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An enantioselective approach to bis-α-amino acids

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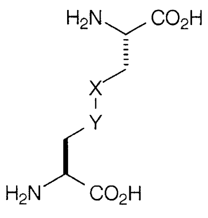
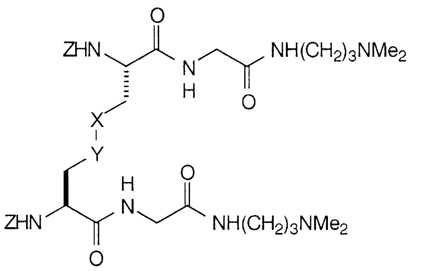
Abstract—In this paper, we describe details of a study into the asymmetric synthesis of bis-α-amino acids via alkylation of a benzophenone-derived glycine imine under phase-transfer conditions. By employing chiral quaternary ammonium salts derived from cinchona alkaloids it was found that the target bis-amino acids can be produced in good overall yield, and with high levels of stereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

In recent years, there has been significant interest in the development of synthetic methods that allow access to bis-amino acids with the general structure **1**.[1,2] These materials have attracted attention largely because they are of use in the synthesis of novel analogues of biologically-active peptides, most commonly being employed as replacements for cystine (**1**, X–Y=S–S).[3] For example, SK and F 107647 **4**,[4] an analogue of the known haemoregulatory peptide HP-5b **5**,[5] has been shown to have haematoregulatory activity, and peptides **2** and **3**, trypanothione disulfide analogues, have been shown to have inhibitory activity towards trypanothione reductase.[2s]

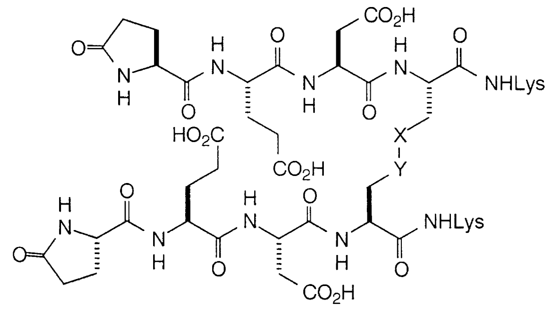


(**1**)



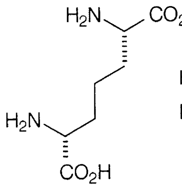
(**2**), X-Y = *E*-CH=CH
(**3**), X-Y = CH_2-CH_2

In addition, synthetic bis-amino acids have proved useful as cross-linking elements for the control of peptide secondary structure, leading to the stabilisation of α-helical,[2q] β-turn[2e] and γ-turn[2h] conformations.

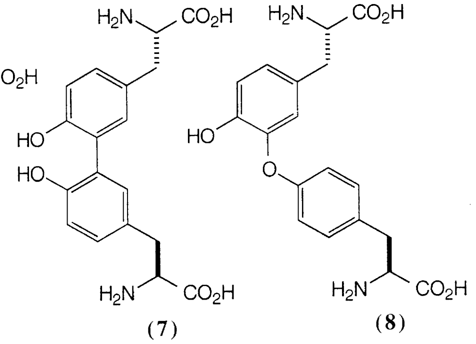


(**4**), X-Y = CH_2CH_2
(**5**), X-Y = S-S

Bis-amino acids of type **1** have also been found in nature. For example *meso*-diaminopimelic acid, **6**[6] dityrosine **7**, and isodityrosine **8**[7] all occur naturally and appear to act as cross-linking agents which help stabilise structural proteins in bacteria and plants. Isodityrosine **8** is also a key structural subunit in a number of bio-active peptides which include the potent ACE inhibitor K-13[8] and the anti-tumour antibiotic deoxybouvardin.[9]



(**6**)



(**7**) (**8**)

Recently, it has been established by both ourselves[10] and

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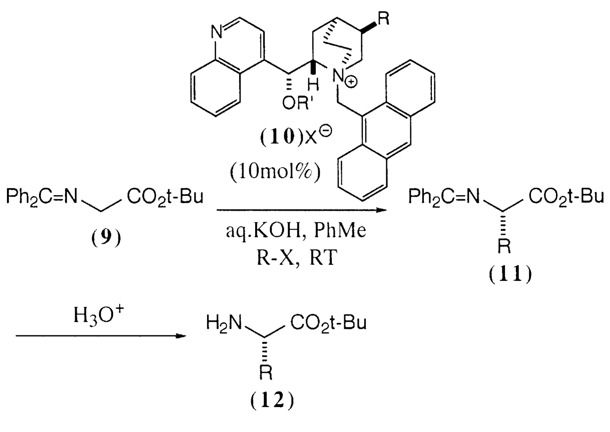
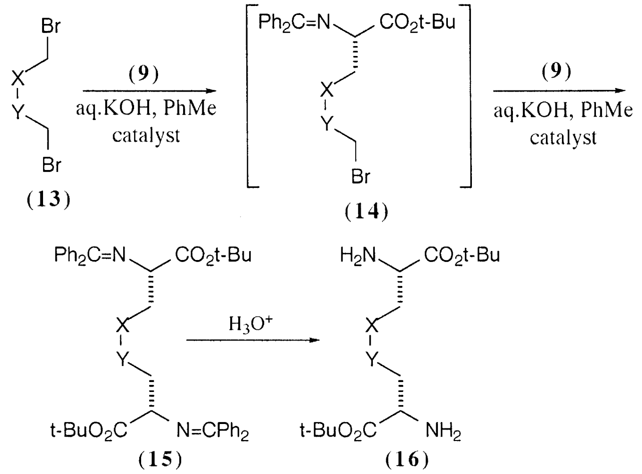


Scheme 1.

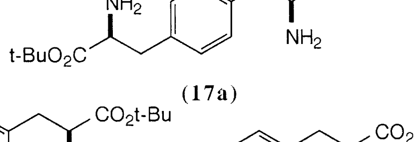


Scheme 2.

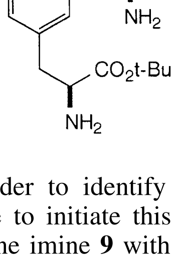
others,[11] that *N*-anthracenylmethyl cinchona alkaloid salts (e.g. **10**) are effective catalysts for the alkylation of amino-acid derived imines (e.g. **9**), leading to an efficient method for the generation of amino acid esters (e.g. **12**).[12,13] As part of a continuation of this work we have recently been investigating whether this alkylation chemistry can be extended to the preparation of bis-amino acids[10d] and in this paper we report details of this study.

In principle, direct extension of the above chemistry (Scheme 1) to the synthesis of bis-amino acid esters **16** simply requires the use of a bis-alkyl halide **13** (Scheme 2), however because the electrophilic reaction component increases in complexity as the reaction progresses (**13**–**14**) a number of issues needed to be addressed. For example, it is likely that reaction of the imine enolate with intermediate **14** will be significantly slower than reaction with the starting dihalide **13**, and the newly created chiral centre in **14** may influence the stereoselectivity of the second alkylation event.

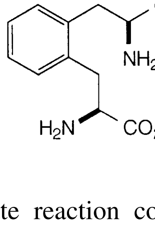
Since both these effects are likely to be influenced by the proximity of the two alkylation sites, we chose to investigate the synthesis of bis-amino acid esters **17a**–**c**. Amino acid derivatives of this type have previously been prepared using a variety of methods,[1,2] and so it was envisaged that the study would also allow evaluation of the effectiveness of this methodology.



(17a)



(17b)



(17c)

In order to identify appropriate reaction conditions, we chose to initiate this study by examining the reaction of glycine imine **9** with dibromide **18**. We were rapidly able to establish that stoichiometric amounts of dihalide **18**, gave high selectivity for the desired bis-imine product **19**,[10d] and so investigations into the stereoselectivity of this process were undertaken (Table 1). For this purpose we employed *n*-Bu_4NBr as an achiral catalyst, and the cinchona alkaloid-derived salts **20**–**22** which had proved effective in previous alkylation studies.[10,14]

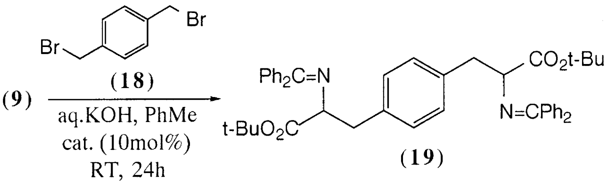
As can be seen from the results presented, with *n*-Bu_4NBr no stereoselectivity is observed. Thus, it appears that, in this system, the initially formed chiral centre has little influence on the stereoselectivity of the second alkylation event. Catalysts **20**–**22** all led to high levels of stereoselectivity, with cinchonidine-derived catalysts **20** and **21** favouring formation of the *S*,*S*-isomer and cinchonine-derived catalyst **22** favouring the *R*,*R*-isomer. This sense of selectivity is the same as that previously observed with these catalysts,[10,11] as is the observation that the dihydro-catalyst **21** gives slightly higher selectivity than the corresponding vinyl-substituted catalyst **20**.

The levels of stereoselectivity obtained using catalysts **20**–**22** are consistent with both alkylation steps occurring under catalyst control. Of course this is perhaps not too surprising, since the dibromide **18** employed in this study has the two bromomethyl functions held rigidly away from each other. Therefore, in order to examine this issue further we compared the stereoselectivity obtained using catalyst **21** in the alkylation of imine **9** with the isomeric dibromides **23**, and **24** (Table 2).

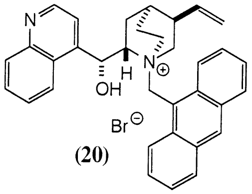
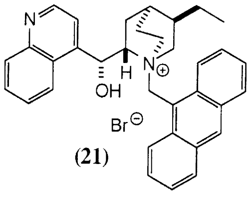
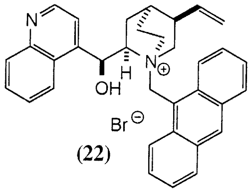
The amino acid esters were all obtained with similar levels of diastereoselectivity (70–75% d.e.) and enantioselectivity (≥95% e.e.). This suggests that, even in the case of dibromide **24**, the quaternary ammonium catalyst dominates the stereoselectivity of the second alkylation step. In this context, it is worth noting that a previous synthetic approach to amino acid derivatives of type **17c** utilised the Schöllkopf auxiliary, and this led to significantly lower levels of stereoselectivity in the second alkylation step.[2f]

The results shown in Table 2 suggest that this approach should be applicable to a wide range of bis-α-amino acid derivatives, and to further illustrate this we investigated synthesis of the most commonly employed cystine analogues **27** and **28** (Scheme 3).

Table 1.



$$\xrightarrow{H_3O^+} \mathbf{(17a)}$$

Catalyst	Distribution (%)[a]		
	(*S*,*S*)[b]	(*meso*)	(*R*,*R*)[b]
n-Bu_4NBr	25	50	25
 **(20)**	80	18	2
 **(21)**	85	14	1
 **(22)**	1	14	85

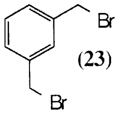
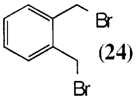
[a] ±5% via HPLC analysis of the *N*-benzoyl derivative of **17a**.

[b] Stereochemistry assigned based on established stereoselectivity of catalysts (**20**)–(**22**).[11,12]

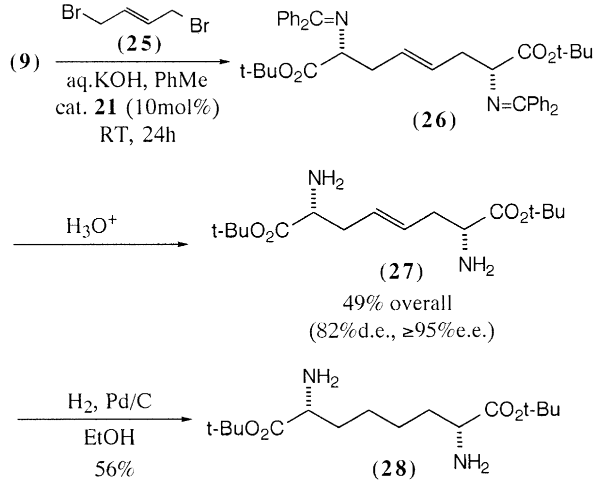
In this case alkylation of imine **9** with dibromide **25**, followed by hydrolysis gave the desired amino acid ester **27** in reasonable overall yield. Again HPLC analysis of the corresponding *N*-benzoyl derivatives demonstrated that high levels of diastereo- and enantioselectivity had been obtained. As might be expected, hydrogenation of **27** also provided straightforward access to the target amino acid **28**.

Table 2.

$$(\mathbf{9}) \xrightarrow[\substack{\text{aq.KOH, PhMe} \\ \text{cat. } \mathbf{21} \text{ (10mol\%)} \\ \text{RT, 24h} \\ \text{2. } H_3O^+}]{\text{1. dibromide}} (S,S)\text{-}(\mathbf{17})$$

Dibromide	Product	d.e. (%)[a]	e.e. (%)[a]	Yield (%)
(**18**)	(**17a**)	72	≥95	55
 (**23**)	(**17b**)	70	≥95	52
 (**24**)	(**17c**)	75	≥95	48

[a] ±5% via HPLC analysis of the *N*-benzoyl derivatives of **17a–c**.



Scheme 3.

In conclusion, we have demonstrated that the asymmetric phase-transfer alkylation of glycine imine **9** provides rapid access to a range of bis-α-amino acid esters with high levels of enantioselectivity. The straightforward nature of the reaction conditions employed make this a useful alternative to previous approaches to compounds of this type.

1. Experimental

Infra-red absorption spectra were recorded on Perkin–Elmer 1600 and 1710 Fourier-transform spectrometers. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded at 300 or 400 MHz and ^{13}C nuclear magnetic resonance spectra at 75 or 100 MHz on a Bruker AC300 or Bruker Avance 400 spectrometer. All chemical shifts (δ) were referenced to the deuterium lock and are reported in parts per million (ppm). The following abbreviations have been used to describe the signal multiplicity: br (broad), s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and J (coupling constant in Hz). Mass spectra (MS) were recorded at low resolution on a Finnigan 4500 instrument with chemical ionisation (CI) using ammonia. Accurate mass measurement (high resolution) and fast atom bombardment (FAB) mass spectra were recorded on a Kratos Concept 1-S instrument. Melting points (mp) were determined using an electrothermal apparatus and are uncorrected. High performance liquid chromatography (HPLC) was performed using either Gilson or Hewlett Packard apparatus with the columns and conditions outlined in the relevant experimental procedures. Enantiomeric and diastereoisomeric excesses determined by HPLC as described in the experimental section were reproducible to ±5%. Thin layer chromatography (TLC) was performed either on plates pre-coated (0.25 mm) with CAMLAB DC-Fertigplatten SIL G-25 UV254 (silica) or plates pre-coated (0.2 mm) with CAMLAB DC-Fertigfolien ALOX N UV254 (neutral alumina). The plates were visualised by the use of a combination of ultraviolet light, iodine, ethanolic vanillin, or aqueous potassium permanganate. Silica gel 60 (particle sizes 40–63 μm) or aluminium oxide 90 active neutral (1077), both supplied by Merck, were employed for flash chromatography. Where necessary, solvents and reagents were dried and purified according to recommended procedures.[15]

1.1. General procedure for the preparation of bis-amino acid *tert*-butyl esters

A mixture of *tert*-butyl *N*-(diphenylmethylene)glycinate **9** (500 mg, 1.7 mmol) and the appropriate catalyst (0.17 mmol) in toluene (15 ml) was treated sequentially with the appropriate dibromide (0.94 mmol) and 50% aqueous potassium hydroxide (4 ml). The mixture was stirred (magnetic stirring, ca. 1000 rmp) for 24 h at room temperature, then water (5 ml) was added. The aqueous layer was extracted with ethyl acetate (15 ml), and the combined organics dried over sodium sulfate. The solvent was then removed under reduced pressure to give crude bis-imine.

The crude bis-imine was then dissolved in dry THF (6 ml) and 15% aqueous citric acid solution (3 ml) added. The resulting mixture was stirred at room temperature for 18 h, then the mixture was diluted with diethyl ether (10 ml) and extracted with 1 M hydrochloric acid (3×10 ml). The combined aqueous layers were washed with diethyl ether (10 ml), basified with solid potassium carbonate, and then extracted with ethyl acetate (3×15 ml). The ethyl acetate extracts were dried over anhydrous magnesium sulphate and then concentrated under reduced pressure to yield the crude bis-amino acid.

1.1.1. Preparation of (2*R*,2″*R*)-2-amino-3-[4-(2-amino-2-*tert*-butoxycarbonylethyl)phenyl]propanonic acid *tert*-butyl ester (*R*,*R*-17a). According to the general procedure, glycine imine **9** was reacted with α,α-dibromo *p*-xylene **18** in the presence of catalyst **22**, to give the crude bis-imine (*R*,*R*)-**19** as a yellow oil. R_f (silica gel) 0.5 (90% petroleum ether/10% ethyl acetate). ν_{max} (neat): 2977, 1732, 1622 cm^{-1}. ^{1}H NMR: δ (300 MHz, CDCl$_3$) *major isomer*, 7.60–6.54 (24H, m, Ar–H), 4.05(2H, dd, J=5.5, 9.0 Hz, 2×CH), 3.19 (2H, dd, J=4.5, 13.5 Hz, 2×C*Ha*Hb), 3.03 (2H, dd, J=9.0, 13.5 Hz, 2×CHa*Hb*), 1.36 (18H, s, 2×C(CH$_3$)$_3$). *m*/*z* (CI, NH$_3$) 694 (M+H$^+$, 1%), 486 (25%), 416 (100%). Found [M+H]$^+$ 693.3684, $C_{46}H_{49}N_2O_4$ requires 693.3692. This material was then hydrolysed according to the general procedure described earlier and the resulting residue purified by chromatography on silica gel to give bis-amino acid ester (*R*,*R*)-**17a** as a colourless oil (53% yield, ≥95% e.e., 72% d.e.). R_f (silica gel) 0.3 (7% methanol/93% chloroform). ν_{max} (neat): 3373, 2977, 1729 cm^{-1}. ^{1}H NMR: δ (300 MHz, CDCl$_3$) *major isomer*, 7.10 (4H, br.s, Ar–H), 3.56–3.51 (2H, br.m, 2×CH), 2.98 (2H, br.dd, J=5.5, 13.5 Hz, 2×C*Ha*Hb), 2.75 (2H, br.dd, J=8.0, 13.5 Hz 2×CHa*Hb*), 1.62 (4H, br.s, 2×NH$_2$), 1.39 (18H, s, 2×C(CH$_3$)$_3$). ^{13}C NMR δ (75 MHz, CDCl$_3$) *major isomer*, 174.2 (2C), 135.9 (2C), 129.4 (4C), 81.1 (2C), 56.2 (2C), 40.7 (2C), 27.9 (6C). *m*/*z* (CI, NH$_3$) 365 (M+H$^+$, 8%), 93 (60%), 76 (100%). Found [M+H]$^+$ 365.2440, $C_{20}H_{33}N_2O_4$ requires 365.2440.

1.1.2. Preparation of (2*S*,2″*S*)-2-amino-3-[4-(2-amino-2-*tert*-butoxycarbonylethyl)phenyl]propanonic acid *tert*-butyl ester (*S*,*S*-17a). According to the general procedure described before, glycine imine **9** was reacted with α,α-dibromo *p*-xylene **18** in the presence of catalyst **21**, to give the crude bis-imine (*S*,*S*)-**19** as a yellow semi-solid. This material was then hydrolysed according to the general procedure above and the resulting residue purified by chromatography on silica gel to give bis-amino acid ester (*S*,*S*)-**17a** as a colourless oil (55% overall yield, ≥95% e.e., 72% d.e.). Spectroscopic data were in agreement with that reported for the enantiomer above.

1.1.3. Preparation of (2*S*,2″*S*)-2-amino-3-[3-(2-amino-2-*tert*-butoxycarbonylethyl)phenyl]propanonic acid *tert*-butyl ester (17b). According to the general procedure described before, glycine imine **9** was reacted with α,α-dibromo *m*-xylene **23** in the presence of catalyst **21**, to give the crude bis-imine as a yellow oil. R_f (silica gel) 0.3 (10% ethyl acetate/90% petroleum ether). ν_{max} (neat): 2976, 1732, 1623 cm^{-1}. ^{1}H NMR: δ (300 MHz, $\mathrm{CDCl_3}$) *major isomer*, 7.55–6.56 (24H, m, Ar–H), 4.02 (2H, dd, J=5.0, 8.5 Hz 2×CH), 3.12–2.97 (4H, m, 2×$\mathrm{CH_2}$), 1.41 (18H, s, 2×$\mathrm{C(CH_3)_3}$). m/z (CI, $\mathrm{NH_3}$) 693 (M+H$^+$, 21%), 297 (48%), 182 (100%). Found [M+H]$^+$ 693.3674, $\mathrm{C_{46}H_{49}N_2O_4}$ requires 693.3692. This material was then hydrolysed according to the general procedure above and the resulting residue purified by chromatography on silica gel to give bis-amino acid ester **17b** as a pale yellow oil (52% overall yield, ≥95% e.e., 70% d.e.). R_f (silica gel) 0.2 (7% methanol/93% chloroform). ν_{max} (neat): 3370, 2977, 1728 cm^{-1}. ^{1}H NMR: δ (400 MHz, $\mathrm{CDCl_3}$) *major isomer*, 7.25–7.04 (4H, m, Ar–H), 3.61–3.57 (2H, m, 2×CH), 3.02 (2H, dd, J=5.0, 13.5 Hz, 2×C*Ha*Hb), 2.79 (2H, dd, J=8.0, 13.5 Hz, 2×CHa*Hb*), 1.52 (4H, 2×$\mathrm{NH_2}$), 1.44 (18H, s, 2×$\mathrm{C(CH_3)_3}$).^{13}C NMR δ (75 MHz, $\mathrm{CDCl_3}$) *major isomer*, 174.2 (2C), 137.7 (2C), 130.3, 128.4, 127.7 (2C), 81.1 (2C), 56.2 (2C), 41.0 (2C), 28.0 (6C). m/z (CI, $\mathrm{NH_3}$) 365 (M+H$^+$, 28%), 200 (100%), 183 (21%). Found [M+H]$^+$ 365.2433, $\mathrm{C_{20}H_{33}N_2O_4}$ requires 365.2400.

1.1.4. Preparation of (2*S*,2″*S*)-2-amino-3-[2-(2-amino-2-*tert*-butoxycarbonylethyl)phenyl]propanonic acid *tert*-butyl ester (17c). According to the general procedure described before, glycine imine **9** was reacted with α,α-dibromo *o*-xylene **24** in the presence of catalyst **21**, to give the crude bis-imine as a yellow oil. R_f (silica gel) 0.3 (10% ethyl acetate/90% petroleum ether). ν_{max} (neat): 2977, 1733, 1660 cm^{-1}. ^{1}H NMR: δ (300 MHz, $\mathrm{CDCl_3}$) *major isomer*, 7.56–7.52 (4H, m, Ar–H), 7.36–7.15 (12H, m, Ar–H), 6.98–6.85 (4H, m, Ar–H), 6.43–6.40 (4H, m, Ar–H), 4.01 (2H, dd, J=4.0, 9.5 Hz 2×CH), 3.07 (2H, dd, J=9.5, 13.5 Hz, 2×C*Ha*Hb), 2.94 (2H, dd, J=4.0, 13.5 Hz, 2×CHa*Hb*), 1.40 (18H, s, 2×$\mathrm{C(CH_3)_3}$). m/z (ES+) 715 (M+Na$^+$, 100%), 693 (M+H$^+$, 85%). Found [M+H]$^+$ 693.3714, $\mathrm{C_{46}H_{49}N_2O_4}$ requires 693.3692. This material was then hydrolysed according to the general procedure above and the resulting residue purified by chromatography on silica gel to give bis-amino acid ester **17c** as a colourless oil (48% overall yield, ≥95% e.e., 75% d.e.). R_f (silica gel) 0.3 (7% methanol/93% chloroform). ν_{max} (neat): 3377, 2976, 1729, 1660 cm^{-1}. ^{1}H NMR: δ (400 MHz, $\mathrm{CDCl_3}$) *major isomer*, 7.23–7.17 (4H, m, Ar–H), 3.64–3.60 (2H, m, 2×CH), 3.16 (2H, dd, J=6.0, 14.0 Hz, 2×C*Ha*Hb), 2.82 (2H, dd, J=8.5, 14.0 Hz, 2×CHa*Hb*), 1.53 (4H, br.s, 2×$\mathrm{NH_2}$), 1.42 (18H, s, 2×$\mathrm{C(CH_3)_3}$). ^{13}C NMR δ (75 MHz, $\mathrm{CDCl_3}$) *major isomer*, 174.5 (2C), 136.6 (2C), 130.4 (2C), 126.7 (2C), 81.1 (2C), 56.2 (2C), 38.3 (2C), 27.9 (6C). m/z (ES+) 387 (M+Na$^+$, 5%), 365 (M+H$^+$, 20%), 309 (24%), 253 (100%). Found [M+Na]$^+$ 387.2254 $\mathrm{C_{20}H_{32}N_2O_4Na}$ requires 387.2260.

1.1.5. Preparation of *E*-(2*S*,7*S*)-2,7-diamino-oct-4-enedioic acid di-*tert*-butyl ester (27). According to the general procedure described earlier, glycine imine **9** was reacted with *E*-1,4-dibromobut-2-ene **25** in the presence of catalyst **21**, to give the crude bis-imine **26** as a pale yellow solid. R_f (silica gel) 0.4 (10% ethyl acetate/90% petroleum ether). ν_{max} (neat): 2977, 1733, 1661 cm^{-1}. ^{1}H NMR: δ (300 MHz, $\mathrm{CDCl_3}$) *major isomer*, 7.80–7.06 (20H, m, Ar–H), 5.35–5.32 (2H, m, 2×C*H*═C), 3.9 0(2H, dd, J= 5.5, 7.5 Hz, 2×CH), 2.59–2.43(4H, m, 2×$\mathrm{CH_2}$), 1.39(18H, s, 2×$\mathrm{C(CH_3)_3}$). m/z (ES+) 665 (M+Na$^+$, 100%), 643 (M+H$^+$, 63%). Found [M+H]$^+$ 643.3514, $\mathrm{C_{42}H_{47}N_2O_4}$ requires 643.3536. This material was then hydrolysed according to the general procedure above and the resulting residue purified by chromatography on silica gel to give bis-amino acid ester **27** as a colourless oil (49% overall yield, ≥95% e.e., 82% d.e.). R_f (silica gel) 0.4 (7% methanol/93% chloroform). ν_{max} (neat): 3382, 2933, 1729, 1675 cm^{-1}. ^{1}H NMR: δ (300 MHz, $\mathrm{CDCl_3}$) *major isomer*, 5.44–5.41 (2H, m, 2×C*H*═C), 3.34–3.30 (2H, m, 2×CH), 2.43–2.34 (2H, m, 2×C*Ha*Hb), 2.30–2.11 (2H, m, 2×CHa*Hb*), 1.52 (4H, br.s, 2×$\mathrm{NH_2}$), 1.40 (18H, s, 2×$\mathrm{C(CH_3)_3}$). ^{13}C NMR δ (75 MHz, $\mathrm{CDCl_3}$) *major isomer*, 174.5 (2C), 129.0 (2C), 80.9 (2C), 54.5 (2C), 38.0 (2C), 28.0 (6C). m/z (CI, $\mathrm{NH_3}$) 337 (M+Na$^+$, 31%), 315 (M+H$^+$, 100%). Found [M+H]$^+$ 315.2260, $\mathrm{C_{16}H_{31}N_2O_4}$ requires 315.2284.

1.1.6. Preparation of (2*S*, 7*S*)-2,7-diaminooctanedioic acid di-*tert*-butyl ester (28). (4*E*, 2*S*, 7*S*)-2,7-Diamino-oct-4-enedioic acid di-*tert*-butyl ester **27** (142 mg, 0.45 mmol) was dissolved in ethanol (5 ml), 5% palladium-on-carbon (50 mg) added and the mixture placed under an atmosphere of hydrogen (balloon). After stirring at room temperature for 2 h, the reaction mixture was filtered through a pad of Celite and the solvent removed under reduced pressure. The residue was purified by chromatography on silica gel (5% methanol/95% chloroform), to give the product **28** as a colourless oil (80 mg, 56%). R_f (silica gel) 0.4 (7% methanol/93% chloroform). $[\alpha]_D$= +26 (c=1, $\mathrm{CHCl_3}$, ≥95% e.e., 82% d.e.). ν_{max} (neat): 3373, 2978, 1728 cm^{-1}. ^{1}H NMR: δ (300 MHz, $\mathrm{CDCl_3}$) *major isomer*, 3.28–3.23 (2H, m, 2×CH), 1.78 (4H, br.s, 2×$\mathrm{NH_2}$), 1.62–1.23 (8H, m, 4×$\mathrm{CH_2}$), 1.40 (18H, s, 2×$\mathrm{C(CH_3)_3}$). ^{13}C NMR δ (100 MHz, $\mathrm{CDCl_3}$) *major isomer*, 175.5 (2C), 80.9 (2C), 54.9 (2C), 34.8 (2C), 28.1 (6C), 25.4 (2C). (m/z (CI, $\mathrm{NH_3}$) 317(M+H$^+$, 100%). Found [M+H]$^+$ 317.2430, $\mathrm{C_{16}H_{33}N_2O_4}$ requires 317.2440.

1.2. General procedure for *N*-benzoylation of bis-amino acid di-*tert*-butyl esters

A solution of the amino acid ester (0.30 mmol) and triethylamine (0.33 mmol) in chloroform (1 ml) was cooled to 0°C under argon. Benzoyl chloride (0.33 mmol) was then added and the solution stirred at 0°C for 20 min and then at room temperature for 1 h. The solution was then washed with 3 M hydrochloric acid (1 ml), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude product. HPLC analysis was performed on the crude isomeric mixture. For other analytical purposes sample of this material was then purified by chromatography on silica gel.

1.2.1. *N*-Benzoylation of (2*R*, 2″*R*)-2-amino-3-[4-(2-amino-2-*tert*-butoxycarbonylethyl)phenyl] propanonic acid *tert*-butyl ester. Bis-amino acid ester (*R*,*R*)-**17a** was reacted with benzoyl chloride according to the general procedure above. The residue was purified by chromatography on silica gel (10% ethyl acetate/90% petroleum ether) to give the product as a white solid. R_f (silica gel) 0.2 (10% ethyl acetate/90% petroleum ether). ν_{max} (neat): 3340, 2978, 1733, 1646 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$) *major isomer*, 7.72–7.68 (4H, m, Ar–H), 7.50–7.36 (6H, m, Ar–H), 7.08 (4H, br.s, Ar–H), 6.61 (2H, br.d, *J*=7.5 Hz, 2×NH), 4.91 (2H, ddd, *J*=6.0, 6.0, 7.5 Hz, 2×CH), 3.26–3.17 (4H, m, $2\times CH_2$), 1.41 (18H, s, $2\times C(CH_3)_3$). *m/z* (CI, NH_3) 573 ($M+H^+$, 9%), 373 (45%), 365 (85%), 317 (100%), 300 (48%), 105 (40%). Found $[M+H]^+$ 573.2966, $C_{34}H_{41}N_2O_6$ requires 573.2964. R_t HPLC (Chiralcel OD-H, 70:30, hexane/ethanol, 232 nm, 0.5 ml/min) 7.2 min (*R*,*R*), 8.4 min (*meso*), 11.5 min (*S*,*S*).

1.2.2. *N*-Benzoylation of (2*S*, 2″*S*)-2-amino-3-[4-(2-amino-2-*tert*-butoxycarbonylethyl)phenyl] propanonic acid *tert*-butyl ester. Bis-amino acid ester (*S*,*S*)-**17a** was reacted with benzoyl chloride according to the general procedure above. The residue was purified by chromatography on silica gel (10% ethyl acetate/90% petroleum ether) to give the product as a white solid, $[\alpha]_D=+84$ (*c*=1, $CHCl_3$, ≥95% e.e., 72% d.e.). Spectroscopic data were in agreement with reported for the enantiomer above.

1.2.3. *N*-Benzoylation of (2*S*, 2″*S*)-2-amino-3-[3-(2-amino-2-*tert*-butoxycarbonylethyl)phenyl] propanonic acid *tert*-butyl ester. Bis-amino acid ester **17b** was reacted with benzoyl chloride according to the general procedure above. The residue was purified by chromatography on silica gel (10% ethyl acetate/90% petroleum ether) to give the product as a white solid. R_f (silica gel) 0.4 (10% ethyl acetate/90% petroleum ether). $[\alpha]_D=+58$ (*c*=1, $CHCl_3$, ≥95% e.e., 70% d.e.) ν_{max} (neat): 3338, 1729, 1651 cm^{-1}. ^{1}H NMR: δ (300 MHz, $CDCl_3$) *major isomer*, 7.71–7.67 (4H, m, Ar–H), 7.46–7.34 (6H, m, Ar–H), 7.18–7.13 (1H, m, Ar–H), 7.06–7.02 (3H, m, Ar–H), 6.65 (2H, br.d, *J*=7.5 Hz, 2×NH), 4.89 (2H, ddd, *J*=6.0, 6.0, 7.5 Hz, 2×CH), 3.14 (4H, app.d, *J*=6.0 Hz, $2\times CH_2$), 1.40 (18H, s, $2\times C(CH_3)_3$). *m/z* (CI, NH_3) 573 ($M+H^+$, 33%), 183 (65%), 166 (100%), 139 (38%). Found $[M+H]^+$ 573.2967, $C_{34}H_{41}N_2O_6$ requires 573.2964. R_t HPLC (Chiralcel OD-H, 80:20, hexane/ethanol, 232 nm, 0.5 ml/min) 8.0 min (*R*,*R*), 8.8 min (*meso*), 12.0 min (*S*,*S*).

1.2.4. *N*-Benzoylation of (2*S*, 2″*S*)-2-amino-3-[2-(2-amino-2-*tert*-butoxycarbonylethyl)phenyl] propanonic acid *tert*-butyl ester. Bis-amino acid ester **17c** was reacted with benzoyl chloride according to the general procedure above. The residue was purified by chromatography on silica gel (10% ethyl acetate/90% petroleum ether) or by recrystallisation from ethanol/water to give the product as a white solid. R_f (silica gel) 0.4 (10% ethyl acetate/90% petroleum ether). mp: 181–183°C. $[\alpha]_D=+37$ (*c*=1, $CHCl_3$, ≥95% e.e., 75% d.e.). ν_{max} (neat): 3313, 2978, 1731, 1643 cm^{-1}. ^{1}H NMR: δ (400 MHz, $CDCl_3$) *major isomer*, 7.73–7.70 (4H, m, Ar–H), 7.49–7.15 (10H, m, Ar–H), 6.91 (2H, br.d, *J*=6.5 Hz, 2×NH), 5.01–4.95 (2H, m, 2×CH), 3.33 (2H, dd, *J*=7.0, 14.5 Hz, 2×C*Ha*Hb), 3.26 (2H, dd, *J*=7.5, 14.5 Hz, 2×CHa*Hb*), 1.43 (18H, s, $2\times C(CH_3)_3$). *m/z* (ES+) 595 ($M+Na^+$, 100%), 461 (41%). Found $[M+Na]^+$ 595.2773, $C_{34}H_{40}N_2O_6Na$ requires 595.2784. R_t HPLC (Chiralcel OD-H, 97:3, hexane/ethanol, 232 nm, 0.5 ml/min) 19.7 min (*R*,*R*), 28.8 min (*meso*), 50.3 min (*S*,*S*).

1.2.5. *N*-Benzoylation of *E*-(2*S*, 7*S*)-2,7-diamino-oct-4-enedioic acid di-*tert*-butyl ester. Bis-amino acid ester **27** was reacted with benzoyl chloride according to the general procedure above. The residue can be purified by chromatography on silica gel (10% ethyl acetate/90% petroleum ether) or by recrystallisation from ethanol/water to give the product as a white solid. R_f (silica gel) 0.2 (20% ethyl acetate/80% petroleum ether). mp: 132–134°C. $[\alpha]_D=+47$ (*c*=1, $CHCl_3$, ≥95% e.e., 82% d.e.). ν_{max} (neat): 3340, 2976, 1732, 1644 cm^{-1}. ^{1}H NMR: δ (400 MHz, $CDCl_3$) *major isomer*, 7.84–7.81 (4H, m, Ar–H), 7.51–7.39 (6H, m, Ar–H), 6.89 (2H, br.d, *J*=7.5 Hz, 2×NH), 5.51–5.46 (2H, m, CH=CH), 4.77 (2H, ddd, *J*=5.0, 5.0, 7.5 Hz, 2×CH), 2.66–2.54 (4H, m, $2\times CH_2$), 1.41 (18H, s, $2\times C(CH_3)_3$). *m/z* (ES+) 545 ($M+Na^+$, 100%), 411 (69%). Found $[M+Na]^+$ 545.2638, $C_{30}H_{38}N_2O_6Na$ requires 545.2627. R_t HPLC (Chiralcel OD-H, 90:10, hexane: ethanol, 232 nm, 0.5 ml/min) 10.2 min (*R*,*R*), 12.6 min (*meso*), 15.3 min (*S*,*S*).

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