# Asymmetric synthesis of β-amino acid scaffolds

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Addition of two or three equivalents of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to conjugate acceptors containing two or three α,β-unsaturated ester fragments respectively and subsequent hydrogenolytic deprotection afford homochiral bis- or tris-β-amino esters containing two or three new stereogenic centres in high de and ee.

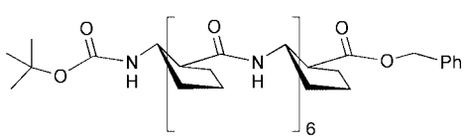
## Introduction

There has been much interest in recent years directed towards the development of new methodology for the asymmetric synthesis of β-amino acids[1] since derivatives thereof often occur as fragments within peptidic natural products that exhibit potent biological activity.[2] While the pharmacological activity of β-amino acid derivatives has often been the focal point of these studies, there has been increasing recognition of the importance of the β-amino acid structural motif in generating pseudopeptide sequences as tools for the generation of structures containing novel secondary and tertiary structures.[3] For example, Gellman *et al.* have shown that β-peptides derived from *trans*-2-aminocyclopentanecarboxylic acid **1** and *trans*-2-aminocyclohexanecarboxylic acid **2** adopt 12- and 14-membered helical stuctures both in the solid state and in solution,[4] while Seebach *et al.* have demonstrated that hexapeptide **3** adopts a 14-membered helix in a range of polar solvents (Fig. 1).[5] The ability of these small β-pseudopeptide fragments to elicit secondary structure is remarkable when they are compared with conventional α-peptides which generally require between fifteen and twenty α-amino acid residues before they begin to demonstrate any noticeable secondary structure.[6]

While much effort has been directed towards understanding the factors that control the secondary structure of α-peptides, only limited success has been achieved in developing models which enable the conformation of a protein to be predicted simply from knowledge of its primary structure. In order to provide tools to help delineate the factors which are responsible for controlling the folding of α-peptide fragments Mutter *et al.* have introduced an elegant concept into the arena of protein folding: the concept of "template assisted synthetic proteins" (TASPs).[7] This approach uses highly functionalised scaffold molecules which act as topological templates upon which to build higher order molecular architectures. Thus, these TASPs serve to constrain the conformational and translational freedom of attached peptide fragments, facilitating the formation of α-helical and β-pleated sheet derived secondary structures. In light of these developments we were interested in preparing the set of β,β′-diamino diacid derivatives **4**, **5**, and **6** as potential scaffolds for probing the secondary structure of attached α- and β-pseudopeptidic fragments (Fig. 2).

The potential of this class of β,β′-diamino diacid has recently been recognised by Adamczyk and Reddy who reported that β,β′-diamino diacid derivatives may be prepared *via* a protocol involving the addition of the sodium enolate of methyl acetate to the chiral bis-sulfinylimines such as **7** to afford bis-*N*,*N*′-sulfinylamide diamino diester **8**, which on treatment with trifluoroacetic acid affords the desired β,β′-diamino derivative **9** (Scheme 1).[8]

Whilst serving to provide access to β,β′-diamino diacid **9**, this methodology is unsatisfactory due to the poor yield and low

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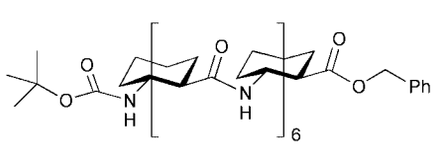


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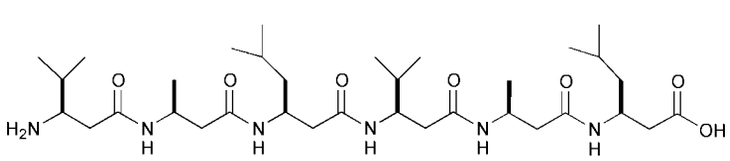


**3**

**Fig. 1**

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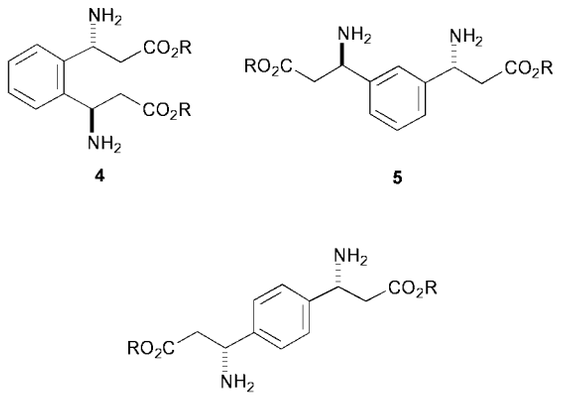
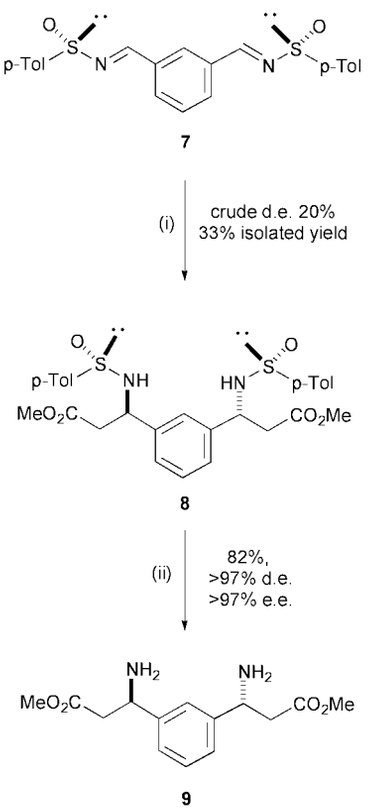


**Fig. 2**

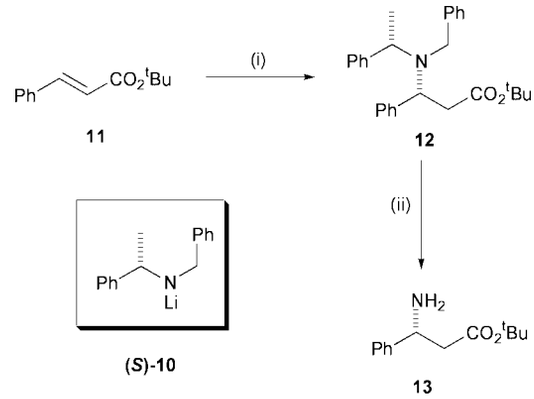


**Scheme 1** *Reagents and conditions*: (i) MeOAc, NaHMDS, THF, −78 °C; (ii) TFA, MeOH, 0 °C.

diastereoselectivity observed during the imine addition stage and the need for preparative reverse phase HPLC to purify the major diastereoisomer **8** to homogeneity. We now wish to report herein our approach towards the asymmetric synthesis of β,β′-diamino diacids which employs a strategy involving the stereoselective conjugate addition of a homochiral ammonia equivalent to substrates containing two α,β-unsaturated esters.

## Results and discussion

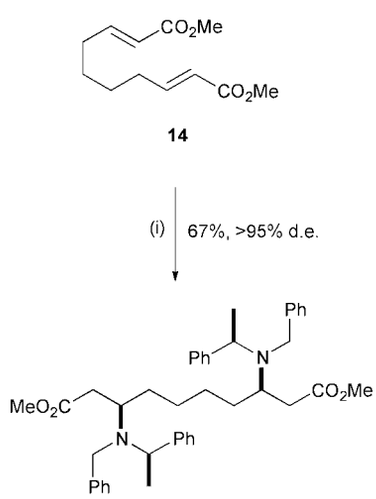
In 1991 we first reported on the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **10** to α,β-unsaturated esters as methodology for the asymmetric synthesis of β-amino acids. For example, addition of lithium amide (*S*)-**10** to *tert*-butyl cinnamate **11** affords (3*R*,α*S*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate **12** in >95% de, which on hydrogenolytic deprotection affords homochiral (*R*)-*tert*-butyl 3-amino-3-phenylpropanoate **13** (Scheme 2).[9] The universally high diastereoselectivity of this conjugate addition protocol is reflected by the number of reports which have appeared to date that employ this methodology for the



**Scheme 2** *Reagents and conditions*: (i) (*S*)-**10** (1.6 equiv.), THF, −78 °C; (ii) $Pd(OH)_2$/C, MeOH, 5 atm $H_2$.

asymmetric synthesis of a wide range of β-amino acids, β-lactams, pseudopeptides and natural products containing this functionality.[10]

It was proposed that this methodology could be employed as the cornerstone of a synthetic strategy for the asymmetric synthesis of β,β′-diamino diacids involving addition of two equivalents of (*S*)-**10** to a substrate containing two α,β-unsaturated ester fragments to afford bis-addition products in high de. Indeed, we have recently demonstrated the validity of this tandem addition approach for the asymmetric synthesis of β,β′-diamino diesters in which addition of (*E*,*E*)-dimethyl nona-2,7-dienedioate **14** to an excess of lithium amide (*R*)-**10** gave homochiral bis-adduct **15** in 67% yield (Scheme 3).[11]



**Scheme 3** *Reagents and conditions*: (i) (*R*)-**10** (12 equiv.), THF, −78 °C.

Consequently, our initial synthetic efforts in this area were directed towards the synthesis of suitably bis-functionalised Michael acceptors **17**, **19** and **21**, which were prepared from the parent *o*-, *m*- and *p*-aryl dihalides **16**, **18** and **20** respectively *via* palladium mediated Heck methodology in good yield (Scheme 4).[12]

### Asymmetric synthesis of β,β′-diamino diesters

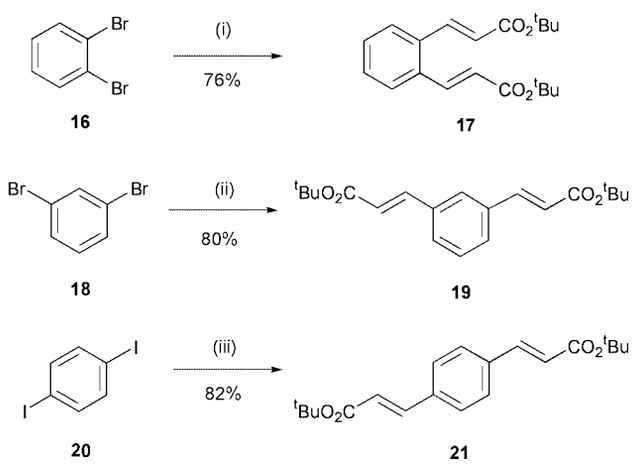
Addition of three equivalents of homochiral lithium amide (*S*)-**10**[13] to acceptors **19** and **21** afforded the desired bis-addition products [3*R*,α*S*,3′*R*,α′*S*]-**22** and [3*R*,α*S*,3′*R*,α′*S*]-**24** in good yield and in 95% de. The absolute configurations of the two new stereogenic centres in **22** and **24** were assigned as (*R*,′*R*) by analogy with previous models developed to explain the stereoselectivity observed during addition of lithium amide **10** to α,β-unsaturated acceptors.[14] Furthermore, the $C_2$ symmetry of **22** and **24** was evident from analysis of the number of resonances observed in their $^1H$ and $^{13}C$ NMR spectra. Hydrogen-

ation of **22** and **24** using $Pd(OH)_2$ on C in MeOH yielded bis-β-amino esters **23** and **25** respectively. As numerous reports have demonstrated that hydrogenation of *N*-benzyl-*N*-α-methylbenzyl β-amino esters occurs without loss of stereochemical integrity,[9,10] it is possible to conclude that bis-β-amino esters **23** and **25** have been prepared in 95% de, and due to the operation of a double asymmetric synthesis,[15] with a calculated ee of >99.9%[16] (Scheme 5).

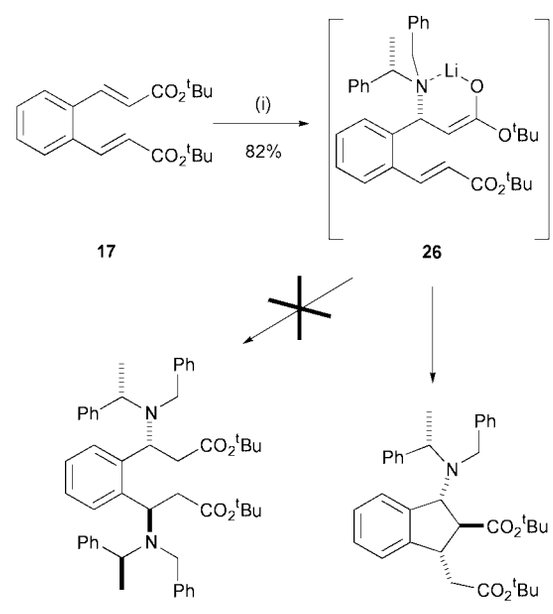
Attempts to prepare the corresponding *o*-substituted bis-β-amino derivative **28** *via* a similar strategy proved unsuccessful since addition of three equivalents of lithium amide (*S*)-**10** to acceptor **17** afforded the benzo *trans*-pentacin analogue **27** as the only product. This observation is consistent with results first reported by de Meijere *et al.* who proposed a mechanism in which the intermediate enolate **26** generated by addition of one equivalent of lithium amide (*S*)-**10** to acceptor **17** undergoes intramolecular conjugate addition to the α,β-unsaturated ester fragment to afford **27** at a much greater rate than addition of a second equivalent of lithium amide (*S*)-**10** to afford **28** (Scheme 6).[17]

Attempts to prepare the double addition product **28** *via* addition of α,β-unsaturated acceptor **17** to an excess (10 equiv.) of lithium amide (*S*)-**10** were unsuccessful,[11] only furnishing the cyclised product **27**. A stepwise strategy toward **28** was therefore adopted, involving addition of (*S*)-**10** to (*E*)-*tert*-butyl 3-(2-iodophenyl)prop-2-enoate **29** which furnished (3*R*,α*S*)-*tert*-butyl 3-(2-iodophenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate **30** in 88% yield and in >95% de. Treatment of β-amino ester **30** under Heck conditions furnished conjugate acceptor (3*R*,α*S*,*E*)-*tert*-butyl 3-[2-(3-*tert*-butoxy-3-oxoprop-1-enyl)phenyl]-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate **31** in 88% yield as a single diastereoisomer after column chromatography (Scheme 7).

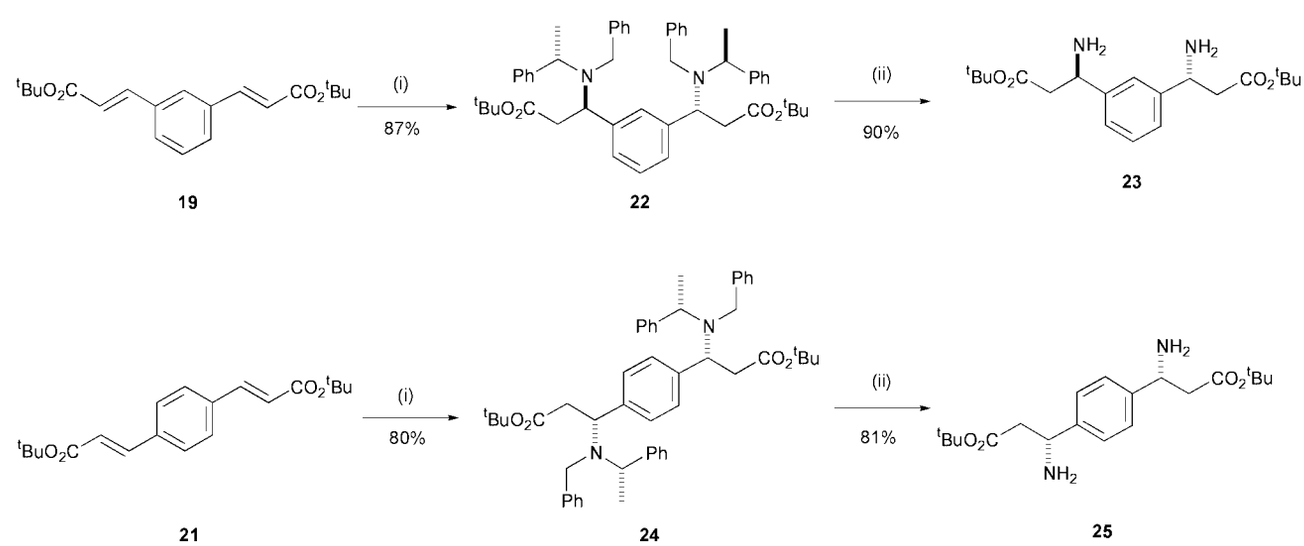
Treatment of α,β-unsaturated acceptor **31** with three equivalents of (*S*)-**10** at −78 °C in THF afforded a 50 : 30 : 20 mixture of diamino diester **28** and the cyclised diastereoisomers **27** and **32** respectively. Presumably (*S*)-**10** promotes deprotonation at the α-position of the β-amino *tert*-butyl ester fragment (thus facilitating intramolecular cyclisation to afford **27** and **32**) or adds in a conjugate fashion to form diamino diester **28**. Chromatographic purification gave **28** in 42% yield and >95% de, the $C_2$ symmetry of which was evident from the number of resonances observed by $^1H$ and $^{13}C$ NMR spectroscopic analysis. The structures of **27** and **32** were proven by treatment of α,β-unsaturated ester **31** with LiHMDS in THF at 0 °C, which furnished an inseparable 62 : 38 mixture of **27** : **32** in 92% yield. $^1H$ NMR spectroscopic analysis of the crude reaction mixture showed that the major diastereoisomer **27** obtained from this protocol was identical to that obtained previously from addition of (*S*)-**10** to **17** (Scheme 8). The different stereochemical outcome of this deprotonation induced cyclisation of **31** to **27** and **32** (Scheme 8) compared with the cyclisation of the



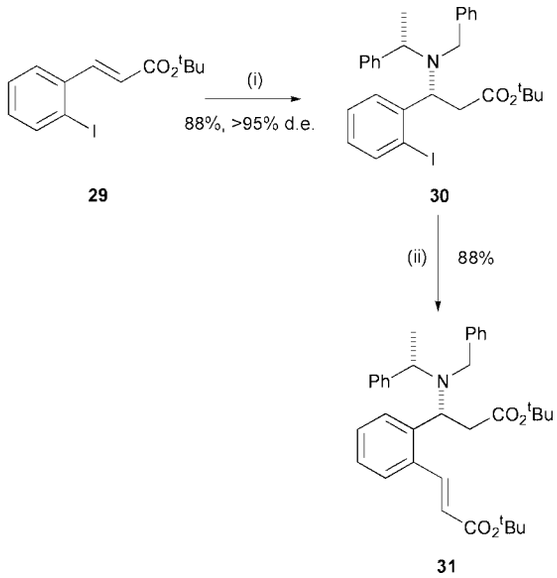

**Scheme 4** *Reagents and conditions*: (i) $Pd(OAc)_2$, *tert*-butyl acrylate, LiCl, $Bu_4NCl$, $K_2CO_3$, DMF, Δ; (ii) $Pd(OAc)_2$, *tert*-butyl acrylate, tri-*o*-tolylphosphine, $NEt_3$, Δ; (iii) $Pd(OAc)_2$, *tert*-butyl acrylate, $PPh_3$, *n*-$Bu_4NHSO_4$, $K_2CO_3$, MeCN–$H_2O$ (1 : 10), 50 °C.




**Scheme 6** *Reagents and conditions*: (i) (*S*)-**10** (3.0 equiv.), THF, −78 °C.




**Scheme 5** *Reagents and conditions*: (i) (*S*)-**10** (3.0 equiv.), THF, −78 °C; (ii) $Pd(OH)_2$/C, MeOH, 5 atm $H_2$.




**Scheme 7** *Reagents and conditions*: (i) (*S*)-**10** (1.6 equiv.), THF, −78 °C; (ii) $Pd(OAc)_2$, *tert*-butyl acrylate, tri-*o*-tolylphosphine, $NEt_3$, Δ.

enolate **26** (Scheme 6) generated by conjugate addition is presumably due to the different enolate geometries involved in these two protocols.[10g]

While the (1*R*,2*S*,3*S*,α*S*) stereochemistry of the major diastereoisomer **27** has previously been unambiguously proven by X-ray crystallographic analysis,[17] the (1*R*,2*S*,3*R*,α*S*) stereochemistry of the minor diastereoisomer **32** was assigned according to the $^1$H NOE enhancements described in Fig. 3.

Notably, while both diastereoisomers exhibited a ~3.5% NOE enhancement between their $H^1$ and $H^2$ protons, the 10.3% enhancement between $H^2$ and $H^3$ of the minor diastereoisomer **32** was absent for the known major diastereoisomer **27**. This indicates that both diastereoisomers **27** and **32** have the same *anti*-configuration between $H^1$ and $H^2$, but that the minor diastereoisomer **32** has a *syn*-relationship between $H^2$ and $H^3$. Hydrogenation of **28** with $Pd(OH)_2$ on C in MeOH yielded the required bis-β-amino ester **33** in 68% yield (Scheme 9).

### Asymmetric synthesis of β,β′,β″-triamino triester 36

Having demonstrated a route towards (*R*,′*R*)-bis-β-amino esters, our attention turned towards the asymmetric synthesis of a (*R*,′*R*,″*R*)-tris-β-amino ester derivative. Thus, according to our general protocol, repeated twice in this case to achieve satisfactory conversion, Heck reaction of 1,3,5-tribromobenzene with *tert*-butyl acrylate gave the tris-acceptor **34** in 62% yield. Treatment of α,β-unsaturated acceptor **34** with lithium amide (*S*)-**10** (6 equiv.) afforded β,β′,β″-triamino triester **35** in

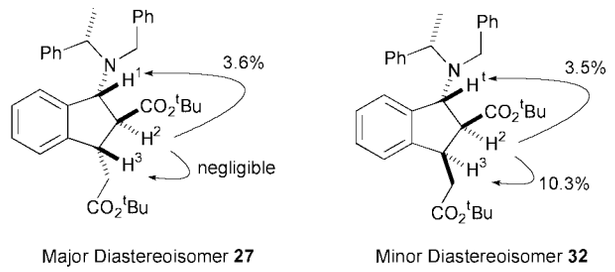
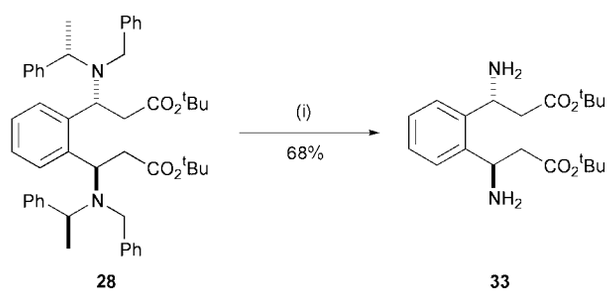



**Fig. 3** Selected NOE difference enhancements for major diastereoisomer **27** and minor diastereoisomer **32**; other NOE enhancements are omitted for clarity.




**Scheme 9** *Reagents and conditions*: (i) $Pd(OH)_2$/C, MeOH, 5 atm $H_2$.

89% de and in 78% yield. Hydrogenolytic deprotection of **35** afforded tri-β-amino triester **36** in 65% yield with a calculated ee of >99.9%[18] (Scheme 10).

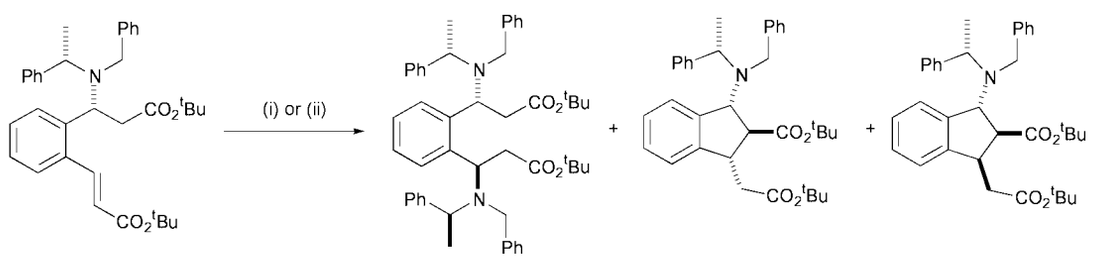
## Conclusion

In summary, we have developed a synthetic strategy for the asymmetric synthesis of a set of β,β′-diamino diesters and a β,β′,β″-triamino triester, which are currently being investigated as homochiral scaffolds for peptide synthesis.

## Experimental

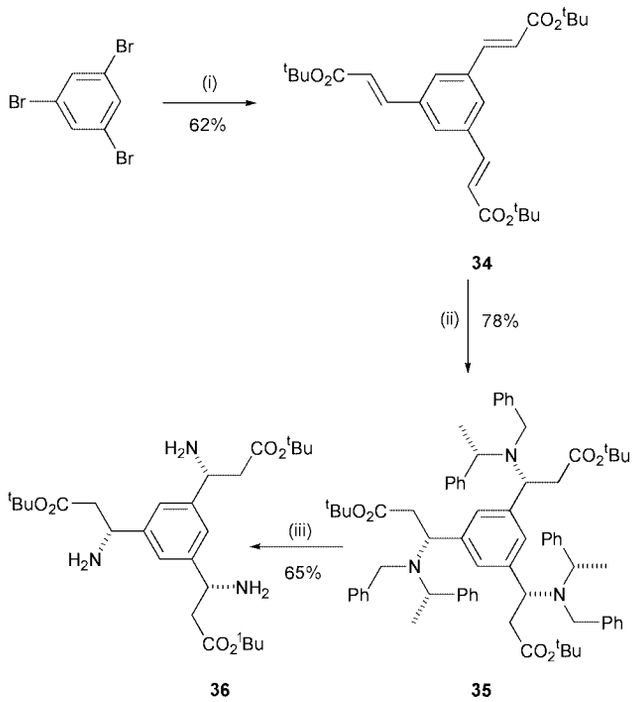
### General

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of nitrogen *via* standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. *n*-Butyllithium was used as a solution in hexanes at the molarity stated. All other solvents and reagents were used as supplied (Analytical or HPLC grade), without prior purification. Reactions were dried with $MgSO_4$. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 $F_{254}$ silica. Sheets were




| Conditions | 28 | 27 | 32 |
|---|---|---|---|
| (i) | 50 | 30 | 20 |
| (ii) | 0 | 62 | 38 |

**Scheme 8** *Reagents and conditions*: (i) (*S*)-**10** (3 equiv.), THF, −78 °C; (ii) LiHMDS (3 equiv.), THF, 0 °C, 3 hours.



**Scheme 10** *Reagents and conditions*: (i) $Pd(OAc)_2$, *tert*-butyl acrylate, tri-*o*-tolylphosphine, $NEt_3$, Δ; (ii) (*S*)-**10** (6 equiv.), THF, −78 °C; (iii) $Pd(OH)_2$/C, MeOH, 5 atm $H_2$.

visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 ($^1$H: 400 MHz and $^{13}$C: 100.6 MHz) or where stated on a Bruker AMX 500 ($^1$H: 500 MHz and $^{13}$C: 125.3 MHz) spectrometer in the deuterated solvent stated. All chemical shifts ($\delta$) are quoted in ppm and coupling constants ($J$) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. $^{13}$C multiplicities were assigned using a DEPT sequence. In all cases, the reaction diastereoselectivity was assessed by peak integration of the $^1$H NMR spectrum of the crude reaction mixture. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted. Low resolution mass spectra (*m*/*z*) were recorded on VG MassLab 20–250 or Micromass Platform 1 spectrometers and high resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer or on a Waters 2790 Micromass LCT Exact Mass Electrospray Ionisation Mass Spectrometer. Techniques used were chemical ionisation (CI, $NH_3$), atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ESI) using partial purification by HPLC with methanol–acetonitrile–water (40 : 40 : 20) as eluent. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell and are given in units of $10^{-1}$ deg cm$^2$ g$^{-1}$. Concentrations are quoted in g per 100 ml. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Dyson Perrins Laboratory, Oxford or the Inorganic Chemistry Laboratory, Oxford.

### Representative procedure 1 for lithium amide addition

*n*-BuLi (2.95 equiv.) was added dropwise to a stirred solution of (*S*)-**10** (3.0 equiv.) in anhydrous THF at −78 °C and stirred for thirty minutes under nitrogen. A solution of the bis-α,β-unsaturated ester (1.0 equiv.) in anhydrous THF at −78 °C was added dropwise *via* cannula and stirred at −78 °C for twelve hours before the addition of saturated aqueous ammonium chloride and was warmed to RT. The resultant solution was partitioned between brine and 1 : 1 DCM–$Et_2O$; the combined organic extracts were dried, filtered and concentrated *in vacuo* before purification by column chromatography.

### Preparation of (*E*,*E*′)-di-*tert*-butyl benzene-1,2-dipropenoate 17

1,2-Dibromobenzene **16** (2.36 g, 10.0 mmol) and *tert*-butyl acrylate (6.40 g, 50 mmol) were added to a suspension of $Pd(OAc)_2$ (180 mg, 0.8 mmol), *n*-$Bu_4NCl$ (3.70 g, 10.0 mmol), $K_2CO_3$ (6.9 g, 50 mmol) and LiCl (420 mg, 10.0 mmol) in DMF (50 ml). The solution was purged with $N_2$ and heated overnight at 100 °C. The mixture was cooled, washed with water (50 ml), extracted with $Et_2O$ (3 × 100 ml), dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 20 : 1) to give **17** as a white solid (2.76 g, 76%). A sample was further purified by recrystallisation ($Et_2O$–hexane) giving **17** as white needles; mp 97 °C ($Et_2O$–hexane), lit.[12] mp 78 °C (EtOH); $\delta_H$ (200 MHz, $CDCl_3$) 1.57 (18H, s, $(CO_2C(Me)_3)$, 6.28 (2H, d, *J* 16.1, PhCH=C*H*), 7.32–7.40 (2H, m, *Ph*), 7.51–7.60 (2H, m, *Ph*), 7.92 (2H, d, *J* 16.1, PhC*H*=CH).[12]

### Preparation of (*E*,*E*′)-di-*tert*-butyl benzene-1,3-dipropenoate 19

A mixture of 1,3-dibromobenzene **18** (5.0 g, 21.2 mmol), *tert*-butyl acrylate (8.1 g, 63.6 mmol), tri-*o*-tolylphosphine (0.52 g, 1.70 mmol) and $Pd(OAc)_2$ (96 mg, 0.42 mmol) in $NEt_3$ (25 ml) was refluxed overnight. The resultant mixture was filtered through Celite (eluent $Et_2O$), washed with water (50 ml), extracted with DCM (3 × 100 ml), dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 20 : 1) to give **19** as a white solid (5.6 g, 80%). A sample was further purified by recrystallisation ($Et_2O$–hexane) for analysis; mp 80 °C ($Et_2O$–hexane); $C_{20}H_{26}O_4$ requires C, 72.7; H 7.9%; found C, 72.6; H, 7.95%; $\nu_{max}$/cm$^{-1}$ (KBr) 2975 (C–H), 1700 (C=O), 1635 (C=C), 1149 (C–O); $\delta_H$ (200 MHz, $CDCl_3$) 1.54 (18H, s, $(CO_2C(Me)_3)$, 6.40 (2H, d, *J* 16.1, PhCH=C*H*), 7.34–7.65 (4H, m, *Ph*), 7.57 (2H, d, *J* 16.1, PhC*H*=CH); $\delta_C$ (50 MHz, $CDCl_3$) 28.1, 80.5, 121.0, 127.2, 129.0, 129.3, 135.2, 142.6, 165.9; *m*/*z* Probe CI ($NH_3$) 331 ($MH^+$, 20%).

### Preparation of (*E*,*E*′)-di-*tert*-butyl benzene-1,4-dipropenoate 21

$Pd(OAc)_2$ (67 mg, 0.3 mmol) was added to a mixture of 1,4-diiodobenzene **20** (0.99 g, 3 mmol), *tert*-butyl acrylate (1.54 g, 12 mmol), $PPh_3$ (79 mg, 0.6 mmol), *n*-$Bu_4NHSO_4$ (1.0 g, 3 mmol) and $K_2CO_3$ (2.1 g, 15 mmol) in MeCN–$H_2O$ (1 : 10, 5 ml) and stirred overnight at 50 °C. After cooling, the mixture was filtered through Celite (eluent $Et_2O$), washed with $H_2O$ (30 ml), extracted with DCM (3 × 100 ml), dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane–EtOAc 20 : 1) to give a separable mixture of compounds. The least polar fraction gave (*E*)-*tert*-butyl 3-(4-iodophenyl)prop-2-enoate as a white solid (142 mg, 14%); $\delta_H$ (200 MHz, $CDCl_3$) 1.53 (9H, s, $(CO_2C(Me)_3)$, 6.36 (1H, d, *J* 16.0, PhCH=C*H*), 7.22 (2H, m, *Ph*), 7.49 (1H, d, *J* 16.0, PhC*H*=CH), 7.70 (2H, m, *Ph*).[19] A more polar fraction gave **21** (0.82 g, 82%) as a white solid; $C_{20}H_{26}O_4$ requires C, 72.7; H, 7.9%; found C, 72.5; H, 8.1%; $\nu_{max}$/cm$^{-1}$ (KBr) 2973 (C–H), 1705 (C=O), 1633 (C=C), 1149 (C–O); $\delta_H$ (200 MHz, $CDCl_3$) 1.54 (18H, s, $CO_2C(Me)_3$), 6.40 (2H, d, *J* 16.1, PhCH=C*H*), 7.51 (4H, s, *Ph*), 7.57 (2H, d, *J* 16.1, PhC*H*=CH); $\delta_C$ (50 MHz, $CDCl_3$) 28.1, 80.6, 121.1, 128.3, 136.1, 142.2, 166.0; *m*/*z* ($APCI^+$) 331 ($MH^+$, 10%).

### Preparation of (3*R*,α*S*,3′*R*,α′*S*)-di-*tert*-butyl benzene-1,3-bis[3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate] 22

Following representative procedure 1, *n*-butyllithium (1.6 M,

1.45 ml, 2.32 mmol), (*S*)-**10** (500 mg, 2.36 mmol) in anhydrous THF (5 ml) and **19** (261 mg, 0.79 mmol) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane–$Et_2O$ 15 : 1) **22** (518 mg, 87%) as a white foam; $[\alpha]_D^{24}$ −11.0 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (KBr) 2975 (C–H), 1729 (C=O), 1141 (C–H); $\delta_H$ (400 MHz, $CDCl_3$) 1.23 (18H, s, $CO_2C(Me)_3$), 1.31 (6H, d, *J* 6.9, C(α)*Me*), 2.56 (2H, dd, $J_{2A,2B}$ 14.6, $J_{2A,3}$ 9.7, C(2)$H_A$), 2.64 (2H, dd, $J_{2B,2A}$ 14.6, $J_{2B,3}$ 5.1, C(2)$H_B$), 3.76 (4H, app s, NC$H_2$), 4.06 (2H, q, *J* 6.9, C(α)*H*), 4.51 (2H, dd, $J_{3,2A}$ 9.7, $J_{3,2B}$ 5.1, C(3)*H*), 7.20–7.38 (19H, m, *Ph*), 7.48–7.50 (4H, m, *Ph*), 7.70 (1H, s, Ph(2)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 16.3, 27.8, 38.8, 50.9, 57.2, 59.2, 80.1, 126.5, 126.8, 127.3, 127.8, 128.1, 140.5, 141.6, 144.2, 171.1; *m*/*z* ($APCI^+$) 754 ($MH^+$, 100%), 776 ($MNa^+$, 10%); HRMS ($CI^+$) $C_{50}H_{61}N_2O_4$ requires 753.4631; found 753.4609.

### Preparation of (3*R*,3′*R*)-di-*tert*-butyl benzene-1,3-bis(3-aminopropanoate) 23

$Pd(OH)_2$ on C (150 mg) was added to a solution of **22** (150 mg, 0.20 mmol) in a mixture of degassed MeOH–acetic acid (5 : 1, 5 ml) and the resultant black suspension stirred under a hydrogen atmosphere (5 atm) for 16 hours. The reaction mixture was filtered through a plug of Celite (eluent MeOH) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH 6 : 1) to give **23** (65 mg, 90%) as a colourless oil; $[\alpha]_D^{24}$ +10.8 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (KBr) 3438 (NH), 2975 (C–H), 1736 (C=O), 1159 (C–O); $\delta_H$ (400 MHz, $CD_3CN$) 1.41 (18H, s, $CO_2C(Me)_3$), 2.75 (2H, dd, $J_{2A,2B}$ 16.2, $J_{2A,3}$ 6.6, C(2)$H_A$), 2.85 (2H, dd, $J_{2B,2A}$ 16.2, $J_{2B,3}$ 7.5, C(2)$H_B$), 4.46 (2H, br s, C(3)*H*), 7.38–7.46 (4H, m, *Ph*); $\delta_C$ (50 MHz, $CD_3CN$) 28.3, 43.5, 53.5, 82.5, 126.6, 127.9, 130.4, 171.7; *m*/*z* ($APCI^+$) 365 ($MH^+$, 100%); HRMS ($CI^+$) $C_{20}H_{33}N_2O_4$ requires 365.2440, found 365.2441.

### Preparation of (3*R*,α*S*,3′*R*,α′*S*)-di-*tert*-butyl benzene-1,4-bis[3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate] 24

Following representative procedure 1, *n*-butyllithium (2.5 M, 0.72 ml, 1.81 mmol, 2.95 equiv.), (*S*)-**10** (388 mg, 1.78 mmol, 3.0 equiv.) in anhydrous THF (5 ml) and **21** (200 mg, 0.61 mmol, 1 equiv.) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane–$Et_2O$ 12 : 1), **24** (367 mg, 80%) as a hygroscopic white foam; $[\alpha]_D^{24}$ +11.8 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 2976, 2920 (C–H), 1726 (C=O), 1149 (C–O); $\delta_H$ (400 MHz, $CDCl_3$) 1.17 (18H, s, $CO_2C(Me)_3$), 1.21 (6H, d, *J* 6.8, C(α)*Me*), 2.49–2.57 (4H, m, C(2)$H_2$), 3.66 (4H, app s, NC$H_2$), 3.97 (2H, q, *J* 6.8, C(α)*H*), 4.39 (2H, dd, $J_{3,2A}$ 9.0, $J_{3,2B}$ 6.1, C(3)*H*), 7.14–7.42 (24H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 16.6, 27.8, 38.2, 50.7, 57.0, 59.2, 80.1, 126.5, 126.8, 127.8, 128.1, 140.5, 141.6, 144.2, 171.1; *m*/*z* ($APCI^+$) 754 ($MH^+$, 100%), 776 ($MNa^+$, 10%); HRMS ($CI^+$) $C_{50}H_{61}N_2O_4$ requires 753.4631; found 753.4608.

### Preparation of (3*R*,3′*R*)-di-*tert*-butyl benzene-1,4-bis(3-aminopropanoate) 25

$Pd(OH)_2$ on C (Pearlman's catalyst, 90 mg) was added to a solution of **24** (180 mg, 0.24 mmol) in degassed MeOH and the resultant black suspension stirred under a hydrogen atmosphere (5 atm) for 16 hours. The reaction mixture was filtered through a plug of Celite (eluent MeOH) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH 10 : 1) to give **25** (71 mg, 81%) as a colourless oil; $[\alpha]_D^{24}$ −9.1 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 2977, 2920 (C–H), 1726 (C=O), 1149 (C–O); $\delta_H$ (400 MHz, $CDCl_3$) 1.42 (18H, s, $CO_2C(Me)_3$), 2.00 (4H, br s, N*H*), 2.55–2.58 (4H, m, C(2)$H_2$), 4.35–4.38 (2H, m, C(3)*H*), 7.32 (4H, app s, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 28.0, 45.0, 52.3, 80.8, 126.5, 171.3; *m*/*z* ($APCI^+$) 365.2 ($MH^+$, 100%), 387.1 ($MNa^+$, 80%); HRMS ($CI^+$) $C_{20}H_{33}N_2O_4$ requires 365.2440, found 365.2441.

### Preparation of (1*R*,2*S*,3*S*)-*tert*-butyl 1-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[(*tert*-butoxycarbonyl)methyl]indane-2-carboxylate 27

Following representative procedure 1, *n*-butyllithium (2.5 M, 0.36 ml, 0.90 mmol), (*S*)-**10** (192 mg, 0.91 mmol) in anhydrous THF (5 ml) and **17** (100 mg, 0.30 mmol) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane–$Et_2O$ 10 : 1), **27** (134 mg, 82%) as a white foam; $[\alpha]_D^{23}$ +81.4 (*c* 1.0, $CHCl_3$), lit.[17] $[\alpha]_D^{20}$ +77.4 (*c* 0.94, $CHCl_3$); $\delta_H$ (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.9, C(α)*Me*), 1.50, 1.53 (2 × 9H, s, $CO_2C(Me)_3$), 2.58–2.70 (2H, m, C(1′)$H_2$), 3.01 (1H, app t, *J* 7.5, C(2)*H*), 3.67 (1H, app q, *J* 7.2, C(3)*H*), 3.72 (1H, d, *J* 15.1, NC$H_A$), 3.82 (1H, d, *J* 15.1, NC$H_B$), 4.18 (1H, q, *J* 6.9, C(α)*H*), 4.94 (1H, d, *J* 7.2, C(1)*H*), 7.15–7.39 (10H, m, *Ph*), 7.43–7.51 (4H, m, *Ph*).

### Preparation of (*E*)-*tert*-butyl 3-(2-iodophenyl)prop-2-enoate 29

*n*-Butyllithium (1.6 M, 11.9 ml, 19.0 mmol) was added to a solution of *tert*-butyl diethylphosphonoacetate (5.0 g, 19.8 mmol) in THF (20 ml) at −78 °C under nitrogen. After thirty minutes, this solution was added dropwise *via* a cannula to a stirred solution of 2-iodobenzaldehyde (4.0 g, 17.2 mmol) in THF (10 ml) at −78 °C and warmed to RT after stirring for thirty minutes at −78 °C. After two hours, the solution was recooled to −78 °C and quenched by the addition of saturated aqueous ammonium chloride (5 ml). After warming to RT, the solution was partitioned between brine (20 ml) and DCM (3 × 100 ml), dried and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane–$Et_2O$ 60 : 1) gave **29** (5.3 g, 93%) as a yellow oil; $\nu_{max}/cm^{-1}$ (film) 2977 (C–H), 1708 (C=O), 1637 (C=C); $\delta_H$ (400 MHz, $CDCl_3$) 1.55 (9H, s, $OC(Me)_3$), 6.25 (1H, d, *J* 15.7, C(2)*H*), 7.04 (1H, t, *J* 7.6, Ph(4)H $C_6H_4I$), 7.34 (1H, t, *J* 7.6, Ph(5)H $C_6H_4I$), 7.56 (1H, d, *J* 7.6, Ph(6)H $C_6H_4I$), 7.83 (1H, d, *J* 15.7, C(3)*H*), 7.90 (1H, d, *J* 7.6, Ph(3)H $C_6H_4I$); $\delta_C$ (100 MHz, $CDCl_3$) 28.6, 81.2, 101.7, 123.4, 127.7, 128.9, 130.7, 135.9, 140.4, 147.1, 166.0; *m*/*z* ($APCI^+$) 331 ($MH^+$, 10%), 348 ($MNH_4^+$, 30%); HRMS ($CI^+$) $C_{13}H_{16}IO_2$ requires 331.0195, found 331.0194.

### Preparation of (3*R*,α*S*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(2-iodophenyl)propanoate 30

Following representative procedure 1, *n*-butyllithium (2.5 M, 5.6 ml, 14.1 mmol), (*S*)-**10** (3.1 g, 14.5 mmol) in anhydrous THF (20 ml) and **29** (3.0 g, 9.1 mmol) in THF (20 ml) gave, after purification by column chromatography on silica gel (hexane–$Et_2O$ 12 : 1) and recrystallisation (hexane–$Et_2O$), **30** (4.3 g, 88%) as white needles; mp 88 °C; $C_{28}H_{32}INO_2$ requires C, 62.1; H, 6.0; N, 2.6%; found C, 62.1; H, 6.0; N, 2.5%; $[\alpha]_D^{24}$ −24.5 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (KBr) 2972 (C–H), 1717 (C=O), 1148 (C-O); $\delta_H$ (400 MHz, $CDCl_3$) 1.18 (9H, s, $CO_2C(Me)_3$), 1.51 (3H, d, *J* 6.7, C(α)*Me*), 2.17 (1H, dd, $J_{2A,2B}$ 13.7, $J_{2A,3}$ 9.7, C(2)$H_A$), 2.60 (1H, dd, $J_{2B,2A}$ 13.7, $J_{2B,3}$ 5.6, C(2)$H_B$), 3.72 (1H, d, *J* 15.5, NC$H_A$), 3.82 (1H, d, *J* 15.5, NC$H_B$), 3.92 (1H, q, *J* 6.7, C(α)H), 4.75 (1H, dd, $J_{3,2A}$ 9.7, $J_{3,2B}$ 5.5, C(3)*H*), 6.93–6.97 (1H, m, Ph(4)*H* $C_6H_4I$), 7.11–7.44 (11H, m, Ph and Ph(6)*H* $C_6H_4I$), 7.66–7.68 (1H, dd, *J* 7.9, *J* 1.1, Ph(5)*H* $C_6H_4I$), 7.81–7.83 (1H, dd, *J* 7.9, *J* 1.1, Ph(3)*H* $C_6H_4I$); $\delta_C$ (100 MHz, $CDCl_3$) 12.5, 27.7, 42.9, 50.5, 56.7, 66.3, 80.3, 101.7, 126.3, 126.7, 127.5, 127.8, 128.0, 128.3, 129.0, 129.8, 139.6, 142.6, 143.7, 145.2, 170.1; *m*/*z* ($APCI^+$) 542.2 ($MH^+$, 100%).

### Preparation of (3*R*,α*S*,*E*)-*tert*-butyl 3-[2-(3-*tert*-butoxy-3-oxoprop-1-enyl)phenyl]-3-(*N*-benzyl-*N*-α-methylbenzylamino)-propanoate 31

A mixture of **30** (1.75 g, 3.23 mmol), *tert*-butyl acrylate (0.98 ml, 6.47 mmol), $PPh_3$ (168 mg, 0.64 mmol) and $Pd(OAc)_2$ (70 mg, 0.32 mmol) in $NEt_3$ (35 ml) was refluxed overnight. The resultant mixture was filtered through Celite (eluent $Et_2O$),

washed with water (50 ml), extracted with DCM (3 × 100 ml), dried and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane–$Et_2O$ 20 : 1) gave **31** (1.54 g, 88%) as a hygroscopic white foam; $[\alpha]_D^{24}$ +15.0 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 2976 (C–H), 1725, 1710 (C=O), 1632 (C=C), 1149 (C–O); $\delta_H$ (400 MHz, $CDCl_3$) 1.11 (9H, s, $CO_2C(Me)_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.60 (9H, s, $CO_2C(Me)_3$), 2.37 (1H, dd, $J_{2A,2B}$ 14.0, $J_{2A,3}$ 11.0, C(2)$H_A$), 2.61 (1H, dd, $J_{2B,2A}$ 14.0, $J_{2B,3}$ 4.9, C(2)$H_B$), 3.62 (1H, d, *J* 15.4, NC$H_A$), 3.82 (1H, d, *J* 15.4, NC$H_B$), 3.92 (1H, q, *J* 6.8, C(α)H), 4.65 (1H, dd, $J_{3,2A}$ 11.0, $J_{3,2B}$ 4.9, C(3)*H*), 6.30 (1H, d, *J* 15.8, ArHC=C*H*), 7.12–7.60 (14H, m, Ph), 8.47 (1H, d, *J* 15.8, Ar*H*C=CH); $\delta_C$ (100 MHz, $CDCl_3$) 12.6, 27.6, 28.3, 41.3, 51.6, 57.0, 80.2, 80.3, 122.1, 126.3, 126.8, 127.0, 127.5, 127.6, 128.0, 128.1, 129.0, 129.5, 134.8, 140.9, 142.1, 142.2, 143.5, 166.0, 170.4; *m*/*z* APCI$^+$ 542.5 ($MH^+$, 90%); 564.4 ($MNa^+$, 30%); HRMS ($ES^+$) $C_{35}H_{44}NO_4$ requires 542.3270; found 542.3254.

### Preparation of (3*R*,α*S*,3′*R*,α′*S*)-di-*tert*-butyl benzene-1,2-bis-[3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate] 28, (1*R*,2*S*,3*S*,α*S*)-*tert*-butyl 1-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[(*tert*-butoxycarbonyl)methyl]indane-2-carboxylate 27 and (1*R*,2*S*,3*R*,α*S*)-*tert*-butyl 1-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[(*tert*-butoxycarbonyl)methyl]indane-2-carboxylate 32

Following representative procedure 1, *n*-butyllithium (2.5 M, 0.22 ml, 0.54 mmol), (*S*)-**10** (118 mg, 0.55 mmol) in anhydrous THF (5 ml) and **31** (100 mg, 0.18 mmol) in THF (2 ml) gave, after work up, a 50 : 30 : 20 mixture of **28**–**27**–**32**. Purification by column chromatography on silica gel (hexane–$Et_2O$ 20 : 1) gave **28** (58 mg, 42%) as a colourless oil and an inseparable mixture of **27** and **32** (46 mg, 46%). Data for **28**; $[\alpha]_D^{24}$ −23.4 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ ($CHCl_3$) 2974 (C–H), 1728 (C=O), 1149 (C–O); $\delta_H$ (400 MHz, $CDCl_3$) 1.06–1.08 (24H, m, $CO_2C(Me)_3$ and C(α)*Me*), 2.04 (2H, dd, $J_{2A,2B}$ 17.5, $J_{2A,3}$ 3.8, C(2)$H_A$), 2.38 (2H, dd, $J_{2B,2A}$ 17.5, $J_{2B,3}$ 8.3, C(2)$H_B$), 3.43 (2H, d, *J* 15.6, NC$H_A$), 3.52 (2H, q, *J* 6.6, C(α)*H*), 3.65 (2H, d, *J* 15.6, NC$H_B$), 4.84 (2H, dd, $J_{3,2B}$ 8.3, $J_{3,2A}$ 3.8, C(3)*H*), 6.84–7.07 (22H, m, *Ph*), 7.43–7.46 (2H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 12.6, 27.7, 40.1, 48.8, 55.5, 57.1, 79.9, 125.9, 126.3, 126.7, 127.5, 127.6, 127.8, 128.3, 142.1, 142.7, 143.6, 171.0; *m*/*z* ($APCI^+$) 754.4 ($MH^+$, 80%); HRMS ($ES^+$) $C_{50}H_{61}N_2O_4$ requires 753.4631; found 753.4634.

### Preparation of (1*R*,2*S*,3*S*,α*S*)-*tert*-butyl 1-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[(*tert*-butoxycarbonyl)methyl]indane-2-carboxylate 27 and (1*R*,2*S*,3*R*,α*S*)-*tert*-butyl 1-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[(*tert*-butoxycarbonyl)methyl]indane-2-carboxylate 32

LiHMDS (1.0 M, 1.10 mmol) was added dropwise *via* syringe to a stirred solution of **31** (200 mg, 0.37 mmol) in THF (3 ml) at 0 °C under nitrogen. After three hours, saturated aqueous ammonium chloride (5 ml) was added and the solution warmed to RT, partitioned between brine (10 ml) and DCM (3 × 60 ml), dried and concentrated *in vacuo*. $^1H$ NMR spectroscopic analysis of the crude reaction mixture indicated a 62 : 38 mixture of diastereoisomers **27** and **32**. The data for **27** were consistent with those previously reported; selected data for minor diastereoisomer **32**: $\delta_H$ (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.7, C(α)*Me*), 1.42, 1.48 (2 × 9H, s, $CO_2C(Me)_3$), 2.52–2.57 (2H, m, C(1′)*H*), 3.30 (1H, dd, $J_{2,3}$ 9.0, $J_{2,1}$ 4.9, C(2)H), 3.88 (1H. app q, *J* 7.8, C(3)*H*), 4.06 (1H, q, *J* 6.7, C(α)*H*), 4.84 (1H, d, $J_{1,2}$ 4.9, C(1)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 22.5, 28.0, 28.1, 37.1, 42.1, 49.9, 50.9, 61.1, 67.6, 80.5, 80.6, 143.1, 144.1, 145.1, 171.8, 173.0.

### Preparation of (3*R*,3′*R*)-di-*tert*-butyl benzene-1,2-bis(3-amino-propanoate) 33

$Pd(OH)_2$ on C (50 mg) was added to a solution of **28** (100 mg, 0.13 mmol) in degassed MeOH and the resultant black suspension stirred under a hydrogen atmosphere (5 atm) for 16 hours. The reaction mixture was filtered through a plug of Celite (eluent MeOH) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH 20 : 1) to give **33** (33 mg, 68%) as a colourless oil; $[\alpha]_D^{24}$ +23.4 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 2977, 2930 (C–H), 1723 (C=O), 1147 (C–O); $\delta_H$ (400 MHz, $CDCl_3$) 1.49 (18H, s, $CO_2C(Me)_3$), 1.76 (4H, br s, N*H*), 2.62–2.66 (4H, m, C(2)$H_2$), 4.78–4.82 (2H, m, C(3)*H*), 7.25–7.28, 7.45–7.48 (2 × 2H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 28.0, 44.7, 47.4, 80.7, 125.9, 127.1, 141.4, 171.3; *m*/*z* APCI$^+$ 365.3 ($MH^+$, 100%), 309.3 ($MH^+ - C_4H_8$, 80%); HRMS ($CI^+$) $C_{20}H_{33}N_2O_4$ requires 365.2440, found 365.2451.

### Preparation of (*E*,*E*′,*E*″)-1,3,5-tri-*tert*-butyl benzene-1,3,5-tripropenoate 34

A mixture of 1,3,5-tribromobenzene (5.0 g, 15.9 mmol), *tert*-butyl acrylate (8.1 g, 63.6 mmol), tri-*o*-tolylphosphine (0.58 g, 1.91 mmol) and $Pd(OAc)_2$ (108 mg, 0.48 mmol) in $NEt_3$ (15 ml) was refluxed overnight. The resultant mixture was filtered through Celite (eluent $Et_2O$), washed with water (50 ml), extracted with DCM (3 × 100 ml), dried and concentrated *in vacuo*. This procedure was repeated to ensure good conversion to the required product. The residue was purified by column chromatography on silica gel (hexane–$Et_2O$ 20 : 1) and then recrystallisation ($Et_2O$–hexane) to give **34** (4.6 g, 62%) as a white solid; mp 158 °C ($Et_2O$–hexane); $C_{27}H_{36}O_6$ requires C, 71.0; H, 7.95%; found C, 71.0; H, 8.0%; $\nu_{max}/cm^{-1}$ (KBr) 2980, 2929 (C–H), 1690 (C=O), 1639 (C=C), 1149 (C–O); $\delta_H$ (200 MHz, $CDCl_3$) 1.54 (27H, s, $CO_2C(Me)_3$), 6.42 (3H, d, *J* 16.1, PhCH=C*H*), 7.56 (3H, d, *J* 16.1, PhC*H*=CH), 7.60 (3H, s, *Ph*); $\delta_C$ (50 MHz, $CDCl_3$) 28.1, 80.8, 121.9, 128.1, 135.9, 141.9, 165.7.

### Preparation of (3*R*,α*S*,3′*R*,α′*S*,3″*R*,α″*S*)-1,3,5-tri-*tert*-butyl benzene-1,3,5-tris[3-(*N*-benzyl-*N*-α-methylbenzylamino)-propanoate] 35

Following representative procedure 1, *n*-butyllithium (1.6 M, 1.86 ml, 2.98 mmol), (*S*)-**10** (636 mg, 3.0 mmol, 6.0 equiv.) in anhydrous THF (5 ml) and **34** (228 mg, 0.50 mmol) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane–$Et_2O$ 10 : 1), **35** (425 mg, 78%) as a white foam; $[\alpha]_D^{24}$ +15.0 (*c* 1.0, $CHCl_3$); $C_{72}H_{87}N_3O_6$ requires C, 79.3; H 8.0; N 3.85%; found C, 79.3; H, 7.9; N, 3.75%; $\nu_{max}/cm^{-1}$ (KBr) 2975, 2928 (C–H), 1725 (C=O), 1151 (C–O); $\delta_H$ (400 MHz, $CDCl_3$) 1.21 (9H, d, *J* 6.8, C(α)*Me*), 1.23 (27H, s, $CO_2C(Me)_3$), 2.55 (3H, dd, $J_{2A,2B}$ 15.0, $J_{2A,3}$ 8.8, C(2)$H_A$), 2.64 (2H, dd, $J_{2B,2A}$ 15.0, $J_{2B,3}$ 5.6, C(2)$H_B$), 3.76 (6H, ABq, NC$H_2$), 4.00 (3H, q, *J* 6.8, C(α)*H*), 4.48 (3H, dd, $J_{3,2A}$ 8.8, $J_{3,2B}$ 5.6, C(3)*H*), 7.13–7.44 (33H, m, *Ph*); $\delta_C$ (50 MHz, $CDCl_3$) 17.7, 27.9, 37.7, 50.8, 57.3, 58.7, 80.0, 126.5, 126.8, 126.9, 127.9, 128.1, 141.4, 141.6, 144.2, 171.0; *m*/*z* ($APCI^+$) 1090.3 ($MH^+$, 100%), 1113.1 ($MNa^+$, 30%).

### Preparation of (3*R*,3′*R*,3″*R*)-1,3,5-tris-*tert*-butyl benzene-1,3,5-tris(3-aminopropanoate) 36

To a solution of **35** (150 mg, 0.14 mmol) in degassed MeOH (5 ml) in a Fischer–Porter bottle was added $Pd(OH)_2$ on C (150 mg) and the resultant black suspension stirred under a hydrogen atmosphere (5 atm) for 16 hours. The reaction mixture was then filtered through a plug of Celite (eluent MeOH) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH 10 : 1) to give **36** (45 mg, 65%) as a colourless oil; $[\alpha]_D^{24}$ +15.3 (*c* 1.0, $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 3368 (NH), 2977 (C–H), 1724 (C=O), 1151 (C–O); $\delta_H$ (400 MHz, $CDCl_3$) 1.41 (27H, s, $CO_2C(Me)_3$), 1.79 (6H, br s, N*H*), 2.55 (6H, ABm, C(2)$H_2$), 4.35 (3H, br m, C(3)*H*), 7.35 (3H, m,

*Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 28.0, 45.4, 52.7, 80.7, 123.2, 171.3; *m*/*z* Probe CI ($NH_3$) 508.1 ($MH^+$, 100%), 522.1 ($MNH_3^+$, 5%), 452.1 ($MH^+ - C_4H_8$, 30%); HRMS ($CI^+$) $C_{27}H_{46}N_3O_6$ required 508.3387; found 508.3381.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