Cyclic sulfamidates as versatile lactam precursors. An evaluation of synthetic strategies towards (−)-aphanorphine

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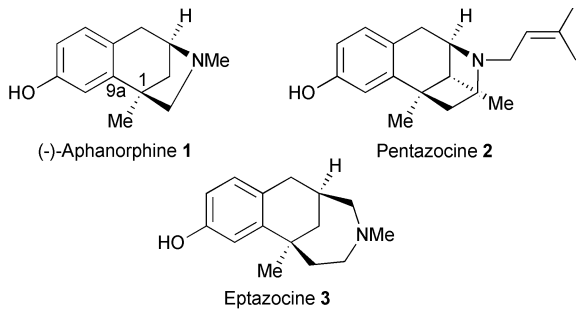
A full account of studies which led to the efficient asymmetric synthesis of (−)-aphanorphine **1** is reported. Two routes to the key cyclic sulfamidate intermediate **5** are described, the first was based on a chiral auxiliary approach and the second utilised asymmetric hydrogenation methodology. A range of *C*(3)-substituted lactams (**4**, **22** and **25**) were synthesised and evaluated as precursors for Pd(0) catalysed entries (based on (i) α-arylation of a lactam enolate and (ii) reductive Heck reaction) to the 3-benzazepine core of **1**. These approaches were less effective than an aryl radical cyclisation which allowed the completion of a synthesis of **1** in 12 steps from anisaldehyde.

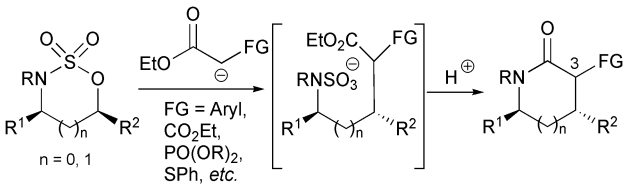
Introduction

(−)-Aphanorphine **1** is a tricyclic alkaloid isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*.[1] The structural resemblance of **1** to benzomorphan analgesics[2] such as pentazocine **2** and eptazocine **3** has led to widespread synthetic attention culminating in several approaches to both racemic and enantiopure **1**.[3]



As part of a programme to develop cyclic sulfamidates as *N*-heterocycle building blocks, we have recently outlined versatile methodologies for the synthesis of a range of enantiopure 5- and 6-ring *N*-heterocyclic derivatives.[4] In particular, the reactions of 1,2- and 1,3-cyclic sulfamidates with functionalised enolates offer a facile and modular entry to α-functionalised pyrrolidinones and piperidinones respectively (Scheme 1).[4b,c] We have investigated the incorporation of a variety of functionalities at *C*(3), including esters, phosphonates and sulfides, which then provide a handle for further manipulation and access to other highly functionalised lactam variants.

In order to define further the scope and robustness of this cyclic sulfamidate based methodology we recently reported an efficient asymmetric entry to (−)-aphanorphine **1**.[5] In this paper we describe full studies directed towards this target molecule and

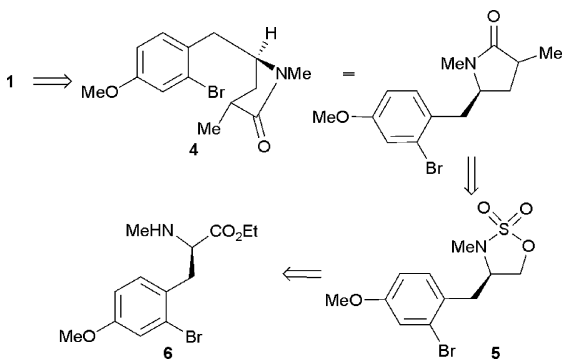


Scheme 1

in so doing also provide a further demonstration of the versatility of the heterocyclic strategy that we have developed.

Results and discussion

Our initial approach to (−)-aphanorphine is outlined in Scheme 2 and called for the formation of α-methylated lactam **4** as a precursor for the construction of the core ring system *via* a palladium-catalysed α-arylation reaction to form the *C*(1)–*C*(9a) bond associated with **1**. Lactam **4** would in turn be synthesised from cyclic sulfamidate **5** which would be derived from amino acid derivative **6**.



Scheme 2 Retrosynthetic analysis of (−)-aphanorphine **1**.

Our first generation approach to cyclic sulfamidate **5** is depicted in Scheme 3. Bromination of *p*-anisaldehyde was achieved in 62% yield in accordance with the procedure described by Durst which employs Comins' methodology for directed *ortho*-lithiation of

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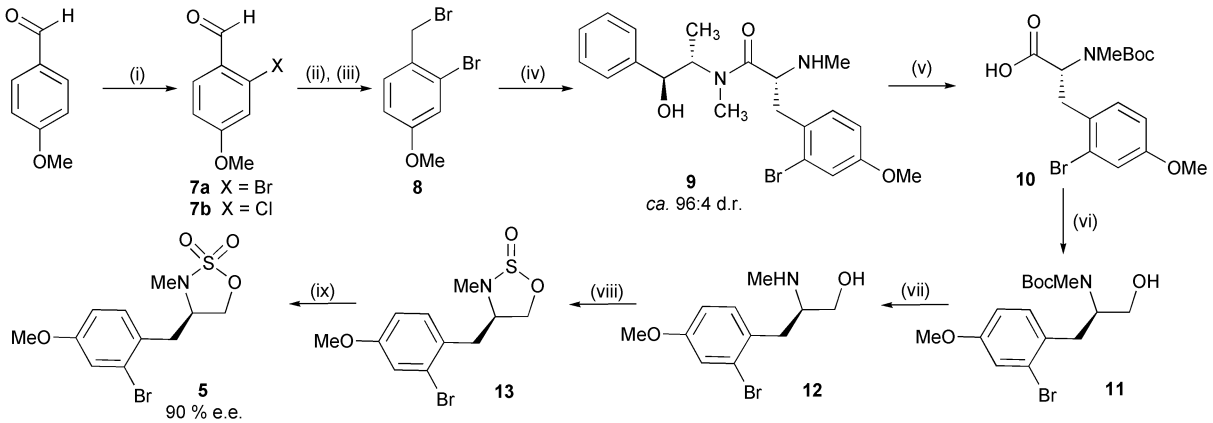


Scheme 3 *Reagents and conditions*: i, *n*-BuLi, trimethylethylenediamine, THF, −20 °C, then *n*-BuLi, −20 °C, then CBr_4 (62%) (see Table 1), −78 °C to r.t.; ii, $NaBH_4$, MeOH, THF, r.t.; iii, PBr_3, Et_2O, 0 °C to r.t. (95% from **7a**); iv, (*S*,*S*)-(+)-pseudoephedrine sarcosinamide, LDA (1.95 eq.), LiCl (6 eq.), THF, 0 °C, 1 h then bromide **8** (1.05 eq.), 0 °C, (77%); v, NaOH, MeOH, H_2O, reflux, then Boc_2O, $NaHCO_3$, dioxane, 0 °C to r.t., (99%); vi, $EtCO_2Cl$, Et_3N, THF, 0 °C, then $NaBH_4$, H_2O; vii, TFA, CH_2Cl_2, (85% from **10**); viii, $SOCl_2$, imidazole, Et_3N, CH_2Cl_2, 0 °C; ix, $RuCl_3$ (0.15 mol%), $NaIO_4$, H_2O, EtOAc, 0 °C (81% from **12**).

Table 1 Brominating agents screened for the formation of **7a**

Entry[a]	Brominating agent	Yield[b]
1	Br_2	18% (+ 70% SM)
2	$BrCH_2CH_2Br$	6% (+ 81% SM)
3	CBr_4	62% (+ 22% SM)
4	$BrCCl_2CCl_2Br$	42% (+ 11% SM & 30% **7b**)[c]

[a] All reactions were performed on a 1.00 mmol scale. [b] Isolated yield (SM = starting material). [c] **7a** and **7b** were not separable by chromatography, distillation or crystallisation.

Table 2 Optimisation of oxidation conditions for the synthesis of **5**

Entry[a]	Solvent	$NaIO_4$ eq.	Scale	Time	Yield[b]
1	1 : 1 MeCN–H_2O	1.5	0.78 mmol	2.5 hrs	14%
2	1 : 1 MeCN–H_2O	1.0	0.26 mmol	50 min	55%
3	1 : 1 MeCN–H_2O	1.0	1.14 mmol	30 min	18%
4	2 : 1 MeCN–H_2O	1.0	0.98 mmol	20 min	40%
5	1 : 1 EtOAc–H_2O	1.0	0.80 mmol	10 min	82%

[a] All reactions were performed at 0 °C using 0.15 mol% $RuCl_3$. [b] Isolated yield.

aromatic aldehydes.[6] A screen of commonly employed electrophilic brominating agents revealed CBr_4 to be optimal (Table 1, entry 3).†

Aldehyde **7a** was reduced ($NaBH_4$) and brominated (PBr_3) to afford benzyl bromide **8** in 95% yield over the two steps.‡ We initially chose to employ an auxiliary controlled protocol to install the key stereocentre present in sulfamidate **5**; Myers has previously outlined the use of pseudoephedrine sarcosinamide as a precursor to *N*-methylated amino acid derivatives.[7] Accordingly, alkylation of the dianion derived from (*S*,*S*)-(+)-pseudoephedrine sarcosinamide with bromide **8** generated adduct **9** in 77% yield and in approximately 92% d.e. (as estimated by HPLC analysis of peracetylated material).§ Direct hydrolytic cleavage (H_2O, dioxane, reflux) of the auxiliary was possible but we were only able to isolate the corresponding amino acid in moderate (45%) yield. In addition, attempted reduction of this species with $LiAlH_4$ to the requisite amino alcohol **12** was unsuccessful due to concomitant reductive debromination. We therefore chose to employ Myers' alternative base-induced auxiliary cleavage protocol and, after requisite Boc protection, were able to isolate adduct **10** in excellent yield (99%). Reduction of this substrate (to **11**) was successful under mixed anhydride conditions and, following Boc deprotection, amino alcohol **12** was isolated in 85% overall yield from **10**. This material was converted to cyclic sulfamidate **5** *via* the corresponding cyclic sulfamidite **13** in good overall yield (81%). Critically, the use of EtOAc–H_2O[8] as solvent for the oxidation step was absolutely essential.¶ When we employed a more commonly used MeCN–H_2O solvent system, yields of **5** were significantly lower (14–55%) and irreproducible, presumably due to competing oxidation of the 4-methoxybromobenzyl substituent (Table 2). It therefore appears that the chemoselectivity and/or reactivity of the oxidation step can be tailored *via* judicious choice of reaction solvent. At this stage we were able to determine the enantiopurity of **5** as 90% e.e. by chiral HPLC (using the corresponding racemate as a standard); this reflects upon the diastereoselectivity of the alkylation step (**8** → **9**). The route outlined in Scheme 3 proceeds in 9 steps and in 29% overall yield.

Given the level of enantiomeric excess (90%) associated with **5** and the length of the sequence, we chose to focus upon an alternative hydrogenation strategy to synthesise the key amino alcohol **12**. Condensation of bromide **7a** with ethyl isocyanoacetate afforded Knoevenagel adduct **14** in 41% yield and as a mixture of geometric

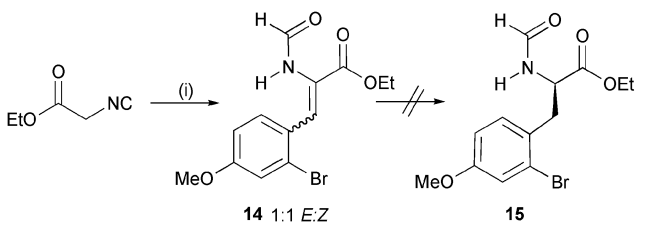
† 1,2-Dibromotetrachloroethane was effective on a smaller scale (0.3 mmol) and only traces of chlorinated adduct **7b** were observed (<10%). On a larger scale, chlorination is most likely promoted by inferior reaction exotherm control during addition of the brominating agent.

‡ Bromination is best conducted using reagent grade Et_2O; anhydrous Et_2O slows the reaction and results in slightly diminished yields of **8** (85% *vs.* 95%).

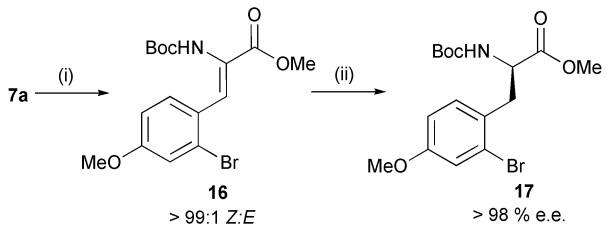
§ We have been unable to enrich this d.e. by chromatography or crystallisation.

¶ The oxidation step is most efficient on a small scale (100 mg; 82%) but can be conducted on larger scales (2 g) although yields were more variable (57–74%).

isomers (1 : 1 *E*–*Z*) (Scheme 4). Unfortunately we were unable to achieve reduction of this substrate (to give **15**) with a variety of RhL* systems.[9] * Hydrogenation of an *N*-Boc variant **16** was, however, successful (Scheme 5).



Scheme 4 *Reagents and conditions*: i, **7a**, NaH, THF, 0 °C to r.t. (41%).



Scheme 5 *Reagents and conditions* i, $BocNHCH(PO(OMe_2))CO_2Me$, *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG), CH_2Cl_2 (99%); ii, [((*R*,*R*)–Et-DuPHOS)Rh(COD)]BF_4 (1.5 mol%), H_2 (5 bar), MeOH (100%).

Reaction of bromide **7a** with Boc-α-phosphonoglycine trimethyl ester in the presence of TMG yielded Boc protected dehydroamino ester **16** in essentially quantitative yield and as a single geometric isomer (>99 : 1 *Z*–*E*) which was assigned on the basis of extensive literature precedent.[10] Reduction of this species was possible and, of the catalysts evaluated (Table 3), a Rh-Et-DuPHOS system delivered the best conversion and asymmetric induction (>98% e.e. as determined by chiral HPLC) to afford amino acid derivative **17** in quantitative yield.[11]

Reduction of both the ester and *N*-Boc moieties of **17** directly to amino alcohol **12** with $LiAlH_4$ was not possible, due again to concomitant debromination. We therefore examined the possibility of an *N*-methylation,[12] Boc deprotection and chemoselective (0 °C) ester reduction sequence. Although we were able to obtain amino alcohol **12** in 77% yield over these three steps, it was evident upon conversion to the cyclic sulfamidate **5** (62% e.e.) and analysis by chiral HPLC that some epimerisation had occurred, presumably during the base-mediated *N*-methylation step (Scheme 6).

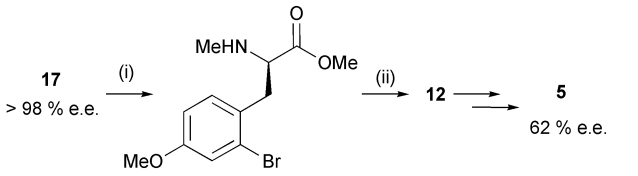
An alternative strategy for the conversion of amino ester **17** to the target amino alcohol **12** was devised (Scheme 7).

Table 3 Hydrogenation catalysts screened for the conversion of **16** → **17**

Entry[a]	Catalyst	e.e.[b]	Yield[c]
1	((*R*,*R*)–Et-DuPHOS)Rh(COD)]BF_4	>98%	100%
2	((*S*,*S*)–i-Pr-DuPHOS)Rh(COD)]BF_4	n.d.	8% (+ 92% **16**)
3	((*R*,*R*)–Me-BPE)Rh(COD)]BF_4	55%	100%

[a] Reaction conditions: catalyst (1.5 mol%), H_2 (5 bar), r.t., MeOH, 36 h. [b] Determined by chiral HPLC using a racemic standard prepared with Wilkinson's catalyst. [c] Isolated yield.

* The reason for the failure of this reaction is at present unclear.[9]



Scheme 6 *Reagents and conditions*: i, NaH (1.2 eq.), MeI, DMF, r.t. then TFA (82%); ii, $LiAlH_4$, THF, 0 °C, (93%).

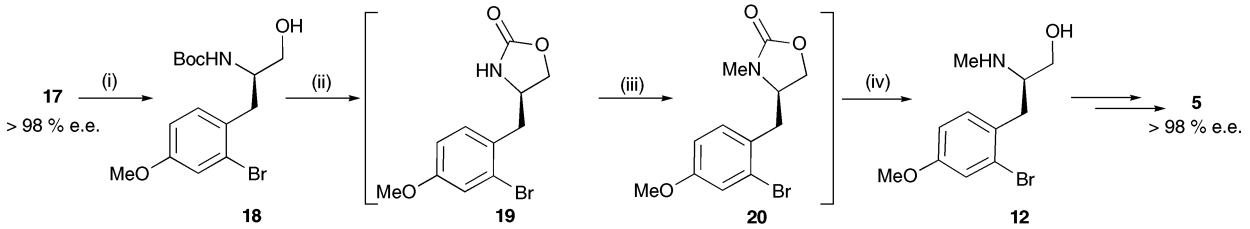
Chemoselective reduction of ester **17** with $LiAlH_4$ (0 °C) proceeded smoothly to afford alcohol **18** in 96% yield with the Ar–Br bond (and *N*-Boc group) still intact. Treatment of this species with NaH effected cyclisation to cyclic carbamate **19**. Once this step was complete, as judged by TLC, methyl iodide and further NaH were added to achieve methylation to afford **20**.†† This intermediate was cleaved hydrolytically and the resulting amino alcohol **12** was isolated in 92% overall yield. Conversion of **12** to cyclic sulfamidate **5** proceeded smoothly using our previously developed conditions and at this stage the enantiopurity of **5** was confirmed as >98% e.e. by chiral HPLC. This sequence allowed us to synthesise the key intermediate **5** in 48% overall yield over 7 steps from *p*-anisaldehyde (compare against Scheme 3).

Attention now turned to the synthesis of α-methyl lactam **4**. Although we have previously reported reactions of structurally representative cyclic sulfamidates with stabilised enolates as a route to *C*(3)-substituted lactams, the direct introduction of α-alkyl groups, *via* simple alkyl ester enolates, has been unsuccessful.[4b] Sulfamidate **5** did, however, react efficiently with the sodium enolate of α-methyl diethyl malonate to deliver lactam **21** after hydrolysis (to cleave the intermediate *N*-sulfate) and lactamisation (Scheme 8). Hydrolysis and subsequent decarboxylation afforded lactam **4** as a 2 : 1 mixture of diastereomers in 65% yield from cyclic sulfamidate **5**; this sequence was conducted efficiently without purification of intermediate **21**. Attempted cyclisation by exposure of lactam **4** to a variety of Pd-catalysed α-arylation protocols was unsuccessful.[13] At lower temperatures (<100 °C) starting material remained intact and at higher temperatures (110–140 °C) only debromination was observed under a variety of conditions, including those previously employed by Cossy to α-arylate piperidinones.[14a,b] We also briefly investigated the possibility of cyclisation *via* a benzyne intermediate by treating **4** with 2 equivalents of LiTMP but this led to decomposition.[15]

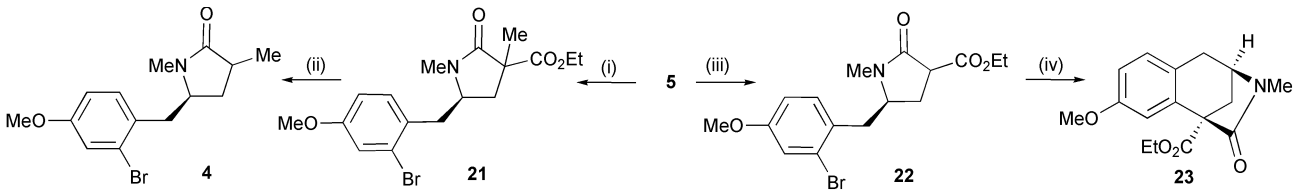
More stabilised enolates are generally better coupling partners for Pd-catalysed α-arylation. To this end we treated cyclic sulfamidate **5** with diethyl malonate to afford α-ester lactam **22** in 80% yield and as a 2 : 1 mixture of diastereomers. This species did indeed undergo successful Pd-catalysed cyclisation at higher temperatures to afford tricycle **23** but the reaction was disappointingly inefficient.‡‡ A screen of Pd source ($Pd(OAc)_2$, $Pd(dba)_2$), solvent (DMF, dioxane, *p*-xylene, toluene), base (Cs_2CO_3, *t*-BuONa, *t*-BuOK), temperature (100–150 °C) and ligand (dppf, dppp, dppe, Xantphos, BINAP) failed to rectify this problem and at best we were able to obtain the tricyclic adduct **23** in only 17% yield (Scheme 8). In all cases, the main byproducts were debrominated

†† The intermediacy of **19** and **20** is inferred although analogous intermediates have been isolated on a model *des*-bromo series.

‡‡ At lower temperature (<100 °C) either oxidative addition of Pd(0) into the Ar–Br bond is slow or cyclisation does not occur.



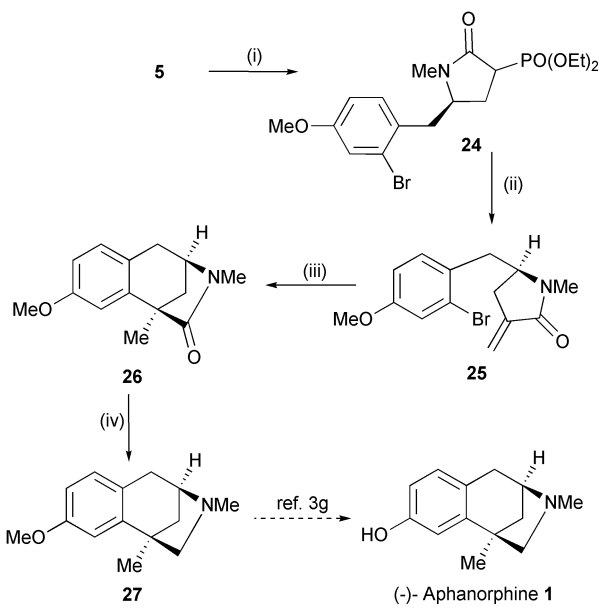
Scheme 7 *Reagents and conditions*: i, $LiAlH_4$, THF, 0 °C (96%); ii, NaH, THF; iii, NaH, MeI, THF; iv, NaOH, MeOH, reflux (92% from **18**).



Scheme 8 *Reagents and conditions*: i, methyl diethylmalonate, NaH, DMF, 40 °C then 5 M HCl; ii KOH, dioxane, reflux, then *p*-xylene, reflux (65% from **5**); iii, diethylmalonate, NaH, DMF, r.t. then 5 M HCl (80%); iv, $Pd(dba)_2$ (12 mol%), dppp (18 mol%), *t*-BuOK, PhMe, 130 °C (17%).

and decarboxylated adducts. Decarboxylation could potentially occur either *via* hydrolysis of ester of **22** to the corresponding acid (due to adventitious water) or *via* a Krapcho-type process promoted by released bromide.[16]§§

A potentially more robust approach to **1** involves Pd catalysed cyclisation *via* an alkene (*i.e.* an intramolecular reductive Heck reaction). Cyclic sulfamidate **5** thus reacted with the potassium enolate of triethylphosphonoacetate to afford, after hydrolysis and lactamisation, α-phosphono lactam **24** in 84% yield (2 : 1 d.r. at *C*(3)) (Scheme 9). This compound then underwent efficient Horner–Wadsworth–Emmons reaction with paraformaldehyde to

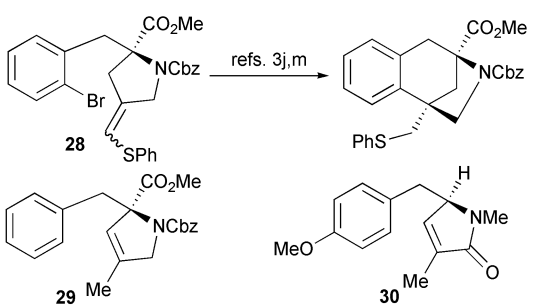


Scheme 9 *Reagents and conditions*: i, $(EtO)_2OPCH_2CO_2Et$, *t*-BuOK, THF, 40 °C then 5 M HCl (84%); ii, NaH, paraformaldehyde, THF (74%); iii, Bu_3SnH–AIBN (added over 1.5 h), PhH, reflux (62% + 18% of **30**); iv, $LiAlH_4$, THF (93%).

§§ An attempt was made to sequester released bromide by addition of AgOTf but this led to decomposition.

afford *exo*-alkene **25** in 74% yield; in our hands **25** proved to be sensitive to chromatography and was used in subsequent stages without purification. Exposure of **25** to reductive Heck conditions did not lead to cyclisation but routinely resulted in debromination and/or double bond isomerisation within the starting material.[17] However, the desired cyclisation could be achieved under radical conditions. Generation of the requisite aryl radical by slow addition (over 1.5 h) of a solution of Bu_3SnH and AIBN in PhH to **25** under high dilution conditions resulted in cyclisation to deliver the target tricycle **26** in 62% yield. Reduction of the lactam carbonyl using conditions previously reported by Funk on a synthesis of racemic **1** yielded amine **27** ($[\alpha]_D^{20}$ +8.3 (*c* 0.5, $CHCl_3$); lit. $[\alpha]_D^{28}$ +8.1 (*c* 1.2, $CHCl_3$),[3h] $[\alpha]_D^{20}$ +9.4 (*c* 0.3, $CHCl_3$),[3j] $[\alpha]_D^{20}$ +8.7 (*c* 1.06, $CHCl_3$)[3n]). This constitutes a formal asymmetric synthesis of (−)-**1**; *O*-demethylation of amine **27** has been reported by a number of groups in yields ranging from 57–86%.

The aryl radical cyclisation (**25** → **26**) is noteworthy, particularly in light of previous related work by Ishibashi[3j,m] who used a similar strategy to access the tricyclic core of **1**. In their system a thio-substituted radical acceptor, as in **28**, was required to achieve an efficient cyclisation (Scheme 10). Model studies on the corresponding *des*-methoxy series had shown that in the absence of such an activating group, 1,5-hydrogen atom abstraction competed leading to the isolation of *endo*-alkene **29**. We also observe the formation of a similar byproduct **30** but in our system there is no requirement for additional activation of the alkene to achieve an



Scheme 10

efficient cyclisation to form **26**. Interestingly the amount of **30** does increase if the Bu_3SnH is added over a shorter time period (*e.g.* addition over 45 minutes affords **26** in 50% yield along with 25% of **30**). This observation strongly suggests that 1,5-hydrogen atom abstraction may not be the only pathway corresponding to the formation of **30** and that direct isomerisation may also contribute. We have also briefly investigated using TMS_3SiH to carry out this cyclisation but this has proved to be less efficient.[18]

Conclusions

In summary, we have demonstrated the applicability of cyclic sulfamidate **5** as a key intermediate for the facile synthesis and evaluation of a range of cyclisation precursors leading to the tricyclic core of **1**. The availability of enantioenriched alkylating agents, such as **5**, was also demonstrated by applying two efficient and general literature methods for the asymmetric synthesis of amino acids. Pd-catalysed cyclisation of the three different precursors investigated was largely unsuccessful and is perhaps a reflection of the steric demands of forming the *C*(1)–*C*(9a) bond associated with **1**. Aryl radical cyclisation was, however, effective and allowed the completion of an efficient asymmetric synthesis of **1** in 15% overall yield in 12 steps from a commercial starting material. This demonstration of the versatile and modular nature of this cyclic sulfamidate mediated lactam methodology should open the way to its application in other target directed projects.

Experimental

General

General experimental details have been reported recently.[4c,5] Experimental procedures associated with the synthesis of (−)-**1** which were included as Electronic Supporting Information within ref. 5 have been omitted from here.

[19]

(2-Bromo-4-methoxyphenyl)methanol. To a solution of **7a** (10.0 g, 46.5 mmol) in THF (10 mL) and MeOH (10 mL) at r.t. was added $NaBH_4$ (879 mg, 23.25 mmol) portionwise over 5 minutes, causing vigorous gas evolution. The reaction mixture was stirred at r.t. for 1.5 h and then concentrated *in vacuo.* The residue was dissolved in Et_2O (100 mL), water (100 mL) and aq. 2 M HCl (10 mL) and the organic portion was isolated, washed with water (2 × 70 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the alcohol (10.09 g, 100%) as a colourless oil; ν_{max}/cm^{-1} (film) 3329 (br), 1603 (m), 1490 (m), 1234 (s), 1030 (s); δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, ArOCH_3), 4.69 (2H, d, $J = 6.5$, Ar CH_2OH), 6.87 (1H, dd, $J = 9.0$ and 3.0, C5-*H*), 7.12 (1H, d, $J = 3.0$, C3–*H*), 7.35 (1H, d, $J = 9.0$, C6–*H*), a signal attributable to –O*H* was not observed. The spectroscopic properties of this compound were consistent with the data available in the literature.

[20]

2-Bromo-1-bromomethyl-4-methoxybenzene 8. To an ice-cooled (0 °C) solution of alcohol (10.09 g, 46.5 mmol) in Et_2O (150 mL) was added PBr_3 (8.61 mL, 90.6 mmol) (*N.B.* anhydrous conditions impair the reaction efficiency). The mixture was placed under a N_2 atmosphere and allowed to warm slowly to r.t. overnight. The resulting orange solution was then cautiously poured into vigorously stirred ice-cooled (0 °C) water (200 mL) and the organic portion was isolated, washed with saturated aq. $NaHCO_3$ solution (100 mL) and then brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford bromide **8** (12.37 g, 95%) as a colourless crystalline solid; m.p. 58–59 °C (Et_2O) [Lit.[20] 59–60 °C (CCl_4–hexanes)]; ν_{max}/cm^{-1} (film) 1602 (s), 1494 (m), 1245 (s), 1029 (m); δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, ArOCH_3), 4.61 (2H, s, ArCH_2Br), 6.84 (1H, dd, $J = 9.0$ and 2.5, C5–*H*), 7.12 (1H, d, $J = 2.5$, C3–*H*), 7.36 (1H, d, $J = 9.0$, C6–*H*. The spectroscopic properties of this compound were consistent with the data available in the literature.

(*R*)-3-(2-Bromo-4-methoxyphenyl)-*N*-((1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl-2-methylaminopropionamide 9. Anhydrous LiCl (8.90 g, 210 mmol, obtained by heating commercially available LiCl at 150 °C and 0.01 mmHg for 12 h) was added to a 3 necked, 500 mL round bottomed flask fitted with a thermometer. The reaction vessel was then evacuated (0.01 mmHg) and, with vigorous stirring, the LiCl was further dried using a heatgun. The vessel was allowed to cool to r.t. and then purged with N_2. (*S*,*S*)-(+)-Pseudoephedrine sarcosinamide[7] (8.11 g, 34.4 mmol) was added and the contents of the flask were suspended in anhydrous THF (75 mL) and cooled to 0 °C. The mixture was then deoxygenated by careful evacuation followed by N_2 purge (3 cycles). In a separate flask LDA solution was prepared as follows. Anhydrous diisopropylamine (9.64 mL, 68.76 mmol) was dissolved in anhydrous THF (30 mL) and the resulting solution was cooled to 0 °C and then deoxygenated (see earlier). *n*-BuLi in hexanes (2.49 M, 67.08 mmol) (*N.B.* the molarity of the *n*-BuLi solution was accurately determined using the procedure of Watson and Eastham,[21] as recommended by Myers) was then added dropwise, *via* syringe, over 8 minutes and the mixture was stirred at 0 °C for 20 minutes. The LDA solution was then added dropwise *via* cannula (5 mL THF line wash) to the flask containing the sarcosinamide–LiCl slurry over 28 minutes to form a bright yellow suspension (*N.B.* the addition rate was maintained such that the internal temperature of the receiving flask did not exceed 5 °C). The mixture was stirred at 0 °C for 35 minutes and then a solution of bromide **8** (10.1 g, 36.1 mmol) in anhydrous THF (20 mL) was added dropwise *via* syringe over 10 minutes (*N.B.* the addition rate was maintained such that the internal temperature of the receiving flask did not exceed 5 °C). The mixture was stirred at 0 °C for a further 3 h, during which time it became almost colourless. The mixture was then poured into aq. 1 M HCl (200 mL) and diluted with EtOAc (200 mL). The aqueous portion was isolated and the organic portion was washed with aq. 1 M HCl (200 mL). The combined aqueous portions were then basified to pH 14 by addition of aq. 12.5 M NaOH (during this addition the solution temperature was maintained below 25 °C by use of an ice bath). The mixture was then extracted with CH_2Cl_2 (5 × 200 mL) and the combined organic extracts were dried (K_2CO_3) and concentrated *in vacuo* to afford a pale yellow oil. This crude residue was then purified by FCC (EtOAc–MeOH–Et_3N 74 : 3 : 3) to yield the product **9** (11.55 g, 77%, 92% d.e.) as a colourless foam. Crystallisation of this material was unsuccessful under a variety of conditions and diastereomeric enrichment could also not be achieved conveniently by chromatography. NMR analysis of this material was complex due to the presence of two diastereomers, each

existing as a mixture of rotamers (one major and one minor) and so full characterisation is presented for the major rotamer of the major diastereomer only; ν_{max}/cm^{-1} (film) 3318 (br), 1604 (s), 1492 (m), 1241 (m), 1027 (m), 907 (m); δ_H (400 MHz, $CDCl_3$) 0.77 (3H, d, $J = 7.0$, CH–CH_3), 2.14 (3H, s, NCH_3), 2.52 (3H, s, NCH_3), 2.67 (1H, dd, $J = 13.0$ and 9.0, C3–*H*), 3.04 (1H, dd, $J = 13.0$ and 6.0, C3–*H*), 3.71 (3H, s, ArOCH_3), 3.76 (1H, dd, $J = 9.0$ and 6.0, C2–*H*), 4.47 (1H, d, $J = 8.0$, C*H*OH), 4.70 (1H, m, C*H*–CH_3), 6.69 (1H, dd, $J = 8.5$ and 2.5, ArC*H*), 7.03 (1H, d, $J = 8.5$, ArC*H*), 7.04 (1H, d, $J = 2.5$, ArC*H*), 7.10–7.36 (5H, m, ArC*H*), signals attributable to –O*H* and –N*H*CH_3 were not observed; δ_C (100 MHz, $CDCl_3$) 14.2 (CH–*C*H_3), 30.5 and 34.4 (NCH_3 × 2), 39.5 (*C*-3), 55.5 (ArO*C*H_3), 56.2 (*C*H–CH_3), 59.2 (*C*-2), 75.7 (*C*OH), 113.4, 117.8 and 124.9 (Ar*C* × 3), 126.7, 127.8 and 128.4 (Ar*C*H × 5), 129.0 (Ar*C*), 132.4 (Ar*C*H), 142.3 and 159.0 (Ar*C* × 2), 176.1 (*C*-1); *m/z* (CI^+) 435 and 437 ([M + H]$^+$, 100 and 73%); HRMS: (CI^+) Found: [M + H]$^+$ 435.1284, $C_{21}H_{28}N_2O_3{}^{79}Br$ requires 435.1283; Anal. Calcd for $C_{21}H_{28}N_2O_3Br$: C, 57.94; H, 6.25; N, 6.43. Found: C, 58.31; H, 6.17; N, 6.25%. Characteristic ^1H NMR signals for minor rotamers/diastereomers: 2.22, 2.34, 2.36, 2.58, 2.82 and 2.88 (6 × NCH_3 signals). The diastereomeric purity of this compound was estimated by HPLC of a peracetylated derivative (Ac_2O, pyridine) of **9** (Chiralpak AD-H, isocratic hexanes-i-PrOH 80 : 20, 1.0 mL min^{-1}, 25 °C); t_R (major) = 10.2 min and t_R (minor) = 8.2 min.

(*R*)-3-(2-Bromo-4-methoxyphenyl)-2-(*tert*-butoxycarbonyl-methyl-amino)propionic acid 10. NaOH pellets (2.88 g, 71.9 mmol) were added to a solution of alkylation adduct **9** (7.136 g, 16.37 mmol) in MeOH (46 mL) and water (33 mL) and the resulting mixture was heated at reflux (*ca.* 90 °C oil bath temperature) for 22.5 h. The mixture was then cooled to r.t. and MeOH was removed *in vacuo* causing the formation of a pseudoephedrine precipitate. The mixture was diluted with water (150 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were then washed with water (150 mL). The aqueous portions were combined and concentrated to *ca.* 150 mL. Dioxane (200 mL) and $NaHCO_3$ (6.04 g, 71.9 mmol) were added and the resulting fine suspension was cooled to 0 °C prior to the addition of Boc_2O (4.29 g, 19.7 mmol). The mixture was stirred at 0 °C for 50 minutes and then subsequently stirred at r.t. for 2 h. The mixture was then diluted with water (200 mL) and extracted with EtOAc (200 mL). The organic portion was extracted with aq. 0.2 M $NaHCO_3$ (150 mL) and the aqueous portions were combined before being acidified to pH 3 by careful addition of aq. 1 M HCl. The solution was then extracted with EtOAc (3 × 250 mL) and the organic extracts were combined, washed with water (200 mL) and then brine (100 mL), dried (Na_2SO_4) and then concentrated *in vacuo* to afford acid **10** (6.08 g, 99%, 3 : 2 rotamer ratio *A*–*B*) as a pale yellow oil; $[\alpha]_D^{20}$ +73.3 ($c = 1.8$, $CHCl_3$); ν_{max}/cm^{-1} (film) 2976 (br), 1697 (s), 1494 (s), 1243 (m), 1150 (s); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, $NCH_3CO_2C(CH_3)_3$ *of A*), 1.42 (9H, s, $NCH_3CO_2C(CH_3)_3$ *of B*), 2.69 (3H, s, NCH_3Boc *of B*), 2.77 (3H, s, NCH_3Boc *of A*), 3.05 (1H, dd, $J = 14.0$ and 11.0, C3–*H of A*), 3.26 (1H, s, $J = 13.5$ and 10.5, C3–*H of B*), 3.37–3.47 (2H, m, C3–*H of A and B*), 3.78 (6H, s, ArOCH_3 *of A and B*), 4.64–4.79 (2H, m, C2–*H of A and B*), 6.76–6.82 (2H, m, ArC*H*), 7.03–7.16 (4H, m, ArC*H*), signals attributable to CO_2H were not observed; δ_C (100 MHz, $CDCl_3$) 28.2 ($NCH_3CO_2C(CH_3)_3$ *of A*), 28.3 ($NCH_3CO_2C(CH_3)_3$ *of B*), 33.1 (NCH_3Boc *of A*), 34.2 (*C*-3 *of B*), 34.6 (NCH_3Boc *of B*), 34.9 (*C*-3 *of A*), 55.5 (ArOCH_3 *of B*), 55.6 (ArOCH_3 *of A*), 59.6 (*C*-2 *of A*), 60.2 (*C*-2 *of B*), 80.7 ($NCH_3CO_2C(CH_3)_3$ *of B*), 80.8 ($NCH_3CO_2C(CH_3)_3$ *of A*), 113.5 (Ar*C*H *of A*), 113.6 (Ar*C*H *of B*), 117.9 (Ar*C*H *of B*), 118.3 (Ar*C*H *of A*), 124.7 (2 signals) and 128.6 (2 signals) (Ar*C* × 4), 131.7 (Ar*C*H *of A*), 131.9 (Ar*C*H *of B*), 154.9 (Ar*C of A*), 156.1 (Ar*C of B*), 159.0 ($NCH_3CO_2C(CH_3)_3$ *of B*), 159.1 ($NCH_3CO_2C(CH_3)_3$ *of A*), 175.6 (*C*O$_2$H *of B*), 176.1 (*C*O$_2$H *of A*); *m/z* (CI^+) 390 and 388 ([M + H]$^+$, 18 and 20%), 290 and 288 ([M + H-Boc]$^+$, 93 and 100); HRMS: (CI^+) Found: [M + H]$^+$ 388.0753, $C_{16}H_{23}NO_5{}^{79}Br$ requires 388.0760.

(*E*) and (*Z*) 3-(2-Bromo-4-methoxyphenyl)-2-formylamino-acrylic acid ethyl ester 14. To a suspension of NaH (60% dispersion in mineral oil, 223 mg, 5.58 mmol) in anhydrous THF (5 mL) at 35 °C was added, *via* syringe, a solution of ethyl isocyanoacetate (526 mg, 4.65 mmol) and bromide **7a** (1.00 g, 4.65 mmol) in anhydrous THF (5 mL) dropwise over 5 minutes to form an orange suspension which was stirred at r.t. for 3 h. After cooling to 0 °C, aq. 1.6 M AcOH (5 mL) was added and the mixture was concentrated *in vacuo.* The residue was dissolved in CH_2Cl_2 (50 mL), washed with water (2 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford an orange solid. Purification by FCC (EtOAc—hexanes 1 : 1–1 : 0) afforded **14** (625 mg, 41%, 1 : 1 mixture of geometric isomers *A*–*B*) as a colourless solid; ν_{max}/cm^{-1} (solid) 3274 (br m), 2940 (br), 1694 (s), 1597 (s), 1488 (s), 1291 (m), 1235 (s), 1027 (s); δ_H (400 MHz, $CDCl_3$) 1.31–1.42 (6H, m, $CO_2CH_2CH_3$ *of A and B*), 3.77–3.82 (6H, m, ArOCH_3 *of A and B*), 4.25–4.38 (4H, m, $CO_2CH_2CH_3$ *of A and B*), 6.79 (1H, d, $J = 8.0$, ArC*H of B*), 6.86 (1H, d, $J = 8.0$, ArC*H of A*), 7.11–7.19 (2H, m, ArC*H of A and B*), 7.36–7.52 (4H, m, ArC*H* and C3–*H*), 7.55 (1H, br s, N*H of B*), 7.68 (1H, br s, N*H of A*), 8.10–8.19 (2H, m, NCO*H of A and B*); δ_C (100 MHz, $CDCl_3$) 14.2 and 14.3 ($CO_2CH_2CH_3$), 55.6 and 55.7 (ArOCH_3), 62.1 and 62.4 ($CO_2CH_2CH_3$), 113.6, 114.3, 118.0 and 118.6 (Ar*C*H × 4), 122.9, 124.8, 125.6, 125.8 (2 signals) and 126.5 (*C*-2 × 2 and Ar*C* × 4), 126.3 (2 signals), 130.2 and 130.6 (Ar*C*H × 2 and *C*-3 × 2), 159.1 (N*C*OH), 160.5 (2 signals) (ArC × 2), 163.8 (N*C*OH), 164.2 and 164.9 ($CO_2CH_2CH_3$ × 2); *m/z* (CI^+) 323 and 328 ([M + H]$^+$, 78% and 80%), 284 (100), 282 (98); HRMS: (CI^+) Found: [M + H]$^+$ 328.0179, $C_{13}H_{15}NO_4{}^{79}Br$ requires 328.0184.

(*R*)-3-(2-Bromo-4-methoxyphenyl)-2-methylaminopropionic acid methyl ester. To an ice-cooled (0 °C) solution of ester **17** (284 mg, 0.73 mmol) in anhydrous DMF (2.6 mL) was added MeI (92 μL, 1.47 mmol) and then NaH (60% dispersion in mineral oil, 38 mg, 0.95 mmol) to form a fine suspension which was stirred at r.t. for 14 h. TFA (0.75 mL) was then added and the mixture was stirred for a further 22 h. The mixture was diluted with aq. 1 M HCl (15 mL) and washed with Et_2O (2 × 10 mL). The aqueous portion was then neutralised with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford the amine (180 mg, 82%) as a pale yellow oil; $[\alpha]_D^{20}$ −13.6 ($c = 0.9$, $CHCl_3$); ν_{max}/cm^{-1} (film) 2949 (m), 1734 (s), 1606 (s), 1495 (s), 1439 (m), 1242 (s), 1030 (s); δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, NHCH_3), 2.97 (1H, dd, $J = 13.5$ and 7.5, C3–*H*), 3.03 (1H, dd, $J = 13.5$ and 7.0, C3–*H*), 3.53 (1H, dd, $J = 7.5$ and 7.0, C2–*H*), 3.66 (3H, s, CO_2CH_3), 3.77 (3H, s, ArOCH_3), 6.78 (1H, dd, $J = 8.5$ and 2.5,

ArC*H*), 7.07–7.13 (2H, m, ArC*H*), no signal attributable to N*H* was observed; δ_C (100 MHz, $CDCl_3$) 34.7 (NH*C*H_3), 38.7 (*C*-3), 51.6 (CO_2*C*H_3), 55.4 (ArO*C*H_3), 63.2 (*C*-2), 113.4 and 118.0 (Ar*C*H × 2), 127.8 and 128.7 (Ar*C* × 2), 131.6 (Ar*C*H), 158.8 (Ar*C*), 174.8 (*C*-1); *m/z* (CI^+) 303 ([M + H]$^+$, 100%); HRMS: (CI^+) Found: [M + H]$^+$ 302.0383, $C_{12}H_{17}NO_3{}^{79}Br$ requires 302.0392. This material was converted to amino alcohol **12** as follows: to an ice-cooled (0 °C) solution of amine (113 mg, 0.37 mmol) in anhydrous THF (2.1 mL) was added, *via* syringe, a solution of $LiAlH_4$ in THF (1 M, 0.56 mmol) dropwise over 1 minute. The mixture was stirred at 0 °C for 15 minutes and then quenched by sequential addition of water (21 μL), aq. 4 M NaOH (21 μL) and then water (63 μL) to form a colourless precipitate. The mixture was filtered through Celite®, washing with CH_2Cl_2 (20 mL), and concentrated *in vacuo* to afford amino alcohol **12** (95 mg, 93%, 62% e.e.) as a pale yellow wax. The enantiomeric purity of this material was determined by conversion to cyclic sulfamidate **5** and subsequent analysis by chiral HPLC.

(*R*)-3-(2-Bromo-4-methoxyphenyl)-2-methylaminopropan-1-ol 12. *Via Compound **10**.* To a solution of acid **10** (6.06 g, 16.1 mmol) in THF (37 mL) at 0 °C was added Et_3N (2.47 mL, 17.7 mmol) and then ethyl chloroformate (1.70 mL, 17.7 mmol) causing the immediate formation of a colourless precipitate. The mixture was stirred at 0 °C for 50 minutes and was then filtered (washing with THF (37 mL)). The filtrate was then added dropwise to an ice-cooled (0 °C) suspension of $NaBH_4$ (1.53 g, 40.3 mmol) in water (37 mL) causing vigorous gas evolution. The mixture was stirred at 0 °C for 2.5 h and was then poured into aq. 0.5 M HCl (120 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and then concentrated *in vacuo* to afford **11** as a colourless oil. This residue was dissolved in CH_2Cl_2 (30 mL) and then TFA (30 mL) was added resulting in immediate bubbling. The mixture was stirred at r.t. for 0.5 h and then concentrated *in vacuo.* The residue was partitioned between CH_2Cl_2 (100 mL), saturated aq. $NaHCO_3$ (100 mL) and water (50 mL). The organic portion was isolated and the aqueous portion was further extracted with CH_2Cl_2 (2 × 80 mL). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to afford amino alcohol **12** (3.77 g, 85%) as a colourless wax. This material was used for the synthesis of cyclic sulfamidate **5** (90% e.e.) without further purification.[5]

Characterisation of **12** (in >98% e.e.) has been reported previously.[5]

(*S*)-5-(2-Bromo-4-methoxybenzyl)-1,3-dimethylpyrrolidin-2-one 4. To a solution of methylated diethylmalonate (154 μL, 0.89 mmol) in anhydrous DMF (5 mL) was added, at r.t., NaH (60% dispersion in mineral oil, 35 mg, 0.89 mmol) to form a colourless solution. After 20 minutes sulfamidate **5** (142 mg, 0.42 mmol) was added and the mixture was heated at 40 °C for 17 h. The mixture was then cooled to r.t. and aq. 5 M HCl (0.45 mL) was added. After stirring for 3 h, the mixture was neutralised with saturated aq. $NaHCO_3$ and stirred for a further 0.5 h prior to extraction with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (3 × 20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil. This residue was dissolved in dioxane (1 mL) and water (1 mL) and KOH (33 mg, 0.58 mmol) was added. The mixture was then heated at reflux for 1.5 h, cooled to r.t., diluted with aq. 1 M HCl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo.* The residue was dissolved in *p*-xylene (2 mL) and heated at reflux for 14 h. The mixture was then cooled to r.t. and concentrated *in vacuo.* The residue was then purified by FCC (EtOAc–petrol 1 : 1) to afford the lactam **4** (87 mg, 65%, 2 : 1 d.r. *A*–*B*) as a colourless oil; ν_{max}/cm^{-1} (film) 1686 (s), 1605 (m), 1493 (m), 1242 (m), 1028 (m); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* = 7.0, C3–CH_3 *of B*), 1.21 (3H, d, *J* = 7.0, C3–CH_3 *of A*), 1.33 (1H, ddd, *J* = 13.0, 9.0 and 8.0, C4–*H of A*), 1.59 (1H, ddd, *J* = 13.0, 9.0 and 8.0, C4–*H of B*), 2.06 (1H, ddd, *J* = 13.0, 8.5 and 2.5, C4–*H of B*), 2.15 (1H, ddd, *J* = 13.0, 9.0 and 7.0, C4–*H of A*), 2.31–2.42 (1H, m, C3–*H of A*), 2.45–2.54 (2H, m, C3–*H of B* and C5–CH_2 *of A*), 2.57 (1H, dd, *J* = 13.5 and 9.0, C5–CH_2 *of B*), 2.88 (3H, s, NCH_3 *of B*), 2.91 (3H, s, NCH_3 *of A*), 3.18 (1H, dd, *J* = 13.5 and 4.5, C5–CH_2 *of B*), 3.41 (1H, dd, *J* = 13.0 and 4.5, C5–CH_2 *of A*), 3.67–3.75 (2H, m, C5–*H of A and B*), 6.81–6.84 (2H, m, ArC*H*), 7.70–7.13 (4H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 16.3 and 16.9 (C2–*C*H_3 *of A and B*), 28.2 (NCH_3 *of A*), 28.5 (NCH_3 *of B*), 32.3 (*C*-4 *of A*), 33.6 (*C*-4 *of B*), 34.7 (C5–*C*H_2 *of B*), 36.3 (C5–*C*H_2 *of A*), 37.8 (*C*-3 *of A*), 40.0 (*C*-3 *of B*), 55.5 (2 signals) (ArO*C*H_3 *of A and B*), 57.7 (*C*-5 *of B*), 58.2 (*C*-5 *of A*), 113.7 and 113.8 and 118.3 (2 signals) (Ar*C*H × 4), 124.8, 124.9, 128.4 and 128.8 (Ar*C* × 4), 131.7 (2 signals) (Ar*C*H × 2), 159.0 (2 signals) (Ar*C* × 2), 177.2 (*C*-2 *of A*), 177.8 (*C*-2 *of B*); *m/z* (CI^+) 314 and 312 ([M + H]$^+$, 90 and 100%); HRMS: (CI^+) Found: [M + H]$^+$ 312.0584, $C_{14}H_{19}NO_2{}^{79}Br$ requires 312.0599.

(*S*)-5-(2-Bromo-4-methoxybenzyl)-1-methyl-2-oxopyrrolidine-3-carboxylic acid ethyl ester 22. To a solution of diethylmalonate (452 μL, 2.98 mmol) in anhydrous DMF (17 mL) was added NaH (60% dispersion in mineral oil, 119 mg, 2.98 mmol) to form a colourless solution which was stirred at r.t. for 30 minutes. Sulfamidate **5** (500 mg, 1.49 mmol) was then added and the mixture was stirred at r.t. for 15 h. Aq. 5 M HCl (1.5 mL) was then added and, after stirring at r.t. for 3 h, the mixture was neutralised with saturated aq. $NaHCO_3$ and extracted with Et_2O (3 × 25 mL). The combined organic portions were washed with water (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale yellow oil which was purified by FCC (EtOAc–petrol 3 : 2) to yield lactam **22** (441 mg, 80%, 2 : 1 d.r. *A*–*B*) as a colourless, amorphous solid; m.p. 58–60.5 °C (Et_2O–CH_2Cl_2); ν_{max}/cm^{-1} (film) 1735 (m), 1690 (s), 1493 (m), 1241 (m), 1031 (m); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* = 7.0, OCH_2CH_3 *of A*), 1.33 (3H, t, *J* = 7.0, $CO_2CH_2CH_3$ *of B*), 2.00–2.24 (3H, m, C4–*H of A and B*), 2.35 (1H, dt, *J* = 13.0 and 8.0, C4–*H of A*), 2.57 (1H, dd, *J* = 13.5 and 9.0, C5–CH_2 *of A*), 2.68 (1H, dd, *J* = 13.5 and 10.5, C5–CH_2 *of B*), 2.92 (3H, s, NCH_3 *of A*), 2.94 (3H, s, NCH_3 *of B*), 3.24 (1H, dd, *J* = 13.5 and 4.5, C5–CH_2 *of A*), 3.35–3.43 (3H, m, C5–CH_2 *of B* and C3–*H of A and B*), 3.79 (6H, s, ArOCH_3 *of A and B*), 3.74–3.86 (1H, m, C5–*H of B*), 3.86–3.94 (1H, m, C5–*H of A*), 4.24–4.29 (4H, m, $CO_2CH_2CH_3$ *of A and B*), 6.80–6.86 (2H, m, ArC*H of A and B*), 7.07 (1H, d, *J* = 8.5, ArC*H of A*), 7.11–7.15 (2H, m, ArC*H of A and B*), 7.25 (1H, d, *J* = 8.5, ArC*H of B*); δ_C (100 MHz, $CDCl_3$) 14.1 and 14.2 ($CO_2CH_2CH_3$ *of A and B*), 27.0 (*C*-4 *of B*), 27.8 (*C*-4 *of A*), 28.7 (2 signals) (NCH_3 *of A and B*), 38.3 (C5–*C*H_2 *of B*), 39.2 (C5–*C*H_2 *of A*), 47.3 (*C*-3 *of A*), 47.9 (*C*-3 *of B*), 55.6 (2 signals)

(ArO*C*H$_3$ *of A and B*), 58.0 (*C*-5 *of B*), 58.5 (*C*-5 *of A*), 61.6 ($CO_2CH_2CH_3$ *of A*), 61.8 ($CO_2CH_2CH_3$ *of B*), 113.7, 113.9, 118.3 and 118.4 (Ar*C*H × 4), 124.7, 125.0, 128.0 and 128.3 (Ar*C* × 4), 131.6 and 132.3 (Ar*C*H × 2), 159.2 (2 signals) (Ar*C* × 2), 169.7, 169.9, 170.3 and 170.6 (*C*-2 and $CO_2CH_2CH_3$ *of A and B*); *m*/*z* (CI$^+$) 372 and 370 ([M + H]$^+$, 87 and 100%); HRMS: (CI$^+$) Found: [M + H]$^+$ 370.0654, $C_{16}H_{20}NO_4{}^{79}Br$ requires 370.0654; Anal. Calcd for $C_{16}H_{20}NO_4Br$: C, 51.91; H, 5.44; N, 4.12. Found: C, 52.10; H, 5.70; N, 3.88%.

(1*S*,9*R*)-4-Methoxy-10-methyl-11-oxo-10-azatricyclo-[7.2.1.0^{2,7}]-dodeca-2,4,6-triene-1-carboxylic acid ethyl ester 23. Bromide **22** (40 mg, 0.10 mmol), *t*-BuOK (20 mg, 0.18 mmol, freshly sublimed at 180 °C and *ca.* 0.01 mmHg), Pd(dba)$_2$ (6.9 mg, 0.012 mmol) and dppp (7.4 mg, 0.018 mmol) were placed in a re-sealable tube, dissolved in anhydrous toluene (0.5 mL, degassed by three freeze–pump–thaw cycles) and heated at 130 °C for 15 h. The reaction mixture was then cooled to r.t., diluted with saturated aq. NH_4Cl solution (2 mL) and extracted with EtOAc (3 × 2 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford a pale brown oil which was then purified by preparative TLC (EtOAc–hexanes 1 : 1) to afford tricycle **23** (5.8 mg, 17%) as a colourless oil; $[\alpha]_D^{20}$ +40.0 (*c* = 0.4, $CHCl_3$); ν_{max}/cm^{-1} (film) 1739 (s), 1695 (m), 1232 (m); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* = 7.2, $CO_2CH_2CH_3$), 2.27 (1H, d, *J* = 11.0, C1–C*H*$_2$), 2.72 (1H, dd, *J* = 11.0 and 5.5, C1–C*H*$_2$), 2.83 (3H, s, NC*H*$_3$), 2.94 (2H, d, *J* = 2.5, C8–*H*), 3.78 (3H, s, ArOC*H*$_3$), 3.92 (1H, dt, *J* = 5.5 and 2.5, C9–*H*), 4.32–4.42 (2H, m, $CO_2CH_2CH_3$), 6.79 (1H, dd, *J* = 8.5 and 2.5, C5–*H*), 7.01 (1H, d, *J* = 8.5, C6–*H*), 7.22 (1H, d, *J* = 2.5, C3–*H*); δ_C (125 MHz, $CDCl_3$) 14.4 ($CO_2CH_2CH_3$), 27.9 (NCH$_3$), 29.8 (*C*-8), 37.9 (C1–CH$_2$), 54.6 (ArOCH$_3$), 55.4 (*C*-9), 56.2 (*C*-1), 61.5 ($CO_2CH_2CH_3$), 111.4 (*C*-3), 114.8 (*C*-5), 123.8 (*C*-7), 131.2 (*C*-6), 135.7 (*C*-2), 158.2 (*C*-4), 169.6 and 171.5 (*C*-11 and $CO_2CH_2CH_3$); *m*/*z* (CI$^+$) 290 ([M + H]$^+$, 100%); HRMS: (CI$^+$) Found: [M + H]$^+$ 290.1382, $C_{16}H_{20}NO_4$ requires 290.1392.

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