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Asymmetric synthesis of the *cis*- and *trans*-stereoisomers of 4-aminopyrrolidine-3-carboxylic acid and 4-aminotetrahydrofuran-3-carboxylic acid

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The diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide has been successfully applied to the first asymmetric syntheses of *cis*-(3*S*,4*R*)- and *trans*-(3*R*,4*R*)-4-aminotetrahydrofuran-3-carboxylic acids (26% and 25% overall yield respectively, >98% d.e. and >97% e.e. in each case). Furthermore, the most efficient asymmetric synthesis to date of *cis*-(3*R*,4*R*)- and *trans*-(3*R*,4*S*)-4-aminopyrrolidine carboxylic acids is delineated: for *cis*-(3*R*,4*R*), four steps, >98% d.e., 52% overall yield; for *trans*-(3*R*,4*S*), five steps, >98% d.e., 50% overall yield.

Introduction

Heterocyclic β-amino acid derivatives of *cis*-(1*R*,2*S*)-2-aminocyclopentane-1-carboxylate **1** (cispentacin) are a medicinally interesting and much studied molecular class. While cispentacin is a potent antifungal agent,[1] the incorporation of an oxygen or sulfur heteroatom within the carbocyclic skeleton to generate the corresponding (±)-4-aminotetrahydrofuran- and (±)-4-aminotetrahydrothiophene-3-carboxylates **2** and **3** results in a significant reduction of biological activity.[2] However, racemic *cis*-4-aminopyrrolidine-3-carboxylic acid **4** has been used to probe the structure of the GABA receptor,[3] while *cis*-*N*-Boc-4-aminopyrrolidine-3-carboxylic acid **5** is a modestly active influenza neuramidase inhibitor. Using *N*-Boc-**5** as a lead structure, Wang *et al.* have employed a combination of combinatorial chemistry and structure based drug design to discover the trisubstituted pyrrolidine carboxylic acid A-192558 **6** as a potent influenza neuramidase inhibitor.[4] Furthermore, water soluble short chain peptides such as **8** containing both transpentacin and *trans*-(3*R*,4*S*)-4-aminopyrrolidine-3-carboxylic acid **7** residues have been shown to adopt distinct helical secondary structures in solution (Fig. 1).[5]

Despite recent interest in the preparation of this structural class, only limited methods for the asymmetric synthesis of these heterocyclic β-amino acid derivatives in enantiomerically pure form exist. For instance, the asymmetric synthesis of *cis*-4-aminopyrrolidine-3-carboxylic acid derivatives has been achieved using enantioselective hydrogenation[6] and 1,3-dipolar cycloaddition of nitrones,[7,8] while the synthesis of *trans*-4-aminopyrrolidine-3-carboxylic acid has been achieved diastereoselectively using radical addition[9] and in an asymmetric fashion through reductive amination.[10] However, there is no single methodology that allows the selective asymmetric synthesis of both *cis*- and *trans*-diastereoisomers. Previous investigations from this laboratory have shown that conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **9** to *tert*-butyl cyclopentene-1-carboxylate **10** and subsequent *N*-deprotection and ester hydrolysis allows an efficient synthesis of cispentacin **12**. Selective epimerisation of β-amino ester *cis*-(1*R*,2*S*,α*S*)-**11** to the thermodynamic epimer *trans*-(1*S*,2*S*,α*S*)-**13** leads to (1*S*,2*S*)-transpentacin **14** (Scheme 1).[11]

As an extension of this methodology, it was envisaged that the conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **9** to a range of dihydrofuran, *N*-protected dihydropyrrole and dihydrothiophene α,β-unsaturated esters would facilitate the asymmetric synthesis of both *cis*- and *trans*-stereoisomers of the corresponding β-amino acid derivatives, and we delineate herein our investigations within this area.

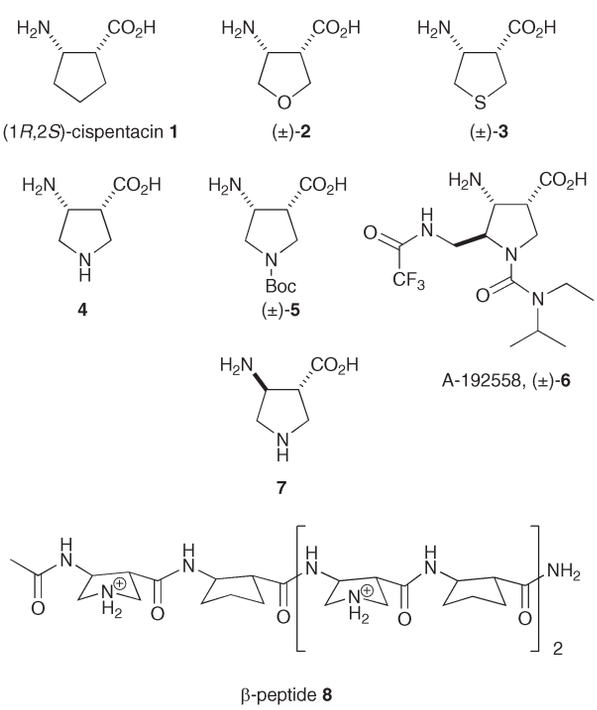

Fig. 1 Heterocyclic β-amino acids.

Results and discussion

Synthesis of heterocyclic α,β-unsaturated esters

Initial investigations centred upon a simple and general route for the synthesis of a range of *tert*-butyl dihydrofuran, *N*-protected dihydropyrrole and dihydrothiophene α,β-unsaturated esters. As *tert*-butyl (*RS*)-3-alkylcyclopentene-1-carboxylates may be readily prepared from the corresponding β-keto esters,[12] an analogous disconnection in the heterocyclic series leads to the requirement for an efficient synthesis of the corresponding heterocyclic β-keto esters **15**. It was envisaged that this structural framework could be regioselectively assembled in a 'one pot' procedure by a tandem conjugate addition–Dieckmann cyclisation protocol (Fig. 2).

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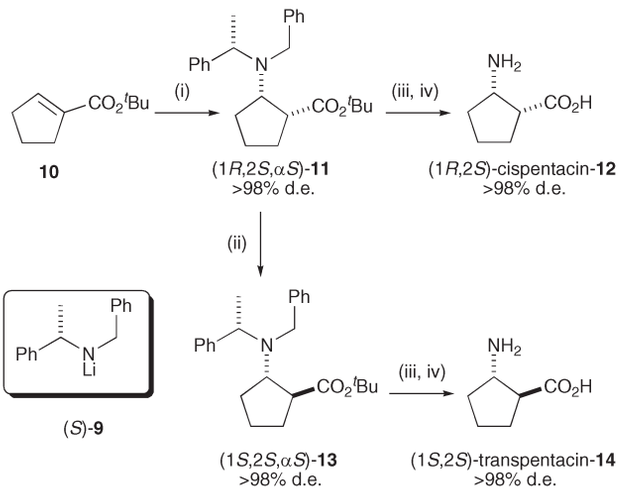


Scheme 1 Reagents and conditions: (i). Lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **9**, THF, −95 °C then 2,6-di-*tert*-butyl phenol; (ii). KO^{t}Bu, ^{t}BuOH, rt; (iii). Pd–C, MeOH, H_2 (5 atm), rt; (iv). TFA then Dowex 50WX8-200.

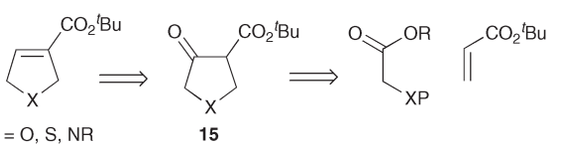
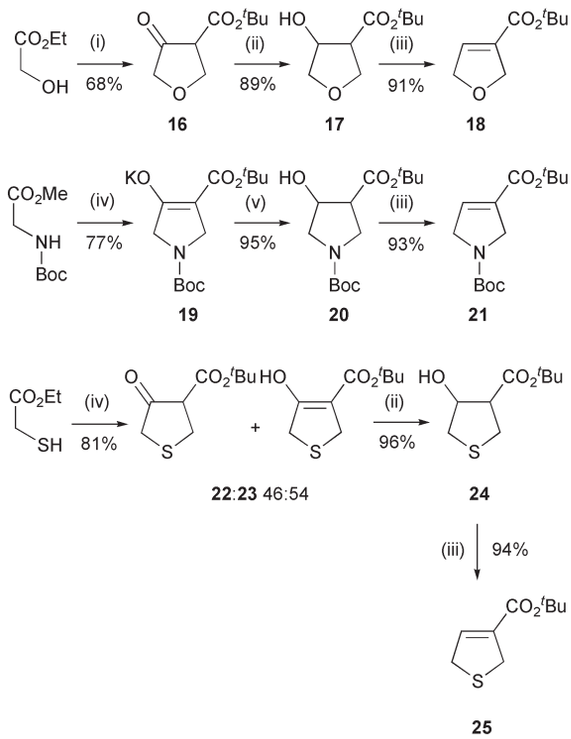


Fig. 2 Retrosynthetic analysis of *tert*-butyl dihydrofuran, *N*-protected dihydropyrrole and dihydrothiophene α,β-unsaturated esters.

In a model study, and using a modification of the literature procedure,[13] *tert*-butyl 4-oxotetrahydrofuran-3-carboxylate **16** was obtained in 68% yield by reaction of the anion of ethyl glycolate with *tert*-butyl acrylate in DMSO at rt. This experimentally simple procedure was subsequently adapted to the synthesis of *tert*-butyl 4-oxotetrahydrothiophene-3-carboxylate **22** which was obtained in 81% overall yield as a 46 : 54 mixture with its enol tautomer **23**, and the corresponding pyrrolidine β-keto ester which was isolated as its stable potassium enolate salt **19** in 77% yield from the reaction of the anion of *N*-Boc-glycine methyl ester and *tert*-butyl acrylate.[4] These heterocyclic β-keto esters **16**, **19** and **22** : **23** were subsequently chemoselectively reduced using either sodium borohydride or sodium cyanoborohydride[14] to the corresponding alcohols **17**, **20** and **24**, which underwent facile dehydration upon treatment with PPh_3/diisopropyl azodicarboxylate (DIAD), furnishing the desired α,β-unsaturated acceptors **18**, **21** and **25** (Scheme 2).

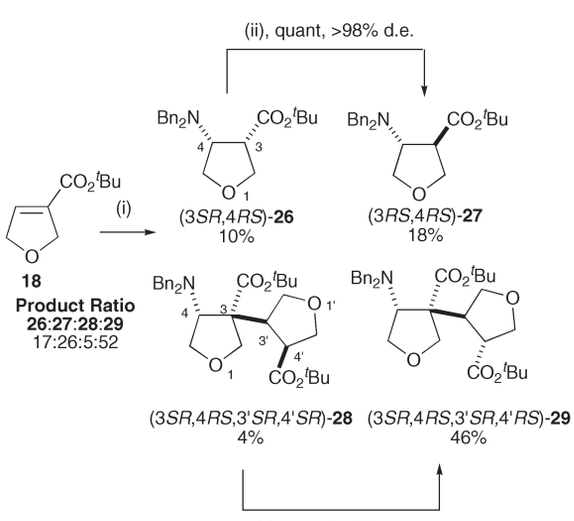
Probing the reactivity of heterocyclic α,β-unsaturated acceptors: conjugate addition of lithium dibenzylamide

With efficient routes to heterocyclic α,β-unsaturated esters **18**, **21** and **25** in hand, attention turned to studying the conjugate addition reactions of lithium amides to these substrates. In order to quantify the reactivity of the heterocyclic α,β-unsaturated esters in this reaction manifold, initial model studies were concerned with the addition of achiral lithium dibenzylamide. Addition of *tert*-butyl 2,5-dihydrofuran-3-carboxylate **18** to lithium dibenzylamide (1.6 eq) gave a complex mixture of four products **26** : **27** : **28** : **29** in a 17 : 26 : 5 : 52 ratio, with chromatographic purification allowing separation of all four compounds. The expected C(3)-epimeric β-amino esters **26** and **27** were obtained in 10% and 18% isolated yield respectively, and in >98% d.e. in each case. Subsequent treatment of (3*SR*,4*RS*)-**26** (>98% d.e.) with KO^{t}Bu in ^{t}BuOH gave quantitatively the thermodynamic β-amino ester (3*RS*,4*RS*)-**27** (>98% d.e.), allowing assignment of the relative configuration within **26** and **27**. The two other products of the conjugate addition reaction were the oligomeric β-amino esters **28** and **29**, isolated in 4% and 46% yield respectively, which presumably derive from conjugate addition of the *in situ* generated (*Z*)-β-amino lithium enolate to



Scheme 2 Reagents and conditions: (i). NaH (1.0 eq), Et_2O, rt, 0.5 h then *tert*-butyl acrylate (1.2 eq), DMSO, rt, 0.5 h; (ii). $NaBH_4$ (1.0 eq), ^{i}PrOH, 0 °C to rt; (iii). PPh_3 (1.5 eq), DIAD (1.3 eq), THF, 0 °C to rt; (iv). *tert*-butyl acrylate (1.0 eq), KO^{t}Bu (1.1 eq), THF, 0 °C, 0.5 h, then rt, 16 h; (v). $NaBH_3CN$ (1.1 eq), MeOH, pH 3–4, rt.

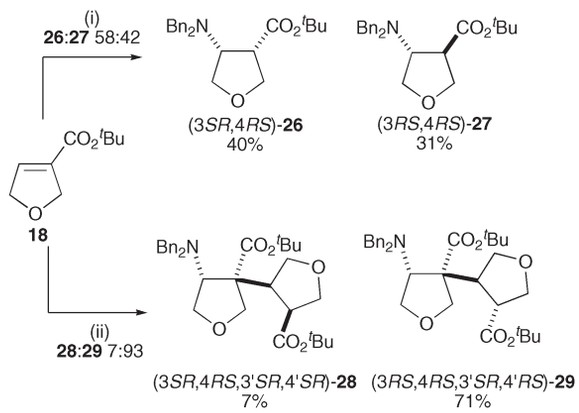
18. The relative configuration at C(3) within oligomeric β-amino esters **28** and **29** was assigned by assuming the known *anti*-facial bias for the reaction of cyclic β-amino enolates derived from lithium amide conjugate addition with electrophiles.[15] The relative *cis*- configuration at C(3′) and C(4′) within oligomeric β-amino ester **28** was verified independently by ^{1}H NOE difference analysis, while the epimeric nature of **28** and **29** was confirmed through conversion of (3*SR*,4*RS*,3′*SR*,4′*SR*)-**28** to the thermodynamic adduct (3*SR*,4*RS*,3′*SR*,4′*RS*)-**29** (>98% d.e.) upon treatment with KO^{t}Bu in ^{t}BuOH. (Scheme 3).



Scheme 3 Reagents and conditions: (i). lithium dibenzylamide (1.6 eq), THF, −78 °C then $NH_4Cl_{(aq)}$, −78 °C to rt; (ii). KO^{t}Bu, ^{t}BuOH, Δ, 3 h.

Although low levels of diastereoselectivity upon protonation of the β-amino enolates generated in this reaction with NH_4Cl may be expected,[11] the formation of oligomeric products in the reaction was unexpected, as during our extensive research utilising the conjugate addition of lithium amides this reaction manifold has not been identified under these standard conditions. In

order to bias the reaction toward the formation of the desired β-amino esters **26** and **27** it was predicted that slow addition of ester **18** to lithium dibenzylamide would disfavour the formation of the oligomeric products. Thus, dropwise addition of a dilute solution of ester **18** to lithium dibenzylamide (1.6 eq) at −78 °C, followed by addition of NH_4Cl gave a 58 : 42 mixture of only the C(3)-epimeric β-amino esters **26** and **27**, in 40% and 31% isolated yield respectively. Conversely, addition of ester **18** in THF to 0.5 eq of lithium dibenzylamide gave a 7 : 93 mixture of only the C(4′)-epimeric oligomeric esters **28** and **29** in 7% and 71% isolated yield respectively (Scheme 4).

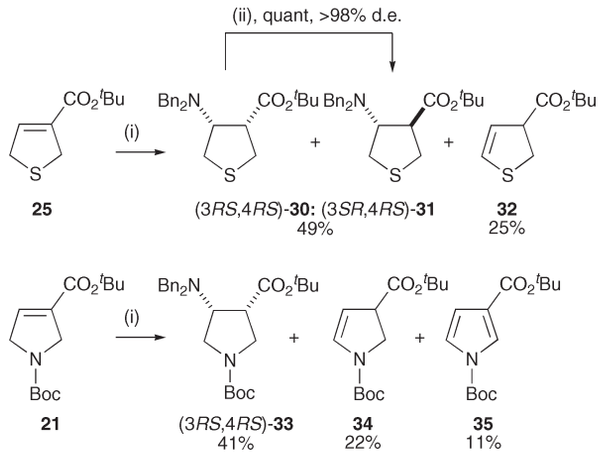


Scheme 4 Reagents and conditions: (i). lithium dibenzylamide (1.6 eq), **18** (1.0 eq), dilute solution added over 2 h, THF, −78 °C then $NH_4Cl_{(aq)}$, −78 °C to rt; (ii). lithium dibenzylamide (0.5 eq), **18** (1.0 eq), THF, −78 °C then $NH_4Cl_{(aq)}$, −78 °C to rt.

Subsequent studies were concerned with evaluating the product distribution arising from addition of *tert*-butyl 2,5-dihydrothiophene-3-carboxylate **25** and *tert*-butyl *N*-Boc-2,5-dihydropyrrole-3-carboxylate **21** to lithium dibenzylamide. Addition of **25** to lithium dibenzylamide under standard conditions gave a complex mixture of products, which contained the C(3)-epimeric β-amino esters (3*RS*,4*RS*)-**30** and (3*SR*,4*RS*)-**31** in a 54 : 46 ratio, although there was no evidence of the formation of oligomeric products. Chromatographic purification yielded an inseparable mixture of β-amino esters (3*RS*,4*RS*)-**30** and (3*SR*,4*RS*)-**31** (54 : 46) in 49% yield, with treatment of this isolated mixture with KO^{t}Bu in ^{t}BuOH allowing quantitative conversion to (3*SR*,4*RS*)-**31** in >98% d.e. Chromatography also allowed the isolation of the deconjugated ester *tert*-butyl 2,3-dihydrothiophene-3-carboxylate **32** in 25% yield, consistent with γ-deprotonation competing with lithium amide addition in this case. Similarly, addition of **21** to lithium dibenzylamide again gave a complex mixture, containing β-amino ester (3*RS*,4*RS*)-**33** as the sole C(3)-epimer, with chromatography furnishing rotameric (3*RS*,4*RS*)-**33** in 41% isolated yield. Attempted conversion of (3*RS*,4*RS*)-**33** to its C(3)-epimer with KO^{t}Bu in ^{t}BuOH proved unsuccessful, leading instead to extensive decomposition, although an 8.1% NOE enhancement from C(4)–H to C(3)–H was indicative of a *syn* relationship between the amino and carboxylate functionalities within **33**. Chromatographic purification also allowed the isolation and identification of the deconjugated adduct *tert*-butyl *N*-Boc-2,3-dihydropyrrole-3-carboxylate **34** in 22% yield and *tert*-butyl *N*-Boc pyrrole-1,3-dicarboxylate **35** in 11% yield, again consistent with γ-deprotonation competing with lithium amide addition. It is notable that *N*-Boc amino protection has been used by Beak *et al.* as an activating and directing group for lithiation in the deprotonation of a variety of cyclic and allylic amines, which may explain the facile γ-deprotonation observed in this case (Scheme 5).[16]

Asymmetric synthesis of heterocyclic β-amino esters: conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide

With model studies complete, the asymmetric synthesis of the heterocyclic β-amino esters was investigated. Slow addition



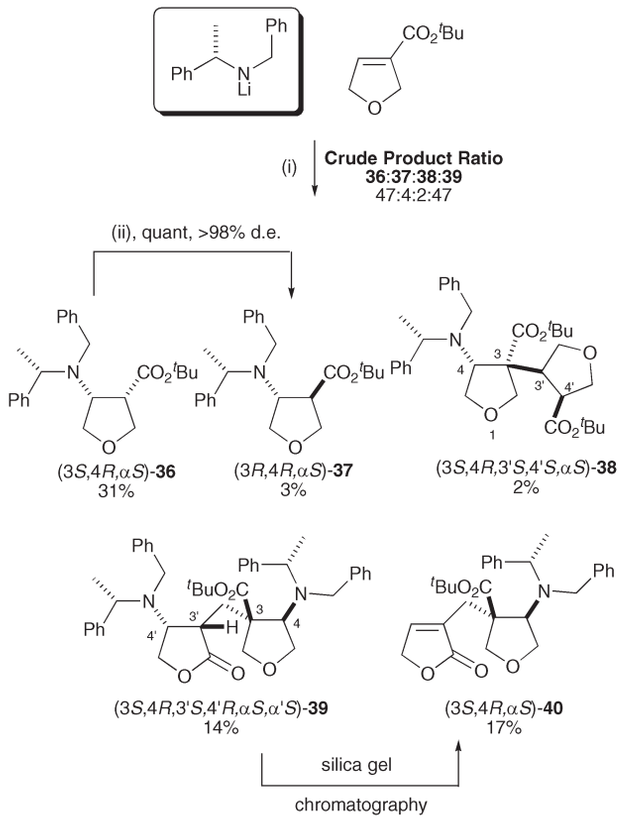
Scheme 5 Reagents and conditions: (i). lithium dibenzylamide (1.6 eq), THF, −78 °C then $NH_4Cl_{(aq)}$, −78 °C to rt; (ii). KO^{t}Bu, ^{t}BuOH, Δ, 3 h.

of dihydrofuran carboxylate **18** to a solution of homochiral lithium-(*S*)-*N*-benzyl-*N*-α-methylbenzylamide **9** gave a crude reaction mixture containing four products **36** : **37** : **38** : **39** in a 47 : 4 : 2 : 47 ratio. Purification by chromatography on silica gave the separable C(3)-epimeric β-amino esters (3*S*,4*R*,α*S*)-**36** and (3*R*,4*R*,α*S*)-**37** in 31% and 3% yield respectively. The configuration at C(4) within **36** and **37** relative to the *N*-α-methylbenzyl stereocentre was assigned by analogy with the model previously used to explain the stereoselectivity observed during addition of lithium amide **9** to α,β-unsaturated esters,[17] with the relative configuration at C(4) and C(3) confirmed by quantitative conversion of **36** to the thermodynamic epimer **37**. The oligomeric product **38** was obtained as a minor reaction component in 2% yield,[18] with further elution giving **39**, a product containing two *N*-benzyl-*N*-α-methylbenzylamino functionalities in 14% yield, and the related product **40** in 17% yield. The α,β-unsaturated lactone **40** was not present in the crude reaction mixture, and is presumed to arise from the retro-conjugate addition of *N*-benzyl-*N*-α-methylbenzylamine under the mildly acidic conditions of the purification medium (Scheme 6).[19] The relative configuration within **40** was unambiguously established by single crystal X-ray analysis, with the absolute (3*S*,4*R*,α*S*) configuration derived from the known configuration of the (*S*)-*N*-α-methylbenzyl stereocentre (Fig. 3).

Diamino ester **39** presumably arises as a result of slow ring opening of the initially formed (*Z*)-β-amino enolate **41** arising from conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, followed by 5-*exo*-*trig* ring-closure to give α,β-unsaturated lactone **42**.[20] Subsequent diastereoselective conjugate addition of β-amino enolate **41** *anti*- to its stereodirecting amino substituent, and protonation of the resulting enolate *anti*- to the neighbouring C(4)-amino group will furnish the diamino ester **39** (Fig. 4).

On the basis of this mechanistic hypothesis, it was envisaged that minimisation of the undesired oligomeric fragmentation products in this reaction could be achieved provided that the reaction was quenched sufficiently quickly so as to allow conjugate addition to occur, but not promote fragmentation. In this manner, addition of ester **18** to an excess of lithium amide (*S*)-**9** (5 eq) followed by addition of aqueous NH_4Cl after 10 min gave a mixture containing an 89 : 11 ratio of β-amino esters **36** : **37** and less than 3% of oligomeric products, with chromatography furnishing β-amino esters (3*S*,4*R*,α*S*)-**36** and (3*R*,4*R*,α*S*)-**37** in 68% and 9% yield respectively and in >98% d.e. in each case (Scheme 7).

Having optimised the conjugate addition of homochiral lithium amide **9** to ester **18**, the corresponding conjugate additions to dihydrothiophene and dihydropyrrole esters **25** and **21** were investigated. Addition of thiophene ester **25** to lithium amide (*S*)-**9** gave, after addition of aqueous NH_4Cl, a mixture which contained the expected C(3)-epimeric β-amino esters (3*R*,4*R*,α*S*)-**43** and (3*S*,4*R*,α*S*)-**44** in a 69 : 31 ratio, with subsequent purification giving an inseparable 69 : 31



Scheme 6 Reagents and conditions: (i). lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **9**, THF, −78 °C then $NH_4Cl_{(aq)}$, −78 °C to rt; (ii). KO^{t}Bu, ^{t}BuOH, Δ, 3 h.

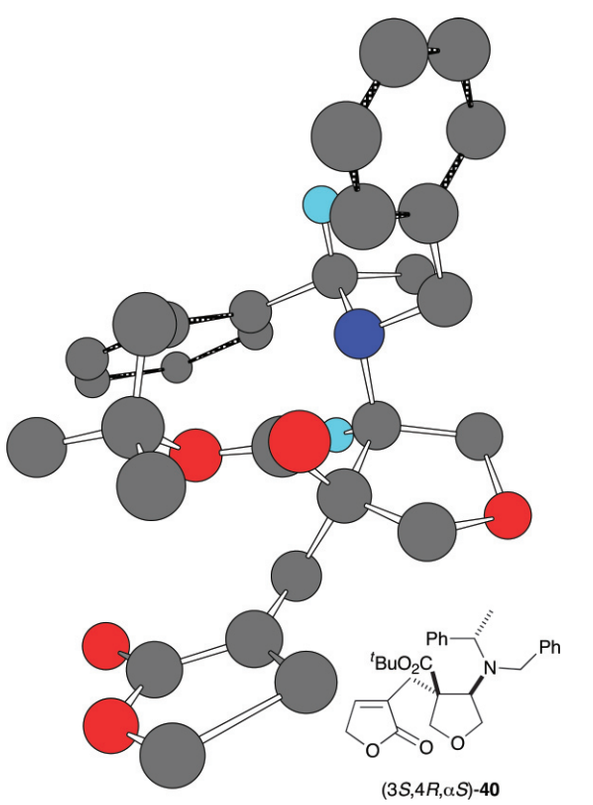


Fig. 3 Chem 3D representation of the X-ray crystal structure of (3*S*,4*R*,α*S*)-**40** (some H omitted for clarity).

mixture of (3*R*,4*R*,α*S*)-**43** and (3*S*,4*R*,α*S*)-**44** in 52% yield, and the deconjugated ester **32** in 29% yield. The purified 69 : 31 mixture of (3*R*,4*R*,α*S*)-**43** and (3*S*,4*R*,α*S*)-**44** was subjected to equilibrating conditions, furnishing the thermodynamic *trans*-diastereoisomer (3*S*,4*R*,α*S*)-**44** in >98% d.e. The use of the hindered proton source 2,6-di-*tert*-butyl phenol in the

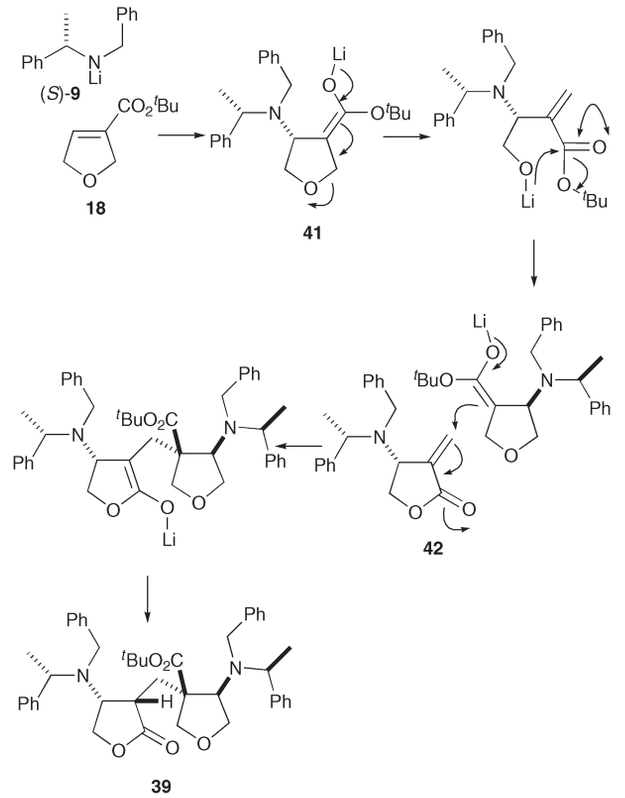
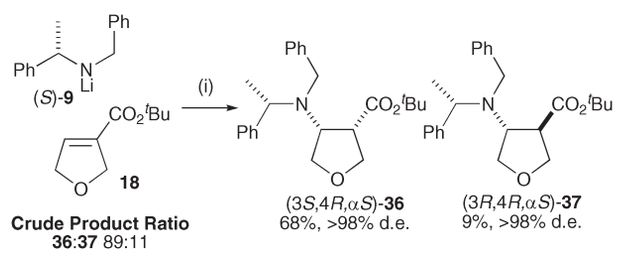


Fig. 4 Proposed mechanism for the synthesis of diamino ester **39**.

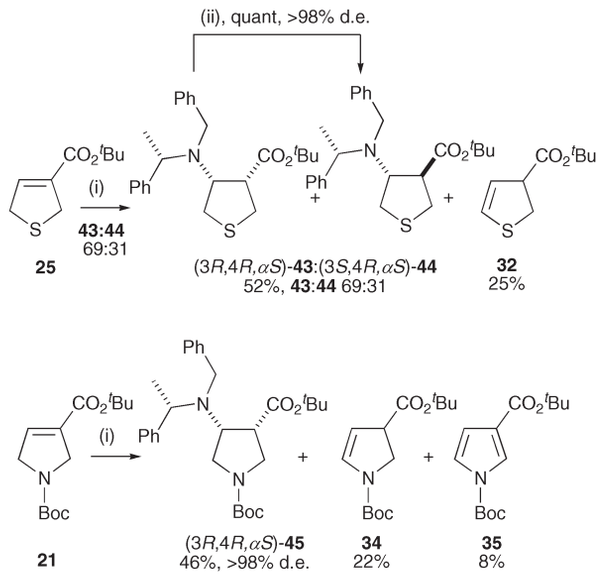


Scheme 7 Reagents and conditions: (i). lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **9** (5 eq), THF, −78 °C, 10 min; (ii). $NH_4Cl_{(aq)}$, −78 °C to rt.

reaction, which has previously been used to give high selectivity upon protonation of carbocyclic β-amino enolates,[11] did not improve the diastereoisomeric ratio, giving an identical product distribution. Conjugate addition of lithium amide (*S*)-**9** to dihydropyrrole ester **21** gave a mixture containing (3*R*,4*R*,α*S*)-**45** in >98% d.e., with chromatography giving (3*R*,4*R*,α*S*)-**45** in 46% isolated yield, plus the deconjugated ester **34** and the aromatic pyrrole **35** in 22% and 8% yield respectively. Attempted epimerisation of *cis*-**45** to the corresponding *trans*-β-amino ester proved unsuccessful, with the relative (3*R*,4*R*,α*S*)-configuration within **45** being assigned by analogy with that obtained from the addition of lithium dibenzylamide to **21**, and by its conversion into the known *cis*-4-amino-3-carboxylic acid (*vide infra*) (Scheme 8).

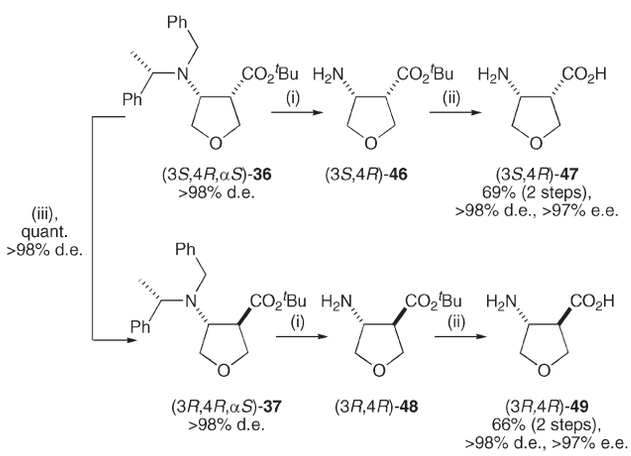
Deprotection: synthesis of *cis*-(3*R*,4*R*)- and *trans*-(3*S*,4*R*)-4-pyrrolidine-3-carboxylic acid and *cis*-(3*S*,4*R*)- and *trans*-(3*R*,4*R*)-4-tetrahydrofuran-3-carboxylic acid

With a range of heterocyclic β-amino esters prepared diastereoselectively, deprotection to the corresponding carboxylic acids was investigated. Attempted *N*-deprotection of the *trans*-dihydrothiophene β-amino ester **44** using a variety of palladium-based hydrogenolytic methods only returned predominantly starting material, while treatment with HBr[21] led to complete decomposition. However, palladium-mediated hydrogenolytic *N*-debenzylation of *cis*-dihydrofuran β-amino ester (3*S*,4*R*,α*S*)-**36** gave the corresponding primary β-amino



Scheme 8 Reagents and conditions: (i). lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide **9** (1.6 eq), THF, −78 °C then $NH_4Cl_{(aq)}$, −78 °C to rt; (ii). KO^{t}Bu, ^{t}BuOH, Δ, 3 h.

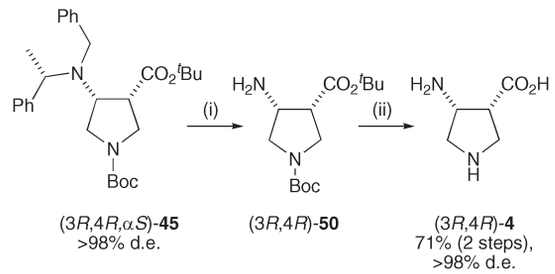
ester (3*S*,4*R*)-**46**, with subsequent treatment with TFA and purification by ion exchange chromatography furnishing acid (3*S*,4*R*)-**47** in good yield (69% over two steps) and >98% d.e. and >97% e.e.[22] Similarly, *N*-deprotection of *trans*-dihydrofuran β-amino ester (3*R*,4*R*,α*S*)-**37**, isolated either as the minor reaction component from the lithium amide conjugate addition reaction, or *via* quantitative epimerisation of *cis*-(3*S*,4*R*,α*S*)-**36**, gave the corresponding β-amino ester (3*R*,4*R*)-**48**, with ester hydrolysis and ion exchange chromatography giving (3*R*,4*R*)-**49** in >98% d.e. and >97% e.e.[22] (Scheme 9).



Scheme 9 Reagents and conditions: (i). $Pd(OH)_2$ on C, MeOH, H_2 (5 atm); (ii). TFA, rt then Dowex 50WX8-200; (iii). KO^{t}Bu, ^{t}BuOH, Δ, 3 h.

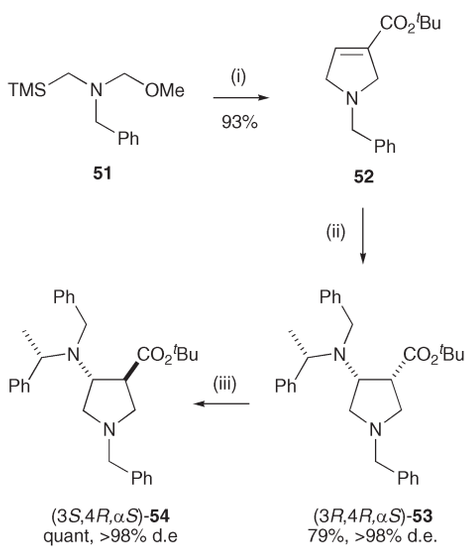
Similarly, palladium-mediated *N*-debenzylation of *cis*-dihydropyrrole β-amino ester (3*R*,4*R*,α*S*)-**45** gave primary β-amino ester (3*R*,4*R*)-**50** in which the two amines are differentially protected, with subsequent treatment with TFA achieving concomitant ester and *N*-Boc deprotection, giving, after purification by ion exchange chromatography, (3*R*,4*R*)-**4** in >98% d.e. (Scheme 10).

As this methodology only allows the asymmetric synthesis of the *cis*-stereoisomer of 4-pyrrolidine-3-carboxylic acid, an alternative strategy was investigated that would be amenable to the stereoselective synthesis of both *cis*- and *trans*-stereoisomers. It was envisaged that *N*-benzyl protection of the dihydropyrrole α,β-unsaturated ester would minimise γ-deprotonation, while being readily deprotected by hydrogenolysis. Thus, *tert*-butyl-*N*-benzyl-2,5-dihydropyrrole-3-carboxylate **52** was prepared in 93% isolated yield *via* 1,3-dipolar cycloaddition,



Scheme 10 Reagents and conditions: (i). $Pd(OH)_2$ on C, MeOH, H_2 (5 atm); (ii). TFA, rt then Dowex 50WX8-200.

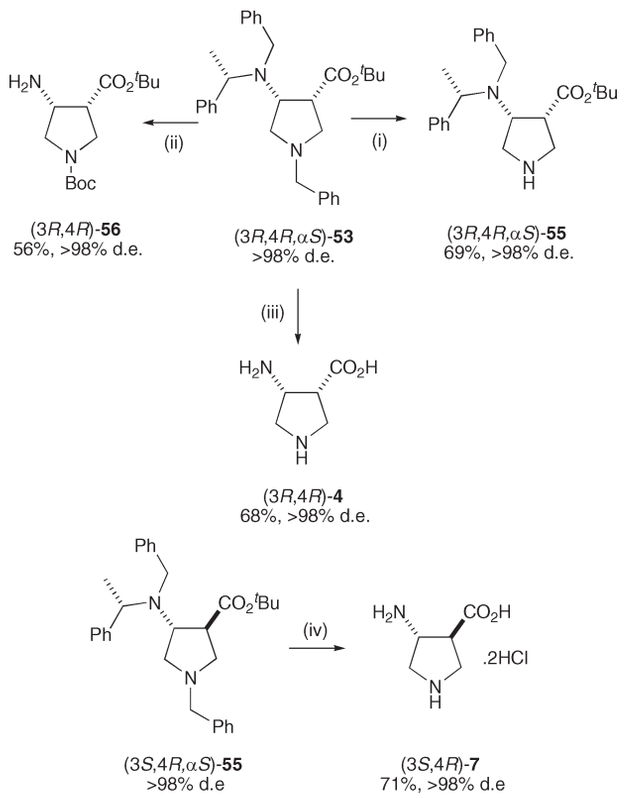
following the method of Sakurai and Achiwa,[23] through treatment of commercially available *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine **51** with a catalytic amount of acetic acid and *in situ* reaction with *tert*-butyl propiolate. Conjugate addition of lithium amide (*S*)-**9** to *N*-benzyl-**52** gave *cis*-(3*R*,4*R*,α*S*)-**53** in >98% d.e., with purification furnishing *cis*-(3*R*,4*R*,α*S*)-**53** in 79% isolated yield as a single stereoisomer (>98% d.e.). Subsequent treatment with KO^{t}Bu in ^{t}BuOH allowed quantitative conversion of **53** to the thermodynamic epimer *trans*-(3*S*,4*R*,α*S*)-**54** (Scheme 11).



Scheme 11 Reagents and conditions: (i). CH_3CO_2H, DCM, 0 °C then *tert*-butyl propiolate, 0 °C to rt, 4 h; (ii). lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C then $NH_4Cl_{(aq)}$, −78 °C to rt; (iii). KO^{t}Bu, ^{t}BuOH, Δ, 3 h.

With an efficient asymmetric route to *N*-protected *cis*- and *trans*-4-aminopyrrolidine carboxylic esters in hand, methodology for the global and differential protection of the pyrrolidine scaffolds was investigated. Treatment of *cis*-(3*R*,4*R*,α*S*)-**53** under standard palladium-mediated hydrogenolysis conditions {$Pd(OH)_2$ on C, H_2 (5 atm), using either MeOH, or MeOH : AcOH : H_2O (40 : 4 : 1) as solvent} cleaved selectively the pyrrolidine *N*-benzyl group, giving (3*R*,4*R*,α*S*)-**55** in 69% yield, while hydrogenolysis in the presence of Boc_2O (1.05 eq) allowed the isolation of *N*-Boc-(3*R*,4*R*)-**56** in 59% yield. Alternatively, global *N*-deprotection could be achieved using the method of Nakayama *et al.*,[24] with palladium-mediated hydrogenolysis of (3*R*,4*R*,α*S*)-**53** in a mixture of EtOH, water and HCl (conc) effecting simultaneous cleavage of all three *N*-benzyl groups. Hydrolysis of the *in situ* made ethyl ester and purification by ion exchange chromatography gave *cis*-(3*R*,4*R*)-**56** in >98% d.e. and 71% yield. Application of this global deprotection protocol to the *trans*-isomer (3*S*,4*R*,α*S*)-**54** gave *trans*-(3*S*,4*R*)-**7** as its hydrochloride salt in >98% d.e. and 68% overall yield (Scheme 12).

In conclusion, the conjugate addition of achiral and homochiral lithium amides to a range of dihydrofuran, *N*-protected dihydropyrrole and dihydrothiophene α,β-unsaturated esters has



Scheme 12 Reagents and conditions: (i). $Pd(OH)_2$ on C, MeOH, H_2 (5 atm) or $Pd(OH)_2$ on C, MeOH : AcOH : H_2O (40 : 4 : 1), H_2 (5 atm); (ii). $Pd(OH)_2$ on C, Boc_2O (1.05 eq), MeOH, H_2 (5 atm); (iii). $Pd(OH)_2$ on C, EtOH, H_2O, HCl (conc), H_2 (5 atm) then 1 M $HCl_{(aq)}$, Δ, 4 h then Dowex 50WX8-200; (iv). $Pd(OH)_2$ on C, EtOH, H_2O, HCl (conc), H_2 (5 atm) then 1 M $HCl_{(aq)}$, Δ, 4 h.

been investigated. The diastereoselective conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide has been successfully applied to the first asymmetric syntheses of *cis*-(3*S*,4*R*)- and *trans*-(3*R*,4*R*)-4-aminotetrahydrofuran-3-carboxylic acids in 26% and 25% overall yield, and to a new and straightforward synthesis of *cis*- and *trans*-4-aminopyrrolidine carboxylic acids. The four step synthesis of *cis*-(3*R*,4*R*)-4-aminopyrrolidine-3-carboxylic acid **4** in 50% overall yield compares favourably with the only previously reported asymmetric synthesis by Aggarwal *et al.*,[8] (nine steps, 15% overall yield). Similarly, the five step approach to *trans*-(3*R*,4*S*)-4-aminopyrrolidine-3-carboxylic acid hydrochloride **7** in 52% overall yield is more efficient than the ten step route (12% overall yield) towards (3*S*,4*R*)-**7** detailed by Naito *et al.*[9] As both enantiomers of lithium *N*-benzyl-*N*-α-methylbenzylamide are readily available in homochiral form, this methodology should be equally applicable to the asymmetric synthesis of any stereoisomer of these heterocyclic β-amino acids. The further application of the conjugate addition of homochiral lithium amides towards a variety of heterocyclic natural products is currently underway in our laboratory.

Experimental

General experimental

All reactions were carried out under nitrogen or argon using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen. THF was distilled from sodium/benzophenone ketyl; *n*-butyllithium was used as a solution in hexanes and was titrated against diphenylacetic acid prior to use. All other reagents were used as supplied without further purification. Flash column chromatography was performed on silica gel (Kieselgel 60). T.l.c was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F_{254}. Plates were visualised either by UV light (254 nm), iodine, ammonium molybdate (7% solution in ethanol) or potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate). Infra red spectra were recorded as thin films or KBr discs using a Perkin-Elmer PARAGON 1000 FT-IR spectrometer, with selected peaks reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 200 (^1H 200 MHz, ^{13}C 50 MHz), Bruker DPX-200 (^1H 200 MHz, ^{13}C 50 MHz), Bruker DPX-400 (^1H 400 MHz, ^{13}C 100 MHz), or Bruker AM-500 (^1H 500 MHz, ^{13}C 125 MHz) spectrometers. Chemical shifts (δ_H) are reported in parts per million (p.p.m.) and are referenced to the residual solvent peak, with coupling constants (*J*) measured in Hertz. Low resolution mass spectra (*m*/*z*) were recorded on either a VG Masslab 20-250 instrument (CI, NH_3) or Platform instrument (APCI). MALDI spectra were recorded on a Micromass MALDI TOF SPEC 2E spectrometer. Major peaks are listed with intensities quoted as percentages of the base peak. Accurate mass measurements were recorded on a VG Autospec and a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer operating at a resolution of 5000 full width half height. Positive ion spectra were calibrated relative to PEG with tetraoctylammonium bromide as the internal lock mass. Negative ion spectra were calibrated relative to poly-DL-alanine with leucine enkephalin as the internal lock mass. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, using a path length of 10 cm, in spectroscopic grade solvents (Aldrich), with concentrations (*c*) given in g per 100 cm^3, solvent and temperature as recorded. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected.

General procedure 1: PPh_3/DIAD mediated elimination to furnish α,β-unsaturated acceptors

A solution of the β-hydroxy ester and PPh_3 (1.5 eq) in anhydrous THF was cooled to 0 °C prior to the dropwise addition of DIAD (1.3 eq). The reaction mixture was warmed to rt, whereat it was stirred overnight. The solvent was removed *in vacuo* and *n*-pentane (50 ml) added. After stirring at rt for 0.5 h, the precipitate was removed by filtration and the filtrate concentrated *in vacuo*. Additional *n*-pentane was added and the process repeated a further two times. Concentration *in vacuo* of the resultant filtrate furnished a yellow oil, which was passed through a silica gel plug (eluting 2% Et_2O/*n*-pentane) to give the requisite α,β-unsaturated acceptor.

General procedure 2: lithium amide conjugate additions

A solution of the amine in anhydrous THF under an inert atmosphere was cooled to −78 °C, prior to the slow addition of *n*-butyllithium (titrated before use, 1 eq). The resultant pink solution was stirred for 1 h at this temperature before the requisite α,β-unsaturated acceptor as a solution in anhydrous THF was added dropwise *via* syringe. The resulting mixture was stirred for 3 h at −78 °C after which time the reaction was quenched by addition of either (a) a precooled solution of 2,6-di-*tert*-butylphenol in anhydrous THF; or (b) NH_4Cl (aq, sat) solution. The resultant mixture was kept at −78 °C for 0.5 h and then allowed to warm to rt over 1 h. NH_4Cl (aq, sat) solution was added and the mixture diluted with Et_2O. The organic layer was separated and the aqueous layer extracted with Et_2O (3×). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products. The individual products were purified as described.

General procedure 3: epimerisation of lithium amide adducts

To a solution of the substrate in *tert*-butanol was added a catalytic quantity of potassium *tert*-butoxide (≈20 mg). The resultant mixture was heated at reflux for 3 h then allowed to cool. The reaction was quenched by addition of NH_4Cl (aq, sat) and the mixture diluted with Et_2O. The organic layer was separated and the aqueous layer extracted with Et_2O (3×). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. The individual products were purified as described.

***General procedure 4*: hydrogenolysis of lithium amide adducts using Pearlman's catalyst**

A solution of the substrate in MeOH was placed in a Fischer–Porter bottle. The vessel was pump-filled five times with nitrogen prior to charging with $Pd(OH)_2$ (20% wt on carbon, 20% by mass of substrate used). The reaction mixture was stirred rapidly at rt overnight, after which time the solution was filtered through a pad of Celite®, washed through with MeOH and concentrated *in vacuo* to give the crude product. The individual products were purified as described.

***General procedure 5*: TFA cleavage furnishing free amino acids**

TFA was added to a solution of the crude β-amino ester at rt and stirred for 16 h. Concentration *in vacuo* gave an oil, which was dissolved in MeOH (2 ml) and HCl in Et_2O (sat, 2 ml). Concentration *in vacuo* gave a pale brown solid, which was partitioned between Et_2O (4 ml) and H_2O (4 ml). The aqueous phase was separated and concentrated to a quarter of its volume and chromatographed using Dowex® 50WX8-200 resin to give the free amino acid.

Preparation of *tert*-butyl 4-oxotetrahydrofuran-3-carboxylate 16

In a modification of the literature procedure,[25] sodium hydride (60% suspension in mineral oil, 8.0 g, 0.20 mol) was first prepared for use by careful washing with *n*-pentane (3 × 50 ml) and discarding the supernatant. The liberated sodium hydride was suspended in Et_2O (150 ml) and ethyl glycolate (18.02 g, 0.20 mol) added neat, dropwise. The reaction mixture was stirred for an additional 0.5 h after the evolution of H_2 gas had ceased. The Et_2O was removed *in vacuo* to give the sodium derivative as a white powder. *tert*-Butyl acrylate (35.2 ml, 0.24 mol) in anhydrous DMSO (150 ml) was added to this derivative in one lot, while the reaction flask was kept immersed in an ice bath. After 15 min, the cooling bath was removed and the reaction mixture stirred for an additional 0.5 h at rt, filtered, poured into ice-cold H_2SO_4 (5% aq, 100 ml) and extracted with Et_2O (3 × 150 ml). The combined organic layers were washed with brine (aq, sat, 200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product as an oil. Purification by flash chromatography on silica gel (10→15% EtOAc/*n*-pentane) gave **16** (25.3 g, 68%) as a white crystalline solid; m.p. 38–40 °C; elemental analysis, found C, 58.4; H, 7.4%; $C_9H_{14}O_4$ requires C, 58.1; H, 7.6%; ν_{max} ($CHCl_3$) 3028s, 2983s, 2936m, 2883m, 1774s, 1724s, 1370s, 1330s, 1157s; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, $OC(CH_3)_3$), 3.39 (1H, t, *J* 8.3, C(3)*H*), 3.92 and 3.99 (2 × 1H, AB system, J_{AB} 16.9, C(5)H_2), 4.38 and 4.46 (2 × 1H, AB system, J_{AB} 8.0, C(2)H_2); δ_C (100 MHz, $CDCl_3$) 27.9 ($OC(CH_3)_3$), 54.2 (*C*(3)), 69.6 (*C*(2)), 70.6 (*C*(5)), 82.8 ($OC(CH_3)_3$), 165.7 ($CO_2{}^t$Bu), 207.9 (*C*(4)O); *m*/*z* (GCMS, CI$^+$) 204 (MH^+, 100), 187 (MH^+, 10), 148 ($MNH_4^+ - C_4H_8$, 65%); HRMS, found 187.0968; $C_9H_{15}O_4$ (MH^+) requires 187.0970.

Preparation of *tert*-butyl 4-hydroxytetrahydrofuran-3-carboxylate 17

To a solution of β-keto ester **16** (20.0 g, 0.107 mol) in ^{i}PrOH (300 ml) at 0 °C was added portionwise $NaBH_4$ (1.62 g, 42.8 mmol). After 2 h, $NaBH_4$ (1.62 g, 42.8 mmol) was again added portionwise and the temperature allowed to rise to rt. $NaBH_4$ (0.81 g, 21.4 mmol) was added again and stirring continued for 0.5 h. The reaction mixture was diluted with Et_2O (200 ml) and poured into brine (aq, sat, 200 ml). The aqueous layer was separated and extracted with Et_2O (2 × 200 ml). The combined organic extracts were washed with $NaHCO_3$ (aq, sat, 2 × 100 ml) and brine (aq, sat, 100 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish crude **17** (17.8 g, 89%) as a colourless oil. This material was used without purification, although for the purposes of analysis a small quantity was subjected to flash chromatography on silica gel (5→20→50% Et_2O/*n*-pentane) to give **17**, a colourless oil, as a 1 : 1 mixture of diastereoisomers; ν_{max} (film) 3430br s, 2978s, 2936m, 1728s, 1369s, 1158s; δ_H (400 MHz, $CDCl_3$) 1.43 and 1.45 (2 × 9H, 2 × s, 2 × $OC(CH_3)_3$), 2.93 (1H, m, C(3)*H* diastereoisomer A), 3.06 (1H, br s, O*H*) overlays 3.04 (1H, m, C(3)*H* diastereoisomer B), 3.44 (1H, br s, O*H*), 3.72 (1H, dd, *J* 9.6, 2.5, C(5)H_A B), 3.81–3.89 (4H, m, C(2)H_A A, C(5)H_2 A and C(5)H_B B), 4.02 (2H, m, C(2)H_2 B), 4.15 (1H, app t, *J* 7.0, C(2)H_B A), 4.54–4.58 (2H, m, C(4)*H* A and C(4)*H* B); δ_C (100 MHz, $CDCl_3$) 28.0 (2 × $OC(CH_3)_3$), 50.3 (*C*(3) diastereoisomer B), 54.5 (*C*(3) diastereoisomer A), 67.7 (*C*(2) B), 69.4 (*C*(2) A), 72.1 (*C*(4) A), 74.7 (*C*(4) B), 74.9 (*C*(5) B), 75.3 (*C*(5) A), 81.5 and 82.2 (2 × $OC(CH_3)_3$), 170.5 and 171.5 (2 × $CO_2{}^t$Bu); *m*/*z* (GCMS, CI$^+$) 206 (MNH_4^+, 100), 189 (MH^+, 40), 150 ($MNH_4^+ - C_4H_8$, 90), 133 ($MH^+ - C_4H_8$, 15%); HRMS, found 189.1129; $C_9H_{17}O_4$ (MH^+) requires 189.1127.

Preparation of *tert*-butyl 2,5-dihydrofuran-3-carboxylate 18

The β-hydroxy ester **17** (15.0 g, 79.8 mmol) in THF (50 ml) was treated with PPh_3 (31.5 g, 0.12 mol) and DIAD (20.4 ml, 0.104 mol) in accordance with *general procedure 1*, giving **18** (12.4 g, 91%) as a volatile, colourless liquid; ν_{max} (film) 2980s, 2935m, 2876m, 1714s, 1647m, 1370s, 1284s, 1166s; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, $OC(CH_3)_3$), 4.72–4.79 (4H, m, C(2)H_2 and C(5)H_2), 6.71 (1H, t, *J* 1.9, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 ($OC(CH_3)_3$), 74.1 and 76.1 (*C*(2) and *C*(5)), 81.2 ($OC(CH_3)_3$), 134.6 (*C*(2)), 136.7 (*C*(3)), 161.8 ($CO_2{}^t$Bu); *m*/*z* (GCMS, CI$^+$) 188 (MNH_4^+, 100), 171 (MH^+, 55), 132 ($MNH_4^+ - C_4H_8$, 60), 115 ($MH^+ - C_4H_8$, 30%); HRMS, found 171.1020; $C_9H_{15}O_3$ (MH^+) requires 171.1021.

Preparation of *tert*-butyl 4-oxotetrahydrothiophene-3-carboxylate 22 and *tert*-butyl 4-hydroxy-2,5-dihydrothiophene-3-carboxylate 23

A solution of ethyl thioglycolate (3.20 ml, 29.2 mmol) and *tert*-butyl acrylate (4.28 ml, 29.2 mmol) in THF (30 ml) was cooled to 0 °C. KO^{t}Bu (3.81 g, 32.1 mmol) was added portionwise and the mixture allowed to warm to rt whereat it was stirred for 3 d. The crude reaction mixture was poured into ice-cold H_2SO_4 (5% aq, 30 ml) and extracted with Et_2O (3 × 30 ml). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash chromatography on silica gel (5% Et_2O/*n*-pentane) gave **22** and **23** (4.78 g, 81%), a 46 : 54 mixture of tautomers, as a white crystalline solid; m.p. 42–44 °C; ν_{max} ($CHCl_3$) 3030m, 3006m, 2983s, 2935m, 1749s, 1724s, 1663s, 1395s, 1370s, 1334s, 1280s, 1247s, 1149s, 1110s, 842m; δ_H (400 MHz, $CDCl_3$) 1.48 (7.65H, s, $OC(CH_3)_3$ keto), 1.50 (9H, s, $OC(CH_3)_3$ enol), 3.18 (0.85H, dd, *J* 11.3, 7.5, C(2)H_A keto), 3.32 (1.7H, d, *J* 12.5, C(5)H_2 keto), 3.35 (0.85H, dd, *J* 11.3, 9.0, C(2)H_B keto), 3.39 (0.85H, dd, *J* 9.0, 7.5, C(3)*H* keto), 3.72 (2H, t, *J* 3.3, C(2)H_2 enol), 3.79 (2H, t, *J* 3.3, C(5)H_2 enol), 11.15 (1H, br s, O*H* enol); δ_C (100 MHz, $CDCl_3$) 27.9 and 28.2 (2 × $OC(CH_3)_3$), 29.1 (*C*(2) keto), 31.8 (*C*(2) enol), 36.1 (*C*(5) enol), 37.4 (*C*(5) keto), 56.4 (*C*(3) keto), 82.0 and 82.8 (2 × $OC(CH_3)_3$), 100.5 (*C*(3) enol), 166.9 and 169.0 (2 × $CO_2{}^t$Bu), 171.4 (*C*(4) enol), 206.2 (*C*(4)O keto); *m*/*z* (GCMS, CI$^+$) 220 (MNH_4^+, 35), 203 (MH^+, 30), 164 ($MN_4^+ - C_4H_8$, 40), 102 (100%); HRMS, found 203.0735; $C_9H_{15}O_3S$ (MH^+) requires 203.0742.

Preparation of *tert*-butyl 4-hydroxytetrahydrothiophene-3-carboxylate 24

To a solution of the keto–enol mixture **22** and **23** (2.45 g, 12.1 mmol) in ^{i}PrOH (40 ml) at 0 °C was added portionwise $NaBH_4$ (246 mg, 6.50 mmol). After 2 h, $NaBH_4$ (246 mg, 6.50 mmol) was again added portionwise and the temperature allowed to rise to rt. $NaBH_4$ (123 mg, 3.25 mmol) was added again and stirring continued for 0.5 h. The reaction mixture was diluted with Et_2O (50 ml) and poured into brine (aq, sat, 50 ml). The aqueous layer was separated and extracted with

Et_2O (2 × 50 ml). The combined organic extracts were washed with $NaHCO_3$ (aq, sat, 2 × 50 ml) and brine (aq, sat, 50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish the crude product **24** (2.37 g, 96%), a colourless oil, as a 1 : 1 mixture of diastereoisomers. This material was used without purification, although for the purposes of analysis a small quantity was subjected to flash chromatography on silica gel (5→10→20% Et_2O/*n*-pentane) to give the separable diastereoisomers: diastereoisomer A (first to elute) was obtained as a colourless oil; ν_{max} (film) 3432br s, 2978s, 2937m, 1725s, 1155s, 1023m, 847m; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, OC(CH_3)$_3$), 2.92 and 3.06 (2 × 1H, ABX system, J_{AB} 11.7, J_{AX} 3.7, J_{BX} 1.7, C(5)H_2), 2.88–2.91 (1H, m, C(3)*H*), 3.03 (1H, app t, *J* 10.4, C(2)H_A), 3.17 (1H, app t, *J* 10.7, C(2)H_B), 3.24 (1H, d, *J* 0.8, O*H*), 4.68–4.73 (1H, m, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (OC(CH_3)$_3$), 29.7 (*C*(2)), 38.4 (*C*(5)), 53.7 (*C*(3)), 74.8 (*C*(4)), 82.2 (O*C*(CH$_3$)$_3$), 171.5 (*C*O$_2$^{t}Bu); *m*/*z* (GCMS, CI$^+$) 222 (MNH_4^+, 15), 205 (MH^+, 100), 166 (MNH_4^+–C_4H_8, 60), 149 (MH^+–C_4H_8, 10%); HRMS, found 205.0902; $C_9H_{17}O_3S$ (MH^+) requires 205.0898; diastereoisomer B (second to elute) was obtained as a white, waxy solid; m.p. 38–40 °C; ν_{max} ($CHCl_3$) 3507br m, 3008m, 2983m, 2941m, 1708s, 1152s, 1030m; δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, OC(CH_3)$_3$), 2.81 (1H, m, C(5)H_A), 2.92–2.97 (2H, m, C(3)*H* and O*H*), 3.03–3.07 (3H, m, C(2)H_2 and C(5)H_B), 4.56 (1H, m, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (OC(*C*H$_3$)$_3$), 29.4 (*C*(2)), 36.6 (*C*(5)), 54.5 (*C*(3)), 76.2 (*C*(4)), 81.9 (O*C*(CH$_3$)$_3$), 171.4 (*C*O$_2$^{t}Bu); *m*/*z* (GCMS, CI$^+$) 222 (MNH_4^+, 65), 205 (MH^+, 100), 166 (MNH_4^+ − C_4H_8, 70), 149 (MH^+ − C_4H_8, 30%); HRMS, found 205.0892; $C_9H_{17}O_3S$ (MH^+) requires 205.0898.

Preparation of *tert*-butyl 2,5-dihydrothiophene-3-carboxylate 25

The β-hydroxy ester **24** (1.77 g, 8.65 mmol) in THF (50 ml) was treated with PPh_3 (3.40 g, 13.0 mmol) and DIAD (2.22 ml, 11.25 mmol) in accordance with *general procedure 1*, giving **25** (1.51 g, 94%) as a volatile, colourless liquid; ν_{max} (film) 2977s, 2929m, 1708s, 1646m, 1368m, 1343m, 1273s, 1166s, 1079m, 857m; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, OC(CH_3)$_3$), 3.88–3.96 (4H, m, C(2)H_2 and C(4)H_2), 6.78 (1H, m, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (OC(*C*H$_3$)$_3$), 37.2 and 38.8 (*C*(2) and *C*(5)), 81.2 (O*C*(CH$_3$)$_3$), 137.1 (*C*(3)), 139.5 (*C*(4)), 163.2 (*C*O$_2$^{t}Bu); *m*/*z* (GCMS, CI$^+$) 204 (MNH_4^+, 15), 187 (MH_4^+, 100%); HRMS, found 187.0791; $C_9H_{15}O_2S$ (MH^+) requires 187.0793.

Preparation of *tert*-butyl *N*-*tert*-butyloxycarbonyl-4-oxopyrrolidine-3-carboxylate potassium salt 19

tert-Butyl *N*-*tert*-butyloxycarbonyl-4-oxopyrrolidine-3-carboxylate potassium salt **19** was prepared according to the literature procedure.[4] Thus, a solution of Boc-glycine methyl ester (22.8 g, 0.112 mol) and *tert*-butyl acrylate (16.4 ml, 0.112 mol) in THF (200 ml) was cooled to 0 °C, and KO^{t}Bu (14.6 g, 0.123 mol) added portionwise. The mixture was warmed to rt, whereat it was stirred for 24 h. Hexane was added to the thick mixture and the solid collected by filtration and washed with Et_2O (2 × 50 ml). The potassium salt **19** (27.9 g, 77%) was obtained as a pale yellow powder; m.p. 118–120 °C (decomposes); *m*/*z* (GCMS, CI$^+$) 303 (MNH_4^+, 100), 286 (MH^+, 45), 247 (MNH_4^+ − C_4H_8, 60), 228 (MH^+ − C_4H_8, 25%).

Preparation of *tert*-butyl *N*-*tert*-butyloxycarbonyl-4-hydroxypyrrolidine-3-carboxylate 20

The potassium salt **19** (15.5 g, 50 mmol), $NaBH_3CN$ (3.46 g, 55 mmol) and bromocresol green (pH 3.8 yellow, pH 5.4 blue) were dissolved in MeOH (200 ml). HCl (1 M, aq) was added dropwise while stirring to maintain pH 3–4. After 15–20 min, the pH change slowed. The mixture was stirred for an additional 1 h, during which time HCl (1 M, aq) was added occasionally to maintain pH 3–4. Water (20 ml) was added and the mixture extracted with Et_2O (3 × 100 ml). The combined organic layers were washed with $NaHCO_3$ (aq, sat, 100 ml), brine (aq, sat, 100 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to furnish the crude product as a waxy solid (13.6 g, 95%). This material was used without purification, although for the purposes of analysis a small quantity was subjected to flash chromatography on silica gel (5→20% EtOAc/*n*-pentane) to give **20**, a 60 : 40 mixture of diastereoisomers, as a white waxy solid; m.p. 120–122 °C; ν_{max} ($CHCl_3$) 3446br s, 3008s, 2982s, 2935m, 1690br s, 1417s, 1369s, 1246m, 1155s; δ_H (400 MHz, $CDCl_3$, rotameric at 298 K) 1.48 and 1.50 (30H, 2 × s, 4 × OC(CH_3)$_3$ minor diastereoisomer + major diastereoisomer) 3.11 (1H, ddd, *J* 14.3, 8.6, 4.1, C(3)*H* major), 3.27 (0.67H, m, C(3)*H* minor), 3.33 (0.67H, m, C(5)H_A minor), 3.42 (1H, m, C(5)H_A major), 3.46 (1H, dd, *J* 12.4, 3.8, C(5)H_B major), 3.53 (1H, dd, *J* 10.6, 8.7, C(2)H_A major) overlays 3.51–3.54 (1.33H, m, C(2)H_2 minor), 3.65 (1H, app t, *J* 10.5, C(2)H_B major) overlays 3.63 (0.67H, m, C(5)H_B minor), 4.49 (0.67H, m, C(4)*H* minor) overlays 4.51 (1H, m, C(4)*H* major); δ_C (100 MHz, $CDCl_3$, rotameric at 298 K) 28.7/28.8 and 29.0/29.2 (4 × OC(*C*H$_3$)$_3$ minor diastereoisomer + major diastereoisomer), 46.4 and 46.7 (*C*(2) major and *C*(2) minor), 51.0 and 51.7 (*C*(3) major and *C*(3) minor), 55.8 and 56.1 (*C*(5) major and *C*(5) minor), 72.2 and 72.9 (*C*(4) major and *C*(4) minor), 81.4/81.5 and 82.7/82.9 (4 × O*C*(CH$_3$)$_3$), 156.8 and 156.9 (2 × N*C*O$_2$^{t}Bu), 171.4 and 173.0 (2 × C(3)*C*O$_2$^{t}Bu); *m*/*z* (GCMS, CI$^+$) 288 (MH^+, 5), 232 (MH^+ − C_4H_8, 10), 188 (100%); HRMS, found 288.1806; $C_{14}H_{26}NO_5$ (MH^+) requires 288.1811.

Preparation of *tert*-butyl *N*-*tert*-butyloxycarbonyl-2,5-dihydropyrrole-3-carboxylate 21

The β-hydroxy ester **20** (12.5 g, 43.5 mmol) in THF (300 ml) was treated with PPh_3 (17.1 g, 65.3 mmol) and DIAD (11.1 ml, 56.6 mmol) in accordance with *general procedure 1*, giving **21** (10.9 g, 93%) as a white solid; m.p. 54–56 °C; ν_{max} ($CHCl_3$) 3026m, 3009s, 2982s, 2933m, 1701s, 1693s, 1412s, 1394s, 1300s, 1163s, 1095s; δ_H (400 MHz, $CDCl_3$, rotameric at 298 K) 1.47/1.48 and 1.49/1.51 (18H, 4 × s, OC(CH_3)$_3$), 4.23 and 4.28 (2 × 2H, 2 × m, C(2)H_2 and C(5)H_2), 6.60 and 6.63 (2 × 1H, 2 × t, *J* 1.9, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 and 28.4 (2 × OC(*C*H$_3$)$_3$), 51.8/52.0 and 53.5/53.7 (*C*(2) and *C*(5)), 79.7/53.7 and 81.2/81.3 (2 × O*C*(CH$_3$)$_3$), 133.7/133.8 (*C*(3)), 135.4/135.5 (*C*(4)), 153.9/154.1 (N*C*O$_2$^{t}Bu), 162.1/162.2 (C(3)*C*O$_2$^{t}Bu); *m*/*z* (GCMS, CI$^+$) 270 (MH^+, 15), 214 (MH^+ − C_4H_8, 10), 170 (100%); HRMS, found 270.1713; $C_{14}H_{24}NO_4$ (MH^+) requires 270.1705.

Preparation of *tert*-butyl (3*SR*,4*RS*)-4-(*N*,*N*-dibenzylamino)-tetrahydrofuran-3-carboxylate 26, *tert*-butyl (3*RS*,4*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydrofuran-3-carboxylate 27, di-*tert*-butyl (3*SR*, 4*RS*,3′*SR*,4′*SR*)-4-(*N*,*N*-dibenzylamino)tetrahydro-[3,3′]-bifuranyl-3,4′-dicarboxylate 28 and di-*tert*-butyl (3*SR*,4*RS*,3′*SR*,4′*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydro-[3,3′]-bifuranyl-3,4′-dicarboxylate 29

Following *general procedure 2*, *n*-BuLi (1.6 M, 2.94 ml, 4.70 mmol), dibenzylamine (927 mg, 4.70 mmol) in THF (25 ml) and **18** (500 mg, 2.94 mmol) in THF (5 ml) gave, after quenching with NH_4Cl (aq, sat, 10 ml) the adducts **26** : **27** : **28** : **29** in a 17 : 26 : 52 : 5 ratio. Purification by flash chromatography on silica gel (2→4→6→8→10→20→40% EtOAc : *n*-pentane) gave the products: (3*RS*,4*RS*)-**27** (177 mg, 18%) as a white crystalline solid; m.p. 82–84 °C; elemental analysis, found C, 75.5; H, 8.1; N, 3.8%; $C_{23}H_{29}NO_3$ requires C, 75.2; H, 8.0; N, 3.8%; ν_{max} (KBr) 2977m, 2932w, 2867w, 1723s, 1454m, 1368s, 1159s; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, OC(CH_3)$_3$), 3.19 (1H, app td, *J* 8.0, 4.0, C(3)*H*), 3.56 and 3.75 (2 × 2H, AB system, J_{AB} 14.0, N(CH_2Ph)$_2$), 3.78–3.84 (3H, m, C(2)H_A, C(4)*H* and C(5)H_A), 3.93 (1H, m, C(5)H_B), 4.18 (1H, app t, *J* 8.7, C(2)H_B), 7.22–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.0 (OC(*C*H$_3$)$_3$), 46.6 (*C*(3)), 54.7 (N(*C*H$_2$Ph)$_2$), 65.2 (*C*(4)), 71.0 (*C*(2) and *C*(5)), 81.0 (O*C*(CH$_3$)$_3$), 127.0 (*p*-Ph),

128.2 and 128.6 (*o*-, *m*-Ph), 139.3 (*ipso*-Ph), 173.0 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 368 (MH^+, 40), 312 ($MH^+ - C_4H_8$, 80), 311 ($M^+ - C_4H_8$, 100%); HRMS, found 368.2221; $C_{23}H_{30}NO_3$ (MH^+) requires 368.2226; (3*SR*,4*RS*)-**26** (113 mg, 10%) as a white crystalline solid; m.p. 82–84 °C; ν_{max} (KBr) 3011m, 2981m, 2888w, 1723s, 1369s, 1155s; δ_H (400 MHz, $CDCl_3$) 1.58 (9H, s, $OC(CH_3)_3$), 3.28 (1H, m, C(3)*H*), 3.64 and 3.80 (2 × 2H, AB system, J_{AB} 14.1, $N(CH_2Ph)_2$) overlays 3.64–3.70 (2H, m, C(4)*H* and C(5)H_A), 4.00 (1H, app t, *J* 8.9, C(2)H_A), 4.09 (1H, m, C(5)H_B), 4.27 (1H, dd, *J* 8.9, 6.1, C(2)H_B), 7.22–7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.3 ($OC(CH_3)_3$), 49.3 (*C*(3)), 55.7 ($N(CH_2Ph)_2$), 63.8 (*C*(4)), 68.8 (*C*(5)), 69.8 (*C*(2)), 81.1 ($OC(CH_3)_3$), 126.9 (*p*-Ph), 128.1 and 128.9 (*o*-, *m*-Ph), 138.9 (*ipso*-Ph), 170.8 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 368 (MH^+, 15), 367 (M^+, 15), 312 ($MH^+ - C_4H_8$, 85), 311 ($MH^+ - C_4H_8$, 100%); HRMS, found 368.2225; $C_{23}H_{30}NO_3$ (MH^+) requires 368.2226; **29** (363 mg, 46%) as a white crystalline solid; m.p. 86–88 °C; ν_{max} (KBr) 3029m, 3011s, 2981s, 2934m, 1721s, 1369s, 1251s, 1153s, 1076m; δ_H (400 MHz, $CDCl_3$) 1.40 and 1.54 (2 × 9H, 2 × s, 2 × $OC(CH_3)_3$), 2.94 (1H, m, C(3′)*H*), 3.11 (1H, m, C(4′)*H*), 3.59 (1H, m, C(4)*H*) overlays 3.62 and 3.89 (2 × 2H, AB system, J_{AB} 14.5, $N(CH_2Ph)_2$), 3.74–3.78 (2H, m, C(2′)H_A and C(5′)H_A), 3.85–3.92 (3H, m, C(2)H_A, C(5)H_A and C(5′)H_B), 3.96–4.03 (2H, m, C(2′)H_B and C(5)H_B), 4.38 (1H, d, C(2)H_B), 7.19–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.0 and 28.2 (2 × $OC(CH_3)_3$), 47.4 (*C*(3′)), 49.3 (*C*(4′)), 54.9 ($N(CH_2Ph)_2$), 60.8 (*C*(3)), 67.5 (*C*(4)), 68.5 (*C*(5)), 71.6 and 71.9 (*C*(2′) and *C*(5′)), 73.2 (*C*(2)), 81.2 and 82.1 (2 × $OC(CH_3)_3$), 127.0 (*p*-Ph), 128.2 and 128.7 (*o*-, *m*-Ph), 139.0 (*ipso*-Ph), 170.9 and 172.7 (2 × $CO_2{}^tBu$); *m*/*z* (APCI$^+$) 538 (MH^+, 100), 537 (M^+, 100), 482 ($MH^+ - C_4H_8$, 40), 481 ($M^+ - C_4H_8$, 70%); HRMS, found 538.3161; $C_{32}H_{44}NO_6$ (MH^+) requires 538.3169; **28** (31 mg, 4%) as a white crystalline solid; m.p. 80–82 °C; elemental analysis, found C, 71.7; H, 8.0; N, 8.1%; $C_{32}H_{43}NO_6$ requires C, 71.5; H, 8.1; N, 2.6%; ν_{max} (KBr) 3010m, 2980s, 2936m, 1718s, 1369s, 1254m, 1152s; δ_H (400 MHz, $CDCl_3$) 1.45 and 1.47 (2 × 9H, 2 × s, 2 × $OC(CH_3)_3$), 2.14 (1H, m, C(3′)*H*), 2.88 (1H, dt, *J* 11.1, 7.3, C(4′)*H*), 3.56 and 3.92 (2 × 2H, AB system, J_{AB} 14.0, $N(CH_2Ph)_2$), 3.72 (1H, dd, *J* 8.6, 6.0, C(2′)H_A), 3.80 (1H, dd, *J* 11.3, 7.6, C(5′)H_A), 3.84–3.96 (4H, m, C(2)H_A, C(2′)H_B, C(4)*H* and C(5′)H_B), 3.99–4.07 (2H, m, C(5)H_2), 4.22 (1H, d, *J* 9.9, C(2)H_B), 7.23–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 and 28.1 (2 × $OC(CH_3)_3$), 45.3 (*C*(3′)), 48.5 (*C*(4′)), 55.5 ($N(CH_2Ph)_2$), 56.7 (*C*(3)), 66.0 (*C*(5)), 68.2 (*C*(4)), 68.6 (*C*(5′)), 71.2 (*C*(2)), 71.4 (*C*(2′)), 81.4 and 82.4 (2 × $OC(CH_3)_3$), 127.1 (*p*-Ph), 128.0 and 128.8 (*o*-, *m*-Ph), 139.2 (*ipso*-Ph), 171.4 and 172.3 (2 × $CO_2{}^tBu$); *m*/*z* (APCI$^+$) 538 (MH^+, 90), 537 (M^+, 100), 482 ($MH^+ - C_4H_8$, 10), 481 ($M^+ - C_4H_8$, 10%); HRMS, found 538.3168; $C_{32}H_{44}NO_6$ (MH^+) requires 538.3169.

Selective preparation of *tert*-butyl (3*RS*,4*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydrofuran-3-carboxylate 27 and *tert*-butyl (3*SR*,4*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydrofuran-3-carboxylate 26

Following *general procedure 2*, the lithium amide was prepared by addition of *n*-BuLi (2.5 M, 0.75 ml, 1.88 mmol) to a solution of dibenzylamine (371 mg, 1.88 mmol) in THF (10 ml) at −78 °C. A solution of **18** (200 mg, 1.18 mmol) in THF (5 ml) was added dropwise, *via* syringe pump, over 2 h. After addition was complete the reaction was stirred for a further 0.5 h, then quenched by addition of NH_4Cl (aq, sat, 10 ml). Following warming to rt, the aqueous phase was separated and extracted with Et_2O (3 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give (3*RS*,4*RS*)-**27** and (3*SR*,4*RS*)-**26** as a 42 : 58 mixture of diastereoisomers. Purification by flash chromatography on silica gel (2→4→6→8→10% EtOAc : *n*-pentane) gave the products (3*RS*,4*RS*)-**27** (132 mg, 31%) and (3*SR*,4*RS*)-**26** (171 mg, 40%), with spectroscopic data identical to that reported above.

Selective preparation of di-*tert*-butyl (3*SR*,4*RS*,3′*SR*,4′*SR*)-4-(*N*,*N*-dibenzylamino)tetrahydro-[3,3′]-bifuranyl-3,4′-dicarboxylate 28 and di-*tert*-butyl (3*SR*,4*RS*,3′*SR*,4′*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydro-[3,3′]-bifuranyl-3,4′-dicarboxylate 29

Following *general procedure 2*, the lithium amide was prepared by addition of *n*-BuLi (2.5 M, 0.24 ml, 0.59 mmol) to a solution of dibenzylamine (116 mg, 0.59 mmol) in THF (5 ml) at −78 °C. A solution of **18** (200 mg, 1.18 mmol) in THF (5 ml) was added dropwise and the reaction mixture stirred at the reduced temperature for 5 h, then quenched by addition of NH_4Cl (aq, sat, 10 ml). Following warming to rt, the aqueous phase was separated and extracted with Et_2O (3 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **29** and **28** as a 93 : 7 mixture of diastereoisomers. Purification by flash chromatography on silica gel (2→10→20→40% EtOAc : *n*-pentane) gave the products **29** (203 mg, 71%) and **28** (21 mg, 7%), with spectroscopic data identical to that reported above.

Preparation of (3*RS*,4*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydrofuran-3-carboxylate 7 *via* epimerisation

Following *general procedure 3*, a solution of (3*SR*,4*RS*)-**26** (50 mg, 0.14 mmol) in ^{t}BuOH (5 ml) was treated with KO^{t}Bu and heated at reflux for 3 h. Purification by flash chromatography on silica gel (10% EtOAc : *n*-pentane) gave (3*RS*,4*RS*)-**27** (50 mg, quantitative) in >98% d.e., with spectroscopic data identical to that reported above.

Preparation of di-*tert*-butyl (3*SR*,4*RS*,3′*SR*,4′*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydro-[3,3′]-bifuranyl-3,4′-dicarboxylate 29 *via* epimerisation

Following *general procedure 3*, a solution of **28** (50 mg, 0.09 mmol) in ^{t}BuOH (5 ml) was treated with KO^{t}Bu and heated at reflux for 3 h. Purification by flash chromatography on silica gel (30% EtOAc : *n*-pentane) gave **29** (49 mg, quantitative) in >98% d.e., with spectroscopic data identical to that reported above.

Preparation of *tert*-butyl (3*RS*,4*RS*)-4-(*N*,*N*-dibenzylamino)-tetrahydrothiophene-3-carboxylate 30 and *tert*-butyl (3*SR*,4*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydrothiophene-3-carboxylate 31

Following *general procedure 2*, *n*-BuLi (1.5 M, 0.57 ml, 0.86 mmol), dibenzylamine (170 mg, 0.86 mmol) in THF (5 ml) and **25** (100 mg, 0.54 mmol) in THF (2 ml) gave, after quenching with NH_4Cl (aq, sat, 10 ml), the adducts (3*RS*,4*RS*)-**30** and (3*SR*,4*RS*)-**31** in a 54 : 46 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (3*RS*,4*RS*)-**30** and (3*SR*,4*RS*)-**31** (99 mg, 49%), an inseparable mixture of diastereoisomers, as a colourless oil. The mixture of (3*RS*,4*RS*)-**30** and (3*SR*,4*RS*)-**31** (99 mg, 0.26 mmol) was redissolved in *tert*-butanol and epimerised under thermodynamic conditions in accordance with *general procedure 3*. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (3*SR*,4*RS*)-**31** (98 mg, quantitative) in >98% d.e. as a colourless oil; ν_{max} (film) 2978s, 2931s, 2856m, 1711s, 1394m, 1368s, 1278s, 1257s, 1163s, 1106s, 839m; δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, $OC(CH_3)_3$), 2.88 (2H, m, C(2)H_2), 2.91–2.93 (2H, m, C(5)H_2), 3.13 (1H, m, C(3)*H*), 3.49 and 3.57 (2 × 2H, AB system, J_{AB} 13.6, $N(CH_2Ph)_2$), 3.84 (1H, m, C(4)*H*), 7.23–7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.0 ($OC(CH_3)_3$), 30.8 (*C*(2)), 32.1 (*C*(5)), 51.9 (*C*(3)), 54.1 ($N(CH_2Ph)_2$), 55.7 (*C*(4)), 80.8 ($OC(CH_3)_3$), 127.0, 128.1, 128.4 (*o*-, *m*-, *p*-Ph), 138.7 (*ipso*-Ph), 171.1 ($CO_2{}^tBu$); *m*/*z* (APCI$^+$) 384 (MH^+, 20), 328 ($MH^+ - C_4H_8$, 100%); HRMS, found 384.1995; $C_{23}H_{29}NO_2S$ (MH^+) requires 384.1997. Also isolated was the deconjugated adduct *tert*-butyl 2,3-dihydrothiophene-3-carboxylate **32** as a colourless oil (25 mg, 25%); ν_{max} (film) 2952s, 2857m, 2844m, 1716s, 1631m, 1436s, 1297s, 1267s, 1197s, 1090s, 741m; δ_H

(400 MHz, $CDCl_3$) 1.47 (9H, s, OC(CH_3)$_3$), 3.36 (1H, dd, *J* 11.5, 10.1, C(2)H_A), 3.59 (1H, dd, *J* 11.5, 8.4, C(2)H_B), 3.86 (1H, m, C(3)*H*), 5.61 (1H, dd, *J* 5.9, 2.8, C(4)*H*), 6.25 (1H, dd, *J* 5.9, 2.5, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 28.0 (OC(CH_3)$_3$), 33.1 (*C*(2)), 53.9 (*C*(3)), 81.4 (O*C*(CH_3)$_3$), 120.7 (*C*(4)), 128.7 (*C*(5)), 171.2 (*C*O_2*t*Bu); *m*/*z* (GCMS, CI$^+$) 204 (MNH_4^+, 15), 187 (MH^+, 100%); HRMS, found 187.0789; $C_9H_{15}O_2S$ (MH^+) requires 187.0793.

Preparation of *tert*-butyl *N*-*tert*-butyloxycarbonyl-(3*RS*,4*RS*)-4-(*N*,*N*-dibenzylamino)tetrahydropyrrole-3-carboxylate 33

Following *general procedure 2*, *n*-BuLi (1.6 M, 0.74 ml, 1.19 mmol), dibenzylamine (234 mg, 1.19 mmol) in THF (8 ml) and **21** (200 mg, 0.74 mmol) in THF (2 ml) gave, after quenching with NH_4Cl (aq, sat, 10 ml), (3*RS*,4*RS*)-**33** in >98% d.e. Purification by flash chromatography on silica gel (5→10→20% EtOAc/*n*-pentane) gave (3*RS*,4*RS*)-**33** (141 mg, 41%) as a pale yellow crystalline solid; m.p. 61–63 °C; ν_{max} ($CHCl_3$) 3009m, 2980m, 2933m, 1722s, 1687s, 1411s, 1368s, 1145s, 778s, 741s; δ_H (400 MHz, $CDCl_3$, rotameric at 298 K) 1.44/1.47 and 1.53/1.56 (18H, 4 × s, 2 × OC(CH_3)$_3$), 3.24 (1H, m, C(3)*H*), 3.37 (1H, dd, *J* 10.1, 6.7, C(5)H_A), 3.41–3.52 (1.5H, m, C(2)H_A and C(4)*H*), 3.58 and 3.75 (2 × 1H, AB system, J_{AB} 13.6, N(CH_2Ph)$_2$) overlays 3.58 (0.5H, m, C(4)*H*), 3.65 and 3.74 (2 × 1H, AB system, J_{AB} 13.9, N(CH_2Ph)$_2$) overlays 3.72–3.79 (2H, m, C(2)H_B and C(5)H_B), 7.22–7.34 (10H, m, *Ph*); δ_H (400 MHz, d_8-toluene, 363 K) 1.45 and 1.46 (2 × 9H, 2 × s, 2 × OC(CH_3)$_3$), 2.90 (1H, m, C(3)*H*), 3.28 (1H, dd, *J* 11.0, 7.5, C(2)H_A), 3.32 (2H, br, C(5)H_2), 3.64 (4H, br, N(CH_2Ph)$_2$), 3.81–3.86 (2H, br, C(2)H_B and C(4)*H*), 7.01–7.27 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$, rotameric at 298 K) 28.2/28.3 and 28.4/28.5 (2 × O*C*(CH_3)$_3$), 46.5 and 47.1 (*C*(5)), 47.5 (*C*(3)), 47.9 and 48.2 (*C*(2)), 55.0 and 55.4 (N(*C*H_2Ph)$_2$), 61.1 and 62.9 (*C*(4)), 79.3/79.5 and 81.0/81.1 (2 × O*C*(CH_3)$_3$), 127.0, 127.1, 127.9, 128.1, 128.8 and 129.0 (*o*-, *m*-, *p*-Ph), 138.5/138.6 (*ipso*-Ph), 154.2/154.4 (N*C*O_2*t*Bu), 170.7/171.2 (C(3)*C*O_2*t*Bu); δ_C (100 MHz, d_8-toluene, 363 K) 28.3 and 28.6 (2 × OC(*C*H_3)$_3$), 48.2 (*C*(4), N(*C*H_2Ph)$_2$, *C*(5) and *C*(2)), 56.0 (*C*(3)), 78.7 and 80.5 (2 × O*C*(CH_3)$_3$), 127.1, 127.7, 127.8, 128.0, 128.1, 128.3, 128.5, 128.9, 129.0 and 129.4 (*o*-, *m*-, *p*-Ph), 137.4 and 139.4 (*ipso*-Ph), 154.1 (N*C*O_2*t*Bu), 178.0 (C(3)*C*O_2*t*Bu); *m*/*z* (APCI$^+$) 467 (MH^+, 100), 466 (M^+, 95), 411 ($MH^+ - C_4H_8$, 40), 410 ($M^+ - C_4H_8$, 75%); HRMS, found 467.2908; $C_{28}H_{39}N_2O_4$ (MH^+) requires 467.2910. Also isolated was the deconjugated adduct *tert*-butyl *N*-*tert*-butyloxycarbonyl-2,3-dihydropyrrole-3-carboxylate **34** (44 mg, 22%) as a white solid; m.p. 58–60 °C; ν_{max} (KBr) 3026w, 3009m, 2982s, 2933m, 1726s, 1697s, 1413s, 1369s, 1139s, 888m; δ_H (400 MHz, d_8-toluene, rotameric at 298 K) 1.32/1.33 and 1.39/1.41 (18H, 4 × s, 2 × OC(CH_3)$_3$), 3.33–3.37 (0.5H, m, C(3)*H*), 3.40–3.44 (0.5H, m, C(3)*H*) overlays 3.47 (0.5H, t, *J* 11.3, C(2)H_A), 3.66 (0.5H, t, *J* 11.6, C(2)H_A), 4.21 (0.5H, dd, *J* 9.4, 4.7, C(2)H_B), 4.31 (0.5H, dd, *J* 11.7, 6.6, C(2)H_B), 4.86 (1H, dd, *J* 4.2, 2.6, C(4)*H*), 6.47 (0.5H, m, C(5)*H*), 6.77 (0.5H, m, C(5)*H*); δ_H (500 MHz, d_8-toluene, 363 K) 1.33 and 1.40 (2 × 9H, 2 × s, 2 × OC(CH_3)$_3$), 3.42 (1H, m, C(3)*H*), 3.63 (1H, t, *J* 11.5, C(2)H_A), 4.16 (1H, dd, *J* 11.5, 6.5, C(2)H_B), 4.86 (1H, dd, *J* 4.0, 3.0, C(4)*H*), 6.59 (1H, br, C(5)*H*); δ_C (100 MHz, d_8-toluene, rotameric at 298 K) 28.1/28.3 and 28.4/28.6 (2 × OC(*C*H_3)$_3$), 47.7 (*C*(2)), 48.3/49.5 (*C*(3)), 80.2 and 80.8 (2 × O*C*(CH_3)$_3$), 105.6/105.7 (*C*(4)), 131.8/12.1 (*C*(5)), 151.8/152.8 (N*C*O_2*t*Bu), 171.2/171.3 (C(3)*C*O_2*t*Bu); δ_C (125 MHz, d_8-toluene, 363 K) 28.0 and 28.3 (2 × OC(*C*H_3)$_3$), 47.8 (*C*(2)), 48.7 (*C*(3)), 79.8 and 80.4 (2 × O*C*(CH_3)$_3$), 105.3 (*C*(4)), 131.8 (*C*(5)), 151.2 (N*C*O_2*t*Bu), 170.8 (C(3)*C*O_2*t*Bu); *m*/*z* (GCMS, CI$^+$) 270 (MH^+, 10%), 214 ($MH^+ - C_4H_8$, 20), 170 (100%); HRMS, found 270.1703; $C_{14}H_{24}NO_4$ (MH^+) requires 270.1705; and the aromatised adduct *tert*-butyl *N*-Boc pyrrole-1,3-dicarboxylate **35** (22 mg, 11%) as a white crystalline solid; m.p. 70–72 °C; ν_{max} (KBr) 3028m, 3009m, 2983s, 2935m, 1749s, 1703s, 1561s, 1496s, 1389s, 1369s, 1289s, 1254s, 1147s, 1100s, 1067s, 975s, 963s, 848s, 831s; δ_H (400 MHz, $CDCl_3$) 1.55 and 1.60 (2 × 9H, 2 × s, (2 × OC(CH_3)$_3$), 6.55 (1H, dd, *J* 3.3, 1.6, C(4)*H*), 7.17 (1H, dd, *J* 3.3, 2.2, C(5)*H*), 7.74 (1H, dd, *J* 2.2, 1.6, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 27.9 and 28.2 (2 × OC(*C*H_3)$_3$), 80.3 and 84.8 (2 × O*C*(CH_3)$_3$), 112.0 (*C*(4)), 120.3 (*C*(3)), 121.2 (*C*(5)), 124.3 (*C*(2)), 148.2 (N*C*O_2*t*Bu), 163.5 (C(3)*C*O_2*t*Bu); *m*/*z* (GCMS, CI$^+$) 268 (MH^+, 15), 212 ($MH^+ - C_4H_8$, 100%); HRMS, found 268.1541; $C_{14}H_{22}NO_4$ (MH^+) requires 268.1549.

Preparation of *tert*-butyl (3*R*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)tetrahydrofuran-3-carboxylate 37, *tert*-butyl (3*S*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)tetrahydrofuran-3-carboxylate 36, di-*tert*-butyl (3*S*,4*R*,3′*S*,4′*S*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)tetrahydro-[3,3′]-bifuranyl-3,4′-dicarboxylate 38 and *tert*-butyl (3*S*,4*R*,3′*S*,4′*R*,α*S*,α′*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)-3-[4′-(*N*-benzyl-*N*-α-methylbenzylamino)-2′-oxotetrahydrofuran-3′-ylmethyl]-tetrahydrofuran-3-carboxylate 39

Following *general procedure 2*, *n*-BuLi (2.5 M, 3.76 ml, 9.40 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.99 g, 9.40 mmol) in THF (50 ml) and **18** (1.00 g, 5.88 mmol) in THF (10 ml) gave, after quenching with NH_4Cl (aq, sat, 20 ml), the adducts **37**:**36**:**38**:**39** in a 4:47:2:47 ratio. Purification by flash chromatography on silica gel (2→4→6→8→10→20→40% EtOAc:*n*-pentane) gave the products: (3*R*,4*R*,α*S*)-**37** as a white crystalline solid (67 mg, 3%); m.p. 68–70 °C; $[\alpha]_D^{24}$ +67.7 (*c*1.5, $CHCl_3$); ν_{max} (KBr) 3011m, 2980s, 2935m, 2872m, 1718s, 1369s, 1149s; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.9, C(α)*Me*), 1.39 (9H, s, OC(CH_3)$_3$), 2.94 (1H, app q, *J* 8.0, C(3)*H*), 3.65 (1H, app t, *J* 8.5, C(2)H_A), 3.77 (1H, m, C(5)H_A), 3.85–3.91 (2H, m, C(4)*H* and C(5)H_B) overlays 3.85 (2H, app s, NCH_2Ph), 4.06 (1H, app t, *J* 8.5, C(2)H_B), 4.15 (1H, q, *J* 6.8, C(α)*H*), 7.21–7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.3 (C(α)*Me*), 28.0 (OC(*C*H_3)$_3$), 50.1 (*C*(3) and N*C*H_2Ph), 58.0 (*C*(α)H), 63.3 (*C*(4)), 70.7 (*C*(2) and *C*(5)), 80.7 (O*C*(CH_3)$_3$), 126.8 (*p*-Ph), 127.7, 128.1, 128.3 and 128.3 (*o*, *m*-Ph), 141.2 and 143.7 (*ipso*-Ph), 172.6 (*C*O_2*t*Bu); *m*/*z* (APCI$^+$) 382 (MH^+, 30), 381 (M^+, 50), 326 ($MH^+ - C_4H_8$, 15), 222 (30), 221 (100%); HRMS, found 382.2381; $C_{24}H_{32}NO_3$ (MH^+) requires 382.2382; (3*S*,4*R*,α*S*)-**36** as a white crystalline solid (694 mg, 31%); m.p. 84–86 °C; $[\alpha]_D^{24}$ −48.0 (*c* 1.5, $CHCl_3$); elemental analysis, found C, 75.4; H, 8.1; N, 8.2%; $C_{24}H_{31}NO_3$ requires C, 75.6; H, 8.2; N, 3.8%; ν_{max} (KBr) 3029w, 3010m, 2980s, 2936w, 1721s, 1369s, 1153s; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.54 (9H, s, OC(CH_3)$_3$), 3.16 (1H, td, *J* 7.7, 4.8, C(3)*H*), 3.55–3.64 (2H, m, C(4)*H* and C(5)H_A), 3.61 and 4.03 (2 × 1H, AB system, J_{AB} 14.8, NCH_2Ph), 3.83 (1H, app t, *J* 7.8, C(5)H_B), 3.92 (1H, dd, *J* 8.8, 7.8, C(2)H_A), 4.11 (1H, dd, *J* 8.8, 4.8, C(2)H_B), 4.23 (1H, q, *J* 6.9, C(α)*H*), 7.23–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.3 (C(α)*Me*), 28.2 (OC(*C*H_3)$_3$), 49.3 (*C*(3)), 51.9 (N*C*H_2Ph), 57.7 (*C*(α)H), 63.4 (*C*(4)), 69.7 (*C*(5)), 70.1 (*C*(2)), 81.0 (O*C*(CH_3)$_3$), 126.7 and 127.0 (*p*-Ph), 128.0, 128.1 and 128.2 (*o*-, *m*-Ph), 141.1 and 141.8 (*ipso*-Ph), 171.7 (*C*O_2*t*Bu); *m*/*z* (APCI$^+$) 382 (MH^+, 70), 381 (M^+, 60), 326 (MH^+–C_4H_8, 65), 325 (M^+–C_4H_8, 100), 222 (45), 221 (100%); HRMS, found 382.2372; $C_{24}H_{32}NO_3$ (MH^+) requires 382.2382; **38** as a white crystalline solid (32 mg, 2%); m.p. 82–84 °C; $[\alpha]_D^{24}$ −38.0 (*c* 0.25, $CHCl_3$); ν_{max} (KBr) 3011m, 2980s, 2936m, 2889m, 1721s, 1369s, 1153s; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.9, C(α)*Me*), 1.42 and 1.46 (2 × 9H, 2 × s, 2 × OC(CH_3)$_3$), 2.81–2.90 (2H, m, C(3′)*H* and C(4′)*H*), 3.51 (1H, dd, *J* 7.4, 5.3, C(4)*H*), 3.60 (2H, app d, *J* 7.0, C(5′)H_2), 3.66 (1H, dd, *J* 8.8, 6.3, C(2′)H_A), 3.80 (1H, d, *J* 9.8, C(2)H_A) overlays 3.82 (1H, m, C(2′)H_B), 3.87 and 4.00 (2 × 1H, AB system, J_{AB} 14.5, NCH_2Ph), 3.95 (1H, dd, *J* 9.8, 7.6, C(5)H_A), 4.07–4.12 (2H, m, C(α)*H* and C(5)H_B), 4.27 (1H, d, *J* 9.8, C(2)H_B), 7.46–7.51 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 28.0 and 28.2 (2 × OC(*C*H_3)$_3$), 47.6 (*C*(3′)), 49.6 (*C*(4′)), 51.4 (N*C*H_2Ph), 57.5 (*C*(α)H), 60.3 (*C*(3)) 64.8 (*C*(4)), 69.1 (*C*(5)), 71.1 (*C*(5′)), 71.8 (*C*(2′)), 73.9 (*C*(2)), 81.0 and 81.9 (2 × O*C*(CH_3)$_3$), 126.7 and 126.9 (*p*-Ph), 128.0, 128.2, 128.4 and 128.5 (*o*-, *m*-Ph), 140.4 and 143.9 (*ipso*-Ph), 170.4 and 172.8

(2 × $CO_2{}^t$Bu); *m*/*z* (APCI$^+$) 552 (MH^+, 100), 551 (M^+, 95), 496 ($MH^+ - C_4H_8$, 30), 495 ($MH^+ - C_4H_8$, 35%); HRMS, found 552.3319; $C_{33}H_{46}NO_6$ (MH^+) requires 552.3325; **39** as a white crystalline solid (283 mg, 14%); m.p. 122–124 °C; $[\alpha]_D^{24}$ −34.8 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 3028m, 3012m, 2976m, 1770s, 1721s, 1494m, 1451m, 1153s; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8, C(α)*Me*), 1.27 (3H, d, *J* 6.9, C(α′)*Me*), 1.44 (9H, s, OC(CH_3)$_3$), 1.87 (1H, dd, *J* 14.6, 4.5, C(3)CH_AH$_B$C(3′)), 2.30 (1H, dd, *J* 14.6, 2.9, C(3)CH$_A$$H_B$C(3′)), 2.39 (1H, m, C(3′)*H*), 2.70–2.74 (2H, m, C(4)*H* and C(4′)*H*), 3.30 and 3.50 (2 × 1H, AB system, J_{AB} 13.1, NCH_2Ph), 3.58 (1H, app d, *J* 9.6, C(5)H_A) overlays 3.62 (1H, dd, *J* 10.0, 7.5, C(5′)H_A), 3.79–3.86 (4H, m, C(α)*H*, C(α′)*H* and NCH_2Ph), 3.86–3.94 (2H, m, C(2)H_A and C(5′)H_B), 4.23 (1H, app d, *J* 9.6, C(5)H_B), 4.36 (1H, d, *J* 10.0, C(2)H_B), 7.21–7.53 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.3 (C(α′)*Me*), 14.2 (C(α)*Me*), 28.2 (OC(*C*H_3)$_3$), 31.5 (C(3)*C*H$_2$C(3′)), 38.7 (*C*(3′)), 50.2 and 51.1 (2 × N*C*H$_2$Ph), 54.3 (*C*(3)), 55.3 and 56.6 (*C*(α)H and *C*(α′)H), 56.7 and 62.3 (*C*(4) and *C*(4′)), 68.2 (*C*(5′)), 69.0 (*C*(2)), 76.0 (*C*(5)), 81.6 (O*C*(CH$_3$)$_3$), 126.4, 127.0, 127.5 and 127.8 (*p*-Ph), 128.0, 128.2, 128.3, 128.4, 128.6, 128.7, 128.9 and 129.1 (*o*-, *m*-Ph), 138.2, 139.4, 142.7 and 143.9 (*ipso*-Ph), 170.2 (*C*O$_2{}^t$Bu), 179.4 (*C*(2′)O); *m*/*z* (APCI$^+$) 689 (MH^+, 50), 688 (M^+, 100%); HRMS, found 689.3952; $C_{44}H_{53}N_2O_5$ (MH^+) requires 689.3954.

A fifth product was also isolated from the column and was identified as being *tert*-butyl (3*S*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(2′-oxo-2′,5′-dihydrofuran-3′-ylmethyl)tetrahydrofuran-3-carboxylate **40**. (3*S*,4*R*,α*S*)-**40** was obtained as clear crystals (238 mg, 17%); m.p. 110–112 °C; $[\alpha]_D^{24}$ −47.8 (*c* 0.90, $CHCl_3$); elemental analysis, found C, 73.0; H, 7.6; N, 2.9%; $C_{29}H_{35}NO_5$ requires C, 72.9; H, 7.4; N, 2.9%; ν_{max} (KBr) 3028m, 3012m, 2977m, 1757s, 1714s, 1369m, 1231m, 1149s, 1069s; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.38 (9H, s, OC(CH_3)$_3$), 1.70 (1H, dd, *J* 15.8, 1.6, C(3)CH_AH$_B$C(3′)), 2.70 (1H, dd, *J* 15.8, 1.2, C(3)CH$_A$CH_BC(3′)), 3.39 (1H, app t, *J* 7.4, C(4)*H*), 3.66 (1H, d, *J* 9.2, C(2)H_A), 3.78 and 4.02 (2 × 1H, AB system, J_{AB} 14.1, NCH_2Ph), 3.92 (1H, dd, *J* 8.9, 7.3, C(5)H_A), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.10 (1H, dd, *J* 8.9, 7.7, C(5)H_B), 4.25 (1H, d, *J* 9.2, C(2)H_B), 4.65 (2H, app d, *J* 1.8, C(5′)H_2), 6.83 (1H, t, *J* 1.5, C(4′)*H*), 7.23–7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.7 (C(α)*Me*), 28.0 (OC(*C*H_3)$_3$), 31.7 (C(3)*C*H$_2$C(3′)), 51.5 (N*C*H$_2$Ph), 56.2 and 56.7 (*C*(α)H and *C*(3)), 66.6 (*C*(4)), 67.2 (*C*(5)), 69.9 (*C*(5′)), 73.8 (*C*(2)), 82.0 (O*C*(CH$_3$)$_3$), 127.1 (*p*-Ph), 128.1, 128.2, 128.3 and 128.9 (*o*-, *m*-Ph), 131.0 (*C*(3′)), 139.9 and 143.4 (*ipso*-Ph), 145.9 (*C*(4′)), 171.7 (*C*O$_2{}^t$Bu), 174.2 (*C*(2′)O); *m*/*z* (APCI$^+$) 478 (MH^+, 80), 477 (M^+, 100), 422 ($MH^+ - C_4H_8$, 45), 421 ($M^+ - C_4H_8$, 80%); HRMS, found 478.2593; $C_{29}H_{36}NO_5$ (MH^+) requires 478.2593.

X-Ray crystal structure determination for 40

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Cu–Kα radiation using standard procedures at 190 K. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[26] X-Ray crystal structure data for **40** [$C_{29}H_{35}NO_5$]: M = 477.60, orthorhombic, space group $P2_12_12_1$, a = 8.8594(1) Å, b = 10.0807(2) Å, c = 28.3944(5) Å, V = 2535.87(7) Å^3, Z = 4, μ = 0.085 mm^{-1}, colourless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm. A total of 3252 unique reflections were measured for 5° < θ < 27° and 2713 reflections were used in the refinement. The final parameters were wR_2 = 0.040 and R_1 = 0.035 [$I > 2\sigma(I)$]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-237687. See http://www.rsc.org/suppdata/ob/b4/b407558g/ for crystallographic data in .cif format.

Selective preparation of *tert*-butyl (3*R*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)tetrahydrofuran-3-carboxylate 37 and *tert*-butyl (3*S*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)-tetrahydrofuran-3-carboxylate 36

Following *general procedure 2*, the lithium amide was prepared by addition of *n*-BuLi (2.5 M, 1.18 ml, 2.94 mmol) to a solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (623 mg, 2.94 mmol) in THF (10 ml) at −78 °C. A cooled (−78 °C) solution of **18** (100 mg, 0.59 mmol) in THF (2 ml) was added rapidly *via* cannula and the reaction mixture stirred at the reduced temperature for 10 min. The reaction was quenched by addition of NH_4Cl (aq, sat, 10 ml), warmed to rt and the aqueous phase separated and extracted with Et_2O (3 × 20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give (3*R*,4*R*,α*S*)-**37**, (3*S*,4*R*,α*S*)-**36** and **39** in an 11 : 86 : 3 ratio. Purification by flash chromatography on silica gel (2→4→6→8% EtOAc : *n*-pentane) gave the products (3*R*,4*R*,α*S*)-**37** (20 mg, 9%) and (3*S*,4*R*,α*S*)-**36** (153 mg, 68%), with spectroscopic data identical to that reported above.

Preparation of *tert*-butyl (3*R*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)tetrahydrofuran-3-carboxylate 37 *via* epimerisation

Following *general procedure 3*, a solution of (3*S*,4*R*,α*S*)-**36** (65 mg, 0.17 mmol) in ^{t}BuOH (5 ml) was treated with KO^{t}Bu and heated at reflux for 3 h. Purification by flash chromatography on silica gel (10% EtOAc : *n*-pentane) gave (3*R*,4*R*,α*S*)-**37** (64 mg, quantitative) in >98% d.e., with spectroscopic data identical to that reported above.

Preparation of *tert*-butyl (3*R*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)tetrahydrothiophene-3-carboxylate 43 and *tert*-butyl (3*S*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)tetrahydrothiophene-3-carboxylate 44

Following *general procedure 2*, *n*-BuLi (1.6 M, 2.70 ml, 4.32 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (916 mg, 4.32 mmol) in THF (30 ml) and **25** (500 mg, 2.70 mmol) in THF (5 ml) gave, after quenching with NH_4Cl (aq, sat, 20 ml), (3*R*,4*R*,α*S*)-**43** and (3*S*,4*R*,α*S*)-**44** in a 69 : 31 ratio. Purification by flash chromatography on silica gel (2% Et_2O : *n*-pentane) gave (3*R*,4*R*,α*S*)-**43** and (3*S*,4*R*,α*S*)-**44** (557 mg, 52%), an inseparable mixture of diastereoisomers, as a colourless oil; NMR data for (3*R*,4*R*,α*S*)-**43** (assigned from the diastereoisomeric mixture): δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.9, C(α)*Me*), 1.49 (9H, s, OC(CH_3)$_3$), 2.73 (1H, dd, *J* 10.1, 6.2, C(5)H_A), 2.86 (2H, app d, *J* 13.3, C(2)H_2), 3.07 (1H, dd, *J* 11.3, 5.3, C(3)*H*), 3.14 (1H, app t, *J* 10.1, C(5)H_B), 3.51 (1H, m, C(4)*H*), 3.79 and 3.96 (2 × 1H, AB system, J_{AB} 14.9, NCH_2Ph), 4.20 (1H, q, *J* 6.9, C(α)*H*), 7.24–7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 28.0 (OC(*C*H_3)$_3$), 30.6 (*C*(2)), 31.8 (*C*(5)), 49.9 (*C*(3)), 51.7 (N*C*H$_2$Ph), 57.8 (*C*(α)H), 66.9 (*C*(4)), 81.0 (O*C*(CH$_3$)$_3$), 126.7, 127.0, 127.9 and 128.1 (*o*-, *m*-, *p*-Ph), 141.4 and 142.3 (*ipso*-Ph), 172.2 (*C*O$_2{}^t$Bu). Also isolated was the deconjugated adduct *tert*-butyl 2,3-dihydrothiophene-3-carboxylate **32** as a colourless oil (140 mg, 28%), with spectroscopic data identical to that reported above.

The mixture of (3*R*,4*R*,α*S*)-**43** and (3*S*,4*R*,α*S*)-**44** (300 mg, 0.76 mmol) was re-dissolved in *tert*-butanol and epimerised under thermodynamic conditions in accordance with *general procedure 3.* Purification by flash chromatography on silica (2% Et_2O : *n*-pentane) gave (3*S*,4*R*,α*S*)-**44** (257 mg, 86%) as a colourless oil; $[\alpha]_D^{24}$ +109.0 (*c* 0.60, $CHCl_3$); ν_{max} (film) 3085m, 3061m, 3027s, 2975s, 2934s, 2874m, 1724s, 1453s, 1367s, 1279s, 1254s, 1150s, 1028s, 846s, 749s; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 7.0, C(α)*Me*), 1.44 (9H, s, OC(CH_3)$_3$), 2.80 (2H, app d, *J* 8.7, C(2)H_2), 2.84–2.89 (2H, m, C(5)H_2), 2.98 (1H, app q, *J* 9.0, C(3)*H*), 3.74 and 3.94 (2 × 1H, AB system, J_{AB} 14.4, NCH_2Ph), 3.87 (1H, m, C(4)*H*), 3.98 (1H, q, *J* 7.0, C(α)*H*), 7.25–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 28.0 (OC(*C*H_3)$_3$), 29.5 and 30.7 (*C*(2) and *C*(5)), 49.6 (N*C*H$_2$Ph), 52.1 (*C*(3)), 57.9 (*C*(α)H),

66.2 (*C*(4)), 80.8 (O*C*(CH_3)$_3$), 126.9, 128.0, 128.1 and 128.6 (*o*-, *m*-, *p*-Ph), 140.8 and 143.3 (*ipso*-Ph), 171.9 (*C*O$_2^t$Bu); *m*/*z* (GCMS, CI$^+$) 398 (MH$^+$, 100), 342 (MH$^+$ − C_4H_8, 10%); HRMS, found 398.2152; $C_{24}H_{31}NO_2S$ (MH$^+$) requires 398.2154.

Preparation of *tert*-butyl *N*-*tert*-butyloxycarbonyl-(3*R*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)tetrahydropyrrole-3-carboxylate 45

Following *general procedure 2*, *n*-BuLi (1.6 M, 3.72 ml, 5.94 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.26 g, 5.94 mmol) in THF (40 ml) and **21** (1.00 g, 3.72 mmol) in THF (10 ml) gave, after quenching with NH_4Cl (aq, sat, 40 ml), (3*R*,4*R*,α*S*)-**45** in >98% d.e. Purification by flash chromatography on silica gel (5→10→20% EtOAc/*n*-pentane) gave (3*R*,4*R*,α*S*)-**45** (821 mg, 46%) as a colourless oil; $[\alpha]_D^{25}$ −18.5 (*c* 1.8, $CHCl_3$); ν_{max} ($CHCl_3$) 3008m, 2980s, 2934m, 1719s, 1687s, 1412s, 1368s, 1152s; δ_H (400 MHz, d_8-toluene, rotameric at 298 K) 1.20 (1.5H, d, *J* 6.9, C(α)*Me*), 1.29 (1.5H, d, *J* 6.9, C(α)*Me*), 1.41/1.42 and 1.43/1.46 (18H, 4 × s, 2 × OC(CH_3)$_3$), 2.82 (0.5H, m, C(3)*H*), 2.87 (0.5H, m, C(3)*H*), 3.03–3.11 (1.5H, m, C(2)H_A and C(5)H_A), 3.17 and 3.84 (2 × 0.5H, AB system, J_{AB} 14.9, NCH_2Ph), 3.19 (0.5H, m, C(4)*H*), 3.27–3.32 (1H, m, C(2)H_B and C(4)*H*), 3.38 (0.5H, dd, *J* 10.5, 7.1, C(5)H_A), 3.52 and 3.74 (2 × 0.5H, AB system, J_{AB} 14.6, NCH_2Ph), 3.61–3.66 (1H, m, C(2)H_B and C(5)H_B), 3.76 (0.5H, dd, *J* 11.6, 10.1, C(5)H_B), 4.16 (0.5H, q, *J* 6.9, C(α)*H*), 4.30 (0.5H, q, *J* 6.9, C(α)*H*), 7.06–7.38 (10H, m, *Ph*); δ_H (500 MHz, d_8-toluene, 363 K) 1.28 (3H, d, *J* 6.5, C(α)*Me*), 1.40 and 1.43 (2 × 9H, 2 × s, 2 × OC(CH_3)$_3$), 2.83 (1H, m, C(3)*H*), 3.13 (1H, app dd, *J* 11.5, 7.0, C(4)*H*), 3.36 (2H, m, C(2)H_2), 3.59–3.64 (2H, br, NCH_AH$_B$Ph and C(5)H_A), 3.66 (1H, br, C(5)H_B), 3.88 (1H, d, *J* 14.5, NCH$_A$$H_B$Ph), 4.25 (1H, q, *J* 6.5, C(α)*H*), 7.15–7.33 (10H, m, *Ph*); δ_C (100 MHz, d_8-toluene, rotameric at 298 K) 15.9/17.7 (C(α)*Me*), 28.4/28.5 and 28.8/28.9 (2 × OC(*C*H_3)$_3$), 47.9 and 48.0 (*C*(5) and *C*(3)), 48.3 and 48.4 (*C*(5) and *C*(2)), 49.2 (*C*(2) and *C*(3)), 52.3/52.5 (N*C*H$_2$Ph), 57.7/58.2 (*C*(α)H), 61.4/63.6 (*C*(4)), 78.8/79.0 and 80.6/80.7 (2 × O*C*(CH_3)$_3$), 127.3, 127.4, 127.5, 127.7, 128.1, 128.3, 128.6, 128.7, 128.8, 129.0, 129.2 and 129.5 (*o*-, *m*-, *p*-Ph), 141.8 and 142.5/142.9 (*ipso*-Ph), 154.2/154.6 (N*C*O$_2^t$Bu), 171.8/172.0 (C(3)*C*O$_2^t$Bu); δ_C (125 MHz, d_8-toluene, 363 K) 28.4/28.5 and 28.7/28.9 (2 × OC(*C*H_3)$_3$), 48.2 and 48.7 (*C*(2), *C*(3), *C*(4) and *C*(5)), 52.5 (N*C*H$_2$Ph), 58.4 (*C*(α)H), 78.8 and 80.6 (2 × O*C*(CH_3)$_3$), 127.1, 127.3, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0 and 129.2 (*o*-, *m*-, *p*-Ph), 141.3 and 141.9 (*ipso*-Ph), 154.3 (N*C*O$_2^t$Bu), 171.7 (C(3)*C*O$_2^t$Bu); *m*/*z* (APCI$^+$) 481 (MH$^+$, 100), 425 (MH$^+$ − C_4H_8, 20%); HRMS, found 481.3166; $C_{29}H_{41}N_2O_2$ (MH$^+$) requires 481.3168. Also isolated was the deconjugated adduct *tert*-butyl *N*-Boc-2,3-dihydropyrrole-3-carboxylate **34** (220 mg, 22%) as a white solid and the aromatised adduct *tert*-butyl *N*-Boc pyrrole-1,3-dicarboxylate **35** (79 mg, 8%) as a white crystalline solid, both with spectroscopic data identical to that reported above.

Preparation of *tert*-butyl (3*S*,4*R*)-4-aminotetrahydrofuran-3-carboxylate 46

Following *general procedure 4*, $Pd(OH)_2$ on C (60 mg) was added to a stirred degassed solution of (3*S*,4*R*,α*S*)-**36** (300 mg, 0.79 mmol) in MeOH (5 ml) and stirred under H_2 (5 atm) overnight. Filtration through Celite® and concentration *in vacuo* gave the crude β-amino ester. Although this material was used without purification, flash chromatography on silica gel (Et_2O) gave an analytical sample of (3*S*,4*R*)-**46** as a colourless oil; $[\alpha]_D^{24}$ −3.2 (*c*1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2982m, 2877w, 1720s, 1370m, 1154s; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, OC(CH_3)$_3$) overlays 1.50 (2H, br s, NH_2), 3.01 (1H, app q, *J* 7.7, C(3)*H*), 3.59 (1H, dd, *J* 8.9, 3.8, C(5)H_A), 3.76 (1H, br m, C(4)*H*), 3.93 (1H, dd, *J* 8.9, 5.4, C(5)H_B), 3.98 (1H, t, *J* 8.7, C(2)H_A), 4.07 (1H, t, *J* 8.7, C(2)H_B); δ_C (100 MHz, $CDCl_3$) 28.2 (OC(*C*H_3)$_3$), 50.9 (*C*(3)), 54.2 (*C*(4)), 68.2 (*C*(2)), 75.4 (*C*(5)), 81.3 (O*C*(CH_3)$_3$), 170.4 (*C*O$_2^t$Bu); *m*/*z* (GCMS, CI$^+$) 188 (MH$^+$, 50), 132 (MH$^+$–C_4H_8, 100%); HRMS, found 188.1280; $C_9H_{18}NO_3$ (MH$^+$) requires 188.1287.

Preparation of *tert*-butyl (3*R*,4*R*)-4-aminotetrahydrofuran-3-carboxylate 48

Following *general procedure 4*, $Pd(OH)_2$ on C (50 mg) was added to a stirred degassed solution of (3*S*,4*R*,α*S*)-**37** (250 mg, 0.66 mmol) in MeOH (5 ml) and stirred under H_2 (5 atm) overnight. Filtration through Celite® and concentration *in vacuo* gave the crude β-amino ester. Although this material was used without purification, flash chromatography on silica gel (Et_2O) gave an analytical sample of (3*R*,4*R*)-**48** as a colourless oil; $[\alpha]_D^{24}$ +61.9 (*c* 2.1, $CHCl_3$); ν_{max} ($CHCl_3$) 2982m, 2872w, 1721s, 1370m, 1154s; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, OC(CH_3)$_3$), 1.72 (2H, br s, NH_2), 2.66–2.71 (1H, m, C(3)*H*), 3.46 (1H, dd, *J* 8.8, 5.2, C(5)H_A), 3.72 (1H, app q, *J* 5.4, C(4)*H*), 3.89 (1H, dd, *J* 9.0, 6.8, C(2)H_A), 3.95 (1H, dd, *J* 8.8, 6.2, C(5)H_B), 4.10 (1H, app t, *J* 8.7, C(2)H_B); δ_C (100 MHz, $CDCl_3$) 28.0 (OC(*C*H_3)$_3$), 55.0 (*C*(3)), 56.1 (*C*(4)), 69.7 (*C*(2)), 75.3 (*C*(5)), 81.2 (O*C*(CH_3)$_3$), 171.8 (*C*O$_2^t$Bu); *m*/*z* (GCMS, CI$^+$) 188 (MH$^+$, 15), 132 (MH$^+$ − C_4H_8, 100%); HRMS, found 188.1289; $C_9H_{18}NO_3$ (MH$^+$) requires 188.1287.

Preparation of (3*S*,4*R*)-4-aminotetrahydrofuran-3-carboxylic acid 47

Following *general procedure 5*, TFA (5 ml) was added to a solution of crude β-amino ester (3*S*,4*R*)-**46** (80 mg, 0.43 mmol) at rt and stirred for 16 h. Purification using Dowex® 50X8-200 resin gave (3*S*,4*R*)-**47** (39 mg, 69% from **36**) as a white solid; m.p. 198–200 °C (decomposes); $[\alpha]_D^{23}$ +19.3 (*c* 0.80, H_2O); ν_{max} (KBr) 3482br s, 3081–2794br s, 2572m, 2182br s, 1620s, 1562s, 1408s, 1185s, 1093s, 901s, 777s; δ_H (400 MHz, D_2O) 3.30 (1H, app qd, *J* 9.0, 2.4, C(3)*H*), 3.85–3.91 (3H, m, C(2)H_A and C(5)H_2), 3.93 (1H, m, C(4)*H*), 4.05 (1H, app t, *J* 9.2, C(2)H_B); δ_C (100 MHz, D_2O) 47.3 (*C*(3)), 52.1 (*C*(4)), 69.2 (*C*(2)), 71.0 (*C*(5)), 176.8 (*C*O$_2$H); *m*/*z* (ESI$^+$) 132 (MH$^+$, 100%); HRMS, found 132.0656; $C_5H_{10}NO_5$ (MH$^+$) requires 132.0661.

Preparation of (3*R*,4*R*)-4-aminotetrahydrofuran-3-carboxylic acid 49

Following *general procedure 5*, TFA (5 ml) was added to a solution of crude β-amino ester (3*R*,4*R*)-**48** (75 mg, 0.40 mmol) at rt and stirred for 16 h. Purification using Dowex® 50X8-200 resin gave (3*R*,4*R*)-**49** (35 mg, 66% from **37**) as a white solid; m.p. 213–215 °C (decomposes); $[\alpha]_D^{23}$ +17.8 (*c* 1.0, H_2O); ν_{max} (KBr) 3462br s, 3021–2763br s, 2347–1931br s, 1623s, 1565s, 1396s, 1372s, 1077s, 901s, 856s; δ_H (400 MHz, D_2O) 2.93–2.97 (1H, m, C(3)*H*), 3.71 (1H, app t, *J* 7.8, C(2)H_A), 3.80–3.88 (2H, m, C(5)H_2), 4.03 (1H, m, C(4)*H*), 4.17 (1H, app t, *J* 8.8, C(2)H_B); δ_C (100 MHz, D_2O) 51.8 (*C*(3)), 54.8 (*C*(4)), 71.0 and 71.1 (*C*(2) and *C*(5)), 177.9 (*C*O$_2$H); *m*/*z* (ESI$^+$) 132 (MH$^+$, 100%); HRMS, found 132.0663; $C_5H_{10}NO_3$ (MH$^+$) requires 132.0661.

Preparation of *tert*-butyl (3*R*,4*R*)-*N*-*tert*-butyloxycarbonyl-4-aminopyrrolidine-3-carboxylate 50

Following *general procedure 4*, $Pd(OH)_2$ on C (120 mg) was added to a stirred degassed solution of (3*R*,4*R*,α*S*)-**45** (600 mg, 1.25 mmol) in MeOH (8 ml) and stirred under H_2 (5 atm) overnight. Filtration through Celite® and concentration *in vacuo* gave the crude β-amino ester. Although this material was used without purification, flash chromatography on silica gel (Et_2O) gave an analytical sample of (3*R*,4*R*)-**50** (211 mg, 59%) as a white solid; m.p. 55–57 °C; $[\alpha]_D^{24}$ +4.7 (*c* 0.90, $CHCl_3$); ν_{max} ($CHCl_3$) 3005m, 2981s, 2935m, 1722s, 1689s, 1414s, 1368s, 1154s; δ_H (400 MHz, d_4-MeOH, rotameric at 298 K) 1.43/1.44 and 1.51 (18H, 3 × s, 2 × OC(CH_3)$_3$), 3.14 (1H, m, C(3)*H*), 3.30 (1H, dd, *J* 11.1, 2.6, C(5)H_A), 3.50–3.55 (2H, m, C(2)H_A and C(5)H_B),

3.64 (1H, m, C(2)H_B), 3.73 (1H, m, C(4)*H*); δ_C (100 MHz, d_4-MeOH, rotameric at 298 K) 28.6/28.7 and 29.2 (2 × OC(CH_3)$_3$), 47.3/47.5 (*C*(2)), 48.8/49.0 (*C*(3)), 53.0/53.8 (*C*(4)), 54.3/54.6 (*C*(5)), 81.5 and 83.3 (2 × O*C*(CH_3)$_3$), 156.7 (N*C*$O_2{}^t$Bu), 172.3 (C(3)*C*$O_2{}^t$Bu); *m*/*z* (GCMS, CI$^+$) 287 (MH^+, 60), 231 ($MH^+ - C_4H_8$, 80), 175 ($MH^+ - C_8H_{16}$, 100%); HRMS, found 287.1970; $C_{14}H_{27}N_2O_4$ (MH^+) requires 287.1971.

Preparation of (3*R*,4*R*)-4-aminopyrrolidine-3-carboxylic acid 4

Following *general procedure 5*, TFA (5 ml) was added to a solution of crude β-amino ester (3*R*,4*R*)-**50** (200 mg, 0.70 mmol) at rt and stirred for 16 h. Purification using Dowex® 50X8-200 resin gave (3*R*,4*R*)-**4** (65 mg, 71% from **45**) as a pale yellow solid; m.p. 164–166 °C (decomposes) (lit.[8] 166–167 °C); $[\alpha]_D^{25}$ +17.1 (*c* 2.5, H_2O) {lit.[8] $[\alpha]_D^{22}$ +25.9 (*c* 0.9, MeOH)}; ν_{max} (KBr) 3581–2372br s, 3420s, 1576s, 1410s, 1127m, 618m; δ_H (400 MHz, D_2O) 3.05 (1H, br m, C(3)*H*) overlays 3.10 (1H, dd, *J* 11.9, 4.3, C(5)H_A), 3.32–3.43 (3H, m, C(2)H_2 and C(5)H_B), 3.77 (1H, m, C(4)*H*); δ_C (100 MHz, D_2O) 46.6 (*C*(2)), 49.9 (*C*(3)), 50.9 (*C*(5)), 51.4 (*C*(4)), 176.6 (*C*O_2H); *m*/*z* (ESI$^+$) 153 (MNa^+, 70), 131 (MH^+, 100%); HRMS, found 131.0818; $C_5H_{11}N_2O_2$ (MH^+) requires 131.0821.

Preparation of *tert*-butyl propiolate

A solution of propiolic acid (25.0 g, 0.36 mol) in Et_2O (100 ml) was cooled to −78 °C and ≈100 ml of isobutylene (condensed by passing the gas into a conical flask held at −78 °C) added, followed by H_2SO_4 (98%, 1 drop). The reaction mixture was held at −78 °C for 4 h, then allowed to warm to rt overnight. The mixture was diluted with water (100 ml) and the aqueous layer separated and extracted with Et_2O (3 × 100 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* Purification by flash chromatography on silica gel (5% Et_2O/*n*-pentane) gave the title compound (33.6 g, 74%) as a crystalline solid; δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, OC(CH_3)$_3$), 2.76 (1H, s, C≡C*H*), with all other spectroscopic data identical to the commercially available material.[27]

Preparation of *tert*-butyl *N*-benzyl-2,5-dihydropyrrole-3-carboxylate 52

To a solution of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-benzylamine **51**[22] (5.0 g, 19.8 mmol) in DCM (75 ml) at 0 °C was added dropwise a solution of *tert*-butyl propiolate (2.1 g, 16.5 mmol) in DCM (10 ml). Acetic acid (0.09 ml, 1.65 mmol) was added neat, dropwise, and the reaction mixture allowed to warm to rt, whereat it was stirred for 4 h. The reaction was neutralized by addition $NaHCO_3$ (aq, sat, 50 ml) and the organic phase separated, washed with brine (aq, sat, 50 ml) and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (20% EtOAc : *n*-pentane)-gave **52** (3.97 g, 93%) as a colourless oil; ν_{max} (film) 3003m, 2976s, 2932m, 1706s, 1455m, 1367s, 1246s, 1166s, 762m, 731m, 701m; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, OC(CH_3)$_3$), 3.61–3.68 (4H, m, C(2)H_2 and C(5)H_2), 3.82 (2H, s, N*C*H_2Ph), 6.66 (1H, m, C(4)*H*), 7.23–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.1 (OC(CH_3)$_3$), 58.3 and 60.0 (*C*(2) and *C*(5)), 80.6 (O*C*(CH_3)$_3$), 127.2 (*p*-Ph), 128.4 and 128.6 (*o*-, *m*-Ph), 135.6 (*C*(3)), 138.1 (*ipso*-Ph), 138.9 (*C*(4)), 162.9 (*C*$O_2{}^t$Bu); *m*/*z* (GCMS, CI$^+$) 260 (MH^+, 100%); HRMS, found 260.1648; $C_{16}H_{22}NO_2$ (MH^+) requires 260.1651.

Preparation of *tert*-butyl *N*-benzyl (3*R*,4*R*,α*S*)-4-(*N*′-benzyl-*N*′-α-methylbenzylamino)tetrahydropyrrole-3-carboxylate 53

Following *general procedure 2*, *n*-BuLi (2.5 M, 2.5 ml, 6.2 mmol), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.31 g, 6.2 mmol) in THF (50 ml) and **52** (1.00 g, 3.9 mmol) in THF (10 ml) gave, after quenching with NH_4Cl (aq, sat, 40 ml), (3*R*,4*R*,α*S*)-**53** in >98% d.e. Purification by flash chromatography on silica gel (5→10→20% EtOAc/*n*-pentane) gave (3*R*,4*R*,α*S*)-**53** (1.45 g, 79%) as a pale yellow solid; m.p. 66–68 °C; $[\alpha]_D^{25}$ +32.0 (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 3061m, 3030m, 2977s, 2934s, 1724s, 1455s, 1368s, 1152s, 750m, 701s; δ_H (400 MHz, $CDCl_3$) 1.52 (3H, d, *J* 6.8, C(α)*Me*), 1.60 (9H, s, OC(CH_3)$_3$), 2.70 (1H, dd, *J* 15.3, 3.9, C(2)H_A), 2.77–2.83 (2H, m, C(2)H_B and C(5)H_A), 2.96 (1H, m, C(3)*H*), 3.09 and 4.07 (2 × 1H, AB system, J_{AB} 15.4, NCH_2Ph), 3.11 (1H, m, C(5)H_B), 3.67 (1H, m, C(4)*H*), 4.08 and 4.26 (2 × 1H, AB system, J_{AB} 14.1, N′CH_2Ph), 4.29 (1H, d, *J* 6.8, C(α)*H*), 7.12–7.32 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 28.2 (OC(*C*H_3)$_3$), 46.7 (*C*(2)), 51.3 (N*C*H_2Ph), 53.9 and 54.1 (*C*(3) and *C*(5)), 58.2 (*C*(α)H), 59.5 (N′*C*H_2Ph), 62.2 (*C*(4)), 82.9 (O*C*(CH_3)$_3$), 127.0, 127.1, 127.7, 128.0, 128.2, 128.4, 128.5, 128.6, 129.1, 129.3, 129.5, 129.8, 130.0, 130.5, 130.7 (*o*-, *m*-, *p*-Ph), 138.9 and 140.7 (*ipso*-Ph), 172.4 (*C*$O_2{}^t$Bu); *m*/*z* (APCI$^+$) 471 (MH^+, 100), 470 (M^+, 65), 415 ($MH^+ - C_4H_8$, 15), 414 ($M^+ - C_4H_8$, 20%); HRMS, found 471.2989; $C_{31}H_{39}N_2O_2$ (MH^+) requires 471.3012.

Preparation of *tert*-butyl *N*-benzyl (3*S*,4*R*,α*S*)-4-(*N*′-benzyl-*N*′-α-methylbenzylamino)tetrahydropyrrole-3-carboxylate 54 *via* epimerisation

Following *general procedure 3*, a solution of (3*R*,4*R*,α*S*)-**53** (700 mg, 1.49 mmol) in ^{t}BuOH (10 ml) was treated with KO^{t}Bu and heated at reflux for 3 h. Purification by flash chromatography on silica gel (20% EtOAc : *n*-pentane) gave (3*S*,4*R*,α*S*)-**54** (695 mg, quantitative) in >98% d.e. as a colourless oil; $[\alpha]_D^{25}$ +51.6 (*c* 1.1, $CHCl_3$); ν_{max} (film) 3028m, 2974s, 2928s, 1725s, 1453s, 1367s, 1150s, 747s, 699s; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.8, C(α)*Me*), 1.40 (9H, s, OC(CH_3)$_3$), 2.35 (1H, m, C(2)H_A), 2.51 (1H, app t, *J* 9.1, C(5)H_A), 2.92–3.00 (3H, m, C(2)H_B, C(3)*H* and C(5)H_B), 3.57 and 3.63 (2 × 1H, AB system, J_{AB} 13.2, NCH_2Ph), 3.81 (1H, m, C(4)*H*), 3.92 and 4.08 (2 × 1H, AB system, J_{AB} 15.3, N′CH_2Ph), 3.94 (1H, q, *J* 6.8, C(α)*H*), 7.21–7.52 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 28.0 (OC(*C*H_3)$_3$), 49.6 (*C*(3)), 50.3 (N*C*H_2Ph), 56.6 (*C*(2)), 57.3 (*C*(5)), 57.9 (*C*(α)H), 59.9 (N′*C*H_2Ph), 61.3 (*C*(4)), 80.2 (O*C*(CH_3)$_3$), 126.6, 126.8 and 126.9 (*p*-Ph), 127.2, 127.8, 128.0, 128.2, 128.4, 128.6 (*o*-, *m*-Ph), 138.9, 142.0, 144.3 (*ipso*-Ph), 173.6 (*C*$O_2{}^t$Bu); *m*/*z* (ESI$^+$) 471 (MH^+, 100), 415 ($MH^+ - C_4H_8$, 15%); HRMS, found 471.3011; $C_{31}H_{39}N_2O_2$ (MH^+) requires 471.3012.

Preparation of *tert*-butyl (3*R*,4*R*,α*S*)-4-(*N*-benzyl-*N*-α-methylbenzylamino)pyrrolidine-3-carboxylate 55

Following *general procedure 4*, $Pd(OH)_2$ on C (70 mg) was added to a stirred degassed solution of (3*R*,4*R*,α*S*)-**53** (344 mg, 0.73 mmol) in MeOH (5 ml) and stirred under H_2 (5 atm) overnight. Filtration through Celite® and concentration *in vacuo* gave the crude pyrrolidine as a yellow oil. Purification by flash chromatography on silica gel (20→40% EtOAc/*n*-pentane) gave (3*R*,4*R*,α*S*)-**55** (191 mg, 69%) as a clear oil; $[\alpha]_D^{25}$ −35.7 (*c* 2.0, $CHCl_3$); ν_{max} (film) 3421br w, 2978s, 2932s, 1725s, 1602w, 1454m, 1369s, 1153s, 910s, 744s, 701s; δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.53 (9H, s, OC(CH_3)$_3$), 3.10–3.21 (3H, m, C(2)H_2 and C(5)H_A), 3.27 (1H, dd, *J* 12.2, 6.9, C(5)H_B), 3.35 and 4.07 (2 × 1H, AB system, J_{AB} 15.4, NCH_2Ph), 3.47–3.59 (2H, m, C(3)*H* and C(4)*H*), 4.24 (1H, q, *J* 6.8, C(α)*H*), 7.22–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1 (C(α)*Me*), 28.1 (OC(*C*H_3)$_3$), 45.9 and 45.7 (*C*(2) and *C*(5)), 47.0 (*C*(3)), 51.7 (N*C*H_2Ph), 57.9 (*C*(α)H), 62.6 (*C*(4)), 83.0 (O*C*(CH_3)$_3$), 126.6 and 127.2 (*p*-Ph), 127.4, 127.6, 128.4 and 128.5 (*o*-, *m*-Ph), 140.2 (*ipso*-Ph), 170.4 (*C*$O_2{}^t$Bu); *m*/*z* (ESI$^+$) 381 (MH^+, 100%); HRMS, found 381.2546; $C_{24}H_{33}N_2O_2$ (MH^+) requires 381.2542.

Alternative preparation of *tert*-butyl (3*R*,4*R*)-*N*-*tert*-butyloxycarbonyl-4-aminopyrrolidine-3-carboxylate 56

Following *general procedure 4*, $Pd(OH)_2$ on C (40 mg) was added to a stirred degassed solution of (3*R*,4*R*,α*S*)-**53** (200 mg, 0.43 mmol) and di-*tert*-butyl dicarbonate (98 mg, 0.45 mmol)

in MeOH (5 ml) and stirred under H_2 (5 atm) overnight. Filtration through Celite® and concentration *in vacuo* gave the crude β-amino ester. Purification by flash chromatography on silica gel (Et_2O) gave an analytical sample of (3*R*,4*R*,α*S*)-**56** (69 mg, 56%) as a white solid, with spectroscopic data identical to that reported above.

Alternative preparation of (3*R*,4*R*)-4-aminopyrrolidine-3-carboxylic acid 4

Following *general procedure 4*, $Pd(OH)_2$ on C (30 mg) was added to a stirred degassed solution of (3*R*,4*R*,α*S*)-**53** (150 mg, 0.43 mmol) in a mixture of EtOH (2 ml), H_2O (1 ml) and HCl (conc, 0.5 ml). The reaction mixture was stirred under H_2 (5 atm) overnight, then filtered through Celite® and concentrated *in vacuo* to give the crude (3*R*,4*R*) β-amino ester as a yellow oil (65 mg). This material was subsequently re-dissolved in HCl (1 M aq, 5 ml) and heated at 70 °C for 4 h. Following cooling to room temperature, the solution was concentrated to a quarter of its volume and chromatographed using Dowex® 50X8-200 resin to give the free amino acid (3*R*,4*R*)-**4** (38 mg, 68% from **53**) as a pale yellow solid, with spectroscopic data identical to that reported above.

Preparation of (3*S*,4*R*)-4-aminopyrrolidine-3-carboxylic acid hydrochloride 7.HCl

Following *general procedure 4*, $Pd(OH)_2$ on C (20 mg) was added to a stirred degassed solution of (3*S*,4*R*,α*S*)-**54** (100 mg, 0.26 mmol) in a mixture of EtOH (2 ml), H_2O (1.0 ml) and HCl (conc, 0.5 ml). The reaction mixture was stirred under H_2 (5 atm) overnight, then filtered through Celite® and concentrated *in vacuo* to give the crude (3*S*,4*R*)-β-amino ester as a yellow oil (37 mg). This material was subsequently re-dissolved in HCl (1 M aq, 5 ml) and heated at 70 °C for 4 h. Following cooling to room temperature, the solution was washed with Et_2O and the aqueous phase concentrated *in vacuo* to afford the *trans* amino acid hydrochloride salt (3*S*,4*R*)-**7**.HCl (24 mg, 71% from **54**) as a clear glass; $[\alpha]_D^{25}$ +22.9 (*c* 0.50, H_2O); ν_{max} (film) 3592–2333br s, 3405s, 2924s, 1729s, 1606m, 1544m, 1515s, 1455m, 1394s, 1296m, 1260m, 1221s, 1197s, 1130m, 843m; δ_H (400 MHz, D_2O) 3.37–3.47 (2H, m, C(3)*H* and C(5)H_A), 3.58 (1H, dd, *J* 12.0, 7.2, C(2)H_A), 3.69 (1H, dd, *J* 12.0, 8.4, C(2)H_B), 3.79 (1H, dd, *J* 12.4, 8.8, C(5)H_B), 4.25 (1H, q, *J* 6.8, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 40.6 (*C*(3)), 46.6 (*C*(5)), 47.9 (*C*(2)), 51.1 (*C*(4)), 176.1 (*C*O_2H); *m*/*z* (ESI^+) 131 (MH^+, 100%); HRMS, found 131.0821; $C_5H_{11}N_2O_2$ (MH^+) requires 131.0821.

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