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tert-Butyl esters of peptides as organocatalysts for the asymmetric aldol reaction

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ABSTRACT

Enantioselective aldol reactions between ketones and aldehydes were shown to be catalysed by a variety of *tert*-butyl esters of peptides. Amongst the peptides tested, Pro-Glu(O^{t}Bu)-O^{t}Bu proved to be the best, affording the product in good to excellent yields, diastereoselectivities and enantioselectivities.

1. Introduction

Since List, Lerner and Barbas employed proline, a natural amino acid, as a catalyst for intermolecular aldol reactions,[1] organocatalysis has flourished to such an extent that it is nowadays recognized as the third major pillar of asymmetric catalysis, alongside transition metal complex catalysis and biocatalysis.[2,3] Amongst the various reactions for the enantioselective formation of a C–C bond, the asymmetric aldol reaction is one of the most important.[4] Thus, researchers have designed and synthesized a number of proline derivatives, either containing bioisosteric groups such as sulfonamides and tetrazoles,[5] or prolinamides which contain additional chiral functionalities that are able to act as hydrogen bond donors.[6] The family of peptides has also been studied for their potential as organocatalysts.[7] Peptides were amongst the first molecules to be used as catalysts in asymmetric aldol reactions, however, they led to low to moderate enantioselectivities in most cases.[8,9] In most of the above cases, DMSO or an organic solvent was utilized as the reaction medium. Over the last few years, water has attracted attention as the reaction medium, since it is an abundant, safe and environmentally friendly solvent. Hayashi et al. and Barbas et al. were amongst the first to report on successful organocatalytic protocols in the presence of water.[10] Since then, a variety of proline derivatives[11] and amino acid derivatives[12] have been designed and employed successfully in aqueous environments.

2. Results and discussion

In our previous endeavours on enantioselective aldol reactions, we have concluded that prolinamides bearing either a thiourea[6f,g] or a urea moiety,[6h] were excellent organocatalysts in promoting the aldol reaction; however these molecules were only active in organic solvents. More recently, we introduced a number of Pro-Phe tripeptides bearing a *tert*-butyl ester of an amino acid at the C-terminus, where depending on the amino acid employed, these molecules could catalyse the aldol reaction either in an organic solvent or in an aqueous medium.[13] Bearing these results in mind and our previous involvement in organocatalysis,[14] we further questioned whether we could employ *tert*-butyl esters of dipeptides or tripeptides as potential organocatalysts. The synthesis of these peptides is shown in Scheme 1.

Starting from the Cbz-protected amino acid at the N-terminus, a standard peptide coupling employing carbodiimide chemistry led to protected dipeptides or tripeptides; after hydrogenation under Pd/C, the deprotected peptides **1a**–**4b** were obtained in moderate to high yields in two steps. To fully demonstrate the potential of peptides bearing *tert*-butyl esters, we tested four different categories of peptides: (i) dipeptides bearing the primary amine of phenylalanine and an amide at the α-carboxylic acid, H-Phe-Phe-O^{t}Bu **1a**, H-Phe-Phg-O^{t}Bu **1b** and H-Phe-Glu(O^{t}Bu)-O^{t}Bu **1c**; (ii) dipeptides bearing the primary amine of α-*tert*-butyl aspartate and an amide at the β-carboxylic acid, H-Asp(Phe-O^{t}Bu)-O^{t}Bu **2a**, H-Asp(Gly-O^{t}Bu)-O^{t}Bu **2b** and H-Asp(Val-O^{t}Bu)-O^{t}Bu **2c**; (iii) tripeptides bearing the primary amine of aspartic acid and two amides at the α- and the β-carboxylic acids, H-Asp[Asp(O^{t}Bu)-O^{t}Bu]-Asp(O^{t}Bu)-O^{t}Bu **3a** and H-Asp[Glu(O^{t}Bu)-O^{t}Bu]-Glu(O^{t}Bu)-O^{t}Bu **3b** and finally (iv) dipeptides bearing the secondary amine of proline, Pro-Ala-O^{t}Bu **4a** and Pro-Glu(O^{t}Bu)-O^{t}Bu **4b**. In order to test organic solvents and aqueous media, all of the catalysts were tested under both reaction conditions (Table 1).

The dipeptides based on phenylalanines **1a**–**c** afforded the aldol products in excellent yields in almost all cases, however, the diastereoselectivity and the enantioselectivity were low (entries 1–6, Table 1). We had previously shown that the tripeptide

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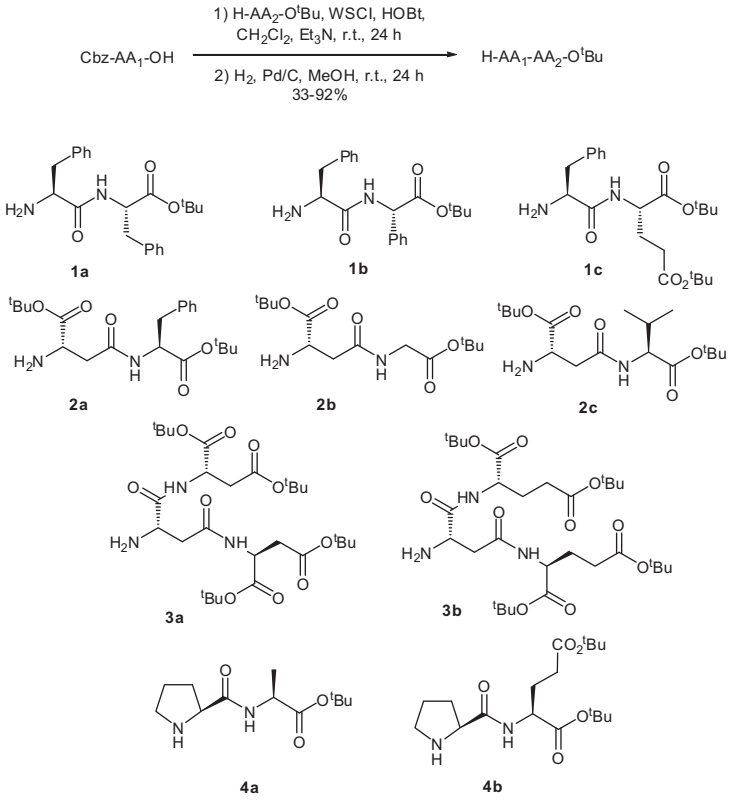
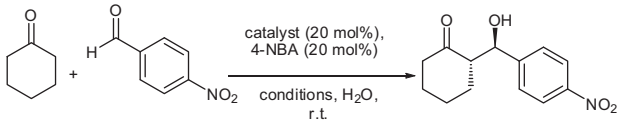


Scheme 1. Synthesis of *tert*-butyl esters of peptides **1a**–**4b**.

Pro-Phe-Phg-O^{t}Bu was an excellent catalyst for aldol reactions both in organic and aqueous media.[13] Unfortunately, the high importance of the proline unit is evident, since catalyst **1b** lost its ability to provide high diastereo- and enantiocontrol. Moving forward to the α-*tert*-butyl aspartate peptides **2a**–**c**, where the amide bond is one carbon atom further away, poor selectivities were also obtained in aqueous solvents, while in toluene, the reactions were sluggish (entries 7–12, Table 1). It has been shown that more having than one hydrogen bond site in an organocatalyst has a positive effect on the properties of the catalyst.[6,13] Unfortunately, although catalysts **3a** and **3b** provided the aldol product with higher enantioselectivities than catalysts **2a**–**c**, the selectivities were moderate (entries 13–16, Table 1). In order to recover the high levels of diastereoselectivity and enantioselectivity, the privileged structure of proline had to be employed (entries 17–20, Table 1). Although Pro-Ala-O^{t}Bu **4a** proved to be sluggish in promoting the aldol reaction, Pro-Glu(O^{t}Bu)-O^{t}Bu **4b** provided the aldol product with high enantiomeric excess under both reaction conditions. In particular, utilizing brine as the reaction medium, a quantitative yield of the product was obtained along with high diastereoselectivity (entry 20, Table 1). It should be noted that similar high yields and selectivities have been reported using tripeptides.[13]

After identifying the optimum catalyst, the reaction conditions were scrutinized (Table 2). Amongst the various solvents tested, acetonitrile provided the best results, while aqueous media led to slightly inferior selectivities (entries 1–14, Table 2). The acid additive was next studied (entries 15–20, Table 2). Strong acids did not provide any product, because they deactivate the catalyst via salt formation, while it seems that there is a small window of pK_a for the acid to provide both high diastereoselectivity and enantioselectivity. Furthermore, the beneficial role of water was highlighted (entry 5 vs 21, Table 2). Finally, a lower temperature, lower ketone/aldehyde ratio or lower catalyst loading proved to be dentrimental for the efficiency of the reaction (entries 22–25,

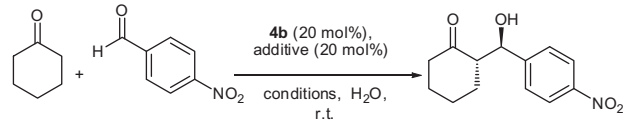
Table 1
Catalyst screening for the enantioselective aldol reaction



Entry	Catalyst	Conditions	Yield[a] (%)	dr[b]	ee[c] (%)
1	**1a**	Toluene, 48 h	22	69:31	80
2	**1a**	Brine, 24 h	97	54:46	49
3	**1b**	Toluene, 48 h	100	50:50	8
4	**1b**	Brine, 24 h	100	38:62	38
5	**1c**	Toluene, 48 h	90	50:50	9
6	**1c**	Brine, 24 h	98	39:61	30
7	**2a**	Toluene, 48 h	100	30:70	16
8	**2a**	Brine, 24 h	95	36:64	37
9	**2b**	Toluene, 72 h	n.r.	—	—
10	**2b**	Brine, 72 h	43	38:62	39
11	**2c**	Toluene, 72 h	n.r.	—	—
12	**2c**	Brine, 72 h	35	42:58	33
13	**3a**	Toluene, 48 h	43	45:55	67
14	**3a**	Brine, 24 h	97	42:58	66
15	**3b**	Toluene, 48 h	90	33:67	40
16	**3b**	Brine, 24 h	94	50:50	37
17	**4a**	Toluene, 72 h	26	70:30	70
18	**4a**	Brine, 72 h	n.r.	—	—
19	**4b**	Toluene, 48 h	38	76:24	90
20	**4b**	Brine, 24 h	100	90:10	87

[a] Isolated yield.
[b] The diastereomeric ratio (dr) *anti*:*syn* was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[c] The enantiomeric excess (ee) for the *anti*-diastereomer was determined by chiral HPLC. 4-NBA: 4-nitrobenzoic acid.

Table 2
Enantioselective aldol reaction of cyclohexanone with 4-nitrobenzaldehyde using catalyst **4b**



5a 6a 7a

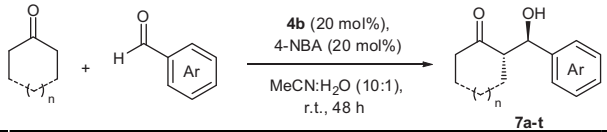
Entry	Conditions	Yield[a] (%)	dr[b]	ee[c] (%)
1	Toluene, 4-NBA, rt, 48 h	38	76:24	90
2	Pet. Ether, 4-NBA, rt, 48 h	37	87:13	86
3	Et_2O, 4-NBA, rt, 24 h	100	86:14	78
4	THF, 4-NBA, rt, 48 h	100	88:12	76
5	MeCN, 4-NBA, rt, 48 h	100	91:9	92
6	$CHCl_3$, 4-NBA, rt, 48 h	95	85:15	72
7	CH_2Cl_2, 4-NBA, rt, 48 h	97	83:17	74
8	AcOEt, 4-NBA, rt, 48 h	95	85:15	76
9	DMSO, 4-NBA, rt, 48 h	100	80:20	73
10	MeOH, 4-NBA, rt, 48 h	100	83;17	80
11	Neat, 4-NBA, rt, 48 h	100	65:35	54
12	H_2O, 4-NBA, rt, 24 h	100	77:23	71
13	Brine, 4-NBA, rt, 24 h	100	90:10	87
14	aq NaBr, 4-NBA, rt, 24 h	100	77:23	78
15	MeCN, PhCOOH, rt, 48 h	78	83:17	85
16	MeCN, 4-Fphenol, rt, 48 h	n.r.	—	—
17	MeCN, AcOH, rt, 48 h	98	77:23	79
18	MeCN, TFA, rt, 48 h	n.r.	—	—
19	MeCN, CSA, rt, 48 h	n.r.	—	—
20	MeCN, 4-CF_3BA, rt, 48 h	100	85:15	85
21[d]	MeCN, 4-NBA, rt, 48 h	68	77:23	80
22	MeCN, 4-NBA, 0 °C, 48 h	88	89:11	90
23[e]	MeCN, 4-NBA, rt, 48 h	54	89:11	80
24[f]	MeCN, 4-NBA, rt, 48 h	48	91:9	89
25[g]	MeCN, 4-NBA, rt, 48 h	27	90:10	88

[a] Isolated yield.
[b] The diastereomeric ratio (dr) *anti*:*syn* was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[c] The enantiomeric excess (ee) for the *anti*-diastereomer was determined by chiral HPLC.
[d] No H_2O.
[e] 5 equiv of cyclohexanone.
[f] 10 mol % of catalyst.
[g] 5 mol % of catalyst. 4-NBA: 4-nitrobenzoic acid. CSA: camphorsulfonic acid. 4-CF_3BA: 4-trifluoromethylbenzoic acid.

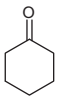
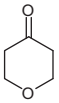
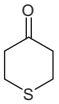
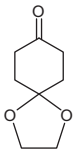
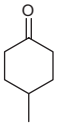
Table 2). We next turned our attention to exploring the substrate scope of the enantioselective aldol reaction (Table 3).

A variety of substituted aromatic aldehydes were employed with cyclohexanone to provide the aldol product (entries 1–14, Table 3). Electron-withdrawing groups at any position of the aromatic group gave high to excellent yields and excellent selectivities (entries 1–5, Table 3). Aromatic aldehydes bearing halogen substituents either at the *para*- or the *ortho*-position led to lower yields and selectivities in general (entries 6–11, Table 3). Benzaldehyde required prolonged reaction times to afford the product in high yield and selectivities, while heteroaromatic aldehydes could be employed with some success (entries 12–14, Table 3). In particular, 4-pyridinyl carboxaldehyde led to lower diastereoselectivity, while 3-thiophenyl carboxaldehyde led to low yield and lower enantioselectivity. Tetrahydropyran-4-one and tetrahydrothiopyran-4-one required longer reaction times to afford the product in high yields and selectivities (entries 15 and 16, Table 3). Disubstituted cyclohexanone (at the 4-position) provided the product in lower yield, but both the diastereoselectivity and enantioselectivity were excellent, while desymmetrization of ketones is also possible, since 4-methyl-cyclohexanone gave the product in excellent yield and enantioselectivity and high diastereoselectivity (entries 17 and 18, Table 3). Cyclopentanone, which is a difficult substrate to use in the organocatalysed aldol reactions, was also utilized with some success (entry 19, Table 3). Moreover, acetone was also investigated as the ketone counterpart, leading to excellent yield but moderate enantioselectivity (entry 20, Table 3). In comparison to tripeptides as organocatalysts to promote the enantioselective

Table 3
Enantioselective aldol reaction between ketones and aldehydes using catalyst **4b**



7a-t

Entry	Ketone	Ar	Product	Yield[a] (%)	dr[b]	ee[c] (%)
1		4-$NO_2C_6H_4$	**7a**	100	91:9	92
2		3-$NO_2C_6H_4$	**7b**	98	92:8	90
3		2-$NO_2C_6H_4$	**7c**	97	86:14	97
4[d]		4-$CF_3C_6H_4$	**7d**	76	93:7	90
5[e]		3-CNC_6H_4	**7e**	77	94:6	95
6[d]		4-FC_6H_4	**7f**	52	86:14	88
7[e]		2-FC_6H_4	**7g**	97	90:10	99
8[d]		4-BrC_6H_4	**7h**	42	86:14	90
9[e]		2-BrC_6H_4	**7i**	78	87:13	94
10[d]		4-ClC_6H_4	**7g**	61	85:15	80
11[e]		2-ClC_6H_4	**7k**	83	91:9	95
12[f]		C_6H_5	**7l**	78	90:10	94
13[e]		4-Pyridinyl	**7m**	100	78:22	91
14[e]		3-Thiophenyl	**7n**	25	85:15	81
15[f]		4-$NO_2C_6H_4$	**7o**	77	90:10	85
16[d]		4-$NO_2C_6H_4$	**7p**	97	89:11	93
17[d]		4-$NO_2C_6H_4$	**7q**	54	98:2	95
18		4-$NO_2C_6H_4$	**7r**	92	84:16	97
19		4-$NO_2C_6H_4$	**7s**	100	40:60	>99
20[d]		4-$NO_2C_6H_4$	**7t**	100	—	73

[a] Isolated yield.
[b] The diastereomeric ratio (dr) *anti*:*syn* was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[c] The enantiomeric excess (ee) for the *anti*-diastereomer was determined by chiral HPLC.
[d] Reaction time: 96 h.
[e] Reaction time: 72 h.
[f] Reaction time: 120 h.

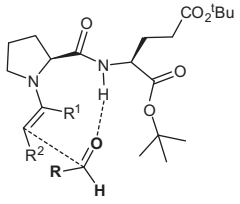


Figure 1. Proposed transition state model for the aldol reaction.

aldol reaction,[13] Pro-Glu(O^{t}Bu)-O^{t}Bu, which is faster and easier to synthesize, led to similar yields and selectivities.

A plausible transition state model is proposed in Figure 1. The free amine from the dipeptide activates the ketone via enamine formation, while the electrophile is activated via hydrogen bonding from the amide proton.

3. Conclusion

In conclusion, the synthesis of four different groups of dipeptides and tripeptides based either on phenylalanine, α-*tert*-butyl aspartate, aspartic acid or proline and a series of *tert*-butyl esters of amino acids was carried out. The design was based on the propensity of primary and secondary amines to activate ketones via enamine formation, while the amide proton could activate the electrophile. All compounds in these families promoted the aldol reaction, however proline dipeptides provided the best results with the dipeptide Pro-Glu(O^{t}Bu)-O^{t}Bu affording the best results both in organic and aqueous media. After screening various reaction conditions, wet acetonitrile provided the best results. A variety of aromatic aldehydes and ketones were utilized successfully leading to products in mediocre to excellent yields, and with good to excellent diastereoselectivities and enantioselectivities. These results build on our previous results, where tripeptides were found to be excellent organocatalysts.[13] Herein we have highlighted that even proline dipeptides can lead to excellent organocatalytic results and provide better catalytic properties than proline itself, since they can be employed in a variety of organic solvents and aqueous media leading to high yields and selectivities.

4. Experimental

4.1. General

Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of the products was accomplished using forced-flow chromatography on Merck Kieselgel 60 F254 230–400 mesh. Thin-layer chromatography (TLC) was performed on aluminium backed silica plates (0.2 mm, 60 F254). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid stains, anisaldehyde or ninhydrin stains. Optical rotations were measured on a Perkin Elmer 343 polarimeter. ^{1}H NMR spectra were recorded on Varian Mercury (200 MHz) and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal), coupling constant and assignment. ^{13}C NMR spectra were recorded on Varian Mercury (50 MHz) and are internally referenced to residual protio solvent signals. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Wherever rotamers exist, they are cited in parenthesis. ^{19}F NMR spectra were recorded on Varian Mercury (188 MHz) and are internally referenced to trifluoroacetic acid. Mass spectra were recorded on a Finnigan Surveyor MSQ Plus, with only molecular ions and major peaks being reported with intensities quoted as percentages of the base peak. HRMS spectra were recorded on Thermo® Orbitrap Velos spectrometer. Chiral High Performance Liquid Chromatography (HPLC) analyses were performed using an Agilent 1100 Series apparatus and Chiralpak® AD-H, OD-H and AS-H columns. The configuration of the products has been assigned by comparison to the literature data or assigned by analogy.

4.1.1. (*S*)-*tert*-Butyl-2-[(*S*)-2-amino-3-phenylpropanamido]-3-phenylpropanoate 1a[15]

To a stirring solution of Cbz-phenylalanine (0.56 g, 2.00 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C, HCl·H-Phe-O^{t}Bu (0.52 g, 2.00 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (WSCI·HCl) (0.38 g, 2.00 mmol), 1-hydroxybenzotriazole (HOBt) (0.27 g, 2.00 mmol) and Et_3N (1.06 mL, 8.00 mmol), were added consecutively. The reaction mixture was left stirring at 0 °C for 1 h, and then warmed to room temperature and left stirring for 18 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with aq HCl 1 M (2 × 30 mL), brine (30 mL), aq NaOH 1 M (2 × 30 mL) and brine (30 mL). The solvents were evaporated in vacuo and the crude product was used in the next reaction.

The crude product was dissolved in MeOH (15 mL) and 10% Pd/C (10 mol %) was added and the reaction mixture was left stirring at room temperature for 24 h under a hydrogen atmosphere. After filtration through Celite, the solvent was evaporated in vacuo and the crude product was purified by column chromatography eluting with $CHCl_3$/MeOH (95:5) (0.49 g, 66% yield); Colourless oil; $[\alpha]_D^{25} = -9.8$ (*c* 1.0, CH_3OH); ^{1}H NMR (200 MHz, CD_3OD): δ 7.38–7.17 (10H, m, ArH), 4.58 (1H, t, *J* = 6.9 Hz, NCH), 4.17–4.02 (1H, m, NCH), 3.28–2.92 (4H, m, 2× $PhCH_2$), 1.38 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, CD_3OD): δ 170.5, 169.3, 136.8, 134.7, 129.5, 129.3, 128.9, 128.4, 127.6, 126.8, 82.0, 54.9, 54.4, 37.9, 37.5, 27.1; MS (ESI) 369 (M+H$^+$, 100%).

4.1.2. (*S*)-*tert*-Butyl-2-[(*S*)-2-amino-3-phenylpropanamido]-2-phenylacetate 1b

Same procedure as above utilizing (*S*)-H-Phg-O^{t}Bu (0.44 g, 62% yield); Colourless oil; $[\alpha]_D^{25} = +57.0$ (*c* 0.33, CH_3OH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.24 (1H, d, *J* = 7.2 Hz, NH), 7.38–7.06 (10H, m, ArH), 5.46 (1H, d, *J* = 7.2 Hz, NCH), 3.81–3.57 (1H, m, NCH), 3.22–3.05 (1H, m, PhC*H*H), 2.79–2.51 (1H, m, PhC*H*H), 1.85 (2H, br s, NH_2), 1.38 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.0 (173.2), 169.8 (169.6), 137.4 (137.8), 137.1 (137.2), 129.3 (129.0), 128.7 (128.6), 128.0, 127.0, 126.9, 126.7, 82.4, 56.5, 56.1, 40.6, 28.0; MS (ESI) 355 (M+H$^+$, 100%); HRMS exact mass calcd for $[M+H]^+$ $(C_{21}H_{27}O_3N_2)^+$ requires *m*/*z* 355.2016, found *m*/*z* 355.2017.

4.1.3. (*S*)-Di-*tert*-butyl-2-[(*S*)-2-amino-3-phenylpropanamido] pentanedioate 1c

Same procedure as above utilizing HCl·H-Glu(O^{t}Bu)-O^{t}Bu (0.40 g, 49% yield); Colourless oil; $[\alpha]_D^{25} = -11.8$ (*c* 0.33, CH_3OH); ^{1}H NMR (200 MHz, CD_3OD): δ 7.38–7.06 (5H, m, ArH), 4.42–4.23 (1H, m, NCH), 4.18–3.71 (1H, m, NCH), 3.46–3.13 (1H, m, PhC*H*H), 3.07–2.78 (1H, m, PhC*H*H), 2.32–1.67 (4H, m, 2× CH_2), 1.45 [18H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, CD_3OD): δ 172.5 (172.6), 172.4 (172.5), 170.3 (170.8), 135.2 (134.9), 129.5 (129.7), 128.7 (128.5), 126.7 (127.0), 82.0, 80.7, 52.5, 52.4, 42.9, 31.3, 27.4, 27.3, 22.4; MS (ESI) 407 (M+H$^+$, 100%); HRMS exact mass calcd for $[M+H]^+$ $(C_{22}H_{35}O_5N_2)^+$ requires *m*/*z* 407.2540, found *m*/*z* 407.2544.

4.1.4. (*S*)-*tert*-Butyl 2-amino-4-{[(*S*)-1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl]amino}-4-oxobutanoate 2a

To a stirred solution of Cbz-Asp-O^{t}Bu (0.32 g, 1.00 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C, HCl·H-Phe-O^{t}Bu (0.26 g, 1.00 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (WSCI·HCl) (0.19 g, 1.00 mmol), 1-hydroxybenzotriazole (HOBt) (0.14 g, 1.00 mmol) and Et_3N (0.53 mL, 4.00 mmol), were added consecutively. The reaction mixture was left stirring at 0 °C for 1 h, and then warmed to room temperature and left stirring for 18 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with aq HCl 1 M (2 × 20 mL), brine (20 mL), aq NaOH 1 M (2 × 20 mL) and brine (20 mL). The solvents were evaporated in vacuo and the crude product was used in the next reaction step.

The crude product was dissolved in MeOH (15 mL) and 10% Pd/C (10 mol %) was added after which the reaction mixture was left stirring at room temperature for 24 h under a hydrogen atmosphere. After filtration through Celite, the solvent was evaporated in vacuo and the crude product was purified by column chromatography eluting with $CHCl_3$/MeOH (98:2) (0.15 g, 37% yield); Colourless oil; $[\alpha]_D^{25} = -1.2$ (*c* 0.5, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$): δ 7.77 (1H, br s, NH), 7.41–7.08 (5H, m, ArH), 4.71–4.61 (1H, m, NCH), 4.25–4.08 (1H, m, NCH), 3.72 (2H, br s, NH_2), 3.12–2.92 (2H, m, $PhCH_2$), 2.88–2.31 (2H, m, $COCH_2$), 1.42–1.37 [18H, m, $2 \times C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.7 (171.8), 170.9 (171.0), 169.8 (169.7), 136.3 (136.5), 129.4, 128.3, 126.8, 82.3 (82.5), 82.2 (82.1), 53.9 (52.7), 51.5 (51.4), 37.8 (38.3), 37.6 (38.0), 27.8; MS (ESI) 393 ($M+H^+$, 100%); HRMS exact mass calcd for $[M+H]^+$ $(C_{21}H_{33}O_5N_2)^+$ requires *m*/*z* 393.2384, found *m*/*z* 393.2394.

4.1.5. (*S*)-*tert*-Butyl 2-amino-4-{[2-(*tert*-butoxy)-2-oxoethyl] amino}-4-oxobutanoate 2b

Same procedure as above utilizing HCl·H-Gly-O^{t}Bu (0.28 g, 92% yield); Colourless oil; $[\alpha]_D^{25} = -0.95$ (*c* 0.1, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$): δ 7.85 (1H, br s, NH), 3.93 (2H, t, *J* = 5.0 Hz, NCH_2), 3.69 (1H, dd, *J* = 9.4 and 3.1 Hz, NCH), 2.67 (1H, dd, *J* = 15.6 and 3.1 Hz, COC*H*H), 2.41 (1H, dd, *J* = 15.6 and 9.4 Hz, COC*H*H), 1.89 (2H, br s, NH_2), 1.48–1.38 [18H, m, $2\times C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.5, 170.7, 169.2, 82.2, 81.9, 51.9, 41.9, 39.6, 28.0, 27.9; MS (ESI) 303 ($M+H^+$, 100%); HRMS exact mass calcd for $[M+Na]^+$ $(C_{14}H_{26}O_5N_2Na)^+$ requires *m*/*z* 325.1734, found *m*/*z* 325.1737.

4.1.6. (*S*)-*tert*-Butyl 2-amino-4-{[(*S*)-1-(*tert*-butoxy)-3-methyl-1oxobutan-2-yl]amino}-4-oxobutanoate 2c

Same procedure as above utilizing HCl·H-Val-O^{t}Bu (0.11 g, 33% yield); Colourless oil; $[\alpha]_D^{25} = +2.8$ (*c* 0.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.76 (1H, d, *J* = 8.3 Hz, NH), 4.45 (1H, dd, *J* = 8.8 and 4.4 Hz, NCH), 3.70–3.63 (1H, m, NCH), 2.70 (1H, dd, *J* = 15.9 and 3.1 Hz, COC*H*H), 2.40 (1H, dd, *J* = 15.9 and 9.6 Hz, COC*H*H), 2.22–2.07 (1H, m, CH), 2.00 (2H, br s, NH_2), 1.44 [18H, s, $2\times C(CH_3)_3$], 0.90 (3H, d, *J* = 6.8 Hz, CH_3), 0.87 (3H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.5, 171.1, 170.4, 81.8, 57.2, 52.1, 39.7, 31.3, 28.0, 27.9, 19.0, 17.6; MS (ESI) 345 ($M+H^+$, 100%); HRMS exact mass calcd for $[M+Na]^+$ $(C_{17}H_{31}O_5N_2Na)^+$ requires *m*/*z* 366.2125, found *m*/*z* 366.2130.

4.1.7. (2*S*,2′*S*)-Tetra-*tert*-butyl 2,2′-{[(*S*)-2-aminosuccinyl] bis(azanediyl)}disuccinate 3a

To a stirred solution of Cbz-Asp-OH (0.27 g, 1.00 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C, HCl·H-Asp(O^{t}Bu)-O^{t}Bu (0.62 g, 2.20 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (WSCI·HCl) (0.42 g, 2.20 mmol), 1-hydroxybenzotriazole (HOBt) (0.31 g, 2.20 mmol) and Et_3N (0.53 mL, 4.00 mmol), were added consecutively. The reaction mixture was left stirring at 0 °C for 1 h, and then warmed to room temperature and left stirring for 18 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with aq HCl 1 M (2×20 mL), brine (20 mL), aq NaOH 1 M (2×20 mL) and brine (20 mL). The solvents were evaporated in vacuo and the crude product was used in the next reaction step.

The crude product was dissolved in MeOH (15 mL) and 10% Pd/C (10 mol %) was added after which the reaction mixture was left stirring at room temperature for 24 h under a hydrogen atmosphere. After filtration through Celite, the solvent was evaporated in vacuo and the crude product was purified by column chromatography eluting with $CHCl_3$/MeOH (95:5) (0.45 g, 77% yield); Colourless oil; $[\alpha]_D^{25} = -14.0$ (*c* 1.0, CH_3OH); ^1H NMR (200 MHz, CD_3OD): δ 4.78–4.61 (2H, m, $2\times$ NCH), 4.30–3.84 (1H, m, NCH), 2.98–2.58 (6H, m, $3\times$ CH_2CO), 1.44 [36H, s, $4\times$ $C(CH_3)_3$]; ^{13}C NMR (50 MHz, CD_3OD): δ 174.7 (174.3), 171.6 (171.5), 170.2 (170.3), 170.1 (170.2), 169.9 (170.0), 169.8 (169.7), 82.2, 82.0, 81.4, 81.2, 52.1, 49.8, 49.5, 40.3, 37.1, 37.0, 27.2, 27.0; MS (ESI) 588 ($M+H^+$, 100%); HRMS exact mass calcd for $[M-H]^-$ $(C_{28}H_{48}O_{10}N_3)^-$ requires *m*/*z* 586.3340, found *m*/*z* 586.3341.

4.1.8. (2*S*,2′*S*)-Tetra-*tert*-butyl 2,2′-{[(*S*)-2-aminosuccinyl] bis(azanediyl)}dipentanedioate 3b

Same procedure as above utilizing HCl·H-Glu(O^{t}Bu)-O^{t}Bu (0.41 g, 67% yield); Colourless oil; $[\alpha]_D^{25} = -16.0$ (*c* 0.1, CH_3OH); ^1H NMR (200 MHz, CD_3OD): δ 4.38–4.24 (1H, m, NCH), 3.37–3.28 (2H, m, $2\times$ NCH), 2.68–2.43 (2H, m, $2\times$ C*H*H), 2.42–2.23 (4H, m, $4\times$ C*H*H), 2.21–1.96 (2H, m, $2\times$ C*H*H), 1.95–1.71 (2H, m, $2\times$ C*H*H), 1.48–1.38 [36H, m, $4\times C(CH_3)_3$]; ^{13}C NMR (50 MHz, CD_3OD): δ 175.8 (175.9), 173.6 (174.5), 174.0 (174.1), 173.8 (173.9), 173.7 (173.8), 173.0 (172.5), 83.1 (83.2), 83.0 (83.1), 81.8 (81.9), 81.8 (81.9), 60.2, 53.7, 53.4, 39.7, 32.5, 32.4, 28.3, 28.2, 22.6, 22.3; MS (ESI) 616 ($M+H^+$, 100%); HRMS exact mass calcd for $[M+H]^+$ $(C_{30}H_{54}O_{10}N_5)^+$ requires *m*/*z* 616.3809, found *m*/*z* 616.3782.

4.1.9. (*S*)-*tert*-Butyl 2-[(*S*)-pyrrolidine-2-carboxamido]propanoate 4a

To a stirred solution of Cbz-Pro-OH (0.25 g, 1.00 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C, HCl·H-Ala-O^{t}Bu (0.18 g, 1.00 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (WSCI·HCl) (0.19 g, 1.00 mmol), 1-hydroxybenzotriazole (HOBt) (0.14 g, 1.00 mmol) and Et_3N (0.53 mL, 4.00 mmol), were added consecutively. The reaction mixture was left stirring at 0 °C for 1 h, and then warmed to room temperature and left stirring for 18 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with aq HCl 1 M (2×20 mL), brine (20 mL), aq NaOH 1 N (2×20 mL) and brine (20 mL). The solvents were evaporated in vacuo and the crude product was used in the next reaction step.

The crude product was dissolved in MeOH (15 mL) and 10% Pd/C (10 mol %) was added after which the reaction mixture was left stirring at room temperature for 24 h under a hydrogen atmosphere. After filtration through Celite, the solvent was evaporated under vacuo and the crude product was purified by column chromatography eluting with $CHCl_3$/MeOH (95:5) (0.18 g, 74% yield); Colourless oil; $[\alpha]_D^{25} = -38.8$ (*c* 0.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.12 (1H, d, *J* = 7.6 Hz, NH), 4.37 (1H, quint, *J* = 7.3 Hz, NCH), 3.83 (1H, dd, *J* = 8.7 and 5.4 Hz, NCH), 3.41 (1H, br s, NH), 3.10–2.88 (2H, m, NCH_2), 2.22–2.06 (1H, m, C*H*H), 1.98–1.61 (3H, m, $3\times$ C*H*H), 1.42 [9H, s, $C(CH_3)_3$], 1.33 (3H, d, *J* = 7.2 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.9, 172.1, 81.6, 60.1, 48.1, 47.0, 30.6, 27.8, 25.8, 18.4; MS (ESI) 243 ($M+H^+$, 100%); HRMS exact mass calcd for $[M+H]^+$ $(C_{12}H_{22}O_3N_2Na)^+$ requires *m*/*z* 265.1523, found *m*/*z* 265.1521.

4.1.10. (*S*)-Di-*tert*-butyl 2-[(*S*)-pyrrolidine-2-carboxamido] pentanedioate 4b

Same procedure as above utilizing HCl·H-Glu(O^{t}Bu)-O^{t}Bu (0.22 g, 63% yield); Colourless oil; $[\alpha]_D^{25} = -25.8$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.60 (1H, br s, NH), 4.97–4.64 (1H, m, NCH), 4.46–4.19 (1H, m, NCH), 3.63–3.34 (2H, m, NCH_2), 2.71–2.45 (1H, m, C*H*H), 2.45–2.24 (3H, m, $3\times$ C*H*H), 2.22–1.83 (5H, m, $4\times$ C*H*H and NH), 1.40 [18H, s, $2\times$ $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.5, 170.1, 168.7, 82.0, 80.9, 59.5, 53.1, 46.7, 31.7, 30.4, 28.0, 27.9, 26.5, 24.3; MS (ESI) 357 ($M+H^+$, 100%); HRMS exact mass calcd for $[M+H]^+$ $(C_{18}H_{33}O_5N_2)^+$ requires *m*/*z* 357.2384, found *m*/*z* 357.2393.

4.2. General procedure for the enantioselective aldol reaction

To a round-bottomed flask, Pro-Glu(O^{t}Bu)-O^{t}Bu (10 mg, 0.028 mmol), 4-NBA (4.7 mg, 0.028 mmol) and aldehyde

(0.14 mmol) were added. After the addition of MeCN (1 mL) and H_2O (0.1 mL), the ketone (1.40 mmol) was added and the reaction mixture was stirred for 24–120 h at room temperature. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with the appropriate mixture of petroleum ether (40–60 °C)/ethyl acetate to afford the desired product.

4.2.1. (*S*)-2-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]-cyclohexanone 7a

See Ref. 13.

4.2.2. (*S*)-2-[(*R*)-Hydroxy-(3-nitrophenyl)methyl]-cyclohexanone 7b

See Ref. 13.

4.2.3. (*S*)-2-[(*R*)-Hydroxy-(2-nitrophenyl)methyl]-cyclohexanone 7c

See Ref. 13.

4.2.4. (*S*)-2-[(*R*)-Hydroxy-(4-trifluoromethylphenyl)methyl]-cyclohexanone 7d

See Ref. 13.

4.2.5. (*R*)-3-[Hydroxy-(2-(*S*)-oxocyclohexyl)methyl]-benzonitrile 7e

See Ref. 13.

4.2.6. (*S*)-2-[(*R*)-Hydroxy-(4-fluorophenyl)methyl]-cyclohexanone 7f

See Ref. 13.

4.2.7. (*S*)-2-[(*R*)-Hydroxy-(2-fluorophenyl)methyl]-cyclohexanone 7g

See Ref. 13.

4.2.8. (*S*)-2-[(*R*)-Hydroxy-(4-bromophenyl)methyl]-cyclohexanone 7h

See Ref. 13.

4.2.9. (*S*)-2-[(*R*)-Hydroxy-(2-bromophenyl)methyl]-cyclohexanone 7i

See Ref. 17.

4.2.10. (*S*)-2-[(*R*)-Hydroxy-(4-chlorophenyl)methyl]-cyclohexanone 7j

See Ref. 18.

4.2.11. (*S*)-2-[(*R*)-Hydroxy-(2-chlorophenyl)methyl]-cyclohexanone 7k

See Ref. 18.

4.2.12. (*S*)-2-[(*R*)-Hydroxy-(phenyl)methyl]-cyclohexanone 7l

See Ref. 13.

4.2.13. (*S*)-2-[(*R*)-Hydroxy-(pyridine-4-yl)methyl]-cyclohexanone 7m

See Ref. 16.

4.2.14. (*S*)-2-[(*R*)-Hydroxy-(thiophen-3-yl)methyl]-cyclohexanone 7n

25% yield; $[\alpha]_D^{25}$ = +9.2 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): *anti* δ 7.36–7.26 (1H, m, ArH), 7.19 (1H, d, *J* = 2.4 Hz, ArH), 7.08 (1H, d, *J* = 5.0 Hz, ArH), 4.92 (1H, d, *J* = 8.4 Hz, OCH), 3.90 (1H, br s, OH), 2.74–2.22 (3H, m, COCH and CHH), 2.17–2.04 (1H, m, C*H*H), 1.86–1.44 (5H, m, 5× C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 215.3, 142.3, 126.0, 125.9, 122.2, 70.6, 57.1, 42.6, 30.8, 27.8, 24.7; HPLC analysis: Diacel Chiralpak AD-H, hexane/^{i}PrOH 90:10, flow rate 1.0 mL/min, retention time: 15.88 (minor) and 21.54 (major).

4.2.15. (*S*)-3-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]dihydro-2*H*-pyran-4(3*H*)-one 7o

See Ref. 13.

4.2.16. (*S*)-3-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]dihydro-2*H*-thiopyran-4(3*H*)-one 7p

See Ref. 13.

4.2.17. (*S*)-7-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]-1,4-dioxospiro[4.5]decan-8-one 7q

See Ref. 13.

4.2.18. (2*S*,4*R*)-2-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]-4-methyl cyclohexanone 7r

See Ref. 13.

4.2.19. (*S*)-2-[(*R*)-Hydroxy-(4-nitrophenyl)methyl]-cyclopentanone 7s

See Ref. 13.

4.2.20. (*R*)-4-Hydroxy-4-(4-nitrophenyl)-butan-2-one 7t

See Ref. 13.

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