Highly Functionalized 1,2–Diamino Compounds through Reductive Amination of Amino Acid-Derived β–Keto Esters

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Introduction

Reducive amination of carbonyl compounds is one of the most useful and versatile methods for the synthesis of different kinds of amines, key intermediates in organic synthesis and in the preparation of important building blocks for drug discovery [1–3]. Reductive amination proceeds upon reaction of a carbonyl compound with ammonia, a primary amine or a secondary amine, through the formation of a carbinolamine, which normally dehydrates to form an imine or an iminium ion intermediate, followed by in situ reduction to the corresponding amine alkylated product [2]. The process could be direct, when all components and reactives are mixed without prior formation of intermediates, or indirect, with pre-formation of intermediates (imine/iminium/enamine) and reduction in separate consecutive steps [3,4].

Regarding the reduction process, the most used methods are catalytic hydrogenation and hydride agents [1–4], although some other reagents have been developed [5–7]. Reductive amination of aldehydes and ketones with primary amines are typically easy, fast, and high-yielding reactions with many examples documented in the literature [1–4]. However, difficulties have been described for some aromatic and acyclic ketones, with slower reaction rates and lower isolated yields than those found for alicyclic ketones and aldehydes [4]. The rate of reaction also depends on the steric and electronic factors of the reactant amine, and the process usually requires the addition of AcOH, the use of 5–10% excess of the amine, and a large excess of the reducing agent [3,4].

Examples of reductive amination using β-ketoesters as the carbonyl component are scarce, despite the final products, β-amino acid derivatives, have interesting synthetic and biological applications [8,9]. A few reported examples describe the reduction of simple β-enamino esters by either catalytic hydrogenation or treatment with hydrides [10–12]. Other examples report the direct or indirect reductive amination of β-keto esters with ammonium acetate, different amines or the chiral ammonia equivalent α-methylbenzylamine [13–16].

In addition, both inter- and intramolecular processes have been applied to the efficient preparation of bioactive and natural compounds of high added value [17,18]. Despite the well documented use of amino acids in the reductive amination of aldehydes (i.e. in the formation of peptide reduced bonds) [19], to the best of our knowledge, only two reports describe the application of amino acid derivatives with ketones and β-keto esters [20,21]. In close relation to these preceedents, we have previously studied the intramolecular reductive amination of Orn-derived β-keto esters (I, R₁ = (CH₂)₄NH₂ and some dippeptide analogues for the preparation of piperidine and piperazines bicyclic systems [22,23]. These compounds were used as versatile chemical intermediates for the synthesis of highly substituted dioxoperhydropyrido[1,2-c]pyrimidine and trioxoperhydropyrazino[1,2-f]pyrimidine bicyclic systems [24,25], the former successfully used as the central core of selective CCK1 receptor antagonists.

Owing to this versatility, we decided to investigate the intermolecular version of this process starting from amino acid derivatives.
acid-derived β-ketoesters. A suitable method for the reductive amination of compounds I could provide highly functionalized β,γ-diamino esters II (Figure 1), which can be seen as interesting intermediates for the generation of molecular diversity (i.e., cyclization to different heterocyclic systems can easily be envisaged). Moreover, compounds II could bear additional reactive functions at R³ (starting amino acid side-chain) and amine R⁴ substituent, thus amplifying the possibilities of additional chemical manipulation. As the use of β-ketoesters in reductive amination processes is underdeveloped, many questions remain to be answered: Could amino acid-derived β-ketoesters I be applied to such an intermolecular process? Will the initial amino acid chiral center survive under the reductive amination conditions? Can amino acids be used as the amino component to incorporate additional complexity in final compounds? To answer these queries, we now describe our attempts to synthesize compounds II, through reductive amination, and the careful examination of the stereochemical issues.

Results and Discussion

To explore the reaction between amino acid-derived β-ketoesters and amines we selected compound I, easily prepared from Z-Phe-OH following a previously described method from our lab [26]. Two primary amines (BnNH₂ and n-BuNH₂) and two α-amino esters (H-Ala-O-Bu and H-Gly-O-Bu) were chosen as amines for the reductive amination (Figure 2). H-Ala-O-Bu was selected for the initial exploratory study, since it could be the most demanding amino component. It is chiral, sterically congested due to α-substitution, and the lower pKa of its amino group (calculated pKa = 7.82) should normally imply a weaker nucleophilic character, and hence a lower reactivity than simple alkyl/benzyl amines (n-BuNH₂, pKa = 10.87; BnNH₂, pKa = 9.33).

Starting from I and H-Ala-O-Bu, we first investigated a battery of different conditions described for the reductive amination of ketones and β-keto esters, both using direct and indirect protocols. Direct reductive amination assays (Ti(OiPr)₄ or AcOH as additive and NaBH₄CN or NaBH(OAc)₃ as reducing agent failed, recovering the starting β-keto ester or leading to alcohols 2a,b in different yield and diastereomeric ratio (Table S1, supporting information). Probably, the low reactivity of both carbonyl and amino species could take account for the disappointing results and, in fact, the diamino derivatives 3 were only detected, although in low yield, in the direct reaction at 50°C with AcOH/NaBH₄CN. Using indirect procedures, first the reaction was allowed to stand at room temperature or at 50°C for the formation of the imine/enamine intermediates (completion monitored by tlc), in the presence of different additives commonly used in reductive aminations [Ti(OiPr)₄, AcOH, CAN, IaCl₃, ZnCl₂] [20,27 – 30]. Then, NaBH₄CN, NaBH(OAc)₃, NaBH₄, or H₂/Pd-C were considered for the reduction of formed intermediates (Table S2, supporting information). The results of the two-step methods were more satisfactory, especially for the combination of AcOH and NaBH₄CN, although the process required long reaction times, both for the intermediate formation and for the reduction step. Under the best conditions, (1. AcOH (1 equiv), CHCl₃, 50°C; 2. NaBH₄CN), the reaction of I and H-Ala-O-Bu afforded three diastereomeric compounds 3 (crude HPLC a,b,c ratio, 10:13:17), which were chromatographically separated and their configuration established as indicated later on. Although it has been pointed out that the reductive amination of α-substituted β-keto esters apparently occurs with control of the stereochemistry at both α and β-positions [4], the formation of the 4R-configured isomer 3c indicates that the stereochemical integrity at γ-position of the starting β-keto ester I was partially lost during the process. The reaction between I and H-Ala-O-Bu in the presence of Ti(OiPr)₄, followed by reduction with a mixture of NaBH(OAc)₃ and NaBH₄CN, afforded low yield of diastereoisomers 3a and 3b, along with alcohols 2a,b as major products. In this case, the lack of 3c suggests that most probably the intermediate species for reduction are hemiaminal titinate derivatives and not imine/enamine species [27]. In fact, the imine/enamine intermediates were detected by HPLC-MS in the Ti(OiPr)₄-promoted reactions in MeOH but not in the experiments performed in aprotic solvents (dichloromethane and dichloroethane, Table S2). Unfortunately, an attempt to optimize this Ti(OiPr)₄-mediated process, which included heating the mixture of the ketoester and the amine in neat Ti(OiPr)₄ (no solvent), was unsuccessful (Table S2, entry 8). The assay to reduce the preformed imine/enamine intermediates in the presence of a heterogeneous hydrogenation catalyst (Pd-C, 50°C, 45 psi), a method that have worked very well for other substrates [23,31], was also unproductive in this case, resulting in the partial reversion to the initial β-ketoester (Table S2, entry 17).

Application of the AcOH/NaBH₄CN optimized conditions to the reaction of I with H-Gly-O-Bu resulted in an approximately 1:1 mixture of the expected diastereoisomers 4a and 4b (Figure 2, Table 1). Almost equimolecular mixtures of 3S,4S and 3R,4S diastereoisomers were also formed in the reaction with benzyl and butyl amines, although the total yield of the corresponding compounds 5a,b and 6a,b were slightly lower than those obtained with amino acids. Taking into account the higher pKa of these amines in relation to amino esters, this result seems to suggest that the amino acid-derived β-keto ester is the principal responsible of the low reactivity found. We might speculate that the existence of the ZNH group at the γ-position, neighboring to the reactive carbonyl, hampers the attack of the amine component. Finally, according to chiral HPLC experiments, compounds 4–6 were obtained as racemic mixtures, while a 70:30 ratio of enantiomers was observed for Ala derivatives 3a–c (Figures S1 and S2).

To provide some insight into the mechanism of the two-step reductive amination process, we follow first the formation of reaction intermediates by ¹H NMR. The reaction of I and H-Gly-O-Bu in CDCl₃ and AcOH (1 equiv) gave a mixture of E and Z enamines B1 and B2 in a 3:4 ratio, as deduced from the singlet

![Figure 1. Intermolecular reductive amination of amino acid-derived β-ketoesters.](doi:10.1371/journal.pone.0053231.g001)
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Figure 2. Synthetic procedure for β,γ-diamino esters by reductive amination of Phe-derived β-ketoester 1.
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signals at 4.68 and 4.45 ppm, respectively [29] (Figure S3). However the spectrum of the crude reaction with H-Ala-O'Bu showed four signals of enamine proton (at 4.68, 4.62, 4.56 and 4.52 ppm, relative ratio 5:8:9:11), which were supposed to be two E- (B1 and B1') and two Z-isomers (B2 and B2'), having 4S and 4R-configuration. From this result, we reasoned that the initially formed imines A should isomerize to the most stable conjugated enamines B, and that enamines C should also be present in the equilibrium and could be responsible for the stereochemical integrity loss (Figure 3). The observed epimerization at the 1'-position of final diamino esters indicated that conjugated-imines D must also be present among the possible intermediates of the reaction. While the imine-enamine tautomerism (A → B and/or A → C) was expected to occur in some extent, as previously reported for intramolecular processes [24,32], the A → D interconversion was unanticipated, since the chiral integrity of the amino acid derivative acting as the amino component is normally preserved in reductive amination reactions of α-amino esters with aldehydes, α-aminoaaldoxyde and even ketones [33–36].

When the intermediates formed between 1 and H-Ala-O'Bu or H-Gly-O'Bu were reduced with NaBD₃CN the measured incorporation of deuterium (Table 2) corroborated the presence of intermediates B, C and D, although imines A are predominantly reduced by the hydride, as deduced from the high percentage of deuterium found at position 3 (Figures S4 and S5). The formation of all possible intermediates could be favored by the temperature and long times needed in the first step, due to the low reactivity of the starting materials, and to the slow speed of reduction in the second. Here, the more stable conjugated enamines B are reduced in low extent, but the transitory short-life imine A is the main intermediate trapped by the hydride.

In the ¹H NMR spectra, compounds 3a, 3c and 4a showed a small value of the 3,4 coupling constant (0–2.9 Hz), indicating a preferred conformation in which the 3 and 4 protons form a dihedral angle close to 90°, while for isomers b this J value is higher (~6.2 Hz). Although simple Chem3D calculation suggested a threo disposition for isomers a and c and erythro for b, this data did not afford any conclusive experimental information about the configuration at C3 and C4 chiral centers. The configurational assignment was done in an indirect way through the formation of pyrrolidinone derivatives. To this end, compounds 3 and 4 were deprotected at the 4-NH group and cyclized to the corresponding five-membered heterocycles 7 and 8, respectively (Figure 4). These cyclic compounds can illustrate one example of the application of the described diamino esters in the creation of diverse heterocyclic scaffolds of interest. Related pyrrolidinone derivatives, having an unsubstituted 4-amino group, have been prepared through the Zinc-mediated homologation of α-aminonitriles and subsequent acidic hydrolysis [37]. The J₄,₅ in derivatives 7a, 7c and 8a (~6.5 Hz) was higher than in their corresponding distereoisomers 7b and 8b (~4.5 ppm). Knowing that in this type of heterocyclic system the coupling constant are J₃₄,J₃₅< J₃₅,J₄₅ [38], we can anticipate the syn- and anti-relative stereochemistry for isomers a (c) and b, respectively. Similarly, NOE experiments indicated a syn-relationship between H4 and H5 protons in 7a, 7c and 8a and an anti-disposition in the respective isomers b. The exclusive formation of isomers 3a and 3b in a Ti(OiPr)₄ experiment, which probably occurs through titanate intermediates, allowed to distinguish between 3a and 3c syn-diastereoisomers. 4,5-Syn- and 4,5-anti-pyrrolidinones showed a different pattern of chemical shifts in ¹³C-NMR, with C-4, C-5, and especially 5-CH₂ carbons notoriously shielded for syn-isomers a and c (~55, 59, and 36 ppm) [39] with respect to their corresponding anti analogues b (57.5, 62, and 41 ppm). Just the opposite behavior was observed for the C-5 carbon in the linear precursors 3 and 4, for which the most shielded signal corresponds to the threo-isomers b (~37 ppm for threo, and ~39 ppm for erythro). A comparison of these values with

Table 1. Result of the reductive amination of Phe-derived β-ketoester 1.

| Final Compd. | Diastereoisomer (%)a |
|--------------|----------------------|
|              | a   | b   | c   |
| 3            | 18  | 20  | 30  |
| 4            | 33  | 34  | −   |
| 5            | 16  | 19  | −   |
| 6            | 23  | 27  | −   |

*Yield of isolated compounds.
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those of J, between distereoisomers a and b in compounds 5 and 6 allowed us the stereochemical assignment of these compounds.

Fortunately, we succeed in getting crystal structures of a couple of the pyrrolidinone derivatives, 7a and 7b, corroborating the syn and anti disposition between substituents at 4 and 5 positions in these compound, and hence the previous assignment performed by NMR (Figures 5 and 6). Structures have been deposited at the Cambridge Crystallographic Data Centre, CCDC number: 880360 (7a) and 877464 (7b). Despite the 70:30 enantiomeric mixture observed in chiral HPLC of these compounds, each crystal contains a racemic 1:1 mixture of enantiomers. For 7a, these enantiomers, related by a pseudocenter of symmetry [40], are forming dimers through N101-H101…O201 and N201-H201…O101 hydrogen bonds. Strong chains are created via a number of CH…p and CH…O = C contacts (C104-H104…Cen2, C103-H103…Cen2, C204-H204…Cen1, C203-H203…Cen1, C105-H105…O101, C205-H205…O201). These chains form (001) layers through CH…p interactions and the 3D structure is build up through CH…O weak interactions (C10-H10a…O1 and C13-H132…O1). The crystal is formed by the union of these sheets through CH…π (C12-H12A…CenPh) contacts (Figure S7).

Figure 3. Reaction Intermediates. Possible intermediates in the reductive amination of 1 with H-Gly-O’tBu (R1 = H) or H-Ala-O’tBu (R1 = Me). For clarity, only 4S and 1’5 isomers are depicted (A–D), but 4R and 1’R containing intermediates (A’–D’) are also possible if all the indicated species are present in equilibrium.

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Table 2. Incorporation of deuterium in the reduction with NaBD3CN.

| Final Compd. | %D* |
|--------------|-----|
|              | H2  | H3  | H4  | H1’ |
| 3a           | 11  | 90  | 5   | 4   |
| 3b           | 5   | 90  | 3   | 6   |
| 3c           | 10  | >90 | 5   | 3   |
| 4a           | 4   | >90 | 4   | 5   |
| 4b           | 3   | >90 | 3   | 5.5 |

*Measured by 1H NMR (d1 = 10) in CDCl3 at 25 °C. Reduction of imines A: incorporation of D at H3; Enamines B: D at H2, H3; Enamines C: D at H3, H4; Imines D: D at H1’.

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Conclusions

In summary, we describe a procedure for the preparation of $\beta,\gamma$-diamino esters from reaction of amino acid-derived $\beta$-ketoesters with both simple amines as well as $\alpha$-amino esters. To the best of our knowledge, this represents the first reductive amination protocol ever described using amino acid-derived $\beta$-ketoesters. This requires a first step of formation of intermediates with AcOH, and the subsequent reduction with NaBH$_3$CN. In this method, the diastero- and enantioselectivities were compromised by the existence of different imine-enamine equilibria, as demonstrated by $^1$H NMR and deuteration experiments. These equilibria are favored by the long reaction times required, probably derived from the low reactivity of the hindered carbonyl component. The separated diastereoisomeric $\beta,\gamma$-diamino esters can be transformed into the corresponding pyrrolidinone derivatives by cyclization between the 4-amino and the 1-carboxylate groups. These pyrrolidinones serve as reliable clue in the configurational assignment (NMR, X-ray) of the linear precursors, and represent a first example of the potential of the described diamino esters for the preparation of different heterocycles.

Materials and Methods

All reagents were of commercial quality. Solvents were dried and purified according to standard methods. Flash chromatography was performed on silica gel 60 (230–400 mesh). NMR spectra were recorded on spectrometers operating at 300 and 75 MHz for $^1$H and $^{13}$C, respectively, using TMS as internal standard (Figure S8). Chemical shifts are given in ppm and $J$ values in Hz. The C attributions are supported by HSQC experiments. Electrospray mass spectra (positive mode) were also recorded. Analytical HPLC were performed on a Eclipse Plus C$_{18}$ (5 $\mu$m, 4.6×150 mm) column using a UV detector at 220 nm. Mixtures of CH$_3$CN (0.05% TFA, solvent A) and H$_2$O (solvent B) were used in the mobile phase, and the corresponding mixture was specified in each

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Synthetic procedure for 4,5-disubstituted 2-pyrrolidinones from $\beta,\gamma$-diamino ester derivatives.
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![Figure 5](https://example.com/figure5.png)

**Figure 5.** X-Ray molecular structure of 2-pyrrolidinone derivative 4R*,5R*–7a.
Atom labeling for molecule 1 or 2 can be obtained by adding 100 or 200 respectively to the label of the atom shown in this figure, i.e. O1 is labelled O101 in molecule 1 and O201 in molecule 2. Thermal ellipsoids are drawn at 50% probability level of non-H atoms, and the H atoms are denoted as spheres of 0.1 Å radius.
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![Figure 6](https://example.com/figure6.png)

**Figure 6.** X-Ray molecular structure of 2-pyrrolidinone derivative 4R*,5S*–7b showing the atomic numbering scheme.
Thermal ellipsoids are drawn at 50% probability level of non-H atoms, and the H atoms are denoted as spheres of 0.1 Å radius.
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case (flow rate 1 mL/min). HPLC-MS was performed in a X-Bridge C18 (3.5 μm, 2.1 × 100 mm) column, eluent CH3CN (0.06% formic acid, solvent A) and H2O (0.1% formic acid, solvent B); flow rate 0.5 mL/min. Chiral HPLC was performed on a Chiralpak IA column (0.4 × 25 cm) using the mixtures of solvents indicated in each case (isocratic conditions). β-Ketoester 1 was prepared as previously described [41,42].

General Procedure for the Reductive Amination

Method A (One step-procedure). To a stirred solution of β-ketoester 1 (57 mg, 0.15 mmol) in the appropriate solvent (2 mL), H-Ala-OBu (0.30 mmol), TEA (41 μL, 0.30 mmol) the corresponding additive (0.5–2 equiv.) and the reducing agent (20 mg, 0.30 mmol) were added. The mixture was stirred at room temperature or 50 °C for 1–3 days. After evaporation, the residue was dissolved in EtOAc and washed with 10% NaHCO3 and brine, dried over Na2SO4 and concentrated in vacuum. The resulting residue was purified by HPLC-MS (Table S1), and in one case purified on a silica gel column using hexane:EtOAc 4:1 to characterize alcohol derivatives 2.

(3R,4S)-Methyl 4-(benzoylcarbonyl)amino-3-hydroxy-5-phenylpentanoate (2a)

HPLC tR = 10.78 min (X-Bridge, gradient 20–100 A in 15 min.). 1H NMR (CDCl3) δ: 7.44–7.74 (m, 10H, Ar), 5.22 (bd, 1H, J = 7.4, NH Z), 5.11 and 5.06 (d, 1H, J = 12.4 Hz, CH2 Z), 4.01 (bd, 1H, J = 7.9, 3-H), 3.82 (q, 1H, J = 7.9, 4-H), 3.67 (s, 3H, OCH3), 3.42 (bs, 1H, OH), 2.94 (bd, 2H, J = 7.6, 2-H), 2.59 (dd, 1H, J = 16.9, 10.2, 5-H), 2.39 (bd, 1H, J = 16.9, 2.3, 5-H). 13C NMR (CDCl3) δ: 173.8 (CO2), 156.3 (CO Z), 137.9, 136.5 (C Ar), 129.4, 128.9, 128.3, 128.1, 127.9, 126.5 (CH Ar), 66.9 (C-3), 66.8 (CH2 Z), 55.9 (4-C), 51.9 (OCH3), 38.6 (2-C), 38.3 (5-C). [α]D = +12.5 (c 0.8, MeOH).

(3S,4S)-Methyl 4-(benzoylcarbonyl)amino-3-hydroxy-5-phenylpentanoate (2b)

Mp: 123–126 °C. HPLC tR = 10.5 min (X-Bridge, gradient 20–100 A in 15 min.). 1H NMR (CDCl3) δ: 7.46–7.10 (m, 10H, Ar), 5.02 (s, 2H, CH2 Z) 4.82 (m, 1H, NH Z), 4.03 (m, 1H, 3-H), 3.95 (m, 1H, 4-H), 3.71 (s, 3H, OCH3), 3.48 (bs, 1H, OH), 3.00 (dd, 1H, J = 14.1, 4.5, 5.1), 2.86 (bd, 1H, J = 5.1), 2.68 (bd, 1H, J = 5.1), 2.50 (dd, 1H, J = 16.6, 3.5, 2-H), 2.52 (dd, 1H, J = 16.6, 8.6, 2-H). 13C NMR (CDCl3) δ: 172.3 (CO2), 156.1 (CO Z), 137.3, 136.3 (C Ar), 129.4, 128.9, 128.4, 128.0, 127.9, 126.5 (CH Ar), 69.9 (3-C), 66.7 (CH2 Z), 55.8 (4-C), 51.9 (OCH3), 38.0 (5-C), 35.6 (2-C). [α]D = –40.0 (c 0.5, MeOH).

Method B (Two step-procedure, ACOH). To a stirred solution of β-ketoester 1 (0.57 g, 1.6 mmol) in CHCl3 (10 mL), the corresponding amine (4.8 mmol) and ACOH (91 μL, 1.6 mmol) were added. The mixture was stirred at 50 °C until the total formation of imine/enamine intermediates was observed. Then, NaBH4·CN (0.2 g, 3.2 mmol) was added, and the mixture was stirred at room temperature until complete reduction of the imine/enamine intermediates. After evaporation, the residue was dissolved in EtOAc and washed with 10% NaHCO3 and brine, dried over Na2SO4 and concentrated in vacuum. The resulting residue was purified on a silica gel column using the solvent system indicated in each case.

Method C (Two step-procedure, Ti(OiPr)4). To a stirred solution of β-ketoester 1 (0.1 g, 0.28 mmol) in CH2Cl2 (3 mL), was added a solution of H-Ala-OBu·HCl (0.218 mmol) and TEA (0.218 mmol) in CH2Cl2 (3 mL). The mixture was stirred at room temperature overnight. Then the reaction was cooled to 0 °C and NaBH4·CN (0.363 mmol) and NaBH(OAc)2 (0.363 mmol) were added. The reaction was stirred overnight. After evaporation, the residue was dissolved in EtOAc and washed with H2O and brine, dried over Na2SO4 and concentrated in vacuum. The resulting residue was purified on a silica gel column using EtOAc:hexane (1:8 to 1:4) as eluents. Alcohols 2a (47.3 mg) and 2b (27.5 mg) were isolated along with compounds 3a (8.8 mg) and 3b (5.6 mg).

Methyl 1-(4-benzoylcarbonyl)amino-3-[[tert-butoxycarbonyl]ethyl-1-yl]amino-5-phenylpentanoate (3a)

Diastereomer 3a (3S*,4S*,1'R*): (CH3)2C=Et2H,3Ox,

Method C (Two step-procedure, Ti(OiPr)4). To a stirred solution of β-ketoester 1 (0.1 g, 0.28 mmol) in CH2Cl2 (3 mL), was added a solution of H-Ala-OBu·HCl (0.218 mmol) and TEA (0.218 mmol) in CH2Cl2 (3 mL). The mixture was stirred at room temperature overnight. Then the reaction was cooled to 0 °C and NaBH4·CN (0.363 mmol) and NaBH(OAc)2 (0.363 mmol) were added. The reaction was stirred overnight. After evaporation, the residue was dissolved in EtOAc and washed with H2O and brine, dried over Na2SO4 and concentrated in vacuum. The resulting residue was purified on a silica gel column using EtOAc:hexane (1:8 to 1:4) as eluents. Alcohols 2a (47.3 mg) and 2b (27.5 mg) were isolated along with compounds 3a (8.8 mg) and 3b (5.6 mg).
**Diastereomer 4b (3R*,4S*).** (CH32Et2O:hexahexane, 1:1:1): Yield: 27% (syn). HPLC 4f = 7.72 min (20 to 100% A in 20 min).

**Diastereomer 6b (3R*,4S*).** (CH32Et2O:hexahexane, 1:1:1): Yield: 27% (syn). HPLC 4f = 7.72 min (20 to 100% A in 20 min).
(4S*,5S*,1'R*,5'R*)-5-Benzy1-4-[(1'R*-tert-butyloxy carbonyl)methyl]amino-2-pyridolineinone (7c)

Eluent: CH2Cl2:MeOH (50:1). 48% (oil). HPLC tR = 6.28 min (20 to 100% A in 20 min). 1H NMR (CDCl3) δ 7.27-7.11 (m, 5H, H Ar), 3.58 (bs, 1H, 1-NH), 3.81 (dd, dddd, 1H, J = 11.1, 6.6, 3.4, 0.8 Hz, 5-H), 3.56 (m, 1H, J = 8.4, 7.5, 6.6 Hz, 4-H), 3.28 (bs, 2H, CH2 G1, G2), 2.94 (dd, 1H, J = 13.5, 3.5 Hz, 5-CH2), 2.56 (dd, 1H, J = 13.5, 11.1 Hz, 5-CH2), 2.45 (dd, 1H, J = 16.5, 7.5 Hz, 3-H), 2.25 (dd, 1H, J = 16.4, 8.3 Hz, 5-H), 1.77 (bs, 1H, 4-NH), 1.42 (s, 9H, CH3 Bu). 13C NMR (CDCl3) δ: 174.8, 171.1 (CO), 137.7, 129.1, 128.9, 126.8 (C and H Ar), 81.3 (C Bu), 58.7 (5-C), 56.3 (4-C), 50.0 (CH2 G1, G2), 36.4 (3-C), 36.2 (5-CH2), 28.1 (CH3 Bu). MS: 305.4 [M+1]+. Anal. cal. for C21H23N2O3: C 67.08, H 7.95, N 9.20, found C 66.88, H 8.08, N 8.97.

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Conceived and designed the experiments: RGM AFM. Performed the experiments: PFF MTGL LI. Analyzed the data: RGM JMG AFM LI. Contributed reagents/materials/analysis tools: RGM MTGL JMGR. Wrote the paper: RGM AFM LI.
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