a**	**4a**	PhH	17	62	1:4
7	(*S*)-**2b**	**4a**	THF	12	10	1:2
8	(*S*)-**2b**	**4a**	CH_2Cl_2	30	28	1:2
9	(*S*)-**2b**	**4a**	PhH	17	40	1:2.5
10	(*S*)-**2c**	**4a**	THF	15	[c]	—
11	(*S*)-**2c**	**4a**	PhH	18	[c]	—
12	(*S*)-**2c**	**4a**	PhH	18	38[d]	1:2
13	(*S*)-**2a**	(*S*)-**4b**	THF	11	54	1:3
14	(*S*)-**2b**	(*S*)-**4b**	PhH	43	38	1:2
15	(*S*)-**2b**	(*S*)-**4b**	PhH	16	33[d]	1:1
16	(*S*)-**2b**	(*S*)-**4b**	CH_2Cl_2	13.5	25[d]	1:1.5
17	(*S*)-**2c**	(*S*)-**4b**	PhH	35	56	1:2.5
18	(*S*)-**2a**	(*R*)-**4b**	PhH	18	72	1:14
19	(*S*)-**2b**	(*R*)-**4b**	PhH	58	51	1:5
20	(*S*)-**2c**	(*R*)-**4b**	PhH	44	60	1:2.5
21	(*S*)-**3a**	**4a**	PhH	11	37	1:3
22	(*S*)-**3b**	**4a**	PhH	18	20	1:2
23	(*S*)-**3c**	**4a**	PhH	23	41	1:3
24	(*S*)-**3a**	(*S*)-**4b**	PhH	10.5	48	1:8
25	(*S*)-**3b**	(*S*)-**4b**	PhH	63	22	1:4
26	(*S*)-**3c**	(*S*)-**4b**	PhH	45	58	1:7
27	(*S*)-**3a**	(*R*)-**4b**	PhH	16	59	1:16
28	(*S*)-**3b**	(*R*)-**4b**	PhH	64	30	1:6
29	(*S*)-**3c**	(*R*)-**4b**	PhH	40	52	1:9
30	(*R*)-**3a**	(*S*)-**4b**	PhH	16	49	1:15
31	(*R*)-**3c**	(*S*)-**4b**	PhH	51	50	1:9

[a] To complete consumption of **4**.
[b] Isolated yield.
[c] Little or no product was formed.
[d] BCl_3 instead of BF_3.

In an effort to improve the dr results, double stereodifferentiation was explored, initially by employing combinations of (*S*)-**2** with (*S*)-**4b** (runs 13–17). This afforded low de values, which were, in general, even smaller than those obtained from the use of achiral **4a**. The situation was significantly improved, however, when (*S*)-**2** and (*R*)-**4b** combinations were investigated (runs 18–20). Here, de values ranged from 43% to 87%, with the added advantage that all imines now afforded improved yields of adducts. These last two sets of runs (13–17 and 18–20) therefore appear to reflect the use of, respectively, 'mismatched' and 'matched' pairs of chiral reactants, which exert their influence on both the stereoselectivity and yield of the reaction. Although a detailed mechanism of these transformations is undetermined, stereodifferentiation is often enhanced by the presence of more sterically-demanding groups, as conformational preferences are thereby exaggerated. Our attention thus turned to the use of the chiral *N*-[1-(1-naphthyl)ethyl]imines **3a**–**c** as reaction partners. Again, initial results with **4a** were disappointing (runs 21–23), with dr values similar to those obtained with the corresponding *N*-(1-phenylethyl)imines (runs 5–12). When the (*S*)-'naphthyl' imines were paired with (*S*)-**4b**, however (runs 24–26), a considerable enhancement in the de was observed (de = 60–78%), when compared with the 'phenyl' [(*S*)-**2**, (*S*)-**4b**] pairings (de = 20–50%). The expected 'matched' pairings of (*S*)-**3** and (*R*)-**4b** (runs 27–29) were then examined. The de values obtained (71–88%) were uniformly higher than with the 'phenyl' counterparts. As a check on these values, the 'reversed' pairings (*R*)-**3a**, (*S*)-**4b** and (*R*)-**3c**, (*S*)-**4b** were investigated and found to give parallel dr values (runs 30, 31).

As proof of the method, the major diastereomer from Table 1, run 29, was isolated from a preparative run (52% yield) and deprotected by hydrogenolysis of the naphthylethyl group. The resulting α-aminoamide was then subjected to acidic hydrolysis.[5] The hydrochloride of the phenylglycine thus obtained showed $[\alpha]_D^{24} = -134.0$, compared to an authentic sample of L-phenylglycine hydrochloride with $[\alpha]_D^{24} = +136.6$. This result indicates that the chiral auxiliaries employed in run 29 predominantly gave *R* stereochemistry in the adduct.

3. Conclusions

Chiral auxiliaries have been shown to be effective in inducing diastereoselectivity in the addition of carbamoylsilanes to imines. The effect is negligible when only the carbamoylsilane bears a chiral *N*-(1-phenylethyl) group, but modest, and approximately equal, stereoselection is observed when either *N*-(1-phenylethyl) or *N*-[1-(1-naphthyl)ethyl] substituents are present on the imine alone. Double diastereoselection, employing chiral substituents in both carbamoylsilane and imine coreactants, proved effective in enhancing dr values only when 'matched' sets of (*S*)-imines and (*R*)-carbamoylsilanes (or vice versa) were employed. *N*-[1-(1-Naphthyl)ethyl] substituted imines were found to be superior to *N*-(1-phenylethyl) substituted imines in this regard. Many of the diastereomeric mixtures of **5** were

separable by column chromatography, thus suggesting a possible route to enantiopure α-aminoamides.

4. Experimental

4.1. General

All NMR spectra were obtained at 11.75 T in $CDCl_3$ unless otherwise indicated. A JASCO P-1010 polarimeter was used to determine optical rotations. The procedure for additions of carbamoylsilanes to the imines and subsequent product isolation was identical to that reported earlier.[1] An imine–BF_3–carbamoylsilane molar ratio of 1:1:1.2, respectively, was employed. (*S*)- and (*R*)-α-Methylbenzylamine and (*S*)- and (*R*)-α-(1-naphthyl)ethylamine, each 99+% ee, were obtained from the Aldrich Chemical Co.

4.2. Imines

These were prepared as reported (^{1}H NMR). Compound **1a**:[6] δ 7.83 (t, 1H, J = 4 Hz); 7.2–7.4 (m, 5H); 4.60 (s, 2H); 2.35 (m, 2H); 1.16 (t, 3H, J = 7 Hz). Compound **1b**:[6] δ 7.69 (d, 1H, J = 4.5 Hz); 7.2–7.4 (m, 5H); 2.53 (m, 1H); 1.14 (d, 6H, J = 7 Hz). Compound **1c**:[7] δ 8.44 (s, 1H); 7.3–7.8 (m, 10H); 4.87 (s, 2H). Compound **2a**:[8] δ 7.78 (t, 1H, J = 4.5 Hz); 7.2–7.4 (m, 5H); 4.31 (q, 1H, J = 6.5 Hz); 2.31 (m, 2H); 1.52 (d, 3H, J = 6.5); 1.13 (t, 3H, J = 7.5 Hz). Compound **2b**:[8] δ 7.63 (d, 1H, J = 5.5 Hz); 7.2–7.4 (m, 5H); 4.29 (q, J = 7 Hz); 2.50 (m, 1H); 1.51 (d, J = 7 Hz); 1.14 (d, 3H, J = 7 Hz); 1.11 (d, 3H, J = 7 Hz). Compound **2c**:[8] δ 8.43 (s, 1H); 7.84 (m, 2H); 7.3–7.5 (m, 8H); 4.60 (q, 1H, J = 7 Hz); 1,65 (d, 3H, J = 7 Hz). Compound **3a**:[9] δ 8.17 (d, 1H, J = 8.5 Hz); 7.7–7.9 (m, 4H); 7.4–7.6 (m, 3H); 5.14 (q, 1H, J = 7 Hz); 2.34 (m, 2H); 1.66 (d, 3H, J = 7 Hz); 1.12 (t, 3H, J = 7 Hz). Compound **3b**:[9] δ 8.17 (d, 1H, J = 8 Hz); 7.89 (d, 1H, J = 8 Hz); 7.7–7.8 (m, 3H); 7.5–7.6 (m, 3H); 5.11 (q, 1H, J = 7 Hz); 2.53 (m, 1H); 1.65 (d, 3H, J = 7 Hz); 1.13 (d, 3H, J = 7 Hz); 1.10 (d, 3H, J = 7 Hz). Compound **3c**:[10] δ 8.47 (s, 1H); 8.30 (d, 1H, J = 8 Hz); 7.8–7.9 (m, 5H); 7.4–7.6 (m, 6H); 5.40 (q, 1H, J = 7 Hz); 1.79 (d, 3H, J = 7 Hz).

4.3. Carbamoylsilane 4b: (*S*)- and (*R*)-*N*-methyl-*N*-(1-phenylethyl)-1-(trimethylsilyl)methanamide

These were individually prepared by the general method[11] starting from ⩾99.5:0.5 er 1-phenylethylamines and existed as a 45:55 mixture of *syn* and *anti* forms at 25 °C as indicated by NMR spectroscopy. Compound (*R*)-**4b**: $[\alpha]_D^{24} = +113.2$ (c 1.0, CH_2Cl_2). Their spectral data were identical with those of **4b** prepared from racemic 1-phenylethylamine. Major *syn*/*anti* isomer. ^{1}H NMR (CD_2Cl_2): δ 7.35–7.45 (m, 5H); 5.22 (q, 1H, J = 7 Hz); 2.61 (s, 3H); 1.71 (d, 3H, J = 7 Hz); 0.379 (s, 9H). ^{13}C NMR (CD_2Cl_2): δ 186.7, 140.5, 128.3, 127.2, 126.7, 54.8, 25.7, 17.7, −1.0. Minor *syn*/*anti* isomer. ^{1}H NMR (CD_2Cl_2): δ 7.35–7.45 (m, 5H); 6.17 (q, 1H, J = 7 Hz); 2.79 (s, 3H); 1.52 (d, 3H, J = 7 Hz); 0.376 (s, 9H). ^{13}C NMR (CD_2Cl_2): δ 186.2, 141.1, 128.3, 127.3, 126.9, 47.6, 29.7, 15.3, −1.3. IR: 1567, 1384, 1249, 842 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NOSi$: C, 66.33; H, 8.99; N, 5.95. Found: C, 66.02; H, 8.78; N, 6.26.

4.4. Aminoamides 5

Characterization data for these compounds follow, identified by imine and carbamoylsilane source. All IR spectra of **5** were obtained on neat liquids and exhibited the expected N–H (3310–3330 cm^{-1}) and C=O (1635–1642 cm^{-1}) stretching frequencies.

4.5. Compounds 1b and (*S*)-4b: *N*-methyl-*N*-[(*S*)-1-phenylethyl]-2-(*N*-benzylamino)-3-methylbutanamide

Inseparable mixture of diastereomers; major *syn*/*anti* isomer. ^{1}H NMR: δ 7.15–7.45 (m, 10H); 6.26, 6.21 (2q, 1H, J = 7 Hz); 3.93, 3.59 (2 apparent t [2 overlapped AB patterns], 2H, J = 14 Hz); 3.23, 3.21 (2d, 1H, J = 7 Hz); 2.53 (coincident s, 3H); 2.34 (br s, 1H); 1.88 (m, 1H); 1.55, 1.51 (2d, 3H, J = 7 Hz); 1.08, 1.05 (2d, 3H, J = 7 Hz); 1.00, 0.99 (2d, 3H, J = 6.5 Hz). ^{13}C NMR: δ 175.3, 175.0, 140.6, 140.5 (coincident?), 140.4, 128.7–126.9 (overlapped peaks), 62.4, 62.2, 52.4, 52.2, 50.7, 50.6, 31.9, 31.6, 29.1 (coincident?), 20.0, 19.8, 18.6, 18.1, 15.8, 15.6. Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.53; H, 8.73; N, 8.54.

4.6. Compounds 1c and (*S*)-4b: *N*-methyl-*N*-[(*S*)-1-phenylethyl]-2-(*N*-benzylamino)-2-phenylethanamide

Inseparable mixture of diastereomers; *syn*/*anti* mixture. ^{1}H NMR: δ 6.6–7.4 (m, 15H); 6.19, 6.17, 5.11, 5.02 (4q, 1H, J = 7 Hz); 4.70, 4.65, 4.50, 4.48 (4s, 1H); 3.80 (m, overlapping AB patterns, 2H); 2.87 (br s, 1H); 2.73, 2.60, 2.46, 2.42 (4s, 3H); 1.55, 1.52, 1.39, 1.05 (4d, 3H, J = 7 Hz). Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.28; H, 7.08; N, 7.65.

4.7. Compounds (*S*)-2a and 4a: *N*,*N*-dimethyl-2-{*N*-[(*S*)-1-phenylethyl]amino}butanamide

Major diastereomer. ^{1}H NMR: δ 7.2–7.4 (m, 5H); 3.77 (q, 1H, J = 6 Hz); 3.41 (t, 1H, J = 6.5 Hz); 2.86 (s, 3H); 2.80 (s, 3H); 2.3 (br s, 1H); 1.60 (m, 2H); 1.36 (d, 3H, J = 6.5 Hz); 0.93 (t, 3H, J = 7 Hz). ^{13}C NMR: δ 174.8, 145.4, 128.3, 128.2, 127.0, 56.5, 56.2, 36.7, 35.4, 26.4, 23.3, 10.2. Minor diastereomer. ^{1}H NMR: δ 7.2–7.4 (m, 5H); 3.59 (q, 1H, J = 6.5 Hz); 3.19 (t, 1H, J = 6.5 Hz); 3.02 (s, 3H); 2.71 (s, 3H); 2.15 (br s, 1H); 1.51 (m, 2H); 1.33 (d, 3H, J = 6.5 Hz); 0.92 (t, 3H, J = 7 Hz). ^{13}C NMR: δ 175.6, 145.6, 128.3, 127.0, 126.9, 56.6, 56.4, 36.5, 35.6, 27.0, 25.7, 10.5. Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.62; H, 9.51; N, 11.70.

4.8. Compounds (*S*)-2b and 4a: *N*,*N*-dimethyl-2-{*N*-[(*S*)-1-phenylethyl]amino}-3-methylbutanamide

Major diastereomer. ^{1}H NMR: δ 7.2–7.4 (m, 5H); 3.66 (q, 1H, J = 6.5 Hz); 3.21 (d, 1H, J = 6.5 Hz); 2.82 (s, 3H); 2.72 (s, 3H); 2.20 (br s, 1H); 1.78 (m, 1H); 1.33 (d, 3H, J = 6.5 Hz); 0.99 (d, 3H, J = 6.5 Hz); 0.94 (d,

3H, $J = 6.5$ Hz). ^{13}C NMR: δ 175.3, 146.2, 128.3, 127.0, 126.8, 60.6, 57.8, 36.8, 35.4, 32.3, 23.3, 19.5, 18.4. Minor diastereomer. ^{1}H NMR: δ 7.2–7.4 (m, 5H); 3.55 (q, 1H, $J = 6$ Hz); 3.02 (s, 3H + overlapped d, 1H); 2.70 (s, 3H); 2.2 (br s, 1H); 1.73 (m, 1H); 1.32 (d, 3H, $J = 6.5$ Hz); 1.00 (d, 3H, $J = 7$ Hz); 0.85 (d, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.7, 145.9, 128.5, 128.3, 127.1, 60.5, 56.7, 36.8, 35.5, 31.8, 25.9, 19.7, 18.5. Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found: C, 72.27; H, 10.01; N, 11.09.

4.9. Compounds (*S*)-2c and 4a: *N*,*N*-dimethyl-2-phenyl-2-{*N*-[(*S*)-1-phenylethyl]amino}ethanamide

Major diastereomer. ^{1}H NMR: δ 7.2–7.4 (m, 10H); 4.37 (s, 1H); 3.52 (q, 1H, $J = 6.5$ Hz); 2.89 (s, 3H); 2.7 (br s, 1H); 2.69 (s, 3H); 1.31 (d, 3H, $J = 6.5$ Hz). ^{13}C NMR: δ 172.0, 145.1, 138.6, 128.7, 128.4, 128.0, 127.7, 127.1, 126.9, 59.6, 54.2, 36.6, 35.9, 24.9. Minor diastereomer. ^{1}H NMR: δ 7.3–7.45 (m, 10H); 4.30 (s, 1H); 3.77 (q, 1H, $J = 6.5$ Hz); 3.03 (s, 3H); 2.66 (s, 3H); 2.6 (br s, 1H); 1.40 (d, 3H, $J = 6.5$ Hz). ^{13}C NMR: δ 172.7, 145.4, 139.0, 128.9, 128.5, 127.7, 127.5, 127.2, 127.1, 60.4, 57.1, 36.5, 35.8, 25.0. Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 75.94; H, 7.62; N, 10.28.

4.10. Compounds (*S*)-2a and (*S*)-4b: *N*-methyl-*N*-[(*S*)-1-phenylethyl]-2-{*N*-[(*S*)-1-phenylethyl]amino}butanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.1–7.4 (m, 10H); 6.09, 4.87 (2q, 1H, $J = 7$ Hz); 3.85, 3.81 (2q, 1H, $J = 7$ Hz); 3.43 (t, 1H, $J = 6.5$ Hz); 2.66, 2.49 (2s, 3H); 2.30 (br s, 1H); 1.65 (m, 2H); 1.46, 1.40 (2d, 3H, $J = 7$ Hz); 1.39, 1.37 (2d, 3H, $J = 7$ Hz); 1.02, 0.92 (2t, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.0, 174.9, 145.9, 145.8, 128.6–126.4 (overlapped peaks), 56.8, 56.6, 56.4, 56.3, 54.1, 50.5, 29.0, 28.4, 26.8, 26.2, 23.9, 23.4, 17.9, 15.6, 10.4, 10.3. Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.1–7.4 (m, 10H); 6.18, 4.85 (2q, 1H, $J = 7$ Hz); 3.68, 3.68 (2 coincident q, 1H, $J = 7$ Hz); 3.17 (t, 1H, $J = 6.5$ Hz); 2.74, 2.30 (2s, 3H); 2.2 (br s, 1H); 1.60 (m, 2H); 1.56, 1.54 (2d, 3H, $J = 7$ Hz); 1.37 (2 overlapped d, 3H, $J = 7$ Hz); 1.05, 0.94 (2t, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.5, 175.4, 145.7, 145.6, 140.5, 139.9, 128.5–125.5 (overlapped peaks), 57.4, 56.9, 56.6, 53.3, 50.5, 30.3, 28.7, 27.8, 27.6, 27.0, 26.2, 25.8, 17.4, 15.8, 10.8, 10.6. Anal. Calcd for $C_{19}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.53; H, 8.46; N, 8.50.

4.11. Compounds (*S*)-2b and (*S*)-4b: *N*-methyl-*N*-[(*S*)-1-phenylethyl]-3-methyl-2-{*N*-[(*S*)-1-phenylethyl]amino}-butanamide

Inseparable mixture of diastereomers; *syn*/*anti* isomers: ^{1}H NMR: δ 7.0–7.4 (m, 10H); 6.22, 6.11, 4.92, 4.84 (4q, 1H, $J = 7$ Hz); 3.72, 3.65, 3.60 (4q, last 2 overlapped, 1H, $J = 7$ Hz); 3.38 and 3.32, 3.26 and 3.01 (2d, $J = 4$ Hz and 2d, $J = 6.5$ Hz, 1H); 2.76, 2.59, 2.47, 2.46 (4s, 3H); 2.25 (br s, 1H); 1.87, 1.79 (2m, 1H); 1.56, 1.55, 1.46, 1.35, 1.34 (4d, 6H, $J = 7$ Hz); 1.00–1.05 and 0.88 (3 overlapped d + d, 6H, $J = 7$ Hz). ^{13}C NMR (major *syn*/*anti* only): δ 175.5, 175.2, 146.4, 145.8, 140.6, 140.4, 128.6–126.4 (overlapped peaks), 61.0, 60.9, 57.6, 56.7, 50.6, 50.4, 32.4, 31.7, 29.1, 28.9, 26.1, 23.3, 19.8, 19.7, 18.4, 18.2, 15.9, 15.6. Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 77.91; H, 8.99; N, 8.15.

4.12. Compounds (*S*)-2c and (*S*)-4b: *N*-methyl-*N*-[(*S*)-1-phenylethyl]-2-phenyl-2-{*N*-[(*S*)-1-phenylethyl]amino}-ethanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.5–7.4 (m, 15H); 6.09, 4.97 (2q, 1H, $J = 7$ Hz); 4.50, 4.37 (2s, 1H); 3.59; 3.56 (2q, 1H, $J = 7$ Hz); 2.85 (br s, 1H); 2.54, 2.31 (2s, 3H); 1.44, 1.37 (2d, 3H, $J = 7$ Hz); 1.38, 1.29 (2d, 3H, $J = 7$ Hz). ^{13}C NMR: δ 172.0, 171.8, 145.2, 145,1, 140.0, 139.9, 139.2, 138.5, 126.6–128.9 (overlapped peaks), 60.4, 59.8, 54.4, 54.3, 53.6, 50.9, 28.9, 28.1, 25.0, 24.9, 16.8, 15.1. Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.0–7.5 (m, 15H); 6.21, 4.80 (2q, 1H, $J = 7$ Hz); 4.57, 4.28 (2s, 1H); 3.91, 3.86 (2q, 1H, $J = 7$ Hz); 2.73, 2.27 (2s, 3H); 2.7 (br s, 1H); 1.57, 1.43 (2d, 3H, $J = 7$ Hz); 1.40, 0.96 (2d, 3H, $J = 7$ Hz). ^{13}C NMR: δ 172.6, 172.1, 145.4, 145.3, 140.4, 139.8, 139.6, 138.7, 129.1–126.5 (overlapped peaks), 61.4, 60.9, 57.5, 57.1, 53.4, 50.8, 28.7, 27.8, 25.8, 25.0, 16.1, 16.0. HRMS (CI) calcd for $C_{25}H_{29}N_2O$ [MH^+] 373.2276; found 373.2274.

4.13. Compounds (*S*)-2a and (*R*)-4b: *N*-methyl-*N*-[(*R*)-1-phenylethyl]-2-{*N*-[(*S*)-1-phenylethyl]amino}butanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.1–7.4 (m, 10H); 6.00, 4.98 (2q, 1H, $J = 7$ Hz); 3.80 (m, 1H); 3.56, 3.37 (2t, 1H, $J = 7$ Hz); 2.68, 2.41 (2s, 3H); 2.4 (br s, 1H); 1.6–1.7 (m, 2H); 1.54, 1.40 (2d, 3H, $J = 7$ Hz); 1.37, 1.28 (2d, 3H, $J = 7$ Hz); 1.00, 0.98 (2t, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.1, 174.7, 145.8, 145.7, 140.7, 140.2, 128.6–126.4 (overlapped peaks), 57.0, 56.9, 56.4, 55.9, 53.6, 50.4, 28.9, 28.0, 26.8, 26.4, 23.5, 23.4, 17.7, 15.3, 10.4, 10.3. Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.1–7.4 (m, 10H); 6.19, 4.75 (2q, 1H, $J = 7$ Hz); 3.69, 3.50 (2q, 1H, $J = 7$ Hz); 3.30, 3.16 (2t, 1H, $J = 7$ Hz); 2.70, 2.29 (2s, 3H); 2.0 (br s, 1H); 1.7–1.2 (m, 8H); 0.9–1.5 (m, 3H). Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.74; H, 8.70; N, 8.63. Found: C, 77.71; H, 8.99; N, 8.53.

4.14. Compounds (*S*)-2b and (*R*)-4b: *N*-methyl-*N*-[(*R*)-1-phenylethyl]-3-methyl-2-{*N*-[(*S*)-1-phenylethyl]amino}-butanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.0–7.4 (m, 10H); 6.00, 5.02 (2q, 1H, $J = 7$ Hz); 3.71, 3.66 (2q, 1H, $J = 7$ Hz); 3.51, 3.21 (d, $J = 4$ Hz, d, $J = 6$ Hz, 1H); 2.70, 2.37 (2s, 3H); 2.3 (br s, 1H); 1.82 (m, 1H); 1.61, 1.38 (2d, 3H, $J = 7$ Hz); 1.33, 1.21 (2d, 3H, $J = 7$ Hz); 1.11, 1.00, 0.99, 0.93 (4d, 6H, $J = 7$ Hz). ^{13}C NMR: δ 175.2, 174.8, 146.5, 146.4, 140.7, 140.4, 128.7–126.2 (overlapped peaks), 61.1, 60.3, 58.2, 57.3, 53.7, 50.5. Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.0–7.4 (m, 10H); 6.23, 4.78 (2d, 1H, $J = 5.5$ Hz); 3.68 (m, 1H); 2.98 (d, 1H, $J = 7.5$ Hz, sec-

ond d obscured); 2.72, 2.28 (2s, 3H); 2.3 (br s, 1H); 1.8–1.9 (m, 1H); 1.47, 1.87 (2d, 3H, $J = 7$ Hz); 1.32, 1.29 (2d, 3H, $J = 7$ Hz); 1.05, 1.01 (2d, 3H, $J = 7$ Hz); 0.98, 0.89 (2d, 3H, $J = 7$ Hz). Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 77.96; H, 9.26; N, 8.32.

4.15. Compounds (*S*)-2c and (*R*)-4b: *N*-methyl-*N*-[(*R*)-1-phenylethyl]-2-phenyl-2-{*N*-[(*S*)-1-phenylethyl]amino}-ethanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.0–7.4 (m, 15H); 6.08, 4.94 (2q, 1H, $J = 7$ Hz); 4.62, 4.39 (2s, 1H); 3.61, 3.57 (2q, 1H, $J = 7$ Hz); 2.9 (br s, 1H); 2.64, 2.32 (2s, 3H); 1.48, 1.33 (2d, 3H, $J = 7$ Hz); 1.36, 0.98 (2d, 3H, $J = 7$ Hz). ^{13}C NMR: δ 172.1, 171.7, 145.1 (coincident?), 140.4, 139.9, 139.2, 138.3, 128.9–126,4 (overlapped peaks), 60.4, 60.1, 54.4, 54.3, 53.6, 50.6, 28.9, 28.0, 25.0 (coincident?), 16.0, 15.5. Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.5–7.5 (m, 15H); 6.22, 4.84 (2q, 1H, $J = 7$ Hz); 4.46, 4.26 (2s, 1H); 3.88 (m, 1H); 2.75 (br s, 1H); 2.60, 2.23 (2s, 3H); 1.3–1.5 (m, 6H). ^{13}C NMR: δ 172.5, 172.1, 145.4, 145.2, 140.2, 139.6, 138.9, 138.8, 129.2–126.9 (overlapped peaks), 61.0, 60.7, 57.4, 57.3, 53.6, 51.0, 28.7, 27.9, 25.3, 25.2, 16.6, 15.3. Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.61; H, 7.58; N, 7.52. Found: C, 80.36; H, 7.92; N, 7.73.

4.16. Compounds (*S*)-3a and 4a: *N*,*N*-dimethyl-2-{*N*-[(*S*)-1-(1-naphthyl)ethyl]amino}butanamide

Major diastereomer: ^{1}H NMR: δ 7.45–8.31 (m, 7H); 4.69 (q, 1H, $J = 6.5$ Hz); 3.53 (t, 1H, $J = 6.5$ Hz); 2.90 (s, 3H); 2.72 (s, 3H); 2.2 (br s, 1H); 1.62 (m, 2H); 1.55 (d, 3H, $J = 6.5$ Hz); 0.94 (t, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.0, 141.4, 133.9, 131.3, 128.8, 127.2, 125.8, 125.6, 125.3, 123.5, 123.2, 55.9, 51.2, 36.7, 35.5, 26.6, 23.0, 10.2. Minor diastereomer: ^{1}H NMR: δ 7.45–8.3 (m, 7H); 4.47 (q, 1H, $J = 6.5$ Hz); 3.23 (t, 1H, $J = 6.5$ Hz); 2.96 (s, 3H); 2.39 (s, 3H); 1.65 (br s, 1H); 1.54 (m, 2H); 1.48 (d, 3H, $J = 6.5$ Hz); 0.94 (t, 3H, $J = 6.5$ Hz). ^{13}C NMR: δ 175.7, 140.9, 133.9, 131.6, 128.8, 127.2, 125.7, 125.5, 125.2, 124.0, 123.2, 56.5, 52.1, 36.4, 35.5, 27.0, 24.7, 10.6. Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.07; H, 8.51; N, 9.85. Found: C, 75.94; H, 8.74; N, 9.83.

4.17. Compounds (*S*)-3b and 4a: *N*,*N*-dimethyl-2-{*N*-[(*S*)-1-(1-naphthyl)ethyl]amino}-3-methylbutanamide

Major diastereomer: ^{1}H NMR: δ 7.4–8.3 (m, 7H); 4.59 (q, 1H, $J = 6.5$ Hz); 3.30 (d, 1H; $J = 6.5$ Hz); 2.85 (s, 3H); 2.63 (s, 3H); 2.20 (br s, 1H); 1.83 (m, 1H); 1.49 (d, 3H, $J = 6.5$ Hz); 1.01 (d, 3H, $J = 6.5$ Hz); 0.94 (d, 3H, $J = 6.5$ Hz). ^{13}C NMR: δ 175.2, 142.0, 133.8, 131.2, 128.8, 127.1, 125.7, 125.5, 125.2, 123.5, 123.3, 60.5, 52.6, 36.8, 35.4, 32.3, 22.8, 19.5, 18.5. Minor diastereomer: ^{1}H NMR: δ 7.4–8.3 (m, 7H); 4.42 (q, 1H, $J = 7$ Hz); 2.97 (s, 3H); 2.34 (s, 3H); 2.20 (br s, 1H); 1.78 (m, 1H); 1.48 (d, 3H, $J = 7$ Hz); 1.06 (d, 3H, $J = 7$ Hz); 0.85 (d, 3H, $J = 7$ Hz). Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47: H, 8.78; N, 9.39. Found: C, 76.11; H, 8.78; N, 9.55.

4.18. Compounds (*S*)-3c and 4a: *N*,*N*-dimethyl-2-{*N*-[(*S*)-1-(1-naphthyl)ethyl]amino}-2-phenylethanamide

Major diastereomer: ^{1}H NMR: δ 7.1–8.0 (m, 12H); 4.48 (s, 1H); 4.40 (q, 1H, $J = 6.5$ Hz); 2.95 (s, 3H); 2.7 (br s, 1H); 2.67 (s, 3H); 1.44 (d, 3H, $J = 6.5$ Hz). ^{13}C NMR: δ 172.0, 140.6, 136.6, 134.0, 131.3, 128.8, 128.7, 128.1, 127.7, 127.2, 125.8, 125.6, 125.2, 123.6, 123.1, 59.6, 49.3, 36.6, 35.9, 24.4. Minor diastereomer: ^{1}H NMR: δ 7.2–8.25 (m, 12H); 4.65 (q, 1H, $J = 6.5$ Hz); 4.33 (s, 1H); 3.00 (s, 3H); 2.44 (s, 3H); 1.6 (br s, 1H); 1.54 (d, 3H, $J = 6.5$ Hz). ^{13}C NMR: δ 172.8, 140.7, 139.1, 134.0, 131.6, 128.9 (coincident?), 127.7, 127.5, 127.4, 125.8, 125.6, 125.3, 124.2, 123.2, 60.6, 52.7, 36.4, 35.8, 24.2. Anal. Calcd for $C_{22}H_{24}N_2O + C_6H_3N_3O_7$ (picrate, mp 199.0–200.5 °C): C, 59.89; H, 4.85; N, 12.47. Found: C, 59.73; H, 4.93; N, 12.42.

4.19. Compounds (*S*)-3a + (*S*)-4b: *N*-methyl-*N*-[(*S*)-1-phenylethyl]-2-{*N*-[(*S*)-1-(1-naphthyl)ethyl]amino}-butanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.05–8.35 (m, 12H); 6.19, 4.82 (2q, 1H, $J = 7$ Hz); 4.75, 4.73 (2 superimposed q, 1H, $J = 6.5$ Hz); 3.59, 3.54 (2t, $J = 6.5$, 6 Hz, 1H); 2.70, 2.52 (2s, 3H); 2.45 (br s, 1H); 1.73 (m, 2H); 1.57, 1.53 (2d, 3H, $J = 6.5$ Hz); 1.50, 1.27 (2d, 3H, $J = 7$ Hz); 1.03, 0.95 (2t, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.14, 175.08, 141.6, 141.5, 140.54, 140.45, 134.0, 133.9, 131.4, 131.3, 128.9–123.3 (overlapped peaks), 56.6, 56.4, 54.2, 51.7 (br), 51.5 (br), 50.5, 29.1, 28.5, 27.0, 26.4, 23.6, 22.9, 18.0, 15.6, 10.4 (coincident?). Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.65–8.35 (m, 12H); 6.18, 4.72 (2q, 1H, $J = 7$ Hz); 4.56 (2 overlapped q, 1H, $J = 6.5$ Hz); [3.63 (dd, $J = 8.5$, 3.5 Hz), 3.22 (t, $J = 7$ Hz), 1H]; 2.66, 2.03 (2s, 3H); 2.0 (br s, 1H); 1.59 (m, 2H); 1.40, 1.28 (2 overlapped d, 3H, $J = 6$ Hz); 1.87, 1.47 (2 overlapped d, 3H, $J = 7$ Hz); 1.17, 0.97 (2t, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.7, 175.2, 140.8 (coincident?), 140.5, 139.2, 134.1, 133.9, 131.5 (coincident?), 128.9–123.2 (overlapped peaks), 57.4, 57.0, 53.0, 52.4 (br), 50.5, 28.6, 27.6, 27.5, 27.0, 25.1, 24.8, 16.9, 15.7, 10.9, 10.7. Anal. Calcd for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 79.97; H, 8.39; N, 7.40.

4.20. Compounds (*R*)-3a and (*R*)-4b: *N*-methyl-*N*-[(*R*)-1-phenylethyl]-2-{*N*-[(*R*)-1-(1-naphthyl)ethyl]amino}-butanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.0–8.35 (m, 12H); 6.17, 4.81 (2q, 1H, $J = 7$ Hz); 4.73, 4.70 (2 superimposed q, 1H, $J = 6.5$ Hz); 3.57, 3.51 (2t, 1H, $J = 6.5$, 6 Hz); 2.68, 2.50 (2s, 3H); 2.35 (br s, 1H); 1.71 (m, 2H); 1.55, 1.48 (2d, 3H, $J = 7$ Hz); 1.51, 1.25 (2d, 3H, $J = 6.5$ Hz); 1.01, 0.92 (2t, 3H, $J = 6.5$ Hz). ^{13}C NMR: δ 175.54, 175.47, 142.0, 141.9, 140.95. 140.89, 134.4, 134.3, 131.8, 131.7, 129.3–123.7 (overlapped peaks), 57.0, 56.9, 54.6, 52.2, 51.9, 50.9, 29.5, 28.9, 27.4, 26.8, 24.0, 23.3, 18.4, 16.1, 10.8 (coincident?). Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.65–8.35 (m, 12H); 6.18, 4.73 (2q, 1H, $J = 7$ Hz); 4.57 (2 overlapped q, 1H, $J = 7$ Hz); [3.62 (dd, $J = 8.5$,

3.5 Hz), 3.22 (t, $J = 7$ Hz), 1H]; 2.66, 2.03 (2s, 3H); 2.0 (br s, 1H); 1.58 (m, 2H); 1.45–1.55 (m, 6H); 1.17, 0.97 (2t, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.7, 175.2, 140.9, 140.8, 140.5, 139.2, 134.1, 133.9, 131.5 (coincident?), 129.0–123.2 (overlapped peaks), 57.4, 57.0, 53.0, 52.4 (br), 50.5, 28.6, 27.6, 27.5, 27.0, 25.1, 24.8, 16.9, 15.7, 10.9, 10.7. Anal. Calcd for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 79.93; H, 8.26; N, 7.32.

4.21. Compounds (*S*)-3b and (*S*)-4b: *N*-methyl-*N*-[(*S*)-1-phenylethyl]-3-methyl-2-{N-[(*S*)-1-(1-naphthyl)ethyl]-amino}butanamide

Inseparable mixture of diastereomers; *syn*/*anti* isomers: ^{1}H NMR: δ 7.0–8.3 (m, 12H); 6.22, 4.85, 4.73 (2 overlapped q, q, q, 1H, $J = 7$ Hz); 4.61, 4.51 (2 overlapped q, 2 overlapped q, 1H, $J = 6.5$ Hz); 3.57, 3.44, 3.37, 3.06 (2d, $J = 4$ Hz, 2d, $J = 7$ Hz, 1H); 2.68, 2.62, 2.51, 1.99 (4s, 3H); 1.80–1.95 (m, 1H); 1.9 (br s, 1H); 1.95–1.55 (m, 6H); 0.85–1.20 (m, 6H). Anal. Calcd for $C_{26}H_{32}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 79.93; H, 8.26; N, 7.32.

4.22. Compounds (*S*)-3c and (*S*)-4b: *N*-methyl-*N*-[(*S*)-1-phenylethyl]-2-phenyl-2-{*N*-[(*S*)-1-(1-naphthyl)ethyl]-amino}ethanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.45–8.0 (17H); 6.15, 4.89 (2q, 1H, $J = 7$ Hz); 4.59, 4.47 (2s, 1H); 4.44 (2 overlapped q, 1H); 2.95 (br s, 1H); 2.56, 2.27 (2s, 3H); 1.47 (2 overlapped d, 3H, $J = 7$ Hz); 1.38, 1.31 (2d, 3H, $J = 7$ Hz). ^{13}C NMR: δ 172.1, 171.8, 140.7, 140.5, 140.2, 139.2, 139.1, 138.5, 134.1, 134.0, 131.4, 131.3, 128.8–123.1 (overlapped peaks), 60.3, 59.8, 53.6, 50.9, 49.6 (br), 28.9, 28.1, 24.4, 24.3, 16.7, 15.1. Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.6–8.3 (17H); 6.20, 4.72 (2q, 1H, $J = 7$ Hz); 4.67, 4.30 (2s, 1H); 4.42 (m, 1H); 3.0 (br s, 1H); 2.66, 2.07 (2s, 3H); 0.9–1.7 (m, 6H). Anal. Calcd for $C_{29}H_{30}N_2O$: C, 82.43; H, 7.16; N, 6.63. Found: C, 82.23; H, 7.32; N, 6.63.

4.23. Compounds (*S*)-3a and (*R*)-4b: *N*-methyl-*N*-[(*R*)-1-phenylethyl]-2-{*N*-[(*S*)-1-(1-naphthyl)ethyl]amino}-butanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 7.1–8.35 (m, 12H); 6.06, 4.49 (2q, 1H, $J = 7$ Hz); 4.71, 4.18 (2q, 1H, 7 Hz); 3.67, 3.49 (2t, 1H, $J = 6.5$ Hz); 2.73, 2.35 (2s, 3H); 2.53 (br s, 1H); 1.65 (m, 2H); 1.55 (2d, 3H, $J = 7$ Hz); 1.40 (2d, 3H, $J = 7$ Hz); 1.02, 0.99 (2t, 3H, $J = 7$ Hz). ^{13}C NMR: δ 175.1, 174.9, 141.7, 141.6, 140.7, 140.3, 133.95, 133.94, 131.3, 131.2, 128.9–123.2 (overlapped peaks), 56.8, 56.3, 53.8, 51.7, 51.3, 50.5, 28.9, 28.1, 26.9, 26.6, 23.5, 23.1, 17.8, 15.4, 10.4, 10.3. Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.95–8.2 (m, 12H); 6.21, 4.46 (2q, 1H, $J = 7$ Hz); 4.52 (2 overlapped q, 1H, $J = 6.5$ Hz); 3.35, 3.25 (2t, 1H, $J = 7$ Hz); 2.63, 2.07 (2s, 3H); 2.35 (br s, 1H); 1.45–1.65 (m, 8H); 0.99, 0.97 (2t, 3H, $J = 7$ Hz). ^{13}C NMR: δ (*syn* or *anti* only): 175.8, 140.8, 140.4, 133.9, 131.4, 128.8–123.9 (overlapped peaks), 57.0, 52.4 (br), 50.6, 28.7, 27.2, 24.9, 15.6, 10.7. Anal. Calcd for $C_{25}H_{30}N_2O$: C, 80.17; H, 8.07; N, 7.48. Found: C, 79.94; H, 8.40; N, 7.38.

4.24. Compounds (*S*)-3b and (*R*)-4b: *N*-methyl-*N*-[(*R*)-1-phenylethyl]-3-methyl-2-{*N*-[(*S*)-1-(1-naphthyl)ethyl]-amino}butanamide

Major diastereomer only; *syn*/*anti* isomers: ^{1}H NMR: δ 7.0–8.3 (m, 12H); 6.06, 5.05 (2q, 1H, $J = 7$ Hz); 4.64, 4.52 (2q, 1H, $J = 7$ Hz); 3.58, 3.31 (2d, 1H, $J = 4$, 6 Hz); 2.77, 2.31 (2s, 3H); 1.87 (m, 1H); 1.62, 1.52 (2d, 3H, $J = 7$ Hz); 1.37, 1.33 (2d, 3H, $J = 7$ Hz); 1.13, 1.05 (2d, 3H, $J = 7$ Hz); 1.00 (2 superimposed d, 3H, $J = 7$ Hz). ^{13}C NMR: δ 176.0, 175.2, 142.5, 142.3, 140.7, 140.6, 133.9 (coincident?), 131.3, 131.2, 128.8–123.2 (overlapped peaks), 61.1, 60.3, 53.9, 52.9 (br), 50.5, 32.3, 31.9, 29.1, 28.2, 25.0, 23.0, 20.3, 19.8, 18.2, 18.1, 17.2, 15.3.

4.25. Compounds (*S*)-3c and (*R*)-4b: *N*-methyl-*N*-[(*R*)-1-phenylethyl]-2-phenyl-2-{*N*-[(*S*)-1-(1-naphthyl)ethyl]-amino}ethanamide

Major diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.95–8.05 (m, 17H); 6.12, 4.86 (2q, 1H, $J = 7$ Hz); 4.69, 4.47 (2s, 1H); 4.42 (2 coincident q, 1H, $J = 7$ Hz); 3.0 (br s, 1H); 2.66, 2.28 (2s, 3H); 1.50, 1.44 (2d, 3H, $J = 7$ Hz); 1.43, 0.92 (2d, 3H, $J = 7$ Hz). ^{13}C NMR: δ 172.1, 171.8, 140.7, 140.5, 140.4, 139.8, 139.2, 138.4, 134.04, 134.01, 131.36, 131.33, 128.9–123.1 (overlapped peaks), 60.4, 60.1, 53.6, 50.6, 49.7 (br), 49.4 (br), 28.9, 28.0, 24.5, 24.4, 16.0, 15.6. Minor diastereomer, *syn*/*anti* mixture: ^{1}H NMR: δ 6.45–8.3 (m, 17H); 6.23, 4.66 (2q, 1H, $J = 7$ Hz); 4.75 (2 coincident q, 1H, $J = 6.5$ Hz); 4.46, 4.34 (2s, 1H); 2.95 (br s, 1H); 2.56, 2.08 (2s, 3H); 1.58 (2 superimposed d, 3H, $J = 7$ Hz); 1.47, 0.87 (2d, 3H, $J = 7$ Hz). ^{13}C NMR: δ 172.7, 172.3, 140.6 (coincident?), 140.1, 136.6, 139.0, 138.8, 134.05, 134.00, 131.7, 131.6, 129.1–123.0 (overlapped peaks), 61.03, 60.98, 53.5, 53.1 (br), 52.9 (br), 51.0, 28.7, 27.9, 24.4, 24.3, 15.9, 15.3.

4.26. Deprotection of the major diastereomer of run 29 [(*S*)-3c + (*R*)-4b]

A mixture of 1.4 g (5.3 mmol) of imine, 0.77 g $BF_3{\cdot}Et_2O$ and 1.6 g (6.4 mmol) of carbamoylsilane in 38 mL of benzene afforded (48 h) 1.2 g (52%) of the major diastereomer, obtained from flash chromatography (15% EtOAc/hexane), $[\alpha]_D^{24} = +42.6$ (*c* 0.51, $CHCl_3$). Hydrogenolysis of 0.25 g of this material in 5 mL methanol containing 50 mg of 10 wt % Pd/C under 1 atm at 25 °C for 10 h afforded 0.12 g (80%) of the aminoamide from chromatography (EtOH–MeOH, 9:1), which ^{1}H NMR indicated was totally amine deprotected. Further characterization was carried out on the hydrochloride. Thus, in another run, 0.80 g of the aminoamide was similarly hydrogenated and the reaction mixture filtered through Celite and concentrated. The residue was dissolved in 15 mL Et_2O, and a solution of hydrogen chloride in diethyl ether added dropwise with stirring to pH 3. The resulting precipitate was filtered, washed with ether and dried under vacuum to give 0.52 g (90%) of the hydrochloride, mp 120–125 °C. This material showed

$[\alpha]_D^{24} = +3.0$ (*c* 2.2, $CHCl_3$). ^1H NMR (mixture of *syn* and *anti*): δ (major stereoisomer) 8.96 (s, 3H), 7.0–7.8 (m, 10H), 5.85 (q, $J = 6$ Hz, 1H), 5.72 (s, 1H), 2.50 (s, 3H), 1.42 (d, $J = 6$ Hz, 3H); δ (minor stereoisomer) 9.05 (s, 3H), 7.0–7.8 (m, 10H), 6.02 (s, 1H), 5.08 (q, $J = 6$ Hz, 1H), 2.48 (s, 3H), 0.88 (d, $J = 6$ Hz, 3H). ^{13}C NMR (mixture of *syn* and *anti*): δ (major stereoisomer) 167.8, 139.8, 127.0–131.5 (overlapped peaks), 55.9, 51.7, 29.3, 15.6; δ (minor stereoisomer) 167.0, 138.7, 127.0–131.5 (overlapped peaks), 55.7, 54.4, 28.4, 15.3. Anal. Calcd for $C_{17}H_{21}ClN_2O$: C, 66.76; H, 6.92; N, 9.16. Found: C, 66.20; H, 7.07; N, 9.20.

Hydrolysis of the aminoamide obtained above was accomplished by dissolving 120 mg in 2.0 mL of 6 M HCl and heating at 110 °C in a sealed tube for 20 h.[5] The solution was concentrated and the solid washed with EtOAc, kept at 60 °C (1 mmHg) for 15 h followed by storage over P_2O_5 (1 mmHg) for 24 h. We obtained 63 mg (75%) of phenylglycine hydrochloride, which had $[\alpha]_D^{24} = -134.0$ (*c* 0.10, MeOH).

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