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# Norstatines from Aldehydes by Sequential Organocatalytic α-Amination and Passerini Reaction

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**Keywords:** Asymmetric synthesis / Asymmetric catalysis / Organocatalysis / Passerini reaction / Proline / β-Secretase / Alzheimer's disease

The combination of the enantioselective, organocatalytic α-amination of aldehydes by diazodicarboxylates and the Passerini reaction provides rapid access to norstatine-based peptidomimetics. These intermediates were elaborated further by deprotection and cleavage of the N–N bond to provide useful building blocks for aspartic protease inhibitors. Coupling of the compounds **76**–**86** with the mono-isophthalamide **91** provided moderate inhibitors of human β-secretase (BACE) **92**–**102**.



## Introduction

Alzheimer's disease (AD) is a progressive, irreversible brain disorder with neither a definitely assigned cause nor an available causal therapy. One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques between nerve cells (neurons) in the brain.[1] β-Amyloid (Aβ) peptide, the major constituent of amyloid plaques, is believed to play a central role in the neuropathology of AD. Aβ is generated from the amyloid precursor protein (APP) by two proteases, β-secretase (BACE) and γ-secretase. BACE has been identified and validated as an aspartic protease.[2] and BACE inhibition is currently perceived as a promising target for the treatment of AD.[3–4]

The X-ray structure of BACE and the structure-activity relationship (SAR) of transition-state-like inhibitors[5] facilitate the design of hydroxyethylene- and norstatine-based scaffolds. Unfortunately, 80% of all aspartic proteases accept phenylalanine at the P1 pocket of the enzyme, thus, selectivity has to derive from either the flanking amino acids or non-natural phenylalanine derivatives. Such non-natural phenylalanines may be presented as norstatine or as hydroxyethylene isosteres. *S*-α-Amino aldehydes are common intermediates for the synthesis of such transition state mimetics and are thus extremely versatile building blocks.

We herein report the enantioselective synthesis of non-natural amino acid derivatives, their elaboration to the targeted norstatines derivatives and their activity as BACE inhibitors. The norstatine derivative **1a** was identified as a lead structure for BACE inhibition in a fluorescence resonance energy transfer (FRET) assay ($IC_{50}$ = 20 μM, Scheme 1) with isolated BACE.[6] The first synthetic approach utilized L-phenylalaninol and provided both hydroxy diastereomers **1a** and **1b** in a 1:1 ratio. These diastereomers were isolated and tested separately, but the relative stereochemistry of the hydroxy group was not established. The compound assigned as **1b** displayed much weaker inhibition ($IC_{50}$ >200 μM). This result stimulated the two-step synthesis of further norstatine intermediates (Scheme 2). Preferentially, high enantioselectivity in the α-amination should be accompanied by low diastereoselectivity in the Passerini reaction to allow simultaneous profiling of diastereomeric mixtures, thereby minimizing efforts towards inactive compounds. An edge-on-face stacking of the S1-phenylalanine on the tyrosyl residue in the active site was observed for the similar Astex inhibitor **2**[7] (Scheme 1 and Figure 1), which was identified in a high-throughput crystallisation screen. This compound displays similar activity toward BACE as the Elan compound **3** but adopts an unpredicted orientation for the benzylamine. The phenylalanine-binding P1 pocket suggested electron-deficient peptidomimetics for this position. The next steps in the variation of the lead structure **1a** ($IC_{50}$ = 20 μM) are depicted in Scheme 6 (Table 3, Entry 11). This compound acknowledges the SAR of the Elan inhibitors,[8] which feature a difluorophenylalanine moiety for P1. The trifluoromethyl group was introduced to interact with the polar P2′ pocket. These pockets can be occupied by carboxylic acids, but the resulting diacids display low membrane penetration, and thus, only moderate inhibition in cellular assays.[9]

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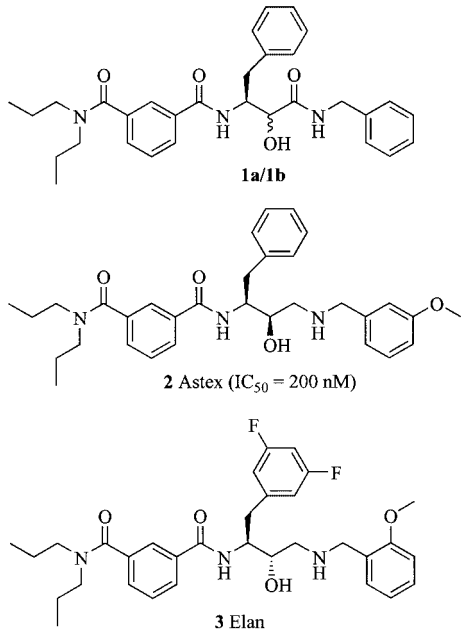
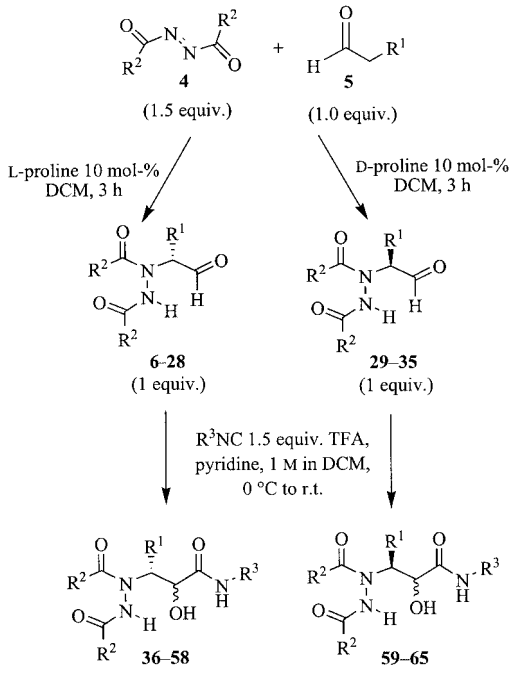



Scheme 1. **1a/1b**, **2** (from Astex) and **3** (from Elan).




Scheme 2. Two-step synthesis of norstatine intermediates.

A plethora of procedures is known for the asymmetric, catalytic synthesis of optically active amino acids.[10] Several stereoselective transformations are based on the robust and inexpensive proline[11] catalysts. The organocatalytic, enantioselective, direct C–N bond formation with aldehydes and a nitrogen source, such as azodicarboxylates, constitutes one of the simplest procedures for the construction of a stereogenic carbon centre attached to a nitrogen atom (Scheme 2). The direct introduction of a nitrogen or an oxygen atom adjacent to a carbonyl group in a catalytic, enantioselective manner using both chiral Lewis-acid and Lewis-base catalysis has been reported recently.[12] The α-amination of aldehydes and ketones was pioneered by B. List[13] and K.A. Jørgensen.[14] It offers the potential to obtain the desired diversity (Scheme 2) in multiparallel reactions. A very important aspect of the direct α-amination reaction is the easy access to optically active nonproteogenic α-amino acids it provides. The homologous α-hydroxy-β-amino amides are found in numerous pharmaceuticals and natural products with potent biological activity.[15]

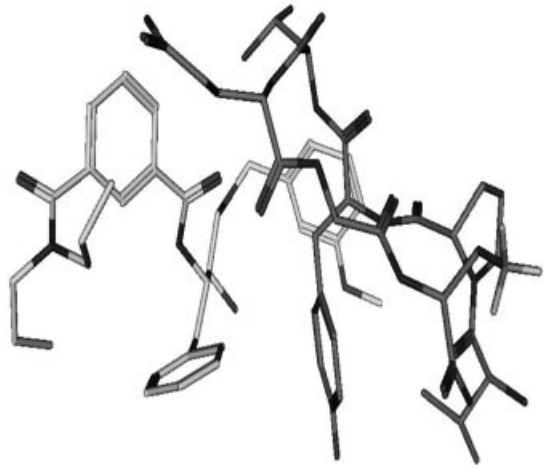


Figure 1. An edge-on-face stacking of the S1-phenylalanine on the tyrosyl residue in the active site was observed for the Astex inhibitor (PDB: 1W51, 1TQF); software: Molecular Operating Environment, MOE, 2004.10.

## Results and Discussion

The aldehydes were treated with azodicarboxylates and 10 mol-% of D- or L-proline at room temperature under ambient conditions in $CH_2Cl_2$ (Scheme 2), and the α-aminated products **6**–**35** were formed in 70–93% yield (Table 1). Even the notorious phenyl acetaldehyde reacted in moderate yields, if freshly distilled. The isolation of the α-aminated product was remarkably easy; the reaction mixture was filtered through a Solid Phase Extraction (SPE) C18 column with $CH_2Cl_2$ and acetonitrile. The solvent and the excess aldehyde were removed in vacuo to provide the pure α-aminated products **6**–**35**. When complete removal of the aldehyde was not possible in vacuo, the azodicarboxylates were reacted at a stoichiometry of 1.5 to 1 versus the aldehydes. Excess azodicarboxylate was scavenged by polystyrene-supported Trisamine (PS-Trisamine) after complete conversion of the aldehyde. The L-proline displays poor solubility in $CH_2Cl_2$ and is easily separated or recovered. This poor solubility of amino acids in polar solvents may lead to chiral amplification.[16] Reactions run in acetonitrile, where proline is readily soluble, were much faster, but catalyst removal required elaborate work up. The catalyst removal is important, as it will undergo an Ugi reaction in the following sequence and will eventually contaminate the desired product.

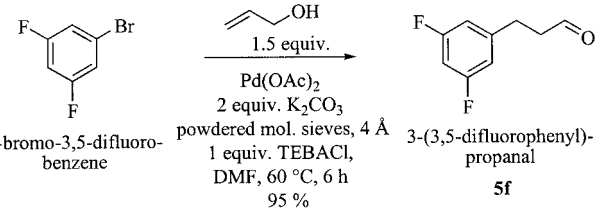
  

Table 1. Two-step enantioselective amination and Passerini reaction of aldehydes.

| Entry | $R^1$ | Aldehyde | $R^2$ | $R^3$ | Product | Yield [%][a] | *dr* [%][b] | Catalyst |
|---|---|---|---|---|---|---|---|---|
| 1 | Me | **5a** | *t*BuO | *c*Hex | **36a,b** | 88 | 80:20 | L-*proline* |
| 2 | Me | **5a** | *t*BuO | 2-morpholinoethyl | **37a,b** | 90 | 80:20 | L-*proline* |
| 3 | Me | **5a** | *i*PrO | *c*Hex | **38a,b** | 70 | 40:60 | L-*proline* |
| 4 | Me | **5a** | *i*PrO | 2-morpholinoethyl | **39a,b** | 50 | 80:20 | L-*proline* |
| 5 | Me | **5a** | morpholino | 2-morpholinoethyl | **40a,b** | 36 | 80:20 | L-*proline* |
| 6 | Et | **5b** | *t*BuO | *c*Hex | **41a,b** | 80 | 80:20 | L-*proline* |
| 7 | Et | **5b** | *t*BuO | 2-morpholinoethyl | **42a,b** | 97 | 80:20 | L-*proline* |
| 8 | Et | **5b** | *i*PrO | 2-morpholinoethyl | **43a,b** | 73 | 60:40 | L-*proline* |
| 9 | Et | **5b** | *i*PrO | *c*Hex | **44a,b** | 97 | 80:20 | L-*proline* |
| 10 | Et | **5b** | morpholino | 2-morpholinoethyl | **45a,b** | 60 | 60:40 | L-*proline* |
| 11 | *i*Pr | **5c** | *t*BuO | *c*Hex | **46a,b** | 81 | 80:20 | L-*proline* |
| 12 | *i*Pr | **5c** | *t*BuO | 2-morpholinoethyl | **47a,b** | 78 | 70:30 | L-*proline* |
| 13 | *i*Pr | **5c** | *i*PrO | *c*Hex | **48a,b** | 70 | 40:60 | L-*proline* |
| 14 | *i*Pr | **5c** | *i*PrO | 2-morpholinoethyl | **49a,b** | 72 | 60:40 | L-*proline* |
| 15 | *i*Pr | **5c** | morpholino | 2-morpholinoethyl | **50** | 20 | – | L-*proline* |
| 16 | Ph | **5d** | *t*BuO | *c*Hex | **51a,b** | 98 | 80:20 | L-*proline* |
| 17 | Ph | **5d** | *t*BuO | 2-morpholinoethyl | **52a,b** | 72 | 80:20 | L-*proline* |
| 18 | Ph | **5d** | *i*PrO | *c*Hex | **53a,b** | 78 | 90:10 | L-*proline* |
| 19 | Ph | **5d** | *i*PrO | 2-morpholinoethyl | **54a,b** | 80 | 90:10 | L-*proline* |
| 20 | Ph | **5d** | morpholino | 2-morpholinoethyl | **55** | 30 | – | L-*proline* |
| 21 | Bn | **5e** | *t*BuO | *c*Hex | **56a,b** | 61 | 80:20 | L-*proline* |
| 22 | Bn | **5e** | *t*BuO | Bn | **57a,b** | 86 | 50:50 | L-*proline* |
| 23 | 3,5-difluorobenzyl | **5f** | *t*BuO | Bn | **58a,b** | 86 | 80:20 | L-*proline* |
| 24 | methyl | **5a** | *t*BuO | Bn | **59a,b** | 86 | 50:50 | D-*proline* |
| 25 | ethyl | **5b** | *t*BuO | Bn | **60a,b** | 91 | 60:40 | D-*proline* |
| 26 | *i*Pr | **5c** | *t*BuO | Bn | **61a,b** | 97 | 50:50 | D-*proline* |
| 27 | Ph | **5d** | *t*BuO | *c*Hex | **62a,b** | 93 | 80:20 | D-*proline* |
| 28 | Ph | **5d** | *t*BuO | Bn | **63a,b** | 93 | 50:50 | D-*proline* |
| 29 | Bn | **5e** | *t*BuO | Bn | **64a,b** | 86 | 80:20 | D-*proline* |
| 30 | 3,5-difluorobenzyl | **5f** | BnO | Bn | **65a,b** | 86 | 80:20 | D-*proline* |

[a] Isolated yield of diastereomeric mixtures of **36**–**65**. [b] The diastereomeric ratio (*dr*) was determined by $^1$H NMR spectroscopic analysis of the crude product.

The 3-(3,5-difluorophenyl)propanal **5f** was obtained by the Heck reaction of 1-bromo-3,5-difluorobenzene (Scheme 3) and allyl alcohol with palladium acetate. It was reacted further with dibenzyl azodicarboxylate in the presence of D-proline (10 mol-%) to provide the bis-*N*-Cbz-protected difluorophenylalaninal analogue **35** in 86% yield (Table 1).




Scheme 3. Synthesis of 3-(3,5-difluorophenyl)propanal (**5f**).

The enantiomeric purity of the α-aminated aldehydes is known to decrease upon storage, extended reaction times or isolation on acidic media. This problem was avoided by the rapid conversion of the α-aminated aldehydes in Passerini reactions, which are powerful, economical, multiple-component reactions[17] (MCR). The reaction of the protected α-amino aldehydes **6**–**35**, isonitriles, trifluoroacetic acid and pyridine[18] lead directly to the diverse α-hydroxy-β-amino amides **36**–**65** in moderate to excellent yields, usually with no or very little diastereoselectivity (Scheme 2, Table 1. The descriptors **a** and **b** relate to the polarity in chromatography, they do not assign stereochemistry. Compound **a** is less polar than compound **b**). The reactions proceeded under mild, nearly neutral conditions, typically between 0 °C and ambient temperature, through a trifluoroacetoxy intermediate,[19] which underwent hydrolysis upon extractive workup with saturated aqueous sodium hydrogen carbonate. $CH_2Cl_2$ was the solvent of choice; it was superior to acetonitrile and tetrahydrofuran in reaction rate and yield. The diastereomeric ratios of the hydroxyamides were observed in the range of 1:1 to 1:4 by NMR and HPLC analysis. The diastereoselectivities observed were very similar to those reported for the Passerini reaction by Zhu et al.; there was no racemisation of the aldehyde during the Passerini reaction, as determined by chiral HPLC analysis.[20] $^1$H NMR investigation of compounds **38a**, **38b**, **48a** and **48b** with the chiral shift reagent Eu(tfc)$_3$ did not reveal any significant racemisation.

### Relative Configuration of 48a and 48b

The compound **48b** derived from the enantioselective L-proline-catalyzed amination and the subsequent unselective Passerini reaction in the same yield as the less polar **48a**. **48b** crystallized readily from MeOH/DMF/$H_2O$ (10:20:1).

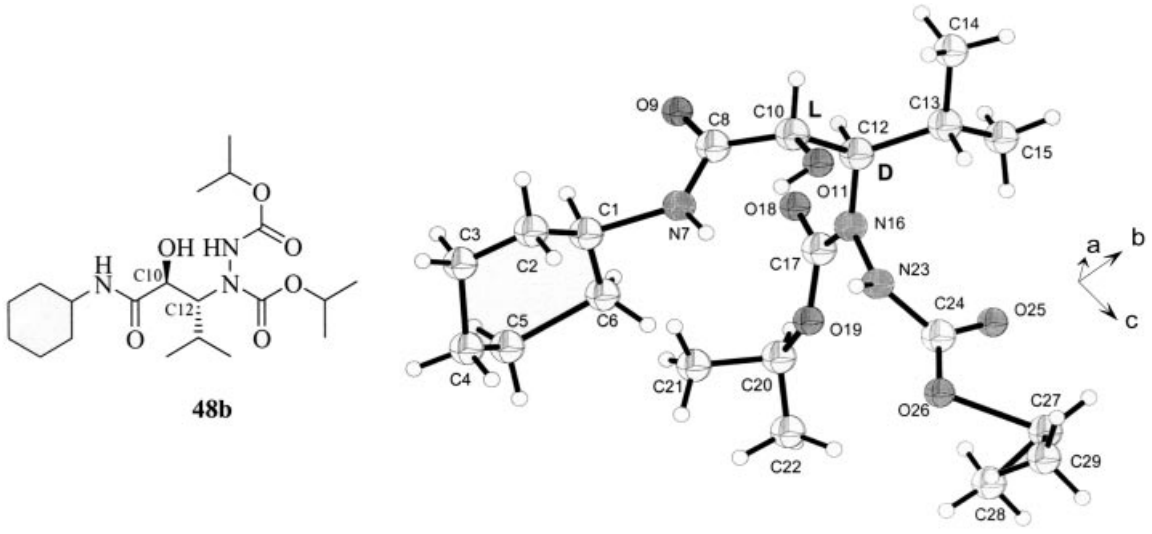
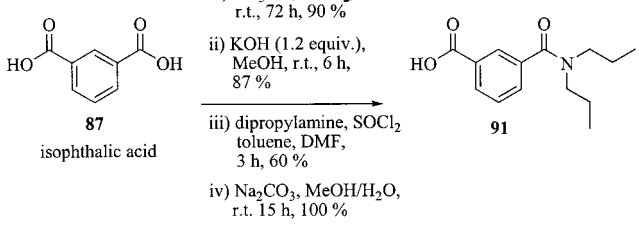


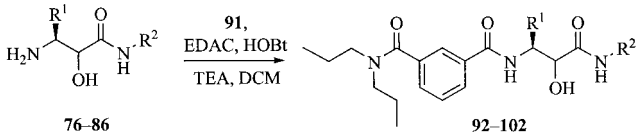

Figure 2. View of the ordered independent **48b** showing an arbitrary atomic labeling scheme.

Single-crystal X-ray analysis was performed to assign the relative configurations of the two chiral centres labelled in Figure 2 as C10 and C12. The relative configuration of C10/C12 was found to be *syn*. The absolute stereochemistry of C12 should thus be *R* (or D) and *S* for C10. We thus assigned the absolute stereochemistry of the diastereomer **48a** to be *R* at C12 and *S* at C10.

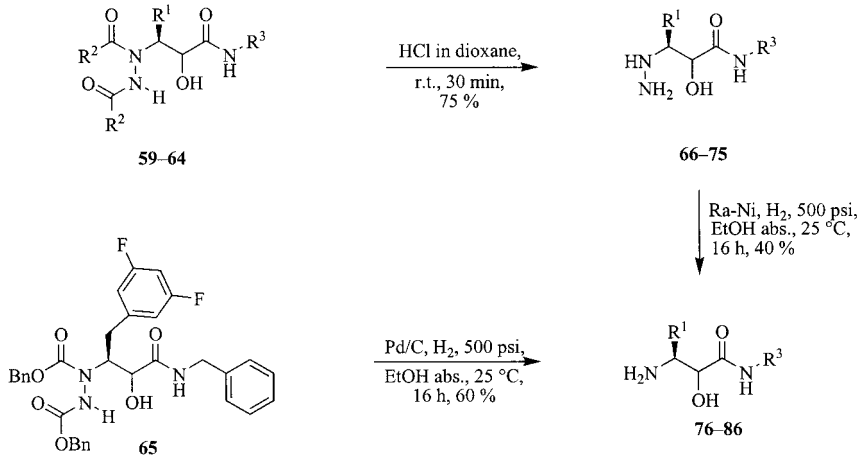
The application of these methods to a concise synthesis of a BACE inhibitor is illustrated in Schemes 2, 3, 4, 5 and 6. The *N*-protecting groups and the N–N bonds in compounds **59**–**65** were removed and cleaved, respectively, and converted to norstatine derivatives **76**–**86** (Table 2). Compounds **59**–**64** were first treated with 1 mL of 18% HCl in dioxane and stirred at room temp. for 30 min, and then submitted to Raney-Ni at 34 bar of $H_2$ to afford the compounds **76**–**85** in a 70% average overall yield. Simultaneous Cbz deprotection and N–N bond cleavage of **65** was achieved in a single step by treatment with $H_2$ over palladium on charcoal at 34 bar. The compounds **76**–**86** were treated with 3-(dipropylcarbamoyl)benzoic acid (**91**) by with EDAC and HOBt as coupling reagents, to result in the potential BACE inhibitors **92**–**102** (Table 3). The compounds were profiled in the FRET-based assay with soluble, truncated BACE.[6] Compound **101** displayed poor inhibi-




Scheme 5. Synthesis of 3-(dipropylcarbamoyl)benzoic acid (**91**).




Scheme 6. Synthesis of phthalamides **92**–**102**.




Scheme 4. Synthesis of norstatine derivatives.

Table 2. Synthesis of norstatine derivatives **76**–**86** by deprotection and N–N bond cleavage.

| Entry | Substrate | Intermediate | Product | $R^1$ | $R^2$ | $R^3$ | Yield [%][a] |
|---|---|---|---|---|---|---|---|
| 1 | **59a** | **66** | **76** | Me | *t*BuO | Bn | 86 |
| 2 | **59b** | **67** | **77** | Me | *t*BuO | Bn | 86 |
| 3 | **60a** | **68** | **78** | Et | *t*BuO | Bn | 40 |
| 4 | **60b** | **69** | **79** | Et | *t*BuO | Bn | 60 |
| 5 | **61a** | **70** | **80** | *i*Pr | *t*BuO | Bn | 55 |
| 6 | **61b** | **71** | **81** | *i*Pr | *t*BuO | Bn | 81 |
| 7 | **62** | **72** | **82** | Ph | *t*BuO | *c*Hex | 73 |
| 8 | **63a** | **73** | **83** | Ph | *t*BuO | Bn | 90 |
| 9 | **63b** | **74** | **84** | Ph | *t*BuO | Bn | 93 |
| 10 | **64** | **75** | **85** | Bn | *t*BuO | Bn | 86 |
| 11 | **65** | – | **86** | 3,5-difluorobenzyl | BnO | Bn | 98 |

[a] Isolated yield of **76**–**86** after silica gel column chromatography.

tion ($IC_{50}$ >200 μM) in all three assays: FRET BACE, RLBA (radioactive ligand binding assay/Tween) and RLBA in the presence of bovine serum albumin (BSA). The difluorophenylalanine **102** displayed some inhibition in the FRET and RLBA (BSA) assays with $IC_{50}$ values of 220 μM and >200 μM, respectively. This weak activity does not confirm our hypothesis of an edge-on-face interaction of two aromatic residues. The compounds **92**–**99** lacked activity in all three assays (Table 4).

Table 3. Synthesis of potential BACE inhibitors.

| Entry | Substrate | Product | $R^1$ | $R^2$ | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | **76** | **92** | Me | Bn | 86 |
| 2 | **77** | **93** | Me | Bn | 86 |
| 3 | **78** | **94** | Et | Bn | 91 |
| 4 | **79** | **95** | Et | Bn | 91 |
| 5 | **80** | **96** | *i*Pr | Bn | 97 |
| 6 | **81** | **97** | *i*Pr | Bn | 81 |
| 7 | **82** | **98** | Ph | *c*Hex | 93 |
| 8 | **83** | **99** | Ph | Bn | 86 |
| 9 | **84** | **100** | Ph | Bn | 86 |
| 10 | **85** | **101** | Bn | Bn | 86 |
| 11 | **86** | **102** | 3,5-difluorobenzyl | Bn | 77 |

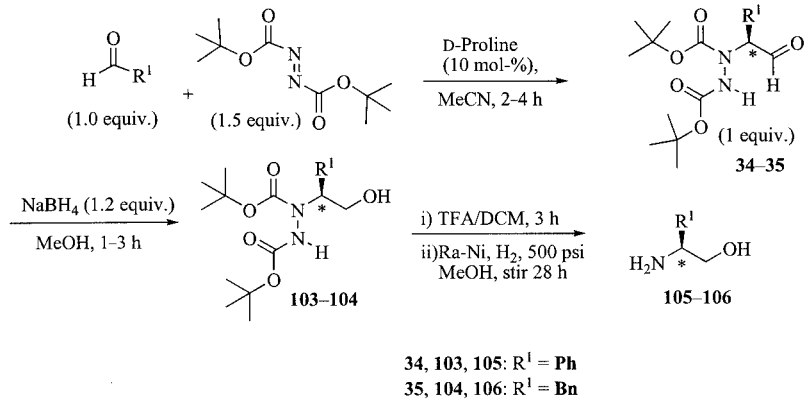
[a] Isolated yield after silica gel column chromatography.

Table 4. Biological data (n.a.: not active) of compounds **1a**, **1b** and **92**–**102**.

| Entry | Compound | FRET (BACE) $IC_{50}$ [μM] | RLBA (Tween) $IC_{50}$ [μM] | RLBA (BSA) $IC_{50}$ [μM] |
|---|---|---|---|---|
| 1 | **92** | n.a. | n.a. | n.a. |
| 2 | **93** | n.a. | n.a. | n.a. |
| 3 | **94** | n.a. | n.a. | n.a. |
| 4 | **95** | n.a. | n.a. | n.a. |
| 5 | **96** | n.a. | n.a. | n.a. |
| 6 | **97** | n.a. | n.a. | n.a. |
| 7 | **98** | n.a. | n.a. | n.a. |
| 8 | **99** | n.a. | n.a. | n.a. |
| 9 | **101** | >>200 | >200 | >200 |
| 10 | **102** | 220 | n.a. | >200 |
| 11 | **1a** | 20 | >200 | >200 |
| 12 | **1b** | >>200 | n.a. | n.a. |

## Assignment of the Absolute Configuration of Selected Intermediates

In order to assign the absolute stereochemistry of the α carbon (designated by an * in Scheme 7), we synthesized L-phenylglycinol (**105**) and L-phenylalaninol (**106**) by the same route and compared their specific optical rotation-{$[\alpha]_D^{20}$} to the commercial references. Synthesis of **105** and **106** involved different steps (Scheme 7) including α-amin-




Scheme 7. Synthesis of L-phenylalaninol and L-phenylglycinol to measure specific optical rotation against optically pure references; * designates the α C atom.

ation of the respective aldehydes with di-*tert*-butylazodicarboxylate, followed by reduction with $NaBH_4$, Boc deprotection and N–N bond cleavage. The $[\alpha]_D^{20}$ of the products was measured with a Perkin–Elmer 241 instrument. The enantiomeric excess (*ee*) was determined to be between 96–99%. This confirms List's[13] finding that D-proline-catalyzed reactions provide *S*-(or L-)configured amino acid analogues.

In conclusion, we have demonstrated the feasibility of an organocatalytic, direct, asymmetric α-amination in combination with a Passerini reaction to provide diverse norstatines. However, the introduction of a difluorophenylalanine moiety in compound **102** did not result in increased potency over the lead compound **1a**.

## Experimental Section

**General Comments:** $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker AC 300 spectrometer at 300 MHz ($^1H$) and 75 MHz ($^{13}C$). Chemical shifts are reported in ppm downfield from $Me_4Si$. Mass spectrometry was performed with a Bruker–Franzen Esquire LC mass spectrometer. Specific optical rotations were determined with a Perkin–Elmer 241 polarimeter. Flash column chromatography was carried out with Merck silica gel 60 (15–40 μm). Thin-layer chromatography (TLC) was carried out with aluminum sheets precoated with silica gel 60 $F_{254}$ (0.2 mm, E. Merck). Chromatographic spots were visualized by UV and/or spraying with an ethanolic solution of ninhydrin followed by heating. Amino acid derivatives were purchased from Fluka Chemie (Switzerland), Nova-Biochem (Switzerland) and Aldrich. All other commercial chemicals were used without further purification.

**X-ray Crystallography:** The crystals used in the diffraction analysis were grown from a solution of **48b** in DMF/MeOH (1:9). The crystal structure of **48b** was solved by single-crystal X-ray diffraction with the Xcalibur system from Oxford Diffraction, equipped with a CCD detector and the Enhance X-ray source option. The software packages SHELXS[21] and SHELXL[22] were used for structure solution and refinement as included in X-STEP32.[23] Diffraction data were collected with an Xcalibur diffractometer and graphite-monochromated (Mo-$K_a$) radiation ($\lambda$ = 0.71073 Å). Unit cell parameters were determined by least-squares refinement of the optimized setting angles of 634 reflections in the range $1.32 \leq \theta \leq 13.28°$. A total of 9809 reflections, 3020 unique ($R_{int}$ = 0.170), were collected up to $\theta$ = 23.89°.

**Crystal Data:** $C_{20}H_{37}N_3O_6$, $M$ = 415.52, colourless prismatic crystal (0.850 × 0.040 × 0.025 mm), orthorhombic, space group $P22_12_1$, $a$ = 5.590(2), $b$ = 19.615(6) and $c$ = 21.646(5) Å, [$V$ = 2373.4(12) Å$^3$, $Z$ = 4, $D_c$ = 1.163 g cm$^{-3}$, $F(000)$ = 904, $\mu$(Mo-$K_\alpha$) = 0.085 mm$^{-1}$].

CCDC-610628 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**3-(3,5-Difluorophenyl)propanal (5f):** 1-Bromo-3,5-difluorobenzene (1.15 mL, 10 mmol), allyl alcohol (1.02 mL, 15 mmol), $Na_2CO_3$ (2.12 g, 20 mmol), TEBACl (2.28 g, 10 mmol), powdered 4 Å sieves (10 g) and $Pd(OAc)_2$ (0.112 g, 0.5 mmol, 5 mol-%) were added to dry, degassed DMF (60 mL) under a nitrogen atmosphere and heated to 60 °C for 6 h. The reaction mixture was cooled to room temp., diluted with EtOAc (100 mL) and filtered through a pad of Celite. The solvents were removed under reduced pressure. The residue was taken up in $Et_2O$ (200 mL) and filtered again through Celite. The filtrate was washed with $H_2O$ (4 × 50 mL), dried ($MgSO_4$) and condensed to give a pale yellow liquid, which after chromatography on silica gel (6% EtOAc in hexane), gave 3-(3,5-difluorophenyl)propanal (**5f**, 1.54 g, 89%) as a light yellow liquid (Scheme 3). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 9.73 (s, 1 H), 6.66 (d, $^3J$ = 7.0 Hz, 1 H), 6.5 (t, $^3J$ = 7.0 Hz, 1 H), 2.72 (t, $^3J$ = 7.0 Hz, 2 H), 2.85 (t, $^3J$ = 7.0 Hz, 1 H) ppm.$^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 200.5, 164.8, 164.7, 144.4, 111.4, 111.3, 101.5, 44.6, 31.6 ppm. MS (EI): $m/z$ = 170 ($M^+$).

**General Procedure for the Synthesis of α-Amino Aldehydes:** L-Proline (11.5 mg, 0.10 mmol) was suspended in $CH_2Cl_2$ (2.5 mL), followed by the addition of the aldehyde (1.50 mmol) and azodicarboxylates (1.00 mmol). The reaction mixture was stirred at room temperature until the yellow colour of azodicarboxylate had disappeared. The reaction mixture was filtered through a Solid Phase Extraction (SPE) C18 Column. This column was washed with MeOH and acetonitrile. The solvent and the excess aldehyde were removed in vacuo.

**General Procedure for the Passerini Reactions:** Trifluoroacetic acid (2.0 equiv.) was added dropwise to a cooled solution (–10°C to 0 °C) of aldehyde **6**–**35** (1.0 equiv.) and isocyanide (1.2–1.5 equiv.) in $CH_2Cl_2$ under a nitrogen atmosphere while maintaining the temperature at ≤0 °C. After 0.5–2 h at 0 °C, the bath was removed, and the reaction was stirred at ambient temperature for 12–72 h. In cases with sluggish reactions, the solution was concentrated slowly to afford a viscous oil, which was further stirred until TLC or HPLC analysis revealed complete consumption of the α-*N*-protected amino aldehyde. The resultant slurry was dissolved in EtOAc and washed with distilled $H_2O$ and brine. The organic layer was dried with anhydrous $Na_2SO_4$, filtered and concentrated. The crude product was either recrystallized or purified by flash column chromatography on silica gel with EtOAc/hexane or $CH_2Cl_2$/MeOH gradient systems. Pure products **36**–**65** (Scheme 2) were obtained as either nearly colourless solids or as colourless to pale yellow viscous oils.

**(*R*)-Di-*tert*-butyl 1-[3-(Cyclohexylamino)-2-hydroxy-1-methyl-3-oxopropyl]hydrazine-1,2-dicarboxylate (36a):** Yield 0.365 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.22 (br. s, 1 H), 6.74 (br. s, 1 H), 4.23 (d, $^3J$ = 6.3 Hz, 1 H), 4.10–4.03 (m, 1 H), 3.68–3.50 (m, 1 H), 1.85–1.73 (m, 2 H), 1.68–1.56 (m, 2 H), 1.55–1.35 (m, 6 H), 1.40 (s, 18 H), 1.30 (d, $^3J$ = 6.3 Hz, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.6, 156.4, 79.9, 65.5, 51.0, 47.6, 33.8, 28.2, 22.9, 8.9 ppm. MS (EI): $m/z$ = 415 ($M^+$).

**(*R*)-Di-*tert*-butyl 1-[2-Hydroxy-1-methyl-3-(2-morpholinoethylamino)-3-oxopropyl]hydrazine-1,2-dicarboxylate (37a):** Yield 0.322 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.26 (br. s, 1 H), 4.76 (d, $^3J$ = 6.8 Hz, 1 H), 4.10–4.07 (m, 1 H), 3.69 (t, $^3J$ = 7.0 Hz, 2 H), 3.34 (t, $^3J$ = 7.0 Hz, 2 H), 2.67 (t, $^3J$ = 7.0 Hz, 2 H), 2.33 (t, $^3J$ = 7.0 Hz, 2 H), 1.40 (s, 18 H), 1.25 (d, $^3J$ = 6.8 Hz, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.1, 156.6, 79.5, 79.4, 66.9, 54.3, 51.2, 28.5, 8.9 ppm. MS (EI): $m/z$ = 445 ($M^+$).

**(*R*)-Diisopropyl 1-[3-(Cyclohexylamino)-2-hydroxy-1-methyl-3-oxopropyl]hydrazine-1,2-dicarboxylate (38a):** Yield 0.108 g (40%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.02 (br. s, 1 H), 6.80 (br. s, 1 H), 4.93–4.77 (m, 2 H), 4.70 (d, $^3J$ = 6.3 Hz, 1 H), 4.15–4.00 (m, 1 H), 1.85–1.73 (m, 2 H), 1.68–1.56 (m, 2 H), 1.55–1.35 (m, 6 H), 1.24 (d, $^3J$ = 6.3 Hz, 12 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.7, 156.6, 66.9, 66.8, 51.0, 47.6, 33.8, 28.2, 23.6, 22.9, 9.9 ppm. MS (EI): $m/z$ = 387 ($M^+$).

**(*R*)-Diisopropyl 1-[3-(Cyclohexylamino)-2-hydroxy-1-methyl-3-oxopropyl]hydrazine-1,2-dicarboxylate (38b):** Yield 0.162 g (60%). $^1H$

NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.00 (br. s, 1 H), 6.78 (br. s, 1 H), 4.85 (d, $^3J$ = 6.3 Hz, 1 H), 4.59–4.30 (m, 2 H), 4.05–3.93 (m, 1 H), 3.71–3.56 (m, 1 H), 1.90–1.64 (m, 4 H), 1.60–1.56 (m, 6 H), 1.27 (d, $^3J$ = 6.3 Hz, 15 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.7, 156.6, 66.9, 66.5, 51.4, 47.7, 33.8, 28.2, 23.6, 22.5, 12.0 ppm. MS (EI): *m*/*z* = 387 ($M^+$).

**(*R*)-Diisopropyl 1-[2-Hydroxy-1-methyl-3-(2-morpholinoethylamino)-3-oxopropyl]hydrazine-1,2-dicarboxylate (39a):** Yield 0.167 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.26 (br. s, 1 H), 6.55 (br. s, 1 H), 4.78 (d, $^3J$ = 6.8 Hz, 1 H), 4.15–4.07 (m, 1 H), 3.63 (t, $^3J$ = 7.0 Hz, 2 H), 3.34 (t, $^3J$ = 7.0 Hz, 2 H), 2.42 (t, $^3J$ = 7.0 Hz, 2 H), 2.33 (t, $^3J$ = 7.0 Hz, 2 H), 1.35 (d, $^3J$ = 6.8 Hz, 6 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.8, 156.6, 156.1, 71.2, 71.0, 66.9, 54.3, 51.2, 37.8, 23.7, 8.9 ppm. MS (EI): *m*/*z* = 418 ($M^+$).

**(*R*)-Di-*tert*-butyl 1-[3-(Cyclohexylamino)-1-ethyl-2-hydroxy-3-oxopropyl]hydrazine-1,2-dicarboxylate (41a):** Yield 0.274 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.99 (br. s, 1 H), 6.20 (br. s, 1 H), 4.78 (d, $^3J$ = 6.3 Hz, 1 H), 4.15–4.00 (m, 1 H), 3.72–3.60 (m, 1 H), 1.70–1.53 (m, 4 H), 1.55–1.52 (m, 2 H), 1.46–1.43 (m, 6 H), 1.40 (s, 18 H), 0.96 (t, $^3J$ = 6.3 Hz, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.9, 156.6, 79.5, 63.0, 56.7, 47.6, 33.8, 33.6, 28.2, 28.1, 23.6, 22.9, 15.7, 9.9 ppm. MS (EI): *m*/*z* = 429 ($M^+$).

**(*R*)-Di-*tert*-butyl 1-[1-Ethyl-2-hydroxy-3-(2-morpholinoethylamino)-3-oxopropyl]hydrazine-1,2-dicarboxylate (42a):** Yield 0.356 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.07 (br. s, 1 H), 4.75 (d, $^3J$ = 6.7 Hz, 1 H), 4.10–4.07 (m, 1 H), 3.67 (t, $^3J$ = 7.0 Hz, 2 H), 3.33 (t, $^3J$ = 7.0 Hz, 2 H), 2.59 (t, $^3J$ = 7.0 Hz, 2 H), 2.31 (t, $^3J$ = 7.0 Hz, 2 H), 1.55–1.51 (m, 2 H), 1.40 (s, 18 H), 0.96 (t, $^3J$ = 6.8 Hz, 2 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.4, 156.4, 79.5, 79.4, 66.8, 53.7, 51.2, 28.5, 14.9, 8.9 ppm. MS (EI): *m*/*z* = 461 ($M^+$).

**(*R*)-Diisopropyl 1-[1-Ethyl-2-hydroxy-3-(2-morpholinoethylamino)-3-oxopropyl]hydrazine-1,2-dicarboxylate (43a):** Yield 0.189 g (60%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.58 (br. s, 1 H), 7.43 (br. s, 1 H), 4.92 (d, $^3J$ = 6.7 Hz, 1 H), 4.08–4.01 (m, 1 H), 3.65 (t, $^3J$ = 7.0 Hz, 2 H), 3.32 (t, $^3J$ = 7.0 Hz, 2 H), 2.45 (t, $^3J$ = 7.0 Hz, 2 H), 2.31 (t, $^3J$ = 7.0 Hz, 2 H), 1.88–1.86 (m, 2 H), 1.20 (d, $^3J$ = 6.8 Hz, 12 H), 0.89 (t, $^3J$ = 6.8 Hz, 2 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.3, 156.3, 77.5, 77.4, 66.6, 65.9, 57.1, 53.4, 51.2, 35.6, 21.9, 21.0, 14.2, 8.9 ppm. MS (EI): *m*/*z* = 432 ($M^+$).

**(*R*)-Diisopropyl 1-[3-(Cyclohexylamino)-1-ethyl-2-hydroxy-3-oxopropyl]hydrazine-1,2-dicarboxylate (44a):** Yield 0.234 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.01 (br. s, 1 H), 6.80 (br. s, 1 H), 4.90 (d, $^3J$ = 6.3 Hz, 1 H), 4.15–4.00 (m, 2 H), 3.72–3.60 (m, 1 H), 3.54–3.50 (m, 1 H), 1.70–1.53 (m, 4 H), 1.55–1.52 (m, 2 H), 1.50–1.43 (m, 6 H), 1.35 (d, $^3J$ = 6.3 Hz, 12 H), 1.0 (t, $^3J$ = 6.3 Hz, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.8, 156.6, 70.1, 66.9, 63.0, 56.7, 47.6, 32.8, 32.6, 28.2, 23.6, 22.9, 14.2, 10.9 ppm. MS (EI): *m*/*z* = 401 ($M^+$).

**(*R*)-Di-*tert*-butyl 1-[3-(Cyclohexylamino)-2-hydroxy-3-oxo-1-(2-propyl)propyl]hydrazine-1,2-dicarboxylate (46a):** Yield 0.286 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.39 (br. s, 1 H), 6.21 (br. s, 1 H), 4.31 (d, $^3J$ = 6.3 Hz, 1 H), 4.20–4.14 (m, 2 H), 3.68–3.63 (m, 1 H), 2.45–2.32 (m, 1 H), 1.85–1.75 (m, 4 H), 1.68–1.56 (m, 6 H), 1.40 (s, 18 H), 0.89 (d, $^3J$ = 6.3 Hz, 6 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.9, 156.1, 79.1, 61.5, 60.5, 47.7, 33.7, 22.9, 28.0, 27.9, 21.6, 17.3 ppm. MS (EI): *m*/*z* = 443 ($M^+$).

**(*R*)-Di-*tert*-butyl 1-[2-Hydroxy-3-(2-morpholinoethylamino)-3-oxo-1-(2-propyl)propyl]hydrazine-1,2-dicarboxylate (47a):** Yield 0.259 g (70%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.91 (br. s, 1 H), 4.75 (d, $^3J$ = 6.7 Hz, 1 H), 4.90–4.05 (m, 1 H), 3.66 (t, $^3J$ = 7.0 Hz, 2 H), 3.33 (t, $^3J$ = 7.0 Hz, 2 H), 2.59 (t, $^3J$ = 7.0 Hz, 2 H), 2.45–2.42 (m, 1 H), 2.31 (t, $^3J$ = 7.0 Hz, 2 H), 1.40 (s, 9 H), 1.39 (s, 9 H), 1.01 (d, $^3J$ = 6.8 Hz, 6 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.4, 156.4, 79.5, 79.4, 66.8, 61.3, 60.3, 53.6, 51.2, 28.5, 21.6, 17.6 ppm. MS (EI): *m*/*z* = 475 ($M^+$).

**Diisopropyl 1-[(1*R*,2*R*)-3-(Cyclohexylamino)-2-hydroxy-3-oxo-1-(2-propyl)propyl]hydrazine-1,2-dicarboxylate (48a):** Yield 0.116 g (40%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.40 (br. s, 1 H), 6.36 (br. s, 1 H), 4.98–4.80 (m, 2 H), 4.35 (d, $^3J$ = 6.3 Hz, 1 H), 4.19–4.10 (m, 1 H), 3.75–3.60 (m, 1 H), 2.32–2.22 (m, 1 H), 1.85–1.75 (m, 4 H), 1.68–1.56 (m, 6 H), 1.24 (d, $^3J$ = 6.3 Hz, 12 H), 0.89 (d, $^3J$ = 6.3 Hz, 6 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 170.9, 156.5, 65.7, 64.4, 48.2, 48.0, 32.8, 27.6, 25.6, 24.9, 22.0, 19.3 ppm. MS (EI): *m*/*z* = 415 ($M^+$).

**Diisopropyl 1-[(1*R*,2*S*)-3-(Cyclohexylamino)-2-hydroxy-3-oxo-1-(2-propyl)propyl]hydrazine-1,2-dicarboxylate (48b):** Yield 0.174 g (60%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.20 (br. s, 1 H), 6.67 (br. s, 1 H), 4.95–4.75 (m, 2 H), 4.25 (d, $^3J$ = 6.3 Hz, 1 H), 3.78–3.61 (m, 2 H), 2.40–2.29 (m, 1 H), 1.88–1.72 (m, 4 H), 1.68–1.52 (m, 6 H), 1.15 (d, $^3J$ = 6.3 Hz, 12 H), 0.98 (d, $^3J$ = 6.3 Hz, 6 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 170.9, 156.5, 65.7, 64.4, 48.2, 48.0, 33.3, 27.4, 25.6, 24.9, 22.0, 17.9 ppm. MS (EI): *m*/*z* = 415 ($M^+$).

**(*R*)-Diisopropyl 1-[2-Hydroxy-3-(2-morpholinoethylamino)-3-oxo-1-(2-propyl)propyl]hydrazine-1,2-dicarboxylate (49a):** Yield 0.192 g (60%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.11 (br. s, 1 H), 4.95–4.70 (m, 3 H), 3.77–3.58 (m, 5 H), 3.40 (d, $^3J$ = 7.0 Hz, 2 H), 2.68–2.55 (m, 2 H), 2.50–2.37 (m, 5 H), 1.30–1.10 (m, 12 H), 0.90–0.77 (m, 6 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.4, 156.4, 66.9, 66.8, 61.3, 60.3, 53.6, 51.2, 37.9, 23.5, 23.4, 21.6, 17.6 ppm. MS (EI): *m*/*z* = 446 ($M^+$).

**(*R*)-Di-*tert*-butyl 1-[3-(Cyclohexylamino)-2-hydroxy-3-oxo-1-phenylpropyl]hydrazine-1,2-dicarboxylate (51a):** Yield 0.373 g (80%). $^1H$ NMR ([$D_6$]DMSO, 300 MHz): $\delta$ = 8.60 (br. s, 1 H), 7.66 (br. s, 1 H), 7.59–7.43 (m, 5 H), 5.17 (d, $^3J$ = 6.3 Hz, 2 H) 3.54–3.40 (m, 1 H), 1.93–1.45 (m, 10 H), 1.40 (s, 9 H), 1.26 (s, 9 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 170.3, 156.6, 141.6, 129.5, 128.5, 128.4, 128.2, 127.0, 82.5, 77.6, 77.1, 48.6, 47.6, 32.8, 32.6, 28.2, 25.7, 24.9, 24.7 ppm. MS (EI): *m*/*z* = 478 ($M^+$).

**(*R*)-Di-*tert*-butyl 1-[2-Hydroxy-3-(2-morpholinoethylamino)-3-oxo-1-phenylpropyl]hydrazine-1,2-dicarboxylate (52a):** Yield 0.292 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.05 (br. s, 1 H), 7.45–7.12 (m, 5 H), 5.17 (d, $^3J$ = 7.0 Hz, 2 H), 3.65–3.50 (m, 4 H), 3.33–3.28 (m, 2 H), 2.60–2.44 (m, 2 H), 2.40–2.30 (m, 4 H), 1.40 (s, 18 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.4, 156.4, 143.5, 128.5, 128.4, 127.0, 126.8, 80.4, 79.5, 79.4, 66.8, 57.7, 53.6, 51.2, 37.7, 28.5 ppm. MS (EI): *m*/*z* = 508 ($M^+$).

**(*R*)-Di-*tert*-butyl 1-[1-Benzyl-3-(cyclohexylamino)-2-hydroxy-3-oxopropyl]hydrazine-1,2-dicarboxylate (56a):** Yield 0.239 g (80%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.99 (br. s, 1 H), 7.23–7.12 (m, 5 H), 5.90 (br. s, 1 H), 4.60–4.45 (m, 1 H), 4.05 (d, $^3J$ = 6.3 Hz, 1 H), 3.75–3.65 (m, 1 H), 3.15–3.00 (m, 1 H), 2.87–2.79 (m, 1 H), 1.90–1.45 (m, 10 H), 1.40 (s, 9 H), 1.26 (s, 9 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 170.4, 155.6, 138.5, 128.9, 128.7, 126.7, 83.0, 82.6, 71.4, 62.7, 56.6, 48.6, 33.2, 32.8, 32.6, 28.2, 28.0, 25.6, 24.9, 24.6 ppm. MS (EI): *m*/*z* = 491 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Benzylamino)-2-hydroxy-1-methyl-3-oxopropyl]hydrazine-1,2-dicarboxylate (59a):** Yield 0.182 g (50%). $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.67 (br. s, 1 H), 7.27–7.18 (m, 5 H), 6.39 (br. s, 1 H), 4.75 (d, $^3J$ = 6.8 Hz, 1 H), 4.45 (s, 2 H), 4.30–4.20 (m, 1 H), 1.40 (s, 18 H), 1.25 (d, $^3J$ = 6.8 Hz, 3 H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.4, 156.6, 141.6, 128.7, 128.6, 127.8,

127.4, 82.0, 58.0, 51.2, 42.2, 27.8, 11.6 ppm. MS (EI): *m*/*z* = 423.5 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Benzylamino)-2-hydroxy-1-methyl-3-oxopropyl]hydrazine-1,2-dicarboxylate (59b):** Yield 0.182 g (50%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.67 (br. s, 1 H), 7.26–7.15 (m, 5 H), 6.41 (br. s, 1 H), 5.20 (s, 2 H), 4.50–4.42 (m, 1 H), 4.22 (d, $^3J$ = 6.2 Hz, 1 H), 1.39 (s, 18 H), 1.25 (d, $^3J$ = 6.8 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.4, 156.6, 141.6, 128.7, 128.6, 127.8, 127.4, 82.1, 58.0, 53.5, 43.2, 28.2, 11.6 ppm. MS (EI): *m*/*z* = 423.5 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Benzylamino)-1-ethyl-2-hydroxy-3-oxopropyl]hydrazine-1,2-dicarboxylate (60a):** Yield 0.239 g (60%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.23 (br. s, 1 H), 7.20–7.06 (m, 5 H), 6.10 (br. s, 1 H), 4. 60 (d, $^3J$ = 6.8 Hz, 1 H), 4.45 (s, 2 H), 4.15–4.00 (m, 1 H), 1.60–1.54 (m, 2 H), 1.40 (s, 18 H), 0.96 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.4, 156.6, 141.6, 128.4, 127.9, 127.5, 77.5, 62.7, 56.7, 44.6, 28.1, 19.3, 11.6 ppm. MS (EI): *m*/*z* = 437 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Benzylamino)-1-ethyl-2-hydroxy-3-oxopropyl]hydrazine-1,2-dicarboxylate (60b):** Yield 0.159 g (40%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.05 (br. s, 1 H), 7.24–7.19 (m, 5 H), 6.23 (br. s, 1 H), 5.22 (s, 2 H), 4.45 (d, $^3J$ = 6.8 Hz, 1 H), 4.20–4.05 (m, 1 H), 1.62–1.58 (m, 2 H), 1.39 (s, 18 H), 0.89 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.8, 156.6, 141.6, 128.7, 128.6, 127.8, 127.5, 127.4, 77.5, 63.5, 56.7, 43.6, 28.1, 19.3, 11.2 ppm. MS (EI): *m*/*z* = 437 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Benzylamino)-2-hydroxy-3-oxo-1-(2-propyl)-propyl]hydrazine-1,2-dicarboxylate (61a):** Yield 0.219 g (50%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.59 (br. s, 1 H), 7.25–7.14 (m, 5 H), 6.01 (br. s, 1 H), 4.69 (d, $^3J$ = 5.7 Hz, 1 H), 4.59 (s, 2 H), 4.32 (dd, $^3J$ = 8.8 Hz, 3.9 Hz, 1 H), 2.58–2.45 (m, 1 H), 1.45 (s, 18 H), 1.08 (d, $^3J$ = 6.6 Hz, 3 H), 0.82 (d, $^3J$ = 6.6 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 169.7, 141.6, 136.1, 128.4, 128.3, 127.9, 127.5, 77.6, 77.2, 65.1, 63.2, 44.7, 28.4, 21.1, 14.3 ppm. MS (EI): *m*/*z* = 451 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Benzylamino)-2-hydroxy-3-oxo-1-(2-propyl)-propyl]hydrazine-1,2-dicarboxylate (61b):** Yield 0.219 g (50%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.67 (br. s, 1 H), 7.26–7.17 (m, 5 H), 6.25 (br. s, 1 H), 4.44 (s, 2 H), 4.37 (d, $^3J$ = 5.5 Hz, 1 H), 4.1 (dd, $^3J$ = 8.8 Hz, 3.9 Hz, 1 H), 2.26–2.19 (m, 1 H), 1.44 (s, 18 H), 0.93 (d, $^3J$ = 6.7 Hz, 6 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.9, 155.6, 141.6, 138.2, 128.7, 127.9, 127.4, 82.9, 82.6, 66.2, 60.5, 43.4, 28.1, 20.3, 19.4, 19.3 ppm. MS (EI): *m*/*z* = 451 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Cyclohexylamino)-2-hydroxy-3-oxo-1-phenylpropyl]hydrazine-1,2-dicarboxylate (62a):** Yield 0.309 g (80%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.26 (br. s, 1 H), 7.33–7.19 (m, 5 H), 6.06 (br. s, 1 H), 5.22 (d, $^3J$ = 6.3 Hz, 2 H), 3.72–3.65 (m, 1 H), 1.90–1.45 (m, 10 H), 1.40 (s, 9 H), 1.26 (s, 9 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 170.4, 156.6, 141.7, 129.7, 128.7, 128.4, 128.2, 127.0, 82.5, 77.6, 77.1, 48.6, 47.6, 32.8, 32.6, 28.2, 25.7, 24.9, 24.7 ppm. MS (EI): *m*/*z* = 478 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Benzylamino)-2-hydroxy-3-oxo-1-phenylpropyl]hydrazine-1,2-dicarboxylate (63a):** Yield 0.226 g (50%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.01 (br. s, 1 H), 7.59–7.00 (m, 10 H), 5.99 (br. s, 1 H), 5.22 (d, $^3J$ = 6.3 Hz, 2 H), 4.46 (d, $^3J$ = 6.3 Hz, 2 H), 1.40 (s, 18 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 170.4, 156.6, 143.7, 141.6, 129.1, 128.7, 128.4, 128.2, 127.0, 126.3, 81.7, 78.6, 77.1, 57.7, 44.6, 28.4, 28.2 ppm. MS (EI): *m*/*z* = 485 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[3-(Benzylamino)-2-hydroxy-3-oxo-1-phenylpropyl]hydrazine-1,2-dicarboxylate (63b):** Yield 0.226 g (50%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.01 (br. s, 1 H), 7.50–6.99 (m, 10 H), 5.99 (br. s, 1 H), 5.17 (d, $^3J$ = 6.3 Hz, 2 H), 4.47 (d, $^3J$ = 6.3 Hz, 2 H), 1.40 (s, 18 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 170.4, 156.6, 143.7, 141.6, 129.1, 128.7, 128.4, 128.2, 127.0, 126.3, 81.7, 78.6, 77.1, 57.7, 44.6, 28.4, 28.2 ppm. MS (EI): *m*/*z* = 485 ($M^+$).

**(*S*)-Di-*tert*-butyl 1-[1-Benzyl-3-(benzylamino)-2-hydroxy-4-oxopropyl]hydrazine-1,2-dicarboxylate (64a):** Yield 0.343 g (80%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.28 (br. s, 1 H), 7.53–7.08 (m, 10 H), 4.5 (d, $^3J$ = 6.3 Hz, 1 H) 4.32 (d, $^3J$ = 6.5 Hz, 1 H), 3.97–3.90 (m, 1 H), 2.95–2.88 (m, 1 H), 2.87–2.79 (m, 1 H), 1.40 (s, 9 H), 1.26 (s, 9 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.4, 156.6, 141.7, 138.1, 129.3, 129.0, 128.8, 128.7, 128.6, 128.5, 127.9, 127.8, 127.4, 127.0, 126.7, 83.1, 82.6, 62.3, 43.8, 35.6, 28.1 ppm. MS (EI): *m*/*z* = 499 ($M^+$).

**(*S*)-Dibenzyl 1-[3-(Benzylamino)-1-(3,5-difluorobenzyl)-2-hydroxy-3-oxopropyl]hydrazine-1,2-dicarboxylate (65a):** Yield 0.415 g (80%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.82 (br. s, 1 H), 7.39–7.33 (m, 15 H), 6.61 (d, $^3J$ = 5.6 Hz, 2 H), 6.51 (t, $^3J$ = 5.6 Hz, 1 H), 5.35 (s, 4 H), 4.78 (d, $^3J$ = 3.0 Hz, 1 H), 4.46 (s, 2 H), 4.28 (d, $^3J$ = 3.0 Hz, 1 H), 2.89–2.87 (m, 1 H), 2.64–2.62 (m, 1 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.3, 156.2, 164.6, 141.3,141.2, 129.5, 128.8, 128.6, 127.5, 126.6, 110.8, 102.4, 65.8, 65.5, 62.6, 44.5, 30.8 ppm. MS (EI): *m*/*z* = 603 ($M^+$).

**General Procedure for Boc Deprotection:** HCl (1 mL, 18% in dioxane) was added to compounds **59**–**64** in a flask and stirred at room temp. for 30 min. The reaction was monitored by TLC. The solvent was removed, azeotroped three times with hexane, and the solution was evaporated to dryness to yield **66**–**75** (Scheme 4).

**General Procedure for N–N bond Cleavage:** To activated Raney-Ni (1.2 equiv., suspension in absolute ethanol) was added compounds **65**–**75**, and the mixture was hydrogenated at 500 psi in an autoclave for 16 h at 25 °C. The reaction mixture was filtered, and the solution was evaporated to dryness. The crude product was purified by an acid-base workup to afford compounds **76**–**86** (Scheme 4) as a white solid.

**(3*S*)-3-Amino-*N*-benzyl-2-hydroxybutanamide (76):** Yield 0.179 g (86%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.19–7.06 (m, 5 H), 4.45 (d, $^3J$ = 5.7 Hz, 1 H), 4.43 (s, 2 H), 3.64–3.56 (m, 1 H), 1.18 (d, $^3J$ = 5.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.0, 141.6, 128.8, 128.6, 127.1, 127.0, 126.8, 73.0, 47.6, 44.3, 16.5 ppm. MS (EI): *m*/*z* = 208 ($M^+$).

**(3*S*)-3-Amino-*N*-benzyl-2-hydroxybutanamide (77):** Yield 0.179 g (86%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.19–7.07 (m, 5 H), 4.45 (d, $^3J$ = 5.7 Hz, 1 H), 4.44 (s, 2 H), 3.69–3.59 (m, 1 H), 1.18 (d, $^3J$ = 5.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.2, 141.7, 128.8, 128.6, 127.1, 127.0, 126.8, 73.0, 47.6, 44.3, 16.1 ppm. MS (EI): *m*/*z* = 208 ($M^+$).

**(3*S*)-3-Amino-*N*-benzyl-2-hydroxypentanamide (78):** Yield 0.089 g (40%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.25–7.14 (m, 5 H), 4.58 (s, 2 H), 4.45 (d, $^3J$ = 5.7 Hz, 1 H), 3.22 (pent, $^3J$ = 1.68 Hz, 1.55 Hz, 1 H), 1.25–1.21 (m, 2 H), 1.8 (br. s, 2 H), 0.88 (t, 3 H, $^3J$ = 7.7 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.4, 139.9, 128.8, 128.6, 127.1, 127.0, 126.8, 70.8, 54.6, 44.4, 23.9, 8.7 ppm. MS (EI): *m*/*z* = 222 ($M^+$).

**(3*S*)-3-Amino-*N*-benzyl-2-hydroxypentanamide (79):** Yield 0.133 g (60%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.19–7.09 (m, 5 H), 4.55 (s, 2 H), 4.45 (d, $^3J$ = 5.7 Hz, 1 H), 3.22 (pent, $^3J$ = 1.68 Hz, 1.55 Hz, 1 H), 1.25–1.21 (m, 2 H), 1.80 (br. s, 2 H), 0.89 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.2, 141.9, 128.8, 128.6, 127.2, 127.1, 126.8, 70.6, 54.5, 44.4, 23.9, 8.7 ppm. MS (EI): *m*/*z* = 222 ($M^+$).

**(3*S*)-3-Amino-*N*-benzyl-2-hydroxy-4-methylpentanamide (80):** Yield 0.130 g (55%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.29–7.12 (m, 5 H), 4.38 (d, $^3J$ = 5.7 Hz, 1 H), 4.35 (s, 2 H), 2.89 (t, $^3J$ = 6.2 Hz, 1 H), 2.25–2.12 (m, 1 H), 0.95 (d, $^3J$ = 6.7 Hz, 3 H), 0.90 (d, $^3J$ = 6.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.4, 137.4, 131.2, 130.0, 128.9, 127.8, 127.8, 61.6, 55.3, 43.4, 28.8, 19.4, 16.6 ppm. MS (EI): *m*/*z* = 236 ($M^+$).

**(3*S*)-3-Amino-*N*-benzyl-2-hydroxy-4-methylpentanamide (81):** Yield 0.191 g (81%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.27–7.09 (m, 5 H), 4.50 (d, $^3J$ = 5.7 Hz, 1 H), 4.44 (s, 2 H), 2.87 (t, $^3J$ = 6.2 Hz, 1 H), 2.24–2.10 (m, 1 H), 0.95 (d, $^3J$ = 6.7 Hz, 3 H), 0.90 (d, $^3J$ = 6.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.0, 141.4, 131.3, 130.5, 128.9, 127.8, 127.8, 65.6, 55.6, 44.4, 28.8, 17.4, 16.6 ppm. MS (EI): *m*/*z* = 236 ($M^+$).

**Dimethyl Isophthalate (88):** Thionyl chloride (1.7 mL, 24.09 mmol) was added dropwise to a stirred solution of isophthalic acid (**87**, 1.0 g, 6.0 mmol) in anhydrous MeOH (50 mL) at 0 °C under nitrogen. The reaction mixture was allowed to stir at room temperature and monitored by TLC. Solvent was removed after completion of the reaction to give isophthalic dimethyl ester (**88**) as a colourless crystalline solid (1.11 g, 95.7% yield, Scheme 5). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.51 (s, 1 H), 7.99 (dd, $^3J$ = 7.7 Hz, 1.8 Hz, 1 H), 7.89 (dd, $^3J$ = 7.7 Hz, 1.8 Hz, 1 H), 7.50 (t, $^3J$ = 7.7 Hz, 1 H), 3.85 (s, 6 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 169.5, 166.6, 130.8, 130.4, 129.8, 129.0, 128.8, 126.8, 51.6, 51.5 ppm. MS (EI): *m*/*z* = 194 ($M^+$).

**3-(Methoxycarbonyl)benzoic Acid (89):** Isophthalic diester **88** (1 equiv., 1.0 g, 5.15 mmol) and potassium hydroxide (1.2 equiv., 0.347 g, 6.18 mmol) were stirred in ethanol (25 mL) for 15 h at room temperature. The ethanol was removed under vacuum, $H_2O$ (25 mL) was added and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 25 mL). The aqueous phase was neutralized (pH = 3.0) with concentrated hydrochloric acid (37%), and the resulting precipitate was filtered, washed with $H_2O$ (5 mL) and dried to give isophthalic mono ester **89** (0.920 g, 99.2%, Scheme 5) as a white solid. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 11.5 (s, 1 H), 8.51 (s, 1 H), 7.99 (dd, $^3J$ = 7.7 Hz, 1.8 Hz, 1 H), 7.89 (dd, $^3J$ = 7.7 Hz, 1.8 Hz, 1 H), 7.50 (t, $^3J$ = 7.7 Hz, 1 H), 3.85 (s, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 169.5, 166.6, 130.8, 130.4, 129.8, 129.0, 128.8, 126.8, 51.6 ppm. MS (EI): *m*/*z* = 180 ($M^+$).

**Methyl 3-(Dipropylcarbamoyl)benzoate (90):** 1-Ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDAC, 979 mg, 5.11 mmol) and *N*-hydroxybenzotriazole hydrate (HOBt, 828 mg, 6.13 mmol) were added to a solution of 3-(methoxycarbonyl)benzoic acid (**89**, 920 mg, 5.11 mmol), dissolved in $CH_2Cl_2$ (10 mL). The resulting mixture was stirred at ambient temperature for 5 min, then treated with dipropylamine (0.84 mL, 6.13 mmol) and triethylamine (1.42 mL, 10.22 mmol) for 8 h. $CH_2Cl_2$ (20 mL) was added, and the solution was washed with HCl (0.1 N, 5 × 30 mL), NaOH (0.1 N, 3 × 30 mL), brine (1 × 30 mL), dried with $Na_2SO_4$ and concentrated to obtain the product **90** as colourless oil (1.23 g, 92%, Scheme 5). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.51 (s, 1 H), 7.99 (dd, $^3J$ = 7.7 Hz, 1.8 Hz, 1 H), 7.89 (dd, $^3J$ = 7.7 Hz, 1.8 Hz, 1 H), 7.50 (t, $^3J$ = 7.7 Hz, 1 H), 3.85 (s, 3 H), 3.38 (t, $^3J$ = 7.7 Hz, 2 H), 3.10 (t, $^3J$ = 7.7 Hz, 2 H), 1.67 (sext, $^3J$ = 7.6 Hz, 2 H), 1.45 (sext, $^3J$ = 7.6 Hz, 2 H), 1.00 (t, $^3J$ = 7.7 Hz, 3 H), 0.91 (t, $^3J$ = 7.7 Hz, 3 H) ppm.$^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 169.9, 166.6, 130.8, 130.4, 129.8, 129.0, 128.8, 126.8, 51.6, 49.9, 45.6, 21.3, 20.2, 11.2, 10.7 ppm. MS (EI): *m*/*z* = 263 ($M^+$).

**3-(Dipropylcarbamoyl)benzoic Acid (91):** Methyl 3-(dipropylcarbamoyl)benzoate (**90**, 1.0 g, 3.80 mmol) and sodium carbonate (2.0 g, 19.0 mmol) were stirred in MeOH (15 mL) and $H_2O$ (1 mL) for 15 h. MeOH was removed under reduced pressure. The aqueous phase was neutralized carefully at 0 °C (pH = 3.0) with concentrated hydrochloric acid (37%), and the resulting precipitate was filtered, washed with $H_2O$ (5 mL) and dried to give **91** (0.920 g, 97.2% yield) as a white solid (Scheme 5). $^1$H NMR ([$D_6$]DMSO, 300 MHz,): $\delta$ = 13.2 (s, 1 H), 8.52 (s, 1 H), 8.19 (dd, $^3J$ = 7.7 Hz, 1.8 Hz, 1 H), 8.01 (dd, $^3J$ = 7.7 Hz, 1.8 Hz, 1 H), 7.58 (t, $^3J$ = 7.7 Hz, 1 H), 3.38 (t, $^3J$ = 7.7 Hz, 2 H), 3.10 (t, $^3J$ = 7.7 Hz, 2 H), 1.67 (sext, $^3J$ = 7.6 Hz, 2 H), 1.45 (sext, $^3J$ = 7.6 Hz, 2 H), 1.00 (t, $^3J$ = 7.7 Hz, 3 H), 0.91 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ([$D_6$]-DMSO, 75 MHz): $\delta$ = 169.5, 166.6, 130.8, 130.4, 129.8, 129.0, 128.8, 126.8, 49.9, 45.6, 21.3, 20.2, 11.2, 10.7 ppm. MS (EI): *m*/*z* = 249 ($M^+$).

**General Procedure for the Synthesis of Analogues of 1:** 1-Ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (EDAC, 708 mg, 3.69 mmol) and *N*-hydroxybenzotriazole hydrate (HOBt, 598 mg, 4.42 mmol) were added to a solution of 3-(dipropylcarbamoyl)benzoic acid (**91**, 920 mg, 3.69 mmol), dissolved in $CH_2Cl_2$ (10 mL). The resulting mixture was stirred at ambient temperature for 5 min, then treated with compound **76** (1.2 equiv.) and triethylamine (1.03 mL, 7.38 mmol) for 8 h. $CH_2Cl_2$ (20 mL) was added, and the solution was washed with HCl (0.1 N, 5 × 30 mL), saturated aq. $NaHCO_3$ (3 × 30 mL), brine (1 × 30 mL), dried with $Na_2SO_4$ and concentrated to obtain the products **92**–**102** (Scheme 6).

**Compound 92:** Yield 1.39 g (86%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.05 (s, 1 H), 7.98 (d, $^3J$ = 7.7 Hz, 2 H), 7.70–7.69 (m, 1 H), 7.31–7.11 (m, 5 H), 4.49 (d, $^3J$ = 5.7 Hz, 1 H), 4.43 (s, 2 H), 4.30–4.23 (m, 1 H), 3.31 (t, $^3J$ = 7.7 Hz, 2 H), 3.02 (t, $^3J$ = 7.7 Hz, 2 H), 1.60–1.51 (m, 2 H), 1.46–1.37 (m, 2 H), 1.09 (s, 3 H), 0.89 (t, $^3J$ = 7.7 Hz, 3 H), 0.84 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.9, 168.6, 165.0, 138.3, 137.8, 134.9, 134.6, 134.0, 129.8, 129.4, 129.3, 127.9, 126.7, 126.8, 125.1, 73.0, 50.9, 50.8, 46.6, 44.1, 42.3, 22.0, 20.8, 13.9, 11.6, 11.1 ppm. MS (EI): *m*/*z* = 439.5 ($M^+$).

**Compound 93:** Yield 1.39 g (86%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.03 (s, 1 H), 7.97 (d, $^3J$ = 7.7 Hz, 2 H), 7.74–7.69 (m, 1 H), 7.39–7.11 (m, 5 H), 4.50 (d, $^3J$ = 5.7 Hz, 1 H), 4.42 (s, 2 H), 4.30–4.22 (m, 1 H), 3.33 (t, $^3J$ = 7.7 Hz, 2 H), 3.05 (t, $^3J$ = 7.7 Hz, 2 H), 1.59–1.50 (m, 2 H), 1.45–1.37 (m, 2 H), 1.09 (s, 3 H), 1.00 (t, $^3J$ = 7.7 Hz, 3 H), 0.94 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.9, 167.9, 165.0, 138.1, 137.6, 134.7, 134.0, 133.9, 129.7, 129.4, 129.3, 127.9, 126.7, 126.8, 125.1, 71.0, 50.8, 50.6, 46.5, 44.0, 42.1, 22.0, 20.8, 13.9, 11.6, 11.1 ppm. MS (EI): *m*/*z* = 439.5 ($M^+$).

**Compound 94:** Yield 1.52 g (91%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.93 (s, 1 H), 7.55 (d, $^3J$ = 7.7 Hz, 2 H), 7.54–7.51 (m, 1 H), 7.26–7.00 (m, 5 H), 4.60 (d, $^3J$ = 5.7 Hz, 1 H), 4.42 (s, 2 H), 4.30–4.22 (m, 1 H), 3.32 (t, $^3J$ = 7.7 Hz, 2 H), 3.05 (t, $^3J$ = 7.7 Hz, 2 H), 1.67–1.60 (m, 2 H), 1.59–1.50 (m, 2 H), 1.45–1.37 (m, 2 H), 1.00 (t, $^3J$ = 7.7 Hz, 3 H), 0.96 (t, $^3J$ = 7.7 Hz, 3 H), 0.94 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.0, 168.8, 165.6, 139.1, 137.5, 134.6, 134.3, 134.0, 129.7, 129.4, 128.3, 127.9, 126.5, 126.3, 125.9, 67.0, 52.8, 50.6, 49.9, 44.0, 22.0, 21.3, 20.8, 11.6, 11.1, 8.6 ppm. MS (EI): *m*/*z* = 453 ($M^+$).

**Compound 95:** Yield 1.52 g (91%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.01 (s, 1 H), 7.75 (d, $^3J$ = 7.7 Hz, 2 H), 7.70–7.65 (m, 1 H), 7.26–7.01 (m, 5 H), 5.00 (d, $^3J$ = 5.7 Hz, 1 H), 4.44 (s, 2 H), 4.30–4.22 (m, 1 H), 3.30 (t, $^3J$ = 7.7 Hz, 2 H), 3.04 (t, $^3J$ = 7.7 Hz, 2 H), 1.66–1.59 (m, 2 H), 1.58–1.48 (m, 2 H), 1.45–1.37 (m, 2 H), 1.00 (t, $^3J$ = 7.7 Hz, 3 H), 0.97 (t, $^3J$ = 7.7 Hz, 3 H), 0.96 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 171.9, 168.5, 165.0, 139.0, 137.5, 134.4, 134.2, 134.0, 129.6, 129.4, 128.1, 127.8, 126.5,

126.0, 124.9, 67.9, 52.0, 50.3, 49.9, 44.4, 22.0, 21.8, 20.9, 11.7, 11.5, 8.8 ppm. MS (EI): $m/z$ = 453 ($M^+$).

**Compound 96:** Yield 1.67 g (97%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.01 (s, 1 H), 7.97 (d, $^3J$ = 7.7 Hz, 2 H), 7.65–7.60 (m, 1 H), 7.38–7.30 (m, 5 H), 5.00 (d, $^3J$ = 5.7 Hz, 1 H), 4.46 (s, 2 H), 4.30–4.22 (m, 1 H), 3.30 (t, $^3J$ = 7.7 Hz, 2 H), 3.04 (t, $^3J$ = 7.7 Hz, 2 H), 2.45–2.40 (m, 2 H), 1.58–1.48 (m, 2 H), 1.45–1.37 (m, 2 H), 1.03 (t, $^3J$ = 7.7 Hz, 3 H), 1.01 (d, $^3J$ = 7.0 Hz, 6 H), 0.96 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.3, 168.9, 167.0, 141.6 135.5, 134.4, 130.2, 129.9, 129.6, 128.4, 128.1, 127.8, 127.5, 126.0, 124.8, 65.0, 57.0, 50.3, 49.9, 44.4, 26.7, 21.9, 21.8, 17.8, 17.9, 11.7, 11.5 ppm. MS (EI): $m/z$ = 468 ($M^+$).

**Compound 97:** Yield 1.40 g (81%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.01 (s, 1 H), 7.97 (d, $^3J$ = 7.7 Hz, 2 H), 7.65–7.60 (m, 1 H), 7.38–7.30 (m, 5 H), 5.55 (d, $^3J$ = 3.5 Hz, 1 H), 4.46 (s, 2 H), 4.40–4.30 (m, 1 H), 3.35 (t, $^3J$ = 7.7 Hz, 2 H), 3.05 (t, $^3J$ = 7.7 Hz, 2 H), 2.10–1.90 (m, 2 H), 1.65–1.55 (m, 2 H), 1.48–1.35 (m, 2 H), 1.05 (t, $^3J$ = 5.7 Hz, 3 H), 0.93 (t, $^3J$ = 5.7 Hz, 3 H), 0.84 (t, $^3J$ = 7.7 Hz, 3 H), 0.65 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 170.38, 167.7, 165.1, 141.6, 137.6, 134.4, 130.5, 130.0, 129.6, 128.9, 128.1, 127.8, 127.5, 126.0, 124.8, 72.0, 57.7, 50.3, 49.9, 43.6, 30.0, 21.9, 20.8, 19.9, 19.5, 11.5, 11.1 ppm. MS (EI): $m/z$ = 467 ($M^+$).

**Compound 98:** Yield 1.69 g (93%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.01 (s, 1 H), 7.52 (d, $^3J$ = 7.7 Hz, 2 H), 7.51–7.49 (m, 1 H), 7.30–7.15 (m, 5 H), 5.01 (d, $^3J$ = 5.5 Hz, 2 H), 5.00 (d, $^3J$ = 5.5 Hz, 2 H), 3.55 (t, $^3J$ = 7.7 Hz, 2 H), 3.45–3.40 (m, 1 H), 3.18 (t, $^3J$ = 7.7 Hz, 2 H), 1.65–1.50 (m, 4 H), 1.30–1.25 (m, 2 H), 1.22–1.15 (m, 6 H), 1.10–1.00 (m, 2 H), 0.81 (t, $^3J$ = 7.7 Hz, 3 H), 0.65 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.0, 168.1, 167.5, 142.9, 135.6, 134.5, 130.6, 128.8, 128.7, 128.6, 128.5, 127.6, 127.0, 126.7, 124.8, 84.5, 55.8, 49.6, 49.7, 47.8, 33.8, 33.6, 22.6, 22.4, 21.9, 20.9, 11.5, 11.1 ppm. MS (EI): $m/z$ = 493 ($M^+$).

**Compound 101:** Yield 1.63 g (86%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 8.14 (s, 1 H), 7.58 (d, $^3J$ = 7.7 Hz, 2 H), 7.47–7.46 (m, 1 H), 7.33–7.13 (m, 10 H), 4.75 (s, 2 H), 4.42 (d, $^3J$ = 6.4 Hz, 1 H), 4.28–4.20 (m, 1 H), 3.55 (t, $^3J$ = 7.7 Hz, 2 H), 3.45–3.40 (m, 1 H), 3.38–3.31 (m, 1 H), 3.18 (t, $^3J$ = 7.7 Hz, 2 H), 1.65–1.55 (m, 2 H), 1.50–1.40 (m, 2 H), 1.19 (t, $^3J$ = 7.7 Hz, 3 H), 1.11 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.8, 168.5, 167.1, 138.1, 137.6, 137.5, 135.1, 134.0, 129.7, 129.4, 129.3, 129.2, 128.8, 128.6, 128.1, 127.8, 127.6, 127.0, 126.7, 126.6, 125.1, 68.5, 53.0, 49.6, 49.7, 42.3, 35.0, 22.8, 22.7, 11.6, 11.1 ppm. MS (EI): $m/z$ = 515 ($M^+$).

**Compound 102:** Yield 1.56 g (77%). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 7.45 (s, 1 H), 7.61 (d, $^3J$ = 7.7 Hz, 2 H), 7.39–7.24 (m, 1 H), 7.20–7.09 (m, 5 H), 7.01 (s, 2 H), 6.74 (dd, $^3J$ = 7.9, 2.1 Hz, 2 H), 6.54 (tt, $^3J$ = 7.9 Hz, 2.1 Hz, 1 H), 4.50–4.42 (m, 1 H), 4.40 (s, 1 H), 4.22 (d, $^3J$ = 6.2 Hz, 1 H), 3.80 (dd, $^3J$ = 10.2 Hz, $^2J$ = 14.2 Hz, 1 H), 2.20 (td, $^3J$ = 4.0 Hz, $^2J$ = 14.2 Hz, 1 H), 3.45 (t, $^3J$ = 7.7 Hz, 2 H), 3.00 (t, $^3J$ = 7.7 Hz, 2 H), 1.65–1.49 (m, 2 H), 1.59–1.39 (m, 2 H), 0.89 (t, $^3J$ = 7.7 Hz, 3 H), 0.63 (t, $^3J$ = 7.7 Hz, 3 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 172.3, 168.7, 167.4, 164.6, 164.5, 141.5, 141.1, 136.0, 135.7, 134.1, 128.9, 128.7, 128.3, 128.2, 127.8, 127.6, 126.1, 124.7, 110.9, 110.8, 102.0, 67.8, 51.0, 49.7, 49.6, 44.3, 35.0, 21.8, 21.7, 11.5, 11.3 ppm. MS (EI): $m/z$ = 551 ($M^+$).

**General Procedure for the Synthesis of α-Amino Alcohol:** L-Proline (11.5 mg, 0.10 mmol) was suspended in $CH_2Cl_2$ (2.5 mL), followed by the addition of the aldehyde (1.50 mmol) and azodicarboxylate (1.00 mmol). The reaction mixture was stirred at room temperature until the yellow colour of azodicarboxylate had disappeared. MeOH (2.5 mL) was added, followed by the careful addition of $NaBH_4$ (50 mg). The reaction was monitored by TLC, and the solvent was removed in vacuo after 20 min. The aqueous phase was diluted and extracted with EtOAc and washed three times with $NH_4Cl$ (50% aq. solution). The organic phase was dried with anhydrous $Na_2SO_4$ and concentrated in vacuo to give the products **103**–**104** (Table 5, Scheme 7). These underwent Boc deprotection with TFA (20% in DCM), the solvent was evaporated and N–N bond cleavage was performed as described above for compounds **76**–**86** to give compounds **105**–**106** (Scheme 7).

Table 5. Enantioselective synthesis of L-phenylglycinol and L-phenylalaninol.

| Entry | Substrate | Product | $R^1$ | Yield [%][a] | *ee* [%][b] | Config.[c] |
|---|---|---|---|---|---|---|
| 1 | **103** | **105** | Ph | 99 | 96 | *S* |
| 2 | **104** | **106** | Bn | 98 | 99 | *S* |

[a] Isolated yield. [b] Determined by comparison of the $[\alpha]_D^{20}$ of **105** and **106** against optically pure samples of L-phenylglycinol and L-phenylalaninol obtained from Aldrich. [c] The absolute configurations were based on the specific rotations of **105** and **106**.

**(*S*)-2-Amino-2-phenylethanol (105):** Yield 0.136 g (99%). $[\alpha]_D^{20}$ = –49.3 ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.25–7.21 (m, 2 H), 7.13–7.7 (m, 3 H), 4.21 (m, 1 H), 4.0–3.97 (m, 2 H), 2.1 (br. s, 2 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 144.1, 128.7, 128.6, 127.0, 126.8, 67.7, 62.5 ppm. MS (EI): $m/z$ = 137 ($M^+$).

**(*S*)-2-Amino-3-phenylpropan-1-ol (106):** Yield 0.148 g (98%). $[\alpha]_D^{20}$ = –27.0 ($c$ = 1.0, $CHCl_3$). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 7.21–7.19 (m, 2 H), 7.12–7.7 (m, 3 H), 3.88–3.85 (m, 1 H), 3.64–3.62 (m, 2 H), 3.10–3.08 (m, 1 H), 2.91–2.90 (m, 1 H), 2.66–2.64 (m, 1 H), 2.0 (br. s, 2 H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 138.3, 128.9, 128.2, 126.4, 68.7, 54.1 ppm. MS (EI): $m/z$ = 151 ($M^+$).

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