Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 1308–1317

Stereoselective synthesis of enantiopure γ-aminoalcohols by reduction of chiral β-enaminoketones

Cristina Cimarelli, Sandra Giuli and Gianni Palmieri*

Dip. di Scienze Chimiche, v. S. Agostino 1, 62032 Camerino, Italy

Received 2 April 2006; accepted 19 April 2006

Abstract—The results of the reduction of chiral β-enamino ketones with sodium borohydride in acetic acid are reported. The reaction is convenient, stereoselective and high yielding and allows the preparation of enantiopure γ-amino alcohols in *syn* diastereoselectivity. The reaction is easy to perform and does not require expensive or hazardous chemicals. A mechanistic hypothesis is presented. The absolute configuration of the products obtained is attributed by correlating ^{1}H NMR spectral data with conformational analysis performed by molecular modelling, and confirmed by X-ray analysis.

1. Introduction

The synthesis of γ-amino alcohols is a matter of considerable interest because they frequently possess interesting pharmacological properties.[1–3] This functional unit is present in several antibiotics and other biologically active natural products.[4–7] Their synthesis has been achieved by a variety of procedures: addition of amines or ammonia to α,β-unsatured ketones or acrylic esters, followed by reduction;[1,8–11] reduction of β-enamino ketones and β-enamino esters[12–14] or other 1,3-difunctionalized unsaturated compounds.[15–17]

Enaminones constitute very interesting starting materials for the preparation of γ-amino alcohols by reduction and/or alkylation. The reduction of enaminones opens some interesting challenges for the chemo- and diastereoselective reduction of β-enamino ketones and β-enamino esters.[18]

In the past we have found that it is possible to prepare *syn*-γ-amino alcohols by reduction of β-enamino ketones. Dissolving metal reductions of enaminones were explored, with sodium and isopropanol, and resulted in the complete reduction of the unsatured system.[6] β-Enamino ketones afforded to secondary *syn*-γ-amino alcohols predominantly, while β-enamino esters afforded to the corresponding primary γ-aminoalcohols.[19]

Reduction of β-enamino ketones to *syn*-γ-amino alcohols was performed also with the $CeCl_3/LiBH_4$ system in moderate to good yields and de.[20]

Secondary β-enamino ketones were reduced in a mixture of trifluoroacetic acid and isopropanol as solvent, with $NaBH_4$. After workup, α,β-unsaturated ketones were obtained in 60–80% yield, with a *trans*-olefinic structure.[21]

The chemoselective reduction of β-enamino ketones has been performed also with different reducing systems, such as $LiAlH_4$ also in the presence of Cu, PtO_2, for the preparation of β-amino ketones (yields = 35–70%). Side reactions were observed, such as deamination with enone production, especially with $LiAlH_4$, with or without Cu.[22]

Sodium triacetoxy borohydride proved to be a good reagent for the reduction of substrates containing acid protons, such as β-enaminoesters.[18,19,23–25]

Also the reduction of β-enamino ketones is possible with sodium triacetoxy borohydride in glacial acetic acid.[26] γ-Amino alcohols are obtained in 70–98% yields in a *syn* configuration predominantly (de 44–99%) as ascertained by analysis of the corresponding tetrahydro oxazine derivatives. The same authors have also patented this procedure.[27]

* Corresponding author. Tel.: +39 0737402241; fax: +39 0737402285; e-mail: gianni.palmieri@unicam.it

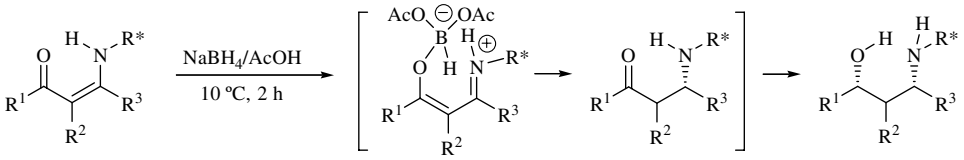
0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.04.009

Owing to our experience in the stereoselective reduction of enaminonic systems, we decided to apply this methodology to the reduction of enantiopure β-enamino ketones. Herein we report the results of the reduction of chiral β-enamino ketones **1** with sodium borohydride in acetic acid.

2. Results and discussion

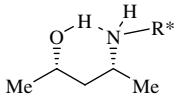
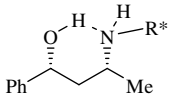
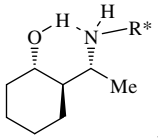
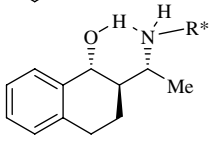
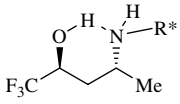
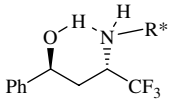
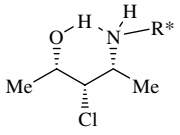
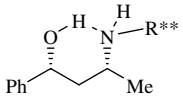
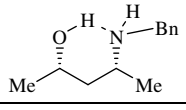
The reduction of β-enamino ketones, performed at room temperature, affords a *syn*/*anti* mixture of the γ-amino alcohols, in which the *syn* isomer **3** is more abundant, with the

Table 1. Reduction of β-enamino ketones **1** to γ-amino alcohols **3**

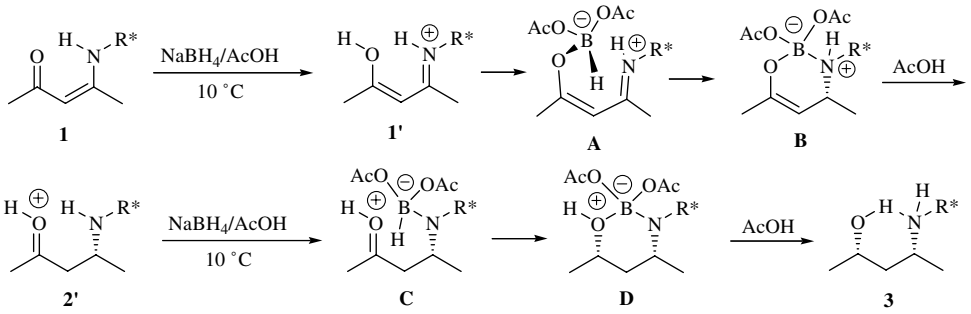


1 **2** **3**

R*-NH_2 = (*R*)-1-phenylethylamine

Entry	**1**	R^1	R^2	R^3	**3**[a]	Yield[a] (%)	dr[b]
1	**1a**	Me	H	Me	 (*S*,*R*,*R*)-**3a**	62	84/16
2	**1b**	Ph	H	Me	 (*R*,*R*,*R*)-**3b**	66	81/19
3	**1c**	$(CH_2)_4$		Me	 (*S*,*R*,*R*,*R*)-**3c**	57	82/18
4	**1d**	*o*-Ph-$(CH_2)_2$		Me	 (*R*,*R*,*R*,*R*)-**3d**	52	69/31
5	**1e**	Me	H	CF_3	 (*S*,*R*,*R*)-**3e**	42	71/29[c]
6	**1f**	Ph	H	CF_3	 (*S*,*S*,*R*)-**3f**	61	76/24[c]
7	**1g**	Me	Cl	Me	 (*S*,S,*R*,*R*)-**3g**	62	83/17
8	**1h**[d]	Ph	H	Me	 (*R*,*R*,*R*)-**3h**[d]	64	83/17
9	**1i**[e]	Me	H	Me	 (*S**,*R**)-**3i**	79	89/11[f]

[a] Yield of the isolated pure major stereoisomer.
[b] Diastereomeric ratio of the *syn* stereoisomers.
[c] Diastereomeric ratio of the *anti* stereoisomers.
[d] R**–NH_2 = (*R*)-1-naphthylethylamine.
[e] R* = Bn.
[f] *syn*/*anti* Diastereomeric ratio.



Scheme 1.

exception of starting materials **1e** and **f** that afford mainly the *anti*-γ-amino alcohol. A possible explanation of this *anti* diastereoselectivity is given later on. In the absence of acetic acid, the reduction does not take place. Generally the stereoisomers can be separated by liquid chromatography, allowing the preparation in good yields of the enantiopure γ-amino alcohols **3** (see Table 1, Scheme 1).

In the acid medium, the starting β-enamino ketone is in the protonated form **1′** (see Fig. 1), from which the formation of a boron–enolate complex takes place by coordination of the boron atom to the carbonyl oxygen and exchange of one acetoxy group of the reducing agent with **1′** itself. Then the hydride is transferred on the iminium carbon atom and the boron coordinates to the nitrogen atom. Solvolysis by acetic acid affords the β-amino ketone **2**. In the subsequent step the nitrogen atom coordinates to a second reducing unit, and the intermediate **D** is obtained, which gives the final γ-aminoalcohol **3**.

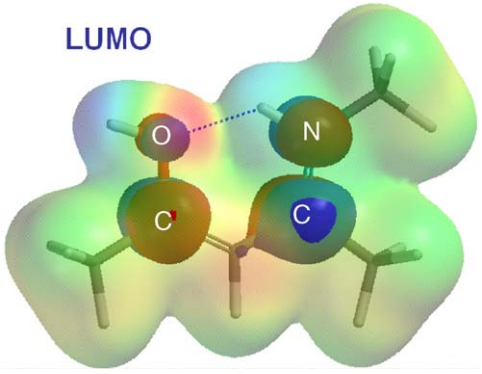


Figure 1. Simultaneous display of the LUMO and the colours code electrostatic potential map on the electron density surface of the protonated enamino ketones **1′**.

In Figure 1 the simultaneous display of the LUMO and the colour coded electrostatic potential map of the electron density surface of the protonated enamino ketones **1′** are reported, showing that the preferential site for nucleophilic attack is the carbon atom of the C=N function.

An interpretation of the stereoselectivity of the reaction can be suggested on the basis of the following considerations. The chiral (*R*)-1-phenylethylamino group bonded to the nitrogen atom induces a high stereoselectivity in the first step of the reduction by directing the hydride transfer on the less hindered face of the C=N double bond, affording to the β-amino ketone **2**. In Figure 2 is depicted the molecular modelling representation of the transition states (TS) for the transfer of the hydride on the *Re* and *Si* face of the C=N double bond, respectively, that show that the *Si*-**TS-2** is stabilized of 1.46 kcal/mol with respect to the *Re*-**TS-2**.[23,24]

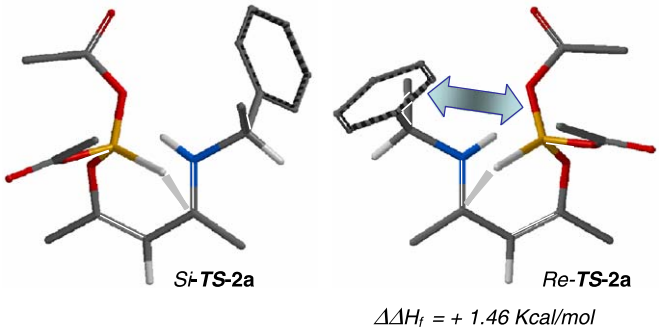


Figure 2. Molecular modelling representation of the diastereoselective transition state (TS) for the first reduction step.

The hypothesis of the boron–enol ester complex **A** as a key intermediate in the first step is confirmed by the experimental evidence that the β-enamino ketone **1j** prepared from dimedone (5,5-dimethylcyclohexan-1,3-dione) and 1-phenylethylamine, is inert in these reduction conditions. This can be explained by considering that, in this molecule, the enone system is constrained in the s-trans geometry, with the borohydride group located too far from the electrophilic carbon atom to transfer the hydride ion to the iminium carbon atom (see Fig. 3), as compared with the corresponding complex **A** derived from **1a**–**i**[23] as depicted in Figure 2.

In the subsequent step the reduction of the carbonyl group takes place, and also in this case the hydride is transferred on the less hindered face of the C=O double bond. Also in this case the molecular modelling representations of the diastereoselective transition states (TS) are depicted in Figure 4 and the *syn*-**TS** is more stable by 1.09 kcal/mol with respect to *anti*-**TS**, consistent with the stereoselectivity observed in the final γ-amino alcohols **3**.

The apparently anomalous *anti* diastereoselectivity observed for starting materials **1e** and **1f** (entries 5 and 6),

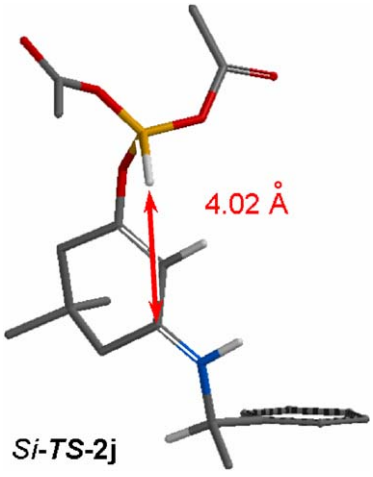


Figure 3. Interatomic distance between the hydrogen atom and the iminic carbon atom in the reduction of **1j**.

is in agreement with the mechanism depicted in Figure 4. In the transition states *syn*-**TS-3e** and **3f**, the CF_3 group is located near to a phenyl group and destabilizes the transition state itself as compared to the *anti*-**TS-3e** and **3f**.

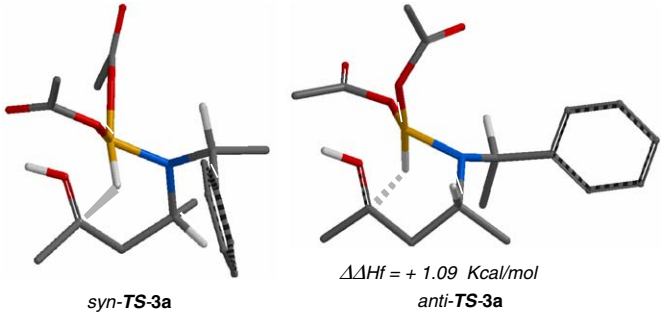


Figure 4. Molecular modelling representation of the diastereoselective transition state (TS) for the second reduction step.

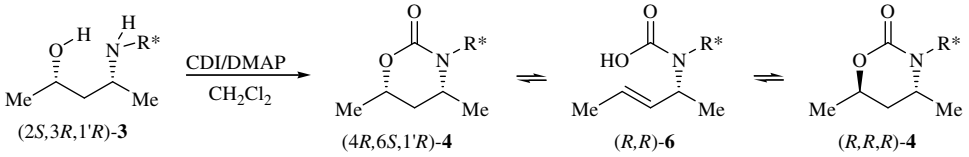
3. Stereochemistry

The absolute configuration of the various diastereomers was attributed by interpreting ^1H and ^{13}C NMR spectra, with the aid of computational methods,[28] and confirmed through X-ray diffraction. With the aim to attribute the absolute configurations with a confidence, oxazinones **4** and oxazines **5** have been prepared, as reported in Scheme 2.

Spectroscopic data and X-ray diffraction show that γ-amino alcohols **3** form rings completed by intramolecular hydrogen bonds, assuming a chair conformation, confirmed by molecular modelling conformational analysis.[29] The discrimination from the *syn*- and *anti*-γ-aminoalcohols was ascertained by ^1H NMR spectra of the isolated pure major isomers or chromatographic fraction for the minor diastereomers. While the *syn*-γ-amino alcohols show J_{aa} and J_{ae} for both the C*H*–O and C*H*–N protons, the *anti*-γ-amino alcohols show J_{aa} and J_{ae} for the C*H*–O and J_{ee} and J_{ae} for C*H*–N proton.[14,30,31] In addition, for the COH–CH_2–CNH methylene, the *syn*-γ-amino alcohols show two triplets (J_{ae} and J_{aa}) and the *anti*-γ-amino alcohols show two double doublets ($J_{ae}J_{aa}$ and $J_{ea}J_{ee}$).[14,30,31]

The discrimination between the major and minor *syn*-γ-amino alcohols was performed on the basis of the chemical shifts observed for the C*H*–O and C*H*–N protons. The magnetic anisotropy of the phenyl group, on the minor *syn*-**3a** exerts a shielding effect on the C*H*–O and as a more relevant measure on the C*H*–N proton nearest to the Ph group ($\Delta\delta = 0.31$ and 0.43 ppm, respectively). This is a general trend observed for both the diastereomers of *syn*-γ-amino alcohols **3** (Fig. 6).

The crystalline γ-amino alcohol **3f** was submitted to X-ray analysis.[32] The structure determined with this technique is



Scheme 2.

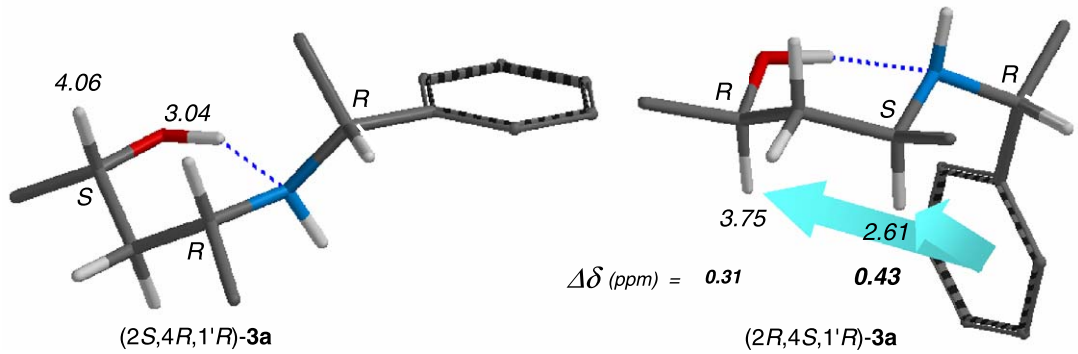


Figure 5. Calculated chair conformations for the major diastereomers *syn*-γ-amino alcohols **3a** and the diagnostic ^1H NMR chemical shifts for the C*H*–O and C*H*–N protons.

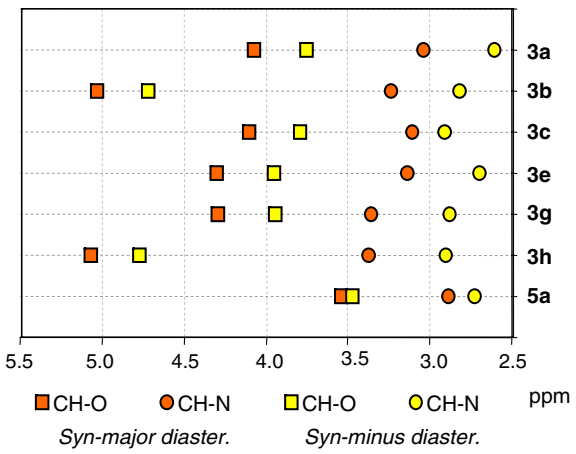


Figure 6. Chemical shifts for the major and minus *syn*-γ-amino alcohols **3**. Note the major upshift of the C*H*–N respect to the C*H*–O proton.

in full agreement with the conclusions based on ^{1}H NMR spectral analysis and on conformational analysis performed on all its possible diastereomers (see Fig. 7). The lowest energy structure obtained with molecular modelling for (*R*,*R*,*R*,*R*)-**3f** has the same conformation of the structure obtained by X-ray analysis, including the conformation of the chiral group R* bonded to the nitrogen atom.

This result validates the methodology used by us for the attribution of the absolute configuration of the various isolated γ-amino alcohols **3** (compare Figs. 5 and 7).

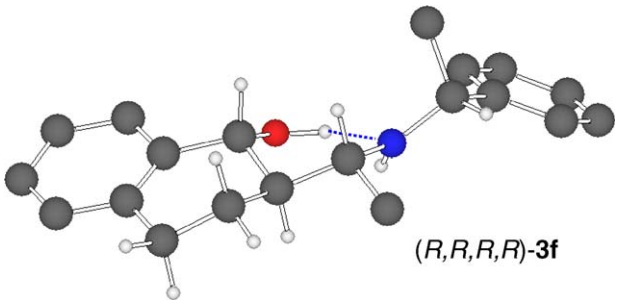
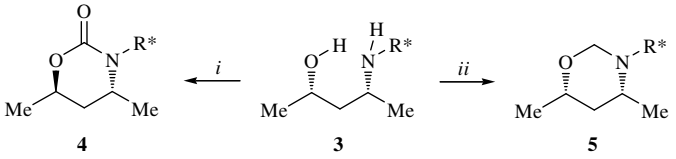
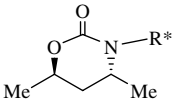
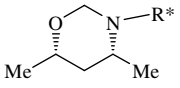
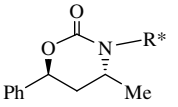
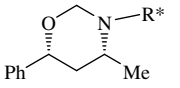
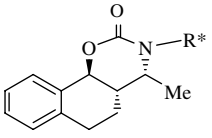
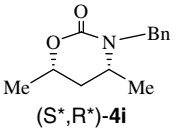
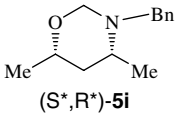


Figure 7. X-ray structure of the γ-amino alcohol (*R*,*R*,*R*,*R*)-**3f** major diastereomer.

Oxazinonic **4** and oxazinic **5** derivatives of γ-amino alcohols **3** were obtained by treating the various γ-amino alcohols with carbonyl diimidazole or formaldehyde, respectively. Their more rigid structure allows assignment of the stereochemistry by ^{1}H NMR spectra. While oxazines are formed without racemization of the stereogenic centres, the cyclization with carbonyl diimidazole to give oxazinones takes place with inversion of the configuration of the stereogenic centre bonded to the hydroxy group (see Table 2).

Table 2. Cyclization of γ-amino alcohols **3** to oxazinones **4** and oxazines **5**



Entry	3	4	Yield[a] (%)	5	Yield[a] (%)
1	(1*S*,3*R*,1′*R*)-**3a**	 (R,R,R)-**4a**	86	 (4R,6S,1'R)-**5a**	93
2	(*R*,*R*,*R*)-**3b**	 (4R,6S,1'R)-**4b**	89	 (R,R,R)-**5b**	91
3	(*R*,*R*,*R*,*R*)-**3d**	 (4R,4aS,10bS,1'R)-**4d**	91		
4	(*S**,*R**)-**3i**	 (S*,R*)-**4i**	84	 (S*,R*)-**5i**	89

Reaction conditions: (i) carbonyl diimidazole, DMAP, CH_2Cl_2, rt, 1 h; (ii) HCHO 35%, THF, rt, 6 h.
R*–NH_2 = (*R*)-1-phenylethylamine.
[a] Yield of the isolated pure stereoisomer.

In this case the less stable *syn* form is in equilibrium with the more stable *anti*, through the open intermediate **6** as depicted in Scheme 2. The calculation of the formation enthalpies, shows that generally the *anti*-**4** isomers are more stable than the *syn*-**4**, justifying the observed epimerization.

4. Conclusion

In summary a convenient, stereoselective and high yielding method for the preparation of enantiopure γ-amino alcohols **3** by the reduction of β-enamino ketones **1** is presented. The reaction is easy to perform and does not require expensive or hazardous chemicals. The absolute configuration of the products obtained was attributed by correlating ^{1}H NMR spectral data with conformational analyses performed by molecular modelling. The conclusions reached on the basis of spectral analysis and molecular modelling are validated by X-ray analysis of product **3f**, which confirms the attributed (*R*,*R*,*R*,*R*) absolute configuration.

5. Experimental

5.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, with $CDCl_3$ as solvent at ambient temperature and were calibrated using residual undeuterated solvents as the internal reference. Coupling constants are given in Hertz. IR spectra were recorded using FTIR apparatus.

5.2. Materials and solvents

All reagents were commercially available, were purchased at the highest quality, and were purified by distillation when necessary. β-Enamino ketones **1a**–**j** were prepared according to the literature methods.

5.3. General procedure for the reduction of β-enamino ketones 1: synthesis of γ-amino alcohols 3

The β-enamino ketones **1a**–**j** (1 mmol) were dissolved in acetic acid (3 mL) at 10 °C, then sodium borohydride was added in portions (4.0 mmol, 0.152 g) and allowed to stand for 2 h. The reaction mixture was quenched with 30% sodium hydroxide solution, until 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 (3:97–20:80 v/v) afforded the pure γ-amino alcohols **3**. Spectral data of products **3** follow.

5.3.1. (2*S*,4*R*)-4-{[(1*R*)-1-Phenylethyl]amino}pentan-2-ol (*S*,*R*,*R*)-3a. Oil; $[\alpha]_D^{20} = -61.3$ (*c* 1.7, $CHCl_3$); IR (neat) 3084, 3055, 1450, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.08 (d, 3H, *J* = 6.2 Hz), 1.16 (d, 3H, *J* = 6.2 Hz), 1.27 (dt, 1H, *J* = 14.3, 10.6 Hz), 1.38 (d, 3H, *J* = 6.6 Hz), 1.57 (ddd, 1H, *J* = 14.3, 2.4, 2.0 Hz), 3.04 (dqd, 1H, *J* = 11.0, 6.4, 2.4 Hz), 3.92 (q, 1H, *J* = 6.6 Hz), 4.06 (dqd, 1H, *J* = 10.2, 6.4, 2.0 Hz), 4.45 (br s, 2H), 7.15–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.7, 22.5, 24.1, 45.5, 52.3, 55.3, 69.2, 126.7, 127.6, 128.9, 145.8. EI-MS: *m*/*z* (%) 207 (M^+, 2), 192 (51), 148 (43), 105 (100). Anal. Calcd for $C_{13}H_{21}NO$ (207.3): C, 75.32; H, 10.21; N, 6.76. Found: C, 75.58; H, 10.39; N, 6.54.

5.3.2. (2*R*,4*S*)-4-{[(1*R*)-1-Phenylethyl]amino}pentan-2-ol (*R*,*S*,*R*)-3a. ^{1}H NMR ($CDCl_3$): δ 1.07 (d, 3H, *J* = 6.2 Hz), 1.09 (d, 3H, *J* = 6.2 Hz), 1.27 (dt, 1H, *J* = 14.3, 10.8 Hz), 1.35 (d, 3H, *J* = 6.6 Hz), 1.44 (ddd, 1H, *J* = 14.3, 2.8, 1.6 Hz), 2.61 (dqd, 1H, *J* = 11.4, 6.2, 2.9 Hz), 3.75 (dqd, 1H, *J* = 10.3, 6.2, 1.5 Hz), 4.01 (q, 1H, *J* = 6.6 Hz), 4.42 (br s, 2H), 7.16–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.8, 23.8, 25.7, 45.7, 51.4, 55.0, 68.9, 127.2, 127.5, 128.9, 144.2.

5.3.3. (*R*,*R*)-1-Phenyl-3-{[(1*R*)-1-phenylethyl]amino}butan-1-ol (*R*,*R*,*R*)-3b. Mp 42–43 °C (CH_2Cl_2–hexane); $[\alpha]_D^{20} = +3.3$ (*c* 4.7, $CHCl_3$); IR (neat) 3084, 3062, 1452, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.14 (d, 3H, *J* = 6.2 Hz), 1.49 (d, 3H, *J* = 6.6 Hz), 1.57 (dt, 1H, *J* = 14.3, 10.6 Hz), 1.81 (dt, 1H, *J* = 14.3, 2.6 Hz), 3.26 (dqd, 1H, *J* = 10.6, 6.6, 2.6 Hz), 4.02 (q, 1H, *J* = 6.6 Hz), 4.40 (br s, 2H), 5.04 (dd, 1H, *J* = 10.6, 2.2 Hz), 7.20–7.48 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.7, 22.5, 46.5, 52.6, 55.5, 75.6, 125.8, 127.1, 127.2, 127.7, 128.5, 129.0, 143.9, 145.6. EI-MS: *m*/*z* (%) 269 (M^+, 10), 254 (16), 148 (49), 132 (35), 105 (100). Anal. Calcd for $C_{18}H_{23}NO$ (269.4): C, 80.26; H, 8.61; N, 5.20. Found: C, 80.47; H, 8.39; N, 4.98.

5.3.4. (1*S*,3*S*)-1-Phenyl-3-{[(1*R*)-1-phenylethyl]amino}-butan-1-ol (*S*,*S*,*R*)-3b. ^{1}H NMR ($CDCl_3$): δ 1.15 (d, 3H, *J* = 6.1 Hz), 1.43 (d, 3H, *J* = 6.6 Hz), 1.51–1.67 (m, 2H), 2.82 (dqd, 1H, *J* = 10.2, 5.9, 3.7 Hz), 4.08 (q, 1H, *J* = 6.6 Hz), 4.40 (br s, 2H), 4.70 (dd, 1H, *J* = 9.9, 2.6 Hz), 7.10–7.80 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 20.8, 25.6, 46.7, 51.8, 55.3, 75.2, 125.7, 126.8, 127.4, 127.7, 128.4, 129.0, 145.2, 145.5.

5.3.5. (1*S*,2*R*)-2-((1*R*)-1-{[(1*R*)-1-Phenylethyl]amino}ethyl)-cyclohexanol (*S*,*R*,*R*,*R*)-3c. Oil; $[\alpha]_D^{20} = -36.4$ (*c* 0.3, $CHCl_3$); IR (neat) 3306, 3062, 3028, 2969, 2928, 2854, 1492, 1453; ^{1}H NMR ($CDCl_3$): δ 1.10–1.84 (m, 9H), 1.15 (d, 3H, *J* = 5.9 Hz), 1.41 (d, 3H, *J* = 6.2 Hz), 3.11 (br s, 1H, $W_{1/2}$ = 7.5 Hz), 3.82 (q, 1H, *J* = 6.6 Hz), 4.10 (q, 1H, *J* = 6.6 Hz), 4.55 (br s, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 18.5, 20.3, 20.5, 22.4, 25.5, 28.8, 45.5, 56.0, 56.5, 72.0, 126.7, 127.6, 128.9, 145.7. Anal. Calcd for $C_{16}H_{25}NO$ (247.4): C, 77.68; H, 10.19; N, 5.66. Found: C, 77.82; H, 10.02; N, 5.41.

5.3.6. (1*R*,2*R*)-2-((1*S*)-1-{[(1*R*)-1-Phenylethyl]amino}ethyl)-cyclohexanol (*R*,*R*,*S*,*R*)-3c. ^{1}H NMR ($CDCl_3$): δ 0.95 (d, 3H, *J* = 6.6 Hz), 1.12–1.75 (m, 9H), 1.44 (d, 3H, *J* = 6.6 Hz), 2.91 (dt, 1H, *J* = 5.8, 3.3 Hz), 3.82 (q, 1H, *J* = 6.5 Hz), 3.94 (q, 1H, *J* = 6.6 Hz), 4.46 (br s, 2H), 7.25–7.40 (m, 5H).

5.3.7. (1*R*,2*R*)-2-((1*R*)-1-{[(1*R*)-1-Phenylethyl]amino}ethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (*R*,*R*,*R*,*R*)-3d. Mp 87–91 °C; $[\alpha]_D^{20} = -159.8$ (*c* 0.8, $CHCl_3$); IR (neat) 3061, 3025, 2922, 1454, 1383 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21 (d, 3H, $J = 6.2$ Hz), 1.36–1.58 (m, 2H), 1.50 (d, 3H, $J = 6.6$ Hz), 1.97 (m, 1H), 2.74–3.00 (m, 3H), 3.89 (q, 1H, $J = 6.6$ Hz), 4.26 (br s, 2H), 4.86 (d, 1H, $J = 8.43$ Hz), 7.05–7.61 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 19.1, 22.7, 25.1, 29.4, 47.9, 56.1, 57.2, 75.1, 126.3, 126.6, 126.7, 126.8, 127.7, 128.0, 129.0, 135.7, 140.0, 145.5. EI-MS: *m*/*z* (%) 295 (M^+, 7), 148 (42), 105 (100). Anal. Calcd for $C_{20}H_{25}NO$ (295.4): C, 81.31; H, 8.53; N, 4.74. Found: C, 81.54; H, 8.66; N, 4.51.

5.3.8. (1*S*,2*S*)-2-((1*S*)-1-{[(1*R*)-1-Phenylethyl]amino}ethyl)-1,2,3,4-tetrahydronaphthalen-1-ol (*S*,*S*,*S*,*R*)-3d. ^1H NMR ($CDCl_3$): δ 1.13 (d, 3H, $J = 6.6$ Hz), 1.35–1.55 (m, 2H), 1.38 (d, 3H, $J = 6.9$ Hz), 2.11 (m, 1H), 2.70–2.94 (m, 3H), 4.06 (q, 1H, $J = 6.9$ Hz), 4.20 (br s, 2H), 4.96 (d, 1H, $J = 10.26$ Hz), 7.02–7.70 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 15.8, 24.6, 25.1, 30.0, 41.1, 54.8, 55.1, 70.0, 126.3, 126.4, 126.6, 126.8, 127.5, 128.4, 129.0, 135.5, 140.5, 144.7.

5.3.9. (2*S*,4*R*)-1,1,1-Trifluoro-4-{[(1*R*)-1-phenylethyl]-amino}-pentan-2-ol (*S*,*R*,*R*)-3e. Yield 42%. Oil; $[\alpha]_D^{20} = +83.5$ (*c* 0.6, $CHCl_3$); IR (neat) 3276, 3065, 3030, 2969, 2929, 2873, 1453; ^1H NMR ($CDCl_3$): δ 1.07 (d, 3H, $J = 6.2$ Hz), 1.39 (d, 3H, $J = 6.6$ Hz), 1.59 (ddd, 1H, $J = 14.8$, 7.3, 4.4 Hz), 1.71 (ddd, 1H, $J = 14.8$, 6.6, 3.3 Hz), 3.04 (quint d, 1H, $J = 6.6$, 3.7 Hz), 3.84 (br s, 2H), 3.94 (q, 1H, $J = 6.6$ Hz), 4.22 (quint d, 1H, $J = 7.3$, 4.4 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 19.6, 24.5, 33.8, 48.1, 55.2, 69.1 (q, $J = 31.2$ Hz), 125.5 (q, $J = 282.1$ Hz), 127.0, 127.7, 128.9, 143.2. EI-MS: *m*/*z* (%) 261 (M^+, 1), 246 (100), 184 (9), 148 (24), 105 (83). Anal. Calcd for $C_{13}H_{18}F_3NO$ (261.3): C, 59.76; H, 6.94; N, 5.36. Found: C, 59.99; H, 6.71; N, 5.18.

5.3.10. (2*R*,4*S*)-1,1,1-Trifluoro-4-{[(1*R*)-1-phenylethyl]-amino}pentan-2-ol (*R*,*S*,*R*)-3e. Yield 17%. Oil; ^1H NMR ($CDCl_3$): δ 1.14 (d, 3H, $J = 6.6$ Hz), 1.38 (d, 3H, $J = 6.6$ Hz), 1.50 (ddd, 1H, $J = 14.6$, 5.9, 3.3 Hz), 1.99 (ddd, 1H, $J = 14.6$, 8.8, 3.3 Hz), 3.14 (quint d, 1H, $J = 6.4$, 3.3 Hz), 3.94 (q, 1H, $J = 6.6$ Hz), 4.12 (br s, 2H), 4.32 (dqd, 1H, $J = 8.8$, 7.3, 3.3 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.2, 23.5, 30.8, 48.4, 55.3, 69.1 (q, $J = 30.7$ Hz), 125.6 (q, $J = 280.0$ Hz), 126.3, 127.7, 129.1, 144.4. EI-MS: *m*/*z* (%) 261 (M^+, 1), 246 (100), 184 (8), 148 (25), 105 (81).

5.3.11. (2*R*,4*R*)-1,1,1-Trifluoro-4-{[(1*R*)-1-phenylethyl]-amino}pentan-2-ol (*R*,*R*,*R*)-3e. Yield 23%. Oil; $[\alpha]_D^{20} = -32.5$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.16 (d, 3H, $J = 6.2$ Hz), 1.40 (d, 3H, $J = 6.6$ Hz), 1.52 (dt, 1H, $J = 14.3$, 11.2 Hz), 1.79 (dt, 1H, $J = 14.3$, 2.6 Hz), 3.14 (d quint d, 1H, $J = 11.0$, 6.2, 2.6 Hz), 3.93 (q, 1H, $J = 6.6$ Hz), 4.09 (br s, 2H), 4.30 (d quint d, 1H, $J = 11.0$, 6.6, 2.6 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.7, 22.1, 35.2, 51.3, 55.4, 71.8 (q, $J = 31.1$ Hz), 125.0 (q, $J = 283.1$ Hz), 126.6, 127.9, 129.1, 145.0. EI-MS: *m*/*z* (%) 261 (M^+, 2), 246 (100), 184 (11), 148 (26), 105 (85). Anal. Calcd for $C_{13}H_{18}F_3NO$ (261.3): C, 59.76; H, 6.94; N, 5.36. Found: C, 59.81; H, 7.03; N, 5.24.

5.3.12. (2*S*,4*S*)-1,1,1-Trifluoro-4-{[(1*R*)-1-phenylethyl]amino}-pentan-2-ol (*S*,*S*,*R*)-3e. Yield 10%. Oil; ^1H NMR ($CDCl_3$): δ 1.18 (d, 3H, $J = 6.2$ Hz), 1.38 (d, 3H, $J = 6.6$ Hz), 1.48 (dt, 1H, $J = 14.1$, 11.0 Hz), 1.66 (dt, 1H, $J = 14.1$, 3.3 Hz), 2.70 (dqd, 1H, $J = 11.3$, 6.2, 2.9 Hz), 3.95 (dqd, 1H, $J = 10.6$, 6.2, 2.6 Hz), 4.02 (q, 1H, $J = 6.6$ Hz), 4.22 (br s, 2H), 7.20–7.45 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.8, 25.3, 35.4, 50.4, 55.1, 71.4 (q, $J = 31.1$ Hz), 124.8 (q, $J = 281.3$ Hz), 127.2, 127.9, 129.1, 143.2. EI-MS: *m*/*z* (%) 261 (M^+, 1), 246 (100), 184 (10), 148 (23), 105 (81).

5.3.13. (1*S*,3*S*)-4,4,4-Trifluoro-1-phenyl-3-{[(1*R*)-1-phenylethyl]amino}butan-1-ol (*S*,*S*,*R*)-3f. Oil; $[\alpha]_D^{20} = +148.6$ (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.35 (d, 3H, $J = 6.6$ Hz), 1.86 (ddd, 1H, $J = 15.0$, 5.5, 3.3 Hz), 2.04 (ddd, 1H, $J = 15.0$, 10.3, 4.4 Hz), 3.57 (q, 1H, $J = 6.6$ Hz), 3.85 (dd, 1H, $J = 10.3$, 3.3 Hz), 4.02 (br s, 2H), 4.19 (qdd, 1H, $J = 7.7$, 5.5, 4.4 Hz), 7.10–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 24.7, 27.1, 55.3, 56.9, 69.3 (q, $J = 30.6$ Hz), 125.6 (q, $J = 280.9$ Hz), 126.7, 127.3, 127.8, 128.0, 128.8, 129.2, 141.7, 143.1. Anal. Calcd for $C_{18}H_{20}F_3NO$ (323.4): C, 66.86; H, 6.23; N, 4.33. Found: C, 66.98; H, 6.34; N, 4.12.

5.3.14. (1*R*,3*R*)-4,4,4-Trifluoro-1-phenyl-3-{[(1*R*)-1-phenylethyl]amino}butan-1-ol (*R*,*R*,*R*)-3f. Oil; $[\alpha]_D^{20} = -20.4$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.43 (d, 3H, $J = 6.6$ Hz), 1.92 (ddd, 1H, $J = 15.0$, 7.9, 4.8 Hz), 2.14 (ddd, 1H, $J = 15.0$, 5.9, 3.1 Hz), 3.79 (q, 1H, $J = 6.6$ Hz), 3.98 (br s, 2H), 4.15 (qdd, 1H, $J = 8.7$, 5.9, 4.8 Hz), 4.27 (dd, 1H, $J = 8.4$, 2.9 Hz), 7.10–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 22.1, 33.5, 54.9, 57.3, 69.4 (q, $J = 30.5$ Hz), 125.8 (q, $J = 300.8$ Hz), 126.4, 126.6, 127.8, 128.1, 129.0, 129.2, 141.1, 141.4. Anal. Calcd for $C_{18}H_{20}F_3NO$ (323.4): C, 66.86; H, 6.23; N, 4.33. Found: C, 66.71; H, 6.28; N, 4.41.

5.3.15. (2*S*,3*S*,4*R*)-3-Chloro-4-{[(1*R*)-1-phenylethyl]amino}-pentan-2-ol (*S*,*S*,*R*,*R*)-3g. Oil; ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, $J = 6.2$ Hz), 1.29 (d, 3H, $J = 6.2$ Hz), 1.41 (d, 3H, $J = 6.6$ Hz), 3.36 (qd, 1H, $J = 6.2$, 1.8 Hz), 3.83 (dd, 1H, $J = 1.8$, 0.7 Hz), 3.92 (q, 1H, $J = 6.6$ Hz), 4.07 (br s, 2H), 4.29 (qd, 1H, $J = 6.2$, 0.7 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.8, 21.5, 23.6, 38.6, 49.2, 66.0, 69.6, 126.8, 127.1, 128.4, 144.9. EI-MS: *m*/*z* (%) 241 (M^+, 1), 226 (4), 148 (36), 105 (100). Anal. Calcd for $C_{13}H_{20}ClNO$ (241.8): C, 64.59; H, 8.34; N, 5.79. Found: C, 64.72; H, 8.13; N, 5.96.

5.3.16. (2*R*,3*R*,4*S*)-3-Chloro-4-{[(1*R*)-1-phenylethyl]amino}-pentan-2-ol (*R*,*R*,*S*,*R*)-3g. Oil; ^1H NMR ($CDCl_3$): δ 1.18 (d, 3H, $J = 6.2$ Hz), 1.23 (d, 3H, $J = 6.2$ Hz), 1.38 (d, 3H, $J = 6.6$ Hz), 2.88 (qd, 1H, $J = 6.2$, 2.2 Hz), 3.27 (br s, 2H), 3.67 (dd, 1H, $J = 2.2$, 1.1 Hz), 3.94 (qd, 1H, $J = 6.2$, 1.1 Hz), 3.98 (q, 1H, $J = 6.6$ Hz), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 17.6, 20.8, 25.2, 54.7, 55.1, 71.1, 72.0, 127.2, 127.9, 129.1, 143.3. EI-MS: *m*/*z* (%) 241 (M^+, 1), 226 (5), 148 (38), 105 (100).

5.3.17. (1*R*,3*R*)-3-{[(1*R*)-1-(1-Naphthyl)ethyl]amino}-1-phenylbutan-1-ol (*R*,*R*,*R*)-3h. Oil; $[\alpha]_D^{20} = -2.5$ (*c* 0.6, $CHCl_3$); IR 3271, 3052, 2965, 1510, 1452 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (d, 3H, $J = 6.2$ Hz), 1.57 (dt, 1H, $J = 14.3$, 10.5 Hz), 1.63 (d, 3H, $J = 6.6$ Hz), 1.85 (dt, 1H, $J = 14.3$, 2.4 Hz), 3.37 (dqd, 1H, $J = 10.3$, 6.6, 2.6 Hz), 4.13 (br s, 2H), 4.88 (q, 1H, $J = 6.6$ Hz), 5.07 (dd, 1H, $J = 10.6$, 2.2 Hz), 7.20–8.16 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 21.6, 22.1, 46.5, 49.7, 52.6, 75.6, 122.5, 123.4, 125.7, 125.8, 126.0, 126.4, 127.1, 127.9, 128.4, 129.4, 130.6, 134.1, 141.4, 145.4. EI-MS: *m*/*z* (%) 319 (M^+, 12), 304 (16), 198 (15), 182 (18), 155 (100). Anal. Calcd for $C_{22}H_{25}NO$ (319.4): C, 82.72; H, 7.89; N, 5.95. Found: C, 82.91; H, 7.66; N, 6.09.

5.3.18. (1*S*,3*S*)-3-{[(1*R*)-1-(1-Naphthyl)ethyl]amino}-1-phenylbutan-1-ol (*S*,*S*,*R*)-3h. Oil; $[\alpha]_D^{20} = -3.42$ (*c* 0.6, $CHCl_3$); IR 3260, 3050, 2955, 1521, 1413 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (d, 3H, $J = 6.2$ Hz), 1.57 (d, 3H, $J = 6.6$ Hz), 1.61–1.73 (m, 2H), 2.90 (d quint, 1H, $J = 8.1$, 6.2 Hz), 4.27 (br s, 2H), 4.77 (dd, 1H, $J = 7.3$, 5.1 Hz), 5.09 (q, 1H, $J = 6.2$ Hz), 7.20–8.16 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 27.1, 30.3, 31.1, 46.6, 52.0, 75.1, 122.3, 124.1, 125.7, 126.2, 126.3, 126.4, 127.2, 127.9, 128.4, 129.4, 131.6, 134.1, 139.1, 145.0. EI-MS: *m*/*z* (%) 319 (M^+, 11), 304 (14), 198 (15), 182 (18), 155 (100). Anal. Calcd for $C_{22}H_{25}NO$ (319.4): C, 82.72; H, 7.89; N, 5.95. Found: C, 82.88; H, 7.96; N, 5.88.

5.3.19. (2*S,3*R**)-4-(Benzylamino)pentan-2-ol (*S**,*R**)-3i.** Oil; IR (neat) 3091, 3046, 1455, 1130 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.13 (d, 3H, $J = 6.2$ Hz), 1.17 (d, 3H, $J = 6.2$ Hz), 1.29 (dt, 1H, $J = 14.0$, 10.6 Hz), 1.52 (ddd, 1H, $J = 14.1$, 2.6, 2.2 Hz), 2.91 (dqd, 1H, $J = 10.9$, 6.2, 2.6 Hz), 3.70 (d, 1H, $J = 12.6$ Hz), 3.94 (d, 1H, $J = 12.6$ Hz), 3.97 (dqd, 1H, $J = 10.3$, 6.2, 2.0 Hz), 4.41 (br s, 2H), 7.15–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 22.8, 24.0, 45.5, 49.7, 52.3, 67.2, 127.5, 128.1, 128.2, 140.6. EI-MS: *m*/*z* (%) 193 (M^+, 2), 178 (46), 134 (41), 91 (100). Anal. Calcd for $C_{12}H_{19}NO$ (193.3): C, 74.57; H, 9.91; N, 7.25. Found: C, 74.81; H, 10.19; N, 6.98.

5.3.20. (2*R,3*R**)-4-(Benzylamino)pentan-2-ol (*S**,*R**)-3i.** Oil; ^1H NMR ($CDCl_3$): δ 1.16 (d, 3H, $J = 7.2$ Hz), 1.23 (d, 3H, $J = 6.4$ Hz), 1.40 (ddd, 1H, $J = 14.2$, 5.2, 2.6 Hz), 1.72 (ddd, 1H, $J = 14.2$, 8.8, 3.2 Hz), 3.10 (qdd, 1H, $J = 6.4$, 3.2, 2.6 Hz), 3.70 (d, 1H, $J = 12.6$ Hz), 3.84 (d, 1H, $J = 12.6$ Hz), 4.17 (dqd, 1H, $J = 8.9$, 7.2, 4.9 Hz), 4.41 (br s, 2H), 7.18–7.35 (m, 5H).

5.4. Preparation of oxazinones 4

γ-Amino alcohols **3a**,**b**,**d**,**i** (2 mmol) in a 50 mL round bottom flask equipped with magnetic stirring, in 10 mL CH_2Cl_2 at rt, were treated with dimethylaminopyridine (DMAP) (0.2 mmol) and cabonyl diimidazole (3 mmol). The reaction mixture was allowed to stand at rt for 1 h, then the mixture was filtered on a thin pad of silica gel affording generally the pure **5**. When necessary the final oxazinones were further purified by recrystallization or chromatographic separation. Spectral data follow.

5.4.1. (4*R*,6*R*)-4,6-Dimethyl-3-[(1*R*)-1-phenylethyl]-1,3-oxazinan-2-one (*R*,*R*,*R*)-4a. Oil; $[\alpha]_D^{20} = +35.5$ (*c* 3.4, $CHCl_3$); IR (neat) 3306, 2966, 2359, 1759, 1454 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (d, 3H, $J = 6.2$ Hz), 1.38 (d, 3H, $J = 6.6$ Hz), 1.42 (d, 3H, $J = 6.2$ Hz), 1.48 (ddd, 1H, $J = 14.4$, 8.4, 4.0 Hz), 2.07 (ddd, 1H, $J = 14.4$, 9.2, 4.7 Hz), 2.65 (dqd, 1H, $J = 8.4$, 6.2, 4.6 Hz), 3.90 (q, 1H, $J = 6.6$ Hz), 5.18 (dqd, 1H, $J = 9.2$, 6.2, 3.9 Hz), 7.00–7.90 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.8, 21.5, 24.5, 42.7, 46.9, 55.0, 74.5, 126.4, 128.7, 130.5, 137.1, 145.8. Anal. Calcd for $C_{14}H_{19}NO_2$ (233.3): C, 72.07; H, 8.21; N, 6.00. Found: C, 71.83; H, 8.03; N, 6.24.

5.4.2. (4*R*,6*S*)-4-Methyl-6-phenyl-3-[(1*R*)-1-phenylethyl]-1,3-oxazinan-2-one (4*R*,6*S*,1′*R*)-4b. Oil; $[\alpha]_D^{20} = +18.3$ (*c* 1.6, $CHCl_3$); IR (neat) ν_{max} 3086, 3062, 3029, 2965, 2927, 2851, 1744, 1493, 1454 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (d, 3H, $J = 6.2$ Hz), 1.28 (d, 3H, $J = 6.6$ Hz), 1.85 (ddd, 1H, $J = 13.9$, 7.3, 5.5 Hz), 2.36 (ddd, 1H, $J = 13.9$, 8.8, 5.5 Hz), 2.67 (sext, 1H, $J = 6.3$ Hz), 3.90 (q, 1H, $J = 6.6$ Hz), 6.07 (dd, 1H, $J = 8.8$, 5.5 Hz), 7.05–8.20 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 18.3, 21.7, 34.0, 56.3, 59.9, 65.0, 125.7, 126.7, 127.77, 127.81, 128.7, 128.9, 135.3, 145.3, 145.7. Anal. Calcd for $C_{19}H_{21}NO_2$ (295.4): C, 77.26; H, 7.17; N, 4.74. Found: C, 77.08; H, 7.32; N, 4.54.

5.4.3. (4*R*,4a*S*,10b*S*)-4-Methyl-3-[(1*R*)-1-phenylethyl]-3,4,4a,5,6,10b-hexahydro-2*H*-naphtho[2,1-*e*][1,3]oxazin-2-one (4*R*,4a*S*,10b*S*,1′*R*)-4d. Oil; $[\alpha]_D^{20} = +126.7$ (*c* 0.8, $CHCl_3$); IR (neat) ν_{max} 3400, 3024, 2928, 2851, 1603, 1454 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.08 (d, 3H, $J = 6.2$ Hz), 1.18 (d, 3H, $J = 6.2$ Hz), 1.38 (tdd, 1H, $J = 13.5$, 5.5, 4.4 Hz), 1.84 (dq, 1H, $J = 13.2$, 2.2 Hz), 2.36 (m, 1H), 2.68 (br d, 1H, $J = 14.6$ Hz), 3.22 (td, 1H, $J = 14.3$, 4.8 Hz), 3.45 (qd, 1H, $J = 6.2$, 4.4 Hz), 3.51 (q, 1H, $J = 6.2$ Hz), 4.55 (d, 1H, $J = 7.7$ Hz), 6.45 (d, 1H, $J = 7.3$ Hz), 6.75–7.30 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 18.6, 25.1, 27.1, 27.8, 30.3, 36.9, 59.4, 61.4, 125.3, 126.7, 127.1, 127.8, 128.1, 128.5, 128.7, 130.3, 136.5, 140.8, 143.5. Anal. Calcd for $C_{21}H_{23}NO_2$ (321.4): C, 78.47; H, 7.21; N, 4.36. Found: C, 78.69; H, 7.03; N, 4.09.

5.4.4. (4*R,6*S**)-3-Benzyl-4,6-dimethyl-1,3-oxazinan-2-one (4*R**,6*S**)-4i.** Oil; IR (neat) 3015, 2966, 1765, 1472 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.09 (d, 3H, $J = 6.2$ Hz), 1.26 (d, 3H, $J = 6.2$ Hz), 1.52 (dt, 1H, $J = 13.9$, 11.3 Hz), 1.95 (ddd, 1H, $J = 13.9$, 5.5, 1.8 Hz), 3.36 (d quint, 1H, $J = 11.3$, 5.9 Hz), 4.19 (d, 1H, $J = 15.7$ Hz), 4.21 (ddd, 1H, $J = 11.3$, 6.2, 2.0 Hz), 5.02 (d, 1H, $J = 15.7$ Hz), 7.10–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.4, 20.6, 38.3, 48.0, 49.3, 71.5, 127.1, 127.3, 128.4, 137.2, 155.0. Anal. Calcd for $C_{13}H_{17}NO_2$ (219.3): C, 71.21; H, 7.81; N, 6.39. Found: C, 71.11; H, 8.02; N, 6.61.

5.5. General procedure for the synthesis of 1,3-tetrahydro oxazines 5

The γ-amino alcohols **3a**,**b**,**i** (0.5 mmol) were dissolved in THF (1 mL), and was added aqueous formaldehyde 35% (0.085 mL, 1 mmol). After 6 h, the solvent was removed under reduced pressure and the crude tetrahydro oxazines

purified by short filtration on a thin pad of silica gel with cyclohexane–AcOEt (97/3 v/v) or CH_2Cl_2/*n*-esano (50/50 v/v) as eluent. Spectral data of tetrahydro oxazines **5** follow.

5.5.1. (4*R*,6*S*)-4,6-Dimethyl-3-[(1*R*)-1-phenylethyl]-1,3-oxazinane (4*R*,6*S*,1′*R*)-5a. Oil; $[\alpha]_D^{20} = -48.1$ (*c* 3.1, $CHCl_3$); IR (neat) 3402, 3028, 2970, 2932, 2905, 2839, 1494, 1448, 1377 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.18 (d, 3H, $J = 6.2$ Hz), 1.23 (d, 3H, $J = 6.2$ Hz), 1.32 (d, 3H, $J = 7.0$ Hz), 1.38 (dt, 1H, $J = 12.8$, 11.0 Hz), 1.58 (dt, 1H, $J = 12.8$, 2.9 Hz), 2.89 (dqd, 1H, $J = 10.6$, 6.2, 3.3 Hz), 3.54 (dqd, 1H, $J = 11.0$, 6.2, 2.6 Hz), 3.95 (d, 1H, $J = 8.1$ Hz), 4.28 (d, 1H, $J = 8.1$ Hz), 4.35 (q, 1H, $J = 7.0$ Hz), 7.15–7.55 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 11.6, 20.4, 21.7, 42.1, 52.5, 53.3, 73.7, 79.6, 126.9, 128.1, 128.3, 143.4. Anal. Calcd for $C_{13}H_{21}NO$ (207.3): C, 75.32; H, 10.21; N, 6.76. Found: C, 75.58; H, 10.39; N, 6.54.

5.5.2. (4*S*,6*R*)-4,6-Dimethyl-3-[(1*R*)-1-phenylethyl]-1,3-oxazinane (4*S*,6*R*,1′*R*)-5a. ^1H NMR ($CDCl_3$) δ 1.15 (d, 3H, $J = 6.2$ Hz), 1.18 (d, 3H, $J = 6.2$ Hz), 1.15–1.50 (m, 2H), 1.54 (d, 3H, $J = 7.0$ Hz), 2.73 (sext, 1H, $J = 6.8$ Hz), 3.47 (sext, 1H, $J = 6.4$ Hz), 3.86 (d, 1H, $J = 9.2$ Hz), 4.28 (q, 1H, $J = 7.0$ Hz), 4.80 (d, 1H, $J = 9.2$ Hz), 7.20–7.50 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 20.3, 20.8, 21.9, 41.0, 53.4, 54.1, 73.5, 80.9, 126.9, 127.8, 128.2, 142.7.

5.5.3. (*R*,*R*)-4-Methyl-6-phenyl-3-[(1*R*)-1-phenylethyl]-1,3-oxazinane (*R*,*R*,*R*)-5b. Oil; $[\alpha]_D^{20} = -32.8$ (*c* 2.0, $CHCl_3$); IR (neat) 3418, 3019, 2975, 1510, 1471, 1327 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 (d, 3H, $J = 6.6$ Hz), 1.42 (d, 3H, $J = 7.0$ Hz), 1.71 (dt, 1H, $J = 13.2$, 10.8 Hz), 1.83 (dt, 1H, $J = 13.2$, 3.7 Hz), 3.12 (dqd, 1H, $J = 10.3$, 6.3, 4.0 Hz), 4.23 (d, 1H, $J = 8.8$ Hz), 4.42 (q, 1H, $J = 6.8$ Hz), 4.50 (dd, 1H, $J = 11.0$, 3.3 Hz), 4.58 (d, 1H, $J = 8.8$ Hz), 7.22–7.60 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.0, 18.3, 20.4, 41.8, 52.9, 53.7, 79.7, 126.0, 127.0, 127.5, 128.1, 128.3, 128.4, 142.6, 143.8. Anal. Calcd for $C_{19}H_{23}NO$ (281.4): C, 81.10; H, 8.24; N, 4.98. Found: C, 81.31; H, 7.97; N, 4.76.

5.5.4. (4*R,6*S**)-3-Benzyl-4,6-dimethyl-1,3-oxazinane (4*R**,6*S**)-5i.** Oil; IR (neat) 3009, 2982, 1615, 1452, 1365, 1055 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, $J = 6.8$ Hz), 1.24 (d, 3H, $J = 6.2$ Hz), 1.35–1.57 (m, 2H), 3.03 (d quint, 1H, $J = 8.1$, 6.6 Hz), 3.56 (d, 1H, $J = 13.8$ Hz), 3.62 (d quint, 1H, $J = 7.7$, 6.2 Hz), 3.93 (d, 1H, $J = 13.8$ Hz), 4.09 (d, 1H, $J = 9.7$ Hz), 4.40 (d, 1H, $J = 9.7$ Hz), 7.15–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.4, 20.6, 38.3, 48.0, 49.3, 71.5, 127.1, 127.3, 128.4, 137.2, 155.0. Anal. Calcd for $C_{13}H_{19}NO$ (205.3): C, 76.06; H, 9.33; N, 6.82. Found: C, 76.29; H, 9.18; N, 7.07.

Acknowledgements

We thanks Dr. Cristina Femoni (University of Bologna—Department of Inorganic and Physic Chemistry) for providing X-ray diffraction data of product **3f**. The financial support of this research by a grant from University of Camerino and from MIUR-PRIN (contract no. 2005037725_001) is gratefully acknowledged.

References

1. Gevorgyan, G. A.; Agababyan, A. G. *Usp. Chim.* **1984**, *53*, 971–1013.
2. Korner, J. K.; Otis, L.; Skinner, W. A. *J. Med. Chem.* **1967**, *10*, 387–391.
3. Robba, M.; Duval, D. *Chim. Ter.* **1973**, *8*, 22–31.
4. Wang, Y. F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465–6466.
5. Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956–3958.
6. Jager, V.; Schwab, W.; Buß, V. *Angew.Chem., Int. Ed. Engl.* **1981**, *20*, 601–603.
7. Heitsch, H.; Konig, W. A.; Decker, H.; Bormann, C.; Fledler, H. P.; Zahner, H. *Antibiotics* **1989**, *42*, 711–717.
8. Tramontini, M. *Synthesis* **1982**, 605–644.
9. English, J.; Blis, A. D. *J. Am. Chem. Soc.* **1956**, *78*, 4057–4060.
10. Barluenga, J.; Aguilar, E.; Fustero, S.; Olano, B.; Viado, A. *J. Org. Chem.* **1992**, *57*, 1219–1223.
11. Katritzky, A.; Harris, P. A. *Tetrahedron* **1990**, *46*, 987–996.
12. Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277–294.
13. Maroni, P.; Cazaux, L.; Tisnes, P.; Zambetti, M. *Bull. Soc. Chim. Fr.* **1980**, 179–186.
14. Bartoli, G.; Cimarelli, C.; Palmieri, G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 537–543.
15. Hendrickson, J. B.; Sufrin, J. R. *Tetrahedron Lett.* **1973**, 1513–1516.
16. Meschino, J. A.; Bond, C. H. *J. Org. Chem.* **1963**, *28*, 3129–3134.
17. Narasaka, K.; Ukaji, S.; Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 525–533.
18. Palmieri, G.; Cimarelli, C.; Bartoli, G. *Tetrahedron: Asymmetry* **1994**, *5*, 1455–1458.
19. Bartoli, G.; Cimarelli, C.; Marcantoni, E.; Palmieri, G.; Petrini, M. *J. Org. Chem.* **1994**, *59*, 5328–5335.
20. Bartoli, G.; Cupone, G.; Dal Pozzo, R.; De Nino, A.; Mariuolo, L.; Procopio, A.; Tagarelli, A. *Tetrahedron Lett.* **2000**, *43*, 7441–7444.
21. Nilsson, L. *Acta Chem. Scand., Ser. B* **1979**, *B33*, 547–550.
22. SanMartin, R.; Martinez de Marigorta, E.; Dominguez, E. *Tetrahedron* **1994**, *50*, 2255–2264.
23. Cimarelli, C.; Palmieri, G. *J. Org. Chem.* **1996**, *61*, 5557–5563.
24. Palmieri, G. *Eur. J. Chem.* **1999**, 805–811.
25. Cimarelli, C.; Palmieri, G.; Volpini, E. *Synth. Commun.* **2001**, *31*, 2943–2953.
26. Harris, M. I. N. C.; Braga, A. C. H. J. *Braz. Chem. Soc.* **2004**, *15*, 971–975.
27. Braga, A. C. H.; Harris, M. I. N. C. BR 9502467 A 19970826 Patent; CAN 128:243740.
28. Semiempirical PM3 calculations were performed with the Spartan 5.0.3, Wavefunction, Inc. 18401 Von Karmen Ave., #370, Irvine, CA 92715.
29. Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759–4765.
30. Gaudemer, A.. In *Determination of Configurations by Spectrometric Methods*; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. 1, p 44.
31. Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1985**, *50*, 4052–4056.

32. The crystallographic data for compound (*R*,*R*,*R*,*R*)-**3d** (Formula: $C_{20}H_{25}NO$ Unit cell parameters: *a* 7.3524(13), *b* 28.645(5), *c* 8.4467(15), beta 100.635(2), space group *P*21) have been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number CCDC 288236. This data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.