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Synthesis of sparteine-like chiral diamines and evaluation in the enantioselective lithiation–substitution of *N*-(*tert*-butoxycarbonyl)-pyrrolidine †

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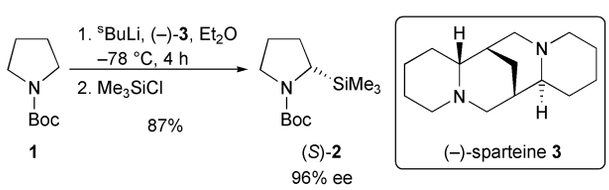
Three chiral diamines were synthesised and evaluated as sparteine surrogates in the lithiation–substitution of *N*-(*tert*-butoxycarbonyl)pyrrolidine. The synthesis and attempted resolution of sparteine-like diamines {(1*S**,2*R**,8*R**)-10-methyl-6,10-diazatricyclo[6.3.1.$0^{2,6}$]dodecane and (1*S**,2*R**,9*R**)-11-methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane} (*via* inclusion complex formation) are reported. Unfortunately, it was only possible to resolve the diazatricyclo-[7.3.1.$0^{2,7}$]tridecane compound. An alternative route to (1*R*,2*S*,9*S*)-11-methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane starting from the natural product, (−)-cytisine, is described. This simple three-step route furnished gram-quantities of a (+)-sparteine surrogate. X-Ray crystallography of an intermediate in the route, (1*R*,5*S*,12*S*)-3-methoxycarbonyl-decahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one, enabled the stereochemistry of all of the tricyclic diamines described in this paper to be unequivocally established. Two other diamines, starting from (*S*)-proline and resolved 2-piperidine ethanol, were prepared using standard methods. These diamines lacked the bispidine framework of (−)-sparteine and were found to impart vastly inferior enantioselectivity. It was concluded that, for the asymmetric lithiation–substitution of *N*-Boc pyrrolidine, a rigid bispidine framework and only three of the four rings of (−)-sparteine are needed for high enantioselectivity. Furthermore, it is shown that diamine (1*R*,2*S*,9*S*)-11-methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane is the first successful (+)-sparteine surrogate.

Introduction

In 1991, Kerrick and Beak reported the conversion of *N*-Boc pyrrolidine **1** into substituted pyrrolidines such as (*S*)-**2** (79–96% ee) *via* enantioselective lithiation with *sec*-butyllithium and (−)-sparteine **3** followed by reaction with a range of electrophiles.[1] The first example of high enantioselectivity in asymmetric lithiation–substitution using *sec*-butyllithium and (−)-sparteine **3** (for the α-functionalisation of *O*-alkyl carbamates) was described by Hoppe *et al.* in the previous year.[2] Since these seminal contributions, a wealth of successful uses of (−)-sparteine **3** in asymmetric synthesis has been documented in reviews[3] and many publications.[4] The impact of (−)-sparteine **3** as a chiral ligand in organolithium chemistry has been incredible and, more recently, the use of (−)-sparteine **3** has been extended to magnesium[5] and palladium.[6] A specific example of the functionalisation of *N*-Boc pyrrolidine **1**, reported by the Beak group, is shown in Scheme 1.[1,7]

Beak's optimised conditions for the conversion of *N*-Boc pyrrolidine **1** into (*S*)-**2** involved treatment of **1** with 1.2 equivalents of *sec*-butyllithium/(−)-sparteine **3** in diethyl ether at −78 °C for 4 h followed by reaction with trimethylsilyl chloride. In this way, an 87% yield of (*S*)-**2** of 96% ee was obtained.[1,7] It was shown that isopropyllithium could also be used for the lithiation but other alkyllithiums, other solvents and the use of sub-stoichiometric amounts of alkyllithum/(−)-sparteine **3** gave considerably lower yields and enantioselectivity. Through a very detailed investigation,[8,9] Beak and co-workers demonstrated that the reaction proceeded through the rapid formation of an alkyllithium–diamine complex and subsequent relatively slow but highly enantioselective lithiation/deprotonation (*via* Boc carbonyl organolithium "delivery"[10]) to give a configurationally stable organolithium species that was trapped by trimethylsilyl chloride. In more recent work, Wiberg and Bailey have calculated a transition state model[11,12] that accounts for the observed enantioselectivity in the lithiation of *N*-Boc pyrrolidine **1**. Key steric interactions were identified to explain the differences in transition state energies for the removal of the *pro*-*R* and *pro*-*S* protons.



Scheme 1

As the sense of asymmetric induction imparted by (−)-sparteine **3** in the α-functionalisation of *N*-Boc pyrrolidine **1** is opposite to that present in natural (*S*)-proline, the (−)-sparteine-mediated methodology is a useful stereochemical complement to synthetic routes from (*S*)-proline. Beak has demonstrated the usefulness of the *N*-Boc pyrrolidine methodology by preparing amino alcohol **4** (>99.5% ee)[13] (precursor to Corey's CBS reagent) and the hydrochloride salt of 2,5-dimethylpyrrolidine **5** (>99% ee)[7] (a well-used chiral auxiliary). Our own group has utilised similar methodology in a new route to diamine **6** (85% ee)[14] whilst Majewski *et al.* used the reaction between lithiated *N*-Boc pyrrolidine and a tartaric acid-derived

† Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of **34**, **37**, *rac*-**25**, **39**, *rac*-**41**, (*R*)-**41**, **44**, (+)-**24** and (*S*)-**48**·CSA. See http://www.rsc.org/suppdata/ob/b3/b308410h/

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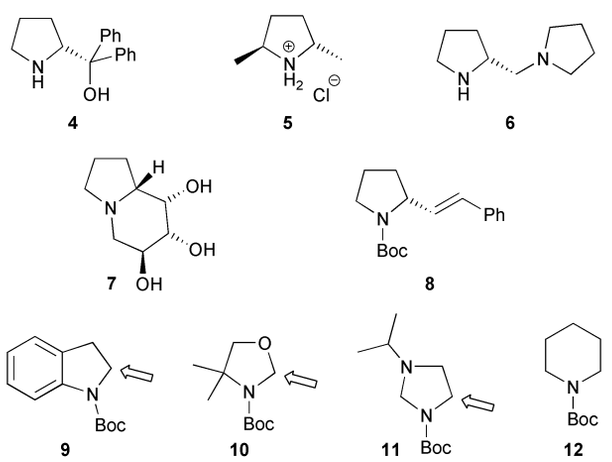
aldehyde as a key step in the synthesis of 8-epi-1-deoxycastanospermine **7**.[15] Most recently, Dieter *et al*. have expanded the synthetic utility of lithiated *N*-Boc pyrrolidine by transmetallating the organolithium to the organocuprate (with very little loss of stereochemical integrity) enabling a wider range of electrophiles to be coupled to the pyrrolidine unit.[16] In this way, vinyl-substituted pyrrolidine **8** was prepared in 86% ee.

Extension of the *N*-Boc-pyrrolidine methodology to other five-membered ring systems has also proved very successful: Beakand co-workers reported the highly enantioselective lithiation–substitution of *N*-Boc indoline **9**,[17] Kise *et al*. described high enantioselectivity in the lithiation of *N*-Boc oxazolidine **10**[18] and Coldham *et al.* developed a new route to chiral diamines *via* α-functionalisation of *N*-Boc imidazoline **11** (at the position indicated by the arrow).[19] In contrast, lithiation–substitution of the corresponding six-membered ring, *N*-Boc piperidine **12**, using *sec*-butyllithum-(−)-sparteine **3** was much less satisfactory: the trimethylsilyl adduct was generated from *N*-Boc piperidine **12** in only 8% yield and with 74% ee.[20] This difference between the five- and six-membered ring systems is dramatic but is not without precedent and has been rationalised using computational methods.[12,20]

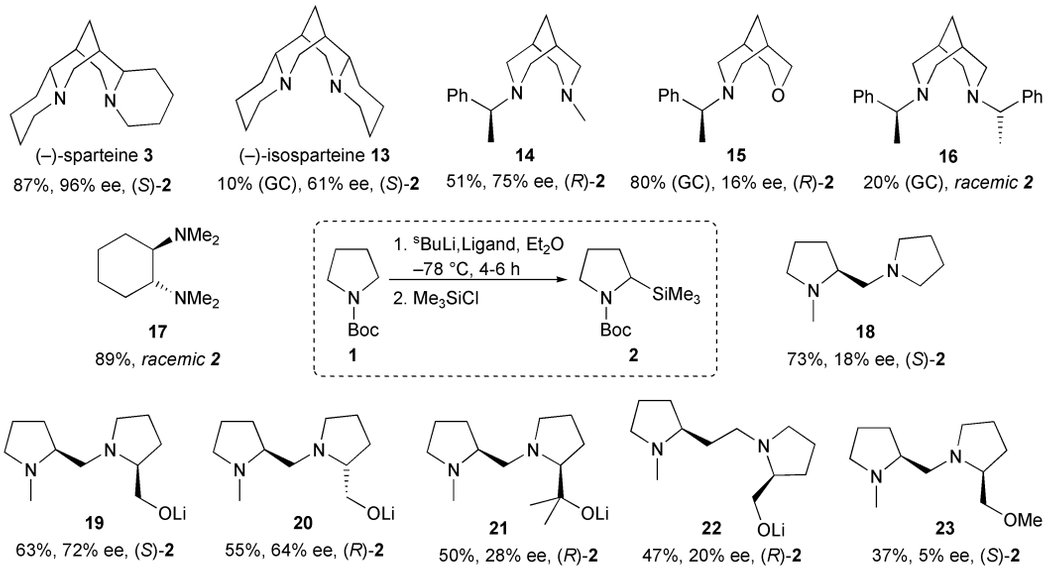


One of the main limitations of using (−)-sparteine **3** in asymmetric synthesis is that it is only commerically available as its (−)-antipode and this limitation has attracted our interest over the last few years. (+)-Sparteine **3**, also reported to be a natural product,[21] can be most easily prepared by resolution of *racemic* lupanine (isolated from the natural source) and subsequent deoxygenation[22] although a resolution of *racemic* sparteine **1** has also been described.[23] An elegant, multi-step, asymmetric synthesis of (+)-sparteine **3** has been recently disclosed by Aubé and co-workers[24] but this route is unlikely to provide multi-gram quantities of (+)-**3**. Due to the lack of ready availability of (+)-sparteine **3**, several groups have developed ingenious strategies for synthesising either enantiomer of a particular compound using (−)-sparteine. These include: (i) changing the solvent;[25] (ii) using electrophiles that react with retention or inversion of configuration;[26] (iii) using a stereodivergent 1,3-elimination process;[27] (iv) using deuterium as a "blocking group";[28] (v) using secondary and tertiary amides;[29] (vi) making use of a transmetallation protocol;[30] (vii) using different chelating groups;[31] and (viii) using a dilithiation protocol.[32] In addition, there are certain reactions which proceed with higher enantioselectivity using bisoxazoline ligands (readily available in either enantiomeric form) compared to (−)-sparteine **3**.[33] With specific reference to the synthesis of enantiomerically enriched pyrrolidines, Gawley *et al.* have described a detailed study on the stereochemistry (retention or inversion) of reaction of a lithiated pyrrolidine with different electrophiles[34] and Coldham *et al.* have recently described an approach based on the dynamic thermodynamic resolution of a racemic organolithium species.[35]

Unfortunately, none of the methods described above provides a general solution to the fact that (+)-sparteine **3** is not readily accessible. Thus, there is still a need to develop a ligand that behaves in an enantiocomplementary fashion to (−)-sparteine **3**. With this in mind, Beak and co-workers investigated a wide range of ligands for the conversion of *N*-Boc pyrrolidine **1** into trimethylsilyl adduct **2**.[36] A detailed overview of the results is presented in Scheme 2 and provides insight into some of the key design features that are required in developing new types of ligand that could function as (+)-sparteine **3** surrogates. The isolated yield (or the GC yield) reflects the degree of lithiation of *N*-Boc pyrrolidine **1** and this is strongly dependent on the steric hindrance of the alkyllithium-chelated ligand. For example, *sec*-butyllithium/TMEDA lithiates *N*-Boc pyrrolidine **1** in 30 min whereas *sec*-butyllithium/(−)-sparteine **3** requires at least 4 h to reach the same degree of lithiation. With (−)-sparteine **3**, an 87% yield of (*S*)-**2** of 96% ee was obtained (after 4 h lithiation time). In contrast, use of (−)-isosparteine **13** led to only 10% lithiation of **1** under the same conditions and (*S*)-**2** was obtained in a reduced 61% ee. Compared to (−)-sparteine **3**, an alkyllithium complexed by (−)-isosparteine **13** is more sterically encumbered as *both* six-membered rings extend outwards towards the organolithium. In (−)-sparteine **3**, one of the rings is held away from the lithium making the resulting organolithium complex more reactive. Increased steric hindrance around the organolithium also correlates with lower enantioselectivity. Related results were also observed in a series of bispidines (**14**–**16**). The best result was obtained with less sterically hindered bispidine **14** (compared to C_2-symmetric **16**): adduct (*R*)-**2** of 75% ee was obtained in 51% yield. Although the reaction mixture was heterogeneous, the result is notable since the sense of induction with bispidine **14** was opposite to that obtained with (−)-sparteine **3**. It was also found that replacing the *N*-methyl group in **14** with an oxygen atom (as in **15**) was unsatisfactory.

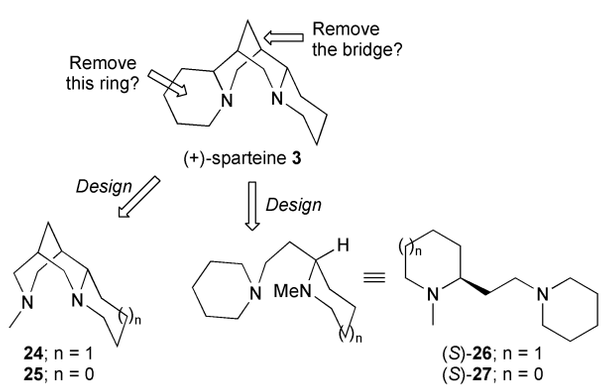
Beak has also studied a series of non-bispidine based ligands. Diamine **17** was a very good ligand for the reaction but furnished adduct **2** in essentially racemic form. This has been rationalised using computational methods.[37] Of the (*S*)-proline-derived ligands **18**–**23**, some interesting trends emerge. Ligands **19** and **20** (containing an O–Li group, generated from the corresponding alcohol using an extra equivalent of alkyllithium) gave the highest enantioselectivity. Interestingly, changing the configuration at the prolinol group led to a reversal in the enantioselectivity indicating that this is the most important chiral centre in the ligands. Use of *sec*-butyllithum/ligand **19** generated a very good 63% yield of (*S*)-**2** of 72% ee (same sense of induction as that obtained with (−)-sparteine **3**). Increased steric hindrance (as in **21**), the presence of an extra CH_2 linker group (as in **22**), replacement of the O–Li group by a methoxy group (as in **23**) or removal of the CH_2O–Li group (as in **18**) all gave significantly inferior enantioselectivity compared to **19** and **20**. In addition, it is of interest to note that ligand **19** was the optimal one for Coldham's dynamic thermodynamic resolution of a racemic lithiated pyrrolidine.[35] More recently, Kozlowski and co-workers have investigated the use of three different 1,5-diaza-*cis*-decalins for the conversion of **1** into **2** and the highest enantioselectivity obtained was a modest 26% ee of (*R*)-**2**[38] (although these ligands were more successful in oxidative biaryl coupling reactions[39]). Based on the results to date, the best ligands for the conversion of *N*-Boc pyrrolidine **1** into trimethylsilyl adduct **2** are **14** and **19**. However, the results with these ligands fall around 20% ee lower than the result obtained with (−)-sparteine **3**.

In this paper, we provide additional information on the effect of ligand structure on the enantioselectivity of converting **1** into **2** and we also specifically address the issue of developing a ligand that behaves in an enantiocomplementary fashion to (−)-sparteine **3**. The new ligands were designed by considering



Scheme 2

the 3-D structure of (+)-sparteine **3** in its lithium-chelating conformation and by studying the calculated transition state for lithiation of *N*-Boc pyrrolidine **1** by an alkyllithium/(−)-sparteine **3** complex[11,12] (Scheme 3). It appeared to us that one of the six-membered rings in (+)-sparteine **3** was held away from the lithium ion and we speculated that it may not be required for high enantioselectivity in sparteine reactions. In this way, we designed (+)-sparteine-like diamines **24** and **25**. On further inspection, we wondered whether the rigid bispidine framework was required for high enantioselectivity. Hence, we designed diamines **26** and **27** which could in principle mimic (+)-sparteine **3**. Diamines **26** and **27** are also analogues of ligand **22** (see Scheme 2), previously studied by Beak. After considerable effort, we succeeded in synthesising ligands **24**, **26** and **27** in enantioenriched forms and were able to test their efficacy in the conversion *N*-Boc pyrrolidine **1** into **2**.[40] Herein we present our results.

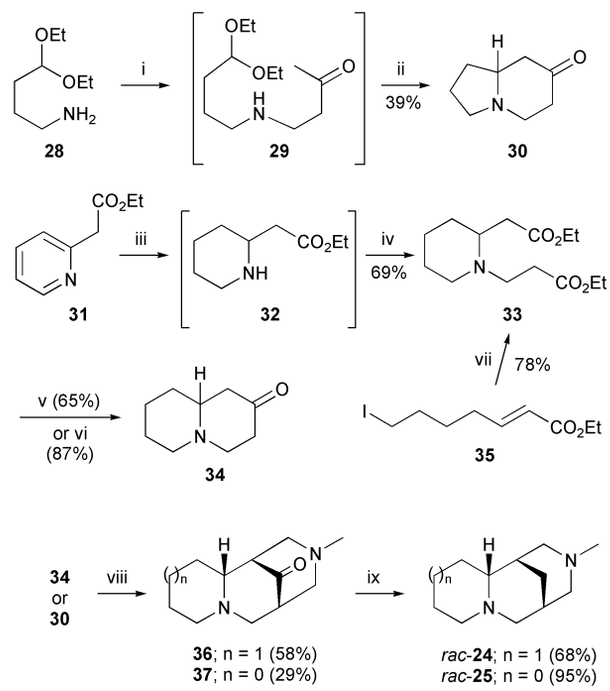


Scheme 3

Results and discussion

Synthesis and resolution of diamines *rac*-24 and *rac*-25

In a previous paper,[41] we reported an approach to enantiomerically enriched diamine **25** starting from (*S*)-proline which was unsuccessful due to racemisation in a double Mannich reaction. Thus, our attention turned to the synthesis of *racemic* diamines **24** and **25** and an investigation of methods for their resolution. We have previously synthesised diamine *rac*-**25**[41] (albeit unintentionally) whilst diamine *rac*-**24** is a known compound, prepared by Scheiber and Nemes.[42] Our optimised methods for the preparation of multi-gram quantities of diamines *rac*-**24** and *rac*-**25** are summarised in Scheme 4.



Scheme 4 *Reagents and conditions:* i, Methyl vinyl ketone, Et_2O, 0 °C, 1 h; ii, $HCl_{(aq)}$, 100 °C, 2.5 h; iii, PtO_2, H_2, $HCl_{(aq)}$, EtOH, rt, 24 h; iv, ethyl acrylate, Et_3N, EtOH, rt, 66 h; v, (a) NaH, NaOEt, xylene, reflux, 5 h; (b) $HCl_{(aq)}$, reflux, 16 h; vi, (a) LHMDS, THF, −78 °C, 2 h; (b) $HCl_{(aq)}$, reflux, 16 h; vii, β-alanine ethyl ester·HCl, K_2CO_3, EtOH, reflux, 60 h; viii, $MeNH_2$, $(CH_2O)_n$, AcOH, MeOH, reflux, 16 h; ix, $N_2H_4{\cdot}H_2O$, KOH, diethylene glycol, reflux, 2 h.

For the synthesis of diamine *rac*-**25**, amino ketone **30** was required and we had most success with an approach described by King.[43] In our hands, commercially available 4,4-diethoxybutan-1-amine **28** was reacted with freshly distilled methyl vinyl ketone to give intermediate **29** which was cyclised *via* an intramolecular Mannich reaction in hydrochloric acid (reaction temperature of 100 °C was essential) to give amino ketone **30**[44] in 39% distilled yield. Despite attempted optimisation (including use of a more recent protocol described by Heathcock and co-workers in their route to petrosins A and B[45]), we were unable to improve the yield of **30** and the reaction was even lower yielding on scales >20 mmol.

The King route is less direct to six-ring amino ketone **34** as the corresponding 5,5-diethoxypentan-1-amine is not commercially available. Thus, based on literature precedent,[46,47] we

optimised a three-step approach to amino ketone **34** starting from ethyl-2-pyridyl acetate **31**. Hydrogenation of pyridine **31** under acidic conditions[46] gave crude piperidine **32** which was reacted with ethyl acrylate in the presence of triethylamine[48] to give bis-ester **33** in 69% yield (after distillation) over the two steps. The Dieckmann condensation of **33** to **34**[44,47] proceeded in 65% yield using Leonard *et al.*'s procedure[47] (sodium hydride/sodium ethoxide in refluxing xylene) but in 87% yield using lithium hexamethyldisilazide (LHMDS) as the base. We prefer the LHMDS procedure and this also scaled up more reliably than Leonard's protocol. In both methods, it is necessary to remove all of the THF (by evaporation) before refluxing overnight in hydrochloric acid. An alternative approach to bis-ester **33** starting from iodo ester **35** (prepared according to the literature route[49–51]) was also briefly investigated. Based on Bunce *et al.*'s approach[49] to cyclic amines, iodo ester **35** and β-alanine ethyl ester hydrochloride underwent an intermolecular substitution reaction followed by an intramolecular conjugate addition in the presence of base to give bis-ester **33**. We found that the use of potassium carbonate in place of triethylamine gave improved yields in this type of reaction and bis-ester **33** was isolated in 78% yield. However, the need for the preparation of iodo ester **35** means that we prefer the three-step route to amino ketone **34** starting from pyridine **31**.

The key step in the route to diamines *rac*-**24** and *rac*-**25** is the double Mannich reaction (*eg* **34** → **36**), precedented in the work of Scheiber and Nemes[42] as it is here that the required relative stereochemistry is established. For the double Mannich reactions of amino ketones **34** and **30**, we discovered that a simple procedure described by Beak and co-workers.[36] gave consistently better results than the more complicated protocol reported by Scheiber and Nemes.[42] Thus, amino ketones **34** and **30** were reacted with methylamine, paraformaldehyde and acetic acid in refluxing methanol to give diazatricyclic ketones **36** (58% yield) and **37** (29% yield), respectively. These compounds were formed as the only isolable diastereomers and their relative stereochemistry was assigned as that depicted in Scheme 4. This has subsequently been unequivocally verified by X-ray crystallography of an intermediate in an independent synthesis of diamine (+)-**24** (*vide infra*). As depicted for the synthesis of **36** (Fig. 1), the observed double Mannich stereochemistry is a consequence of the preferred chair–chair conformation of amino ketone **34** and the fact that the second intramolecular Mannich reaction to form the new ring can only occur *via* an axially oriented iminium ion. Finally, standard Wolff–Kishner reduction removed the carbonyl group in each of **36** and **37** to generate diamines *rac*-**24** and *rac*-**25**. In our opinion, the best ways of synthesising diamines *rac*-**24** and *rac*-**25** are presented in Scheme 4: starting from commercial materials, diamine *rac*-**25** can be prepared in a convenient three-step route whereas diamine *rac*-**24** is synthesised *via* a slightly longer five-step route.

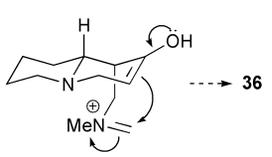
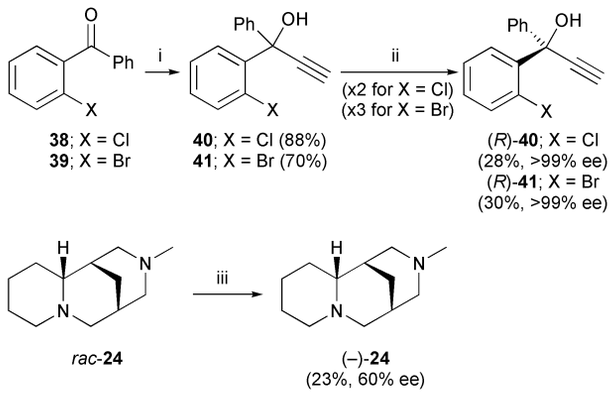


Fig. 1

With multi-gram quantities of racemic **24** and **25** in hand, their resolution was investigated next. Classical resolution methods using tartaric acid (and derivatives), malic acid and camphorsulfonic acid in a range of solvents met with uniform failure. In the few cases where crystal formation was observed, surprisingly, only racemic crystals were isolated. Thus, we sought substrates where (−)-sparteine **3** had been successfully used as a resolving agent and our literature survey revealed only one example. In 1983, Toda *et al.* reported the resolution of a series of acetylinic alcohols (*e.g.* **40** and **41**) *via* inclusion complex formation with (−)-sparteine **3**.[52] Our plan was to use enantioenriched acetylinic alcohols such as **40** and **41** (resolved using (−)-sparteine **3**) to resolve racemic diamines **24** and **25** into their respective enantiomers. As diamines **24** and **25** were significantly "sparteine-like" in structure, we hoped that some success would be obtained in this approach. Our results are summarised in Scheme 5.



Scheme 5 *Reagents and conditions:* i, HC≡CMgBr, THF, reflux, 16 h; ii, (a) (−)-sparteine **3**, acetone, rt, 16 h; (b) filter to collect crystals; (c) treat crystals with 2 M $HCl_{(aq)}$; iii, alcohol (*R*)-**40** (>99% ee), acetone, rt, 16 h; (b) filter to collect crystals; (c) treat crystals with 2 M $HCl_{(aq)}$.

Racemic acetylinic alcohols **40** and **41** were prepared by reaction of commercially available ketone **38** and ketone **39**[53] (prepared by Friedel–Crafts acylation of benzene) with ethynylmagnesium bromide in refluxing THF (Scheme 5). The resolution of alcohols *rac*-**40** and *rac*-**41** was accomplished satisfactorily using Toda's method.[52] As an example, a description of the resolution of *rac*-**40** using (−)-sparteine **3** is provided. An equimolar mixture of alcohol *rac*-**40** and (−)-sparteine **3** was left for 16 h in acetone. During this period, some of the solvent evaporated slowly and crystals of an inclusion complex formed (aided by the addition of light petroleum 40–60 °C). The crystals were collected by filtration, treated with 2 M hydrochloric acid and the resulting enantioenriched alcohol (*R*)-**40** {35% yield, $[\alpha]_D$ −115.2 (*c* 0.6 in MeOH)} was isolated after extraction into diethyl ether. This alcohol was then recomplexed with fresh (−)-sparteine **3** and the process repeated to give alcohol (*R*)-**40** {$[\alpha]_D$ −139.6 (*c* 0.6 in MeOH), lit.,[54] $[\alpha]_D$ −129.0 (*c* 0.2 in MeOH)} of >99% ee as judged by chiral HPLC. The yield of alcohol (*R*)-**40** was 28% from *rac*-**40** (out of a maximum 50%). From the first complexation with (−)-sparteine **3**, a 64% yield of (*S*)-**40** {$[\alpha]_D$ +58.4 (*c* 0.6 in MeOH)} was also obtained. However, it was not possible to improve the enantiomeric excess of alcohol (*S*)-**40** beyond ~50% by further complexation with (−)-sparteine **3**. The resolution of alcohol *rac*-**41** required three complexations to reach >99% ee: alcohol (*R*)-**41** {$[\alpha]_D$ −123.6 (*c* 1.1 in MeOH), lit.,[54] −114 (*c* 0.2 in MeOH)} of >99% ee by chiral HPLC was obtained in 30% yield.

Diamine *rac*-**24** was then partially resolved *via* inclusion complex formation with resolved alcohol (*R*)-**40** (>99% ee) using essentially the same procedure as that described above. After one complexation, we obtained a 23% yield of diamine (−)-**24** {$[\alpha]_D$ −15.7 (*c* 0.5 in EtOH)} of 60% ee and a 68% yield of diamine (+)-**24** {$[\alpha]_D$ +6.1 (*c* 0.6 in EtOH)} of 30% ee. The enantiomeric excess of these diamines was determined using ^{1}H NMR spectroscopy in the presence of the chiral shift reagent, (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Initially, we assigned the absolute stereochemistry of diamine (−)-**24** to be that depicted in Scheme 5 (*i.e.* the same as naturally occurring (−)-sparteine **3**) based on the fact that it was generated from

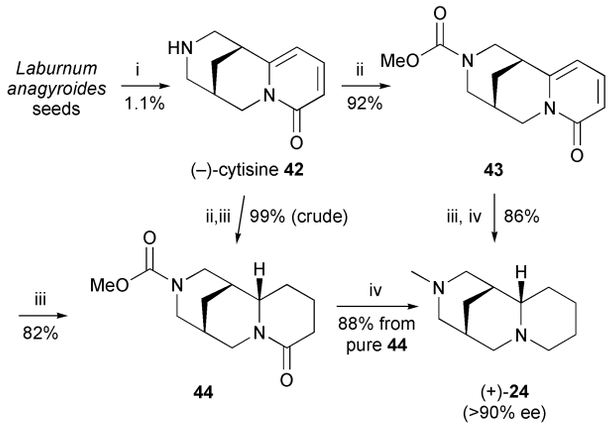
the crystals obtained from *rac*-**24** and alcohol (*R*)-**40** (itself generated from the crystals obtained from *rac*-**40** and (−)-sparteine **3**). This was subsequently confirmed when we synthesised diamine (+)-**24** starting from (−)-cytisine **42** of known absolute stereochemistry (*vide infra*). Presumably, diamine (−)-**24** of 60% ee could be further enriched with additional complexations. However, as supply of alcohol (*R*)-**40** and diamine *rac*-**40** was limited, complexation a second time with (−)-sparteine was not attempted. The resolution was reproducible in the 50–60% ee range and after repeating it a few times, we obtained sufficient quantity of diamine (−)-**24** of 55% ee for its evaluation as a (−)-sparteine **3** mimic. In contrast to diamine *rac*-**24**, the five-ring analogue, diamine *rac*-**25** was completely resistant to resolution using alcohol (*R*)-**40** (no crystals were formed). Even alcohol (*R*)-**41**, which was successfully used to resolve racemic sparteine,[52] did not generate any crystals when combined with *rac*-**25**. As Toda *et al*. found, small changes to the structure of the alcohol or the diamine can affect inclusion complex formation considerably.[52,54]

In summary, diamine (−)-**24** of 55% ee was generated *via* resolution of the racemate (prepared in five steps) using alcohol (*R*)-**40** (itself obtained by resolution using (−)-sparteine **3**). Although this is a fairly inefficient route to diamine (−)-**24** that would only function as a mimic of (−)-sparteine **3**, it does represent the first synthesis of non-racemic diamine **24**. Unfortunately, attempts to prepare diamine (+)-**24** *via* this approach (from either the mother-liquors of the resolution of alcohol *rac*-**40/41** or the mother-liquors of the resolution of diamine *rac*-**24**) never exceeded 30% ee. In addition, the approach could not be extended to prepare enantioenriched five-ring-substituted diamine **25**.

Synthesis of diamine (+)-24 from (−)-cytisine

Due to the limited success in the resolution of diamines *rac*-**24** and *rac*-**25**, we sought an alternative route to the enantioenriched diamines and were attracted to the possibility of starting from (−)-cytisine **42**, another natural product from the same family as (−)-sparteine **3**. Unfortunately, (−)-cytisine **42** is prohibitively expensive from commercial suppliers.[55] However, full details of the extraction of (−)-cytisine **42** from *Laburnum anagyroides* seeds have been recently reported in the supporting information of a communication from Lasne and co-workers that describes the preparation of (−)-cytisine analogues for a study of nicotinic receptors.[56] We found this extraction procedure to be a convenient source of multi-gram quantities of (−)-cytisine **42** suitable for the preparation of diamine (+)-**24** in >90% ee. An overview of the straightforward synthetic route is shown in Scheme 6.

Following the literature protocol,[56] (−)-cytisine **42**[57,58] was extracted in 1.1% mass yield (after crystallisation from acetone) from 200 g of powdered *Laburnum anagyroides* seeds (Vilmorin, France). Next, the free amine was N-protected using 10 equivalents of each of triethylamine and methyl chloroformate to give methyl carbamate **43** in 92% yield.[59] The literature conditions reported for this step utilised the large excess of the reagents but we found that 1.1 equivalents of each worked equally well (see Experimental section for details). Hydrogenation of the pyridone functionality using platinum(IV) oxide (Adams' catalyst)[60,61] was then explored. Reaction of pyridone **43** in ethanol with hydrogen (at atmospheric pressure) and Adams' catalyst furnished lactam **44** in 82% yield after chromatography. Lactam **44** was the only diastereomer produced in this reaction (according to ^{1}H and ^{13}C NMR spectroscopy of the crude product) and its stereochemistry was unequivocally assigned as that indicated by X-ray crystallography (Fig. 2). As shown in Fig. 2, H-12 is *cis* to the methylene bridge between carbons C-1 and C-5 and, crucially, this is the relative stereochemistry required in sparteine-like diamine **24** (see Scheme 3). Thus, hydrogenation



Scheme 6 *Reagents and conditions:* i, (a) $NH_4OH_{(aq)}$, CH_2Cl_2, MeOH, rt, 3 days; (b) 3 M $HCl_{(aq)}$; (c) $NH_4OH_{(aq)}$ then extract into CH_2Cl_2; (d) recrystallise from acetone; ii, Et_3N, MeO_2CCl, CH_2Cl_2, rt, 3.5 h; iii, PtO_2, H_2, EtOH, rt, 5 h (typically); iv, $LiAlH_4$, THF, reflux, 16 h.

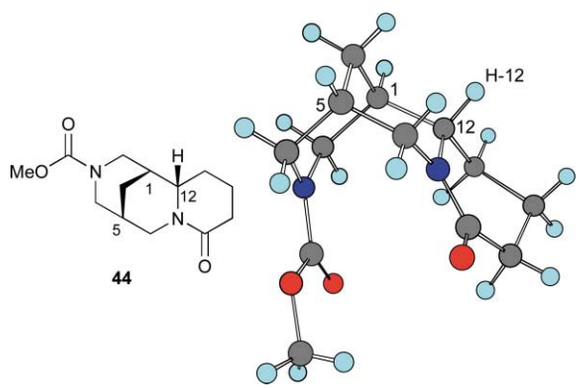


Fig. 2 Chem3-D® representation of the X-ray crystal structure of lactam **44**.

occurred exclusively on the less sterically hindered *exo* face of pyridone **43**, as precedented in the work of Ohmiya and co-workers.[61]

Finally, reduction of lactam **44** with lithium aluminium hydride (in THF at reflux) converted the methyl carbamate protecting group into the required *N*-methyl substituent as well as transforming the lactam into the piperidine ring (Scheme 6). In this way, diamine (+)-**24** {$[\alpha]_D$ +26.5 (*c* 1.0 in EtOH)} of >90% ee (determined using ^{1}H NMR spectroscopy in the presence of the chiral shift reagent, (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) was obtained in 88% yield. As far as can be judged by ^{1}H and ^{13}C NMR spectroscopy, diamine (+)-**24** is diastereomerically pure (as we have previously prepared its diastereomer[62] which has distinguishable NMR spectroscopic data) and the absolute stereochemistry of (+)-**24** was assigned based on the known absolute stereochemistry of (−)-cytisine **42**.

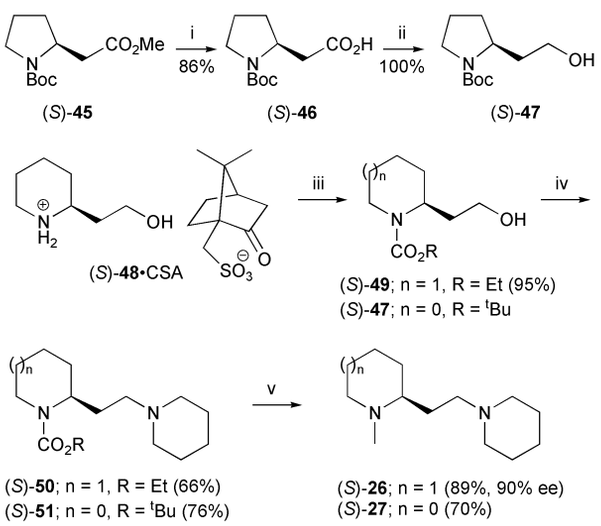
Further optimisation of the three-step route from recrystallised (−)-cytisine **42** was carried out and we have two alternative protocols for preparing diamine (+)-**24**. Chromatography can be avoided throughout the synthesis and crude methyl carbamate **43** can be hydrogenated to give lactam **44** in 99% crude yield. However, subsequent lithium aluminium hydride reduction of crude **44** generated in this way was lower yielding. Thus, we recommend purification of carbamate **43** using chromatography to give >90% yield of high purity **43**. Then, pyridone hydrogenation of pure **43** followed by lithium aluminium hydride reduction (without purification of the intermediate **44**) then gave diamine (+)-**24** in a reproducible 86% yield after purification by distillation.

To summarise, the route to diamine (+)-**24** starting from recrystallised (−)-cytisine (Scheme 6) has several notable features. Firstly, the absolute stereochemistry of (−)-cytisine is suitable for generating a mimic of (+)-sparteine **3**. Secondly,

the pyridone hydrogenation affords the *relative* stereochemistry required in diamine (+)-**24** with complete control. Thirdly, the methyl carbamate group acts as both an N-protecting group and a masked *N*-methyl group (revealed by a late-stage lithium aluminium hydride reduction). And, finally, the simple, three-step route is high yielding (79% overall) and produces gram quantities of diamine (+)-**24**.

Synthesis of diamines (*S*)-26 and (*S*)-27

The preparation of enantioenriched diamines (*S*)-**26** and (*S*)-**27**, lacking the rigid bispidine framework, has also been carried out. The (*S*) absolute configuration was selected as diamines with this configuration were expected to behave as (+)-sparteine mimics (see Scheme 3). Diamine (*S*)-**26** was prepared from the known[63,64] camphorsulfonate salt of piperidine ethanol (*S*)-**48**·CSA and diamine (*S*)-**27** was prepared from known[41] protected amino ester (*S*)-**45**, ultimately derived from (*S*)-proline. The full synthetic routes are depicted in Scheme 7.



Scheme 7 *Reagents and conditions:* i, $LiOH_{(aq)}$, dioxane, rt, 16 h; ii, BH_3·Me_2S, THF, reflux, 1 h iii, (a) $K_2CO_{3(aq)}$, EtO_2CCl, CH_2Cl_2, rt, 20 h; (b) K_2CO_3, MeOH, rt, 16 h; iv, (a) Et_3N, MsCl, CH_2Cl_2, 0 °C then rt for 1 h; (b) piperidine, toluene, DBU (for **49** only), reflux, 16–24 h; v, $LiAlH_4$, THF, rt for 48 h (for **26**) or reflux for 16 h (for **27**) (see Experimental section for details).

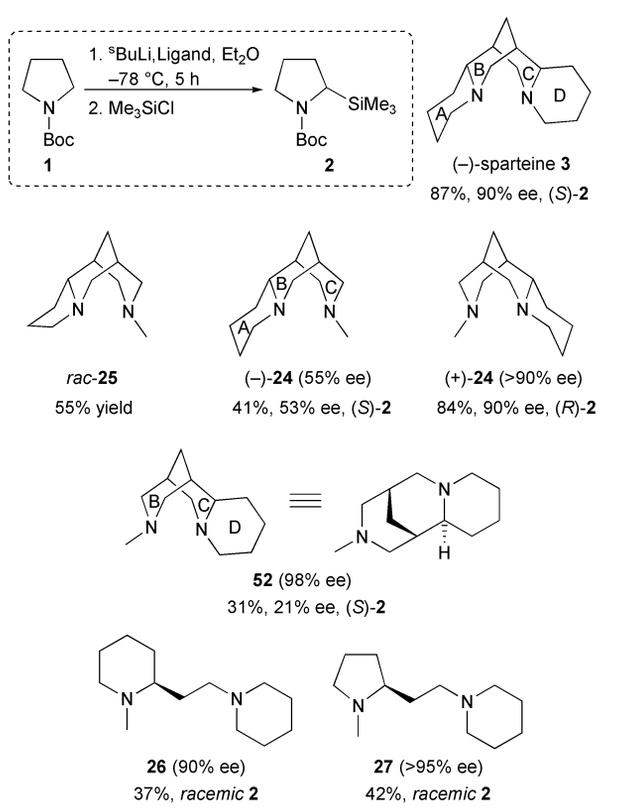
The preparation of Boc-protected amino ester (*S*)-**45** using an Arndt–Eistert homologation method has previously been described by us.[41] It was converted in good yield (86% overall) into Boc-protected amino alcohol (*S*)-**47**[65] *via* acid (*S*)-**46**[66] by ester hydrolysis and borane reduction.[67]

Commercially available 2-piperidine ethanol *rac*-**48** was resolved using (+)-camphorsulfonic acid to give a mediocre 12% yield of (*S*)-**48**·CSA {$[\alpha]_D$ +28.1 (*c* 1.1 in $CHCl_3$) (lit.,[63] +34.0 (*c* 1.0 in $CHCl_3$)} of approximately 90% ee (based on the % ee determined for diamine (*S*)-**26**, *vide infra*). The conversion of salt (*S*)-**48**·CSA into ethyl carbamate-protected amino alcohol (*S*)-**49** was best achieved by simultaneous N- and O-protection using ethyl chloroformate and then subsequent deprotection of the more labile carbonate group. Thus, treatment of salt (*S*)-**48**·CSA with three equivalents of ethyl chloroformate in aqueous potassium carbonate–dichloromethane (based on related literature protocols[68]) afforded the N- and O-protected amino alcohol (characterised by ^1H and ^{13}C NMR spectroscopy). This crude product was then reacted with potassium carbonate in methanol to generate ethyl carbamate-protected amino alcohol (*S*)-**49** in 95% yield.

For the introduction of the second amino group, we planned to activate the hydroxyl groups (*e.g.* as a tosylate or mesylate) in (*S*)-**49** and (*S*)-**47** and displace them with piperidine. A similar route was used by Hendrie and Leonard to prepare diamines containing one less methylene group in the side chain.[69] Standard mesylation of (*S*)-**49** was followed by heating the crude mesylate in toluene with added piperidine and DBU (according to the literature procedure for a similar compound[69]). After purification by chromatography, amino carbamate (*S*)-**50** was isolated in 66% yield. Subsequent reduction using lithium aluminium hydride at room temperature gave diamine (*S*)-**26** in 89% yield after distillation. Diamine (*S*)-**26** was of 90% ee as shown by ^1H NMR spectroscopy in the presence of the chiral shift reagent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol). Essentially the same reactions were used to convert Boc-protected amino alcohol (*S*)-**47** into amino carbamate (*S*)-**51** and thence into diamine (*S*)-**27** (presumed >95% ee). However, it was found that DBU was not required in the substitution step (76% yield of (*S*)-**51** in the absence of DBU) and the lithium aluminium hydride reduction step was carried out at reflux (for reduction of the more sterically hindered Boc group).

Evaluation of the new diamines as sparteine surrogates

With new, enentioenriched diamines in hand, the final objective was to evaluate them as sparteine surrogates in the lithiation–substitution of *N*-Boc pyrrolidine **1**. As a benchmark for direct comparison, we intitially repeated Beak's conversion of *N*-Boc pyrrolidine **1** into trimethylsilyl adduct (*S*)-**2** using 1.3 equivalents of *sec*-butyllithium and (−)-sparteine **3**. In our hands, an 87% yield of (*S*)-**2** of 90% ee (determined by chiral GC) was obtained (Scheme 8).



Scheme 8

The same reaction was repeated using diamines (−)-**24** (55% ee), (+)-**24** (>90% ee), (*S*)-**26** (90% ee) and (*S*)-**27** (>95% ee assumed). In addition, as we were unable to obtain enantioenriched diamine **25**, we evaluated its efficacy *as a ligand* by carrying out the conversion of **1** into *rac*-**2** using diamine *rac*-**25**. The results are presented in Scheme 8 together with the result reported by Lesma, Silvani and co-workers[70] using diamine **52** (which is equivalent to the BCD rings of (−)-sparteine **3** as depicted in Scheme 8). Diamine *rac*-**25** did

support lithiation of *N*-Boc pyrrolidine **1** as judged by the 55% yield of *rac*-**2** obtained. Partially resolved diamine (−)-**24** (55% ee) generated (*S*)-**2** of 53% ee (by chiral GC) indicating that the A-ring of (−)-sparteine **3** is important for high enantioselectivity. This result was subsequently confirmed by Lesma, Silvani and co-workers using diamine (−)-**24** of >98% ee.[70] A comparison with diamine **52** is useful at this point: diamine **52** gave (*S*)-**2** (same sense of induction as with (−)-sparteine **3**) in only 21% ee. This clearly indicates that the ABC rings of (−)-sparteine **3** are needed for high enantioselectivity. This was our prediction based on Chem3-D® modelling of (−)- and (+)-sparteine **3** in its lithium-chelating conformation and subsequently by examination of Wiberg and Bailey's calculated transition state model for lithiation of *N*-Boc pyrrolidine **1** using (−)-sparteine **3**.[11,12] Of most significance, use of the easily prepared diamine (+)-**24** gave an 84% yield of (*R*)-**2** of 90% ee (by chiral GC). This is the first example of a diamine that behaves in an enantiocomplementary fashion to (−)-sparteine **3** and diamine (+)-**24** is also successful as a (+)-sparteine surrogate in other applications.[40]

Unfortunately, the more conformationally flexible diamines (*S*)-**26** and (*S*)-**27** did not lead to any enantioselectivity in the lithiation of *N*-Boc pyrrolidine **1**. Essentially racemic adducts **2** (as judged by very low optical rotation data) were generated in moderate yields from these reactions. We had hoped that diamines (*S*)-**26** and (*S*)-**27** would self-assemble around the lithium counterion to provide a similar chiral architecture to that found in the alkyllithium-(−)–sparteine **3** complex. However, our reasoning in this case was at odds with the experimental results. A comparison with the results obtained in Beak's detailed study (see Scheme 2) shows that the structurally most similar diamines (**18** and **22**) gave a maximum of 20% ee. Our results confirm the importance of the rigid bispidine framework and that Beak's diamine **19** (containing an O–Li group) remains the best non-bispidine-based ligand reported thus far for the asymmetric lithiation–substitution of *N*-Boc pyrrolidine **1**.

Conclusion

In this paper, optimised routes for the preparation of sparteine-like diamines *rac*-**24** and *rac*-**25** have been described. The methods investigated for resolution of these diamines were of limited success. However, recent results from the Hodgson group have demonstrated some examples where *racemic* diamines **24** and **25** outperform (−)-sparteine in terms of *chemical* yield.[71] This may be due to the fact that diamines **24** and **25** are less sterically hindered than (−)-sparteine **3**. Thus, it is likely that *racemic* diamines **24** and **25** could have other useful applications as modified TMEDA ligands.

The results presented in this paper, together with those recently reported by Lesma, Silvani and co-workers[70] provide significant information on exactly which parts of the (−)-sparteine **3** structure are responsible for high enantioselectivity in the enantioselective lithiation of *N*-Boc pyrrolidine. It appears that the rigidity imparted by the bispidine framework is crucial. In addition, we conclude that the ABC rings of (−)-sparteine **3** (as drawn in Scheme 8) are the key structural features necessary for high enantioselectivity. The D-ring of (−)-sparteine is superfluous. On inspection, the results appear to be consistent with the calculated transition state model for lithiation of *N*-Boc pyrrolidine **1** reported by Wiberg and Bailey.[11,12]

Finally, the simple, three-step synthesis of diamine (+)-**24** of >90% ee starting from (−)-cytisine **42** is a major development from this project. Diamine (+)-**24** is the first reported (+)-sparteine surrogate and, as well as the lithiation of *N*-Boc pyrrolidine reported in this paper, we have demonstrated that it is enantiocomplentary to (−)-sparteine **3** in other applications (*e.g.* *a*-functionalisation of *O*-alkyl carbamates, rearrangement of cyclooctene oxide and oxidative kinetic resolutions of alcohols).[40] Future work will be carried out in assessing the full scope and usefulness of diamines such as (+)-**24** derived from (−)-cytisine and in studying the effect of the N-substituent in (−)-cytisine-derived diamines on the enantioselectivity of various reactions/processes. These results will be reported in due course.

Experimental

General

Water is distilled water. Et_2O and THF were freshly distilled from sodium benzophenone ketyl whereas CH_2Cl_2 was freshly distilled from calcium hydride. Triethylamine was stored over potassium hydroxide pellets. *sec*-Butyllithium was titrated against *N*-benzylbenzamide before use.[72] All non-aqueous reactions were carried out under oxygen-free nitrogen using oven-dried glassware. Light petroleum refers to the fraction boiling in the range 40–60 °C. Brine refers to a saturated aqueous solution of sodium chloride. Flash column chromatography was carried out using ICN Biomedicals GmbH silica (60 Å) or Fisher Matrex silica 60, 70–200 micron. Thin layer chromatography was carried out using commercially available Merck F_{254} aluminium-backed silica plates. For Kugelrohr distillations, the temperatures quoted correspond to the oven temperatures.

Proton (270 MHz or 400 MHz) and carbon (67.9 or 100.6 MHz) NMR spectra were recorded on a JEOL EX-270 or a JEOL ECX-400 instrument using an internal deuterium lock. All samples were recorded as solutions in $CDCl_3$ and chemical shifts are quoted in parts per million downfield of tetramethylsilane. Carbon NMR spectra were recorded with broad band proton decoupling and were assigned using DEPT experiments.

Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Microanalyses were carried out at the University of Newcastle on a Carlo Erba 1106 elemental analyser and weighed using a Mettler MT 5 microbalance. Infrared spectra were recorded on an ATI Matteson Genesis FT-IR spectrometer. Chemical ionisation and high resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Optical rotations were recorded at 20 °C on a Jasco DIP-370 polarimeter (using the sodium D line; 589 nm) and $[a]_D$ are given in 10^{-1} deg cm^2 g^{-1}.

Ethyl (*E*)-7-iodohept-2-enoate **35**[49–51] and methyl ester (*S*)-**45**[41] were prepared according to the literature routes.

Hexahydroindolizin-7(1*H*)-one 30

Freshly distilled methyl vinyl ketone (2.1 cm^3, 25.7 mmol) was added dropwise to a stirred solution of 4,4-diethoxybutan-1-amine **28** (3.8 cm^3 of 90% technical grade quality, 19.8 mmol) in Et_2O (10 cm^3) at 0 °C under nitrogen. After stirring for 1 h at 0 °C, 2.5 M hydrochloric acid (50 cm^3) was added and the mixture was warmed to room temperature. The two layers were separated and the aqueous layer was heated at reflux (approx. 100 °C) for 2.5 h *without a reflux condenser*. Then, after cooling to room temperature, the aqueous mixture was evaporated under reduced pressure and saturated aqueous potassium carbonate solution (100 cm^3) was added. The mixture was extracted with $CHCl_3$ (3 × 100 cm^3) and the combined $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave amino ketone **30** (1.1 g, 39%) as a colourless oil, bp 60–65 °C/1.0 mmHg (lit.,[40] 60–63 °C/1.0 mmHg); R_F (9 : 1 $CHCl_3$–MeOH) 0.35. Spectroscopic data identical to that reported in the literature.[41]

Ethyl 3-[2-(2-ethoxy-2-oxoethyl)piperidin-1-yl)propanoate 33

A suspension of platinum(IV) oxide (370 mg, 1.0 mmol), ethyl-2-pyridyl acetate **31** (5.0 cm^3, 32.8 mmol) and 6 M hydrochloric

acid (8.75 cm^3) in EtOH (50 cm^3) was stirred at room temperature under a hydrogen atmosphere (balloon) for 24 h (or until the mixture became colourless). The solvent was evaporated to give an off-white solid. 2 M Ammonium hydroxide solution (50 cm^3) was added and the mixture extracted with Et_2O (6 × 25 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give crude amino ester **32** (4.2 g, 75%) as a colourless oil. A solution of this crude amino ester **32**, ethyl acrylate (7.85 cm^3, 72.4 mmol) and triethylamine (20.2 cm^3, 144.9 mmol) in EtOH (100 cm^3) was stirred at room temperature under nitrogen for 66 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave bis-ester **33** (6.0 g, 92%, 69% from **31**) as a colourless oil, bp 175–180 °C/1.0 mmHg; R_F (97 : 3 CH_2Cl_2–MeOH) 0.3; $\nu_{max}(CHCl_3)/cm^{-1}$ 2939 and 1726 (C=O); δ_H (270 MHz; $CDCl_3$) 4.12 (4 H, q, *J* 7.0, OCH_2), 2.93–2.59 (5 H, m, CHN), 2.45 (2 H, t, *J* 7.0, CH_2CO_2), 2.39–2.27 (2 H, m), 1.75–1.28 (6 H, m) and 1.25 (6 H, t, *J* 7.0, Me); δ_C (67.9 MHz; $CDCl_3$) 172.6 (C=O), 60.4 (OCH_2), 60.3 (OCH_2), 56.3 (CHN), 50.3 (CH_2N), 49.3 (CH_2N), 35.7 (CH_2CO_2), 31.9 (CH_2CO_2), 30.7 (CH_2), 25.2 (CH_2), 22.0 (CH_2) and 14.2 (Me) (two signals not resolved); *m*/*z* (CI; NH_3) 272 [100%, $(M + H)^+$] [Found: $(M + H)^+$, 272.1861. $C_{14}H_{25}NO_4$ requires M + H, 272.1861].

In a separate experiment, a sample of the intermediate amino ester **32** was purified by Kugelrohr distillation. Ethyl piperidin-2-yl acetate **32**: colourless oil, bp 85–90 °C/1.5 mmHg; R_F (4 : 1 CH_2Cl_2–MeOH) 0.5; $\nu_{max}(CHCl_3)/cm^{-1}$ 3327 (NH), 2934 and 1724 (C=O); δ_H (270 MHz; $CDCl_3$) 4.14 (2 H, q, *J* 7.0, OCH_2), 3.09–3.01 (1 H, m, CHN), 3.02–2.86 (1 H, m, CHN), 2.66 (1 H, dt, *J* 3.0 and 12.0, CHN), 2.37–2.33 (2 H, m), 2.11 (1 H, br s, NH), 1.80–1.63 (1 H, m), 1.66–1.51 (2 H, m), 1.49–1.32 (2 H, m) 1.26 (3 H, t, *J* 7.0, Me) and 1.21–1.12 (1 H, m); δ_C (67.9 MHz; $CDCl_3$) 172.3 (C=O), 60.2 (OCH_2), 53.2 (CHN), 46.8 (CH_2N), 41.6 (CH_2), 32.5 (CH_2), 26.0 (CH_2), 24.5 (CH_2) and 14.1 (Me); *m*/*z* (CI; NH_3) 172 [100%, $(M + H)^+$] [Found: $(M + H)^+$, 172.1341. $C_9H_{17}NO_2$ requires M + H, 172.1338].

Ethyl 3-[2-(2-ethoxy-2-oxoethyl)piperidin-1-yl)propanoate 33

A suspension of ethyl (*E*)-7-iodohept-2-enoate **35**[49–51] (100 mg, 0.35 mmol), β-alanine ethyl ester hydrochloride (61 mg, 0.39 mmol) and potassium carbonate (147 mg, 1.06 mmol) in EtOH (2 cm^3) was stirred and heated at reflux under nitrogen for 60 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue dissolved in Et_2O (10 cm^3) and water (10 cm^3). The two layers were separated and the Et_2O layer was washed with 5% aqueous sodium thiosulfate solution (10 cm^3) and brine (10 cm^3). The combined aqueous washings were then extracted with Et_2O (2 × 10 cm^3). The combined Et_2O extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with $CHCl_3$–MeOH (97 : 3) as eluent gave bis-ester **33** (75 mg, 78%) as a colourless oil, identical spectroscopically to that obtained above.

Octahydro-2*H*-quinolizin-2-one 34

LHMDS (17.7 cm^3 of a 1 M solution in THF, 17.7 mmol) was added dropwise to a stirred solution of bis-ester **33** (2.0 g, 7.4 mmol) in THF (5 cm^3) at −78 °C under nitrogen. After stirring for 2 h at −78 °C, 12 M hydrochloric acid (1.8 cm^3) was added and the solution was warmed to room temperature. Water (30 cm^3) was added and the mixture was extracted with Et_2O (3 × 25 cm^3). Then, saturated aqueous potassium carbonate solution was added to the aqueous layer until pH 10 was obtained. The aqueous layer was extracted with Et_2O (3 × 25 cm^3) and the combined Et_2O extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude β-keto ester as a yellow oil. Then, 6 M hydrochloric acid (75 cm^3) was added and the resulting solution was stirred and heated at reflux for 16 h. After cooling to room temperature, the solution was carefully neutralised with solid potassium carbonate until gas evolution stopped and the solution was saturated. The solid was removed by filtration and washed with Et_2O (15 cm^3). The aqueous filtrate was extracted with Et_2O (3 × 10 cm^3). The combined Et_2O extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude amino ketone **34** (960 mg, 87%) as a pale yellow oil, R_F (97 : 3 CH_2Cl_2–MeOH) 0.35; identical spectroscopically to that reported in the literature,[44] and sufficiently pure for use in the next step.

(1*S**,2*R**,9*R**)-11-Methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecan-13-one 36

Methylamine (3.25 cm^3 of a 2.0 M solution in MeOH, 6.6 mmol) was added dropwise to a stirred solution of amino ketone **34** (1.0 g, 6.6 mmol), paraformaldehyde (594 mg, 19.9 mmol) and acetic acid (0.4 cm^3) in MeOH (7.7 cm^3) at room temperature under nitrogen. The resulting solution was heated at reflux for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and 50% aqueous potassium hydroxide solution (30 cm^3) was added to the residue. The aqeuous mixture was extracted with Et_2O (3 × 60 cm^3) and the combined Et_2O extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diazatricyclic ketone **36** (803 mg, 58%) as a colourless oil, bp 140–150 °C/0.8 mmHg (lit.,[42] 120–131 °C/0.1–0.4 mmHg); R_F (4 : 1 CH_2Cl_2–MeOH) 0.2; $\nu_{max}(CHCl_3)/cm^{-1}$ 2942 and 1717 (C=O); δ_H (270 MHz; $CDCl_3$) 3.32–2.73 (5 H, m), 2.58–2.51 (1 H, m), 2.40–2.17 (2 H, m), 2.24 (3 H, s, NMe), 2.14–1.85 (3 H, m), 1.79–1.50 (4 H, m) and 1.41–1.10 (2 H, m); δ_C (67.9 MHz; $CDCl_3$) 214.5 (C=O), 66.7 (NMe), 62.4 (CH_2N), 60.4 (CH_2N), 56.4 (CH_2N), 54.9 (CH_2N), 52.1 (CHN), 47.4 (CH), 45.4 (CH), 29.9 (CH_2), 25.4 (CH_2) and 23.4 (CH_2); *m*/*z* (EI) 208 [28%, M^+], 164 (44), 150 (58) and 98 (100) [Found: M^+, 208.1578. $C_{12}H_{20}N_2O$ requires M, 208.1576].

(1*S**,2*R**,9*R**)-11-Methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane or (1*S**,5*R**,12*R**)-3-methyldecahydro-1,5-methanopyrido[1,2-*a*]diazocine *rac*-24

A solution of diazatricyclic ketone **36** (1.3 g, 6.5 mmol), hydrazine hydrate (1.7 cm^3, 34.1 mmol) and potassium hydroxide (4.7 g, 84.1 mmol) in diethylene glycol (13 cm^3) under nitrogen was stirred and heated at reflux (230 °C) using a silicone oil bath for 2 h. Then, the volatile components were removed by distillation for 1 h at 190 °C. The reaction mixture was cooled to room temperature and combined with the previously distilled fraction. Water (30 cm^3) was added and the aqueous mixture was extracted with Et_2O (4 × 10 cm^3). The combined Et_2O extracts were washed with 20% aqueous sodium hydroxide solution (4 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diamine *rac*-**24** (850 mg, 68%) as a colourless oil, bp 150–160 °C/0.8 mmHg; R_F (4 : 1 $CHCl_3$–MeOH) 0.1; $\nu_{max}(CHCl_3)/cm^{-1}$ 2937 and 2775; δ_H (270 MHz; $CDCl_3$) 3.02–2.82 (4 H, m), 2.23 (1 H, ddd, *J* 2.0, 3.0 and 11.0), 2.18–2.10 (1 H, m), 2.16 (3 H, s, NMe), 1.90–1.45 (11 H, m) and 1.38–1.20 (2 H, m); δ_C (67.9 MHz; $CDCl_3$) 66.4 (CHN), 60.4 (CH_2N), 57.6 (CH_2N), 56.3 (CH_2N), 53.4 (CH_2N), 47.4 (NMe), 35.1 (CH), 33.9 (CH_2), 30.7 (CH_2), 30.5 (CH), 25.6 (CH_2) and 25.0 (CH_2); *m*/*z* (EI) 194 [50%, M^+], 164 (44), 150 (58) and 98 (100) [Found: M^+, 194.1787. $C_{12}H_{22}N_2$ requires M, 194.1783].

1-(2-Chlorophenyl)-1-phenylprop-2-yn-1-ol *rac*-40

A solution of *ortho*-chlorobenzophenone **38** (8.0 g, 37.0 mmol) in THF (10 cm^3) was added dropwise to a stirred solution of

ethynylmagnesium bromide (150 cm^3 of a 0.5 M solution in THF, 75.0 mmol) at room temperature under nitrogen. The resulting solution was heated at reflux for 16 h. After cooling to room temperature, the solution was carefully poured into a mixture of ice (50 cm^3), water (150 cm^3) and 12 M hydrochloric acid (5 cm^3). Then, the aqueous mixture was extracted with Et_2O (3 × 100 cm^3) and the combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with light petroleum–EtOAc (6 : 1) as eluent gave alcohol *rac*-**40** (7.9 g, 88%) as a brown viscous oil, R_F (6 : 1 light petroleum–EtOAc) 0.3; ν_{max}(film)/cm^{-1} 3546 (OH), 3430 (OH), 3292 (C≡CH), 3062, 1656, 1435, 1337, 1180 and 756; δ_H (270 MHz; $CDCl_3$) 8.05–7.99 (1 H, m), 7.56–7.52 (2 H, m), 7.38–7.25 (6 H, m), 3.30 (1 H, br s) and 2.89 (1 H, s); δ_C (67.9 MHz; $CDCl_3$) 142.7 (*ipso*-Ar), 140.2 (*ipso*-Ar), 132.3 (*ipso*-Ar), 131.2, 129.4, 128.2, 128.1, 128.0, 126.6, 126.5, 84.2 (*C*≡CH), 75.9 (C≡*C*H) and 73.6 (COH); *m*/*z* (EI) 242 [21%, $^{35}M^+$] [Found: $(^{35}M - H)^+$, 241.0420. $C_{15}H_{10}{}^{35}ClO$ requires M − H, 241.0420].

(*R*)-1-(2-Chlorophenyl)-1-phenylprop-2-yn-1-ol 40

(−)-Sparteine (7.5 cm^3, 32.6 mmol) was added dropwise to a solution of alcohol *rac*-**40** (7.9 g, 32.6 mmol) in acetone (40 cm^3) at room temperature. After allowing some of the solvent to evaporate over 16 h, colourless crystals formed. Light petroleum (20 cm^3) was added and the crystals were collected by filtration and washed with light petroleum (3 × 30 cm^3). Then, the crystals were dissolved in a mixture of Et_2O (150 cm^3) and 2 M hydrochloric acid (100 cm^3). The two layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give alcohol (*R*)-**40** (2.7 g, 35%) as a brown viscous oil, $[\alpha]_D$ −115.2 (*c* 0.6 in MeOH). To the combined light petroleum washes, a mixture of Et_2O (150 cm^3) and 2 M hydrochloric acid (100 cm^3) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give alcohol (*S*)-**40** (5.0 g, 64%) as a brown viscous oil, $[\alpha]_D$ +58.4 (*c* 0.6 in MeOH).

Using the procedure described above, alcohol (*R*)-**40** {2.7 g, $[\alpha]_D$ −115.2 (*c* 0.6 in MeOH), 11.3 mmol} and (−)-sparteine (2.6 cm^3, 11.3 mmol) in acetone (15 cm^3) gave alcohol (*R*)-**40** (2.2 g, 28% from *rac*-**40**, >99% ee by chiral HPLC) as a brown viscous oil, identical spectroscopically to *rac*-**40**, $[\alpha]_D$ −139.6 (*c* 0.6 in MeOH) (lit.,[54] −129.0 (*c* 0.2 in MeOH)); HPLC: Chiralcel OD-H, 5% ^{i}PrOH in heptane, 1.0 cm^3 min^{-1}, 215 nm, 10.2 [(*R*)-**40**], 11.6 [(*S*)-**40**].

(1*S*,2*R*,9*R*)-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane or (1*S*,5*R*,12*R*)-3-methyldecahydro-1,5-methanopyrido[1,2-*a*]-[1,5]diazocine (−)-24

A solution of diamine *rac*-**24** (742 mg, 3.8 mmol) in acetone (3 cm^3) was added dropwise to a solution of alcohol (*R*)-**40** (929 mg, 3.8 mmol, >99% ee) in acetone (3 cm^3) at room temperature. After allowing all of the solvent to evaporate over 64 h, pale yellow crystals formed. Light petroleum (5 cm^3) was added and the crystals were collected by filtration and washed with light petroleum (3 × 5 cm^3). Then, the crystals were dissolved in a mixture of Et_2O (15 cm^3) and 2 M hydrochloric acid (10 cm^3). The two layers were separated and the Et_2O layer was extracted with 2 M hydrochloric acid (2 × 10 cm^3). To the combined aqeuous extracts, 20% aqueous sodium hydroxide solution was added until pH 9 was obtained. Then, the solution was extracted with Et_2O (3 × 10 cm^3) and the combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give diamine (−)-**24** (171 mg, 23%, 60% ee by ^{1}H NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) as a colourless oil, identical spectroscopically to *rac*-**24**, $[\alpha]_D$ −15.7 (*c* 0.5 in EtOH).

To the combined light petroleum washings from above, a mixture of Et_2O (15 cm^3) and 2 M hydrochloric acid (10 cm^3) was added. The two layers were separated and the Et_2O layer was extracted with 2 M hydrochloric acid (2 × 10 cm^3). To the combined aqeuous extracts, 20% aqueous sodium hydroxide solution was added until pH 9. Then, the solution was extracted with Et_2O (3 × 10 cm^3) and the combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give diamine (+)-**24** (503 mg, 68%, 30% ee by ^{1}H NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol) as a colourless oil, identical spectroscopically to *rac*-**24**, $[\alpha]_D$ +6.1 (*c* 0.6 in EtOH).

(1*R*,5*S*)-1,2,3,4,5,6-Hexahydro-1,5-methanopyrido[1,2-*a*][1,5]-diazocin-8-one or cytisine (−)-42

A suspension of *Cytisus* (*Laburnum anagyroides*) seeds (200 g, powdered in a food blender, Vilmorin, France) in CH_2Cl_2 (300 cm^3), MeOH (85 cm^3) and 35% w/v aqueous ammonium hydroxide solution (32 cm^3) was stirred at room temperature for 67 h. Then, the mixture was filtered and the residue washed with CH_2Cl_2 until the filtrate was colourless. The filtrate was then acidified by dropwise (**CAUTION**) addition of 3 M hydrochloric acid until pH 1 was obtained. The two layers were separated and the aqueous layer was basified by dropwise (**CAUTION**) addition of 35% w/v aqueous ammonium hydroxide solution until pH 11 was obtained. The aqueous layer was extracted with CH_2Cl_2 (10 × 30 cm^3) and the combined CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give crude (−)-cytisine (3.5 g, 1.65%) as a brown solid. Recrystallisation from acetone gave (−)-cytisine **42** (2.3 g, 1.1%, two crops) as a yellow solid, mp 156–157 °C (lit.,[57] 155 °C); $[\alpha]_D$ −67.5 (*c* 1.0 in $CHCl_3$) (lit.,[56] −76.0 (*c* 1.0 in $CHCl_3$)). Spectroscopic data identical to that reported in the literature.[58]

(1*R*,5*S*)-*N*-Methoxycarbonyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one 43

Methyl chloroformate (4.6 cm^3, 58.3 mmol) was added dropwise over 10 min to a stirred solution of (−)-cytisine **42** (1.11 g, 5.8 mmol) and triethylamine (8.2 cm^3, 58.3 mmol) in CH_2Cl_2 (33 cm^3) at 0 °C under nitrogen. After stirring for 3.5 h at room temperature, the solvent was evaporated under reduced pressure. EtOAc (15 cm^3) was added to the residue and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2–MeOH–35% w/v aqueous ammonium hydroxide (90 : 9 : 1) as eluent gave pyridone **43** (1.33 g, 92%) as a colourless gum, $[\alpha]_D$ −207.0 (*c* 1.1 in $CHCl_3$) (lit.,[59] −209.0 (*c* 0.8 in $CHCl_3$)). Spectroscopic data identical to that reported in the literature.[59]

(1*R*,2*S*,9*S*)-11-Methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane or (1*R*,5*S*,12*S*)-3-methyldecahydro-1,5-methanopyrido[1,2-*a*]-[1,5]diazocine (+)-24

A suspension of pyridone **43** (1.37 g, 5.5 mmol) and platinum(IV) oxide (130 mg, 0.55 mmol) in MeOH (25 cm^3) was stirred at room temperature under a hydrogen atmosphere (balloon) for 5 h. The solids were removed by filtration through Celite and the filter cake was washed with 9 : 1 CH_2Cl_2–MeOH (100 cm^3). The filtrate was evaporated under reduced pressure to give the crude product as a white solid. To this crude product in THF (25 cm^3) at 0 °C under nitrogen, lithium aluminium hydride (1.26 g, 33.2 mmol) was added in one portion. The resulting suspension was stirred and heated at reflux for 16 h. After cooling to 0 °C, Et_2O (10 cm^3) was added followed by the portionwise addition (**CAUTION**) of solid hydrated sodium sulfate until effervescence ceased. The solids were removed by

filtration through Celite and the filter cake was washed with 9 : 1 CH_2Cl_2–MeOH (100 cm^3). The filtrate was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a brown oil. Purification by Kugelrohr distillation gave diamine (+)-**24** (920 mg, 86%, >90% ee by ^1H NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) as a colourless oil, identical spectroscopically to *rac*-**24**, bp 95–110 °C/0.8 mmHg; $[\alpha]_D$ +26.5 (*c* 1.0 in EtOH).

(1*R*,5*S*,12*S*)-3-Methoxycarbonyldecahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one 44

A suspension of pyridone **43** (4.84 g, 19.5 mmol) and platinum(IV) oxide (136 mg, 0.60 mmol) in EtOH (55 cm^3) was stirred at room temperature under a hydrogen atmosphere (balloon) for 7 days. The solids were removed by filtration through Celite and the filter cake was washed with 9 : 1 CH_2Cl_2–MeOH (100 cm^3). The filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2–MeOH (98 : 2) (with a few drops of 35% w/v aqueous ammonium hydroxide) as eluent gave lactam **44** (4.06 g, 82%) as a white solid, mp 121–122 °C; $[\alpha]_D$ −180.3 (*c* 1.0 in $CHCl_3$); R_F (97 : 2 : 1 CH_2Cl_2–MeOH–35% w/v aqueous ammonium hydroxide) 0.3; ν_{max}($CHCl_3$)/cm^{-1} 1691 (C=O, CO_2Me) and 1620 (C=O, lactam); δ_H (400 MHz; $CDCl_3$) approx. 4 : 1 mixture of rotamers; signals for major rotamer: 4.78 (1 H, d, *J* 13.5, CHN), 4.62 (1 H, dd, *J* 1.5 and 14.0, CHN), 4.21 (1 H, dd, *J* 1.5 and 13.5, CHN), 3.61 (3 H, s, Me), 3.47 (1 H, br d, *J* 10.5, CHN), 3.09 (1 H, br td, *J* 2.0 and 13.5, CHN), 2.88 (1 H, dd, *J* 2.0 and 14.0, CHN), 2.81 (1 H, br d, *J* 13.5, CHN), 2.48–2.31 (2 H, m), 2.25–2.08 (1 H, m), 2.02–1.76 (5 H, m) and 1.73–1.55 (2 H, m) [resolved signals for minor rotamer: 4.38 (1 H, br d, *J* 13.5, CHN), 4.30 (1 H, br d, *J* 13.0, CHN), 3.68 (3 H, s, Me), 3.02 (1 H, dd, *J* 13.0, CHN) and 2.96 (1 H, br d, *J* 14.0, CHN)]; δ_C (100.6 MHz; $CDCl_3$) 169.8 (C=O, CO_2Me), 156.0 (C=O, lactam), 59.4 (CHN), 52.6 (MeO), 49.0 (CH_2N), 45.7 (CH_2N), 44.3 (CH_2N), 33.3 (CH_2), 33.1 (CH), 32.7 (CH_2), 27.8 (CH), 27.7 (CH_2) and 20.2 (CH_2); *m*/*z* (CI; NH_3) 253 [100%, (M + H)$^+$] [Found: (M + H)$^+$, 253.1553. $C_{13}H_{20}N_2O_3$ requires M + H, 253.1553]; Found: C, 62.0; H, 8.2; N, 11.0%; $C_{13}H_{20}N_2O_3$ requires C, 61.88; H, 7.99; N, 11.10%. Single crystals of compound **44** suitable for X-ray diffraction were grown from $CDCl_3$.

Crystal structure determination of lactam 44

Crystal data. $C_{13}H_{20}N_2O_3$, *M* = 252.31, orthorhombic, *a* = 7.9103(4), *b* = 9.9556(5), *c* = 15.8702(9) Å, *U* = 1249.81(11) Å^3, *T* = 115(2) K, space group $P2_12_12_1$, *Z* = 4, μ(Mo-Kα) = 0.096 mm^{-1}, 10029 reflections measured, 3598 unique (R_{int} = 0.0196) which were used in all calculations. The final $wR(F^2)$ was 0.0898 (all data).

CCDC reference number 215917.

See http://www.rsc.org/suppdata/ob/b3/b308410h/ for crystallographic data in CIF or other electronic format.

(2*S*)-*tert*-Butyl 2-(2-Carboxyethyl)pyrrolidine-1-carboxylate (*S*)-46

A solution of lithium hydroxide (11.6 cm^3 of a 1.0 M aqueous solution, 11.6 mmol) and methyl ester (*S*)-**45**[41] (3.27 g, 13.4 mmol) in dioxane was stirred at room temperature for 16 h. Water (10 cm^3) was added and the mixture was acidified by dropwise addition of 10% aqueous citric acid solution until pH 3–4 was obtained. Then, the dioxane as evaporated under reduced pressure and the aqueous residue was extracted with EtOAc (3 × 35 cm^3). The combined EtOAc extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with light petroleum–EtOAc (1 : 1) as eluent gave acid (*S*)-**46** (2.64 g, 86%) as a white solid, mp 98–100 °C (lit.,[66] 99–100 °C); $[\alpha]_D$ −30.7 (*c* 0.6 in $CHCl_3$); $[\alpha]_D$ −37.8 (*c* 1.4 in DMF) (lit.,[66] −40.5 (*c* 1.9 in DMF); R_F (1 : 1 light petroleum–EtOAc) 0.4; ν_{max}($CHCl_3$)/cm^{-1} 1710 (C=O, CO_2H) and 1685 (C=O, Boc); δ_H (270 MHz; $CDCl_3$) 10.26 (1 H, br s, CO_2H), 4.24–4.04 (1 H, m, CHN), 3.47–3.23 (2 H, m, CH_2N), 3.01–2.81 (1 H, br m), 2.32 (1 H, br dd, *J* 9.5 and 14.5), 2.16–1.99 (1 H, m), 1.90–1.69 (3 H, m) and 1.44 (9 H, CMe_3); δ_C (67.9 MHz; $CDCl_3$) rotamers observed 176.5 (C=O, CO_2H), 154.4 (C=O, Boc), 79.8 (CMe_3), 53.8 (CHN), 46.4 and 46.1 (CH_2N), 38.8 (CH_2), 31.2 and 30.8 (CH_2), 28.4 (CMe_3) and 22.6 and 22.3 (CH_2); *m*/*z* (CI; NH_3) 230 [24%, (M + H)$^+$], 174 (100), 130 (33) and 70 (57) [Found: (M + H)$^+$, 230.1396. $C_{11}H_{19}NO_4$ requires M + H, 230.1392].

(2*S*)-*tert*-Butyl 2-(2-hydroxyethyl)pyrrolidine-1-carboxylate (*S*)-47

Borane dimethyl sulfide (5.6 cm^3 of a 2 M solution in THF, 11.2 mmol) was added dropwise to a stirred solution of acid (*S*)-**46** (2.33 g, 10.2 mmol) in THF (50 cm^3) at room temperature under nitrogen. The resulting mixture was heated at reflux for 1 h. After cooling to room temperature, the THF was evaporated under reduced pressure and the residue was dissolved in a mixture of CH_2Cl_2 (60 cm^3) and water (20 cm^3). The two layers were separated and the CH_2Cl_2 layer was washed with saturated aqueous sodium hydrogencarbonate solution (20 cm^3) and brine (20 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give protected amino alcohol (*S*)-**47** (2.22 g, 100%) as a yellow oil, which was sufficiently pure (by TLC and ^1H NMR spectroscopy) for use in the next step.

In a separate experiment, a sample of amino alcohol (*S*)-**47** was purified by flash column chromatography using 2 : 1 light petroleum–EtOAc as eluent. Amino alcohol (*S*)-**47**: pale yellow oil, $[\alpha]_D$ −13.8 (*c* 1.1 in $CHCl_3$); R_F (2 : 1 light petroleum–EtOAc) 0.3; ν_{max}($CHCl_3$)/cm^{-1} 1670 (C=O); δ_H (270 MHz; $CDCl_3$) 4.45 (1 H, br s), 4.14–4.00 (1 H, m), 3.65–3.41 (2 H, m), 3.25 (2 H, t, *J* 6.5, CH_2O), 2.01–1.70 (4 H, m), 1.65–1.49 (2 H, m) and 1.39 (9 H, CMe_3); δ_C (67.9 MHz; $CDCl_3$) 156.2 (C=O), 79.6 (CMe_3), 58.9 (CH_2O), 53.4 (CHN), 46.3 (CH_2N), 38.1 (CH_2), 30.9 (CH_2), 28.3 (CMe_3) and 23.4 (CH_2); *m*/*z* (CI; NH_3) 216 [37%, (M + H)$^+$], 160 (100), 116 (57) and 70 (32) [Found: (M + H)$^+$, 216.1605. $C_{11}H_{21}NO_3$ requires M + H, 216.1600].

(2*S*)-Ethyl 2-(2-hydroxyethyl)piperidine-1-carboxylate (*S*)-49

Ethyl chloroformate (1.70 cm^3, 17.6 mmol) was added dropwise to a stirred mixture of salt (*S*)-**48**·CSA (2.12 g, 5.86 mmol) in CH_2Cl_2 (100 cm^3) and 5% w/v aqueous potassium carbonate solution (150 cm^3) at 0 °C. After warming to room temperature, the resulting mixture was stirred at room temperature for 20 h. Then, CH_2Cl_2 (50 cm^3) and water (100 cm^3) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 150 cm^3) and the combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the N- and O-diprotected crude product. The crude product was dissolved in 1% w/v methanolic potassium carbonate solution (100 cm^3) and the resulting solution was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure and water (50 cm^3) was added. The mixture was extracted with CH_2Cl_2 (3 × 70 cm^3) and the combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give protected amino alcohol (*S*)-**49** (1.12 g, 95%) as a pale yellow oil, R_F (5 : 2 light petroleum–EtOAc) 0.55; ν_{max}($CHCl_3$)/cm^{-1} 3435 (OH), 2945 and 1660 (C=O); δ_H (270 MHz; $CDCl_3$) 4.43 (1 H, br s), 4.10 (2 H, q, *J* 7.0, OCH_2Me), 3.97 (1 H, br d, *J* 12.5), 3.80–3.52 (2 H, m), 3.51–3.30 (1 H, m), 2.70 (1 H, br t, *J* 13.0), 2.00–1.87 (1 H, m), 1.85–1.34 (7 H, m) and 1.22 (3 H, t, *J* 7.0, Me); δ_C (67.9 MHz; $CDCl_3$) 155.6 (C=O), 61.5 (OCH_2Me), 58.5 (CH_2OH), 46.5 (CHN), 39.0 (CH_2N), 32.2 (CH_2), 29.0 (CH_2), 25.3 (CH_2), 18.9 (CH_2) and 14.5 (Me); *m*/*z* (CI; NH_3) 202

[100%, $(M + H)^+$] and 156 (30) [Found: $(M + H)^+$, 202.1446. $C_{10}H_{19}NO_3$ requires M + H, 202.1443].

(2*S*)-Ethyl 2-[2-(1-piperidinyl)ethyl]-1-piperidinecarboxylate (*S*)-50

Methanesulfonyl chloride (0.58 cm^3, 5.63 mmol) was added dropwise to a stirred solution of protected amino alcohol (*S*)-**49** (1.12 g, 5.59 mmol) and triethylamine (0.86 cm^3, 6.15 mmol) in CH_2Cl_2 (20 cm^3) at 0 °C under nitrogen. After warming to room temperature, the resulting solution was stirred for 1 h. Then, water (20 cm^3) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 cm^3). The combined CH_2Cl_2 extracts were washed with saturated aqueous sodium hydrogencarbonate solution (40 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude mesylate. To a stirred solution of the crude mesylate in toluene (35 cm^3), DBU (0.09 cm^3, 0.56 mmol) and piperidine (2.25 cm^3, 22.7 mmol) were added. The resulting solution was heated at reflux for 24 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica with CH_2Cl_2–MeOH (9 : 1) as eluent to give amino carbamate (*S*)-**50** (981 mg, 66%) as a yellow oil, $[\alpha]_D$ −27.3 (*c* 1.3 in $CHCl_3$); R_F (9 : 1 $CHCl_3$–MeOH) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 2941 and 1675 (C=O); δ_H (270 MHz; $CDCl_3$) 4.32–4.22 (1 H, m), 4.18–3.92 (3 H, m), 2.91–2.78 (1 H, m), 2.76–2.35 (6 H, m), 2.21–2.01 (1 H, m), 1.72–1.25 (13 H, m) and 1.21 (3 H, t, *J* 7.0, Me); δ_C (67.9 MHz; $CDCl_3$) 155.7 (C=O), 61.1 (CH_2O), 55.9 (CH_2N), 54.3 (CH_2N), 49.0 (CHN), 38.9 (CH_2N), 28.8 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 23.3 (CH_2), 18.9 (CH_2) and 14.6 (Me) (one CH_2 not resolved); *m*/*z* (CI; NH_3) 269 [100%, $(M + H)^+$], 112 (20), 86 (55) and 52 (95) [Found: $(M + H)^+$, 269.2234. $C_{15}H_{28}N_2O_2$ requires M + H, 269.2229].

(2*S*)-*tert*-Butyl 2-[2-(1-piperidinyl)ethyl]-1-pyrrolidinecarboxylate (*S*)-51

Using the procedure described above, protected amino alcohol (*S*)-**47** (669 mg, 3.11 mmol), methanesulfonyl chloride (0.27 cm^3, 3.42 mmol) and triethylamine (0.66 cm^3, 4.66 mmol) in CH_2Cl_2 (15 cm^3) followed by refluxing with piperidine (1.25 cm^3, 12.5 mmol) in toluene (16 cm^3) for 16 h (note: no DBU added) gave the crude amino carbamate (670 mg, 76%) as a yellow oil which was sufficiently pure (by TLC and ^1H NMR spectroscopy) for use in the next step.

In a separate experiment, a sample of amino carbamate (*S*)-**51** was purified by flash column chromatography using CH_2Cl_2–MeOH (9 : 1) as eluent. Amino alcohol (*S*)-**51**: yellow solid, $[\alpha]_D$ −58.9 (*c* 1.0 in $CHCl_3$); R_F (9 : 1 CH_2Cl_2–MeOH) 0.35; $\nu_{max}(CHCl_3)/cm^{-1}$ 1680 (C=O); δ_H (270 MHz; $CDCl_3$) 3.72–3.56 (1 H, m), 3.30–3.05 (3 H, m), 3.02–2.65 (5 H, m), 2.13–1.62 (9 H, m), 1.58–1.38 (3 H, m) and 1.26 (9 H, s, CMe_3); δ_C (67.9 MHz; $CDCl_3$) 154.7 (C=O), 79.1 (*C*Me_3), 54.7 (CH_2N), 54.5 (CHN), 52.8 (CH_2N), 46.3 (CH_2N), 30.3 (CH_2), 28.7 (CH_2), 28.0 (C*Me*$_3$), 23.3 (CH_2), 22.3 (CH_2) and 21.7 (CH_2); *m*/*z* (CI; NH_3) 283 [100%, $(M + H)^+$], 183 (27) and 98 (48) [Found: $(M + H)^+$, 283.2384. $C_{16}H_{30}N_2O_2$ requires M + H, 283.2386].

(*S*)-*N*-Methyl-[2-(1-piperidinyl)ethyl]piperidine (*S*)-26

Lithium aluminium hydride (795 mg, 21.0 mmol) was added in one portion to a stirred solution of amino carbamate (*S*)-**50** (936 mg, 3.5 mmol) in THF (40 cm^3) at room temperature under nitrogen. After stirring for 48 h, Et_2O (20 cm^3) was added followed by the portionwise addition (**CAUTION**) of solid hydrated sodium sulfate until effervescence ceased. The resulting suspension was then stirred at room temperature for 3 h and the solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diamine (*S*)-**26** (656 mg, 89%, 90% ee by ^1H NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol) as a colourless oil, bp 145–150 °C/0.6 mmHg; $[\alpha]_D$ −43.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2937, 2856 and 2790; δ_H (270 MHz; $CDCl_3$) 2.74 (1 H, br d, *J* 13.5), 2.42–2.17 (5 H, m), 2.18 (3 H, s, NMe). 2.02–1.92 (1 H, m), 1.84–1.77 (1 H, m) and 1.72–1.15 (15 H, m); δ_C (67.9 MHz; $CDCl_3$) 62.6 (CHN), 57.0 (CH_2N), 55.5 (CH_2N), 54.7 (CH_2N), 43.0 (NMe), 30.8 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 25.8 (CH_2), 24.3 (CH_2) and 24.2 (CH_2); *m*/*z* (CI; NH_3) 211 [100%, $(M + H)^+$], 125 (25) and 98 (35) [Found: $(M + H)^+$, 211.2172. $C_{13}H_{26}N_2$ requires M + H, 211.2174].

(*S*)-*N*-Methyl-[2-(1-piperidinyl)ethyl]pyrrolidine (*S*)-27

Lithium aluminium hydride (1.01 g, 26.4 mmol) was added portionwise to a stirred solution of amino carbamate (*S*)-**51** (1.19 g, 4.22 mmol) in THF (45 cm^3) at 0 °C under nitrogen. The resulting suspension was heated at reflux for 24 h. After cooling to room temperature, Et_2O (20 cm^3) was added followed by the portionwise addition (**CAUTION**) of solid hydrated sodium sulfate until effervescence ceased. The resulting suspension was then stirred at room temperature for 2 h and the solids were removed by filtration through Celite. The filtrate was evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diamine (*S*)-**27** (579 mg, 70%) as a colourless oil, $[\alpha]_D$ −71.5 (*c* 0.6 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1230 and 1201; δ_H (270 MHz; $CDCl_3$) 3.06–2.97 (1 H, m), 2.45–2.21 (6 H, m), 2.27 (3 H, s, NMe), 2.08 (1 H, q, *J* 9.0), 1.99–1.80 (3 H, m), 1.76–1.51 (6 H, m) and 1.49–1.32 (4 H, m); δ_C (67.9 MHz; $CDCl_3$) 63.3 (CHN), 57.4 (CH_2N), 56.9 (CH_2N), 54.9 (CH_2N), 40.6 (NMe), 31.4 (CH_2), 31.0 (CH_2), 26.2 (CH_2), 24.7 (CH_2) and 22.1 (CH_2); *m*/*z* (CI; NH_3) 197 [100%, $(M + H)^+$], 98 (33) and 84 (32) [Found: $(M + H)^+$, 197.2019. $C_{12}H_{24}N_2$ requires M + H, 197.2018].

Representative procedure for evaluating diamines: (*R*)-2-trimethylsilyl-*N*-*tert*-butoxycarbonylpyrrolidine (*R*)-2

sec-Butyllithium (2.3 cm^3 of a 1.1 M solution in hexane, 2.51 mmol) was added dropwise to a stirred solution of freshly distilled diamine (+)-**24** (488 mg, 2.51 mmol) in Et_2O (25 cm^3) at −78 °C under nitrogen. The resulting solution was stirred at −78 °C for 10 min after which a solution of *N*-Boc pyrrolidine **1** (331 mg, 1.93 mmol) in Et_2O (1.3 cm^3) was added dropwise over 10 min *via* a cannula. After stirring for 5 h at −78 °C, Me_3SiCl (0.37 cm^3, 2.90 mmol) was added dropwise and the resulting solution was allowed to warm to room temperature over 16 h. Then, 5% aqueous H_3PO_4 solution (3.2 cm^3) was added and the mixture was stirred for 20 min. The two layers were separated and the organic layer was washed with 5% aqueous H_3PO_4 solution (3 × 3.2 cm^3). The combined aqueous layers were extracted with Et_2O (4 × 4.3 cm^3) and the combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with light petroleum–EtOAc (95 : 5) as eluent gave the trimethylsilyl adduct (*R*)-**2** (394 mg, 84%, 90% ee by chiral GC) as a colourless oil, $[\alpha]_D$ −61.7 (*c* 1.0 in $CHCl_3$) (lit.,[7] $[\alpha]_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**5** of 96% ee); GC: Chiraldex G-PN 20 m × 0.25 mm i.d. (γ-cyclodextrin, propionyl derivative in 3-position), 27.0 min [(*S*)-**2**], 28.0 min [(*R*)-**2**]. Spectroscopic data identical to that reported in the literature.[7]

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