Stereocontrolled synthesis and alkylation of cyclic β-amino esters: asymmetric synthesis of a (−)-sparteine surrogate†‡

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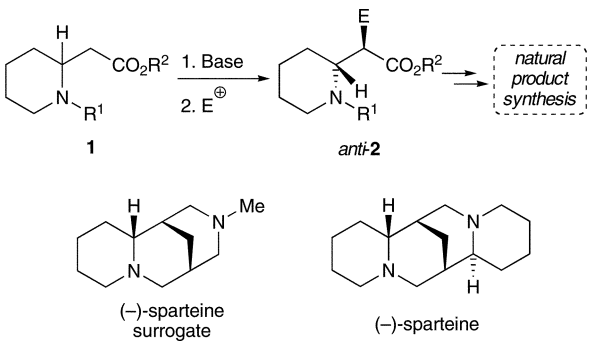
A convenient method for the stereoselective synthesis of cyclic β-amino esters from an iodo αβ-unsaturated ester and α-methylbenzylamine is described. Subsequent enolate generation and alkylation proceeds with complete stereocontrol, with the two stereogenic centres working together. In this way, a functionalised piperidine suitable for alkaloid natural product synthesis was prepared. The usefulness of the methodology is exemplified with the concise synthesis of a (−)-sparteine surrogate.

Introduction

The piperidine structural motif is a common feature of numerous biologically active pharmaceutical compounds and natural products. As a result, the development of new methods for the asymmetric synthesis of chiral piperidines is an important topic that continues to capture the imagination of synthetic chemists.[1] With this in mind, our group has an ongoing interest in the preparation of cyclic β-amino esters **1** and their stereoselective alkylation to amino esters *anti*-**2** (Scheme 1).[2,3] A number of research groups have shown that the conversion of amino esters **1** → *anti*-**2** is a particularly useful reaction for alkaloid natural product synthesis and successful total syntheses of (+)- and (−)-lupinine,[4,5] (−)-stelettamide B[6] and (±)-thermopsine[7] have been successfully reported in recent times. In this paper, we report a simple method for the preparation of either enantiomer of cyclic β-amino esters **1** together with a study of the stereoselective alkylation of amino esters **1** → *anti*-**2** where R^1 = α-methylbenzyl. The usefulness of this methodology is demonstrated with the concise synthesis of a (−)-sparteine surrogate.



Scheme 1

Results and discussion

Stereoselective synthesis of cyclic β-amino esters

Due to the importance of cyclic β-amino esters **1** in natural product synthesis, it is not surprising to find that several approaches for their asymmetric synthesis have been developed. These include chemical[4] and enzymatic resolutions,[8] homologation of pipecolic esters,[9] conjugate addition of chiral amine derivatives to αβ-unsaturated esters and subsequent cyclisation,[2,10,11] S_N2 displacement–cyclisation of αβ-unsaturated esters using a chiral amine,[3,12] stereoselective allylation of a chiral iminium ion[6] and hydrogenation of enamide esters using a chiral auxiliary[13,14] or chiral catalyst.[15]

Previous research in our group has led to the development of two different approaches for the asymmetric synthesis of cyclic β-amino esters: (i) conjugate addition of chiral lithium amides to αβ-unsaturated esters followed by *N*-deprotection and cyclisation[2] and (ii) S_N2 displacement of an iodo-substituted αβ-unsaturated ester using a chiral amine and concomitant cyclisation.[3] Of these two methods for synthesising cyclic β-amino esters **1**, our preferred approach, which we have now optimised, is the diastereoselective Bunce-style[16] S_N2 substitution-cyclisation of iodo-αβ-unsaturated ester **3** and (*S*)-α-methylbenzylamine to amino esters (*R*,*S*)-**4** and (*S*,*S*)-**4** (Scheme 2). The required iodo ester **3** can be readily prepared in gram quantities from 5-chloropentanol *via* Swern oxidation,[17] Horner–Wadsworth–Emmons reaction[18] and Finkelstein reaction[16] (84% yield over 3 steps, see Supporting Information†). The initial conditions examined for the cyclisation process involved refluxing of iodo ester **3** and (*S*)-α-methylbenzylamine in EtOH for 16 hours. This gave a 65 : 35 mixture of diastereomeric amino esters (*R*,*S*)-**4** and (*S*,*S*)-**4**.[3] However, we have recently found that carrying out the reaction in DMF at room temperature for 64 hours (due to a slower cyclisation step at this temperature) led to slightly improved

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‡ CCDC reference number 623452. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b712503h

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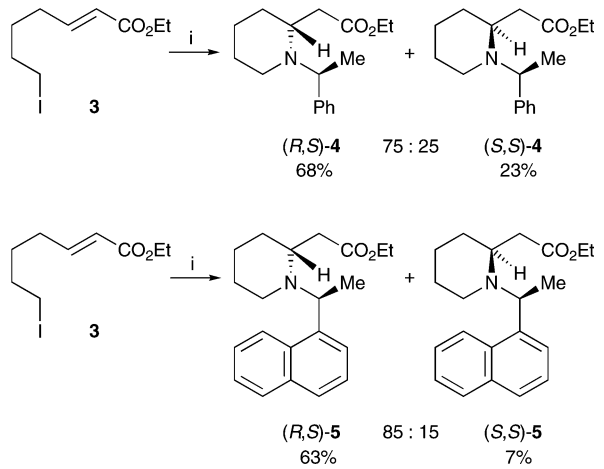


Scheme 2 *Reagents and conditions*: i, (*S*)-α-methylbenzylamine or (*S*)-(1-naphthyl)ethylamine, Et_3N, DMF, rt, 64 h.

stereoselectivity. In this way, a 75 : 25 mixture of (*R*,*S*)-**4** and (*S*,*S*)-**4** was produced from which we isolated a 68% yield of amino ester (*R*,*S*)-**4** after chromatography.[19] Using the same conditions, a 63% yield of amino ester (*R*,*S*)-**5** was obtained using (*S*)-(1-naphthyl)ethylamine (Scheme 2).

In order to rationalise the preferred formation of amino esters (*R*,*S*)-**4**/**5** over (*S*,*S*)-**4**/**5**, we devised the following model (Fig. 1). Bunce *et al.* have already shown that the reaction of benzylamine with iodo ester **3** proceeds *via intermolecular* S_N2 substitution of the iodide followed by *intramolecular* conjugate addition of the amine onto the αβ-unsaturated ester.[16] It is reasonable to assume that the same mechanistic pathway occurs with (*S*)-α-methylbenzylamine and (*S*)-(1-naphthyl)ethylamine and this has allowed us to construct two preferred conformations **A** and **B** for cyclisation to (*R*,*S*)-**4**/**5** and (*S*,*S*)-**4**/**5** respectively (Fig. 1). In both **A** and **B**, the hydrogen of the chiral amine occupies the most sterically hindered "inside" position. The major products (*R*,*S*)-**4**/**5** arise *via* **A** in which the sterically larger aryl (Ar) group minimises its steric clash with the axial hydrogen on the carbon labelled with a *. Thus, better stereoselectivity is obtained with the more sterically demanding 1-naphthyl substituent.

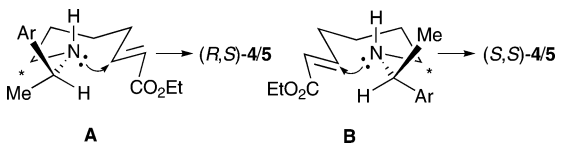
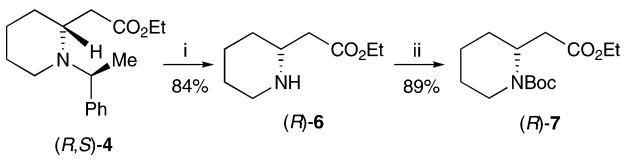


Fig. 1 Model to explain the sense of induction in the S_N2 substitution–intramolecular cyclisation of iodo ester **3**.

To demonstrate the usefulness of the cyclisation methodology, it was necessary to develop suitable conditions for *N*-deprotection of the α-methylbenzyl chiral auxiliary. In our hands, the most useful procedure involved transfer hydrogenolysis using $Pd(OH)_2/C$ and ammonium formate (Scheme 3). Thus, under these conditions, amino ester (*R*,*S*)-**4** was converted into amine (*R*)-**6** (>95 : 5 er by chiral shift NMR spectroscopy) in 84% yield after distillation. Subsequent Boc-protection delivered *N*-Boc protected amino ester (*R*)-**7** in 89% yield. Alternatively, *N*-Boc protected amino ester (*R*)-**7** could be directly prepared in 82% yield from (*R*,*S*)-**4** without isolation of the intermediate amine. The naphthylamino ester



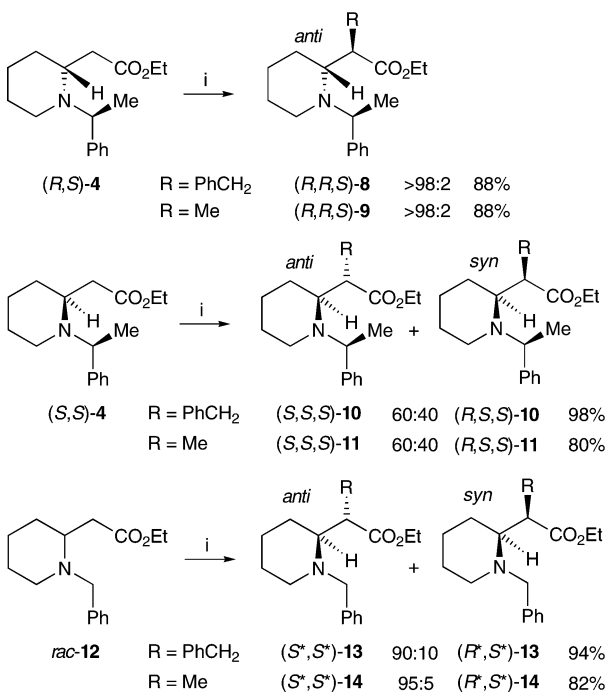
Scheme 3 *Reagents and conditions*: i, $Pd(OH)_2/C$, $NH_4^+HCO_2^-$, EtOH, reflux, 90 min; ii, Boc_2O, Et_3N, CH_2Cl_2, rt, 16 h.

(*R*,*S*)-**5** was similarly deprotected to amine (*R*)-**6** (86% yield). An alternative *N*-deprotection method using reaction with α-chloroethyl chloroformate was lower yielding.

Stereoselective alkylation of cyclic β-amino esters

Next, we studied the stereoselectivity of the alkylation of enolates derived from the cyclic β-amino esters. The *anti*-stereoselective alkylation of enolates generated from amino esters such as (*R*,*S*)-**4** was first reported by Lhommet *et al.* in 1999.[20] Since enolate alkylations of (*R*,*S*)-**4** show better stereoselectivity than similar reactions of *N*-Boc amino esters such as (*R*)- or (*S*)-**7**,[4,6] we speculated that the two stereogenic centres in amino ester (*R*,*S*)-**4** were working together to produce high stereoselectivity. To specifically probe this, the stereoselectivity of enolate alkylation of diastereomeric amino esters (*R*,*S*)-**4** and (*S*,*S*)-**4** was studied; additionally, we included the achiral *N*-benzyl group (amino ester **12**) as part of this study.

Alkylations of amino esters (*R*,*S*)-**4**, (*S*,*S*)-**4** and **12** were carried out by deprotonation using LHMDS at −78 °C and subsequent reaction with benzyl bromide or methyl iodide (Scheme 4). The ratio of diastereomeric alkylation products was determined from the ^1H NMR spectra of the crude products; the yields quoted are of single diastereomers (**8**/**9**) or of mixtures of diastereomeric adducts (**10**/**11**/**13**/**14**) after chromatography. Further



Scheme 4 *Reagents and conditions*: i, (a) LHMDS, −78 °C, THF, 1 h; (b) $PhCH_2Br$ or MeI.

chromatography of the benzylated adducts **10** led to a 48% yield of the major diastereomer which was identified as (*S*,*S*,*S*)-**10** by X-ray crystallography (Fig. 2). A series of *N*-deprotections and NMR spectroscopic correlations (detailed in the Supporting Information†) enabled assignment of the stereochemistry of all of the benzyl adducts and the methyl adducts were assigned by analogy.

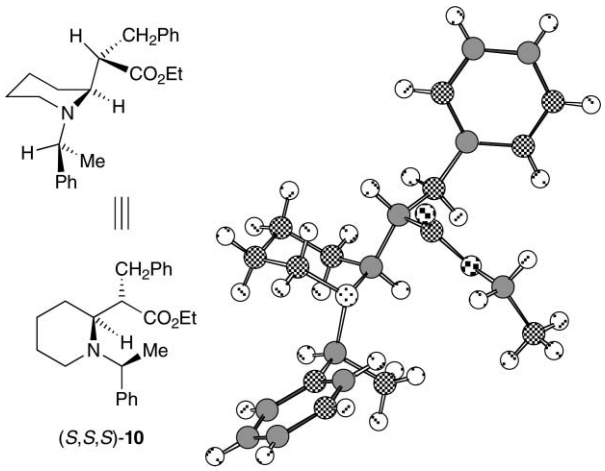


Fig. 2 X-Ray crystal structure of *anti*-**10**.

As shown in Scheme 4, alkylation of amino ester (*R*,*S*)-**4** proceeded with complete *anti*-stereoselectivity (as reported earlier by Lhommet *et al.*[20]) to give adducts (*R*,*R*,*S*)-**8** and (*R*,*R*,*S*)-**9**.[21] This was clearly the situation in which the two stereogenic centres worked together since the analogous reactions with amino ester (*S*,*S*)-**4** generated 60 : 40 mixtures of diastereomeric adducts **10** and **11**. Removal of the stereogenic centre on the *N*-alkyl substituent restored high *anti*-stereoselectivity as shown by the alkylations of amino ester **12** which proceeded in ≥90 : 10 diastereoselectivity. Thus, for alkylations of enolates derived from cyclic β-amino esters, good levels of stereocontrol (~90 : 10 diastereoselectivity) can be obtained using *N*-benzyl- or *N*-Boc-protection[4,6] but *complete* stereoselectivity (>98 : 2) requires the use of the appropriately configured *N*-α-methylbenzyl substituent. Such a pronounced difference with enolate alkylations of the two diastereomers is significant since stereoselective routes to amino esters such as (*S*,*S*)-**4** *via* the conjugate addition of chiral lithium amides to αβ-unsaturated esters (followed by cyclisation) have already been established by ourselves[2] and Davies and co-workers.[11]

Concise total synthesis of a (−)-sparteine surrogate

In order to demonstrate the usefulness of the synthesis and alkylation of cyclic β-amino esters such as (*R*,*S*)-**4**, we elected to carry out the asymmetric synthesis of a (−)-sparteine surrogate (Fig. 3). The intention was to use our new methodology to complete the synthesis in significantly fewer steps than the previously published asymmetric routes.

Due to the lack of availability of (+)-sparteine, we have been actively engaged in the search for a chiral ligand that behaves as the enantiomer of naturally occurring (−)-sparteine. Our efforts culminated with the disclosure in 2002 of a suitable (+)-sparteine surrogate which could be readily synthesised in three steps from

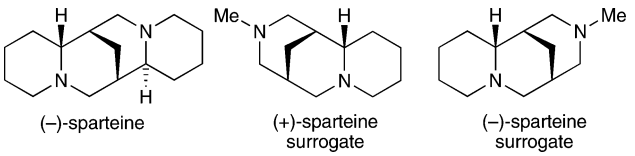
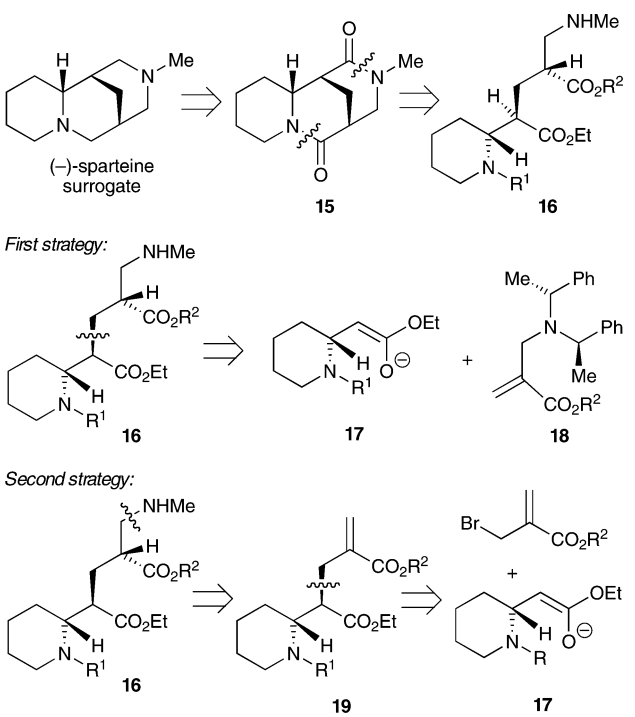


Fig. 3 Structures of (−)-sparteine and the (+)- and (−)-sparteine surrogates.

(−)-cytisine.[22] Work from our group has demonstrated that the (+)-sparteine surrogate behaves in an enantiocomplementary fashion in a wide range of reactions.[23] In addition, other groups have utilised the (+)-sparteine surrogate in syntheses of *P*-stereogenic phosphine boranes, chiral diarylmethanes and (−)-kainic acid.[24] In recent work, we have shown that *sec*-butyllithium complexes of the (+)-sparteine surrogate are not only more reactive than their (−)sparteine counterparts but also more effective in asymmetric catalysis using sub-stoichiometric amounts of chiral diamine ligands.[25] As a result, the development of an efficient route to the (−)-sparteine surrogate is currently of much importance. This is exacerbated by the fact that the previous asymmetric routes for the preparation of the (−)-sparteine surrogate are either long or low yielding.[26]

Our retrosynthetic analysis of the (−)-sparteine surrogate is shown in Scheme 5. It was envisaged that bis-lactam **15** would be a suitable precursor to the (−)-sparteine surrogate. Disconnection of the amides in bis-lactam **15** reveals a bis-β-amino ester **16** which we anticipated disconnecting in two different ways. In the first strategy, a chiral β-amino ester enolate **17** would be reacted with Michael acceptor **18**. By analogy with the highly *anti*-selective enolate alkylations shown in Scheme 4, it was hoped that such a Michael reaction would proceed with high *anti*-stereoselectivity.

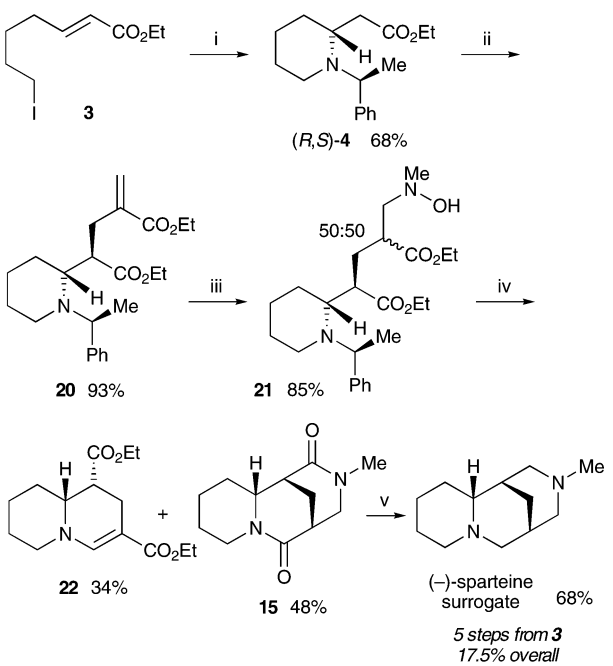


Scheme 5

For stereocontrol at the more remote stereogenic centre, we planned using a chiral auxiliary attached to the amine in the Michael acceptor, as precedented in methodology developed by a group at Pfizer for the synthesis of structurally related β-amino acid derivatives.[27] In the event, this strategy was flawed as we were unable to bring about reaction of the enolate **17** with Michael acceptor **18** under a range of conditions.

Thus, the second strategy (Scheme 5) was eventually adopted. Here, the plan was to introduce an amino substituent by conjugate addition to the αβ-unsaturated ester functionality in amino ester **19**. Amino ester **19** would itself be generated by stereoselective alkylation chiral β-amino ester enolate **17** using an appropriate α-bromomethyl acrylate. Originally, we had hoped to achieve stereocontrol in the amine conjugate addition reaction using a Davies-style chiral lithium amide nucleophile but no products were obtained from any of our attempts. In the end, however, we had to accept a stereorandom incorporation of this amino functionality (*vide infra*).

Our five-step synthesis of the (−)-sparteine surrogate using the second strategy from Scheme 5 is summarised in Scheme 6. Thus, reaction of (*S*)-α-methylbenzylamine with iodo ester **3** under the optimised conditions (Et_3N, DMF, room temperature, 64 hours) gave a 68% yield of cyclic β-amino ester (*R*,*S*)-**4** after chromatography. Next, enolate formation and stereoselective alkylation with ethyl (α-bromomethyl)acrylate proceeded efficiently to give a single diastereomeric alkylated β-amino ester **20** in 93% yield. The second amino functionality in the (−)-sparteine surrogate was introduced using conjugate addition of *N*-methyl hydroxylamine to the αβ-unsaturated ester.[28] The reaction was high yielding (85% yield of **21**) but, unsurprisingly, there was no stereocontrol at the newly-formed stereogenic centre and an inseparable 50 : 50 mixture of diastereomers was generated. All our attempts to introduce chiral lithium amides or simple amines in conjugate addition reactions with **20** were unsuccessful.



Scheme 6 *Reagents and conditions*: i, (*S*)-α-methylbenzylamine, Et_3N, DMF, rt, 64 h; ii, (a) LHMDS, −78 °C, THF, 1 h; (b) ethyl (α-bromomethyl)acrylate; iii, MeHNOH·HCl, Et_3N, CH_2Cl_2, rt, 64 h; iv, $Pd(OH)_2/C$, $NH_4^+HCO_2^-$, EtOH, reflux, 16 h; v, $LiAlH_4$, THF, reflux, 16 h.

Our intention was to carry out transfer hydrogenolysis of **21** using $Pd(OH)_2/C$ and ammonium formate with a view to cleaving both the *N*-α-methylbenzyl and N–O bonds. If successful, this should facilitate double lactamisation to generate the required bis-lactam **15**. Only one of the diastereomeric hydroxylamines **21** possesses the correct relative stereochemistry for bis-lactamisation and we were thus delighted to observe formation of the desired bis-lactam **15** which was isolated in 48% yield after chromatography. Another product was isolated from this reaction and it was eventually identified as a single diastereomer of enamine ester **22** (34% isolated yield).[29] The formation of enamine ester **22** was unexpected and presumably proceeds *via* *N*-α-methylbenzyl cleavage and cyclisation of the unprotected amine onto an imine (that could form by, for example, elimination of the hydroxyl group from the hydroxylamine). Subsequent elimination of the amine would then give the enamine ester. The relative stereochemistry of enamine ester **22** has not been unequivocally proven but is assumed to be as shown in Scheme 6 based on the relative stereochemistry of **21**.

Finally, $LiAlH_4$ reduction of both lactam units in bis-lactam **15** led to the efficient formation of the (−)-sparteine surrogate {$[a]_D$ −29.6 (*c* 1.0 in EtOH) ($[a]_D$ +26.5 (*c* 1.0 in EtOH) for the (+)-sparteine surrogate[26b])}, isolated in 68% yield after Kugelrohr distillation. This five-step synthesis of the (−)-sparteine surrogate from iodo ester **3** is the most efficient (17.5% overall yield) and shortest synthesis to date. The generation of the mixture of diastereomeric hydroxylamines **21** and their subsequent transformation into two products, **22** and **15**, which then need to be separated have thus far precluded synthesis on a multi-gram scale.

Conclusion

To summarise, we have developed a convenient chiral auxiliary-mediated cyclisation method for the preparation of cyclic β-amino esters (*R*,*S*)-**4**. Furthermore, we have exemplified the synthetic utility of the stereoselective alkylation of amino esters such as (*R*,*S*)-**4** with the shortest synthesis of the (−)-sparteine surrogate. We hope that the methodology reported herein will be of use to those involved in the asymmetric synthesis of piperidinyl-containing natural products and pharmaceutical candidates.

Experimental

General

Water is distilled water. Et_2O and THF were freshly distilled from benzophenone ketyl whereas CH_2Cl_2 was freshly distilled from CaH_2. Petrol refers to the fraction of petroleum ether with a boiling point range of 40–60 °C. All reactions were carried out under O_2-free N_2 or Ar using oven-dried and/or flame dried glassware. Flash column chromatography was carried out using Fluka silica gel 60 (0.035–0.070 mm particle size). Thin layer chromatography was carried out using Merck F_{254} alumina-backed silica plates. Proton (270 MHz or 400 MHz) and carbon (67.9

or 100.6 MHz) NMR spectra were recorded using an internal deuterium lock. All samples were recorded in $CDCl_3$. Chemical shifts are quoted in parts per million and referenced to $CHCl_3$ (7.27). Carbon NMR spectra were recorded with broadband proton decoupling and were assigned using DEPT experiments. Infra-red spectra were recorded on an FT-IR spectrometer. Optical rotations were recorded at room temperature (20 °C) and $[\alpha]_D$ measurements are given in units of 10^{-1} deg cm^2 g^{-1}. For Kügelrohr distillation, the temperatures quoted correspond to the oven temperatures.

General procedure for cyclisation of iodoester

A solution of chiral amine (3.85 mmol), iodoester **3** (1.00 g, 3.50 mmol) and Et_3N (3.85 mmol) in DMF (20 mL) under N_2 was stirred at rt for 64 h. Water (20 mL) and Et_2O (20 mL) were added and the two layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

Ethyl {(2*R*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}acetate (*R*,*S*)-4 and ethyl {(2*S*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}acetate (*S*,*S*)-4

Using the general procedure for cyclisation, (*S*)-α-methylbenzylamine (0.5 mL, 3.85 mmol), iodoester **3** (1.00 g, 3.5 mmol) and Et_3N (0.55 mL, 3.85 mmol) in DMF (20 mL) gave the crude product which contained a 75 : 25 mixture (by ^{1}H NMR spectroscopy) of amino esters (*R*,*S*)-**4** and (*S*,*S*)-**4**. Purification by flash chromatography with petrol–EtOAc (9 : 1) as eluent gave amino ester (*R*,*S*)-**4** (720 mg, 68%) as a pale yellow oil, $[\alpha]_D$ −36.1 (*c* 1.0 in $CHCl_3$); R_F(9 : 1 petrol–EtOAc) 0.3; IR ($CDCl_3$): 1730 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (dd, J = 8.0, 1.5 Hz, 2H), 7.30 (td, J = 8.0, 1.5 Hz, 2H), 7.22 (tt, J = 8.0, 1.5 Hz, 1H), 4.20–4.12 (m, 2H), 3.70 (q, J = 6.5 Hz, 1H), 3.51 (dq, J = 9.0, 4.5 Hz, 1H), 2.63–2.52 (m, 2H), 2.32 (dt, J = 12.0, 5.0 Hz, 1H), 2.21 (ddd, J = 12.0, 9.0, 4.0 Hz, 1H), 1.82–1.74 (m, 1H), 1.63–1.52 (m, 2H), 1.50–1.36 (m, 3H), 1.31 (d, J = 6.5 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 173.1 (C=O), 146.1 (*ipso*-Ph), 128.0 (Ph), 127.2 (Ph), 126.4 (Ph), 60.2 (CH_2), 59.2 (C), 52.3 (CH), 44.9 (CH_2), 32.0 (CH_2), 29.9 (CH_2), 25.6 (CH_2), 20.7 (Me), 17.7 (CH_2), 14.1 (Me); MS (CI, NH_3) *m*/*z* 276 [(M + H)$^+$, 100], 188 (80), 172 (40), 105 (50); HRMS (CI, NH_3) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{25}NO_2$, 276.1964; found, 276.1967 and amino ester (*S*,*S*)-**4** (240 mg, 23%) as a pale yellow oil, $[\alpha]_D$ −6.5 (*c* 1.0 in $CHCl_3$); R_F(9:1 petrol–EtOAc) 0.15; IR (film): 1730 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.27 (m, 4H), 7.25–7.20 (m, 1H), 4.07 (q, J = 7.0 Hz, 2H), 3.84 (q, J = 6.5 Hz, 1H), 3.51 (dq, J = 9.0, 4.5 Hz, 1H), 2.69 (dd, J = 14.0, 4.5 Hz, 1H), 2.63–2.51 (m, 2H), 2.45 (dd, J = 14.0, 9.0 Hz, 1H), 1.71–1.38 (m, 6H), 1.34 (d, J = 6.5 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 172.9 (C=O), 144.8 (*ipso*-Ph), 128.1 (Ph), 127.3 (Ph), 126.6 (Ph), 60.0 (CH_2), 59.0 (CH), 52.6 (CH), 43.4 (CH_2), 32.7 (CH_2), 28.9 (CH_2), 24.9 (CH_2), 21.2 (Me), 20.1 (CH_2), 14.1 (Me); MS (EI) *m*/*z* 275 [M$^+$, 20], 260 (65), 105 (100); HRMS (EI) *m*/*z* M$^+$ calcd for $C_{17}H_{25}NO_2$, 275.1885; found, 275.1884.

Ethyl {(2*R*)-1-[(1*S*)-1-(1-naphthyl)ethyl]piperidin-2-yl}acetate (*R*,*S*)-5 and ethyl {(2*S*)-1-[(1*S*)-1-(1-naphthyl)ethyl]piperidin-2-yl}acetate (*S*,*S*)-5

Using the general procedure for cyclisation, (*S*)-(1-naphthyl)-ethylamine (0.32 mL, 1.95 mmol), iodoester **3** (500 mg, 1.77 mmol) and Et_3N (0.21 mL, 1.95 mmol) in DMF (10 mL) gave the crude product which contained an 85 : 15 mixture (by ^{1}H NMR spectroscopy) of amino esters (*R*,*S*)-**5** and (*S*,*S*)-**5**. Purification by flash chromatography with petrol–EtOAc (9 : 1) as eluent gave amino ester (*R*,*S*)-**5** (365 mg, 63%) as a pale yellow oil, $[\alpha]_D$ −84.2 (*c* 1.0 in $CHCl_3$); R_F(9 : 1 petrol–EtOAc) 0.25; IR ($CDCl_3$): 1720 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (br s, 1H), 7.89–7.84 (m, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.66 (br d, J = 6.0 Hz, 1H), 7.52–7.43 (m, 3H), 4.49–4.36 (m, 1H), 4.25–4.13 (m, 2H), 3.73–3.69 (m, 1H), 2.79 (dd, J = 13.5, 3.5 Hz, 1H), 2.68 (dd, J = 13.5, 10.0 Hz, 1H), 2.40 (dt, J = 12.0, 4.5 Hz, 1H), 2.25 (ddd, J = 12.0, 10.0, 3.0 Hz, 1H), 1.92–1.84 (m, 1H), 1.69–1.64 (m, 1H), 1.59–1.26 (m, 4H), 1.49 (d, J = 6.5 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 173.3 (C=O), 141.4 (*ipso*-Ar), 134.0 (*ipso*-Ar), 131.6 (*ipso*-Ar), 128.6 (Ar), 127.1 (Ar), 125.4 (Ar), 125.2 (Ar), 125.1 (Ar), 124.6 (Ar), 124.0 (Ar), 60.3 (CH_2), 57.0 (br, CH), 52.1 (CH), 45.1 (CH_2), 30.6 (CH_2), 29.7 (CH_2), 25.7 (CH_2), 20.2 (CH_2), 18.1 (Me), 14.2 (Me); MS (CI, NH_3) *m*/*z* 326 [(M + H)$^+$, 100], 238 (10); HRMS (CI, NH_3) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{27}NO_2$, 326.2120; found, 326.2125 and amino ester (*S*,*S*)-**5** (40 mg, 7%) as a pale yellow oil, $[\alpha]_D$ +5.5 (*c* 0.75 in $CHCl_3$); R_F(9 : 1 petrol–EtOAc) 0.15; IR ($CDCl_3$): 1720 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57–8.54 (m, 1H), 7.87–7.82 (m, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.57–7.54 (m, 1H), 7.50–7.39 (m, 3H), 4.44 (q, J = 6.5 Hz, 1H), 3.95 (q, J = 7.5 Hz, 2H), 3.47–3.41 (m, 1H), 2.92 (dt, J = 13.0, 3.0 Hz, 1H), 2.71 (dd, J = 13.5, 5.0 Hz, 1H), 2.54 (dt, J = 13.0, 2.5 Hz, 1H), 2.50 (dd, J = 13.5, 9.0 Hz, 1H), 1.77–1.25 (m, 6H), 1.49 (d, J = 6.5 Hz, 3H), 1.08 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 173.1 (C=O), 141.3 (*ipso*-Ar), 134.2 (*ipso*-Ar), 131.5 (*ipso*-Ar), 128.7 (Ar), 127.2 (Ar), 125.5 (Ar), 125.2 (Ar), 125.15 (Ar), 124.9 (Ar), 124.4 (Ar), 60.0 (CH_2), 58.3 (CH), 51.9 (CH), 42.7 (CH_2), 31.4 (CH_2), 27.7 (CH_2), 24.6 (CH_2), 21.0 (Me), 19.2 (CH_2), 14.0 (Me); MS (CI, NH_3) *m*/*z* 326 [(M + H)$^+$, 100], 238 (30); HRMS (CI, NH_3) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{27}NO_2$, 326.2120; found, 326.2122.

(*R*)-Ethyl piperidin-2-ylacetate (*R*)-6

A suspension of 20% $Pd(OH)_2$ on C (35 mg, 0.04 mmol), amino ester (*R*,*S*)-**4** (200 mg, 0.74 mmol) and $NH_4^+HCO_2^-$ (140 mg, 2.22 mmol) in EtOH (2 mL) was stirred and heated at reflux under N_2 for 90 min. After being allowed to cool to rt, the solids were removed by filtration through Celite and washed with Et_2O (50 mL). Then, 2 M $NH_4OH_{(aq)}$ (10 mL) was added to the filtrate and the two layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by Kügelrohr distillation gave amine (*R*)-**6** (104 mg, 84%, >90% ee by NMR spectroscopy in the presence of 7.0 equiv. (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) as a colourless oil, bp 80–85 °C/2.0 mmHg (lit.,[26b] 85–90 °C/1.5 mmHg); $[\alpha]_D$ −10.8 (*c* 1.0 in $CHCl_3$); R_F(9 : 1 CH_2Cl_2–MeOH) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.08 (q,

$J = 7.0$ Hz, 2H), 3.04–2.95 (m, 1H), 2.90–2.81 (m, 1H), 2.60 (td, $J = 11.5$, 3.0 Hz, 1H), 2.33–2.28 (m, 2H), 2.10 (br s, 1H), 1.75–1.64 (m, 1H), 1.58–1.46 (m, 2H), 1.40–1.27 (m, 2H), 1.23 (t, $J = 7.0$ Hz, 3H), 1.21–1.12 (m, 1H). Spectroscopic data consistent with that reported in the literature.[26b]

(*R*)-*tert*-Butyl 2-(2-ethoxy-2-oxoethyl)piperidin-1-carboxylate (*R*)-7

A solution of Boc_2O (421 mg, 1.93 mmol) in CH_2Cl_2 (6 mL) was added dropwise to a stirred solution of amine (*R*)-**6** (150 mg, 0.88 mmol) and Et_3N (1.22 mL, 8.80 mmol) in CH_2Cl_2 (6 mL) at rt under N_2. The resulting solution was stirred at rt for 16 h. Then, 2 M $HCl_{(aq)}$ (5 mL) was added and the two layers were separated. The organic layer was washed with brine (2 × 5 mL) and water (5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography with petrol–EtOAc (3 : 1) as eluent gave *N*-Boc amino ester (*R*)-**7** (212 mg, 89%) as a colourless oil, $[\alpha]_D$ +7.4 (*c* 1.0 in $CHCl_3$); R_F(3 : 1 CH_2Cl_2–MeOH) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.72–4.62 (m, 1H), 4.09 (q, $J = 7.0$ Hz, 2H), 4.00–3.91 (m, 1H), 2.76 (br t, $J = 13.0$ Hz, 1H), 2.55 (dd, $J = 14.0$, 7.5 Hz, 1H), 2.50 (dd, $J = 14.0$, 8.0 Hz, 1H), 1.67–1.47 (m, 6H), 1.43 (s, 9H), 1.23 (t, $J = 7.0$ Hz, 3H), 1.21–1.12 (m, 1H). Spectroscopic data consistent with that reported in the literature.[30]

General procedure for alkylation of amino esters

LHMDS (1.06 M solution in THF, 1.30 mmol) was added dropwise to a stirred solution of the amino ester (250 mg, 0.90 mmol) in THF (6 mL) at −78 °C under N_2. After stirring at −78 °C for 1 h, the alkyl halide (1.30 mmol) was added dropwise. The resulting solution was allowed to warm to rt over 4 h and stirred at rt for 12 h. Then, the solvent was evaporated under reduced pressure. The residue was partitioned between water (10 mL) and 1 : 1 Et_2O–CH_2Cl_2 (10 mL). The two layers were separated and the aqueous layer was extracted with Et_2O–CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil.

Ethyl (2*R*)-3-phenyl-2-{(2*R*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}propionate (*R*,*R*,*S*)-8

Using the general procedure for alkylation, amino ester (*R*,*S*)-**4** (183 mg, 0.66 mmol), LHMDS (0.94 mL of a 1.06 M solution in THF, 1.00 mmol) and benzyl bromide (0.12 mL, 1.00 mmol) in THF (3.7 mL) gave the crude product as a single diastereomer (by ^{1}H NMR spectroscopy). Purification by flash chromatography with petrol–EtOAc–Et_3N (90 : 10 : 1) as eluent gave benzylated amino ester (*R*,*R*,*S*)-**8** (212 mg, 88%) as a colourless oil, $[\alpha]_D$ −6.4 (*c* 1.0 in CH_2Cl_2); R_F(9 : 1 petrol–EtOAc) 0.35; IR ($CHCl_3$): 1720 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (d, $J = 7.5$ Hz, 2H), 7.34 (t, $J = 7.5$ Hz, 2H), 7.28–7.10 (6H, m), 4.30 (q, $J = 6.5$ Hz, 1H), 4.18–3.97 (m, 2H), 3.25 (q, $J = 7.0$ Hz, 1H), 2.96 (d, $J = 7.0$ Hz, 2H), 2.94–2.88 (m, 1H), 2.68 (ddd, $J = 12.5$, 6.0, 3.5 Hz, 1H), 2.40 (ddd, $J = 12.5$, 8.5, 3.0 Hz, 1H), 1.79–1.02 (m, 6H), 1.34 (d, $J = 6.5$ Hz, 3H), 1.16 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 174.1 (C=O), 144.6 (*ipso*-Ph), 140.9 (*ipso*-Ph), 128.8 (Ph), 128.3 (Ph), 128.0 (Ph), 127.6 (Ph), 126.5 (Ph), 125.9 (Ph), 60.2 (CH_2), 58.9 (CH), 55.4 (CH), 49.0 (CH), 44.1 (CH_2), 31.9 (CH_2), 25.1 (CH_2), 24.1 (CH_2), 23.3 (CH_2), 14.1 (Me), 12.7 (Me); MS (CI, NH_3) *m*/*z* 366 [(M + H)$^+$, 100], 188 (40). The optical rotation of benzylated amino ester (*R*,*R*,*S*)-**8** was erroneously reported with a positive sign.[20]

Ethyl (2*R*)-{(2*R*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}propionate (*R*,*R*,*S*)-9

Using the general procedure for alkylation, amino ester (*R*,*S*)-**4** (250 mg, 0.90 mmol), LHMDS (1.28 mL of a 1.06 M solution in THF, 1.30 mmol) and MeI (85 μL, 1.36 mmol) in THF (6 mL) gave the crude product as a single diastereomer (by ^{1}H NMR spectroscopy). Purification by flash chromatography with petrol–EtOAc–Et_3N (90 : 10 : 1) as eluent gave methylated amino ester (*R*,*R*,*S*)-**9** (224 mg, 88%) as a colourless oil, $[\alpha]_D$ −12.2 (*c* 1.1 in CH_2Cl_2); R_F(9 : 1 petrol–EtOAc) 0.3; IR ($CHCl_3$): 1725 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, $J = 7.5$ Hz, 2H), 7.30 (t, $J = 7.5$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 1H), 4.26–4.05 (m, 3H), 3.07 (quintet, $J = 7.0$ Hz, 1H), 2.93–2.85 (m, 1H), 2.60 (ddd, $J = 12.0$, 6.0, 3.5 Hz, 1H), 2.33 (ddd, $J = 12.0$, 9.0, 3.0 Hz, 1H), 1.78–1.20 (m, 6H), 1.32 (d, $J = 6.5$ Hz, 3H), 1.26 (t, $J = 7.0$ Hz, 3H), 1.14 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 175.4 (C=O), 144.7 (*ipso*-Ph), 127.9 (Ph), 127.5 (Ph), 126.3 (Ph), 60.2 (CH_2), 58.8 (CH), 54.9 (CH), 44.3 (CH_2), 40.1 (CH), 24.7 (CH_2), 24.6 (CH_2), 23.5 (CH_2), 14.2 (Me), 12.0 (Me), 10.6 (Me); MS (CI, NH_3) *m*/*z* 290 [(M + H)$^+$, 100], 188 (20); HRMS (CI, NH_3) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{27}NO_2$, 290.2120; found, 290.2121. The optical rotation of benzylated amino ester (*R*,*R*,*S*)-**9** was erroneously reported with a positive sign.[20]

Ethyl (2*S*)-3-phenyl-2-{(2*S*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}propionate *anti*-10 and ethyl (2*R*)-3-phenyl-2-{(2*S*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}propionate *syn*-10

Using the general procedure for alkylation, amino ester (*S*,*S*)-**4** (199 mg, 0.72 mmol), LHMDS (1.03 mL of a 1.06 M solution in THF, 1.09 mmol) and benzyl bromide (0.13 mL, 1.09 mmol) in THF (6 mL) gave the crude product as a 60 : 40 mixture of benzylated amino esters *anti*-**10** and *syn*-**10** (by ^{1}H NMR spectroscopy). Purification by flash chromatography with petrol–EtOAc (97 : 3) as eluent gave benzylated amino ester *anti*-**10** (127 mg, 48%) as a white solid, mp 69–71 °C; $[\alpha]_D$ −44.8 (*c* 1.0 in CH_2Cl_2); R_F(9 : 1 petrol–EtOAc) 0.3; IR ($CHCl_3$): 1725 (C=O) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ: 7.30–7.10 (10H, m), 4.13 (q, $J = 6.5$ Hz, 1H), 4.05 (q, $J = 7.0$ Hz), 3.47–3.25 (m, 2H), 2.98–2.80 (m, 3H), 2.23 (br d, $J = 13.5$ Hz, 1H), 1.75–1.50 (m, 6H), 1.31 (d, $J = 6.5$ Hz, 3H), 1.01 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 174.5 (C=O), 145.9 (*ipso*-Ph), 139.9 (*ipso*-Ph), 128.7 (Ph), 128.3 (Ph), 128.0 (Ph), 127.2 (Ph), 126.5 (Ph), 126.1 (Ph), 59.7 (CH_2), 57.2 (CH), 55.7 (CH), 49.1 (CH), 42.9 (CH_2), 35.5 (CH_2), 21.7 (CH_2), 21.5 (Me), 20.4 (CH_2), 19.9 (CH_2), 14.1 (Me); MS (CI, NH_3) *m*/*z* 366 [(M + H)$^+$, 80], 262 (20), 188 (100), 105 (10), 84 (35); HRMS (CI, NH_3) *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{31}NO_2$, 366.2433; found, 366.2428, a 15 : 85 mixture (by ^{1}H NMR spectroscopy) of benzylated amino esters *anti*-**10** and *syn*-**10** (90 mg, 34%) as a colourless oil and benzylated amino ester *syn*-**10** (44 mg, 16%) as a colourless oil, $[\alpha]_D$ +2.9 (*c* 1.75 in CH_2Cl_2); R_F(9 : 1 petrol–EtOAc) 0.3; IR ($CHCl_3$): 1720

(C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.12 (10H, m), 4.22 (q, $J = 6.5$ Hz, 1H), 3.98 (q, $J = 7.0$ Hz), 3.47–3.25 (m, 3H), 2.80 (dd, $J = 13.5$, 11.0 Hz, 1H), 2.78–2.67 (m, 1H), 2.40 (br d, $J = 14.5$ Hz, 1H), 1.85–1.47 (m, 6H), 1.34 (d, $J = 6.5$ Hz, 3H), 1.04 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 175.2 (C=O), 146.4 (*ipso*-Ph), 140.5 (*ipso*-Ph), 128.8 (Ph), 128.2 (Ph), 127.2 (Ph), 126.7 (Ph), 125.9 (Ph), 59.9 (CH_2), 57.5 (CH), 54.8 (CH), 48.8 (CH), 42.5 (CH_2), 36.9 (CH_2), 22.6 (CH_2), 22.4 (Me), 20.2 (CH_2), 19.9 (CH_2), 14.0 (Me) (one Ph resonance not resolved); MS (CI, NH_3) m/z 366 [$(M + H)^+$, 100], 262 (20), 188 (70), 84 (30); HRMS (CI, NH_3) m/z $[M + H]^+$ calcd for $C_{24}H_{31}NO_2$, 366.2433; found, 366.2428.

Crystal structure determination of ethyl (2*S*)-3-phenyl-2-{(2*S*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}propionate *anti*-10

Crystal data. $C_{24}H_{31}NO_2$, $M = 365.50$, monoclinic, $a = 7.7573(6)$, $b = 6.5351$, $c = 20.5605(15)$ Å, $\beta = 93.341(2)°$, $U = 1040.54(14)$ Å^3, $T = 115(2)$ K, space group $P2_1$, $Z = 2$, μ(Mo-Kα) = 0.073 mm^{-1}, 7226 reflections measured, 4564 unique ($R_{int} = 0.0193$) which were used in all calculations. The final $R1$ was 0.0373 ($I > 2\sigma_I$) and w$R2$ was 0.0889 (all data). CCDC reference number 623452.‡

Ethyl (2*S*)-{(2*S*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}propionate *anti*-11 and ethyl (2*R*)-{(2*S*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}propionate *syn*-11

Using the general procedure for alkylation, amino ester (*S*,*S*)-**4** (204 mg, 0.74 mmol), LHMDS (1.05 mL of a 1.06 M solution in THF, 1.11 mmol) and MeI (70 μL, 1.12 mmol) in THF (6 mL) gave the crude product as a 60 : 40 mixture of methylated amino esters *anti*-**11** and *syn*-**11** (by ^1H NMR spectroscopy). Purification by flash chromatography with petrol–EtOAc (95 : 5) as eluent gave a 65 : 35 mixture (by ^1H NMR spectroscopy) of methylated amino esters *anti*-**11** and *syn*-**11** (172 mg, 80%) as a colourless oil, R_F(9 : 1 petrol–EtOAc) 0.3; IR ($CHCl_3$): 1720 (C=O) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ: 7.34–7.16 (m, 5H), 4.21–4.06 (m, 3H), 3.28–3.11 (m, 2H), 2.87 (ddd, $J = 14.5$, 11.5, 3.0, 0.65H), 2.55 (ddd, $J = 14.5$, 11.5, 3.0, 0.35H), 2.30 (dt, $J = 14.5$, 4.5, 0.35H), 2.24 (dt, $J = 14.5$, 4.0, 0.65H), 1.75–1.42 (m, 6H), 1.25–1.12 (m, 6H), 1.14 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ: 176.7 (C=O), 176.2 (C=O), 146.5 (*ipso*-Ph), 146.0 (*ipso*-Ph), 128.2 (Ph), 128.0 (Ph), 127.2 (Ph), 126.6 (Ph), 126.5 (Ph), 60.0 (CH_2), 59.9 (CH_2), 57.3 (CH), 57.1 (CH), 56.2 (CH), 55.3 (CH), 43.0 (CH_2), 42.5 (CH_2), 40.3 (CH), 39.7 (CH), 22.6 (CH_2), 22.4 (Me), 21.6 (Me), 20.8 (CH_2), 20.4 (CH_2), 20.3 (CH_2), 20.0 (CH_2), 15.5 (Me), 14.3 (Me), 14.2 (Me), 14.0 (Me); MS (CI, NH_3) m/z 290 [$(M + H)^+$, 100], 188 (80), 105 (20), 84 (35); HRMS (CI, NH_3) m/z $[M + H]^+$ calcd for $C_{18}H_{27}NO_2$, 290.2122; found, 290.2121.

Ethyl (1-benzylpiperidin-2-yl)acetate *rac*-12

A stirred solution of benzylamine (0.55 mL, 4.98 mmol), iodoester **3** (1.27 g, 4.49 mmol) and Et_3N (0.70 mL, 4.98 mmol) in EtOH (12.5 mL) under N_2 was heated at reflux for 16 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure. Water (20 mL) was added and the mixture was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with water (30 mL), 5% $Na_2S_2O_{3(aq)}$ (30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography with petrol–EtOAc (9 : 1) as eluent gave amino ester *rac*-**12** (878 mg, 75%) as a pale yellow oil, R_F(9 : 1 petrol–EtOAc) 0.35; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.18 (m, 5H), 4.13 (q, $J = 7.0$ Hz, 2H), 3.80 (d, $J = 13.5$ Hz, 1H), 3.36 (d, $J = 13.5$ Hz, 1H), 3.01–2.93 (m, 1H, CHN), 2.71 (dd, $J = 14.5$, 4.5 Hz, 1H), 2.66–2.58 (m, 1H), 2.44 (dd, $J = 14.5$, 8.0 Hz, 1H), 2.21–2.13 (m, 1H), 1.81–1.70 (m, 1H), 1.69–1.58 (m, 1H), 1.58–1.36 (m, 4H), 1.24 (t, $J = 7.0$ Hz, 3H). Spectroscopic data consistent with that reported in the literature.[16]

Ethyl (2*S**)-2-phenyl-3-[(2*S**)-1-benzylpiperidin-2-yl]propionate *anti*-13 and ethyl (2*R**)-2-phenyl-3-[(2*S**)-1-benzylpiperidin-2-yl]propionate *syn*-13

Using the general procedure for alkylation, amino ester *rac*-**12** (212 mg, 0.81 mmol), LHMDS (1.15 mL of a 1.06 M solution in THF, 1.21 mmol) and benzyl bromide (0.15 mL, 1.21 mmol) in THF (6 mL) gave the crude product as a 90 : 10 mixture of benzylated amino esters *anti*-**13** and *syn*-**13** (by ^1H NMR spectroscopy). Purification by flash chromatography with petrol–EtOAc (9 : 1) as eluent gave a 90 : 10 mixture (by ^1H NMR spectroscopy) of benzylated amino esters *anti*-**13** and *syn*-**13** (269 mg, 94%) as a colourless oil, R_F(9 : 1 petrol–EtOAc) 0.3; IR ($CHCl_3$): 1730 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.10 (10H, m), 4.11–3.94 (m, 3H), 3.52 (d, $J = 13.5$ Hz, 0.1H), 3.45 (d, $J = 13.5$ Hz, 0.9H), 3.26 (ddd, $J = 11.0$, 7.0, 3.0, 1H), 3.00 (dd, $J = 13.5$, 2.5, 1H), 2.92–2.77 (m, 2H), 2.73 (td, $J = 7.5$, 3.5 Hz, 1H), 2.29 (ddd, $J = 12.5$, 9.0, 3.5, 1H), 2.16 (ddd, $J = 12.5$, 9.0, 3.5, 1H), 1.78–1.34 (m, 6H), 1.10 (t, $J = 7.0$ Hz, 2.7H), 1.03 (t, $J = 7.0$ Hz, 0.3H); HRMS (CI, NH_3) m/z $[M + H]^+$ calcd for $C_{23}H_{29}NO_2$, 352.2277; found, 352.2279.

Ethyl (2*S**)-2-[(2*S**)-1-benzylpiperidin-2-yl]propionate *anti*-14 and ethyl (2*R**)-2-[(2*S**)-1-benzylpiperidin-2-yl]propionate *syn*-14

Using the general procedure for alkylation, amino ester *rac*-**12** (110 mg, 0.42 mmol), LHMDS (0.60 mL of a 1.06 M solution in THF, 0.63 mmol) and MeI (39 μL, 0.63 mmol) in THF (2.5 mL) gave the crude product as a 95 : 5 mixture of methylated amino esters *anti*-**14** and *syn*-**14** (by ^1H NMR spectroscopy). Purification by flash chromatography with petrol–EtOAc (9 : 1) as eluent gave a 95 : 5 mixture (by ^1H NMR spectroscopy) of methylated amino esters *anti*-**14** and *syn*-**14** (96 mg, 82%) as a colourless oil, R_F(9 : 1 petrol–EtOAc) 0.35; IR ($CHCl_3$): 1735 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.11 (m, 5H), 4.21–4.08 (m, 2H), 3.94 (d, $J = 13.5$ Hz, 0.95H), 3.76 (d, $J = 13.5$ Hz, 0.05H), 3.33 (d, $J = 13.5$ Hz, 0.95H), 3.21 (d, $J = 13.5$ Hz, 0.05H), 3.10 (quintet, $J = 7.0$ Hz, 1H), 2.85 (ddd, $J = 12.5$, 4.5, 3.5, 1H), 2.76–2.72 (m, 1H), 2.09 (ddd, $J = 12.5$, 9.5, 3.0, 1H), 1.71–1.63 (m, 1H), 1.55–1.20 (m, 5H), 1.24 (t, $J = 7.0$ Hz, 3H), 1.15 (d, $J = 7.0$ Hz, 3H); HRMS (CI, NH_3) m/z $[M + H]^+$ calcd for $C_{17}H_{25}NO_2$, 276.1964; found, 276.1963.

Diethyl (4*R*)-2-methylene-4-{(2*R*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}pentanedioate (*R*,*R*,*S*)-20

Using the general procedure for alkylation, amino ester (*R*,*S*)-**4** (125 mg, 0.46 mmol), LHMDS (0.66 mL of a 1.06 M solution

in THF, 0.69 mmol) and ethyl (α-bromomethyl)acrylate (134 mg, 0.69 mmol) in THF (3 mL) gave the crude product as a single diastereomer (by ^{1}H NMR spectroscopy). Purification by flash chromatography with petrol–EtOAc (9 : 1) as eluent gave alkylated amino ester (*R*,*R*,*S*)-**20** (165 mg, 93%) as a colourless oil, $[\alpha]_D$ −10.7 (*c* 1.0 in $CHCl_3$); R_F(9 : 1 petrol–EtOAc) 0.25; IR (film): 1720 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37 (br d, J = 7.5 Hz, 2H), 7.30 (br t, J = 7.5, Hz, 2H), 7.22 (br t, J = 7.5, Hz, 1H), 6.16 (d, J = 1.0 Hz, 1H), 5.57 (d, J = 1.0 Hz, 1H), 4.28 (q, J = 6.5 Hz, 1H), 4.24–4.02 (m, 4H), 3.30 (ddd, J = 12.0, 7.0, 3.0 Hz, 1H), 2.84 (td, J = 7.0, 3.5 Hz, 1H), 2.77 (ddd, J = 13.0, 8.0, 3.5 Hz, 1H), 2.66 (br d, J = 14.5 Hz, 1H), 2.54–2.44 (m, 2H), 1.76–1.37 (m, 6H), 1.31 (d, J = 6.5 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 173.9 (C=O), 166.8 (C=O), 145.0 (*ipso*-Ph), 138.5 (C), 127.9 (Ph), 127.6 (Ph), 126.6 (CH_2), 126.4 (Ph), 60.6 (CH_2), 60.1 (CH_2), 58.2 (CH), 55.9 (CH), 45.6 (CH), 43.6 (CH_2), 29.5 (CH_2), 23.9 (CH_2), 23.2 (CH_2), 22.5 (CH_2), 14.7 (Me), 14.2 (Me), 14.1 (Me); MS (CI, NH_3) m/z 388 [(M + H)$^+$, 100], 188 (40); HRMS (CI, NH_3) m/z [M + H]$^+$ calcd for $C_{23}H_{33}NO_4$, 388.2488; found, 388.2482.

(4*R*)-Diethyl 2-[(*N*-hydroxy-*N*-methylamino)methyl]-4-{(2*R*)-1-[(1*S*)-1-phenylethyl]piperidin-2-yl}pentanedioate 21

Et_3N (14 μL, 0.1 mmol) was added dropwise to a stirred solution of *N*-methylhydroxylamine hydrochloride (9 mg, 0.1 mmol) in THF (2 mL) at rt under N_2. After stirring for 10 min, a solution of alkylated amino ester (*R*,*R*,*S*)-**20** (40 mg, 0.1 mmol) was added dropwise *via* a cannula and the resulting solution was stirred at rt for 64 h. The solvent was evaporated under reduced pressure and Et_2O (5 mL) was added to the residue. The solids were removed by filtration through a plug of silica and washed with Et_2O (50 mL). The solvent was evaporated under reduced pressure to give the crude product. Purification by flash chromatography with petrol–EtOAc (3 : 1) as eluent gave a 50 : 50 mixture (by ^{1}H NMR spectroscopy) of hydroxylamines **21** (38 mg, 85%) as a colourless oil, R_F(3 : 1 petrol–EtOAc) 0.2; IR (film): 1730 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.34 (m, 2H), 7.33–7.25 (m, 2H), 7.24–7.17 (m, 1H), 6.28 (br s, 0.5H), 5.79 (br s, 0.5H), 4.28–3.97 (m, 4.5H), 3.85 (dq, J = 11.0, 7.5 Hz, 0.5H), 3.20–3.12 (m, 0.5H), 3.08–3.03 (m, 0.5H), 2.88–2.80 (m, 2H), 2.73–2.55 (m, 3H), 2.60 (s, 1.5H), 2.52 (s, 1.5H), 2.42–2.36 (m, 0.5H), 2.32–2.25 (m, 0.5H), 2.04–1.85 (m, 2H), 1.68–1.58 (m, 1H), 1.50–1.05 (m, 11H), 1.20 (t, J = 7.5 Hz, 1.5H), 1.07 (t, J = 7.5 Hz, 1.5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 175.0 (C=O), 174.8 (C=O), 174.7 (C=O), 174.3 (C=O), 144.5 (*ipso*-Ph), 144.3 (*ipso*-Ph), 128.0 (Ph), 127.8 (Ph), 127.6 (Ph), 127.4 (Ph), 126.5 (Ph), 126.3 (Ph), 63.8 (CH_2), 63.0 (CH_2), 60.5 (CH_2), 60.41 (CH_2), 60.38 (CH_2), 60.3 (CH_2), 58.8 (CH), 55.4 (CH), 54.7 (CH), 48.78 (CH), 48.76 (CH), 44.6 (CH), 44.4 (CH), 44.2 (CH_2), 44.0 (CH_2), 42.8 (CH_2), 42.7 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 24.6 (CH_2), 24.3 (CH_2), 23.8 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 14.2 (Me), 14.15 (Me), 14.1 (Me), 14.0 (Me), 13.9 (Me), 13.1 (Me); MS (CI, NH_3) m/z 435 [(M + H)$^+$, 100], 188 (65), 389 (30); HRMS (CI, NH_3) m/z [M + H]$^+$ calcd for $C_{24}H_{38}N_2O_5$, 435.2859; found, 435.2856.

(1*R*,9a*R*)-Diethyl 2,6,7,8,9,9a-hexahydro-1*H*-quinolizine-1,3-dicarboxylate 22 and (1*R*,5*S*,11a*R*)-3-methyl-octahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocine-2,6-dione 15

A suspension of 20% $Pd(OH)_2$ on C (20 mg, 0.02 mmol), a 50 : 50 mixture of hydroxylamines **21** (110 mg, 0.25 mmol) and $NH_4^+HCO_2^-$ (48 mg, 0.75 mmol) in EtOH (1 mL) was stirred and heated at reflux under N_2 for 16 h. After being allowed to cool to rt, the solids were removed by filtration through Celite and washed with CH_2Cl_2 (50 mL). Then, 2 M $NH_4OH_{(aq)}$ (5 mL) was added to the filtrate and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash chromatography with CH_2Cl_2–MeOH (50 : 1) and then CH_2Cl_2–MeOH (9 : 1) as eluent gave quinolizidine **22** (24 mg, 34%) as a colourless oil, $[\alpha]_D$ +94.4 (*c* 1.0 in $CHCl_3$); R_F(9 : 1 CH_2Cl_2–MeOH) 0.75; IR (film): 3015, 1730 (C=O), 1665 (C=O), 1620 (C=C), 1220 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, J = 2.0 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.55–3.50 (m, 1H), 3.45–3.38 (m, 1H), 3.18 (td, J = 13.0, 3.0 Hz, 1H), 2.87 (dt, J = 12.0, 5.5 Hz, 1H), 2.62 (ddd, J = 16.5, 5.5, 1.5 Hz, 1H), 2.40 (ddd, J = 16.5, 12.0, 2.0 Hz, 1H), 1.92–1.87 (m, 1H), 1.73–1.34 (m, 5H), 1.28 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 172.2 (C=O), 168.4 (C=O), 144.7 (CH), 94.9 (C), 60.7 (CH_2), 59.2 (CH_2), 55.7 (CH), 54.6 (CH_2), 41.8 (CH), 26.5 (CH_2), 25.8 (CH_2), 24.6 (CH_2), 19.0 (CH_2), 14.7 (Me), 14.2 (Me); MS (CI, NH_3) m/z 282 [(M + H)$^+$, 100]; HRMS (CI, NH_3) m/z [M + H]$^+$ calcd for $C_{15}H_{23}N_2O_4$, 282.1705; found, 282.1699 and bislactam **15** (27 mg, 48%) as a colourless oil, $[\alpha]_D$ +41.8 (*c* 1.0 in $CHCl_3$); R_F(9 : 1 CH_2Cl_2–MeOH) 0.4; IR (film): 3015, 2940, 1730 (C=O), 1635 (C=O), 1440, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.74 (ddd, J = 13.5, 4.0, 2.0 Hz, 1H), 3.51–3.40 (m, 2H), 3.38 (ddd, J = 12.0, 5.0, 3.0 Hz, 1H), 2.93 (s, 3H), 2.93–2.88 (m, 1H), 2.82–2.78 (m, 1H), 2.49 (td, J = 13.5, 3.5 Hz, 1H), 2.10–2.07 (m, 2H), 1.99–1.92 (m, 1H), 1.87–1.83 (m, 1H), 1.73–1.68 (m, 1H), 1.40–1.20 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 170.0 (C=O), 168.1 (C=O), 59.2 (CH), 52.8 (CH_2), 42.2 (CH_2), 41.7 (CH), 37.1 (CH), 34.0 (Me), 31.3 (CH_2), 25.0 (CH_2), 24.8 (CH_2), 24.1 (CH_2); MS (CI, NH_3) m/z 282 [(M + H)$^+$, 100]; HRMS (CI, NH_3) m/z [M + H]$^+$ calcd for $C_{12}H_{18}N_2O_2$, 223.1447; found, 223.1448.

(1*S*,2*S*,9*S*)-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane, (−)-sparteine surrogate

$LiAlH_4$ (77 mg, 2.03 mmol) was added in one portion to a stirred solution of bislactam **15** (75 mg, 0.34 mmol) in THF (1.5 mL) at 0 °C under N_2. The resulting suspension was stirred and heated at reflux for 16 h. After cooling to rt, Et_2O (1 mL) was added and solid $Na_2SO_4{\cdot}H_2O$ was added portionwise until effervescence ceased. The resulting mixture was stirred at rt for 30 min. The solids were removed by filtration through Celite and washed with 9 : 1 CH_2Cl_2–MeOH (30 mL). The filtrate was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product as a yellow oil. Purification by Kugelrohr distillation gave (−)-sparteine surrogate (44 mg, 68%) as a pale yellow oil, bp 110–115 °C/0.3 mmHg (lit.,[27b] 95–110 °C/0.8 mmHg); $[\alpha]_D$ −29.6 (*c* 1.0 in EtOH) (lit.,[27b] $[\alpha]_D$ +26.5 (*c* 1.0 in EtOH) for (+)-sparteine

surrogate); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.03–2.96 (m, 2H), 2.89 (dt, J = 11.5, 2.0 Hz, 1H), 2.86–2.82 (m, 1H), 2.24 (ddd, J 11.0, 3.5, 1.5 Hz, 1H), 2.18–2.12 (m, 1H), 2.15 (s, 3H), 1.98 (dd, J = 11.5, 3.0 Hz, 1H), 1.94–1.89 (m, 1H), 1.86–1.45 (m, 11H). Spectroscopic data consistent with that reported in the literature.[27b]

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