DOI: 10.1002/ejoc.200500702

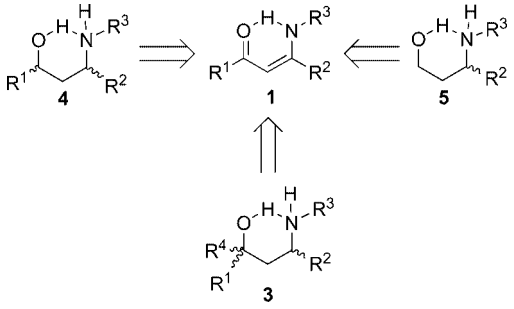
One-Pot Addition/Reduction Procedure for the Synthesis of γ-Amino Alcohols from β-Enamino Ketones

Cristina Cimarelli,*[a] Sandra Giuli,[a] and Gianni Palmieri[a]

Keywords: γ-Amino alcohols / β-Enamino ketones / Alkylation / Reduction / Conformation analysis

γ-Amino alcohols **3** have been synthesized by the addition of organolithium reagents to β-enamino ketones **1** followed by one-pot reduction with sodium triacetoxyborohydride. The method allows the stereoselective synthesis of γ-amino alcohols in which the hydroxy group is bonded to a fully substituted carbon atom. The relative configuration of the chiral product was determined by ^{1}H NMR spectroscopy.

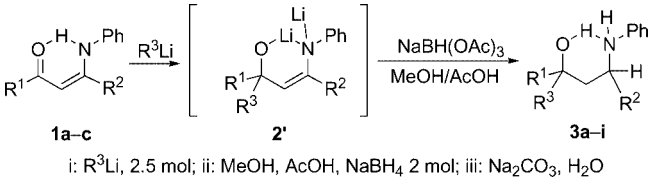
The structural unit of γ-amino alcohols is present with a stereodefined geometry in many compounds that have interesting pharmacological and biological properties.[1] In addition, aminols are often useful building blocks in the synthesis of many natural products.[2] In the past we have developed methodologies for the preparation of γ-amino alcohols **4** and **5** from enamino ketones[3] **1** and β-enamino esters[4] (**1**, R^1 = OR). Such reactions afforded γ-amino alcohols in which the hydroxy function is bonded to a methylene or a methine carbon atom; now this series has been extended through the synthesis of γ-amino alcohols **3** in which the hydroxy group is bonded to a fully substituted carbon atom (Scheme 1).



Scheme 1.

Also, β-enamino ketones appear to be more convenient precursors of γ-amino alcohols. In fact they have been studied for their intrinsic properties[5] and as versatile precursors of several classes of compounds.[6] They can be prepared in a wide variety of ways, including the direct condensation of the appropriate amine with symmetrical β-dicarbonyl compounds in homogeneous and heterogeneous phases,[7] the acylation of lithium imines with esters[8] and recently the addition of organolithium reagents to β-enamino esters,[9] making β-enamino ketones very easily available and cheap starting materials.

In this paper the synthesis of 1,3-amino alcohols **3** by the addition of alkyllithium reagents to β-enamino ketones followed by one-pot reduction is presented (Scheme 2).



Scheme 2.

Results and Discussion

β-Enamino ketone **1** was added to 2.5 equiv. of alkyllithium in *n*-hexane (see Expt. Sect.). The addition reaction was performed at different temperatures and for different times depending on the reactivity of the alkyllithium reagent used. After the addition step, the reaction mixture was quenched with methanol and then acetic acid and sodium borohydride were added, and thus a one-pot reduction with sodium triacetoxyborohydride formed in situ was performed. The final γ-amino alcohol **3** was obtained after quenching with saturated sodium carbonate solution. The reaction conditions, yields and diastereomer ratios are reported in Table 1.

The mechanism proposed for this reaction is given in Scheme 3. First the organolithium reagent acts as a base, extracting the acidic proton of the amino group of the enamino ketones **1a**–**c**. Then a second organolithium molecule attacks the carbonyl group to afford the presumed intermediate **2′**. The β-hydroxyimine tautomer **2** participates in the reduction step; the triacetoxyborohydride coordinates to the oxygen atom and transfers the hydride ion to the imin-

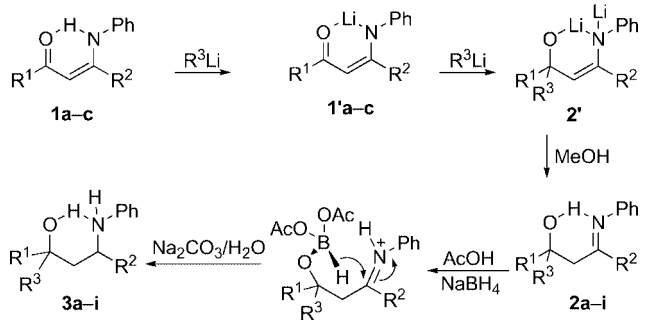
[a] Dipartimento di Scienze Chimiche, Università di Camerino, Via S. Agostino 1, 62032 Camerino, Italy

Table 1. Reaction conditions, yields and diastereomer ratio of the synthesis of γ-amino alcohols **3**.

Entry	**1**	R^1	R^2	**3**	R^3	*T* [°C][a]	*t* [h][a]	Yield [%][b]	*dr*[c]
1	**1a**	Me	Me	**3a**[d]	Me	50	1.5	45	–
2	**1a**	Me	Me	(*R**,*R**)-**3b**	*i*Pr	0	1.20	36	74:26
3	**1a**	Me	Me	(*R**,*S**)-**3c**	*n*Bu	0	2.5	86	64:36
4	**1a**	Me	Me	(*R**,*R**)-**3d**	*t*Bu	50	3	51	72:28
5	**1a**	Me	Me	(*R**,*S**)-**3e**	Ph	50	3	66	62:38
6	**1b**	Ph	Me	(*R**,*R**)-**3f**	*i*Pr	0	1.25	59	52:48
7	**1b**	Ph	Me	(*R**,*S**)-**3g**	*n*Bu	0	3	79	66:34
8	**1c**	Ph	Ph	(*R**,*R**)-**3h**	*i*Pr	0	2.25	57	85:15
9	**1c**	Ph	Ph	(*R**,*S**)-**3i**	*n*Bu	0	1.5	39	71:29

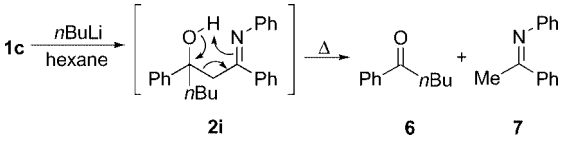
[a] Conditions for the alkylation step. [b] Combined yield of pure isolated diastereomers. [c] Diastereomer ratio was determined by GC analysis of the reaction mixture. [d] See ref.[10]

ium group to afford a diastereomeric mixture of γ-amino alcohols **3**.



Scheme 3.

Several attempts to isolate the hypothetical β-hydroxyimine **2** failed. However, direct evidence for its formation comes from GC-MS analysis, before the reduction step, of the crude reaction mixture of Entry 9 in Table 1. The mixture, treated after the addition step with methanol, was submitted to GC-MS analysis which showed two chromatographic peaks corresponding to 1-phenylpentan-1-one (**6**) and phenyl(1-phenylethylidene)amine (**7**) which result from the thermal decomposition of the hypothetical intermediate **2i**, probably through a retro-aldol reaction (Scheme 4). Such observations are supported by literature data which show the instability of analogous β-hydroxyimines.[11] The subsequent reduction of the mixture with sodium borohydride and acetic acid in methanol afforded the diastereomeric γ-amino alcohol **3i**. The thermal instability of the addition intermediate **2** encouraged us to try a one-pot procedure, with direct reduction of the crude addition mixture, which afforded the desired γ-amino alcohols **3** in satisfactory yields, as reported in Table 1.



Scheme 4.

The use of acetic acid is necessary to obtain a good yield from the reduction step. A mixture of starting material **1a** and *n*-buthyllithium was also treated with sodium borohydride in methanol after the addition step performed under the conditions shown in Entry 3 of Table 1. GC-MS analysis of the crude reaction mixture revealed in this case a lower yield of the final γ-amino alcohol **3c** (23%) and a significant amount of byproducts.

The reaction proceeds with acceptable yields with β-enamino ketones with a phenyl group bonded to the nitrogen atom, probably because of their strong electrophilicity, while (*Z*)-4-(benzylamino)pent-3-en-2-one (**1d**) is reactive under the reaction conditions, but only affords the corresponding γ-amino alcohol in a poor yield. All the organolithium reagents used exhibit good reactivity with the exception of methyllithium, which reacts with β-enamino ketone **1a** in acceptable yields (Table 1, Entry 1), but has very poor reactivity towards starting materials **1b** and **1c**. However, it is possible to obtain the desired γ-amino alcohol **3** through the opportune choice of starting β-enamino ketone **1** and organolithium reagent.

Lithium phenylacetylide and PhMgCl were also used as organometallic reagents in the reaction with β-enamino ketone **1a** but their use proved to be unsuccessful; lithium phenylacetylide did not react under the reaction conditions, while treatment with the Grignard reagent afforded only intractable mixtures.

In same cases alternative conditions for the addition step were used: the reaction was performed in tetrahydrofuran at –80 °C in the presence of cerium trichloride as Lewis acid catalyst. After quenching with methanol and one-pot reduction with sodium borohydride, analysis of the crude mixture revealed that the reaction only occurred with starting material **1a** and *n*-buthyllithium, for which a yield of 64% was obtained and a diastereomer ratio of 67:32, similar to the results obtained under our standard conditions (Table 1, Entry 3).

Stereochemistry

The stereochemical outcome of these reactions can be explained by considering the two consecutive reactions involved in the proposed mechanism (see Scheme 2). While the addition step gives the racemate **2**, in the subsequent reduction step the hydride can attack both the diastereotopic faces of the iminium group to afford two diastereomeric transition states from which either the (*R**,*R**) or the (*R**,*S**) final γ-amino alcohol **3** may form. Theoreti-

cal calculations [at the PM3 and 3-21G(*) levels of theory] conducted on the transition states of the reduction of **2d** (Table 1, Entry 4) show that the most stable conformation assumed by the transition state (*R**,*R**)-**3d TS** is a six-membered cyclic chair in which the more hindered *tert*-butyl and phenylamino groups adopt equatorial positions, as shown in Figure 1. On the other hand, in the transition state (*R**,*S**)-**3d TS** the phenylamino group is axial because only the more hindered *tert*-butyl group can occupy the equatorial position and it locks the transition state in the most stable conformation, as depicted in Figure 1. In this position the phenylamino group exerts such a strong steric effect on both the axially directed γ-methyl and γ′-acetoxy groups that it twists the transition state out of the chair conformation. The energy difference between the two transition states is +0.810 kcal/mol at the PM3 level [+0.922 kcal/mol, 3-21G(*)] and it accounts for the diastereoselectivity observed. The same model can explain the stereoselectivity observed in Entries 2 and 3.

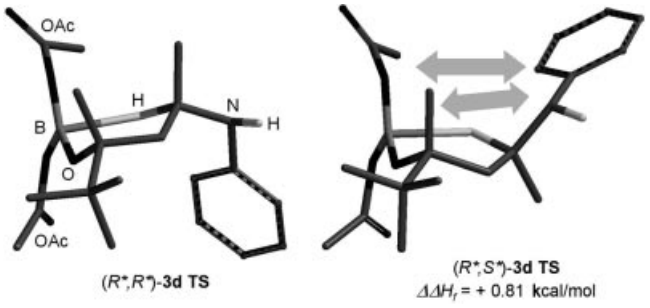


Figure 1. Diasteomeric transition states for the intramolecular reduction step of **2d**.

In Entries 5–7 of Table 1 the diastereoselectivity observed can be explained on the basis of a different transition state in which the phenyl and the phenylamino groups are situated in *trans* positions, which is more stable for stereoelectronic reasons. The most stable transition state calculated for the product **3e** corresponds to an (*R**,*S**) relative configuration of the γ-amino alcohol, as depicted in Figure 2. When a second phenyl group is bonded to the other chiral center, as in Entries 8 and 9, the major diastereomer obtained is derived from a transition state in which the most stable conformation calculated has the two phenyl groups in *trans* positions, as depicted in Figure 2 for (*R**,*R**)-**3h TS**.

Generally, the product obtained is the thermodynamically more stable, as calculated at the semiempirical PM3 level (Table 2).

Table 2. Calculated heats of formation (PM3 level) for the major and minor diastereomers of **3**.

3	Major ΔH_f [kcal/mol]	Minor ΔH_f [kcal/mol]	$\Delta\Delta H_f$ [kcal/mol]
3b	–56.728 (*R**,*R**)	–56.451 (*R**,*S**)	0.277
3c	–63.846 (*R**,*S**)	–63.627 (*R**,*R**)	0.219
3d	–60.204 (*R**,*R**)	–59.191 (*R**,*S**)	1.013
3e	–12.342 (*R**,*S**)	–12.083 (*R**,*R**)	0.259
3f	–19.709 (*R**,*R**)	–18.792 (*R**,*S**)	0.917
3g	–27.270 (*R**,*S**)	–26.706 (*R**,*R**)	0.564
3h	+14.449 (*R**,*R**)	+14.126 (*R**,*S**)	0.323
3i	+5.011 (*R**,*S**)	+6.565 (*R**,*R**)	1.554

The relative configurations of the γ-amino alcohols **3** were assigned by interpreting the general trend in the chemical shifts observed in their ^{1}H NMR spectra assuming the most stable conformations calculated by molecular modelling. It has been reported in the literature[3,4a,12] that a strong intramolecular hydrogen bond exists between the proton of the hydroxy group and the nitrogen atom of γ-amino alcohols, as shown in Figure 3, that makes the cyclic chair conformation rigid and this was also found to be the case in the most stable conformation calculated. Both literature[3,4a,12] and ^{1}H NMR spectroscopic data show that this conformation is analogous to that assumed by 1,3-tetrahydrooxazine derivatives. An X-ray analysis of a β-aminonaphthol (this product is solid in contrast to γ-amino alcohols which are generally liquid) has been reported[13] and proved that the conformation of the product in the crystal is the same as that assumed in the NMR solution and very similar to that observed for similar γ-amino

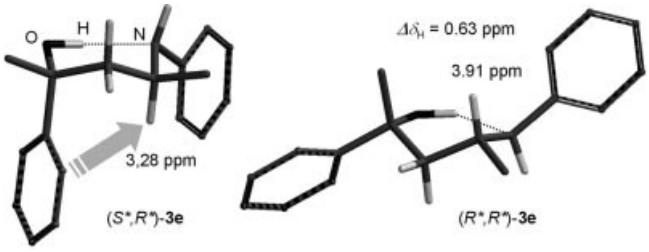


Figure 3. Calculated most stable conformations for both diastereomers of γ-amino alcohol **3e**.

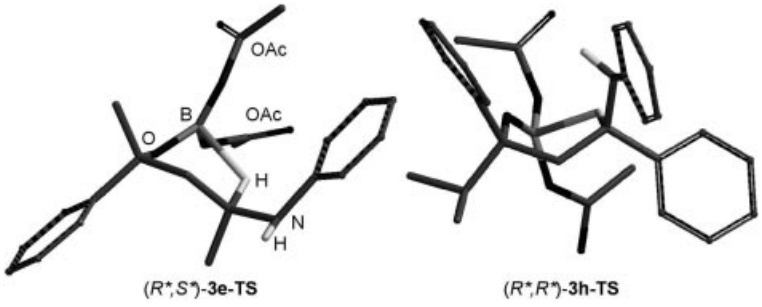


Figure 2. Diasteomeric transition states for the intramolecular reduction of **2e** and **2h**.

alcohols. In the light of this observation the cyclization to oxazines is superfluous. It is useful to confirm the relative configuration of the products, particularly of **3e**–**i**, from the chemical shift of the proton geminal to the amino group which shows very different values depending on the diastereomer, as reported in Table 3.

Table 3. Chemical shifts of the proton geminal to the amino group for the major (M) and minor (m) diastereomers of **3**.

3	δ_H(M) [ppm]	δ_H(m) [ppm]	$\Delta\delta_H$ [ppm]
3b	3.85 (*R**,*R**)	3.84 (*R**,*S**)	0.01
3c	3.85 (*R**,*S**)	3.79 (*R**,*R**)	0.06
3d	3.79 (*R**,*R**)	3.82 (*R**,*S**)	0.03
3e	3.28 (*R**,*S**)	3.91 (*R**,*R**)	0.63
3f	3.26 (*R**,*R**)	3.70 (*R**,*S**)	0.44
3g	3.27 (*R**,*S**)	3.90 (*R**,*R**)	0.62
3h	4.55 (*R**,*R**)	4.13 (*R**,*S**)	0.42
3i	4.68 (*R**,*S**)	4.18 (*R**,*R**)	0.50

The largest difference is registered for products **3e**: in diastereomer (*R**,*S**)-**3e** the phenyl group is in an axial position and exerts a shielding effect of 0.63 ppm with respect to the azomethine proton, while the isomer (*R**,*R**)-**3e** adopts a conformation in which the phenyl group is equatorial and exerts no effects on the other protons of the molecule (see Figure 3). Analogous considerations can be made for the other products (**3f**–**i**) that have a phenyl group at the C-2 position.

Conclusions

In summary, a new synthesis of tertiary γ-amino alcohols by addition of alkyllithium reagents to β-enamino ketones followed by a one-pot reduction procedure with sodium triacetoxyborohydride is reported. Pure diastereomers can be obtained by flash chromatography. In addition the procedure is easy to perform, of practical utility and does not require dangerous or expensive chemicals.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were recorded at 200 or 400 MHz and 50 or 100 MHz, respectively. Coupling constants are given in Hz. IR spectra were recorded using an FTIR apparatus. All reagents were commercially available, purchased at the highest quality and purified by distillation when necessary. THF and *n*-hexane were distilled and stored over sodium wire before use. The following organometallic reagents were used: MeLi (1 M solution in diethyl ether), *i*PrLi (0.7 M solution in pentane), *n*BuLi (2.5 M solution in hexanes), *t*BuLi (1.7 M solution in pentane), PhLi (1.9 M solution in dibutyl ether), PhMgCl (2.0 M solution in THF), lithium phenylacetylide (2.0 M solution in THF). When only the major diastereomer was obtained pure, the ^{1}H NMR signals for the minor diastereomer were deduced from the spectra of the crude reaction mixture or from enriched chromatographic fractions.

One-Pot Addition/Reduction Procedure for the Synthesis of γ-Amino Alcohols from β-Enamino Ketones: β-Enamino ketones **1a**–**d** (2.0 mmol) were dissolved in *n*-hexane (5 mL) under nitrogen and the alkyllithium reagent (5.0 mmol) was added dropwise at 0 °C. Then the reaction mixture was warmed as necessary and after the reaction times reported in Table 1 quenched with methanol (5 mL). Acetic acid (1 mL) was added at 0 °C and $NaBH_4$ (4 mmol) was added portionwise. After 2 h, the mixture was treated with Na_2CO_3 until a basic pH was reached and extracted with dichloromethane (2 × 20 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and the solvent removed under reduced pressure. Chromatographic separation of the crude oil on silica gel with AcOEt/cyclohexane (50:50) as eluent afforded the pure diastereomers.

(3*R,5*R**)-5-Anilino-2,3-dimethylhexan-3-ol [(3*R**,5*R**)-3b]:** Major diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3391, 1602, 1498, 909, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.95 (d, *J* = 7.0 Hz, 6 H), 1.17 (d, *J* = 6.2 Hz, 3 H), 1.23 (s, 3 H), 1.58–1.65 (m, 2 H), 1.69 (sept, *J* = 6.8 Hz, 1 H), 3.75 (br. s, 2 H), 3.85 (dqd, *J* = 9.5, 6.2, 4.0 Hz, 1 H), 6.70–6.90 (m, 3 H), 7.20–7.30 (m, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 17.2, 17.6, 22.3, 23.8, 39.4, 43.6, 48.0, 74.9, 116.0, 119.7, 129.6, 146.8 ppm. EI (70 eV): *m*/*z* (%) = 221 (12) $[M]^+$, 120 (100), 77 (4). $C_{14}H_{23}NO$ (221.342): calcd. C 75.97, H 10.47, N 6.33; found C 75.85, H 10.33, N 6.51.

(3*R,5*S**)-5-Anilino-2,3-dimethylhexan-3-ol [(3*R**,5*S**)-3b]:** Minor diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3392, 1601, 1498, 908, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.91 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 1.06 (s, 3 H), 1.16 (d, *J* = 6.2 Hz, 3 H), 1.60 (dd, *J* = 15.0, 10.6 Hz, 1 H), 1.87 (dd, *J* = 15.0, 2.9 Hz, 1 H), 1.92 (sept, *J* = 6.8 Hz, 1 H), 3.70 (br. s, 2 H), 3.84 (dqd, *J* = 10.6, 6.2, 2.9 Hz, 1 H), 6.70–6.90 (m, 2 H), 7.10–7.60 (m, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 17.1, 18.7, 22.1, 22.7, 36.2, 46.3, 47.2, 75.2, 115.9, 119.7, 129.6, 146.7 ppm. EI (70 eV): *m*/*z* (%) = 221 (14) $[M]^+$, 120 (100), 77 (5). $C_{14}H_{23}NO$ (221.342): calcd. C 75.97, H 10.47, N 6.33; found C 76.15, H 10.64, N 6.11.

(2*R,4*S**)-2-Anilino-4-methyloctan-4-ol [(2*R**,4*S**)-3c]:** Major diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3368, 1602, 1499, 750, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.92 (t, *J* = 7.0 Hz, 3 H), 1.15 (d, *J* = 6.1 Hz, 3 H), 1.26 (s, 3 H), 1.29–1.42 (m, 4 H), 1.44–1.50 (m, 2 H), 1.61 (dd, *J* = 14.6, 4.6 Hz, 1 H), 1.67 (dd, *J* = 14.6, 9.2 Hz, 1 H), 3.85 (dqd, *J* = 9.2, 6.1, 4.6 Hz, 1 H), 4.00 (br. s, 2 H), 6.72–6.85 (m, 2 H), 7.10–7.30 (m, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 14.4, 22.3, 23.6, 26.2, 26.7, 44.2, 47.8, 48.0, 72.8, 115.8, 119.5, 129.6, 147.1 ppm. EI (70 eV): *m*/*z* (%) = 235 (16) $[M]^+$, 120 (100), 77 (5). $C_{15}H_{25}NO$ (235.369): calcd. C 76.55, H 10.71, N 5.95; found C 76.72, H 10.84, N 5.81.

(2*R,4*R**)-2-Anilino-4-methyloctan-4-ol [(2*R**,4*R**)-3c]:** Minor diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3368, 1602, 1498, 750, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.93 (t, *J* = 7.0 Hz, 3 H), 1.17 (d, *J* = 4.8 Hz, 3 H), 1.18 (s, 3 H), 1.18–1.41 (m, 4 H), 1.54–1.61 (m, 2 H), 1.63 (dd, *J* = 15.0, 10.4 Hz, 1 H), 1.72 (dd, *J* = 15.0, 3.7 Hz, 1 H), 3.79 (dqd, *J* = 10.1, 6.1, 3.4 Hz, 1 H), 4.00 (br. s, 2 H), 6.70–6.85 (m, 3 H), 7.15–7.30 (m, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 14.3, 22.2, 23.6, 27.2, 28.2, 41.4, 47.4, 48.0, 72.9, 115.7, 119.4, 129.5, 147.0 ppm. EI (70 eV): *m*/*z* (%) = 235 (16) $[M]^+$, 120 (100), 77 (5). $C_{15}H_{25}NO$ (235.369): calcd. C 76.55, H 10.71, N 5.95; found C 76.39, H 10.58, N 6.13.

(3*R,5*R**)-5-Anilino-2,2,3-trimethylhexan-3-ol [(3*R**,5*R**)-3d]:** Major diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3360, 1602, 1499, 752, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.93 (s, 9 H), 1.14 (d, *J* = 5.9 Hz, 3 H), 1.22 (s, 3 H), 1.59 (dd, *J* = 14.4, 3.3 Hz, 1 H), 1.70 (dd, *J* = 14.4, 10.2 Hz, 1 H), 3.79 (dqd, *J* = 9.9, 6.2, 3.3 Hz, 1 H), 3.96 (br. s, 2 H), 6.70–6.84 (m, 3 H), 7.10–7.28 (m, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 22.1, 22.4, 25.3, 28.7, 38.2, 41.7, 48.3, 116.1, 119.7, 129.5, 146.8 ppm. EI (70 eV): *m*/*z* (%) = 235 (6) $[M]^+$, 120 (100), 77 (7). $C_{15}H_{25}NO$ (235.369): calcd. C 76.55, H 10.71, N 5.95; found C 76.30, H 10.58, N 6.21.

(3*R,5*S**)-5-Anilino-2,2,3-trimethylhexan-3-ol [(3*R**,5*S**)-3d]:** Minor diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3402, 1614, 1437, 739, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.96 (s, 9 H), 1.23 (d, J = 6.2 Hz, 3 H), 1.24 (s, 3 H), 1.63 (dd, J = 14.6, 7.3 Hz, 1 H), 1.80 (dd, J = 14.6, 5.1 Hz, 1 H), 3.10 (br. s, 2 H), 3.82 (dqd, J = 7.2, 6.2, 5.1 Hz, 1 H), 6.60–6.80 (m, 1 H), 7.00–7.40 (m, 4 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 20.1, 22.5, 23.8, 25.4, 29.4, 43.5, 47.1, 125.0, 125.8, 129.3, 147.0 ppm. EI (70 eV): *m*/*z* (%) = 235 (6) [M]$^+$, 120 (100), 77 (7). $C_{15}H_{25}NO$ (235.369): calcd. C 76.55, H 10.71, N 5.95; found C 76.73, H 10.96, N 5.68.

(2*R,4*S**)-4-Anilino-2-phenylpentan-2-ol [(2*R**,4*S**)-3e]:** Major diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3306, 1602, 1498, 767, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.02 (d, J = 6.2 Hz, 3 H), 1.56 (s, 3 H), 1.96 (dd, J = 14.6, 11.0 Hz, 1 H), 2.19 (dd, J = 14.6, 2.6 Hz, 1 H), 3.28 (dqd, J = 11.0, 6.2, 2.6 Hz, 1 H), 4.30 (br. s, 2 H), 6.43–7.60 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 22.0, 32.3, 49.2, 49.6, 75.5, 116.9, 120.4, 125.2, 126.6, 128.4, 129.4, 146.5, 148.3 ppm. EI (70 eV): *m*/*z* (%) = 255 (26) [M]$^+$, 120 (100), 77 (9). $C_{17}H_{21}NO$ (255.359): calcd. C 79.96, H 8.29, N 5.49; found C 79.78, H 8.08, N 5.62.

(2*R,4*R**)-4-Anilino-2-phenylpentan-2-ol [(2*R**,4*R**)-3e]:** Minor diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3368, 1601, 1498, 752, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.18 (d, J = 6.2 Hz, 3 H), 1.68 (s, 3 H), 1.89 (dd, J = 14.8, 9.5 Hz, 1 H), 2.00 (dd, J = 14.8, 4.0 Hz, 1 H), 3.91 (dqd, J = 9.5, 6.2, 4.0 Hz, 1 H), 4.0 (br. s, 2 H), 6.67–7.53 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 22.2, 29.4, 48.2, 50.1, 74.4, 115.8, 119.6, 124.6, 126.7, 128.4, 129.6, 146.7, 149.5 ppm. EI (70 eV): *m*/*z* (%) = 255 (26) [M]$^+$, 120 (100), 77 (9). $C_{17}H_{21}NO$ (255.359): calcd. C 79.96, H 8.29, N 5.49; found C 79.80, H 8.14, N 5.58.

(3*R,5*R**)-5-Anilino-2-methyl-3-phenylhexan-3-ol [(3*R**,5*R**)-3f]:** Major diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3339, 1596, 1498, 1320, 1283 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.72 (d, J = 7.0 Hz, 3 H), 1.02 (d, J = 5.9 Hz, 3 H), 1.05 (d, J = 6.2 Hz, 3 H), 1.95 (sept, J = 7.0 Hz, 1 H), 2.00 (dd, J = 14.8, 9.7 Hz, 1 H), 2.10 (dd, J = 14.3, 3.3 Hz, 1 H), 3.26 (dqd, J = 9.5, 6.6, 3.7 Hz, 1 H), 4.3 (br. s, 2 H), 6.3–7.5 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 17.0, 17.5, 20.6, 22.2, 39.2, 45.2, 49.9, 117.0, 120.4, 126.3, 128.1, 129.3, 131.1, 146.5, 147.0 ppm. EI (70 eV): *m*/*z* (%) = 283 (6) [M]$^+$, 120 (100), 77 (22). $C_{19}H_{25}NO$ (283.408): calcd. C 80.52, H 8.89, N 4.94; found C 80.79, H 9.04, N 4.78.

(3*R,5*S**)-5-Anilino-2-methyl-3-phenylhexan-3-ol [(3*R**,5*S**)-3f]:** Minor diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3392, 1602, 1499, 1448, 1376 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.79 (d, J = 7.0 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H), 1.20 (d, J = 6.6 Hz, 3 H), 1.98 (dd, J = 14.8, 8.6 Hz, 1 H), 2.14 (sept, J = 7.0 Hz, 1 H), 2.30 (dd, J = 14.7, 4.8 Hz, 1 H), 3.62–3.80 (br. s, 2 H), 3.70 (dqd, J = 8.4, 6.2, 4.8 Hz, 1 H), 6.5–7.5 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 17.0, 18.0, 22.0, 27.1, 30.4, 38.4, 45.7, 115.4, 119.3, 125.9, 126.6, 127.9, 129.5, 145.7, 146.0 ppm. EI (70 eV): *m*/*z* (%) = 283 (6) [M]$^+$, 120 (100), 77 (22). $C_{19}H_{25}NO$ (283.408): calcd. C 80.52, H 8.89, N 4.94; found C 80.70, H 9.05, N 4.81.

(2*R,4*S**)-2-Anilino-4-phenyloctan-4-ol [(2*R**,4*S**)-3g]:** Major diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3306, 1602, 1498, 753, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.82 (t, J = 7.4 Hz, 3 H), 1.00 (d, J = 6.3 Hz, 3 H), 1.14–1.30 (m, 4 H), 1.76 (dd, J = 5.5, 3.1 Hz, 1 H), 1.78 (dd, J = 5.9, 3.5 Hz, 1 H), 1.96 (dd, J = 14.5, 11.0 Hz, 1 H), 2.10 (dd, J = 14.5, 2.3 Hz, 1 H), 3.27 (dqd, J = 11.0, 6.3, 2.3 Hz, 1 H), 4.57 (br. s, 2 H), 6.4–7.5 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 14.0, 21.7, 23.1, 25.2, 44.5, 47.8, 49.8, 117.1, 120.7, 125.5, 126.2, 128.2, 129.2, 129.3, 145.7, 147.0 ppm. EI (70 eV): *m*/*z* (%) = 297 (9) [M]$^+$, 120 (100), 77 (18). $C_{20}H_{27}NO$ (297.435): calcd. C 80.76, H 9.15, N 4.71; found C 80.58, H 9.38, N 4.32.

(2*R,4*R**)-2-Anilino-4-phenyloctan-4-ol [(2*R**,4*R**)-3g]:** Minor diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3392, 1602, 1498, 751, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.82 (t, J = 7.0 Hz, 3 H), 0.85–1.02 (m, 1 H), 1.17 (d, J = 6.3 Hz, 3 H), 1.20–1.35 (m, 3 H), 1.86–1.95 (m, 2 H), 1.90 (dd, J = 14.6, 10.0 Hz, 1 H), 2.06 (dd, J = 14.6, 3.5 Hz, 1 H), 3.83 (br. s, 2 H), 3.90 (dqd, J = 9.8, 6.3, 3.5 Hz, 1 H), 6.60–7.50 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 14.2, 22.2, 23.3, 26.0, 41.9, 47.5, 49.5, 115.6, 119.4, 125.1, 127.3, 128.3, 128.5, 129.4, 146.7, 147.6 ppm. EI (70 eV): *m*/*z* (%) = 297 (9) [M]$^+$, 120 (100), 77 (18). $C_{20}H_{27}NO$ (297.435): calcd. C 80.76, H 9.15, N 4.71; found C 80.92, H 9.35, N 4.47.

(1*R,3*R**)-1-Anilino-1,3-diphenyl-4-methylpentan-3-ol [(1*R**,3*R**)-3h]:** Major diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3418, 1601, 1266, 1026, 752, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.77 (d, J = 7.0 Hz, 3 H), 0.91 (d, J = 6.6 Hz, 3 H), 2.11 (sept, J = 6.7 Hz, 1 H), 2.31 (dd, J = 14.8, 8.8 Hz, 1 H), 2.50 (dd, J = 14.8, 4.8 Hz, 1 H), 2.77 (br. s, 2 H), 4.55 (dd, J = 8.8, 4.8 Hz, 1 H), 6.20–6.30 (m, 2 H), 6.54–6.66 (m, 1 H), 6.94–7.08 (m, 2 H), 7.20–7.40 (m, 10 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 16.9, 17.7, 38.4, 47.9, 55.5, 78.2, 114.1, 117.9, 125.9, 126.5, 126.7, 127.3, 128.2, 128.9, 129.0, 144.4, 145.5, 146.8 ppm. EI (70 eV): *m*/*z* (%) = 345 (7) [M]$^+$, 182 (100), 105 (20), 77 (29). $C_{24}H_{27}NO$ (345.8): calcd. C 83.44, H 7.88, N 4.05; found C 83.18, H 7.59, N 4.27.

(1*R,3*S**)-1-Anilino-1,3-diphenyl-4-methylpentan-3-ol [(1*R**,3*S**)-3h]:** Minor diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3379, 1601, 1500, 1314, 1265, 752, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.71 (d, J = 7.0 Hz, 3 H), 1.04 (d, J = 6.6 Hz, 3 H), 2.04 (sept, J = 6.8 Hz, 1 H), 2.26 (dd, J = 14.7, 3.3 Hz, 1 H), 2.37 (dd, J = 14.7, 10.1 Hz, 1 H), 4.13 (dd, J = 10.4, 2.7 Hz, 1 H), 4.20 (br. s, 2 H), 6.15–6.20 (m, 2 H), 6.60–6.80 (m, 1 H), 7.00–7.50 (m, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 16.9, 17.5, 39.2, 47.4, 57.2, 80.0, 116.2, 119.7, 126.2, 126.7, 127.3, 127.7, 128.4, 128.9, 129.2, 143.9, 146.3, 146.5 ppm. EI (70 eV): *m*/*z* (%) = 345 (7) [M]$^+$, 182 (100), 105 (20), 77 (33). $C_{24}H_{27}NO$ (345.8): calcd. C 83.44, H 7.88, N 4.05; found C 83.61, H 7.63, N 4.31.

(1*R,3*S**)-1-Anilino-1,3-diphenylheptan-3-ol [(1*R**,3*S**)-3i]:** Major diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3419, 1601, 1504, 1314, 1266, 751, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.84 (t, J = 6.6 Hz, 3 H), 0.90–1.10 (m, 1 H), 1.15–1.45 (m, 3 H), 1.98 (t, J = 7.7 Hz, 2 H), 2.15–2.40 (m, 2 H), 2.95 (br. s, 1 H), 4.30 (br. s, 1 H), 4.68 (dd, J = 8.1, 5.9 Hz, 1 H), 6.30–6.75 (m, 3 H), 7.00–7.50 (m, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 14.2, 23.2, 25.8, 42.1, 51.6, 55.9, 76.8, 114.6, 118.3, 125.2, 126.4, 126.8, 127.3, 128.2, 128.6, 129.0, 129.2, 144.5, 147.1 ppm. EI (70 eV): *m*/*z* (%) = 359 (3) [M]$^+$, 284 (1), 182 (100), 118 (56), 104 (18), 77 (49). $C_{25}H_{29}NO$ (359.504): calcd. C 83.52, H 8.13, N 3.90; found C 83.67, H 7.82, N 3.62.

(1*R,3*R**)-1-Anilino-1,3-diphenylheptan-3-ol [(1*R**,3*R**)-3i]:** Minor diastereomer: oil. IR (film): $\tilde{\nu}_{max}$ = 3425, 1600, 1505, 1312, 1261, 750, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.85 (t, J = 7.1 Hz, 3 H), 1.75–1.90 (m, 4 H), 2.20–2.40 (m, 4 H), 4.18 (t, J = 6.8 Hz, 1 H), 4.55 (br. s, 2 H), 6.40–6.70 (m, 3 H), 7.00–7.60 (m, 12 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, 25 °C): δ = 14.2, 23.2, 25.5, 44.5, 50.0, 56.8, 78.0, 116.2, 119.7, 125.1, 125.7, 125.8, 125.9, 126.7, 127.2, 128.5, 129.2, 143.7, 146.5 ppm. EI (70 eV): *m*/*z* (%) = 359 (5) [M]$^+$, 284 (2), 182 (100), 118 (51), 105 (15), 77 (43). $C_{25}H_{29}NO$ (359.5): calcd. C 83.52, H 8.13, N 3.90; found C 83.38, H 7.82, N 3.70.

Acknowledgments

Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome and the University of Camerino is gratefully acknowledged.

[1] a) S. Shibahara, S. Kondo, K. Maeda, H. Umezawa, M. Ohno, *J. Am. Chem. Soc.* **1972**, *94*, 4353–4354; b) Y.-F. Wang, T. Izawa, S. Kobayashi, M. Ohno, *J. Am. Chem. Soc.* **1982**, *104*, 6465–6466; c) S. Hashiguchi, A. Kawada, H. Natsugari, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2435–2444; d) S. Knapp, *Chem. Rev.* **1995**, *95*, 1859–1876; e) A. P. Kozikowski, Y.-Y. Chen, *J. Org. Chem.* **1981**, *46*, 5248–5250.

[2] a) V. Jäger, W. Schwab, V. Buss, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 601–603; b) H. Hann, H. Heitsch, R. Rathmann, G. Zimmermann, C. Bormann, H. Zähner, W. A. König, *Liebigs Ann. Chem.* **1987**, 803–807; c) H. Ohfune, *Acc. Chem. Res.* **1992**, *25*, 360–366; d) S. G. Davies, O. Ichihara, *Tetrahedron Lett.* **1999**, *40*, 9313–9316.

[3] G. Bartoli, C. Cimarelli, G. Palmieri, *J. Chem. Soc., Perkin Trans. 1* **1994**, 537–543.

[4] a) G. Bartoli, C. Cimarelli, E. Marcantoni, G. Palmieri, M. Petrini, *J. Org. Chem.* **1994**, *59*, 5328–5335; b) C. Cimarelli, G. Palmieri, G. Bartoli, *Tetrahedron: Asymmetry* **1994**, *5*, 1455–1458.

[5] a) B. F. Kukharev, V. K. Stankevich, G. R. Klimenko, O. N. Bel'kova, S. B. Leonov, I. I. Ivanova, N. V. Kotel'nikov, *Russ. J. Org. Chem.* **1998**, *71*, 639–641; b) P. Ollinger, W. Remp, H. Junck, *Monatsh. Chem.* **1974**, *105*, 346–353.

[6] C. Cimarelli, G. Palmieri, *Recent Res. Dev. Org. Chem.***1997**, *1*, 179–189 and references cited therein.

[7] a) R. V. Singh, J. P. Tandon, *J. Prakt. Chem.* **1979**, *321*, 151; b) R. K. Sharma, R. V. Singh, J. P. Tandon, *Inorg. Nucl. Chem.* **1980**, *42*, 1382; c) J. V. Greenhill, *Chem. Soc. Rev.* **1977**, *6*, 277; d) P. G. Baraldi, D. Simoni, S. Manfredini, *Synthesis* **1983**, 902; e) M. E. F. Braibante, H. S. Braibante, L. Missio, A. Andricopulo, *Synthesis* **1994**, 898–900.

[8] G. Bartoli, C. Cimarelli, G. Palmieri, M. Bosco, R. Dalpozzo, *Synthesis* **1990**, 895–898.

[9] C. Cimarelli, G. Palmieri, E. Volpini, *Tetrahedron Lett.* **2004**, *45*, 6629–6631.

[10] J. Almena, F. Foubelo, M. Yus, *J. Org. Chem.* **1994**, *59*, 3210–3215.

[11] S. J. Veenstra, S. S. Kinderman, *Synlett* **2001**, *7*, 1109–1112.

[12] J. Barluenga, B. Olano, S. Fustero, *J. Org. Chem.* **1985**, *50*, 4052–4056.

[13] C. Cimarelli, A. Mazzanti, E. Volpini, G. Palmieri, *J. Org. Chem.* **2001**, *66*, 4759–4765.

Received: September 15, 2005
Published Online: December 13, 2005

