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Practical and efficient enantioselective synthesis of α-amino acids in aqueous media

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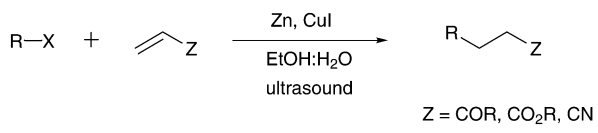
Enantiomerically pure natural and unnatural α-amino acids have been synthesized from a chiral methyleneoxazolidinone by means of a highly diastereoselective 1,4-conjugate addition of alkyl iodides in aqueous media. The zinc–copper conjugate addition reaction exhibits high chemoselectivity, with the possibility of using functionalized iodides, to afford a single diastereomer in short reaction times and with good yields.

Introduction

α-Amino acids are the fundamental building blocks of peptides and proteins and their physiological importance ensures sustained interest in their chemistry.[1] In addition, unnatural α-amino acids are expected to play key roles in improving the original properties and functions of proteins. The development of efficient methods for the preparation of various types of α-amino acids is desired not only in the field of organic chemistry but also in many biologically related areas. The synthesis of α-amino acids can be achieved by several general methods, the most common of which are the alkylation of α-halo acids, cyanide addition to imines (Strecker reaction) and the reduction of amino acrylates.[2] Indeed, asymmetric synthesis based on these methodologies represents a field of great importance.[3]

In recent decades organic chemists have been interested in developing organic synthesis in aqueous media.[4] The use of water as a solvent has particular advantages and these include low cost, safety and environmental compatibility. Moreover, the study of organic reactions in water may also contribute to our understanding of the basic mechanisms of life. A significant number of organic reactions have so far been performed under aqueous conditions, although the stereoselective control of these organic transformations is an issue of current interest.[5]

We recently became interested in studying the stereoselectivity of the aqueous conjugate addition reaction developed by Luche in 1986 (Scheme 1).[6] This methodology allows the 1,4-addition of alkyl halides to α,β-unsaturated carbonyl systems and has several advantages when compared to other methods, including simplicity, mild reaction conditions and high chemoselectivity.



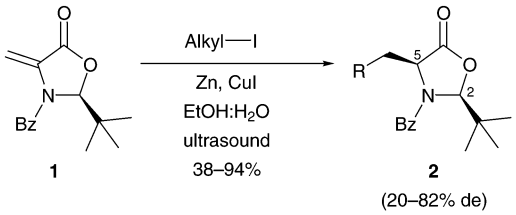
Scheme 1 Luche's conjugate addition.

In our investigation we discovered that achiral alkyl iodides add diastereoselectively to chiral α,β-unsaturated carbonyl compounds in good yields.[7] The stereoselectivity can be achieved using different chiral α,β-unsaturated systems such as methylenedioxolanones or methyleneoxazolidinones[8] and γ-substituted α,β-unsaturated esters. The stereoselectivity obtained in these reactions is consistent with the mechanism proposed by Luche: *i.e.*, single electron transfer (SET) from the metal surface to the carbon–halogen bond to generate an adsorbed radical, followed by 1,4-radical addition to the α,β-unsaturated system, which in turn gives rise to an enolate that is protonated by the solvent.[6]

We recently used this methodology to achieve the stereoselective synthesis of vitamin D_3 metabolites and various analogs.[9] In the work described here, we demonstrated that the conjugate addition products resulting from 1,4-addition to methyleneoxazolidinones can be efficiently transformed into enantiopure α-amino acids. Although several new procedures for the synthesis of racemic α-amino acids in water have recently been developed,[10] the stereoselective synthesis of α-amino acids in aqueous media has not been reported to date.

Results and discussion

In previous studies[7b] we found that the conjugate addition of alkyl iodides to (2*S*)-*N*-benzoyl-5-methyleneoxazolidinone (**1**) generally proceeds with good yields (up to 94%) but with variable diastereoselectivity (20–82% de, Scheme 2). The stereochemistry of the major diastereomer (*cis*) was explained in terms of diastereoselective protonation of the intermediate enolate, which occurs *anti* with respect to the bulky *tert*-butyl group. Unfortunately, the synthesis of enantiomerically pure amino acids was a laborious process since the separation of diastereomers required the use of HPLC techniques. For this reason we explored the possibility of increasing the diastereoselectivity of the reaction by changing the *N*-protecting group. Some years ago, Beckwith reported that, in radical conjugate addition reactions, the nature of the *N*-protecting group in methyleneoxazolidinones has a significant influence on the stereoselectivity.[11]



Scheme 2 Conjugate addition reaction to *N*-Bz methyleneoxazolidinone **1**.

In an effort to explore this stereochemical parameter, we pursued the synthesis of *N*-Cbz methyleneoxazolidinone **3**. Compound **3** was prepared in a four-step synthetic procedure from *S*-methyl-(*R*)-cysteine according to the literature method.[12] It was found that the zinc–copper conjugate addition reaction of alkyl iodides (**4a–f**) with *N*-Cbz oxazolidinone **3** afforded the conjugate addition products **5a–f** in excellent yields with high diatereoselectivity; only one diastereomer can be detected by ^{1}H NMR spectroscopy (Table 1). As in the radical conjugate additions to **3** using organomercuric reagents,[11] the stereochemistry of the products was assigned as *cis* by NOE experiments. As

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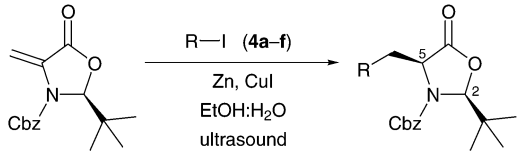
Table 1 Zinc–copper conjugate addition of iodides **4a–f** to *N*-Cbz methyleneoxazolidinone **3**

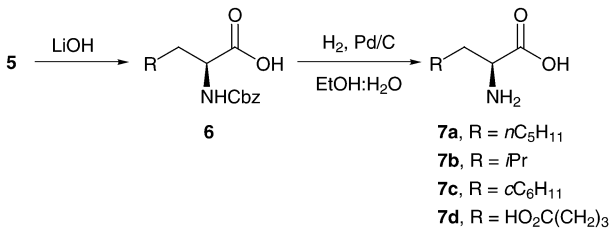


Entry	R–I	Yield (%)[a]	*cis* : *trans*[b]
1	$nC_5H_{11}I$ (**4a**)	96	>98 : 2
2	iC_3H_5I (**4b**)	76	>98 : 2
3	$cC_6H_{11}I$ (**4c**)	98	>98 : 2
4	$MeO_2C(CH_2)_3I$ (**4d**)	99	>98 : 2
5	$HO(CH_2)_3I$ (**4e**)	60	>98 : 2
6	$HO(CH_2)_{12}I$ (**4f**)	96	>98 : 2

[a] Isolated yield. [b] *cis* : *trans* ratio determined by ^{1}H NMR spectroscopy.

shown in Table 1, the reaction exhibited high chemoselectivity and it was possible to use iodides bearing different functional groups such as free hydroxy, ester or amino groups. The reaction also gave high yields in short reaction times (less than 90 minutes).

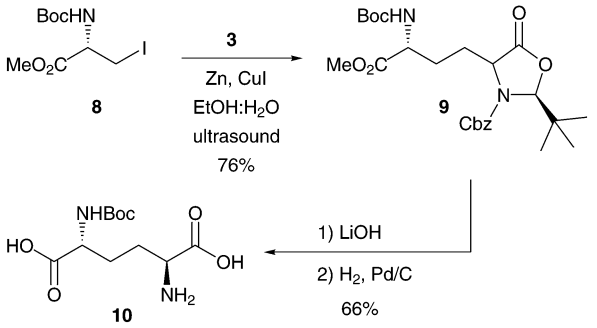
Having obtained the conjugate addition products, we turned our attention to the synthesis of the corresponding enantiomerically pure α-amino acids. The conversion of the oxazolidinone moiety into the α-amino acid can be performed by acid hydrolysis in the case of *N*-Bz oxazolidinones[13] or by direct hydrogenolysis for *N*-Cbz oxazolidinones.[11] In our case we decided to employ a recently reported two-step sequence,[12] using firstly LiOH to obtain *N*-Cbz-α-amino acids, which are suitable for peptide coupling technology, followed by hydrogenolysis with Pd/C in aqueous ethanol (Scheme 3). In this way, natural and unnatural alkylic α-amino acids such as (*S*)-2-aminooctanoic acid (**7a**), (*S*)-leucine (**7b**) or (*S*)-cyclohexyl alanine (**7c**) were obtained in good yields (74–94%) as enantiomerically pure compounds. This experimental procedure was also used to convert the conjugate addition product **5d** into the α-amino acid **7d** (100%), although in this case the ester group was also hydrolyzed. Unfortunately, we were unable to obtain the α-amino acids derived from the hydroxy-free conjugate addition products since the hydrogenolysis reaction was not effective.



Scheme 3 Synthesis of enantiopure α-amino acids **7a–d**.

As part of this study we also exploited the synthetic utility of this methodology by using more complex iodides, such as D-serine iodide derivative **8** (Scheme 4).[14] Interestingly, the reaction of iodide **8** with oxazolidinone **3** afforded the conjugate addition product **9** as the only diastereomer, as detected by ^{1}H NMR spectroscopy, in 76% yield. Basic hydrolysis followed by hydrogenolysis led to the synthesis of *N*-Boc-protected diacid **10**, which is an interesting nor-analog of *meso*-diaminopimelic acid. The latter compound is a naturally occurring amino acid biosynthesized in bacteria and higher plants and is of interest as a target for antibiotic design.[15]

In conclusion, α-amino acids can be synthesized in aqueous media, at room temperature and in short reaction times to give high yields using a short synthetic sequence. The key step of the synthesis is the highly diastereoselective ultrasound-induced conjugate addition (>96% de) of alkyl iodides over the chiral methyleneoxazolidinone **3** in aqueous media. The chiral auxiliary can be efficiently removed to give enantiomerically pure functionalized α-amino acids.



Scheme 4 Synthesis of **10**.

Experimental

Melting points were measured on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-1000 polarimeter using a sodium lamp (589 nm) in cells of 10 cm path length. Concentrations are given in units of 10^{-2} g cm^3. Infrared spectra were recorded on a Matson FTIR spectrophotometer and the frequencies (ν) as absorption maxima are given in wavenumbers (cm^{-1}) relative to polystyrene (1603 cm^{-1}). NMR spectra were acquired on a Bruker AC-200F spectrometer (^{1}H, 200 MHz; ^{13}C, 50 MHz). Chemical shifts (δ) are given in ppm downfield from $SiMe_4$ using the residual solvent signals as reference. The multiplicities of ^{1}H signals are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; m = multiplet. All coupling constants, *J*, are reported in Hz. ^{13}C NMR spectra were acquired on broad band decoupled mode and the carbon types were assigned using DEPT sequences. Mass spectra were recorded on a Fisons VG-Quattro spectrometer using electron ionization (EI) at 70 eV or FAB. FAB spectra were recorded using thioglycerol as a matrix. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh) by Still's method.[16] Thin layer chromatography was carried out on Merck silica gel 60 F_{254} (layer thickness 0.2 mm) and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid or *p*-anisaldehyde reagent followed by heating. Unless stated otherwise, all reactions were conducted in flame-dried glassware under a positive pressure of argon. Reaction temperatures refer to external bath temperatures. All dry solvents were distilled under argon immediately prior to use. Absolute MeOH and EtOH were distilled from Mg turnings. For conjugate addition reactions, Milli-Q water was used and the solvent mixture EtOH : H_2O was deoxygenated by bubbling through a positive pressure of argon during 10 min. Zinc dust (325 mesh) was used without purification and copper iodide was purified by recrystallization from saturated potassium iodide solution.[17] All other reagents were commercial products and were used as received. Sonications were carried out in a Selecta SE3000513 (50 kHz, 150 W) cleaning bath, which was filled with water and the temperature controlled (18–20 °C) by running tap water through a stainless steel coil.

General procedure for conjugate addition of alkyl iodides (4a–f) to chiral oxazolidinone 3

To a sonicated solution of oxazolidinone **3** (1 equiv.) and alkyl iodide (**4a–f**, 2 equiv.) in aqueous EtOH (3 cm^3, 70% v/v) was added CuI (2 equiv.) and Zn (6 equiv.). After a few minutes, more aqueous EtOH (5 cm^3, 70% v/v) was added and sonication was continued for 45–90 min. The mixture was diluted with Et_2O (25 cm^3), sonicated for 10 min, and filtered through a short

pad of Celite, washing the solids with EtOAc (3 × 30 cm^3). The combined organic phases were washed with brine (30 cm^3), dried (Na_2SO_4 anhydrous), filtered, and concentrated under reduced pressure (20–30 mmHg). The residue was purified by flash chromatography to afford, after concentration, the desired 1,4-addition product (76–99% yield).

(2*S*,4*S*)-2-(1,1-Dimethylethyl)-4-hexyl-5-oxo-3-oxazolidinecarboxylic acid phenylmethyl ester (5a)

Following the general experimental procedure, a mixture of oxazolidinone **3** (100 mg, 0.345 mmol) and 1-iodopentane (0.090 cm^3, 0.69 mmol) was treated with CuI (131 mg, 0.69 mmol) and Zn (135 mg, 2.07 mmol) to give, after column chromatography (hexanes : EtOAc, 9 : 1), **5a** (120 mg, 96%) as the only diastereomer (colorless oil). R_f 0.57 (hexanes : EtOAc, 7 : 3); $[\alpha]_D^{20}$ +31.6 (*c* 0.1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2859–2958 (CH), 1794 (CO), 1721, 1482 (C=C), 1466; δ_H (200 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 6.8, CH_3), 0.97 (9 H, s, Me_3C), 1.23–1.95 (10 H, m, 5 × CH_2), 4.26 (1 H, t, *J* 7.3, NCHCO), 5.18 (2 H, s, CH_2Ar), 5.56 (1 H, s, NCHO), 7.37 (5 H, s, ArH); δ_C (50 MHz, $CDCl_3$) 14.0 (CH_3), 22.5 (CH_2), 24.9 (3 × CH_3), 26.3 (CH_2), 28.9 (CH_2), 31.5 (CH_2), 33.4 (CH_2), 36.9 (C), 57.2 (CH), 68.2 (CH_2), 96.3 (CH), 128.4 (2 × CH), 128.59 (CH), 128.64 (2 × CH), 135.3 (C), 156.0 (C), 172.8 (C); *m*/*z* (EI) 361 (1%, M^+), 304 (23 $M^+ - C_4H_9$), 91 (100).

(2*S*,4*S*)-2-(1,1-Dimethylethyl)-4-(2-methylpropyl)-5-oxo-3-oxazolidinecarboxylic acid phenylmethyl ester (5b)

Following the general experimental procedure, a mixture of oxazolidinone **3** (100 mg, 0.345 mmol) and 2-iodopropane (0.07 cm^3, 0.691 mmol) was treated with CuI (131 mg, 0.69 mmol) and Zn (135 mg, 2.07 mmol) to give, after column chromatography (hexanes : EtOAc, 9 : 1), **5b** (87 mg, 76%) as the only diastereomer (colorless oil). R_f 0.56 (hexanes : EtOAc, 7 : 3); $[\alpha]_D^{22}$ +53.0 (*c* 0.1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2872–959 (CH), 1793 (CO), 1721, 1497 (C=C), 1467; δ_H (200 MHz, $CDCl_3$) 0.92 (6 H, d, *J* 6.3, 2 × CH_3), 0.97 (9 H, s, Me_3C), 1.58–2.07 (3 H, m, $CHCH_2$), 4.33 (1 H, dd, *J* 7.8 and 6.3, NCHCO), 5.17 (2 H, s, CH_2Ar), 5.56 (1 H, s, NCHO), 7.37 (5 H, s, ArH); δ_C (50 MHz, $CDCl_3$) 21.9 (CH_3), 22.7 (CH_3), 24.9 (3 × CH_3), 36.9 (C), 42.4 (CH_2), 55.5 (CH), 68.3 (CH_2), 96.3 (CH), 128.6 (5 × CH), 135. 2 (C), 156.0 (C), 173.0 (C), 198.5 (C); *m*/*z* (EI) 333 (1%, M^+), 276 (49, $M^+ - C_4H_9$), 91 (100).

(2*S*,4*S*)-4-(Cyclohexylmethyl)-2-(1,1-dimethylethyl)-5-oxo-3-oxazolidinecarboxylic acid phenylmethyl ester (5c)

Following the general experimental procedure, a mixture of oxazolidinone **3** (60 mg, 0.207 mmol) and iodocyclohexane (0.054 cm^3, 0.415 mmol) was treated with CuI (79 mg, 0.415 mmol) and Zn (81 mg, 1.244 mmol) to give, after column chromatography (hexanes : EtOAc, 9 : 1), **5c** (75 mg, 98%) as the only diastereomer (colorless oil). R_f 0.57 (hexanes : EtOAc, 7 : 3); $[\alpha]_D^{23}$ +54.9 (*c* 0.07 in CH_3Cl); ν_{max} (film)/cm^{-1} 2851–2924 (CH), 1793 (C=O), 1721, 1481 (C=C), 1448; δ_H (200 MHz, $CDCl_3$) 0.97 (9 H, s, Me_3C), 0.89–1.82 (13 H, m, $cC_6H_{11}CH_2$), 4.37 (1 H, dd, *J* 7.8 and 5.4, NCHCO), 5.17 (2 H, dd, *J* 12.2 and 15.6, CH_2Ar), 5.56 (1 H, s, NCHO), 7.37 (5 H, s, ArH); δ_C (50 MHz, $CDCl_3$) 24.9 (3 × CH_3), 25.9 (2 × CH_2), 26.4 (2 × CH_2), 32.8 (CH_2), 33.4 (CH_2), 34.2 (CH), 36.9 (C), 41.1 (CH_2), 54.9 (CH), 96.3 (CH), 128.6 (5 × CH), 135.2 (C), 156.0 (C), 173.1 (C); *m*/*z* (EI) 316 (5%, $M^+ - C_4H_9$), 91 (100).

(2*S*,4*S*)-2-(1,1-Dimethylethyl)-4-(methoxycarbonylbutyl)-5-oxo-3-oxazolidinecarboxylic acid phenylmethyl ester (5d)

Following the general experimental procedure, a mixture of oxazolidinone **3** (60 mg, 0.207 mmol) and methyl 4-iodobutyrate (0.056 cm^3, 0.415 mmol) was treated with CuI (79 mg, 0.415 mmol) and Zn (81 mg, 1.244 mmol) to give, after column chromatography (hexanes : EtOAc, 9 : 1), **5d** (80 mg, 99%) as the only diastereomer (colorless oil). R_f 0.50 (hexanes : EtOAc, 7 : 3); $[\alpha]_D^{21}$ +43.0 (*c* 0.1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2872–2958 (CH), 1792, 1723 (C=O), 1482, 1457 (C=C), 1197; δ_H (200 MHz, $CDCl_3$) 0.97 (9 H, s, Me_3C), 1.52–2.05 (6 H, m, 3 × CH_2), 2.28 (2 H, dd, *J* 7.3 and 6.8, CH_2CO_2), 3.67 (3 H, s, OCH_3), 4.26 (1 H, dd, *J* 7.3 and 6.8, NCHCO), 5.18 (2 H, s, CH_2Ar), 5.56 (1 H, s, NCHO), 7.37 (5 H, s, ArH); δ_C (50 MHz, $CDCl_3$) 24.4 (CH_2), 24.9 (3 × CH_3), 25.8 (CH_2), 33.0 (CH_2), 33.7 (CH_2), 36.9 (C), 51.5 (CH), 56.9 (CH_3), 68.3 (CH_2), 96.3 (CH), 128.5 (2 × CH), 128.6 (CH), 128.7 (2 × CH), 135.2 (C), 156.0 (C), 172.6 (C), 173.7 (C); *m*/*z* (EI) 391 (3%, M^+), 334 (16, $M^+ - C_4H_9$), 91 (100).

(2*S*,4*S*)-2-(1,1-Dimethylethyl)-4-(4-hydroxybutyl)-5-oxo-3-oxazolidinecarboxylic acid phenylmethyl ester (5e)

Following the general experimental procedure, a mixture of oxazolidinone **3** (56 mg, 0.193 mmol) and 3-iodopropanol (0.040 cm^3, 0.415 mmol) was treated with CuI (79 mg, 0.415 mmol) and Zn (81 mg, 1.244 mmol) to give, after column chromatography (hexanes : EtOAc, 9 : 1), **5e** (40 mg, 60%) as the only diastereomer (colorless oil). R_f 0.1 (hexanes : EtOAc, 7 : 3); ν_{max} (film)/cm^{-1} 3441 (OH), 2872–2959 (CH), 1719, 1790 (C=O), 1457, 1482 (C=C), 1326, 1198, 1040; δ_H (200 MHz, $CDCl_3$) 0.96 (9 H, s, Me_3C), 1.55–1.98 (6 H, m, 3 × CH_2), 3.59 (2 H, dd, *J* 6.3 and 5.8, CH_2OH), 4.28 (1 H, dd, *J* 7.3 and 6.8, NCHCO), 5.17 (2 H, s, CH_2Ar), 5.55 (1 H, s, NCHO), 7.37 (5 H, s, ArH); δ_C (50 MHz, $CDCl_3$) 22.6 (CH_2), 24.9 (3 × CH_3), 32.1 (CH_2), 33.0 (CH_2), 36.9 (C), 57.0 (CH), 62.4 (CH_2), 68.4 (CH_2), 96.4 (CH), 128.5 (2 × CH), 128.7 (3 × CH), 135.2 (C), 156.0 (C), 172.7 (C).

(2*S*,4*S*)-2-(1,1-Dimethylethyl)-4-(4-hydroxytridecyl)-5-oxo-3-oxazolidinecarboxylic acid phenylmethyl ester (5f)

Following the general experimental procedure, a mixture of oxazolidinone **3** (60 mg, 0.207 mmol) and 12-iodododecanol (129 mg, 0.415 mmol) was treated with CuI (79 mg, 0.415 mmol) and Zn (81 mg, 1.244 mmol) to give, after column chromatography (hexanes : EtOAc, 9 : 1), **5f** (95 mg, 96%) as the only diastereomer (colorless oil). R_f 0.35 (hexanes : EtOAc, 7 : 3); $[\alpha]_D^{25}$ +26.4 (*c* 0.1 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3440 (OH), 2854–2925 (CH), 1721, 1794 (C=O), 1482 (C=C), 1465, 1325, 1198, 1041; δ_H (200 MHz, $CDCl_3$) 0.97 (9 H, s, Me_3C), 1.26–1.98 (24 H, m, 12 × CH_2), 3.64 (2 H, m, CH_2OH), 4.26 (1 H, t, *J* 7.3, NCHCO), 5.18 (2 H, s, CH_2Ar), 5.55 (1 H, s, NCHO), 7.37 (5 H, s, ArH); δ_C (50 MHz, $CDCl_3$) 24.9 (3 × CH_3), 25.7 (CH_2), 26.4 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 32.8 (CH_2), 33.4 (CH_2), 36.9 (C), 57.2 (CH), 63.1 (CH_2), 63.1 (CH_2), 68.2 (CH_2), 96.3 (CH), 128.4 (2 × CH), 128.6 (CH), 128.6 (2 × CH), 135.3 (C), 156.0 (C), 172.8 (C); *m*/*z* (FAB) 476 (10%, $M^+ + H$).

(α*R*,2*S*,4*S*)-α-{[(1,1-Dimethylethoxy)carbonyl]amino}-2-(1,1-dimethylethyl)-5-oxo-3-[(phenylmethoxy)carbonyl]-4-oxazolidinebutanoic acid methyl ester (9)

Following the general experimental procedure, a mixture of oxazolidinone **3** (100 mg, 0.346 mmol) and iodide **8** (220 mg, 0.691 mmol) was treated with CuI (132 mg, 0.691 mmol) and Zn (135 mg, 2.074 mmol) to give, after column chromatography (hexanes : EtOAc, 8 : 2), **9** (132 mg, 78%) as the only diastereomer (colorless oil). R_f 0.23 (hexanes : EtOAc, 7 : 3); ν_{max} (film)/cm^{-1} 3372 (NH), 2974–2875 (CH), 1791, 1719 (C=O), 1500, 1455 (C=C), 1319, 1170, 1040; δ_H (200 MHz, $CDCl_3$) 0.95 (9 H, s, Me_3CC), 1.44 (9 H, s, Me_3CO), 1.97 (4 H, m, 2 × CH_2), 3.74 (3 H, s, OCH_3), 4.24–4.31 (2 H, m, 2 × NCHCO), 5.06 (1 H, br m, NH), 5.18 (2 H, s, CH_2Ar), 5.55 (1 H, s, O_2CH), 7.33–7.41 (5 H, m, ArH); δ_C (50 MHz, $CDCl_3$) 24.9 (3 × CH_3), 28.3 (3 × CH_3), 29.2 (CH_2), 29.6 (CH_2), 36.8 (C), 52.4 (CH), 53.1 (CH), 56.7 (CH_3), 68.5 (CH_2), 80.0 (C), 96.5 (CH), 128.5 (2 × CH),

128.7 (CH), 128.7 (2 CH), 135.2 (C), 155.3 (C), 155.9 (C), 172.2 (C), 172.6 (C); *m/z* (EI) 391 (5%, $M^+ - C_5H_9O_2$), 91 (100).

General experimental procedure for the preparation of α-amino acids

To a cooled (0 °C) solution of the conjugate addition product **5a–d** or **9** (50–100 mg, 1 equiv.) in THF : H_2O (3 : 1, 8–15 cm^3) was added LiOH (2 equiv.). After 1 h stirring, water (5–8 cm^3) was added and the organic phase was evaporated under reduced pressure. The aqueous layer was neutralized and extracted with EtOAc (3 × 25 cm^3). The combined organic phases were dried, filtered and the solvent evaporated under reduced pressure. The protected amino acid was dissolved in deoxygenated aqueous EtOH (5–10 cm^3, 70% v/v), Pd/C (10%, 0.1 equiv.) was added, and the mixture was stirred at rt under a H_2 atmosphere (balloon) for 1 h. The resulting mixture was filtered through a short pad of Celite washing the solids with aqueous EtOH (3 × 10 cm^3, 70% v/v). The filtrate was concentrated under vacuum to afford the α-amino acids as white solids (74–100% yield).

(2*S*)-2-Aminooctanoic acid (7a)[18]

Following the general experimental procedure, reaction of **5a** (100 mg, 0.277 mmol) with LiOH (23 mg, 0.553 mmol) afforded 71 mg of a colorless oil, which was stirred in a H_2 atmosphere in the presence of Pd/C (10%, 25 mg, 0.024 mmol) to give **7a** (34 mg, 94%) as a white solid, mp 254–256 °C; $[\alpha]_D^{37}$ +16.0 (*c* 0.3 in 1 M HCl) (lit.,[18] +21); δ_H (200 MHz, D_2O) 0.70 (3 H, t, *J* 6.7, CH_3), 1.15 (8 H, m, 4 × CH_2), 1.76 (2 H, m, CH_2), 3.81 (1 H, m, NCHCO); δ_C (50 MHz, D_2O) 14.3 (CH_3), 22.9 (CH_2), 25.1 (CH_2), 28.9 (CH_2), 31.0 (CH_2), 31.7 (CH_2), 54.7 (CH); *m/z* (FAB) 160 (100, $M^+ + H$).

L-Leucine (7b)[19]

Following the general experimental procedure, reaction of **5b** (60 mg, 0.180 mmol) with LiOH (15 mg, 0.360 mmol) afforded 65 mg of a colorless oil, which was stirred in a H_2 atmosphere in the presence of Pd/C (10%, 19 mg, 0.018 mmol) to give **7b** (22 mg, 93%) as a white solid, mp 269–271 °C; $[\alpha]_D^{22}$ +14.5 (*c* 0.7 in 6 M HCl) (lit.,[19] +15.5); δ_H (200 MHz, D_2O) 0.79 (6 H, d, *J* 3.0, 2 × CH_3), 1.46–1.67 (3 H, m, $CHCH_2$), 3.56 (1 H, m, NCHCO); δ_C (50 MHz, D_2O) 21.9 (CH_3), 23.1 (CH_3), 25.2 (CH), 40.8 (CH_2), 54.5 (CH), 176.5 (C); *m/z* (FAB) 132 (100%, $M^+ + H$).

(α*S*)-α-Aminocyclohexanepropanoic acid (7c)[20]

Following the general experimental procedure, reaction of **5c** (52 mg, 0.134 mmol) with LiOH (12 mg, 0.278 mmol) afforded a colorless oil, which was stirred in a H_2 atmosphere in the presence of Pd/C (10%, 15 mg, 0.014 mmol) for 2 days to give **7c** (17 mg, 74%) as a white solid. mp 234–237 °C; $[\alpha]_D^{29}$ +9.1 (*c* 0.1 in 1 M HCl) (lit.,[20] +12 ± 1); δ_H (200 MHz, D_2O) 0.65–1.69 (13 H, m, $cC_6H_{11}CH_2$), 3.60 (1 H, dd, *J* 8.5 and 6.1, NCHCO); δ_C (50 MHz, D_2O) 26.5 (CH_2), 26.7 (CH_2), 26.9 (CH_2), 32.9 (CH_2), 34.1 (CH_2), 34.4 (CH), 39.4 (CH_2), 53.8 (CH), 191.5 (C); *m/z* (FAB) 172 (100, $M^+ + H$).

(2*S*)-Aminoheptanedioic acid (7d)[21]

Following the general experimental procedure, reaction of **5d** (60 mg, 0.153 mmol) with LiOH (19 mg, 0.460 mmol) afforded a colorless oil, which was stirred in a H_2 atmosphere in the presence of Pd/C (10%, 16 mg, 0.015 mmol) to give **7d** (29 mg, 100%) as a white solid, mp 264–267 °C; $[\alpha]_D^{25}$ +19.3 (*c* 0.5 in 1 M HCl) (lit.,[21] +20.5); δ_H (200 MHz, D_2O) 1.27 (2 H, m, CH_2), 1.49 (2 H, m, CH_2), 1.70 (2 H, m, CH_2), 2.24 (2 H, t, *J* 7.3, CH_2CO_2), 3.58 (1 H, t, *J* 6.1, NCHCO); δ_C (50 MHz, D_2O) 24.9 (CH_2), 25.1 (CH_2), 31.1 (CH_2), 34.8 (CH_2), 55.7 (CH), 175.7 (C), 180.2 (C); *m/z* (EI) 144 (23%, $M^+ - CO_2H$), 69 (100).

(2*S*,5*R*)-2-Amino-5-{[(1,1-dimethylethoxy)carbonyl]amino} hexanedioic acid (10)

Following the general experimental procedure, reaction of **9** (100 mg, 0.203 mmol) with LiOH (34 mg, 0.812 mmol) afforded a white solid, which was stirred in a H_2 atmosphere in the presence of Pd/C (10%, 19 mg, 0.018 mmol) for 2 h to give **10** (35 mg, 66%) as a white solid. $[\alpha]_D^{24}$ −8.9 (*c* 0.3 in EtOH); δ_H (200 MHz, D_2O) 1.27 (9 H, s, Me_3CO), 1.58–1.87 (4 H, m, 2 × CH_2), 3.63 (1 H, t, *J* 5.5, NCHCO), 3.92 (1 H, m, NCHCO); δ_C (50 MHz, D_2O) 28.0 (2 × CH_2), 28.7 (3 × CH_3), 30.7 (2 × CH), 55.2 (C), 82.6 (C), 158.7 (C), 174.8 (C); *m/z* (EI) 219 (1%, $M^+ - C_4H_9$), 203 (20, $M^+ - C_4H_9O$), 68 (100); *m/z* (FAB) 277 (25%, $M^+ + H$).

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