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A new and expeditious strategy for the synthesis of β-amino acids from Δ^2-oxazolines

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Abstract—A new, mild two-step synthesis of racemic β-amino acids starting from 2-alkyl-Δ^2-oxazolines is described. The process implies the initial formation of masked *N*-substituted or *N*-unsubstituted β-enamino acid derivatives followed by chemoselective reduction of the enamino moiety. The process takes place with high yields, total chemoselectivity and moderate diastereoselectivity.

1. Introduction

Recently, increasing attention has been focused on β-amino acids, which are 1,3-difunctionalised compounds. This is partly due to the fact that β-peptides, which consist entirely of β-amino acids rather than α-amino acids, are an emerging class of unnatural biopolymers with interesting secondary structures.[1,2] It has also been demonstrated that β-peptides are resistant to the action of proteases,[3] which bodes well for medicinal purposes. In addition, the isolation of naturally occurring molecules containing β-amino acids is also growing. Many cyclic and non-cyclic peptides with important pharmacological properties have been isolated from marine organisms or from plants, and aromatic and aliphatic β-amino acids, as well as proteinogenic amino acids and some unusual acid moieties such as hydroxyacids, have been found to be components of these molecules.[4]

In some cases, the substitution of α-amino acids for their β-isomers in biologically active peptides involves an increase in the activity and enzymatic stability of the resulting peptide.[5] However, together with the widely recognised biological activity as part of peptidic chains, terpenes, alkaloids, macrolides and β-lactam antibiotics, several β-amino acids also show interesting pharmacological properties by themselves.[6] A third reason for the increased development of β-amino acid chemistry is the result of their ample role in several aspects of synthetic organic chemistry, namely their utility as chiral auxiliaries, chiral ligands, chiral building blocks and intermediates in the synthesis of β-lactams.[7]

As a consequence, a variety of procedures for preparing β-amino acids has been described,[4a,8] and can be classified into the following categories: (i) conjugate addition of primary or secondary amines or hydroxyl amines to α,β-unsaturated esters or nitriles,[9] (ii) addition of C-nucleophiles to imines,[10] (iii) alkylation of β-amino ester or amide enolates,[11] (iv) homologation of α-amino acids,[12] (v) transformations of aspartic acid derivatives,[13] including methods that apply Seebach's *self-reproduction of chirality* concept,[14] (vi) chemoenzymatic methods[15] and (vii) selective reduction of 3-aminoacrylic acid derivatives.[16,17] Among all of these procedures, the chemoselective reduction of the enamino moiety in β-enamino acid derivatives has received much less attention due, perhaps, to the high reactivity of the ester function towards a great number of reducing agents, which thus diminishes the regioselectivity of the process.

A simple way to overcome this problem would be to block this functionality through the use of protecting groups. Heterocyclic systems such as Δ^2-thiazolines, Δ^2-imidazolines and especially Δ^2-oxazolines have shown great synthetic potential as both carboxylic acid-protecting groups, chiral auxiliaries in asymmetric reactions and as chiral ligands in metal-catalysed asymmetric synthesis.[18,19] The reaction of commercially available 2-alkyl-2-oxazolines **1** with a variety of nitriles **2**[20] or with imidoyl chlorides **3**[21] has allowed us to devise two different approaches to

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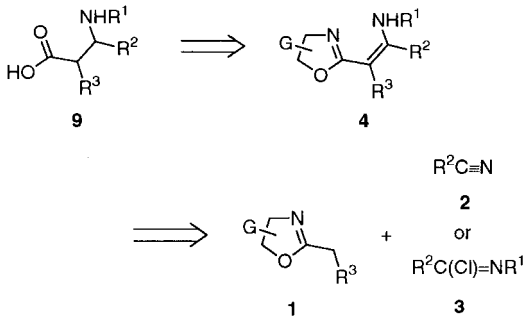


Scheme 1.

masked β-dehydroamino acids **4**, thus extending the reactivity of 2-alkyl-2-oxazolines (Scheme 1). It should also be pointed out that while this manuscript was under preparation, a first report regarding the application of these new derivatives **4** as chiral ligands for asymmetric catalysis was published.[22] In the present paper, we disclose our results regarding the development of a simple two-step strategy for obtaining racemic β-amino acids from masked β-enamino acids **4** through chemoselective reduction of the enamino moiety and deprotection of the carboxylic function.[23]

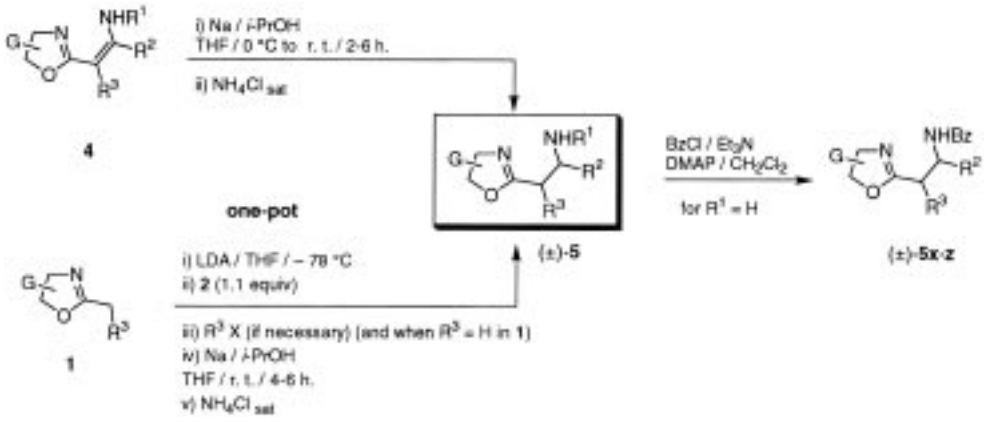
2. Results and discussion

The use of dissolving metals is one of the easiest methods to achieve the reduction of a large number of organic compounds. Since the sodium/*iso*-propanol system has been successfully used to perform the reduction of related systems such as 4-amino-1-aza-1,3-butadienes[24] or β-enaminoesters,[16a] we decided to initiate our research by testing it in compounds **4**. Thus, when *C*-protected β-enamino acids **4** were treated with an excess of sodium in THF as the solvent and *iso*-propanol as the proton source at 0°C and the reaction was allowed to reach room temperature, the corresponding *C*-protected β-amino acids **5** were obtained, after work-up, in the yields reported in Table 1 (Scheme 2). The reaction was finished in under two hours for *N*-substituted **4** ($R^1 \neq H$) and in less than six hours for *N*-unsubstituted **4** ($R^1 = H$). At longer reaction times, intractable mixtures of compounds were obtained as the result of product decomposition; however, the reaction was chemoselective as no reduction of the oxazoline moiety was detected in the ^1H NMR spectrum of the crude residue. Compounds **5** were usually obtained in high yields, independently of the substituents in the oxazoline moiety. The only requirement was that the R^2 substituent be an aromatic or heteroaromatic group; when R^2 was an aliphatic

Table 1. Synthesis of β-amino acid derivatives **5**

Entry	**1**[a]	Sm	R^1	R^2	R^3	Product	*Syn/anti*[b]	Yield (%)[c,d]	One-pot yield (%)[c]
1	**1a**	**4a**	H	Ph	H	**5a**		95 (82)	82
2	**1a**	**4b**	H	*p*-Me–C_6H_4	H	**5b**		90 (85)	96
3	**1a**	**4c**	H	*p*-MeO–C_6H_4	H	**5c**		87 (88)	
4	**1b**	**4d**	H	Ph	Me	**5d**	30/70	75[e]	
5	**1a**	**4e**	Ph	Ph	H	**5e**		99	
6	**1a**	**4f**	*p*-MeO–C_6H_4	*t*-Bu	H	**5f**[h]		75	
7	**1a**	**4g**	H	*p*-Me–C_6H_4	Me	**5g**	18/82	90[e] (80)[e]	90[e] (85)[e,f]
8	**1b**	**4h**	H	*p*-MeO–C_6H_4	Me	**5h**	30/70	95[e]	
9	**1c**	**4i**	H	Ph	H	**5i**		72	88
10	**1c**	**4j**	H	*p*-Me–C_6H_4	H	**5j**		92	97
11	**1c**	**4k**	H	*p*-MeO–C_6H_4	H	**5k**		93	77
12	**1c**	**4l**	H	2-Furyl	H	**5l**		83	92
13	**1a**	**4m**	H	*p*-Me–C_6H_4	Allyl	**5m**	37/63	96[e]	
14	**1d**	**4n**	H	*p*-Me–C_6H_4	H	**5n**		83[g]	
15	**1a**	**4o**	*c*-C_6H_{11}	Ph	H	**5o**		98	
16	**1a**	**4p**	*p*-MeO–C_6H_4	Ph	H	**5p**		99	
17	**1a**	**4q**	(±)-Ph(Me)CH	Ph	H	**5q**		80[g]	
18	**1a**	**4r**	Ph	*p*-MeO–C_6H_4	H	**5r**		98	
19	**1b**	**4s**	Ph	Ph	Me	**5s**	17/83	88[e]	
20	**1b**	**4t**	(±)-Ph(Me)CH	Ph	Me	**5t**		96[i]	
21	**1b**	**4u**	Ph	*p*-MeO–C_6H_4	Me	**5u**	18/82	91[e]	
22	**1a**	**4v**	*p*-Me-C_6H_4	*t*-Bu	H	**5v**[h]		85	
23	**1b**	**4w**	*p*-Me–C_6H_4	*t*-Bu	Me	**5w**[h]	23/77	90[e]	
24	**1a**	**4x**	H	2-Pyridyl	H	-[j]			
25	**1a**	**4y**	*p*-MeO–C_6H_4	CF_3	H	-[j]			
26	**1a**	**5a**	Ph-CO–	Ph	H	**5x**		98[k]	
27	**1b**	**anti-5d**	Ph-CO–	Ph	Me	***anti*-5y**		60[k]	
28	**1c**	**5i**	Ph-CO–	Ph	H	**5z**		75[k]	

[a] Structure of the oxazoline moiety: **1a**, 2-methyl-2-oxazoline; **1b**, 2-ethyl-2-oxazoline; **1c**, 2,4,4-trimethyl-2-oxazoline; **1d**, (4*S*,5*S*)-4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline.
[b] Calculated from crude mixture by ^1H NMR (300 MHz).
[c] Yield of crude product (not optimised).
[d] In brackets, yield of crude product when using *t*-BuOH as proton source.
[e] Yield of the mixture of diastereomers.
[f] Crude yield starting from 2-ethyl-2-oxazoline **1b** (three steps).
[g] Yield of a mixture of diastereomers (1:1) (not separated).
[h] $NaBH_4$/MeOH was used as reducing agent.
[i] Yield of a mixture of 4 diastereomers (1:3:1:3) (not separated).
[j] A complex mixture of products was obtained.
[k] Yield of isolated product after recrystallization.



Scheme 2.

substituent, complex mixtures were obtained and the desired product **5**, although detected, could not be isolated. Also for the fluorinated derivative **4y** and for **4x** (R^2=2-pyridyl) a complex mixture of undefined products was obtained as a result, in the latter case, of partial and/or total reduction of the heteroaromatic substituent (entries 24, 25, Table 1).

N-Unsubstituted β-amino acid derivatives **5** (R^1=H) are very polar and water soluble; therefore, in order to avoid a decrease of the reaction yield, the quenching of the reaction mixture was performed with the minimum (stoichiometric) amount of a NH_4Cl saturated aqueous solution.

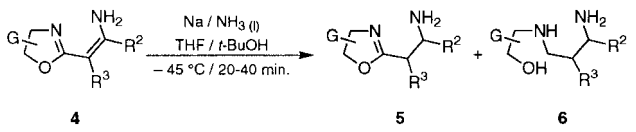
When $R^3 \neq H$ the chemoselective reduction of the enaminic double bond generated mixtures of *syn*/*anti* diastereomers in a moderate and variable (1:1.3 to 1:4.8) ratio, as a new stereocenter was created. Attempts to improve the diastereoselectivity by decreasing the reaction temperature, changing the reaction time, or using another proton source such as *tert*-butanol were completely ineffective. The identification of compounds **5** was carried out by means of ^1H and ^{13}C NMR and HRMS. The value of the coupling constants, as well as the chemical shift for the H in α position to the amino group, was decisive in the elucidation of *syn*/*anti* diastereomers. In related systems, the coupling constant is bigger and the chemical shift located at higher field for the *anti* than for the *syn* diastereomer.[24,25] In our case, the chemical shift and the coupling constant of the H α to the NH_2 group in, for example, compound **5d** are 3.88 ppm and 9.6 Hz, respectively, for the *anti* isomer and 4.15 ppm and 5.2 Hz for the *syn* isomer.

When chiral non-racemic compound **4n**, which bears the chirality in the oxazoline portion, was treated with Na/*i*-PrOH in the conditions described, an equimolecular mixture of diastereomers was obtained. In this case neither diastereomer could be separated and no asymmetric induction was observed.

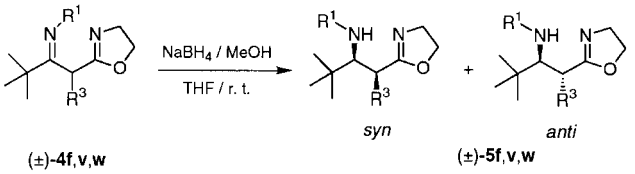
In most instances the crude product showed satisfactory spectroscopic data and could be used in the following step without purification. When necessary, the purification of compounds **5** was carried out either by means of flash chromatography or recrystallisation. However, several *N*-unsubstituted oxazoline-protected β-amino acids **5** (R^1=H), isolated as pale yellow oils, were too unstable for distillation, flash chromatography (silica gel, alumina, florisil) or medium-pressure liquid chromatography (MPLC), as had been previously observed for related *N*-unsubstituted β-amino ketones.[24,25] For this reason and bearing in mind that *N*-substituted oxazoline-protected β-amino acids **5** ($R^1 \neq H$) are more stable, several derivatives **5** (R^1=H) were benzoylated through reaction with $PhCOCl/Et_3N$/DMAP to afford *N*-benzoylated oxazoline-protected β-amino acids **5x**–**z** (R^1=COPh) (entries 26–28, Table 1, Scheme 2).

Closely related conditions ($Na/NH_{3(l)}$/*t*-BuOH) were recently described by Kishi[26] and we decided to test them in an attempt to improve the diastereoselectivity of the reduction process, as the reaction proceeded at lower temperature (−45°C). However, in all cases a mixture of the starting material **4**, the desired reduced compound **5** and another product **6**, resulting from the opening of the oxazoline portion, were obtained in variable proportions. If the reaction was allowed to continue, the amount of **6** was increased, and after 30 min the crude reaction was almost exclusively compound **6** (Scheme 3).

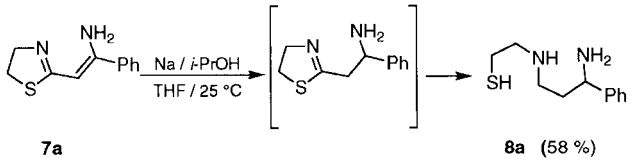
Other reducing agents such as complex metal hydrides (i.e. $NaBH_4$, $NaBH_3CN$, $LiAlH_4$) under different conditions ($NaBH_4/I_2$,[27] $NaBH_4$/MsOH,[28] $NaBH_4$/AcOH,[16a] $NaBH_3CN$/MeOH,[29] $NaBH_3CN$/AcOH,[30] $NaBH_3CN$/CF_3CO_2H[31]) have also been tested, but they were inefficient, yielding either a complex mixture of products or the recovered starting material. One exception to this general behaviour is the case of β-*tert*-leucine derivatives **4f**,**v**,**w**. These compounds generally appear as imino tautomers, because of steric effects between the *t*-butyl and aryl (=R^1) groups;[21] consequently, they can also be reduced by other agents such as complex metal hydrides (Scheme 4). Thus, when **4f**,**v**,**w** were allowed to react with $NaBH_4$ in a THF/MeOH mixture (3:1) at 25°C, the corresponding β-amino derivatives **5f**,**v**,**w** were synthesised in high yields (entries 6, 22, 23, Table 1 and Scheme 4). In the



Scheme 3.



Scheme 4.



Scheme 5.

case of α-substituted derivatives such as **4w**, a separable mixture of *syn/anti* (1:3) diastereomers **5w** was obtained (entry 23, Table 1). The preference for the major diastereoisomer *anti*-**5w** can be easily explained if it is assumed that, in a Felkin–Ahn model, the hydride attacks the imino carbon from the opposite side of the α-methyl group.

It is worth noting that *N*-unsubstituted *C*-protected β-amino acids **5** (R^1=H) can also be obtained in a one-pot procedure starting from 2-alkyl-2-oxazolines **1** (Scheme 2). This reaction involves three or four steps, depending on whether the alkylation is carried out or not, and is convenient since the isolation of intermediates **4** is not necessary, thus saving time and material. Furthermore, in many cases, this one-pot reaction provides higher yields than the stepwise sequence (entries 2, 9, 10, 12, Table 1) making it the method of choice for preparing derivatives **5** (R^1=H).

As the thiazoline ring has also been used as a protective group for the carboxylic function,[32] we analysed the reduction of thiazoline-protected β-enamino derivatives **7**. The treatment of **7** (for example **7a**) with complex metal hydrides ($LiAlH_4$, $NaBH_4$) was inefficient as had been the case with oxazoline derivatives **4** (vide supra), while the use of dissolving metals (Na/*i*-PrOH) in conditions identical to those used for oxazoline derivatives **4** resulted in the complete reduction of the unsaturated system, with concomitant opening of the thiazoline ring to yield compound **8a** (Scheme 5). This disappointing result, although not totally unexpected, led us to focus our research on the reduction of compounds **4**.

The last step in the preparation of β-amino acids **9** involved the deprotection of the carboxylic function of compounds **5** and could be carried out conveniently by means of acidic hydrolysis. Thus, treatment of β-amino oxazolines **5** in refluxing 3N HCl for 2–3 h yielded the desired β-amino acids **9** along with the recovery of β-amino alcohols **10**. Finally, isolation and purification of β-amino acids **9** were achieved by means of flash chromatography and recrystallisation for *N*-substituted β-amino acids **9** ($R^1 \neq H$) and by means of ion-exchange chromatography (Dowex-50, H^+ form) for *N*-unsubstituted β-amino acids **9** (R^1=H), to afford the corresponding derivatives in moderate to good yields (Table 2, Scheme 6).

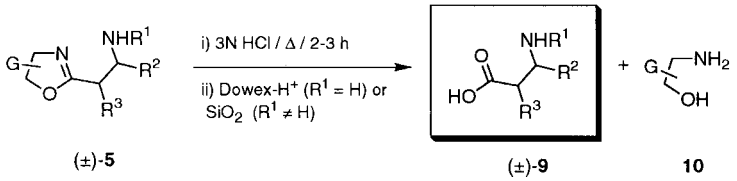
It should also be pointed out that, besides the option of being transformed into β-amino acids, several C-oxazoline protected β-amino acids **5** present latent functionality that can be developed to convert them into interesting organic compounds. Thus, for example, compounds **5** in which R^2=2-Furyl or *p*-MeO–C_6H_4 are potential precursors of α-amino acids (in fact, they can be regarded as synthons of aspartic acid) when standard procedures are used to transform the R^2 group into a carboxyl group.[33] Moreover, in these cases both carboxylic functions are masked behind orthogonal protecting groups.

In summary, we have described our initial studies of a simple and convenient procedure for the regioselective reduction of racemic *C*-protected β-enamino acids **5**. The iminic or enaminic nature of compounds **5** determines the reducing agent to be employed; thus, enaminic tautomers **5** can be reduced by dissolving metals (Na/*i*-PrOH) while complex metal hydrides ($NaBH_4$) can be used for iminic

Table 2. Synthesis of β-amino acids **9**

Entry	Sm	R^1	R^2	R^3	Product	Yield (%)[a]
1	**5a**	H	Ph	H	**9a**	90
2	**5b**	H	*p*-Me–C_6H_4	H	**9b**	73
3	**5c**	H	*p*-MeO–C_6H_4	H	**9c**	51
4	*anti*-**5d**	H	Ph	Me	*anti*-**9d**	46
5	**5e**	Ph	Ph	H	**9e**	90
6	**5f**	*p*-MeO–C_6H_4	*t*-Bu	H	**9f**	88

[a] Isolated yield after purification.



Scheme 6.

tautomers **5**. *N*-Unsubstituted compounds **5** (R^1=H) can also be accessed through a facile one-pot procedure from oxazolines **1** in high yields, thus avoiding the isolation of intermediates **4**. Finally, standard deprotection of the carboxylic function yields the desired β-amino acids **9**. Further work to improve the diastereoselectivity in the reduction step, either by choosing a different chiral auxiliary in the oxazoline portion or by investigating other reduction conditions (i.e. catalytic hydrogenation) is in progress and will be reported at another time.

3. Experimental

3.1. General

THF was distilled under argon from sodium/benzophenone ketyl as drying agent. Diisopropylamine, used to generate LDA, was refluxed over KOH, distilled, and stored under argon in the presence of 4 Å molecular sieves at 4°C. *i*-PrOH and *t*-BuOH were dried by refluxing them over magnesium activated with iodine and distilled. Solvents used in extractions, recrystallisations, and in chromatographic columns were distilled prior to use. β-Enamino acid derivatives **4** and **7** were prepared as described.[20,21] All other reagents were commercially available and were used without further purification. Complete descriptions of the equipment and analytical methods used for the synthesis and characterisation of the described compounds have been previously reported.[20b,21]

3.2. Synthesis of Δ^2-oxazoline protected β-amino acids 5. Two different methods (A and B) were employed depending on which tautomeric form (enamine or imine) was present in the starting material.

3.2.1. Method A: Reduction of Δ^2-oxazoline protected β-enamino acids 4. Isopropanol (3 mL, via syringe) and Na (excess) in small portions were successively added under inert atmosphere to a solution of the starting material **4** (20.0 mmol) in dry THF (10 mL) at 0°C. The reaction mixture was stirred and allowed to reach room temperature. When TLC monitoring indicated complete disappearance of the starting material (2–6 h), the excess of Na was removed and a saturated aqueous solution of NH_4Cl (4–5 mL) was added. [For *N*-unsubstituted β-amino acid derivatives (R^1=H) a minimum (stoichiometric) amount of NH_4Cl was added.] The reaction mixture was extracted with dichloromethane (3×15 mL); the combined organic layer was dried over $MgSO_4$, filtered, and solvents were evaporated under reduced pressure to give a residue that, in most cases, was spectroscopically pure and could be used without further purification. When necessary, purification was carried out either by means of flash chromatography over SiO_2 or by recrystallisation, if solid, to give the corresponding Δ^2-oxazoline protected β-aminoacid **5** in the yield reported in Table 1.

3.2.2. 2-(2-Amino-2-phenyl)ethyl-2-oxazoline (5a). Colourless oil; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.40–7.20 (m, 5H), 4.35 (t, 1H, *J*=7.4 Hz), 4.17 (t, 2H, *J*=9.2 Hz), 3.79 (t, 2H, *J*=9.2 Hz), 2.54 (dd, 2H, *J*=7.4, 6.2 Hz), 1.80 (bs, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 166.6 (s), 144.8 (s), 128.5 (d), 127.3 (d), 126.1 (d), 67.1 (t), 54.3 (t), 53.1 (d), 37.9 (t); HRMS (EI): calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1111.

3.2.3. 2-(2-Amino-2-*p*-tolyl)ethyl-2-oxazoline (5b). White solid. Mp 47–49°C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.25 (d, 2H, *J*=8.0 Hz), 7.15 (d, 2H, *J*=8.0 Hz), 4.36 (t, 1H, *J*=6.4 Hz), 4.26 (t, 2H, *J*=9.1 Hz), 3.84 (t, 2H, *J*= 9.1 Hz), 2.59 (dd, 2H, *J*=7.3 and 6.4 Hz), 2.56 (s, 3H), 2.20–2.00 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 166.4 (s), 141.7 (s), 136.6 (s), 128.9 (d), 125.8 (d), 66.8 (t), 54.0 (t), 52.5 (d), 37.7 (t), 20.7 (q); HRMS (EI): calcd for $C_{12}H_{16}N_2O$ 204.1262, found 204.1267.

3.2.4. 2-(2-Amino-2-*p*-methoxyphenyl)ethyl-2-oxazoline (5c). Pale yellow oil; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.30 (d, 2H, *J*=9.1 Hz), 6.85 (d, 2H, *J*=9.1 Hz), 4.34 (t, 1H, *J*=6.9 Hz), 4.22 (t, 2H, *J*=9.5 Hz), 3.81 (t, 2H, *J*= 9.5 Hz), 3.80 (s, 3H), 2.57 (dd, 2H, *J*=7.6, 6.9 Hz), 2.00 (bs, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 166.6 (s), 158.7 (s), 136.9 (s), 127.1 (d), 113.8 (d), 67.0 (t), 55.2 (q), 54.2 (t), 52.4 (d), 38.0 (t); HRMS (EI): calcd for $C_{12}H_{16}N_2O_2$ 220.1213, found 220.1211. Anal. calcd for $C_{12}H_{16}N_2O_2$: C 65.43, H 7.32, N 12.72; found: C 65.28, H 7.40, N 12.51.

3.2.5. 2-(2-Amino-1-methyl-2-phenyl)ethyl-2-oxazoline (5d). Pale yellow oil, obtained as a *syn*/*anti* mixture of diastereoisomers. Data for the minor isomer were obtained from a diastereomerically enriched mixture. HRMS (EI): calcd for $C_{12}H_{16}N_2O$ 204.1262, found 204.1262.

3.2.6. (1*S,2*R**)-2-(2-Amino-1-methyl-2-phenyl)ethyl-2-oxazoline (*anti*-5d).** ^{1}H NMR ($CDCl_3$,TMS, 250 MHz) δ 7.36–7.21 (m, 5H), 4.10 (t, 2H, *J*=9.2 Hz), 3.88 (d, 1H, *J*=9.6 Hz), 3.71 (t, 2H, *J*=9.2 Hz), 2.71 (m, 1H), 2.00 (bs, 2H), 0.84 (d, 3H, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 170.5 (s), 143.7 (s), 128.4 (d), 127.3 (d), 126.5 (d), 66.9 (t), 59.2 (d), 54.1 (t), 41.7 (d), 15.7 (q).

3.2.7. (1*S,2*S**)-2-(2-Amino-1-methyl-2-phenyl)ethyl-2-oxazoline (*syn*-5d).** ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.36–7.21 (m, 5H), 4.15 (d, 1H, *J*=5.2 Hz), 3.98 (t, 2H, *J*=9.2 Hz), 3.59 (t, 2H, *J*=9.2 Hz), 2.71 (m, 1H), 2.00 (bs, 2H), 1.10 (d, 3H, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 170.5 (s), 143.7 (s), 128.4 (d), 128.1 (d), 127.0 (d), 66.9 (t), 57.3 (d), 54.1 (t), 41.0 (d), 11.9 (q).

3.2.8. 2-(2-Anilino-2-phenyl)ethyl-2-oxazoline (5e). White solid. Mp 137–9°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.41–7.05 (m, 7H), 6.68–6.51 (m, 3H), 4.72 (bs, 1H), 4.70 (m, 1H), 4.20 (t, 2H, *J*=9.5 Hz), 3.81 (t, 2H, *J*=9.5 Hz), 2.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 165.5 (s), 147.3 (s), 142.6 (s), 129.0 (d), 128.7 (d), 127.3 (d), 126.1 (d), 117.5 (d), 113.5 (d), 67.4 (t), 55.3 (t), 54.3 (d), 36.8 (t); HRMS (EI): calcd for $C_{17}H_{18}N_2O$ 266.1419, found 266.1426.

3.2.9. (1*S,2*R**)-2-(2-Amino-1-methyl-2-*p*-tolyl)ethyl-2-oxazoline (*anti*-5g).** White solid. Mp 92–4°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.30–7.10 (m, 4H), 4.27 (t, 2H, *J*=9.6 Hz), 4.00 (d, 1H, *J*=9.4 Hz), 3.88 (t, 2H, *J*=9.6 Hz), 2.69 (m, 1H), 2.34 (s, 3H), 1.75 (bs, 2H), 0.95 (d, 3H, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 170.0

(s), 140.8 (s), 137.1 (s), 129.2 (d), 127.0 (d), 67.1 (t), 59.0 (d), 54.2 (t), 41.8 (d), 21.1 (q), 15.9 (q); HRMS (EI): calcd for $C_{13}H_{18}N_2O$ 218.1413, found 218.1419. Anal. calcd for $C_{13}H_{18}N_2O$: C 71.53, H 8.31, N 12.83; found: C 71.39, H 8.20, N 12.86.

3.2.10. 2-[2-Amino-2-(*p*-methoxyphenyl)-1-methyl]ethyl-2-oxazoline (5h). Pale yellow oil, obtained as a mixture of diastereoisomers that were not separated. Data for each diastereoisomer were obtained from the diastereomeric mixture. HRMS (CI): calcd for $C_{13}H_{16}NO_2$ ($M^+ + 1 - NH_3$) 218.1180, found 218.1181.

3.2.11. (1*S,2*R**)-2-(2-Amino-2-*p*-methoxyphenyl-1-methyl)-ethyl-2-oxazoline (*anti*-5h).** ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.20 (d, 2H, J=6.8 Hz), 6.82 (d, 2H, J=6.8 Hz), 4.25 (t, 2H, J=9.2 Hz), 3.95 (d, 1H, J=9.2 Hz), 3.88 (t, 2H, J=9.2 Hz), 3.76 (s, 3H), 2.71 (m, 1H), 2.00 (bs, 2H), 0.90 (d, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7 (s), 158.8 (s), 135.7 (s), 128.0 (d), 113.8 (d), 67.0 (t), 58.6 (d), 55.2 (q), 54.2 (t), 41.9 (d), 15.8 (q).

3.2.12. (1*S,2*S**)-2-(2-Amino-2-*p*-methoxyphenyl-1-methyl)-ethyl-2-oxazoline (*syn*-5h).** ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.20 (d, 2H, J=6.8 Hz), 6.82 (d, 2H, J=6.8 Hz), 4.17 (t, 2H, J=9.2 Hz), 3.95 (d, 1H, J=9.2 Hz), 3.75 (t, 2H, J=9.2 Hz), 3.76 (s, 3H, 2.73 (m, 1H), 2.00 (bs, 2H), 1.12 (d, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7 (s), 158.8 (s), 135.7 (s), 127.6 (d), 113.5 (d), 75.0 (t), 58.6 (d), 56.9 (q), 54.1 (t), 41.2 (d), 12.2 (q).

3.2.13. 2-(2-Amino-2-phenyl)ethyl-4,4-dimethyl-2-oxazoline (5i). Colourless oil; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.30–7.20 (m, 5H), 4.32 (t, 1H, J=6.9 Hz), 3.82 (s, 2H), 2.56 (d, 2H, J=6.9 Hz), 1.90 (bs, 2H), 1.19 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 163.7 (s), 144.5 (s), 128.3 (d), 127.1 (d), 126.1 (d), 78.6 (d), 66.8 (s), 53.0 (t), 37.9 (t), 28.2 (q); HRMS (EI): calcd for $C_{13}H_{18}N_2O$ 218.1419, found 218.1415. Anal. calcd for $C_{13}H_{18}N_2O$: C 71.53, H 8.31, N 12.83; found: C 71.39, H 8.43, N 12.64.

3.2.14. 2-(2-Amino-2-*p*-tolyl)ethyl-4,4-dimethyl-2-oxazoline (5j). Pale yellow oil; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.23 (d, 2H, J=8.0 Hz), 7.10 (d, 2H, J=8.0 Hz), 4.32 (t, 1H, J=6.9 Hz), 3.78 (s, 2H), 2.53 (d, 2H, J=6.9 Hz), 2.19 (s, 3H), 2.10 (bs, 2H), 1.23 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 164.5 (s), 142.3 (s), 137.3 (s), 129.7 (d), 126.6 (d), 79.2 (d), 67.5 (s), 53.4 (t), 38.7 (t), 28.9 (q), 21.5 (q); HRMS (EI): calcd for $C_{14}H_{20}N_2O$ 232.1575, found 232.1571. Anal. calcd for $C_{14}H_{20}N_2O$: C 72.38, H 8.68, N 12.06; found: C 72.27, H 8.53, N 11.91.

3.2.15. 2-(2-Amino-2-*p*-methoxyphenyl)ethyl-4,4-dimethyl-2-oxazoline (5k). Pale yellow oil; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.22 (d, 2H, J=8.7 Hz), 6.79 (d, 2H, J=8.7 Hz), 4.27 (m, 1H), 3.81 (s, 2H), 3.72 (s, 3H), 2.47 (m, 2), 2.00 (bs, 2H), 1.19 (s, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 165.6 (s), 145.4 (s), 143.9 (s), 129.3 (d), 126.7 (d), 80.4 (d), 68.5 (s), 52.9 (q), 42.6 (t), 35.5 (t), 21.5 (q); HRMS (EI): calcd for $C_{14}H_{20}N_2O_2$ 248.1527, found 248.1524. Anal. calcd for $C_{14}H_{20}N_2O_2$: C 67.72, H 8.12, N 11.28; found: C 67.75, H 8.13, N 11.30.

3.2.16. 2-[2-Amino-2-(2-furyl)]ethyl-4,4-dimethyl-2-oxazoline (5l). Pale yellow oil; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.25 (d, 1H, J=1.8 Hz), 6.20 (dd, 1H, J=2.9, 1.8 Hz), 6.09 (d, 1H, J=2.9 Hz), 4.32 (dd, 1H, J=8.5, 5.0 Hz), 3.82 (s, 2H), 2.65 (dd, 1H, J=8.5, 5.0 Hz), 2.52 (dd, 1H, J=8.5, 8.5 Hz), 2.00 (bs, 2H), 1.18 (s, 3H), 1.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 163.4 (s), 157.2 (s), 141.5 (d), 109.9 (d), 104.6 (d), 78.8 (t), 67.0 (s), 47.2 (d), 35.6 (t), 28.3 (q). Anal. calcd for $C_{11}H_{16}N_2O_2$: C 63.46, H 7.69, N 13.46; found: C 63.38, H 7.80, N 13.37.

3.2.17. 2-(1-Amino-1-*p*-tolyl)but-3-en-1-yl-2-oxazoline (5m). Pale yellow oil; diastereoisomers not separated; data obtained from a 37:63 mixture of diastereoisomers. HRMS (FAB): calcd for $C_{15}H_{20}N_2O$ ($M^+ + 1$) 245.1654, found 245.1657.

3.2.18. (1*S,2*R**)-2-(1-Amino-1-*p*-tolyl)but-3-en-1-yl-2-oxazoline (*anti*-5m).** Major diastereoisomer; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.20–7.00 (m, 4H), 5.60 (m, 1H), 4.88 (m, 2H), 4.12 (t, 2H, J=9.2 Hz), 3.95 (d, 1H, J=9.6 Hz), 3.80 (t, 2H, J=9.2 Hz), 2.65 (m, 1H), 2.23 (s, 3H), 2.00 (m, 2H), 1.80 (bs, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 168.9 (s), 140.6 (s), 137.1 (s), 135.1 (d), 129.2 (d), 126.8 (d), 116.5 (t), 66.9 (d), 57.3 (t), 54.1 (t), 47.3 (t), 34.6 (d), 21.0 (q).

3.2.19. (1*S,2*S**)-2-(1-Amino-1-*p*-tolyl)but-3-en-1-yl-2-oxazoline (*syn*-5m).** Minor diastereoisomer; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.20–7.00 (m, 4H), 5.70 (m, 1H), 5.00 (m, 2H), 4.12 (m, 3H), 3.60 (t, 2H, J=9.2 Hz), 2.65 (m, 1H), 2.25 (s, 3H), 2.05 (m, 2H), 1.80 (bs, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 168.5 (s), 140.2 (s), 136.7 (s), 135.9 (d), 128.8 (d), 126.5 (d), 116.3 (t), 66.8 (d), 57.1 (t), 53.9 (t), 46.9 (t), 32.5 (d), 21.0 (q).

3.2.20. (4*S*,5*S*)-2-(2-Amino-2-*p*-tolyl)ethyl-4-methoxymethyl-5-phenyl-2-oxazoline (5n). Mixture of diastereoisomers; pale yellow oil; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.30–7.00 (m, 18H) 4.29 (m, 2H), 3.32 (s, 3H), 3.31 (s, 3H), 3.25 (m, 4H), 2.85 (m, 2H), 2.44 (m, 2H), 2.31 (s, 6H), 2.10 (bs, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5 (s), 141.62 (s), 141.55 (s), 137.8 (s), 137.7 (s), 136.4 (s), 136.3 (s), 129.0 (d), 128.9 (d), 127.95 (d), 125.95 (d), 125.8 (d), 125.5 (d), 73.0 (t), 72.1 (t), 58.4 (q), 52.3 (d), 49.6 (d), 49.55 (d), 37.0 (t), 36.9 (t), 20.6 (q).

3.2.21. 2-(2-Cyclohexylamino-2-phenyl)ethyl-2-oxazoline (5o). Pale yellow solid. Mp 98–100°C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.34–7.25 (m, 5H), 4.18 (m, 1H), 4.15 (t, 2H, J=9.1 Hz), 3.78 (t, 2H, J=9.4 Hz), 2.60–2.54 (m, 2H), 2.35–1.08 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2 (s), 144.5 (s), 129.2 (d), 128.0 (d), 127.8 (d), 68.0 (t), 57.5 (d), 55.1 (t), 54.1 (d), 38.1 (t), 35.4 (t), 33.5 (t), 26.9 (t), 26.0 (t), 25.6 (t); MS (EI) (*m*/*z*, %): 271 ($M^+ - 1$, 14), 207 ($M^+ - 65$, 100), 188 ($M^+ - 84$, 57). Anal. calcd for $C_{17}H_{24}N_2O$: C 75.00, H 8.82, N 10.29; found: C 75.31, H 8.79, N 10.41.

3.2.22. 2-(2-*p*-Methoxyphenylamino-2-phenyl)ethyl-2-oxazoline (5p). Pale brown solid. Mp 107–9°C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.43–7.21 (m, 5H), 7.70 (d, 2H, J=7.9 Hz), 7.50 (d, 2H, J=7.9 Hz), 4.63 (dd, 1H, J=13.5,

8.2 Hz), 4.50 (bs, 1H), 4.20 (t, 2H, *J*=9.3 Hz), 3.81 (t, 2H, *J*=9.3 Hz), 3.68 (s, 3H), 2.79–1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 165.6 (s), 152.1 (s), 143.0 (s), 141.4 (s), 128.7 (d), 127.3 (d), 126.2 (d), 115.0 (d), 114.7 (d), 67.4 (t), 56.3 (t), 55.7 (q), 54.5 (d), 36.9 (t); MS (EI) (*m*/*z*, %): 296 (M^+, 8), 208 (M^+-88, 89), 196 (M^+-100, 100). Anal. calcd for $C_{18}H_{20}N_2O_2$: C 72.97, H 6.75, N 9.46; found: C 72.80, H 6.61, N 9.31.

3.2.23. 2-[2-Phenyl-2-(*N*-1-phenylethylamino)]ethyl-2-oxazoline (5q). Obtained as a non-separable mixture of diastereoisomers in a 1:1 ratio. Pale yellow oil; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.28–6.96 (m, 20H), 4.10–3.93 (m, 4H), 3.78–3.52 (m, 6H), 3.35 (q, 2H, *J*=7.0 Hz), 2.70–2.30 (m, 4H), 1.20 (d, 3H, *J*=7.0 Hz), 1.12 (d, 3H, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.1 (s), 145.9 (s), 145.4 (s), 143.1 (s), 128.4 (d), 128.3 (d), 128.2 (d), 127.1 (d), 127.0 (d), 126.9 (d), 126.6 (d), 126.5 (d), 67.0 (t), 57.3 (t), 56.9 (t), 54.8 (d), 54.5 (d), 54.3 (d), 36.9 (t), 36.3 (t), 25.0 (q), 22.3 (q). HRMS (FAB): calcd for $C_{19}H_{22}N_2O$ (M^++1) 295.1809, found 295.1810.

3.2.24. 2-(2-Anilino-2-*p*-methoxyphenyl)ethyl-2-oxazoline (5r). White solid. Mp 138–140°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.35–6.46 (m, 9H), 4.70–4.57 (m+bs, 2H), 4.13 (t, 2H, *J*=9.5 Hz), 3.73 (t, 2H, *J*=9.5 Hz), 3.70 (s, 3H), 2.75–2.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 165.5 (s), 158.7 (s), 147.1 (s), 134.6 (s), 129.0 (d), 127.2 (d), 117.4 (d), 114.1 (d), 113.6 (d), 67.3 (t), 55.2 (d), 54.8 (q), 54.4 (t), 36.9 (t); MS (EI) (*m*/*z*, %): 296 (M^+, 7), 212 (M^+-84, 78), 211 (M^+-85, 83), 210 (M^+-86, 100). Anal. calcd for $C_{18}H_{20}N_2O_2$: C 72.97, H 6.75, N 9.46; found: C 72.89, H 6.70, N 9.58.

3.2.25. (1*S,2*R**)-2-(2-Anilino-1-methyl-2-phenyl)ethyl-2-oxazoline (*anti*-5s).** White solid. Mp 163–5°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.22–6.43 (m, 10H), 4.87 (d, 1H, *J*=6.1 Hz), 4.33 (dd, 1H, *J*=6.1 and 6.1 Hz), 4.06 (t, 2H, *J*=9.0 Hz), 3.75 (t, 2H, *J*=9.0 Hz), 2.78 (m, 1H), 1.06 (d, 3H, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 169.4 (s), 147.1 (s), 141.7 (s), 128.9 (d), 128.4 (d), 127.3 (d), 126.9 (d), 117.0 (d), 113.2 (d), 67.2 (t), 60.6 (d), 54.1 (t), 40.7 (d), 15.8 (q); HRMS (EI): calcd for $C_{18}H_{20}N_2O$ 280.1576, found 280.1577.

3.2.26. 2-[1-Methyl-2-phenyl-2-(*N*-1-phenylethylamino)]-ethyl-2-oxazoline (5t). Obtained as a non-separable mixture of four diastereoisomers in a 1:3:1:3 ratio; yellow oil; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.30–7.00 (m, 20H), 4.20 (t, 4H, *J*=7.6 Hz), 4.05–3.35 (m, 8H), 2. 64 (m, 1H), 2.55 (m, 1H), 1.92–1.79 (bs, 2H), 1.18 (d, 3H, *J*=7.0 Hz), 1.08 (d, 3H, *J*=7.0 Hz), 0.86 (d, 3H, *J*=7.0 Hz), 0.75 (d, 3H, *J*=7.0 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 170.6 (s), 169.8 (s), 146.4 (s), 145.6 (s), 142.0 (s), 141.8 (s), 128.2 (d), 128.1(d), 127.7(d), 127.5 (d), 127.4 (d), 127.2 (d), 126.9 (d), 126.7 (d), 126.5 (d), 67.1 (t), 67.0 (t), 66.8 (t), 63.2 (d), 61.5 (d), 54.9 (d), 54.7 (d), 54.5 (d), 54.2 (t), 54.1 (t), 40.8 (d), 40.6 (d), 25.3 (q), 25.0 (q), 22.1 (q), 21.9 (q), 15.3 (q), 13.3 (q), 12.9 (q); HRMS (EI): calcd for $C_{20}H_{25}N_2O$ (M^++1) 309.1967, found 309.1955.

3.2.27. (1*S,2*R**)-2-(2-Anilino-2-*p*-methoxyphenyl-1-methyl)-ethyl-2-oxazoline (*anti*-5u).** White solid. Mp 168–170°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 7.17–6.43 (m, 9H), 4.29 (d, 1H, *J*=7.8 Hz), 4.09 (t, 2H, *J*=9.3 Hz), 3.73 (t, 2H, *J*=9.3 Hz), 3.70 (s, 3H), 2.78 (m, 1H), 1.06 (d, 3H, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 169.5 (s), 158.6 (s), 147.2 (s), 133.6 (s), 128.9 (d), 127.9 (d), 116.9 (d), 113.5 (d), 113.2 (d), 67.1 (t), 60.0 (d), 55.1 (q), 54.1 (t), 40.8 (d), 15.7 (q). Anal. calcd for $C_{19}H_{22}N_2O_2$: C 73.55, H 7.09, N 9.03; found: C 73.71, H 7.01, N 9.18.

3.2.28. Method B: Reduction of Δ^2-oxazoline protected β-imino acids 4f,v,w. MeOH (3 mL) and $NaBH_4$ (30.0 mmol) were added sequentially to a solution of the corresponding iminic derivative **4f**,**v**,**w** (20.0 mmol) in dry THF (10 mL) at 0°C. The reaction mixture was stirred and allowed to reach room temperature. After 30 min the reaction was finished (TLC monitoring) and saturated aqueous solution of NH_4Cl (4-5 mL) was added. The reaction mixture was extracted with dichloromethane (3×15 mL); the combined organic layer was washed with saturated brine, dried over $MgSO_4$, filtered, and solvents were evaporated under reduced pressure to give a residue that was then purified by means of flash chromatography over SiO_2 to give the corresponding Δ^2-oxazoline protected β-amino acid **5f**,**v**,**w** in the yield reported in Table 1.

3.2.29. 2-(2-*p*-Methoxyphenylamino-3,3-dimethyl)butyl-2-oxazoline (5f). White solid. Mp 115–6; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.78–5.59 (m, 4H), 3.89 (m, 1H), 3.72 (s, 3H), 3.67–3.40 (m, 4H), 3.20 (bs, 1H), 2.55 (dd, 1H, *J*=13.8, 3.8 Hz), 2.33 (dd, 1H, *J*=13.8, 10.2 Hz), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 166.9 (s), 151.4 (s), 143.3 (s), 114.5 (d), 114.3 (d), 67.0 (t), 61.5 (d), 55.6 (q), 54.0 (t), 35.3 (s), 30.4 (t), 26.4 (q); MS (EI) (*m*/*z*, %): 276 (M^+, 18), 219 (M^+-t-Bu, 100); HRMS (EI): calcd for $C_{16}H_{24}N_2O_2$ 276.1838, found 276.1836.

3.2.30. 2-[3,3-Dimethyl-2-(*p*-tolylamino)]butyl-2-oxazoline (5v). White solid. Mp 103–5°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.88 (d, 2H, *J*=7.5 Hz), 6.48 (d, 2H, *J*=7.5 Hz), 4.00–3.90 (m, 1H), 3.67–3.40 (m, 4H), 3.30 (bs, 1H), 2.55 (dd, 1H, *J*=13.0, 3.8 Hz), 2.31 (dd, 1H, *J*=13.0, 8.1 Hz), 2.18 (s, 3H), 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 167.1 (s), 146.7 (s), 129.4 (d), 125.9 (s), 113.4 (d), 67.1 (t), 60.6 (d), 54.1 (t), 35.5 (s), 30.4 (t), 26.5 (q), 20.3 (q); MS (EI) (*m*/*z*, %): 260 (M^+, 12), 203 (M^+-t-Bu, 100); HRMS (EI): calcd for $C_{16}H_{24}N_2O$ 260.1889, found 260.1882.

3.2.31. (*anti*)-2-[1,3,3-Trimethyl-2-(*p*-tolylamino)]butyl-2-oxazoline (*anti*-5w). White solid. Mp 117–8°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.86 (d, 2H, *J*=7.5 Hz), 6.45 (d, 2H, *J*=7.5 Hz), 4.75 (bs, 1H), 4.09–3.85 (m, 2H), 3.72–3.45 (m, 3H), 2.75 (m, 1H), 2.13 (s, 3H), 1.18 (d, 3H, *J*=7.1 Hz), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 171.4 (s), 147.1 (s), 129.5 (d), 125.6 (s), 112.9 (d), 67.0 (t), 62.4 (d), 54.1 (t), 37.2 (s), 35.3 (d), 27.4 (q), 20.3 (q), 17.0 (q); MS (EI) (*m*/*z*, %): 274 (M^+, 20), 217 (M^+-t-Bu, 100); HRMS (EI): calcd for $C_{17}H_{26}N_2O$ 274.2045, found 274.2042.

3.2.32. (*syn*)-2-[1,3,3-Trimethyl-2-(*p*-tolylamino)]butyl-2-oxazoline (*syn*-5w). White solid. Mp 130–2°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 6.87 (d, 2H, *J*=7.5 Hz),

6.50 (d, 2H, J=7.5 Hz), 4.99 (bd, 1H, J=9.8 Hz), 4.20–4.03 (m, 2H), 3.85–3.67 (m, 2H), 3.08 (dd, 1H, J=9.8, 2.8 Hz), 2.96 (dd, 1H, J=7.1, 2.8 Hz), 2.12 (s, 3H), 1.06 (d, 3H, J=7.1 Hz), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 170.6 (s), 148.3 (s), 129.7 (d), 124.8 (s), 112.3 (d), 66.6 (t), 65.3 (d), 54.1 (t), 36.8 (s), 34.3 (d), 27.2 (q), 20.3 (q), 18.9 (q); MS (EI) (*m/z*, %): 274 (M^+, 12), 217 (M^+-t-Bu, 100); HRMS (EI): calcd for $C_{17}H_{26}N_2O$ 274.2045, found 274.2045.

3.3. Synthesis of *N*-benzoyl derivatives 5x–z

A solution of 4-*N*,*N*-Dimethylaminopyridine (DMAP) (catalytic amount) and Et_3N (12.0 mmol) in dichloromethane (10 mL) was added dropwise to a solution of the corresponding *N*-unsubstituted compound **5** (11.0 mmol) in dichloromethane (10 mL) at 0°C under inert atmosphere. A solution of benzoyl chloride (11 mmol) in dichloromethane (10 mL) was then added dropwise at 0°C. The reaction was allowed to reach room temperature and stirred for 5–7 h until TLC monitoring indicated complete disappearance of the starting material. Solvents were evaporated under reduced pressure to give a solid residue that was treated with 1N HCl (25 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layer was washed several times with saturated brine, dried over $MgSO_4$, and filtered. After evaporation of the solvents, a solid residue was obtained and then recrystallised with hexane–dichloromethane (3:1) to get *N*-benzoyl derivatives **5x–z** in the yields reported in Table 1.

3.3.1. 2-(2-Phenyl-2-phenylcarboxamido)ethyl-2-oxazoline (5x). White solid. Mp 134–7°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 8.18 (d, 1H, NH, J=7.7 Hz), 7.88–7.24 (m, 10H), 5.63 (m, 1H), 4.18 (t, 2H, J=8.9 Hz), 3.82 (t, 2H, J=8.9 Hz), 2.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 166.4 (s), 165.8 (s), 141.0 (s), 134.5 (s), 131.5 (d), 128.5 (d), 127.4 (d), 127.1 (d), 126.2 (d), 67.1 (d), 54.3 (t), 49.9 (t), 33.7 (t); HRMS (EI): calcd for $C_{18}H_{18}N_2O_2$ 294.1378, found 294.1368. Anal. calcd for $C_{18}H_{18}N_2O_2$: C 73.45, H 6.16, N 9.52; found: C 73.52, H 6.21, N 9.38.

3.3.2. 2-[(1*R,2*S**)-1-Methyl-2-phenyl-2-phenylcarboxamido)ethyl-2-oxazoline (*anti*-5y).** White solid. Mp 126–9°C; ^{1}H NMR ($CDCl_3$, TMS, 250 MHz) δ 8.60 (d, 1H, NH, J=8.7 Hz), 7.84–7.18 (m, 10H), 5.28 (dd, 1H, J=8.7 and 4.6 Hz), 4.10 (m, 2H), 3.75 (m, 2H), 3.01 (m), 1.28 (d, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8 (s), 167.5 (s), 142.0 (s), 135.3 (s), 129.4 (d), 129.2 (d), 129.1 (d), 128.1 (d), 128.0 (d), 127.2 (d), 67.7 (t), 56.4 (t), 55.0 (d), 39.6 (d), 18.0 (q); HRMS (EI): calcd for $C_{19}H_{20}N_2O_2$ 308.1525, found 308.1524. Anal. calcd for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; found: C 74.23, H 6.43, N 9.18.

3.3.3. 4,4-Dimethyl-2-(2-phenyl-2-phenylcarboxamido)-ethyl-2-oxazoline (5z). White solid. Mp 107–110°C; ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.01 (d, 1H, NH, J=8.0 Hz), 7.82–7.15 (m, 10H), 5.53 (m, 1H), 3.78 (s, 2H), 2.79 (d, 2H, J=5.7 Hz), 1.16 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 167.0 (s), 163.8 (s), 156.2.0 (s), 141.6 (s), 135.0 (d), 132.2 (d), 129.2 (d), 128.1 (d), 127.8 (d), 127.0 (d), 79.6 (d), 67.9 (t), 50.7 (t), 34.8 (s), 29.0 (q); HRMS (EI): calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1681. Anal. calcd for $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69; found: C 74.37, H 6.95, N 8.63.

3.3.4. One-pot synthesis of *N*-substituted *C*-protected β-amino acids 5 from Δ^2-oxazolines 1. *n*-BuLi (14.0 mmol, 2.5 M in hexanes) was added dropwise to a solution of diisopropylamine (14.0 mmol) in dry THF (10 mL) at −20°C under inert atmosphere. After 30 min the reaction was cooled down to −78°C and a THF (10 mL) solution of the corresponding 2-alkyl-Δ^2-oxazoline (14.0 mmol) was slowly added. The reaction was stirred at −78°C for 1 h, before the dropwise addition of a solution of the corresponding nitrile **2** (14.23 mmol) in dry THF (10 mL). After two hours of stirring at low temperature, a solution of the alkyl halide (14.23 mmol) in dry THF (10 mL) was added and the reaction was stirred at room temperature for 3 h. When the alkylation was not required, this step was omitted. The progress of the reaction was followed by means of TLC and when the α-alkylated intermediate **4** was observed to be the main product, excess of Na and *i*-PrOH (4 mL) were added. The reaction was again monitored by means of TLC and was completed after 3–4 h. Work-up of the reaction as described above gave *N*-substituted *C*-protected β-amino acids **5** in one-pot from Δ^2-oxazolines **1** in the yields reported in Table 1.

3.3.5. Reduction of Δ^2-thiazoline protected β-enamino acid 7a. Isopropanol (3 mL, via syringe) and Na (excess) in small portions were added sequentially under inert atmosphere to a solution of the starting material **7a** (4.1 g, 20.0 mmol) in dry THF (10 mL) at 0°C. The reaction mixture was stirred and allowed to reach room temperature. When TLC monitoring indicated complete disappearance of the starting material (2–6 h), the reaction was worked-up as described above for the reduction of Δ^2-oxazoline protected β-enaminoacids **4**. The oily residue obtained was identified as diamine thiol **8a** (58%) and was not fully characterised.

3.3.6. 6-Amino-4-aza-6-phenyl-hexanethiol (8a). Yellow oil; ^{1}H NMR ($CDCl_3$, TMS, 200 MHz) δ 7.25–7.10 (m, 5H), 3.90 (t, 2H), 2.65 (m, 1H), 2.53 (t, 2H), 1.76 (m, 2H), 1.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.2 (s), 128.3 (d), 126.8 (d), 126.0 (d), 54.7 (d), 47.6 (t), 46.8 (t), 39.1 (t), 38.5 (t).

3.4. Synthesis of *N*-unsubstituted β-amino acids 9a–d

A solution of the corresponding compound **5a–d** (2.5 mmol) in 3N HCl (50 mL) was refluxed for 2–3 h. The reaction was allowed to cool to room temperature and was extracted with diethyl ether (3×25 mL). The aqueous layer was evaporated under reduced pressure (10^{-2} mmHg) to give a white solid residue. The free β-amino acid **9** was isolated by passing the residue through a Dowex 50wx8 ion-exchange chromatography column. For this procedure, the ion exchange column was first rinsed with distilled water; an aqueous solution of the residue was then deposited on the top of the column and eluted with 1.5 M NH_4OH. Evaporation of the fractions under reduced pressure (10^{-2} mmHg) gave the corresponding free amino acid **9** as a white solid. Yields are listed in Table 2.

3.4.1. 3-Amino-3-phenylpropionic acid 9a. Mp 221–3°C

(dec.); ^{1}H NMR (D_2O, 250 MHz) δ 7.20–7.05 (m, 5H), 4.02 (t, 1H, J=7.5 Hz), 2.35 (d, 2H, J=7.6 Hz); ^{13}C NMR (D_2O, 62.8 MHz) δ 180.9 (s), 145.3 (s), 129.5 (d), 128.1 (d), 127.1 (d), 53.7 (d), 47.7 (t); HRMS (EI): calcd for $C_9H_{11}NO_2$ 165.0789, found 165.0802.

3.4.2. 3-Amino-3-(4-methylphenyl)propionic acid 9b. Mp 240–2°C (dec.); ^{1}H NMR (D_2O, 250 MHz) δ 7.09–6.99 (m, 4H), 3.99 (t, 1H, J=7.6 Hz), 2.37 (d, 2H, J=7.6 Hz), 2.09 (s, 3H); ^{13}C NMR (D_2O, 62.8 MHz) δ 181.0 (s), 142.3 (s), 138.1 (s), 130.0 (d), 127.1 (d), 53.3 (d), 47.1 (t), 20.8 (q); HRMS (EI): calcd for $C_{10}H_{13}NO_2$ 179.0946, found 179.0956. Anal. calcd for $C_{10}H_{13}NO_2$: C 67.02, H 7.31, N 7.82; found: C 67.15, H 7.23, N 7.87.

3.4.3. 3-Amino-3-(4-methoxyphenyl)propionic acid 9c. Mp 238–240°C (dec.); ^{1}H NMR (D_2O, 250 MHz) δ 7.17 (d, 2H, J=8.7 Hz), 6.81 (d, 2H, J=8.7 Hz), 4.36 (t, 1H, J=7.6 Hz), 3.61 (s, 3H), 2.56–2.64 (dq, 2H, J=11.0, 7.0 Hz); ^{13}C NMR (D_2O, 62.8 MHz) δ 177.3 (s), 159.5 (s), 128.6 (d), 114.6 (d), 55.4 (q), 52.3 (d), 40.5 (t)—a C(s) around 138 ppm was not observed; HRMS (EI): calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0897. Anal. calcd for $C_{10}H_{13}NO_3$: C 61.54, H 6.67, N 7.18; found: C 61.59, H 6.73, N 7.15.

3.4.4. (2*R,3*S**)-3-Amino-2-methyl-3-phenylpropionic acid *anti*-9d.** Mp 256–8°C (dec.); ^{1}H NMR (D_2O, 250 MHz) δ 7.20–7.05 (m, 5H), 3.59 (d, 1H, J=8.0 Hz), 2.32–2.25 (m, 1H), 0.57 (d, 3H, J=7.0 Hz); ^{13}C NMR (D_2O, 62.8 MHz) δ 185.2 (s), 143.8 (s), 129.4 (d), 128.2 (d), 59.6 (d), 51.6 (d), 16.1 (q); HRMS (EI): calcd for $C_{10}H_{14}NO_2$ (M^++1) 180.1024, found 180.1022.

3.4.5. Synthesis of *N*-substituted β-amino acids 9e–f. A solution of the corresponding compound **9e–f** (5.0 mmol) in 3N HCl (50 mL) was refluxed for 2.5 h. The reaction was allowed to cool to room temperature, neutralised with 3N NaOH, and extracted with chloroform (3×10 mL). The combined organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The free β-amino acid was purified from the residue by means of flash chromatography over silica gel, with concomitant recovery of the aminoalcohol moiety. Finally, recrystallisation in hexane–chloroform 3:1 afforded the corresponding β-amino acid.

3.4.6. 3-Phenyl-3-*N*-phenylaminopropionic acid 9e. White solid. Mp 135–6°C; ^{1}H NMR ($CDCl_3$, TMS, 200 MHz) δ 7.38–6.58 (m, 10H), 6.10–5.00 (bs, 2H), 4.85 (t, 1H, J=6.2 Hz), 2.85 (d, 2H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$, 62.8 MHz) δ 176.5 (s), 146.4 (s), 141.7 (s), 129.1 (d), 128.8 (d), 127.5 (d), 126.2 (d), 118.2 (d), 114.0 (d), 54.8 (d), 42.4 (t); HRMS (EI): calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1115.

3.4.7. 3-*N*-*p*-Methoxyphenylamino-4,4-dimethylpentanoic acid 9f. White solid. Mp 125–7°C; ^{1}H NMR (CD_3OD, TMS, 250 MHz) δ 6.70 (d, 2H, J=9.0 Hz), 6.59 (d, 2H, J=9.0 Hz), 3.66 (s, 3H), 3.50 (dd, 1H, J=8.7, 4.7 Hz), 2.56 (dd, 1H, J=15.0, 4.7 Hz), 2.27 (dd, 1H, J=15.0, 8.7 Hz), 0.87 (s, 9H); HRMS (EI): calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1517.

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