Studies towards the preparation of sparteine-like diamines for asymmetric synthesis †

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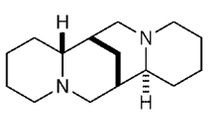
A route for the preparation of sparteine-like diamines starting from naturally occurring amino acids has been explored. Starting from the amino acids (*S*)-proline and (*S*)-phenylalanine, two novel sparteine-like diamines **2** and **3** have been prepared. The synthetic route involves Dieckmann condensation followed by a double Mannich reaction to set up the tricyclic structure with control of the relative stereochemistry. During the Dieckmann and Mannich reactions it was found that racemisation occurred either *via* retro-Michael or retro-Mannich processes. Conditions for preventing racemisation in the Dieckmann reaction were uncovered but it was not possible to prevent racemisation during the double Mannich reaction. Thus, the two novel sparteine-like diamines **2** and **3** have been prepared in racemic form.

Introduction

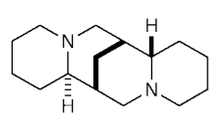
The lupine alkaloid (−)-sparteine, isolated in large quantities by extracting certain papilionaceous plants such as Scotch broom, has found widespread use as a chiral ligand in asymmetric synthesis over the last ten years.[1,2] (+)-Sparteine is also naturally ocurring[3] but is far less easily obtained: it can be synthesised in a long-winded fashion from (−)-lupanine, itself obtained by resolution of isolated *racemic* lupanine.[4] Thus, sparteine is only readily and commercially available as its (−)-antipode and this is a limitation on the use of sparteine as a chiral ligand.



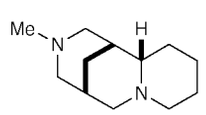
(−)-Sparteine

To address this problem, two attempts to find sparteine surrogates, available in either enantiomeric form, have been reported. Beak *et al.*[5] screened 17 chiral diamines in the asymmetric functionalisation of *N*-Boc pyrrolidine and found that none outperformed (−)-sparteine. In a similar way, Hodgson and Lee have reported that the use of C_2 symmetric bisoxazolines in place of (−)-sparteine gave lower enantioselectivity for the α-deprotonation–rearrangement of cyclooctene oxide.[6] An alternative approach to this problem would be to carry out a synthesis of (+)-sparteine. Such an approach would be particularly demanding not least because only five separate syntheses of *racemic* sparteine have previously been reported.[7] Perhaps surprisingly, there have been no reports of a total asymmetric synthesis of sparteine. An approach to the synthesis of sparteine, described by Wendt and Aubé and which could in principle have been rendered asymmetric, was unfortunately unsuccessful.[8]

Given the difficulty in the synthesis of sparteine encountered by previous workers in the field,[7,8] we decided not to embark on a total synthesis of enantiomerically enriched (+)-sparteine.



(+)-Sparteine



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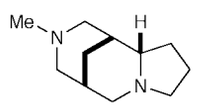

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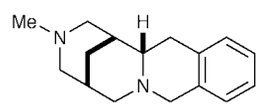

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Instead, our attention has focused on the preparation of chiral diamines **1**–**3** which posses similar chiral architecture (*vide infra*) to (+)-sparteine but which we envisaged would be easier to prepare. In this way, using diamines such as **1**–**3** we would be able to address the limitation of sparteine and hopefully develop chiral ligands capable of functioning as surrogates of (+)-sparteine.

The rationale behind the choice of diamines **1**–**3** as our initial targets was guided by some observations from the Beak laboratory. During work on the effect of ligand structure on the enantioselective deprotonation of *N*-Boc pyrrolidine, Beak *et al.* noted that the use of (−)-α-isosparteine reduced the rate of lithiation and gave lower enantioselectivity when compared with (−)-sparteine.[5] Both of these effects were explained by considering the steric hindrance in the lithium complexes with (−)-α-isosparteine and (−)-sparteine.[9] These complexes are depicted schematically in Fig. 1 and as can be seen, there is greater steric congestion around the lithium cation in the (−)-α-isosparteine complex since both of the peripheral rings extend towards the lithium. In contrast, with the (−)-sparteine complex, one of the rings is held away from the lithium cation thus exposing it for reaction. In the same way, we anticipated that diamine *ent*-**1** would also provide a non-sterically hindered environment around the lithium but at the same time, most of the chiral backbone of sparteine is present for high enantioselectivity.

In this paper, we describe our synthetic work on the attempted synthesis of enantiomerically enriched diamines **2** and **3** starting from the amino acids (*S*)-proline and (*S*)-phenylalanine respectively. The strategy is delineated in full

† Full experimental procedures for the reactions in Tables 1–3 are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/1999/3623

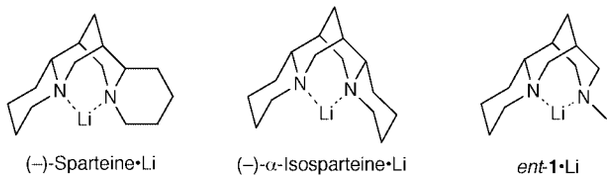
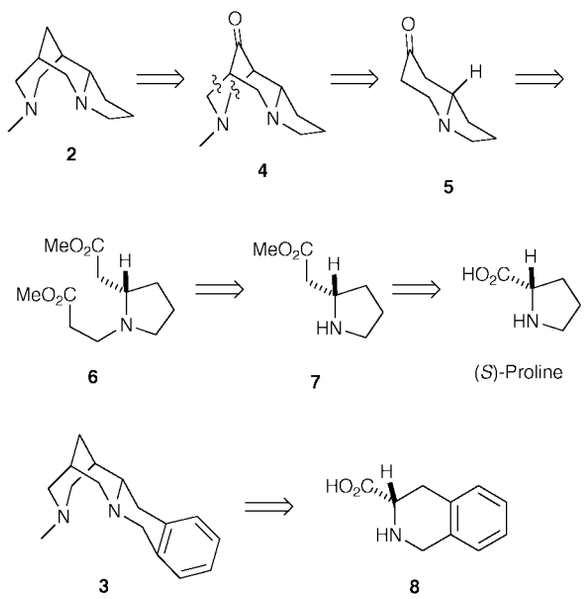


Fig. 1 Lithium chelating conformations of (−)-sparteine, (−)-α-isosparteine and sparteine surrogate *ent*-1.



Scheme 1

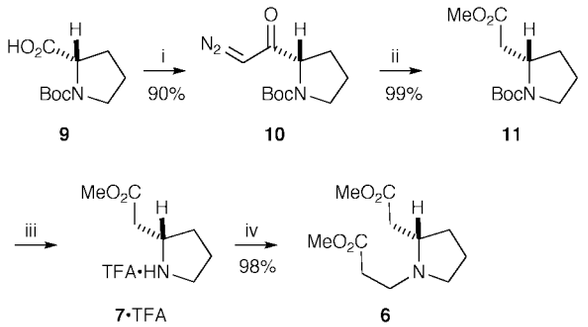
for the proposed preparation of diamine **2** (Scheme 1). These two targets were selected in preference to diamine **1** since the amino acids required are commercially available. In contrast, for the synthesis of diamine **1**, either the preparation of (*S*)-pipecolic acid[10] or of the 6-ring analogue of β-amino acid **7**[11] requires resolution so it was decided to test the methodology on the more readily accessible diamines **2** and **3**.

Our approach to diamine **2** follows the same strategy as that adopted by Scheiber and Nemes for the preparation of *racemic* diamine **1** (Scheme 1).[12] The key intermediate is bicyclic ketone **5** since a double Mannich reaction (to give **4**) followed by Wolff–Kishner reduction should furnish the target molecule in which the relative stereochemistry is controlled by the inherent diastereoselectivity of the second intramolecular Mannich reaction. We envisaged preparing ketone **5** from (*S*)-proline *via N*-protection, Arndt–Eistert homologation, *N*-deprotection, Michael addition to methyl acrylate and finally Dieckmann condensation. A similar retrosynthetic analysis furnishes amino acid **8** (prepared by Pictet–Spengler cyclisation of (*S*)-phenylalanine) as the starting material. Herein we describe the use of this approach for the synthesis of diamines **2** and **3** and the unanticipated problems encountered along the way.

Results and discussion

Synthesis of proline-derived diamine 2

Our approach to sparteine-like diamine **2** required the preparation of the Dieckmann precursor **6**. Its synthesis from (*S*)-proline is outlined in Scheme 2. First of all, the *N*-Boc derivative **9** was prepared from (*S*)-proline in 93% yield using the published procedure (Et_3N, Boc_2O, CH_2Cl_2, 0 °C, 2.5 h).[13] Next, Arndt–Eistert[14] homologation was required to furnish methyl ester **11**. Such an approach to methyl ester **11** has previously been described by O'Neil *et al.*[15] and by Mahboobi *et al.*[16] and we essentially followed their procedures. Thus, the carb-



Scheme 2 *Reagents and conditions*: i, i-BuOCOCl, Et_3N, Et_2O −20 °C ⟶ 0 °C then CH_2N_2, Et_2O, 0 °C ⟶ rt then 16 h; ii, cat AgOBz Et_3N, MeOH, dark, −25 °C ⟶ rt over 3 h; iii, TFA, CH_2Cl_2, 0 °C for 15 min, rt for 1.5 h; iv, methyl acrylate, $FeCl_3$, Et_3N, CH_2Cl_2, rt, 96 h.

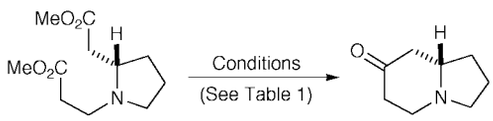
oxylic acid of *N*-Boc proline **9** was converted into the mixed anhydride with isobutyl chloroformate and subsequent treatment with excess diazomethane gave diazoketone **10** in high yield (90%) after chromatography; diazoketone **9** could be stored in the freezer in the absence of light without noticeable degradation. In our hands, the best procedure for the Wolff rearrangement of **10** to methyl ester **11** was that documented by Podlech and Seebach during work on the synthesis of β-amino acids.[17] This involved reaction of a homogeneous solution of catalytic silver benzoate in triethylamine with diazoketone **10** in methanol. Provided light was excluded and the reaction was initiated at low temperatures (−25 °C), an essentially quantitative crude yield of methyl ester **11**, which did not require any purification before use in the next step, was obtained.

Initially, we carried out Boc deprotection of methyl ester **11** and attempted to isolate the resulting amino ester **7**. Unfortunately, only a low (16%) yield of **7** was obtained which presumably reflected either the volatility or water solubility of this compound. Although the subsequent Michael reaction of **7** in refluxing excess methyl acrylate gave a quantitative yield of adduct **6**, this approach was too low yielding to be synthetically useful. Therefore, two changes were made: after the Boc deprotection, the amino ester **7** was isolated as its trifluoroacetate salt (in essentially crude quantitative yield) and the Michael reaction was accomplished by treating this salt with a mixture of triethylamine (to free up the amino ester **7** *in situ*), methyl acrylate and iron(III) chloride[18] in dichloromethane at room temperature for 96 hours. In this way, the Michael addition product **6** was obtained in a much improved 98% yield (after purification by column chromatography) over the two steps (Scheme 2). Essentially the same yield of **6** was obtained if we refluxed the trifluoroacetate salt of **7** in excess methyl acrylate containing some triethylamine.

Racemic bicyclic ketone **5** has previously been prepared on four separate occasions[19–22] (including the use of Dieckmann routes[19–21]). Of the previous approaches, we adopted the Dieckmann[23] route to ketone **5** since it was the only one that should allow enantiomerically enriched ketone **5** to be prepared. We have carried out the Dieckmann reaction of bis ester **6** using sodium hydride with catalytic sodium methoxide or LDA as the base followed by two different methods for subsequent decarboxylation. The full results of this study are presented in Table 1.

The use of sodium hydride together with catalytic sodium methoxide in refluxing xylenes (a procedure described by Leonard *et al.* for the synthesis of the 6-membered ring analogue[24]) or the use of LDA in THF at −78 °C followed by hydrolysis and decarboxylation using refluxing 6 M hydrochloric acid resulted in good yields of ketone **5** after purification by Kugelrohr distillation (Table 1, Entries 1–2). Unfortunately, however, ketone **5** thus obtained was shown to be racemic by optical rotation measurement and by recording

Table 1



6 5

Entry	Base[a]	Method of decarboxylation[a]	Yield (%)[b]	$[\alpha]_D$ (% ee)[c]
1	NaH, NaOMe xylenes	6 M HCl	75	0 (0)
2	LDA, THF	6 M HCl	78	0 (0)
3	NaH, NaOMe xylenes	KOH(aq), MeOH	29	+41.4 (90)
4	LDA, THF	KOH(aq), MeOH	34	+36.5 (84)

[a] For details, see experimental section. [b] Yield of isolated pure ketone **5**. [c] Enantiomeric excess determined using ^{1}H NMR spectroscopy in the presence of a chiral shift reagent.

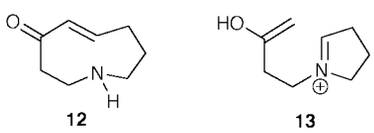
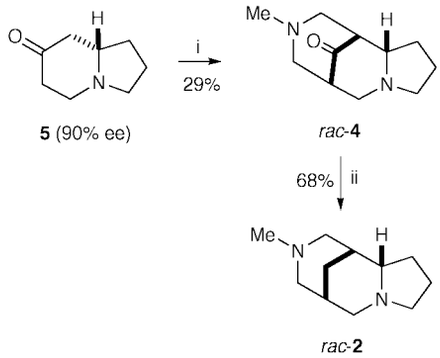


Fig. 2

the ^{1}H NMR spectrum in the presence of the chiral shift reagent[25] (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Presumably the racemisation occurs in the harsh decarboxylation step and can be rationalised by invoking either a retro-Michael reaction to give **12** or a retro-Mannich reaction to give **13** (Fig. 2). Such a loss of stereochemical information is not that uncommon in β-amino ketones and has, for example, been noted previously by Knight *et al.* during the synthesis of lupinine[11] and Slosse and Hootelé during the preparation and subsequent epimerisation of myrtine.[26] In some recent and elegant synthetic work, a closely related epimerisation was used to advantage by Heathcock *et al.* in the synthesis of Petrosins C and D.[27]

In order to prepare enantiomerically enriched ketone **5**, we were encouraged by the fact that Slosse and Hootelé had observed reduced levels of epimerisation of myrtine using dilute aqueous base.[26] Thus, the conditions for the decarboxylation were modified to refluxing with aqueous potassium hydroxide in methanol[28] for 2–3 hours. In this way, enantiomerically enriched ketone (*S*)-**5** (84–90% ee) was obtained albeit in much reduced yield (Table 1, Entries 3–4). Of particular note, we had been successful in minimising racemisation and this is the first time that this ketone has been prepared in non-racemic form.

Initially, the double Mannich reaction[29] of ketone (*S*)-**5** with methylamine was attempted using the conditions reported by Scheiber and Nemes[12] in their synthesis of diamine **1**. However, we were unable to isolate any of the required tricylcic ketone using these conditions. We had more success using conditions reported by Beak for the preparation of bispidines.[5] Thus, a mixture of ketone (*S*)-**5** (90% ee), methylamine, paraformaldehyde and acetic acid in methanol were refluxed for 16 hours to give a 29% yield of ketone **4** after Kugelrohr distillation (Scheme 3). Ketone **4** was isolated as a single diastereoisomer as shown by ^{1}H and ^{13}C NMR spectroscopy and, in line with related double Mannich reactions, we believe it has the relative stereochemistry depicted. Unfortunately, the tricyclic ketone **4** was not optically active and was shown to be racemic by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Racemisation *via* **12** or **13** (Fig. 2) is occurring under these acidic conditions and we have been unable to find racemisation-free double Mannich reaction conditions (*vide infra*).

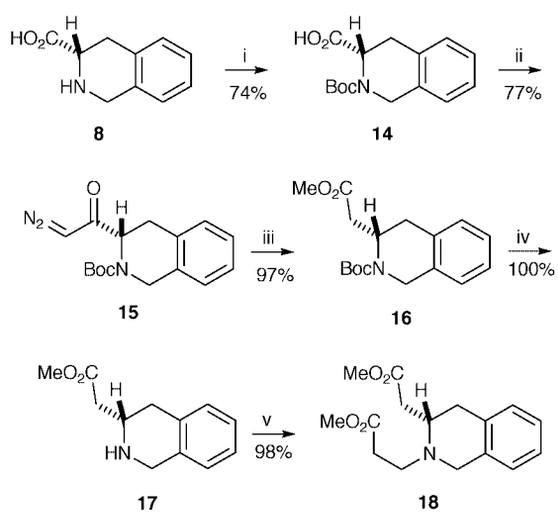


Scheme 3 *Reagents and conditions*: i, $MeNH_2$, $(CH_2O)_n$, AcOH, MeOH, reflux, 16 h; ii, $N_2H_4{\cdot}H_2O$, KOH, diethylene glycol, reflux, 2 h.

Although we were not able to prepare enantiomerically enriched tricyclic ketone **4**, we have converted this into the target diamine **2** using Wolff–Kishner reduction. Thus, treatment of ketone **4** with hydrazine hydrate and potassium hydroxide at high temperature (according to the method of Scheiber and Nemes[12]) afforded a 68% crude yield of the novel diamine *rac*-**2** which was of good purity. Indeed, purification of this diamine by Kugelrohr distillation did not lead to any improvement in its purity as judged by ^{1}H NMR spectroscopy.

Synthesis of phenylalanine-derived diamine 3

Concurrently with the previously described research, we also investigated a similar approach to diamine **3** starting from (*S*)-phenylalanine. In this way, we have established the generality of the racemisation problems encountered in the synthesis of these types of compounds. The preparation of the Dieckmann precursor **18** is outlined in Scheme 4.

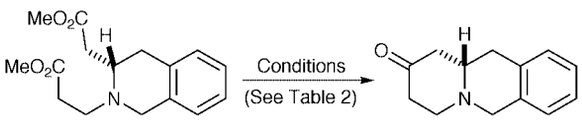


Scheme 4 *Reagents and conditions* i, NaOH, Boc_2O, t-BuOH–water rt, 16 h; ii, i-BuOCOCl, Et_3N, THF, −20 °C ⟶ 0 °C then CH_2N_2, Et_2O 0 °C ⟶ rt then 16 h at rt; iii, cat AgOBz, Et_3N, MeOH, dark, −25 °C ⟶ rt over 3 h; iv, TFA, CH_2Cl_2, rt, 1 h; v, methyl acrylate, reflux, 17 h.

Initially, cyclic amino acid **8** was prepared in 65% crude yield using the known[30] Pictet–Spengler reaction of (*S*)-phenylalanine with aqueous formaldehyde. Next, *N*-Boc protection was accomplished in 74% yield using aqueous sodium hydroxide and Boc_2O, a procedure reported by McMills.[31] A much lower yield was obtained when the conditions used (Et_3N, Boc_2O, CH_2Cl_2) for the preparation of *N*-Boc derivative **9** were employed.

Essentially the same procedure as that used for the Arndt–Eistert homologation of proline derivative **9** was employed for

Table 2



18 **19**

Entry	Base[a]	Method of decarboxylation[a]	Crude yield (%)[b]	$[\alpha]_D$ (% ee)[c]
1	NaH, NaOMe xylenes	6 M HCl	44	0 (0)
2	NaH, NaOMe 1,4-dioxane	6 M HCl	84	0 (0)
3	KO^{t}Bu, ^{t}BuOH	6 M HCl	34	0 (0)
4	LDA, THF	6 M HCl	94	0 (0)
5	NaH, NaOMe 1,4-dioxane	12 M HCl	90 (44)	−33.3 (—)
6	LDA, THF	12 M HCl	—(35)	−46.1 (—)
7	NaH, NaOMe xylenes	NaCl, DMF	—(29[d])	−10.8
8	NaH, NaOMe xylenes	LiCl, DMF	—(7[d])	−19.0
9	NaH, NaOMe xylenes	KOH(aq), MeOH	—(28[d])	−72.2 (—)
10	LDA, THF	KOH(aq), MeOH	59 (19)	−89.7 (≥90)

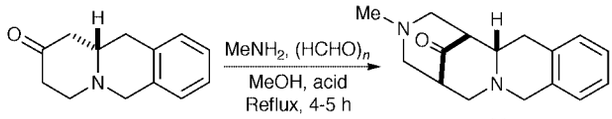
[a] For details, see Experimental section. [b] Yield of crude ketone **5** (isolated yield of pure product in brackets). [c] Optical rotations performed on purified ketone **5**; enantiomeric excess determined using ^{1}H NMR spectroscopy in the presence of a chiral shift reagent. [d] Yield from isolated intermediate obtained from Dieckmann cyclisation with NaH–NaOMe in xylenes.

the conversion of **14** into **16**. However, use of diethyl ether as solvent for the preparation of diazoketone **15** gave only a moderate 52% yield of **15**. We suspected that this low yield was due to precipitation of the triethylaminmonium salt of acid **14** during the mixed anydride preparation. Indeed, carrying out the reaction in THF visibly suppressed salt precipitation and allowed us to obtain an improved 77% yield of diazoketone **15**. Decomposition of the diazoketone **15** to methyl ester **16** (97% yield) was accomplished analogously to that described previously (see Scheme 2). In this series, we found that TFA deprotection of *N*-Boc derivative **16** afforded an isolable amino ester **17** in 98% crude yield which was used directly in the next step. The Michael addition of **17** to methyl acrylate was best carried out by refluxing **17** in methyl acrylate for 17 hours (98% yield after purification by column chromatography).

The Dieckmann condensation of the bis *ethyl* ester analogue of our compound **18** has previously been reported by Yamada and Kunieda.[32] They found that treatment of the bis ethyl ester with sodium hydride in 1,4-dioxane followed by decarboxylation using concentrated hydrochloric acid (at reflux for 10 hours) gave ketone **19** in 80% crude yield. Ketone **19** thus produced exhibited $[\alpha]_D$ −91.0 (*c* 0.26 in EtOH) and the authors presumed that no racemisation had occurred in its preparation. In an attempt to optimise the yield and to minimise any racemisation, we have studied a wide range of conditions for the Dieckmann cyclisation of bis ester **18** to ketone **19**. The results are collected together in Table 2.

Initially, using refluxing 6 M hydrochloric acid for the decarboxylation step, the base was varied in an attempt to optimise the crude yield of ketone **19** (Table 2, Entries 1–4) from the Dieckmann reactions. It was found that sodium hydride in 1,4-dioxane and LDA in THF gave the highest yields of, as expected, racemic ketone **19**. Therefore, these successful conditions were combined with decarboxylation conditions (12 M hydrochloric acid, 2 hours at reflux) similar to those used by Yamada and Kunieda. In this way, optically active product was obtained with both bases but, based on the magnitude of the optical rotation values, it was clear that in our hands racemisation was not completely suppressed (Table 2, Entries 5 and 6).

Table 3



19 *rac*-**20**

Entry	AcOH (equiv.)	HCl (equiv.)	Yield (%)[a]	$[\alpha]_D$	ee (%)[b]
1	1	—	28	−3.9 (EtOH)	0–10
2	2	—	30	−8.4 ($CHCl_3$)	0–10
3	2	1	30	−15.8 ($CHCl_3$)	20–30
4	—	2	30	−7.0 ($CHCl_3$)	—

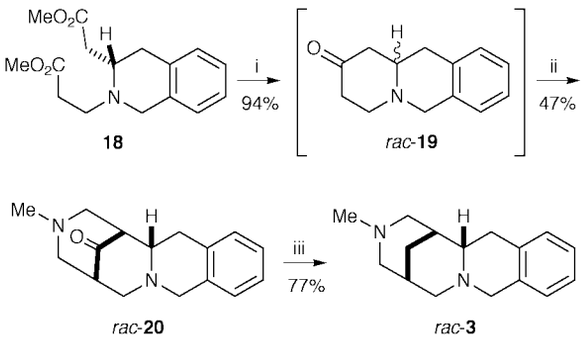
[a] Yield of pure ketone **20** after purification by Kugelrohr distillation. [b] Enantiomeric excess determined using ^{1}H NMR spectroscopy in the presence of a chiral shift reagent.

Attention was switched to alternative methods for decarboxylation.[33] Halide-mediated approaches[34] gave low yields and ketone **19** was obtained in low optical purity (Table 2, Entries 7 and 8). The best results (Table 2, Entries 9 and 10) were obtained using base to perform the hydrolysis and decarboxylation (as we had found in the previous series). Thus, decarboxylation of the sodium hydride- or LDA-mediated Dieckmann condensation products using aqueous potassium hydroxide in methanol generated ketone (*S*)-**19** of high enantiomeric excess. The reaction using LDA (Table 2, Entry 10) reproducibly gave a good crude yield (59%) and ketone (*S*)-**19** was shown to be ≥90% ee using ^{1}H NMR spectroscopy in the presence of the chiral shift reagent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

We found that only low yields of ketone **19** were obtained whenever the crude product was purified by column chromatography (Table 2, Entries 5–10). Thus, for the purposes of assessing the optical and enantiomeric purity of ketone **19** from these reactions, the crude products were purified. However, for investigating the degree of racemisation in the subsequent double Mannich reaction, the *crude* ketone (*S*)-**19** from the LDA–potassium hydroxide reaction (Table 2, Entry 10) was utilised directly.

The double Mannich reaction of ketone (*S*)-**19** with methylamine and formaldehyde has been examined under acetic acid and/or hydrochloric acid conditions (Table 3). Using the conditions used for the synthesis of ketone **4** (see Scheme 3), a 28% yield of tricyclic ketone **20** was obtained after purification by Kugelrohr distillation (Table 3, Entry 1). This ketone **20** was shown to be essentially racemic by polarimetry and ^{1}H NMR spectroscopy in the presence of the chiral shift reagent, a result which is consistent with that obtained in the proline series. Attempts to lower the amount of racemisation by changing the conditions were not very successful (Table 3, Entries 2–4). Use of 2 equivalents of acetic acid in combination with 1 equivalent of hydrochloric acid[35] generated tricyclic ketone **20** in 20% yield with 20–30% ee (Table 3, Entry 3). The low yields and generation of products of low enantiomeric excess in the double Mannich reaction indicated that we should abandon this approach to our intial target molecules.

In order to demonstrate that it was possible to generate the target diamine **3** in racemic form using this approach, we have completed the synthesis as indicated in Scheme 5. Thus, Dieckmann cyclisation using LDA followed by 6 M hydrochloric acid-mediated decarboxylation gave *racemic* ketone **19** in an excellent 94% crude yield. The double Mannich reaction using methylamine, paraformaldehyde and acetic acid in refluxing methanol for 16 hours generated a 47% distilled yield of *racemic* ketone **20**. Finally, Wolff–Kishner reduction using the



Scheme 5 *Reagents and conditions*: i, LDA, THF, −78 °C, 20 min then 6 M HCl, reflux, 16 h; ii, $MeNH_2$, $(CH_2O)_n$, AcOH, MeOH, reflux, 16 h; iii, $N_2H_4{\cdot}H_2O$, KOH, diethylene glycol, reflux, 2 h.

conditions employed previously with ketone **4** produced *racemic* diamine **3** in 77% isolated yield (Scheme 5).

Conclusion

Starting from the amino acids (*S*)-proline and (*S*)-phenylalanine, two novel sparteine-like diamines **2** and **3** have been prepared (albeit in racemic form) and fully characterised. Although it was possible to minimise racemisation in the Dieckmann cyclisation reactions used for their synthesis, we were unable to find racemisation-free double Mannich reaction conditions. β-Amino ketones such as **5** and **19** are susceptible to acid-catalysed racemisation at the elevated temperatures (*via* either retro-Michael or retro-Mannich processes) required for the double Mannich reactions. In addition to racemisation, the yields of the Mannich adducts **4** and **20** (*ca.* 30%) from these reactions are low. Because of these problems, our initial route for the preparation of enantiomerically enriched sparteine-like diamines **1**, **2** and **3** has been abandoned. Alternative approaches to such chiral diamines are currently being investigated and will be reported in due course.

Experimental

General

THF was dried over sodium–benzophenone and distilled before use. CH_2Cl_2 was dried over calcium hydride and distilled before use. Xylene was dried over calcium hydride, distilled and stored over 4 Å molecular sieves before use. Diisopropylamine was dried over calcium hydride, distilled and stored over potassium hydroxide pellets before use. Anhydrous 1,4-dioxane was purchased from Aldrich Chemical Company Ltd. NH_3 refers to a 33% aqueous ammonia solution. *n*-Butyllithium was titrated against *N*-benzylbenzamide before use.[36] Petrol refers to the fraction of petroleum ether boiling in the range 40–60 °C and was redistilled in Winchester quantities before use. (3*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid **8** was prepared in 65% yield according to the literature procedure.[30] All non-aqueous reactions were carried out under oxygen-free nitrogen using oven-dried glassware. Flash column chromatography was carried out using ICN Biomedicals GmbH 33–63 silica (60 Å) or Fisher Matrex silica 60. Thin layer chromatography was carried out on commercially available Merck 5554 aluminium-backed silica plates and the plates were visualised using a 1% ethanolic ninhydrin solution.

Proton (270 MHz) and carbon (67.5 MHz) NMR spectra were recorded on a Jeol EX-270 spectrometer using an internal deuterium lock. All samples were recorded as solutions in deuteriated chloroform and chemical shifts are quoted in parts per million downfield of tetramethylsilane. Coupling constant (*J*) values are given in Hz. Carbon NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments.

For Kugelrohr distillations, the temperatures quoted correspond to the oven temperatures. Melting points were measured on an Electrothermal IA 9100 digital melting point apparatus. Infra red spectra were recorded on an ATI Mattson Genesis FT IR spectrometer as solutions in chloroform. Chemical ionisation and high resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Optical rotations were recorded on a Jasco DIP-370 polarimeter (using the sodium D line; 589 nm) at 20 °C and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Full experimental procedures for all of the reactions described in Tables 1, 2 and 3 are available as supplementary information.

(2*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxylic acid 9

Using the published procedure,[13] (*S*)-proline (5.0 g, 43.5 mmol) gave *N*-Boc proline **9** (8.7 g, 93%) as white crystals, mp 133–135 °C (from petrol) (lit.,[13] 138–140 °C), $[\alpha]_D$ −51.2 (*c* 1.0 in $CHCl_3$) and identical spectroscopically to that previously reported.

(3*S*)-2-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid 14

Amino acid **8** (4.98 g, 28.1 mmol) was added to a stirred solution of sodium hydroxide (1.25 g, 31.0 mmol) in water (120 cm^3) at room temperature. Then, *tert*-butyl alcohol (80 cm^3) was added followed by the dropwise addition of liquid di-*tert*-butyl dicarbonate (6.20 g, 28.4 mmol). After stirring the resulting mixture at room temperature for 16 h, the clear solution was washed with petrol (2 × 50 cm^3). The combined organic layers were extracted with saturated aqueous potassium carbonate solution (2 × 50 cm^3). Then, the aqueous layers and the aqueous reaction mixture were combined and acidified to pH 1 by addition of solid sodium hydrogen sulfate. The acidic aqueous solution was extracted with Et_2O (3 × 100 cm^3) and the combined organic extracts were washed with brine (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a solid. Recrystallisation from EtOAc–hexane gave *N*-Boc amino acid **14** (5.75 g, 74%) as white crystals, mp 113–115 °C (from EtOAc–hexane); $[\alpha]_D$ +3.9 (*c* 1.4 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1718 (C=O, CO_2H), 1692 (C=O, Boc); δ_H(270 MHz; $CDCl_3$) (rotamers) 10.03–9.96 (2 H, br s, 2 × CO_2H), 7.18–7.11 (8 H, m, Ar), 5.13–5.10 (1 H, m, CHN), 4.75–4.64 (3 H, m, CHN and 2 × CH_AH_BN), 4.48 (1 H, d, *J* 16.0, CH_AH_BN), 4.44 (1 H, d, *J* 16.3, CH_AH_BN), 3.26–3.08 (4 H, m, CH_2Ar), 1.50 (9 H, s, CMe_3) and 1.39 (9 H, s, CMe_3); δ_C(67.5 MHz; $CDCl_3$) (rotamers) 177.6 (C=O, CO_2H), 177.4 (C=O, CO_2H), 155.7 (C=O, Boc), 154.8 (C=O, Boc), 133.8, 132.7, 131.9, 131.6 (*ipso*-Ar), 128.5, 127.7, 126.9, 126.7, 126.3, 126.2 (Ar), 80.9 (CMe_3), 54.1, 52.3 (CHN), 44.5, 43.8 (CH_2N), 31.3, 30.9 (CH_2Ar), 28.35 and 28.2 (CMe_3); *m*/*z* (CI, NH_3) 395 [15%, $(M + NH_4)^+$], 278 (45, M + H) and 178 (100) [Found: $(M + H)^+$, 278.1391. $C_{15}H_{19}NO_4$ requires *M* + H, 278.1392].

(2*S*)-*tert*-Butyl 2-diazoacetylpyrrolidine-1-carboxylate 10

Triethylamine (0.66 cm^3, 4.7 mmol) was added dropwise to a stirred solution of *N*-Boc proline **9** (1.0 g, 4.7 mmol) in Et_2O (5.4 cm^3) at −10 °C under nitrogen. After 5 min, the solution was cooled to −20 °C and isobutyl chloroformate (0.74 cm^3, 4.8 mmol) was added dropwise. The mixture was allowed to warm to 0 °C and the precipitate was removed by filtration. To the resulting filtrate, a solution of excess diazomethane in Et_2O ‡ was added and the solution was allowed to warm to room temperature. After stirring at room temperature for 16 h, two to three

‡ For the preparation of diazoketone **10** starting from 5.0 g of *N*-Boc proline **9**, diazomethane prepared from 23.9 g of Diazald® was used (for diazoketone **16** starting from 10.0 g of *N*-Boc amino acid **15**, diazomethane prepared from 26.3 g of Diazald® was used).

drops of acetic acid were added to destroy excess diazomethane. Then, the reaction mixture was washed with 10% aqueous citric acid solution (20 cm^3) (**CAUTION**—vigorous effervescence may occur), saturated aqueous sodium hydrogen carbonate solution (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol–EtOAc (1:1) as eluent gave known[15,16] diazoketone **10** (1.0 g, 90%) as a yellow oil, R_F (1:1 petrol–EtOAc) 0.3; $[\alpha]_D$ −118.0 (*c* 1.0 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 2111 (CHN_2), 1689 (C=O, Boc) and 1649 (C=O, $COCHN_2$); δ_H(270 MHz; $CDCl_3$) (rotamers) 5.49–5.39 (1 H, m, CHN_2), 4.37–4.10 (1 H, m, CHN), 3.60–3.32 (2 H, m, CH_2N), 2.30–1.83 (4 H, m, CH_2CH_2) and 1.46 (9 H, appearing as two singlets, CMe_3); δ_C(67.5 MHz; $CDCl_3$) (rotamers) 196.3, 195.2 (C=O, $COCHN_2$), 154.4, 153.7 (C=O, Boc), 80.4, 77.5 (*C*Me_3), 64.4, 63.3 (CHN_2), 53.3, 52.0 (CHN), 47.1, 46.8 (CH_2N), 31.3, 29.7 (CH_2), 28.4 (C*Me*$_3$), 24.4 and 23.7 (CH_2); *m*/*z* (CI, NH_3) 240 [100%, $(M + H)^+$] and 212 (41, $M - N_2$) [Found: $(M + H)^+$, 240.1352. $C_{11}H_{18}N_3O_3$ requires *M* + H, 240.1348].

(3*S*)-*tert*-Butyl 3-diazoacetyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 15

Using the procedure described above, triethylamine (5.0 cm^3, 36.0 mmol), *N*-Boc amino acid **14** (10.4 g, 34.6 mmol) in THF (100 cm^3), isobutyl chloroformate (4.7 cm^3, 36.0 mmol) and excess diazomethane in Et_2O gave the crude product as a yellow oil. Purification by flash column chromatography on silica with EtOAc–petrol (4:1) as eluent gave diazoketone **15** (8.7 g, 77%) as a yellow oil, R_F (1:1 petrol–EtOAc) 0.5; $[\alpha]_D$ −105.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2112 (CHN_2), 1689 (C=O, Boc), 1641 (C=O, $COCHN_2$); δ_H(270 MHz; $CDCl_3$) (rotamers) 7.26–7.08 (8 H, m, Ar), 5.34 (1 H, s, CHN_2), 5.30 (1 H, s, CHN_2), 4.97–4.94 (1 H, m, CHN), 4.73–4.43 (5 H, m, CHN and 2 × CH_2N), 3.32–3.02 (4 H, m, CH_2Ar), 1.53 (9 H, s, CMe_3) and 1.47 (9 H, s, CMe_3); δ_C(67.5 MHz; $CDCl_3$) (rotamers) 195.5, 194.0 (C=O, $COCHN_2$), 155.1 (C=O, Boc), 154.4 (C=O, Boc), 133.7, 132.9, 132.6 (*ipso*-Ar), 128.4, 127.8, 127.3, 127.0, 126.9, 126.6, 126.1, 125.9 (Ar), 81.1, 80.9 (*C*Me_3), 60.3 (CHN_2), 59.5, 57.4 (CHN), 44.8, 44.1 (CH_2N), 31.5, 30.3 (CH_2Ar) and 28.3 (C*Me*$_3$); *m*/*z* (CI, NH_3) 302 [45%, $(M + H)^+$], 274 (90), 218 (100) [Found: $(M + H)^+$, 302.1505. $C_{16}H_{19}N_3O_3$ requires *M* + H, 302.1505].

(2*S*)-*tert*-Butyl 2-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate 11

A solution of silver benzoate (106 mg, 0.46 mmol) in triethylamine (1.7 cm^3, 12.0 mmol) was added dropwise to a stirred solution of diazoketone **10** (1.0 g, 4.2 mmol) in MeOH (17 cm^3) at −25 °C under nitrogen with the exclusion of light. The mixture was allowed to warm to room temperature over 3 h. Then, the solvent was evaporated under reduced pressure and the residue dissolved in EtOAc (20 cm^3). The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (20 cm^3), saturated ammonium chloride solution (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give known[15,16] methyl ester **11** (1.0 g, 99%) as a pale brown oil, R_F (5:1 petrol–EtOAc) 0.3; $[\alpha]_D$ −43.2 (*c* 1.0 in MeOH){lit.,[16] $[\alpha]_D$ −38.8 (*c* 16 in MeOH)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 1731 (C=O, CO_2Me) and 1683 (C=O, Boc); δ_H(270 MHz; $CDCl_3$) 4.19–4.10 (1 H, m, CHN), 3.67 (3 H, s, MeO), 3.35 [2 H, dd (appearing as a triplet), *J* 6.1 and 6.8, CH_2N], 2.88 (1 H, dd, *J* 3.5 and 15.0, CH_AH_BCO), 2.31 (1 H, dd, *J* 9.7 and 15.0, CH_AH_BCO), 2.10–2.00 (1 H, s, CH), 1.89–1.72 (3 H, m, $CHCH_2$) and 1.49 (9 H, s, CMe_3); δ_C(67.5 MHz; $CDCl_3$) 171.9 (C=O, CO_2Me), 154.2 (C=O, Boc), 79.4 (*C*Me_3), 54.0 (CHN), 51.5 (MeO), 46.3 (CH_2N), 38.7, 30.9 (CH_2), 28.5 (C*Me*$_3$) and 23.1 (CH_2); *m*/*z* (EI) 243 [45%, M^+] [Found: $(M + H)^+$, 244.1543. $C_{12}H_{22}NO_4$ requires *M* + H, 244.1549].

(3*S*)-*tert*-Butyl 3-(2-methoxy-2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 16

Using the procedure described above, silver benzoate (85 mg, 0.37 mmol) in triethylamine (1.2 cm^3, 8.5 mmol) and diazoketone **15** (874 mg, 2.90 mmol) in MeOH (20 cm^3) gave methyl ester **16** (842 mg, 97%) as an oil, R_F (1:1 petrol–EtOAc) 0.55; $[\alpha]_D$ +57.4 (*c* 1.4 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1733 (C=O, CO_2Me) and 1685 (C=O, Boc); δ_H(270 MHz; $CDCl_3$) 7.24–7.17 (2 H, m, Ar), 7.15–7.10 (2 H, m, Ar), 4.97–4.83 (1 H, br m, CHN), 4.77 (1 H, d, *J* 17.0, CH_AH_BN), 4.33 (1 H, d, *J* 17.0, CH_AH_BN), 3.65 (3 H, s, MeO), 3.13 (1 H, dd, *J* 5.6 and 16.0, CH_AH_BCO), 2.75 (1 H, br d, *J* 16.0, CH_AH_BCO), 2.49 (1 H, dd, *J* 6.8 and 14.8, ArCH_AH_B), 2.29 (1 H, dd, *J* 7.7 and 14.8, $ArCH_AH_B$) and 1.50 (9 H, s, CMe_3); δ_C(67.5 MHz; $CDCl_3$) (rotamers) 172.0 (C=O, CO_2Me), 155.0 (C=O, Boc), 133.3, 133.1, 132.6 (*ipso*-Ar), 129.6, 127.1, 126.8, 126.6 (Ar), 80.5 (*C*Me_3), 52.0 (MeO), 47.9, 46.7 (CHN), 43.6, 43.1 (CH_2N), 37.6, 37.2, 33.6 (CH_2) and 28.8 (C*Me*$_3$); *m*/*z* (CI, NH_3) 306 [75%, $(M + H)^+$] 206 (100) [Found: $(M + H)^+$, 306.1709. $C_{17}H_{23}NO_4$ requires *M* + H, 306.1705].

(2*S*)-Methyl 3-[2-(2-methoxy-2-oxoethyl)pyrrolidino]propanoate 6

Trifluoroacetic acid (12.4 cm^3, 161.0 mmol) was added dropwise to a stirred solution of methyl ester **11** (3.6 g, 14.7 mmol) in CH_2Cl_2 (50 cm^3) at 0 °C under nitrogen. After 15 min, the solution was allowed to warm to room temperature and stirred for a further 1.5 h. The solvent was evaporated under reduced pressure and excess trifluoroacetic acid was removed by azeotroping with $CHCl_3$ (6 × 15 cm^3). Then, the residue was dissolved in CH_2Cl_2 (90 cm^3) at 0 °C under nitrogen and to the stirred solution, triethylamine (7.2 cm^3, 50.0 mmol) was added dropwise. The solution was allowed to warm to room temperature and iron(III) chloride (238 mg, 1.5 mmol) and methyl acrylate (1.3 cm^3, 14.7 mmol) were added. The resulting dark mixture was stirred at room temperature for 96 h. Then, the organic layer was washed with saturated aqueous sodium sulfate solution (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a brown oil. Purification by flash column chromatography on silica with $CHCl_3$–MeOH (97:3) as eluent gave diester **6** (3.3 g, 98%) as a pale brown oil, R_F (97:3 $CHCl_3$–MeOH) 0.3; $[\alpha]_D$ −57.2 (*c* 1.2 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1734 (C=O, CO_2Me); δ_H(270 MHz; $CDCl_3$) 3.61 (3 H, s, OMe), 3.60 (3 H, s, OMe), 3.14–2.91 (2 H, m), 2.78–2.67 (1 H, m, CHN), 2.59 (1 H, dd, *J* 4.1 and 15.0, CH_AH_BCO), 2.46–2.37 (3 H, m), 2.22–2.08 (2 H, m), 2.01–1.88 (1 H, m) and 1.72–1.40 (3 H, m); δ_C(67.5 MHz; $CDCl_3$) 172.8, 172.7 (C=O, CO_2Me), 60.7 (CHN), 53.4 (CH_2N), 51.6 (OMe), 51.4 (OMe), 49.5 (CH_2N), 39.4, 33.7, 30.8 and 22.3 (CH_2); *m*/*z* (EI) 229 (58%, M^+) [Found: M^+, 229.1303. $C_{11}H_{19}NO_4$ requires *M*, 229.1314].

(3*S*)-Methyl 3-[3-(2-methoxy-2-oxoethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]propanoate 18

Trifluoroacetic acid (9 cm^3, 120.0 mmol) was added dropwise to a stirred solution of methyl ester **16** (2.89 g, 9.5 mmol) in CH_2Cl_2 (20 cm^3) at room temperature under nitrogen. After stirring at room temperature for 1.5 h, the solvent was evaporated under reduced pressure and the residue dissolved in EtOAc (100 cm^3). The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (75 cm^3). The aqueous layer was back-extracted with EtOAc (100 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Then, the residue was dissolved in methyl acrylate (20 cm^3) and the resulting mixture was heated under reflux for 17 h. The excess methyl acrylate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2–

MeOH–NH_3 (96.5:3.0:0.5) as eluent gave diester **18** (2.69 g, 98%) as a pale brown oil, R_F (94.5:5.0:0.5 CH_2Cl_2–MeOH–NH_3) 0.5; $[a]_D$ +10.7 (*c* 2.7 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1733 (C=O, CO_2Me), 1483 and 1214; δ_H(270 MHz; $CDCl_3$) 7.12–7.08 (4 H, m, Ar), 3.77 (1 H, d, *J* 16.3, CH_AH_BN), 3.63 (1 H, d, *J* 16.3, CH_AH_BN), 3.60 (6 H, s, 2 × OMe), 3.53 (1 H, td, *J* 4.3 and 13.2), 2.87–2.69 (2 H, m), 2.59–2.46 (4 H, m) and 2.22 (1 H, dd, *J* 8.9 and 14.9); δ_C(67.5 MHz; $CDCl_3$) 173.2, 173.1 (C=O, CO_2Me), 133.8, 133.0 (*ipso*-Ar), 129.6, 126.8, 126.6, 126.2 (Ar), 54.1 (OMe), 51.9 (2 signals, CHN and OMe), 50.7, 48.8 (CH_2N), 33.9 (CH_2) and 32.2 ($ArCH_2$); *m*/*z* (CI, NH_3) 292 [100%, $(M + H)^+$] [Found: $(M + H)^+$, 292.1548. $C_{16}H_{21}NO_4$ requires *M* + H, 292.1549].

(2*S*)-Methyl pyrrolidin-2-ylacetate 7

Trifluoroacetic acid (3.5 cm^3, 45.6 mmol) was added dropwise to a stirred solution of methyl ester **11** (1.0 g, 4.2 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C under nitrogen. After 15 min, the solution was allowed to warm to room temperature and stirred for a further 1.5 h. Then, CH_2Cl_2 (50 cm^3) was added and the organic layer was washed with saturated aqueous potassium carbonate solution (50 cm^3). The aqueous layer was back-extracted with CH_2Cl_2 (3 × 50 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a brown oil. Purification by Kugelrohr distillation gave amino ester **7** (96 mg, 16%) as a colourless oil, bp 135–145 °C/1.0 mmHg; R_F (7:3 $CHCl_3$–MeOH) 0.2; $[a]_D$ +7.0 (*c* 2.6 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 (C=O, CO_2Me); δ_H(270 MHz; $CDCl_3$) 3.68 (3 H, s, OMe), 3.48–3.38 (1 H, m, CHN), 3.05–2.85 (2 H, m, CH_2N), 2.56–2.40 (2 H, m, CH_2CO), 2.40 (1 H, s, NH), 2.01–1.67 (3 H, m) and 1.42–1.29 (1 H, m); δ_C(67.5 MHz; $CDCl_3$) 172.9 (C=O, CO_2Me), 55.0 (CHN), 51.6 (OMe), 46.3, 40.7, 31.2 and 25.0 (CH_2).

(3*S*)-Methyl (1,2,3,4-tetrahydroisoquinolin-3-yl)acetate 17

Trifluoroacetic acid (1.3 cm^3, 17.3 mmol) was added dropwise to a stirred solution of methyl ester **16** (606 mg, 2.0 mmol) in CH_2Cl_2 (8 cm^3) at room temperature under nitrogen. After stirring at room temperature for 2.5 h, the solvent was evaporated under reduced pressure and the residue dissolved in EtOAc (20 cm^3). The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (15 cm^3). The aqueous layer was back-extracted with EtOAc (20 cm^3) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with $CHCl_3$–MeOH–NH_3 (95.5:4.0:0.5) as eluent gave amino ester **17** (315 mg, 79%) as an oil, R_F (94.5:5.0:0.5 $CHCl_3$–MeOH–NH_3) 0.3; $[a]_D$ −53.7 (*c* 0.9 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1731 (C=O, CO_2Me); δ_H(270 MHz; $CDCl_3$) 7.15–7.01 (4 H, m, Ar), 4.13 (1 H, d, *J* 16.3, CH_AH_BN), 4.04 (1 H, d, *J* 16.3, CH_AH_BN), 3.73 (3 H, s, MeO), 3.38–3.31 (1 H, br m, CHN), 2.83 (1 H, dd, *J* 4.0 and 16.3), 2.66 (1 H, dd, *J* 4.1 and 17.0) and 2.55–2.51 (2 H, m); δ_C(67.5 MHz; $CDCl_3$) 172.4 (C=O, CO_2Me), 135.1, 133.8 (*ipso*-Ar), 129.0, 126.0, 125.8 (Ar), 51.6 (MeO), 50.4 (CHN), 48.1 (CH_2N), 40.6 and 34.8 (CH_2); *m*/*z* (CI, NH_3) 206 [100%, $(M + H)^+$] [Found: $(M + H)^+$, 206.1181. $C_{12}H_{15}NO_2$ requires *M* + H, 206.1181].

Hexahydroindolizin-7(1*H*)-one 5 (Table 1, Entry 3)

A solution of diester **6** (2.9 g, 12.6 mmol) in xylenes (11 cm^3) was added dropwise over 3 h (using a syringe pump) to a stirred refluxing solution of sodium methoxide (51 mg, 1.0 mmol) and sodium hydride (1.27 g of a 60 wt% dispersion in mineral oil, 9.2 mmol) in xylenes (60 cm^3) under nitrogen. After stirring for a further 2 h at reflux, the reaction mixture was cooled to 0 °C and acetic acid (2.1 g, 35.4 mmol) was added. Then, water (10 cm^3) was added and the organic layer was extracted with 2 M hydrochloric acid (3 × 20 cm^3). The combined aqueous extracts were basified to pH 8 by addition of saturated aqueous sodium hydrogen carbonate solution and extracted with Et_2O (3 × 20 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. To the oily residue was added MeOH (60 cm^3) and 2 M aqueous potassium hydroxide solution (23 cm^3) and the resulting mixture was heated under reflux for 2 h. After cooling to room temperature, the solvent was evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation§ gave ketone (*S*)-**5** (511 mg, 29%, 90% ee) as a colourless oil, bp 60–65 °C/1 mmHg (lit.,[22] 60–63 °C/1 mmHg); R_F (9:1 $CHCl_3$–MeOH) 0.35; $[a]_D$ +41.4 (*c* 0.9 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1713 (C=O); δ_H(270 MHz; $CDCl_3$) 3.36–3.30 (1 H, m), 3.20–3.13 (1 H, m), 2.68–2.51 (2 H, m), 2.40–2.18 (5 H, m), 2.06–1.76 (3 H, m) and 1.60–1.43 (1 H, m); δ_C(67.5 MHz; $CDCl_3$) 209.3 (C=O), 64.1 (CHN), 53.2, 47.3, 40.6, 31.4 and 22.5 (CH_2); *m*/*z* (EI) 139 [100%, M^+] and 96 (89) [Found: M^+, 139.1002. $C_8H_{13}NO$ requires *M*, 139.0997].

(11a*RS*)-1,3,4,6,11,11a-Hexahydro-2*H*-pyrido[1,2-*b*]isoquinolin-2-one 19 (Table 2, Entry 4)

n-Butyllithium (2.75 cm^3 of a 1.58 M solution in hexanes, 4.35 mmol) was added dropwise to a stirred solution of diisopropylamine (0.65 cm^3, 5.0 mmol) in THF (6 cm^3) at 0 °C under nitrogen. After 10 min, the solution was cooled to −78 °C and a solution of the diester **18** (560 mg, 1.9 mmol) in THF (12 cm^3) was added dropwise over 5 min. The reaction mixture was stirred at −78 °C for 1.5 h and then 12 M hydrochloric acid solution (0.4 cm^3, 5.0 mmol) was added. After being allowed to warm to room temperature, the solvent was evaporated under reduced pressure. To the oily residue was added 6 M hydrochloric acid (50 cm^3). The resulting mixture was heated under reflux for 16 h. After cooling to room temperature, the solution was carefully basified by addition of solid potassium carbonate until saturated. The excess solid was removed by filtration and washed with Et_2O. The aqueous filtrate was extracted with Et_2O (3 × 20 cm^3) and the combined organic extracts were dried (K_2CO_3) and evaporated under reduced pressure to give crude *racemic* ketone **19** (363 mg, 94%) as a yellow solid.

(11a*S*)-1,3,4,6,11,11a-Hexahydro-2*H*-pyrido[1,2-*b*]isoquinolin-2-one 19 (Table 2, Entry 10)

n-Butyllithium (1.15 cm^3 of a 1.5 M solution in hexanes, 1.75 mmol) was added dropwise to a stirred solution of diisopropylamine (0.3 cm^3, 2.1 mmol) in THF (3 cm^3) at 0 °C under nitrogen. After 10 min, the solution was cooled to −78 °C and a solution of the diester **18** (232 mg, 0.8 mmol) in THF (3 cm^3) was added dropwise over 5 min. The reaction mixture was stirred at −78 °C for 20 min and then water (0.1 cm^3, 5.5 mmol) was added. After being allowed to warm to room temperature, the solvent was evaporated under reduced pressure. To the oily residue was added MeOH (5 cm^3) and 2 M aqueous potassium hydroxide solution (2 cm^3) and the resulting mixture was heated under reflux for 3 h. After cooling to room temperature, the reaction mixture was worked up using the procedure described previously to give the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2–MeOH as eluent gave ketone (*S*)-**19** (31 mg, 19%) as an off-white solid, mp 101–109 °C (lit.,[32] 119.5–120.5 °C); R_F (96.5:3.0:0.5 CH_2Cl_2–MeOH–NH_3) 0.5; $[a]_D$ −89.7 (*c* 1.55 in EtOH){lit.,[32] $[a]_D$ −91.0 (*c* 0.26 in EtOH)}; $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 (C=O); δ_H(270 MHz; $CDCl_3$) 7.18–7.13 (2 H, m, Ar), 7.11–7.04 (2 H, m, Ar), 4.04 (1 H, d, *J* 15.3, CH_AH_BN), 3.55 (1 H, d, *J* 15.3, CH_AH_BN), 3.36 (1 H, ddd, *J* 2.8, 5.7 and 11.4, CHN), 2.89–2.82 (2 H, m), 2.79–2.74 (2 H, m), 2.61–2.35 (4 H, m); δ_C(67.5 MHz; $CDCl_3$) 207.8 (C=O), 133.2, 132.1 (*ipso*-Ar), 127.9, 126.4, 126.0, 125.9 (Ar), 57.9 (CHN), 56.7, 54.3 (CH_2N), 47.5, 41.1 and 36.6

§ Note that ketone **5** is a relatively volatile compound and care must be taken when isolating it by distillation.

(CH_2); *m/z* (CI, NH_3) 202 [100%, $(M + H)^+$] [Found: $(M + H)^+$, 202.1229. $C_{13}H_{15}NO$ requires *M* + H, 202.1231].

Using the procedure described above, *n*-butyllithium (1.1 cm^3 of a 1.6 M solution in hexanes, 1.7 mmol), diisopropylamine (0.3 cm^3, 2.1 mmol) and diester **18** (234 mg, 0.8 mmol) in THF (7.5 cm^3) followed by treatment with MeOH (5 cm^3) and 2 M aqueous potassium hydroxide solution (2 cm^3) gave the crude ketone (*S*)-**19** (95 mg, 59%) as a yellow solid which was sufficiently pure for direct use in subsequent double Mannich reactions.

10-Methyl-3,10-diazatricyclo[6.3.1.0^{3,7}]dodecan-12-one 4

Methylamine (1.8 cm^3 of a 2.0 M solution in MeOH, 3.8 mmol) was added dropwise to a stirred solution of ketone (*S*)-**5** (510 mg, 3.6 mmol, 90% ee), paraformaldehyde (334 mg, 11.2 mmol) and acetic acid (0.2 cm^3, 3.5 mmol) in MeOH (4.0 cm^3) at room temperature under nitrogen. The resulting solution was heated under reflux for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and 50% aqueous potassium hydroxide solution (17 cm^3) was added to the residue. The aqueous mixture was extracted with Et_2O (3 × 25 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by Kugelrohr distillation gave *racemic* ketone **4** (208 mg, 29%) as a colourless oil, bp 135–145 °C/0.8 mmHg; R_F (4:1 $CHCl_3$–MeOH) 0.1; $\nu_{max}(CHCl_3)/cm^{-1}$ 1713 (C=O); δ_H(270 MHz; $CDCl_3$) 3.43–1.55 (15 H, m) and 2.26 (3 H, s, NMe); δ_C(67.5 MHz; $CDCl_3$) 215.0 (C=O), 68.5 (NMe), 60.3, 56.55, 55.0, 51.9 (CH_2N), 49.6, 45.75, 45.4 (CH), 27.4 and 22.8 (CH_2); *m/z* (EI) 194 [27%, M^+] and 84 (100) [Found: M^+, 194.1428. $C_{11}H_{18}N_2O$ requires *M*, 194.1419].

Tricyclic ketone 20

Methylamine (0.9 cm^3 of a 2.0 M solution in MeOH, 1.8 mmol) was added dropwise to a stirred solution of *racemic* ketone **19** (350 mg, 1.7 mmol), paraformaldehyde (210 mg, 7.0 mmol) and acetic acid (0.12 cm^3, 2.1 mmol) in MeOH (4.0 cm^3) at room temperature under nitrogen. The resulting solution was heated under reflux for 16 h. After cooling to room temperature, 2 M hydrochloric acid (30 cm^3) was added and the aqueous layer was washed with Et_2O (2 × 20 cm^3). The aqueous layer was basified to pH 14 by addition of 20% aqueous sodium hydroxide solution (20 cm^3) and extracted with Et_2O (3 × 10 cm^3). The combined organic extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with $CHCl_3$–MeOH–NH_3 (89:10:1) as eluent gave *racemic* ketone **20** (211 mg, 47%) as a pale yellow oil, R_F (78:20:2 CH_2Cl_2–MeOH–NH_3) 0.5; $\nu_{max}(CHCl_3)/cm^{-1}$ 1737 (C=O); δ_H(270 MHz; $CDCl_3$) 7.10–7.05 (3 H, m, Ar), 7.01 (1 H, dd, *J* 2.9 and 7.1, Ar), 4.04 (1 H, d, *J* 15.0, CH_AH_BN), 3.49 (1 H, dd, *J* 2.2 and 11.6), 3.39 (1 H, br d, *J* 11.6), 3.33–3.21 (3 H, m), 2.86–2.77 (2 H, m), 2.71–2.56 (4 H, m), 2.48–2.44 (1 H, m) and 2.27 (3 H, s, NMe); δ_C(67.5 MHz; $CDCl_3$) 214.1 (C=O), 133.7, 132.6 (*ipso*-Ar), 128.1, 126.2, 126.1, 125.8 (Ar), 62.7 (CHN), 61.9, 61.2, 57.7, 57.0 (CH_2N), 51.0, 47.9 (CH), 45.7 (NMe) and 32.8 ($ArCH_2$); *m/z* (CI, NH_3) 257 [100%, $(M + H)^+$], [Found: $(M + H)^+$, 257.1651. $C_{16}H_{20}N_2O$ requires *M* + H, 257.1654].

10-Methyl-3,10-diazatricyclo[6.3.1.0^{3,7}]dodecane 2

A solution of *racemic* ketone **4** (3.33 g, 17.2 mmol), hydrazine hydrate (4.4 cm^3, 90.2 mmol) and potassium hydroxide (7.58 g, 135.4 mmol) in diethylene glycol (27 cm^3) was heated at reflux using a silicone oil bath (at 230 °C). After stirring at reflux for 2 h, the volatile components were removed by distillation for 1 h at 150–190 °C. The distillation apparatus was rinsed out with water (15 cm^3) and Et_2O (15 cm^3) and the rinsings used to dilute the reaction mixture. The mixture was extracted with Et_2O (5 × 15 cm^3) and the combined organic extracts were washed with 20% aqueous sodium hydroxide solution (5 × 15 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give crude *racemic* diamine **2** (2.12 g, 68%) as a colourless oil which was of high purity by ^{1}H NMR spectroscopy.

In a separate experiment, *racemic* ketone **4** (330 mg, 1.7 mmol), hydrazine hydrate (0.44 cm^3, 9.0 mmol) and potassium hydroxide (752 mg, 13.0 mmol) in diethylene glycol (3.4 cm^3) gave the crude product. Purification by Kugelrohr distillation gave *racemic* diamine **2** (165 mg, 54%) as a colourless oil, bp 140–150 °C/0.5 mmHg; R_F (4:1 $CHCl_3$–MeOH) 0.1; $\nu_{max}(CHCl_3)/cm^{-1}$ 2931 and 2783; δ_H(270 MHz; $CDCl_3$) 3.25–1.20 (17 H, m) and 2.17 (3 H, s, NMe); δ_C(67.5 MHz; $CDCl_3$) 67.4 (CHN), 60.4, 57.3, 54.9, 54.3 (CH_2N), 47.5 (NMe), 33.3 (CH_2), 31.2, 30.0 (CH), 26.7 and 20.7 (CH_2); *m/z* (EI) 180 [60%, M^+] and 122 (35) [Found: M^+, 180.1627. $C_{11}H_{20}N_2$ requires *M*, 180.1626].

Diamine 3

Using the procedure described above, *racemic* ketone **20** (211 mg, 0.8 mmol), hydrazine hydrate (0.2 cm^3, 4.1 mmol) and potassium hydroxide (320 mg, 5.7 mmol) in diethylene glycol (1.7 cm^3) gave the crude product. Purification by Kugelrohr distillation gave *racemic* diamine **3** (154 mg, 77%) as a colourless oil (which solidified on standing overnight at −20 °C), bp 140–150 °C/0.3 mmHg; mp 69–72 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 1588 and 739; δ_H(270 MHz; $CDCl_3$) 7.11–7.02 (3 H, m, Ar), 6.95 (1 H, dd, *J* 2.2 and 6.6, Ar), 3.97 (1 H, d, *J* 15.5, CH_AH_BN), 3.28–3.03 (5 H, m), 2.55 (1 H, q, *J* 2.9), 2.52 (1 H, dd, *J* 3.5 and 6.7), 2.45 (1 H, ddd, *J* 1.7, 3.8 and 11.3), 2.21–2.15 (1 H, m), 2.17 (3 H, s, NMe), 2.04 (1 H, dd, *J* 2.9 and 11.7), 1.99–1.94 (1 H, m), 1.79–1.74 (1 H, m) and 1.66–1.62 (2 H, m); δ_C(67.5 MHz; $CDCl_3$) 134.9 (*ipso*-Ar), 128.1, 125.9, 125.6, 125.3 (Ar), 61.1 (CHN), 60.7, 60.3, 60.2, 58.7 (CH_2N), 47.8 (NMe), 34.1 (CH_2), 33.7 (CH), 33.5 (CH_2) and 30.7 (CH); *m/z* (EI) 242 [100%, M^+], [Found: M^+, 242.1783. $C_{16}H_{22}N_2$ requires *M*, 242.1783].

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