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Synthesis and differential functionalisation of pyrrolidine and piperidine based spirodiamine scaffolds

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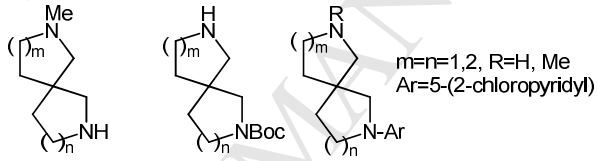

Synthesis and Differential Functionalisation of Pyrrolidine and Piperidine based Spirodiamine Scaffolds

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Abstract

The synthesis and differential substitution/protection of a series of spirodiamine scaffolds is described. Methods for selective access to the two mono-N-methyl isomers based on 2,7-diazaspiro[4.5]decane are also described. Key precursors associated with this chemistry are prone to rearrangement and methods for circumventing this issue are reported. While direct *mono*-carbamoylation (Boc) was not efficient, selective deprotection of doubly Boc-protected derivatives derived from symmetrical diamines provided mono-Boc variants. N-Arylation, exemplified by a series of monosubstituted spirodiamines incorporating the 2-chloro-5-pyridyl moiety, which is a privileged nicotinic agonist substructure, has also been carried out to provide monoarylated secondary and tertiary spirodiamines variants.

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Introduction

Nitrogen-based heterocycles based on spirodiamine scaffolds are of significant interest in medicinal chemistry, catalysis and materials chemistry by providing a well defined and comparatively rigid three dimensional quality to a multisite interaction, be it involving a receptor/enzyme as the target or as the basis of a ligand for a metal-based catalyst. In terms of biologically active molecules,[1a] spiroamines have found application as potential antibacterial[1b] and antitumour drugs,[2] agonists of various protein receptors[3] including neural receptors,[4] and as peptidomimetics.[5] Spiroamine-based scaffolds are also found in Nature, as exemplified by the antimalarial alkaloid manzamine (and related molecules) which are isolated from marine sponges,[6] and have also been identified in a structurally diverse range of natural products derived from plants[7] and fungi.[8] More recently, there has been a significant increase in the awareness of the importance of three dimensionality as a design element within drug candidates.[9] This may involve chirality, but even without explicit consideration of chirality, an increase in the proportion of sp^3 centres, at the expense of more often used sp^2-based structures, can have a profound effect on biological profile that is not just limited to intrinsic activity but will also link to key physicochemical parameters. Consequently, the desirability of sp^3 centres is now recognized as an important critical factor in terms of enhancing a candidate's likelihood of successful translation from laboratory to clinic to market, and new opportunities for chemical methodologies in this area are of value. In this sense, spirodiamines not only offer "three dimensionality" but, and depending on the specific scaffold, also chirality.

In terms of background, a number of spirodiamine scaffolds **A**-**F** (Figure 1; based on 4-, 5- or 6-membered rings) are known, and the various methods for the synthesis of each of these scaffolds (as opposed to specific individual examples) is reviewed briefly here. It is important to appreciate that these spirodiamines are not necessarily reported/available in their "parent" (i.e. unsubstituted on the rings or via N) forms, and we have omitted benzofused variants, as well as comparatively reactive β–lactam derivatives. Aminal (aminoacetal) isomers/variants have been ignored simply because of the susceptibility of such latter systems to isomerisation/ring opening and hence scrambling of the spiro stereocentre.

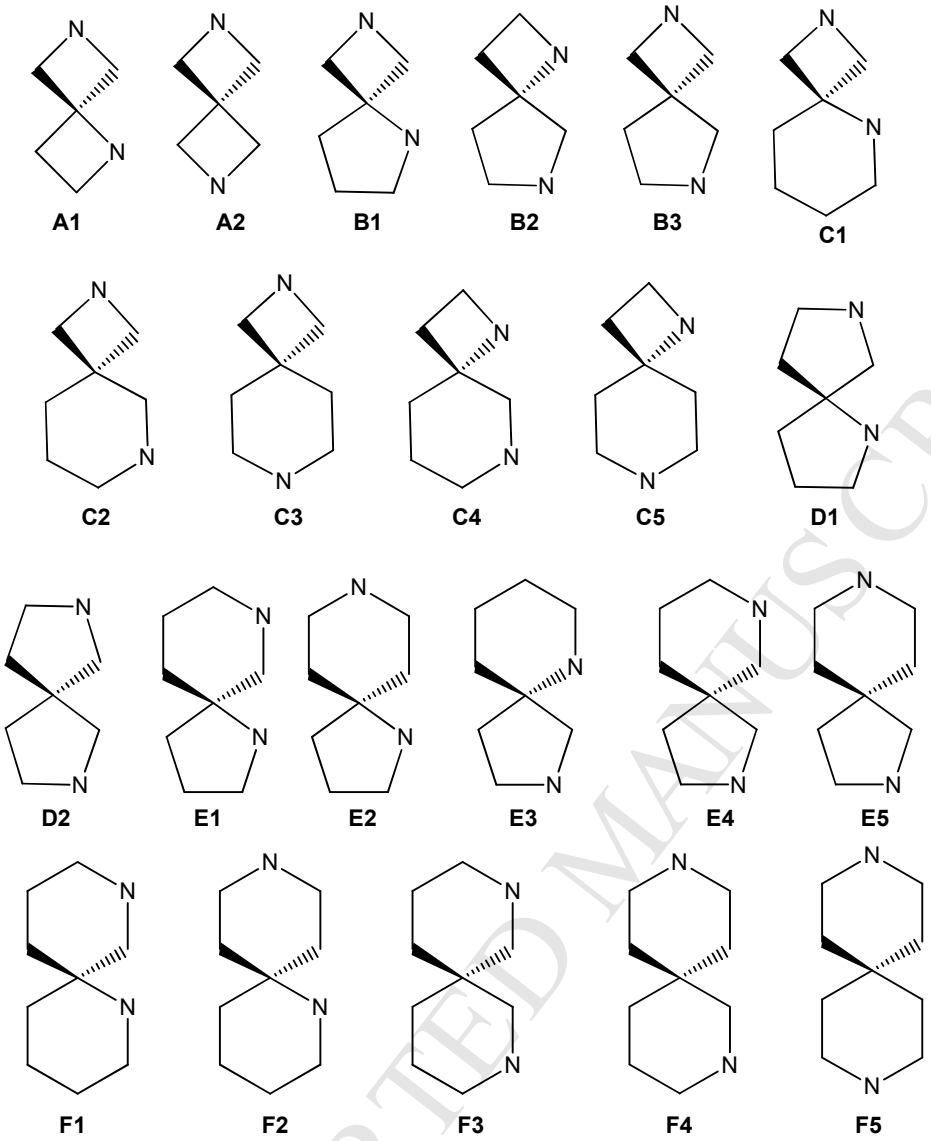


Figure 1. Azetidine/pyrrolidine/piperidine spirodiamine scaffolds. No absolute stereochemistry should be inferred and scaffolds (i.e. molecular frameworks) are shown without substituents or associated functionality. References to specific examples of structures incorporating each scaffold are included in the text below, but generally β–lactam and benzo-fused variants have been excluded. Aziridine variants are not shown, given the comparatively high reactivity of these systems, and configurationally labile aminal isomers are also excluded.

Several synthetic strategies, including stereoselective approaches, have been applied depending on the structure of the target scaffold, and given the utility of these systems as the basis of more complex structures, it is appropriate to provide a brief overview of the more commonly exploited methods available. A number of these and related spiroamine scaffolds have only been reported or otherwise exploited in the patent literature, but this underscores the potential and perceived importance of these units in drug discovery.

The most common stereoselective approach to pyrrolidine variants has involved the alkylation of *L*-proline or its derivatives, followed by the cyclization step to achieve the spirocycle. This provides an entry to pyrrolidine-based scaffolds encompassing 2,5-diazaspiro[3.4]octane **B1**,[5] 1,7-diazaspiro[4.4]nonane **D1**,[10] 1,7-diazaspiro[4.5]decane **E1**[11] and the seven-membered (azepane-based) 1,7-diazaspiro[4.6]undecane (*not shown*)[12] which have been obtained in most cases in enantiopure form.

Other, more varied ways of stereocontrolled construction of diazaspiro systems, often applied in alkaloid synthesis, have included ring-contracting pinacol rearrangements to access 2,7-diazaspiro[4.4]nonane **D2**,[13] synthesis of this same scaffold by electrocyclisation,[14] and synthesis of the core structure of manzamine that contains the 2,7-diazaspiro[4.5]decane **E4** structure via intramolecular stereocontrolled Michael addition to a 2-pyrrolidone derivative.[15]

Spirodiamine skeletons have been obtained via the reaction of geminally disubstituted (i.e. the nascent spiro-centre is already established) azetidine, pyrrolidine or piperidine derivatives with an amine in order to close the second ring, usually involving formation of an amine or an imide. Using this method, 2,6-diazaspiro[3.3]heptane **A2**,[10d,f] 1,6-diazaspiro[3.4]octane **B2**,[10d] 2,6-diazaspiro[3.4]octane **B3**,[10g] 2,5-diazaspiro[3.5]nonane **C1**,[4] 2,5-diazaspiro[3.6]nonane **C2**,[10g] 2,7-diazaspiro[3.5]nonane **C3**,[10e,f] diazaspiro[4.5]decanes **E4**[16] and **E5**,[17] and diazaspiro[5.5]undecanes **F3**,[18] **F4**[19] and **F5**[20] systems have been prepared. One of the geminal substituents can itself already be e.g. an amine or amide so that the cyclization step does not necessarily require an external amine, such as in the syntheses of diamine scaffolds **C4**,[4b] **C5**,[21a-d] **D1**,[21e] **E1**,[21e] **E2**,[21f] **E3**[21e] and **E4**[21g] and **F1**.[21e] Both rings of a nascent spiro system can be also closed in the same step, as in the syntheses of the 2,7-diazaspiro[4.4]nonane scaffold **D2**[22] and the 2,8-diazaspiro[5.5]undecane structure **F3**.[1,23] In several cases, the second ring of a diazaspiro scaffold was established via ring closing metathesis, and this process has been applied successfully to generate the 2,6-diazaspiro[4.5]decane **E3**,[24] 1,8-diazaspiro[5.5]undecane **F1**,[25] 1,9-diazaspiro[5.5]undecane **F2**,[24,25c,25d] and analogous systems based on a pyrrolidine and piperidine spirofused to an azepane moiety (not shown in Figure 1, but included here for completeness), such as 2,7-diazaspiro[4.6]undecane,[24] 3,7-diazaspiro[5.6]dodecane[24] and 3,8-diazaspiro[5.6]dodecane[24] ring systems. One synthesis of the 2,7-diazaspiro[4.4]nonane scaffold **D2** and an example of the 1,6-diazaspiro[3.4]octane **B2** skeleton have been described in which the second heterocyclic ring was constructed *via* dipolar cycloaddition.[10d,26]

Importantly, a major application of spirodiamines is as spacer units within, for example, medicinal chemistry. Carreira[27a-c] has recently provided elegant entries to 1,5-diazaspiro[3.3]heptanes **A1** and 1,6-diazaspiro[3.3]heptanes **A2** and exemplified how the spatial disposition of functionality based on these scaffolds is exploitable. Meyers et al. have made extensive use of spirocycles, including **A1**, **C3**, **D2**, **E5**, and **F5**, within candidates for inhibition of fatty acid amide hydrolase (FAAH), and Lachance,[10f] Tang[21e] and Meyers[27d] have reported the exploitation of mono-Boc variants of various spirodiamines, and this work is relevant to aspects of the studies reported here (see below).

Results and Discussion

Our objective was to define new entries or improve existing methods for the synthesis of a series of spirodiamines based on pyrrolidines and piperidines to provide access to a range of molecular scaffolds that were also amenable to further (and selective) manipulation/substitution. Our aim was to develop a synthetic platform to provide scaffolds/substitution variants that would present the pharmacophore associated nicotinic ligands (a basic amine and a pyridyl-based π-system) and this is discussed in more detail below. Our targets primarily encompassed scaffolds that incorporated a 1,3-diaminopropane relationship between the two amine moieties (e.g. **D2**, **E4**, and **F3**) with a key issue being an ability to differentiate between the two amine centres, in both symmetrical systems (i.e. where the two ring sizes are the same as in **D2** or **F3**) and in cases where the rings sizes are different (e.g. **E4**).

Specific targets showing target substitution patterns are shown in **Figure 2** with **1** and **2** corresponding to scaffold **D2**, **3** and **4** to the bispiperidine-based diazaspirocycle **F3**, and **5-7** to scaffold **E4**; in this latter case, the issue of differentiation (**5** vs. **6**) is more complex because of two differently sized rings are involved. Distinguishing between the two amine sites has been explored either during the construction of the spirocycle (as in **1** and **3** or as in **5** vs. **6**) or once the diazaspirocycle has been established via differential amine protection of e.g. diamines **2** and **4**, both of which were prepared (as racemates) as previously described.[1b]

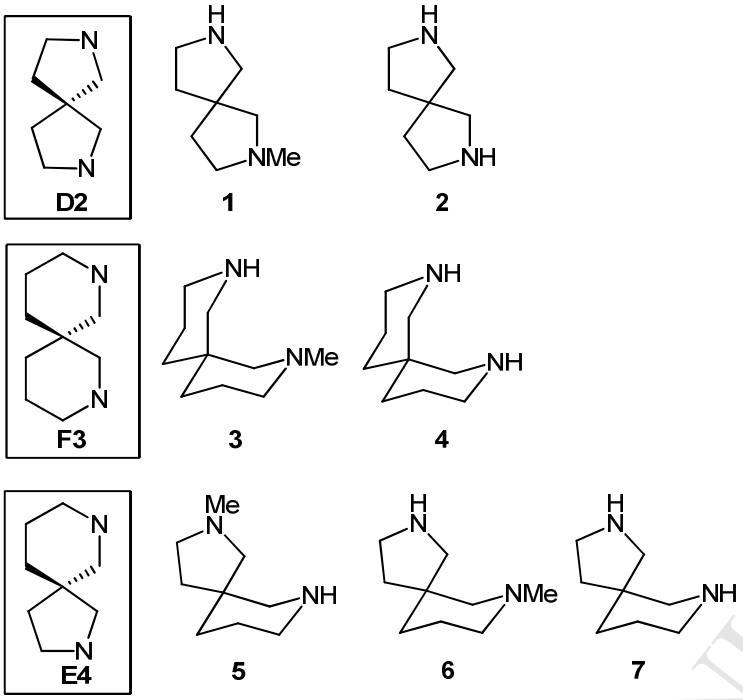
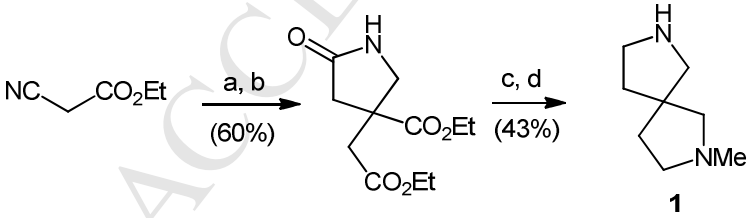


Figure 2. Target spirodiamines **1-7** based on scaffolds **D2**, **E4** and **F3**.

Mono N-methylspirodiamines.

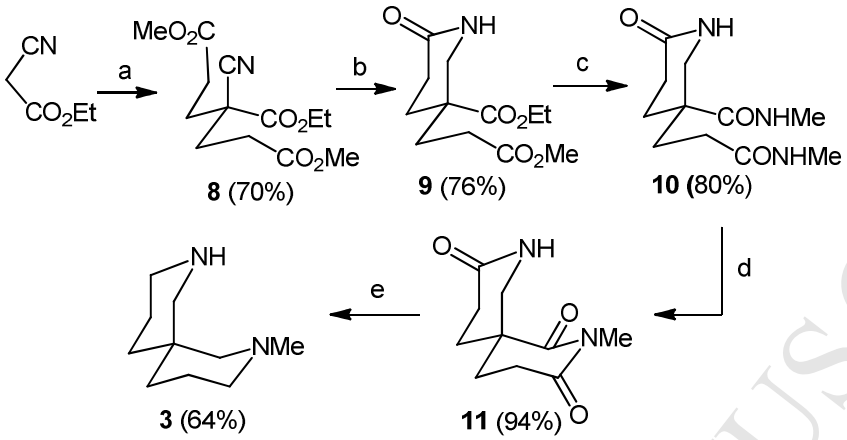
2-Methyl-2,7-diazaspiro[4.4]nonane **1**, in which the two pyrrolidine nitrogen centres are differentiated, was prepared as previously reported[1b] and the sequence used (as shown in **Scheme 1**) has broad applicability. The key steps involved a double alkylation of ethyl cyanoacetate, nitrile reduction and lactamization (to establish the first heterocyclic ring) followed by imide formation; $MeNH_2$ was used but this approach does offer an opportunity to incorporate a series of other N-substituents by judicious choice of the amine reagent. Global reduction then furnished the target mono N-methyl spirodiamine **1**.



Scheme 1.[1] Reagents and conditions: a) ethyl bromoacetate, Et_3N, $EtOH/H_2O$; b) H_2 (4 atm), PtO_2, EtOH/AcOH; c) $MeNH_2$, H_2O; d) $LiAlH_4$, THF.

An analogous approach provided access to 2-methyl-2,8-diazaspiro[5.5]undecane **3** (**Scheme 2**). A double Michael reaction involving ethyl cyanoacetate and methyl acrylate yielded cyanotriester **8**.[18] Catalytic hydrogenation and *in situ* cyclization of the intermediate

aminoester resulted in the formation of the six-membered lactam **9**.[28] Reaction of **9** with N-methylamine did not provide the target imide directly, rather diamide **10** which was cyclized under acidic conditions to give imide **11**.[29] Global reduction of **11** with $LiAlH_4$ led to the racemic monomethylated spirodiamine **3**.



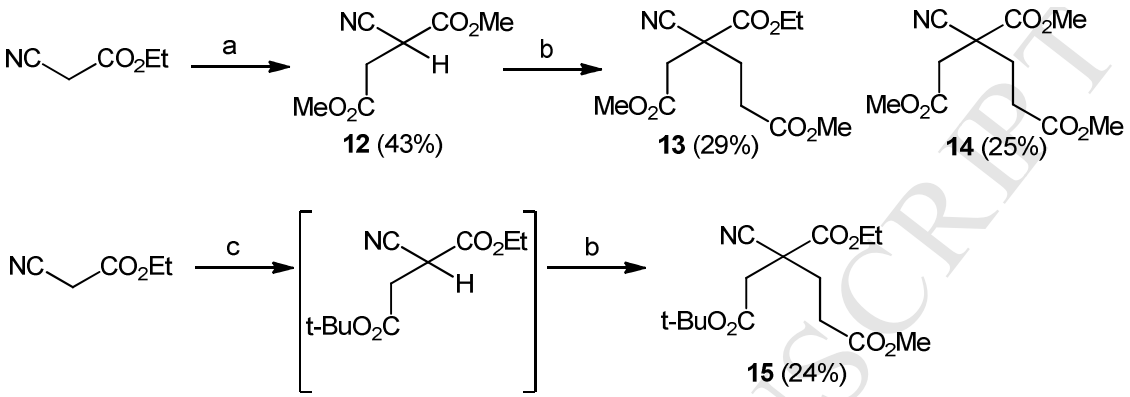
Scheme 2. Reagents and conditions: a) methyl acrylate, Et_3N, $EtOH/H_2O$; b) H_2 (4 atm), PtO_2, EtOH/AcOH; c) $MeNH_2$, H_2O; d) *p*-TsOH · H_2O, *p*-xylene; e) $LiAlH_4$, THF.

Both diamines **1** and **3** are symmetrical in the sense that both rings are the same (pyrrolidine and piperidine respectively) in each case. Targets **5** and **6** (2-methyl-2,7-diazaspiro[4.5]decane and 7-methyl-2,7-diazaspiro[4.5]decane respectively, Figure 2[30]) are not only differentiated in terms of secondary vs. tertiary amines (also the case for **1** and **3**) but here the two constituent rings are of a different size, which raises an important regiocontrol issue.

Our approach to **5** and **6** was based on modification and application of the chemistry outlined in **Schemes 1** and **2**. This involved reaction of ethyl cyanoacetate with two different alkylating agents to achieve the requisite rings sizes and the differential ester substitution/reactivity patterns necessary in order to provide each target selectively.

Cyanotriester **13** provided an entry to **5** and was prepared as shown in **Scheme 4**, together with a more highly differentiated variant **15** required for spirodiamine isomer **6**. Alkylation of ethyl cyanoacetate with ethyl chloroacetate provided, as the main product, the monosubstituted adduct **12**;[31] complete transesterfication was also observed under these conditions. Michael addition of **12** to methyl acrylate (in ethanol and water) gave triesters **13** and **14**, which were separated by flash chromatography. Partial transesterification also took place in this case (see below), but interestingly only at the most hindered ester residue. This outcome was determined by long range $^1H/^{13}C$ NMR correlations and is presumed to reflect

the higher electrophilicity associated with ester moiety adjacent to the cyano residue. Given the added complication associated with transesterification in going from **12** to **13**/**14**, it is pertinent to note that (and in our hands) the Michael addition reaction (**12** → **13**/**14**) was unsuccessful when methanol was used as solvent.[32]



Scheme 3. Reagents and conditions: a) ethyl chloroacetate, Na, MeOH; b) methyl acrylate, Et_3N, EtOH/H_2O; c) ethyl chloroacetate, *t*-BuOK, *t*-BuOH.

A similar, but more controlled sequence was carried out to provide the fully differentiated triester **15** required for the synthesis of **6**, also shown in **Scheme 3**. This involved monoalkyation of ethyl cyanoacetate with *tert*-butyl chloroacetate and use of potassium *tert*-butoxide and *tert*-butanol served to avoid transesterification. Subsequent Michael addition involving methyl acrylate then provided triester **15**.

Triesters **13**, **14** and **15** were individually subjected to nitrile hydrogenation and it was our expectation that five-membered lactams (in preference to six-membered ring isomers) would be favoured in the case of **13** and **14** (**Scheme 4**). However, in all three cases, six-membered lactams **16** (from **13**) and **17** (from **14**), and **18** (in this case the expected product from **15**) were observed exclusively. In the case of **16** and **17**, this outcome was deduced by IR spectroscopy: a carbonyl band below 1666 and 1663 cm^{-1} respectively indicating a six-membered lactam, but also see below. Further evidence came from transesterification of **18** (HCl/MeOH) which provided **16**, identical to the lactam obtained from **13**, as judged by IR, ^1H and ^{13}C NMR.

Both **16** and **17** were exposed individually (and also as a mixture) to aqueous methylamine and subsequent cyclization occurred to give imide **19** as the only product observed, the structure of which was unambiguously established by X-ray crystallography (Figure 3).[33]

Global hydride reduction of **19** then provided the monomethylated target 2-methyl-2,7-diazaspiro[4.5]decane **5**.

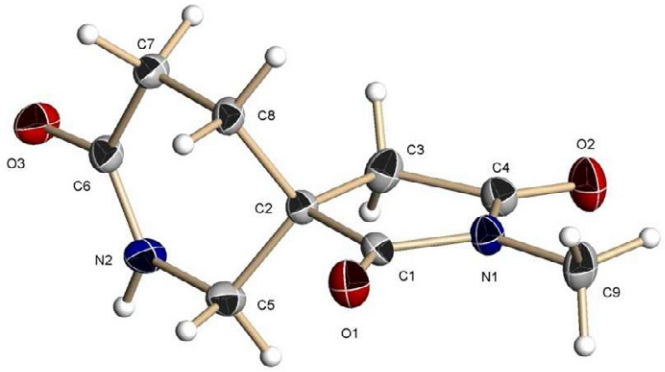
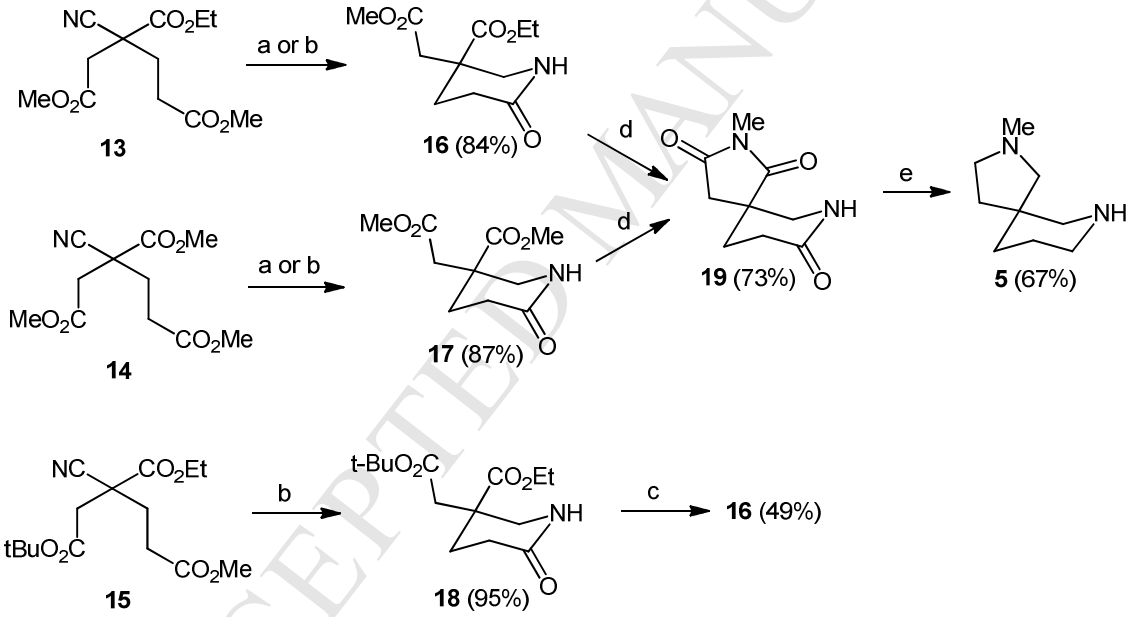
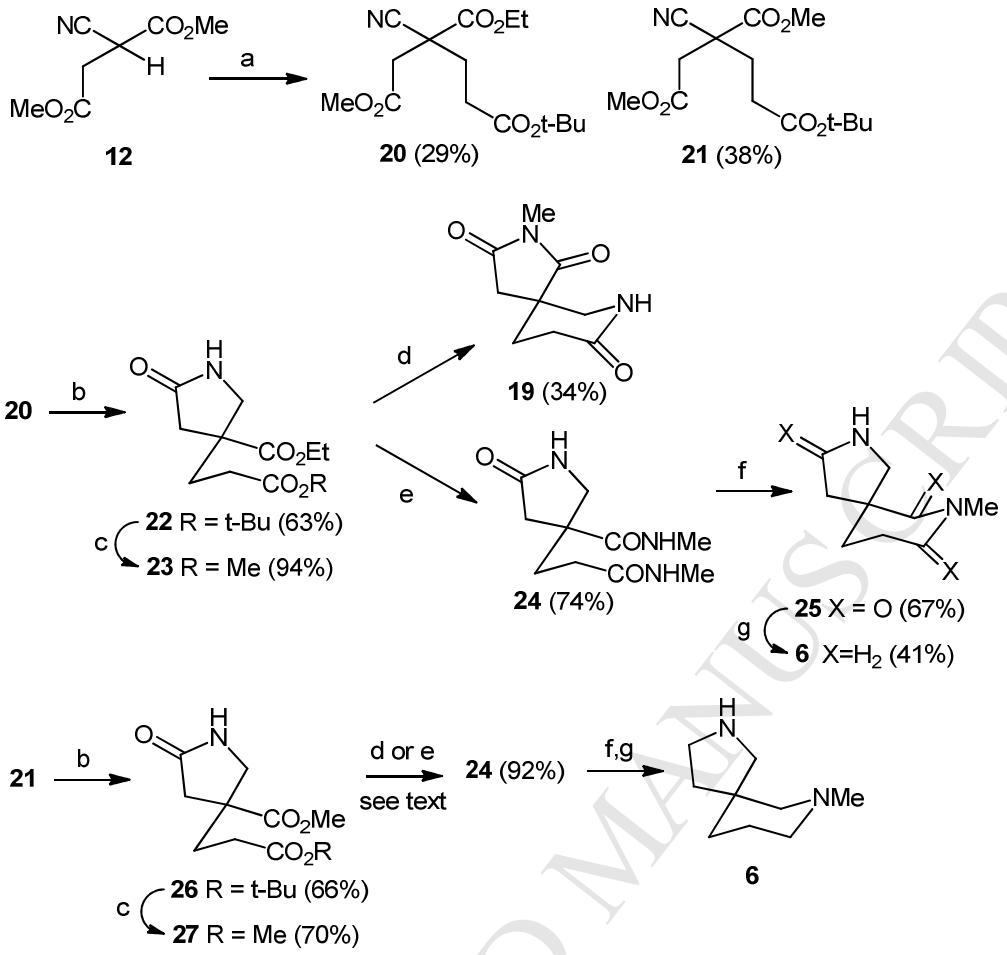


Figure 3. Crystal structure of imide **19**. Thermal ellipsoids are shown at the 50% probability level.



Scheme 4. Reagents and conditions: a) H_2 (4 atm), PtO_2, EtOH/AcOH; b) H_2 (7.5 atm), PtO_2, EtOH (yields shown relate to this procedure); c) HCl, MeOH; d) $MeNH_2$, H_2O; e) $LiAlH_4$, THF.

Based on these observations, in order to direct five rather than six-membered ring lactamization (as in **13** → **16**) to generate the isomeric mono N-methyl diazaspirodiamine **6** we required a cyanotriester variant with a blocking group on the longer alkyl chain (**Scheme 5**). Michael addition of diester **12** to *tert*-butyl acrylate gave triesters **20** and **21**. Again, ethanol was necessary here because the corresponding addition process in methanol failed and these ester products were separated by flash chromatography.



Scheme 5. Reagents and conditions: a) *tert*-butyl acrylate, Et_3N, EtOH/H_2O; b) H_2 (8 atm), PtO_2, EtOH; c) HCl, MeOH; d) $MeNH_2$, H_2O, r.t. to 180°C; e) $MeNH_2$, H_2O, r.t.; f) *p*-TsOH·H_2O, xylene; g) $LiAlH_4$, THF.

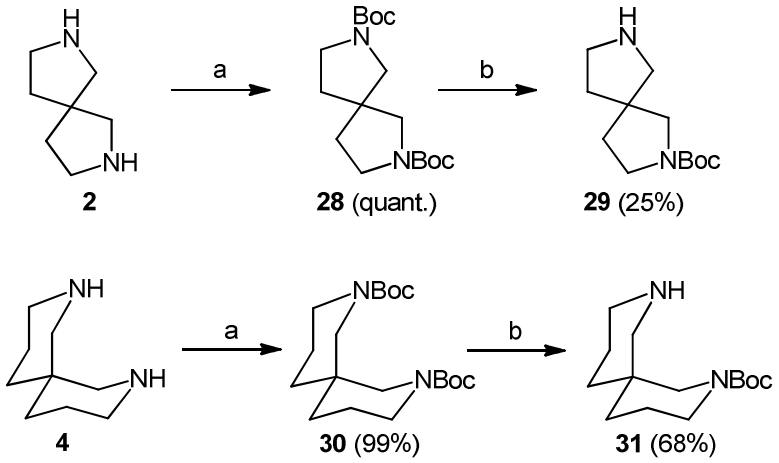
Hydrogenation of **20** and **21** did provide the desired five-membered lactams **22** and **26** respectively, which were transesterified with acidic methanol to give the methyl esters **23** and **27** needed to secure the second (six-membered) ring. The IR spectra of **22/23** and **26/27** showed a band at approx. 1727-1721 cm^{-1}, indicating the presence of a five-membered lactam. In the reactions of lactams **23** and **27** with methylamine, formation of diamide intermediate **24** was anticipated (cf Scheme 2). Surprisingly, while dimethyl ester **27** reacted at elevated temperature (step d; Scheme 5) with methylamine to give **24**, in the case of the mixed methyl/ethyl diester **23**, rearrangement was observed and the only product obtained was the five-membered ring imide **19**. This is the same product as that derived by amine condensation of **16** or **17** (Scheme 4) and this outcome was confirmed by direct and careful comparison of the product obtained by the earlier procedure. The rearrangement associated with **23** → **19** must involve lactam cleavage and subsequent reclosure with the hindered (quaternary centre) ethyl ester associated with **23** presumably more susceptible to

intramolecular rather than intermolecular nucleophilic displacement. This rearrangement was suppressed fully in the case of **23** by conducting the aminolysis step (step e; Scheme 5) at room temperature which cleanly then provided **24** from both **23** and **27**. Conversion of **24** to imide **25** occurred with acid catalysis, although small amounts of rearrangement (to give **19**, which was confirmed by careful comparison, and for which the crystallographic data are available, see Figure 3) were observed here; this reaction has been studied under a series of different conditions (solvents, temperatures and reaction times), and details of this are shown in **Table 2** (see Experimental Section). Hydride reduction of **25** then provided access to the N-methylated piperidine **6**, the regioisomer of the N-methyl pyrrolidine **5**.

It is appropriate to point out that care must be exercised in assigning product structures in this area. While reasonable assumptions regarding ester reactivity may hold generally, these are not universal and the lability and propensity of the heterocyclic ring systems described here to undergo ring opening and reclosure under transamidation conditions, for which a number of mechanistic variants may operate, must be borne in mind.

Mono N-Boc spirodiamines.

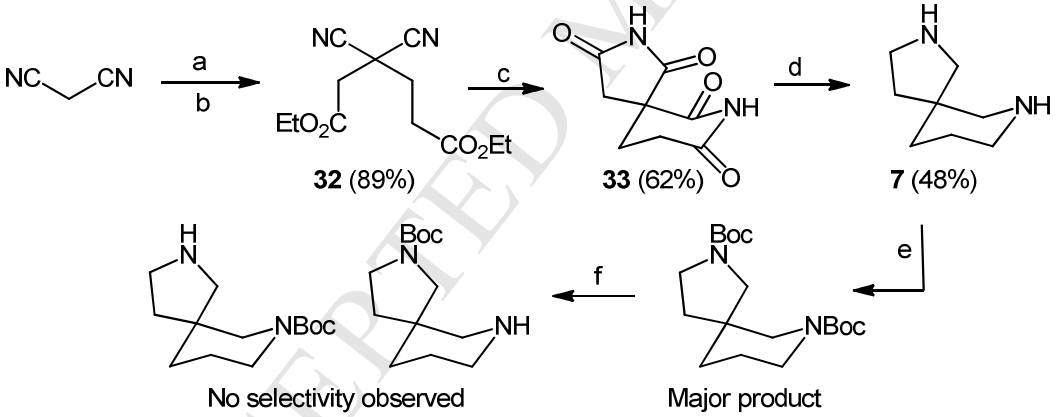
While mono N-methylated variants such as **1**, **3**, **5** and **6** do differentiate the two nitrogen centres as secondary vs. tertiary amines, the ability to release a secondary amine function from, for example, a mono-Boc protected spirodiamine represented an attractive option. Lachance,[10f] Meyers[27d] and Tang[21e] have all reported mono-Boc spirodiamines, and Meyers[27d] has described carbamate **29** (see below), although no experimental details are reported. 2,7-Diazaspiro[4.4]nonane **2** and 2,8-diazaspiro[5.5]undecane **4** were prepared and although methods have been reported to be effective in achieving monoacylation of diamines,[34] in our hands and despite extensive experimentation, bisacylation of these two substrates was always the major reaction pathway observed. The problem of accessing mono Boc-spirodiamines was best overcome by bisacylation (generating **28** and **30**) followed by careful treatment with trifluoroacetic acid which provided the desired mono-Boc protected derivatives **29** and **31** (**Scheme 6**). The yields of the deprotection procedures have not been optimised since a significant advantage here is the marked difference in polarity between e.g. **2**, **28** and **29** which facilitates isolation and purification of **29**.



Scheme 6. Reagents and conditions: a) Boc_2O, EtOH; b) TFA, DCM.

2,7-Diazaspiro[4.5]decanes

2,7-Diazaspiro[4.5]decane **7**, previously only reported in the patent literature, was prepared as shown in **Scheme 7**. Malononitrile was alkylated sequentially with ethyl bromoacetate and ethyl acrylate to give diester **32**, hydrolysed under acidic conditions to provide bisimide **33** which was reduced with $LiAlH_4$ to give spirodiamine **7**.[35]



Scheme 7. Reagents and conditions: a) ethyl bromoacetate, Triton B, THF; b) ethyl acrylate, Triton B, dioxan c) H_2SO_4, AcOH; d) $LiAlH_4$, THF; e) Boc_2O, EtOH; f) TFA, DCM.

As anticipated in this case, monoprotection of **7** gave the bisBoc adduct as the major product. However, there was no obvious selectivity for one mono-Boc isomer over the other and although subsequent cleavage of one Boc residue (cf Scheme 6) was achieved, again no selectivity was observed (**Scheme 7**)[36] This lack of selectivity combined with the issue of separating the isomeric mono-Boc adducts derived from **7** effectively marks a limit to the usefulness of this methodology and further reactions of **7** were not pursued.

Mono N-Arylation of Spirodiamine Scaffolds

Our interest in spirodiamines as scaffolds for medicinal chemistry was prompted in part by the opportunity afforded by the diamine moiety to provide both a secondary amine (anticipated to be protonated at physiological pH) and a means for the ready (and flexible) attachment of a second potential binding moiety, such as a heteroaryl unit. Such a system would provide a means of rapidly exploring ligand space associated with, for example, the binding mode of neuronal nicotinic ligands, such as epibatidine **34**[37] and the anatoxin-a/epibatidine hybrid UB165 **35**,[38] where both an ammonium (via a π-cation interaction) and H-bond accepting π-system (here the 2-chloro-5-pyridyl unit is common) are prerequisites for nicotinic recognition.[39] Using an array of spirodiamines, N-arylation of one amine site would allow ready synthesis of a library of spatially diverse ligands (**Figure 4**).

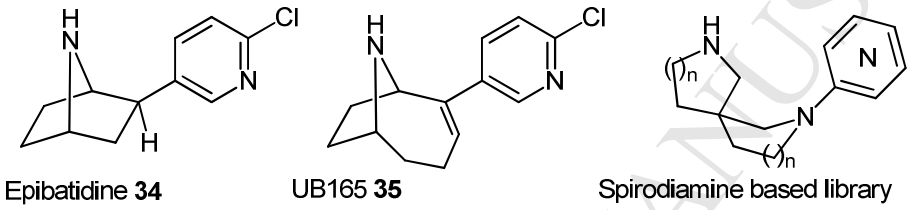


Figure 4. Nicotinic ligands epibatidine **34** and UB165 **35** and variants based on arylation of spirodiamine scaffolds.

With this in mind we have explored the feasibility of N-arylation of N-methyl and N-Boc spirodiamine variants using Pd-catalysed Buchwald-Hartwig arylation of pyridyl halides. A variety of reagents/ligands were examined and either Xantphos or $P(i\text{-}BuNCH_2CH_2)_3N$ (as described for this purpose by Verkade[40]) in the presence of $Pd_2(dba)_3$ proved reliable and efficient combinations to prepare a variety of 2-, 3- and 4-substituted pyridines.[41] These reactions were carried out in the N-methyl and N-Boc series and representative examples were based on use of 2-chloro-5-iodopyridine as the arylating agent (cf Figure 4) are illustrated in **Table 1**. In the case of the N-Boc variants, cleavage of the N-Boc residue following N-arylation was carried out using trifluoroacetic acid to provide the corresponding secondary amine. It should be also noted that we were unsuccessful in achieving a selective monoarylation of either diamine **2** or **4**, and given the lack of regioselectivity seen in Scheme 7, we did not apply this chemistry to diamine **7**.

Spirodiamine	N-Arylated Product (%)	[d]Boc cleavage

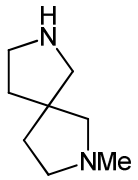
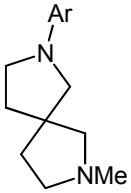
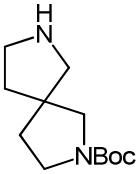
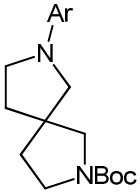
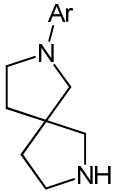
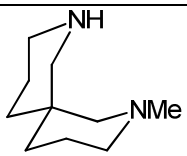
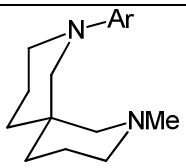
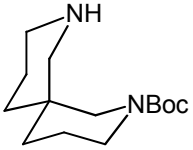
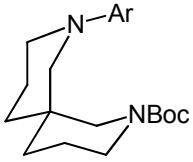
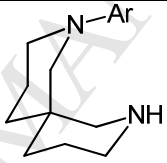
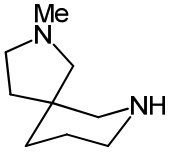
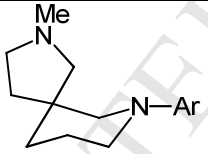
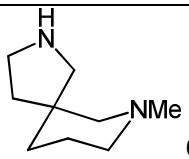
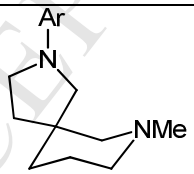
 **1**	 **36** ([a]31%)	N/A
 **29**	 **37** ([b]61%);	 **38** (100%)
 **3**	 **39** ([b]78%; [c]76%)	N/A
 **31**	 **40** ([b]80%)	 **41** (100%)
 **5**	 **42** ([b]84%)	N/A
 **6**	 **43** ([b]34%)	N/A

Table 1. In all cases shown, 2-chloro-5-iodopyridine was used and Ar= 5-(2-chloropyridyl); [a]In this case the result using *rac*-BINAP is shown, which is typical of the lower yields observed with this ligand; [b]Yield using Xantphos; [c]Yield using P(*i*-Bu$NCH_2CH_2)_3N$; [d]Boc cleavage was carried out using CF_3CO_2H in CH_2Cl_2 and in the cases shown was essentially quantitative.

Clearly, the ready accessibility of a secondary amine site allows a range of other, well-established methodologies of library synthesis to be exploited and once again, access to the N-

Boc derivatives allows for efficient “mono” functionalization of the scaffold core and subsequent liberation of a second potential site for further substitution.

Conclusions

In summary, we described the synthesis (and in some cases an alternative synthesis) of a series of spirodiamine scaffolds containing 5- and 6-membered rings, where differentiation of the amine sites can be achieved via either N-methylation or N-Boc protection. In terms of the construction of the diamine scaffold, the care must be taken in terms of predicting/assuming the stereo/regiochemical outcome of cyclization reactions that are inevitably done under equilibrating conditions. This is because rearrangement is not only possible but the feasibility of an alternative pathway has been demonstrated. Accordingly, control of reaction conditions in certain cases is essential, as is careful analysis of product structure. The product diamines are readily amenable to both protection (which allows for differentiation) and N-arylation, and further details of other aspects of this chemistry, in terms of the use of these scaffolds in library generation, will be reported in due course.

Experimental

General

All reactions that involved air/moisture sensitive compounds were performed under an atmosphere of dry nitrogen with either flame dried or oven dried glassware. ^{1}H and ^{13}C NMR spectra were recorded at the specified field strength and in the solvent indicated using standard pulse techniques on Jeol Lambda 300 (300 MHz), Jeol JNM-GX270 (270 MHz), and Jeol JNM-ECP400 (400 MHz) spectrometers at ambient temperatures. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to TMS or the residual solvent peak. Coupling constants (J) are quoted to the nearest 0.1 Hz. Assignments of signals were made where possible, using COSY, DEPT, HMQC and HMBC experiments as necessary. Mass spectra were recorded using a VG Autospec (EI/CI mode) and a VG Quattro (ESI mode) and infrared spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer as a thin film between NaCl plates. Absorptions maxima (υ_{max}) are reported in wavenumbers (cm^{-1}).

2-Methyl-2,7-diazaspiro[4.4]nonane (1)

$LiAlH_4$ in pellets (2.07 g; 54.5 mmol) was stirred vigorously in dry THF (40 mL) under N_2 atmosphere until a suspension of powder was formed (4 h). This suspension was transferred dropwise via a cannula to the stirred suspension of 2-methyl-2,7-diazaspiro[4.4]nonane-1,3,8-trione[1b] (2.27 g; 12.5 mmol) in dry THF (40 mL) under N_2 atmosphere (both suspensions were cooled to 0-5^{o}C during transfer). The mixture was then heated in reflux overnight under N_2 atmosphere, cooled to 0-5^{o}C, diluted with THF (50 mL) and the following were slowly added dropwise in 0-5^{o}C: water (2.5 mL), 15% aq. NaOH (2.5 mL) and water (7.5 mL). The resulting slurry was filtered through Celite, the solids were washed with THF (500 mL) and the combined filtrates were concentrated in vacuo to give a yellow oil which was distilled under vacuum (bp 32-36^{o}C at 1.5 mmHg) to give diamine **1** (0.90 g; 52%) as a colourless oil. δ_H (270 MHz, CD_3OD) 2.94-2.85 (2H, m, $CH_2C\underline{H}_2NMe$), 2.80, 2.71 (2H, 2d, *J* 10.9, $C\underline{H}_2NMe$), 2.68-2.57 (2H, m, $CH_2C\underline{H}_2NH$), 2.57, 2.48 (2H, 2d, *J* 9.6, $C\underline{H}_2NH$), 2.34 (3H, s, CH_3), 1.93-1.70 (4H, m, $C\underline{H}_2CH_2NH$, $C\underline{H}_2CH_2NMe$); δ_C (75.5 MHz, CD_3OD) 68.1 ($\underline{C}H_2NMe$), 59.8 ($\underline{C}H_2NH$), 57.1 ($CH_2\underline{C}H_2NMe$), 50.8 (C4^o), 46.4 ($CH_2\underline{C}H_2NH$), 42.7 (CH_3), 40.9 ($\underline{C}H_2CH_2NH$), 38.4 ($\underline{C}H_2CH_2NMe$); *m/z* (CI) 141 ($M+H^+$); HRMS: Found: $M+H^+$, 141.1384. $C_8H_{17}N_2$ requires 141.1386. The characterisation of **1** as its HCl salt is given elsewhere.[1b]

Methyl 4-(ethoxycarbonyl)-7-oxo-4-piperidinepropionate (9)

3-Ethyl-1,5-dimethyl 3-cyano-1,3,5-pentanetricarboxylate (15.3 g; 53.0 mmol) was dissolved in ethanol (50 mL) and glacial acetic acid (100 mL) and platinum oxide (1.0 g) was added. The mixture was hydrogenated in a Parr-shaker flask (4 atm, room temp.) for 2.5 days. TLC showed a mixture of product and starting material. More PtO_2 (0.5 g) was added and the mixture was further hydrogenated overnight in the same conditions. The mixture was filtered through Celite and the solids were washed with methanol. The combined filtrates were concentrated in vacuo and worked up using AcOEt/sat. $NaHCO_3$. The organic layer was dried with $MgSO_4$ and concentrated to give lactam **9** (10.54 g; 76%) as a pale yellow oil, which solidified when cooled, but was used in the next step without further purification. IR (neat): ν 3242, 2955, 1725, 1663; δ_H (400 MHz, $CDCl_3$) 6.03 (1H, br s, NH), 4.21, 4.20 (2H, 2q, *J* 7.1, $OC\underline{H}_2CH_3$), 3.73 (1H, ddd, *J* 12.2, 3.8, 2.7, $C\underline{H}_2NH$), 3.68 (3H, s, OCH_3), 3.17 (1H, d, *J* 12.2, $C\underline{H}_2NH$), 2.46-2.38 (2H, m, $CH_2C\underline{H}_2CONH$), 2.34-2.22 (3H, m, $CH_2C\underline{H}_2COOMe$ (2H), $C\underline{H}_2CH_2CONH$ (1H)), 2.06-1.92 (2H, m, $C\underline{H}_2CH_2COOMe$), 1.82-1.68 (1H, ddd, *J* 13.7, 9.3, 7.3, $C\underline{H}_2CH_2CONH$), 1.28 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$); δ_C (100.5 MHz, $CDCl_3$) 173.3, 173.2 (COOR), 170.7 (CONH), 61.5 ($O\underline{C}H_2CH_3$), 51.9 ($O\underline{C}H_3$), 48.4 (CH_2NH), 44.4 (C 4^o), 31.5

($\underline{C}H_2CH_2COOMe$), 29.1 ($\underline{C}H_2CH_2CONH$), 28.5 ($CH_2\underline{C}H_2COOMe$), 28.3 ($CH_2\underline{C}H_2CONH$), 14.2 ($OCH_2\underline{C}H_3$); *m/z* (EI+) 257 ($M^+$); HRMS: Found: M^+, 257.1257. $C_{12}H_{19}NO_5$ requires 257.1258.

***N*-Methyl 4-(methylaminocarbonyl)-7-oxo-4-piperidinepropionamide (10)**

A solution of **9** (4.08 g; 15.9 mmol) in 40% aqueous methylamine (8 mL) was stirred overnight at room temp. The mixture was gradually heated in oil bath to 180°C over 1.5 h while the volatiles were distilled off. The yellow solid residue obtained was recrystallised from ethanol to give the bisamide **10** (3.05 g; 80%) as colourless crystals mp 255-256°C (EtOH). IR (neat): ν 3333, 3284, 3095, 1676, 1651, 1634, 1558; δ_H (400 MHz, D_2O) 3.62, 3.19 (2H, 2d, *J* 13.0, $C\underline{H}_2NH$), 2.74 (3H, s, CH_3), 2.67 (3H, s, CH_3), 2.45-2.22 (2H, m, $CH_2C\underline{H}_2CONH$), 2.20-2.06 (3H, m, $CH_2C\underline{H}_2COOMe$ (2H), $C\underline{H}_2CH_2CONH$ (1H)), 1.98-1.77 (3H, m, $C\underline{H}_2CH_2CONHMe$ (2H), $C\underline{H}_2CH_2CONH$ (1H)); δ_C (100.5 MHz, D_2O) 176.9, 175.8, 174.8 (CONH), 47.2 (CH_3), 44.0 (CH_3), 32.6 (C 4°), 30.8 (CH_2NH), 28.0 ($\underline{C}H_2CH_2CONH$), 27.4 ($CH_2\underline{C}H_2CONH$), 26.3 ($\underline{C}H_2CH_2CONHMe$), 26.0 ($CH_2\underline{C}H_2CONHMe$); *m/z* (electrospray, positive) 242 ($M+H^+$); HRMS: Found: $M+H^+$, 242.1497. $C_{11}H_{20}N_3O_3$ requires 242.1499. Anal. calcd. for $C_{11}H_{19}N_2O_3$: C, 54.74; H, 7.94; N, 17.42. Found: C, 54.54; H, 7.94; N, 17.67.

2-Methyl-2,8-diazaspiro[5.5]undecane-1,3,9-trione (11)

A suspension of **10** (9.78 g; 40.6 mmol) and p-TsOH.H_2O (8.53 g; 44.6 mmol) in p-xylene (80 mL) was heated in reflux overnight. The mixture was evaporated to dryness and worked up using water/AcOEt. The aqueous layer was evaporated to dryness and the residue was purified by chromatography (silica gel; DCM:MeOH 9:1) to give spirocycle **11** (7.97 g; 94%) as a colourless solid. mp 169°C (EtOH). IR (neat): ν 3187, 1716, 1671, 1652; δ_H (400 MHz, D_2O) 3.65, 3.27 (2H, 2d, *J* 13.0, $C\underline{H}_2NH$), 3.06 (3H, s, CH_3), 2.91-2.71 (2H, m, $CH_2C\underline{H}_2CONH$), 2.50-2.34 (2H, m, $CH_2C\underline{H}_2CONMe$), 2.26 (1H, ddd, *J* 13.0, 7.0, 5.5 $\underline{C}H_2CH_2CONH$), 2.18-1.87 (3H, m, $C\underline{H}_2CH_2CONH$ (1H), $C\underline{H}_2CH_2CONMe$ (2H)); δ_C (100.5 MHz, D_2O) 177.6 (CONH), 175.4, 174.7 (CONMe), 47.7 (CH_2NH), 39.9 (C 4°), 28.3 ($\underline{C}H_2CH_2CONMe$), 27.0 ($\underline{C}H_2CH_2CONH$), 27.0 ($CH_2\underline{C}H_2CONMe$), 27.0 ($CH_3$), 24.7 ($CH_2\underline{C}H_2CONH$); *m/z* (EI+) 210 ($M^+$); HRMS: Found: M^+, 210.0996. $C_{10}H_{14}N_2O_3$ requires 210.0999. Anal. calcd. for $C_{10}H_{14}N_2O_3$: C, 57.12; H, 6.72; N, 13.33. Found: C, 56.98; H, 6.61; N, 13.46.

2-Methyl-2,8-diazaspiro[5.5]undecane (3)

$LiAlH_4$ in pellets (4.6 g; 121.5 mmol) was stirred vigorously in dry THF (100 mL) under N_2 atmosphere until a suspension of powder was formed (4 h). This suspension was transferred dropwise via a cannula to the stirred suspension of **11** (5.68 g; 27 mmol) in dry THF (110 mL) under N_2 atmosphere (both suspensions were cooled to 0-5^{o}C during transfer). The mixture was then heated in reflux overnight under a N_2 atmosphere, then cooled to 0-5^{o}C, diluted with THF (50 mL) and the following were slowly added dropwise in 0-5^{o}C: water (5 mL), 15% aq. NaOH (5 mL) and water (15 mL). The resulting slurry was filtered through Celite, the solids were washed with thoroughly with THF (500 mL) and the combined filtrates were concentrated in vacuo to give a brown oil which was distilled under vacuum (bp 55-60^{o}C/1.5 mmHg) to give spirodiamine **3** (2.92 g; 64%) as a colourless oil. δ_H (300 MHz, CD_3OD) 2.70-2.40 (4H, m, C$\underline{H}_2$NMe, $CH_2CH_2C\underline{H}_2$NMe), 2.35-1.85 (4H, m, C$\underline{H}_2$NH, $CH_2CH_2C\underline{H}_2$NH), 2.10 (3H, s, CH_3), 1.60-1.10 (8H, m, $CH_2C\underline{H}_2CH_2$NMe, C$\underline{H}_2CH_2CH_2$NMe, $CH_2C\underline{H}_2CH_2$NH, C$\underline{H}_2CH_2CH_2$NH); δ_C (75.5 MHz, CD_3OD) 65.2 ($\underline{C}H_2$NMe), 57.9 ($CH_2CH_2\underline{C}H_2$NMe), 55.2 ($\underline{C}H_2$NH), 47.6 ($CH_2CH_2\underline{C}H_2$NH), 47.2 (CH_3), 35.5 (C 4^o), 33.7 ($\underline{C}H_2CH_2CH_2$NMe), 30.9 ($\underline{C}H_2CH_2CH_2$NH), 22.8 ($CH_2\underline{C}H_2CH_2$NH), 22.3 ($CH_2\underline{C}H_2CH_2$NMe); *m/z* (CI) 169 ($M+H^+$); HRMS: Found: $M+H^+$, 169.1697. $C_{10}H_{21}N_2$ requires 169.1699.

2-Ethyl-1,4-dimethyl 2-cyano-1,2,4-butanetricarboxylate (13) and trimethyl 2-cyano-1,2,4-butanetricarboxylate (14)

Cyanodiester **12**[31] (1.63 g; 9.53 mmol) was dissolved in ethanol-water 1:1 (10 mL) and Et_3N (1.65 mL) was added. The mixture was cooled to 0-5^{o}C and methyl acrylate (0.9 mL; 9.6 mmol) was added dropwise. The mixture was warmed to room temp. and stirred for 3 h. It was then concentrated, acidified with 2M HCl to pH 4 and extracted (3xAcOEt). The combined organic extracts were dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel in hexane:AcOEt 7:3 **13** (742 mg; 29%; R_f 0.24) and **14** (616 mg; 25%; R_f 0.2) as colourless oils. Note that mixed fractions were also obtained which were processed successfully in the following stages. Data for **13**: δ_H (270 MHz, $CDCl_3$) 4.21, 4.20 (2H, 2q, *J* 7.2, $OC\underline{H}_2CH_3$), 3.72 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.07, 2.81 (2H, 2d, *J* 17.0, C$\underline{H}_2$COOMe), 2.62 (1H, ddd, *J* 16.5, 9.2, 6.6, $CH_2C\underline{H}_2$COOMe), 2.46 (1H, ddd, *J* 16.5, 9.8, 6.3, $CH_2C\underline{H}_2$COOMe), 2.35-2.08 (2H, m, C$\underline{H}_2CH_2$COOMe), 1.35 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$); δ_C (100.5 MHz, $CDCl_3$) 171.7, 169.0, 167.4 (COOR), 117.9 (CN), 63.4 ($O\underline{C}H_2CH_3$), 52.4 ($O\underline{C}H_3$), 52.1 ($O\underline{C}H_3$), 45.1 (C 4^o), 40.7 ($\underline{C}H_2$COOMe), 32.0 ($CH_2\underline{C}H_2$COOMe), 29.7 ($\underline{C}H_2CH_2$COOMe), 14.0 ($OCH_2\underline{C}H_3$); *m/z* (electrospray, positive)

289 ($M+NH_4^+$); HRMS: Found: $M+NH_4^+$, 289.1396. $C_{12}H_{21}N_2O_6$ requires 289.1394. Data for **14**: δ_H (270 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.08, 2.83 (2H, 2d, *J* 17.1, C$\underline{H}_2$COOMe), 2.61 (1H, ddd, *J* 16.3, 9.2, 6.7, $CH_2C\underline{H}_2$COOMe), 2.46 (1H, ddd, *J* 16.3 9.7 6.3, $CH_2C\underline{H}_2$COOMe), 2.32-2.10 (2H, m, C$\underline{H}_2CH_2$COOMe); δ_C (100.5 MHz, $CDCl_3$) 171.6, 168.9, 168.3 (C$\underline{O}$OMe), 117.8 (CN), 53.9 (O$\underline{C}H_3$), 52.5 (O$\underline{C}H_3$), 52.1 (O$\underline{C}H_3$), 45.1 (C 4^o), 40.7 ($\underline{C}H_2$COOMe), 32.0 ($CH_2\underline{C}H_2$COOMe), 29.7 ($\underline{C}H_2CH_2$COOMe); *m/z* (electrospray, positive) 275 ($M+NH_4^+$); HRMS: Found: $M+NH_4^+$, 275.1238. $C_{11}H_{19}N_2O_6$ requires 275.1238.

1-*t*-Butyl-2-ethyl-4-methyl 2-cyano-1,2,4-butanetricarboxylate (15)

(i) 1-*t*-Butyl-2-ethyl 2-cyano-1,2-ethanedicarboxylate

Ethyl cyanoacetate (2.4 mL; 22.5 mmol) was dissolved in dry t-butanol (20 mL) at room temp. and Bu^{t}OK (2.52 g; 22.5 mmol) was added. The resulting suspension was stirred for 15 min. and a solution of t-butyl chloroacetate (1.1 mL, 7.5 mmol) in dry t-butanol (4 mL) was added. The mixture was stirred at room temperature overnight, then poured into ice (50 g) with concentrated HCl (2 mL), and water (20 mL) was added. The resulting mixture was extracted (3x DCM), the combined extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was distilled under vacuum (bp 118-125^{o}C at 1.0 mmHg) to give the monoalkylated title compound (0.65 g; 37%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 4.28 (2H, q, *J* 7.0, OC$\underline{H}_2CH_3$), 3.84 (1H, t, *J* 6.5, CH), 2.92 (1H, dd, *J* 16.0, 6.5 C$\underline{H}_2$COOBu^t), 2.84 (1H, dd, *J* 16.0, 6.5, C$\underline{H}_2$COOBu^t), 1.46 (9H, s, $C(CH)_3)_3$), 1.32 (3H, t, *J* 7.0, $OCH_2C\underline{H}_3$); δ_C (100.5 MHz, $CDCl_3$) 168.0, 165.2 (COOR), 116.0 (CN), 82.8 ($\underline{C}(CH_3)_3$), 63.3 (O$\underline{C}H_2CH_3$), 34.8 ($\underline{C}H_2$COOBu^t), 33.2 (CH), 28.0 (C($\underline{C}H_3)_3$), 14.0 ($OCH_2\underline{C}H_3$); *m/z* (CI) 228 ($M+H^+$); HRMS: Found: $M+H^+$, 228.1232. $C_{11}H_{18}NO_4$ requires 228.1236.

(ii) **1-*t*-Butyl-2-ethyl-4-methyl 2-cyano-1,2,4-butanetricarboxylate (15)**

The cyanodiester (from part (i)) (0.30 g; 1.32 mmol) was dissolved in ethanol-water 1:1 (2 mL), cooled to 0-5^{o}C and Et_3N (0.23 mL) was added. After 15 min. of stirring, methyl acrylate (0.13 mL; 1.39 mmol) was added dropwise. The mixture was stirred at 0-5^{o}C for 2 h, allowed to warm to room temperature and stirred for further 4 h. The mixture was then concentrated, diluted with water, acidified with 2M HCl to pH 4 and extracted (3x AcOEt). The combined extracts were dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel in hexane:AcOEt 4:1 to give the bisalkylated ester **15** (242 mg; 64%) as a colourless oil. δ_H (300 MHz, $CDCl_3$) 4.37-4.21 (2H, m, OC$\underline{H}_2CH_3$), 3.70 (3H, s, OCH_3), 3.00,

2.74 (2H, 2d, *J* 16.9, C<u>H</u>$_2$COOBu^t), 2.64 (1H, ddd, *J* 16.4, 9.6, 6.5, CH$_2$C<u>H</u>$_2$COOMe), 2.48 (1H, ddd, *J* 16.4, 10.0, 6.2, CH$_2$C<u>H</u>$_2$COOMe), 2.30-2.10 (2H, m, C<u>H</u>$_2$CH$_2$COOMe), 1.46 (9H, s, C(CH$_3$)$_3$), 1.35 (3H, t, *J* 7.0, OCH$_2$C<u>H</u>$_3$); δ_C (75.5 MHz, CDCl$_3$) 171.8, 171.8, 167.4 (COOR), 118.1 (CN), 82.8 (<u>C</u>(CH$_3$)$_3$), 63.2 (O<u>C</u>H$_2$CH$_3$), 52.0 (O<u>C</u>H$_3$), 45.4 (C 4^o), 42.0 (<u>C</u>H$_2$COOBu^t), 32.0 (CH$_2$<u>C</u>H$_2$COOMe), 29.6 (<u>C</u>H$_2$CH$_2$COOMe), 27.9 (C(<u>C</u>H$_3$)$_3$), 14.0 (OCH$_2$<u>C</u>H$_3$); *m/z* (electrospray, positive) 331 (M+NH$_4^+$); HRMS: Found: M+NH$_4^+$, 331.1865. $C_{15}H_{27}N_2O_6$ requires 331.1865.

Methyl 3-(ethoxycarbonyl)-6-oxo-3-piperidineacetate (16) from triester 13

Cyanotriester **13** (742 mg; 2.74 mmol) was dissolved in ethanol (7 mL) and glacial acetic acid (7 mL), PtO_2 (80 mg) was added and the mixture was hydrogenated in a Parr-shaker flask (4 atm, room temp.) for 4 days. TLC showed the disappearance of starting material. The solution was decanted with a pipette and the catalyst was washed twice with methanol. The combined supernatants were concentrated in vacuo and worked up in AcOEt/sat. $NaHCO_3$aq. The organic layer was dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 19:1) to give lactam **16** (556 mg; 84%) as a pale yellow oil. IR (neat): ν 3231, 2956, 1727, 1666, 1197; δ_H (270 MHz, CDCl$_3$) 6.31 (1H, s, NH), 4.20 (2H, q, *J* 6.9, O<u>C</u>H$_2$CH$_3$) 3.77 (1H, d, *J* 12.9, C<u>H</u>$_2$NH), 3.65 (3H, s, OCH$_3$), 3.31 (1H, d, *J* 12.9, C<u>H</u>$_2$NH), 2.75, 2.65 (2H, 2d, *J* 15.8, C<u>H</u>$_2$COOMe), 2.50-2.30 (2H, m, C<u>H</u>$_2$CONH), 2.30-2.14 (1H, m, <u>C</u>H$_2$CH$_2$CONH), 1.95-1.80 (1H, m, C<u>H</u>$_2$CH$_2$CNH), 1.24 (3H, t, *J* 6.9, OCH$_2$C<u>H</u>$_3$); δ_C (100.5 MHz, CDCl$_3$) 173.2 (CONH), 171.0, 170.6 (COOR), 61.6 (O<u>C</u>H$_2$CH$_3$), 51.8 (O<u>C</u>H$_3$), 47.8 (CH$_2$NH), 43.0 (C 4^o), 39.8 (<u>C</u>H$_2$COOMe), 29.1 (<u>C</u>H$_2$CH$_2$CONH), 28.1 (CH$_2$<u>C</u>H$_2$CONH), 14.1 (OCH$_2$<u>C</u>H$_3$); *m/z* (CI) 244 (M+H$^+$); HRMS: Found: M+H$^+$, 244.1182. $C_{11}H_{18}NO_5$ requires 244.1185.

Cyanotriester **13** (0.92 g; 3.39 mmol) was dissolved in ethanol (20 mL), PtO_2 (0.1 g) was added and the mixture was hydrogenated in an autoclave (7.5 atm) for 2 days. TLC still showed the presence of starting material. PtO_2 (0.05 g) was added and hydrogenation was continued overnight. The solution was decanted with a pipette and the catalyst was washed twice with methanol. The combined supernatants were concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 19:1) to give lactam **16** (0.69 g; 84%) as a colourless oil, identical with that obtained above.

Methyl 3-(methoxycarbonyl)-6-oxo-3-piperidineacetate (17)

Cyanotriester **14** (616 mg; 2.4 mmol) was dissolved in ethanol (6 mL) and glacial acetic acid (6 mL), PtO_2 (70 mg) was added and the mixture was hydrogenated in a Parr-shaker flask (4 atm, room temp.) for 4 days. TLC showed the consumption of starting material. The solution was decanted with a pipette and the catalyst was washed twice with methanol. The combined supernatants were concentrated in vacuo and worked up in AcOEt/sat. $NaHCO_3$aq. The organic layer was dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 19:1) to give lactam **17** (190 mg; 35%) as a low melting solid which proved difficult to recrystallise. IR (neat): ν 3217, 2954, 1728, 1663; δ_H (400 MHz, $CDCl_3$) 5.82 (1H, s, NH), 3.80 (1H, dd, *J* 12.7, 1.8, C$\underline{H}_2$NH), 3.75 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.33 (1H, dd, *J* 12.7, 1.8, C$\underline{H}_2$NH), 2.77, 2.67 (2H, 2d, *J* 15.6, C$\underline{H}_2$COOMe), 2.50-2.34 (2H, m, C$\underline{H}_2$CONH), 2.29-2.18 (1H, m, C$\underline{H}_2$CH$_2$CONH), 1.95-1.85 (1H, m, C$\underline{H}_2$CH$_2$CNH); δ_C (100.5 MHz, $CDCl_3$) 173.7 (CONH), 171.2, 170.6 (COOMe), 52.6 (O$\underline{C}H_3$), 51.9 (O$\underline{C}H_3$), 47.7 (CH_2NH), 43.0 (C 4^o), 39.9 ($\underline{C}H_2$COOMe), 29.1 ($\underline{C}H_2CH_2$CONH), 28.1 ($CH_2\underline{C}H_2$CONH); *m/z* (EI+) 229 (M^+); HRMS: Found: M^+, 229.0941. $C_{10}H_{15}NO_5$ requires 229.0945.

Cyanotriester **14** (1.76 g; 6.85 mmol) was dissolved in ethanol (80 mL), PtO_2 (0.2 g) was added and the mixture was hydrogenated in an autoclave (7.5 atm) for 3 days. TLC still showed the presence of starting material. PtO_2 (0.1 g) was added and hydrogenation was continued overnight. The solution was decanted with a pipette and the catalyst was washed twice with methanol. The combined supernatants were concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 19:1) to give lactam **17** (1.36 g; 87%) as a colourless oil, which was identical to that obtained above.

***t*-Butyl 3-(ethoxycarbonyl)-6-oxo-3-piperidineacetate (18)**

Cyanotriester **15** (0.25 g; 0.8 mmol) was dissolved in ethanol (10 mL), PtO_2 (50 mg) was added and the mixture was hydrogenated in an autoclave (7.5 atm) for 2 days. TLC still showed the presence of starting material. Further PtO_2 (30 mg) was added and hydrogenation was continued overnight. The solution was decanted and the catalyst was washed twice with methanol. The combined supernatants were concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 19:1) to give lactam **18** (217 mg; 95%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 6.61 (1H, s, NH), 4.20 (2H, q, *J* 7.0, OC$\underline{H}_2$CH$_3$) 3.77 (1H, dd, *J* 12.8, 1.6, C$\underline{H}_2$NH), 3.36 (1H, dd, *J* 12.8, 1.6 C$\underline{H}_2$NH), 2.67, 2.58 (2H, 2d, *J* 15.8, C$\underline{H}_2$COOBu^t), 2.45-2.30 (2H, m, C$\underline{H}_2$CONH), 2.21 (1H, ddd, *J* 13.5, 6.0, 6.0, $\underline{C}H_2CH_2$CONH), 1.88 (1H, ddd, *J* 13.5, 7.5, 7.5, C$\underline{H}_2$CH$_2$CNH), 1.43 (9H, s, C(CH$_3$)$_3$), 1.27 (3H, t, *J* 7.0, OCH$_2$C$\underline{H}_3$); δ_C (100.5

MHz, $CDCl_3$) 173.2 (CONH), 171.3, 169.3 (COOR), 81.5 ($\underline{C}(CH_3)_3$), 61.4 ($O\underline{C}H_2CH_3$), 47.8 (CH_2NH), 42.9 (C 4^o), 41.4 ($\underline{C}H_2COOBu^t$), 29.1 ($\underline{C}H_2CH_2CONH$), 28.2 ($CH_2\underline{C}H_2CONH$), 28.0 ($C(\underline{C}H_3)_3$), 14.1 ($OCH_2\underline{C}H_3$); *m/z* (electrospray, positive) 286 ($M+H^+$); HRMS: Found: $M+H^+$, 286.1644. $C_{14}H_{24}NO_5$ requires 286.1649.

Methyl 3-(ethoxycarbonyl)-6-oxo-3-piperidineacetate (16) from 18

Tert-Butyl ester **18** (436 mg; 1.53 mmol) was dissolved in MeOH (10 mL) and concentrated HCl (0.5 mL) was added dropwise while stirring. The mixture was heated in reflux for 5 h. It was concentrated in vacuo and worked up in DCM/sat. $NaHCO_3$aq. The combined organic extracts were dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 9:1) to give lactam **16** (183 mg; 49%) as a pale yellow oil, identical with that obtained above.

2-Methyl-2,7-diazaspiro[4.5]decane-1,3,8-trione (19) from 16

A solution of **16** (547 mg; 2.25 mmol) in 40% aqueous methylamine (3 mL) was stirred overnight at room temp. The mixture was gradually heated in oil bath to 170^{o}C over 1.5 h while the volatiles were distilled off. Work up as above gave lactam **19** (289 mg; 66%) as colourless crystals. For characterization, see below.

2-Methyl-2,7-diazaspiro[4.5]decane-1,3,8-trione (19) from 17

A solution of dimethyl ester **17** (177 mg; 0.77 mmol) in 40% aqueous methylamine (2 mL) was stirred overnight at room temp. The mixture was gradually heated in oil bath to 170^{o}C over 1.5 h while the volatiles were distilled off. The pale pink solid residue obtained was recrystallised from ethanol to give imide **19** (110 mg; 73%) as white crystals mp 185-190^{o}C. IR (neat): ν 3166, 3033, 1772, 1703, 1650, 1410; δ_H (300 MHz, D_2O) 3.48, 3.22 (2H, 2d, *J* 12.8, $C\underline{H}_2NH$), 2.83 (3H, s, CH_3), 2.70 (2H, s, $C\underline{H}_2CONMe$), 2.52-2.22 (2H, m, $CH_2C\underline{H}_2CONH$), 2.09 (1H, ddd, *J* 13.5, 9.5, 7.5, $\underline{C}H_2CH_2CONH$), 1.85 (1H, ddd, *J* 13.5, 6.5, 4.0, $\underline{C}H_2CH_2CONH$); δ_C (75.5 MHz, D_2O) 183.1, 179.6 (CONMe), 175.1 (CONH), 48.4 (CH_2NH), 42.8 (C 4^o), 38.9 ($\underline{C}H_2CONMe$), 28.2 ($\underline{C}H_2CH_2CONH$), 27.7 ($CH_2\underline{C}H_2CONH$), 25.6 (CH_3); *m/z* (EI+) 196 (M^+); HRMS: Found: M^+, 196.0845. $C_9H_{12}N_2O_3$ requires 196.0842.

2-Methyl-2,7-diazaspiro[4.5]decane (5)

Imide **19** (1.43 g; 7.3 mmol) was suspended in dry THF (30 mL) in 0-5^{o}C under N_2 and 1M solution of $LiAlH_4$ in THF (29 mL; 29 mmol) was added dropwise. The ice bath was removed and the mixture was heated in reflux overnight under N_2. It was cooled to 0-5^{o}C and the following were slowly added dropwise in 0-5^{o}C: water (1.5 mL), 15% NaOHaq (1.5 mL) and water (4.5 mL). The resulting slurry was filtered through Celite, the solids were washed with THF (250 mL) and the combined filtrates were concentrated in vacuo to give a yellow oil which was distilled under vacuum (bp 66^{o}C at 2.5 mmHg) to give spirodiamine **4** (755 mg; 67%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 2.77-2.68 (2H, m, $CH_2C\underline{H}_2NMe$), 2.66, 2.59 (2H, 2d, *J* 11.7, $C\underline{H}_2NMe$), 2.59-2.51 (1H, m, $CH_2CH_2C\underline{H}_2NH$), 2.50-2.40 (2H, m, $C\underline{H}_2NH$, $CH_2CH_2C\underline{H}_2NH$), 2.29 (3H, s, CH_3), 2.23 (1H, d, *J* 9.3, $C\underline{H}_2NH$), 1.73 (1H, br s, NH), 1.68-1.39 (6H, m, $C\underline{H}_2CH_2NMe$, $CH_2C\underline{H}_2CH_2NH$, $C\underline{H}_2CH_2CH_2NH$); δ_C (100.5 MHz, CD_3OD) 67.2 ($\underline{C}H_2NMe$), 57.5 ($\underline{C}H_2NH$), 56.0 ($CH_2\underline{C}H_2NMe$), 46.6 ($CH_2CH_2\underline{C}H_2NH$), 42.6 ($CH_3$), 42.1 (C 4^{o}), 37.2 ($\underline{C}H_2CH_2CH_2NH$), 36.9 ($\underline{C}H_2CH_2NMe$), 24.5 ($CH_2\underline{C}H_2CH_2NH$); *m/z* (electrospray, positive) 155 ($M+H^+$); HRMS: Found: $M+H^+$, 155.1541. $C_9H_{19}N_2$ requires 155.1548.

1-*t*-Butyl-3-ethyl-4-methyl 3-cyano-1,3,4-butanetricarboxylate (20) and 1-*t*-butyl-3,4-dimethyl 3-cyano-1,3,4-butanetricarboxylate (21)

Cyanodiester **12** (1.16 g; 6.78 mmol) was dissolved in ethanol-water 1:1 (12 mL), cooled to 0-5^{o}C and Et_3N (1.2 mL) was added dropwise. After 15 min. t-butyl acrylate (1.05 mL; 0.92 g; 7.14 mmol) was added dropwise. The mixture was stirred at 0-5^{o}C for 1.5 h, allowed to warm to room temp. and stirred for further 2 h. It was then concentrated, diluted with water, acidified with 2N HCl to pH 4 and extracted 3x with AcOEt. The combined organic extracts were dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel in hexane:AcOEt 4:1) to give **20** (0.61 g; 29%; R_f 0.27) and **21** (0.77 g; 38%; R_f 0.23) as colourless oils. Data for **20**: δ_H (270 MHz, $CDCl_3$) 4.30, 4.29 (2H, 2q, *J* 6.9, $OC\underline{H}_2CH_3$), 3.72 (3H, s, OCH_3), 3.07, 2.80 (2H, 2d, *J* 17.1, $C\underline{H}_2COOMe$), 2.53 (1H, ddd, *J* 16.2, 9.5, 6.0, $CH_2C\underline{H}_2COOBu^t$), 2.36 (1H, ddd, *J* 16.2, 9.6, 6.6, $CH_2C\underline{H}_2COOBu^t$), 2.26-2.00 (2H, m, $C\underline{H}_2CH_2COOBu^t$), 1.43 (9H, s, $C(CH_3)_3$), 1.34 (3H, t, *J* 6.9, $OCH_2C\underline{H}_3$); δ_C (100.5 MHz, $CDCl_3$) 170.5, 169.0, 167.8 (COOR), 118.0 (CN), 81.4 ($\underline{C}(CH_3)_3$), 63.3 ($O\underline{C}H_2CH_3$), 52.4 ($O\underline{C}H_3$), 45.2 (C 4^{o}), 40.7 ($\underline{C}H_2COOMe$), 32.1 ($\underline{C}H_2CH_2COOBu^t$), 31.0 ($CH_2\underline{C}H_2COOBu^t$), 28.1 ($C(\underline{C}H_3)_3$), 14.0 ($OCH_2\underline{C}H_3$); *m/z* (CI) 314 ($M+H^+$); HRMS: Found: $M+H^+$, 314.1598. $C_{15}H_{24}NO_6$ requires 314.1604. Data for **21**: δ_H (270 MHz, $CDCl_3$) 3.84 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.08, 2.81 (2H, 2d, *J* 17.1, $C\underline{H}_2COOMe$), 2.53 (1H, ddd, *J* 16.0, 9.5, 6.0,

$CH_2C\underline{H}_2COOBu^t$), 2.36 (1H, ddd, *J* 16.0, 10.0, 6.0, $CH_2C\underline{H}_2COOBu^t$), 2.25-2.05 (2H, m, $C\underline{H}_2CH_2COOBu^t$), 1.43 (9H, s, $C(CH_3)_3$); δ_C (100.5 MHz, $CDCl_3$) 170.4, 169.0, 168.4 (COOR), 118.0 (CN), 81.4 ($\underline{C}(CH_3)_3$), 53.9 (OCH_3), 52.4 ($O\underline{C}H_3$), 45.1 (C 4^o), 40.8 ($\underline{C}H_2COOMe$), 32.1 ($\underline{C}H_2CH_2COOBu^t$), 31.0 ($CH_2\underline{C}H_2COOBu^t$), 28.1 ($C(\underline{C}H_3)_3$); *m/z* (CI) 300 ($M+H^+$); HRMS: Found: $M+H^+$, 300.1445. $C_{14}H_{22}NO_6$ requires 300.1447.

***t*-Butyl 4-(ethoxycarbonyl)-6-oxo-4-pyrrolidinepropionate (22)**

Cyanotriester **20** (0.56 g; 1.79 mmol) was dissolved in ethanol (12 mL), PtO_2 (60 mg) was added and the mixture was hydrogenated in an autoclave (8 atm) for 2 days. TLC showed the absence of starting material. The solution was decanted with a pipette and the catalyst was washed twice with methanol. The combined supernatants were concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 19:1) to give lactam **22** (0.32 g; 63%) as a colourless oil which solidified when chilled. An analytical sample was recrystallised from AcOEt/hexane to give pure **22** as white crystals mp 95-97^{o}C. IR (neat): ν 3196, 3102, 2935, 1722, 1712, 1685, 1366; δ_H (400 MHz, $CDCl_3$) 6.11 (1H, s, NH), 4.19 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 3.77, 3.25 (2H, 2d, *J* 10.0, $C\underline{H}_2NH$), 2.85, 2.26 (2H, 2d, *J* 17.1, $C\underline{H}_2CONH$), 2.23-1.98 (4H, m, $C\underline{H}_2C\underline{H}_2COOBu^t$), 1.44 (9H, s, $C(CH_3)_3$), 1.27 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$); δ_C (100.5 MHz, $CDCl_3$) 175.6 (CONH), 173.9, 171.6 (COOR), 80.9 ($\underline{C}(CH_3)_3$), 61.7 ($O\underline{C}H_2CH_3$), 49.8 (CH_2NH), 49.2 (C 4^o), 39.0 ($\underline{C}H_2CONH$), 32.7 ($\underline{C}H_2CH_2COOBu^t$), 31.2 ($CH_2\underline{C}H_2COOBu^t$), 28.1 ($C(\underline{C}H_3)_3$), 14.2 ($OCH_2\underline{C}H_3$); *m/z* (CI) 303 ($M+NH_4^+$); HRMS: Found: $M+NH_4^+$, 303.1913. $C_{14}H_{27}N_2O_5$ requires 303.1914. Anal. calcd. for $C_{14}H_{23}NO_5$: C, 58.91; H, 8.13; N, 4.91. Found: C, 58.90; H, 8.30; N, 5.00.

***t*-Butyl 4-(methoxycarbonyl)-6-oxo-4-pyrrolidinepropionate (26)**

Cyanotriester **21** (0.72 g; 2.41 mmol) was dissolved in ethanol (15 mL), PtO_2 (80 mg) was added and the mixture was hydrogenated in an autoclave (8 atm) for 3 days. TLC still showed the presence of starting material. PtO_2 (50 mg) was added and hydrogenation was continued overnight. The solution was decanted with a pipette and the catalyst was washed twice with methanol. The combined supernatants were concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 19:1) to give lactam **26** (0.43 g; 66%) as a colourless oil which solidified. An analytical sample was recrystallised from AcOEt/hexane to give pure **26** as white crystals mp 117-118^{o}C. IR (neat): ν 3199, 3107, 2886, 1733, 1721, 1682, 1224; δ_H (270 MHz, $CDCl_3$) 6.62 (1H, s, NH), 3.75 (1H, d, *J* 10.2, $C\underline{H}_2NH$), 3.72 (3H, s, OCH_3), 3.24 (1H, d, *J* 10.2, $C\underline{H}_2NH$), 2.83, 2.25 (2H, 2d, *J* 17.1, $C\underline{H}_2CONH$), 2.22-1.92 (4H, m,

$C\underline{H}_2C\underline{H}_2COOBu^t$), 1.41 (9H, s, $C(CH_3)_3$); δ_C (100.5 MHz, $CDCl_3$) 175.9 (CONH), 174.4, 171.6 (COOR), 80.9 ($\underline{C}(CH_3)_3$), 52.7 ($O\underline{C}H_3$), 50.0 (CH_2NH), 49.2 (C 4^o), 39.1 ($\underline{C}H_2CONH$), 32.7 ($\underline{C}H_2CH_2COOBu^t$), 31.2 ($CH_2\underline{C}H_2COOBu^t$), 28.1 ($C(\underline{C}H_3)_3$); *m/z* (CI) 289 ($M+NH_4^+$); HRMS: Found: $M+NH_4^+$, 289.1758. $C_{13}H_{25}N_2O_5$ requires 289.1758.

Methyl 4-(ethoxycarbonyl)-6-oxo-4-pyrrolidinepropionate (23)

Tert-butyl ester **22** (0.26 g; 0.91 mmol) was dissolved in MeOH (7 mL) and concentrated HCl (0.2 mL) was added dropwise while stirring. The mixture was heated in reflux for 2 h, allowed to cool down to room temp. and neutralised with sat. $NaHCO_3$aq (2 mL). Methanol was evaporated in vacuo and the residue was worked up in DCM/water. The combined organic extracts were dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 9:1) to give methyl ester **23** (208 mg; 94%) as a colourless oil. IR (neat): ν 3245, 2955, 1724, 1692; δ_H (400 MHz, $CDCl_3$) 6.08 (1H, s, NH), 4.19 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 3.77 (1H, d, *J* 9.8, $C\underline{H}_2NH$), 3.68 (3H, s, OCH_3), 3.26 (1H, d, *J* 9.8, $C\underline{H}_2NH$), 2.87 (1H, d, *J* 17.1, $C\underline{H}_2CONH$), 2.38-2.04 (5H, m, $C\underline{H}_2CONH$ (1H), $C\underline{H}_2C\underline{H}_2COOBu^t$ (4H)), 1.28 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$); δ_C (100.5 MHz, $CDCl_3$) 175.5 (CONH), 173.7, 172.7 (COOR), 61.8 ($O\underline{C}H_2CH_3$), 49.8 (CH_2NH), 49.2 ($C4^o$), 39.0 ($\underline{C}H_2CONH$), 32.6 ($\underline{C}H_2CH_2COOMe$), 29.8 ($CH_2\underline{C}H_2COOMe$), 14.2 ($OCH_2\underline{C}H_3$); *m/z* (CI) 244 ($M+H^+$); HRMS: Found: $M+H^+$, 244.1186. $C_{11}H_{18}NO_5$ requires 244.1185.

Methyl 4-(methoxycarbonyl)-6-oxo-4-pyrrolidinepropionate (27)

Tert-butyl ester **26** (0.29 g; 1.07 mmol) was dissolved in MeOH (8 mL) and concentrated HCl (0.25 mL) was added dropwise while stirring. The mixture was heated in reflux for 2 h, allowed to cool down to room temp. and neutralised with sat. $NaHCO_3$aq (3 mL). Methanol was evaporated in vacuo and the residue was worked up in DCM/water. The combined organic extracts were dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (DCM:MeOH 9:1) to give lactam **27** (172 mg; 70%) as a colourless oil. IR (neat): ν 3232, 2955, 1727, 1692; δ_H (400 MHz, $CDCl_3$) 6.05 (1H, s, NH), 3.80 (1H, d, *J* 10.0, $C\underline{H}_2NH$), 3.74 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.27 (1H, d, *J* 10.0, $C\underline{H}_2NH$), 2.87 (1H, d, *J* 17.1, $C\underline{H}_2CONH$), 2.37-2.23 (3H, m, $C\underline{H}_2CONH$ (1H), $CH_2C\underline{H}_2COOMe$ (2H)), 2.21-2.06 (2H, m, $C\underline{H}_2CH_2COOMe$); δ_C (100.5 MHz, $CDCl_3$) 175.5 (CONH), 174.2, 172.7 (COOR), 52.7 ($O\underline{C}H_3$), 51.9 ($O\underline{C}H_3$), 49.8 (CH_2NH), 49.2 (C 4^o), 39.0 ($\underline{C}H_2CONH$), 32.6 ($\underline{C}H_2CH_2COOMe$), 29.8 ($CH_2\underline{C}H_2COOMe$); *m/z* (CI) 230 ($M+H^+$); HRMS: Found: $M+H^+$, 230.1028. $C_{10}H_{16}NO_5$ requires 230.1028.

2-Methyl-2,7-diazaspiro[4.5]decane-1,3,8-trione (19) from 23

A solution of ethyl ester **23** (205 mg; 0.84 mmol) in 40% aqueous methylamine (2.5 mL) was stirred overnight at room temp. The mixture was gradually heated in oil bath to 180^{o}C over 1.5 h while the volatiles were distilled off. The solid residue obtained was recrystallised from ethanol to give spirocycle **19** (57 mg; 34%) which was identical in all respects to that obtained above.

***N*-Methyl 4-(methylaminocarbonyl)-6-oxo-4-pyrrolidinepropionamide (24) from 27**

A solution of dimethyl ester **27** (170 mg; 0.74 mmol) in 40% aqueous methylamine (2 mL) was stirred overnight at room temp. The mixture was gradually heated in oil bath to 180^{o}C over 1.5 h while the volatiles were distilled off. A semi-solid residue was obtained, which was recrystallised from ethanol to give bisamide **24** (155 mg; 92%) as white crystals mp 178-180^{o}C. IR (neat): ν 3296, 3087, 2946, 1676, 1632, 1552; δ_H (270 MHz, D_2O) 3.73, 3.37 (2H, m, C$\underline{H}_2$NH), 2.85 (1H, d, *J* 11.5, C$\underline{H}_2$CONH), 2.74 (3H, s, CH_3), 2.69 (3H, s, CH_3), 2.39 (1H, d, *J* 11.5, C$\underline{H}_2$CONH), 2.23-2.12 (2H, m, $CH_2C\underline{H}_2$CONHMe), 2.12-1.97 (2H, m, C$\underline{H}_2CH_2$CONHMe); δ_C (100.5 MHz, D_2O) 178.5, 176.5, 175.6 (CONH), 50.1 (CH_3), 49.6 (CH_3), 39.0 (C 4^{o}), 33.6 (CH_2NH), 31.3 ($\underline{C}H_2$CONH), 26.3 ($\underline{C}H_2CH_2$CONHMe), 26.1 ($CH_2\underline{C}H_2$CONHMe); *m/z* (CI) 228 ($M+H^+$); HRMS: Found: $M+H^+$, 228.1348. $C_{10}H_{18}N_3O_3$ requires 228.1348. Anal. calcd. for $C_{10}H_{17}N_3O_3$: C, 52.83; H, 7.54; N, 18.50. Found: C, 52.81; H, 7.47; N, 18.60.

Bismethyl ester **27** (1.28 g; 5.59 mmol) was dissolved in methanol (15 mL), 40% aqueous methylamine (10 mL; 116 mmol) was added and the mixture was stirred overnight at room temp. TLC showed complete disappearance of starting material. The mixture was concentrated in vacuo and worked up in DCM/water. The aqueous layer was concentrated in vacuo and chromatographed on silica gel ($CHCl_3$:EtOH:NH_3aq 25:25:1) to give biamide **24** (1.10 g; 87%) as a white solid which was identical to that obtained above.

***N*-Methyl 4-(methylaminocarbonyl)-6-oxo-4-pyrrolidinepropionamide (24) from 23**

Methyl ethyl diester **23** (240 mg; 1.0 mmol) was dissolved in methanol (3 mL), 40% aqueous methylamine (0.1 mL; 1.16 mmol) was added and the mixture was stirred overnight at room temp. TLC showed mainly starting material. $MeNH_2$ solution (0.8 mL) was gradually added over 2 days until complete disappearance of starting material on TLC. The mixture was

concentrated in vacuo and worked up in DCM/water. The aqueous layer was concentrated in vacuo and chromatographed on silica gel ($CHCl_3$:EtOH:NH_3aq 25:25:1) to give bisamide **24** (166 mg; 74%) as a white solid which was identical to that obtained above.

Note that in general, bisamide **24** did not require purification and was generally used directly in the next step.

7-Methyl-2,7-diazaspiro[4.5]decane-3,6,8-trione (25)

A suspension of crude **24** (1.7 g; 7.49 mmol) and p-TsOH.H_2O (1.57 g; 8.21 mmol; 1.1 eq) in p-xylene (20 mL) was heated at reflux overnight. The mixture was then evaporated to dryness and worked up in water/AcOEt. The organic phase was concentrated to dryness and the residue was chromatographed on silica gel ($CHCl_3$:EtOH:NH_3aq 25:25:1) to give a white solid (1.30 g; conv. 89%) containing **25** and **19** in 3:1 ratio by ^{1}H NMR. Purification was achieved by recrystallisation from EtOH to give **25** as colourless crystals, mp 186-196^{o}C. IR (neat): ν 3238, 2683, 1669, 1356, 1273, 1112, 1021, 1011; δ_H (400 MHz, D_2O; no trace of **19** detectable) 3.81, 3.49 (2H, 2d, *J* 10.8, C$\underline{H}_2$NH), 3.10 (3H, s, CH_3), 2.84 (1H, d, *J* 17.4, C$\underline{H}_2$CONH), 2.83, 2.79 (2H, 2d, *J* 6.6, $CH_2C\underline{H}_2$CONMe), 2.57 (1H, d, *J* 17.4, C$\underline{H}_2$CONH), 2.16, 2.15 (2H, 2d, *J* 6.6, C$\underline{H}_2CH_2$CONMe); δ_C (100.5 MHz, D_2O) 178.4, 177.7, 175.4 (CONH), 51.0 (CH_2NH), 45.4 (C 4^o), 40.2 ($\underline{C}H_2$CONH) 29.2 ($\underline{C}H_2CH_2$CONMe), 27.4 ($CH_2\underline{C}H_2$CONMe), 25.3 (CH_3); *m/z* (CI) 197 ($M+H^+$); HRMS: Found: $M+H^+$, 197.0925. $C_9H_{13}N_2O_3$ requires 197.0926. Anal. calcd. for $C_9H_{12}N_2O_3$: C, 55.08; H, 6.17; N, 14.28. Found: C, 55.29; H, 5.99; N, 14.22.

Isomers **19** and **25** were purified by crystallisation as these isomers were inseparable by conventional chromatography and HPLC. The extent of isomerisation that occurred depended on the conditions used. This reaction was examined under a series of conditions with conversions and product ratios shown in **Table 2** below. It should also be noted that although trace amounts of **19** were observed in samples of **25**, following reduction and N-arylation, the corresponding N-arylated derivatives (e.g. **42** and **43** below) are readily separated by chromatography.

Table 2.

Solvent (all at reflux)	Amount p-TsOH (eq)	Time (h)	Conversion (%)	**25** : **19** (^{1}H NMR)
p-xylene	1.1	overnight	89	3 : 1
p-xylene	0.3	overnight	<30	-
p-xylene	0.3	4	<30	-
p-xylene	1.0	4	66	9 : 1
p-xylene*	1.1	1.5	93	7 : 1
p-xylene**	1.1	2	74	8 : 1
MeOH	1.1	overnight	73	1 : 1
EtOH	1.1	overnight	51	5.5 : 1

*Enhancement of **25** to >19:1 ratio (starting from 7:1 mixture) was achieved by recrystallisation from EtOH. **Reaction was carried out under gentle N_2 flow with a valve open to release $MeNH_2$.

7-Methyl-2,7-diazaspiro[4.5]decane (6)

To a suspension of **25** (0.79 g; 4.03 mmol) in dry THF (25 mL) in 0-5^{o}C under N_2 was added dropwise $LiAlH_4$ (18 mL; 18 mmol, 1M solution in THF). The ice bath was removed and the mixture was heated in reflux overnight under N_2 after which time it was cooled to 0-5^{o}C and the following were slowly added dropwise in 0-5^{o}C: water (0.8 mL), 15% NaOHaq (0.8 mL) and water (2.5 mL). The resulting slurry was filtered through Celite, the solids were washed with THF (150 mL) and the combined filtrates were concentrated in vacuo to give a yellow oil which was distilled under vacuum (bp 82-85^{o}C at 2.5 mmHg) to give spirodiamine **6** (254 mg; 41%) as a colourless oil. δ_H (400 MHz, CD_3OD) 2.90, 2.88 (2H, 2d, *J* 7.0, C$\underline{H}_2$NMe), 2.81-2.48 (4H, m, $CH_2CH_2C\underline{H}_2NMe$, C$\underline{H}_2$NH), 2.45-2.15 (2H, m, $CH_2C\underline{H}_2NH$), 2.22 (3H, s, CH_3), 1.75-1.35 (6H, m, $CH_2C\underline{H}_2CH_2NMe$, $C\underline{H}_2CH_2CH_2NMe$, $C\underline{H}_2CH_2NH$); δ_C (100.5 MHz, $CDCl_3$) 66.0 ($\underline{C}H_2NH$), 62.4 ($\underline{C}H_2NMe$), 56.2 ($CH_2CH_2\underline{C}H_2NMe$), 47.0 ($CH_3$), 46.3 ($CH_2\underline{C}H_2NH$), 43.2 (C 4^o), 34.8 ($\underline{C}H_2CH_2NH$), 34.3 ($\underline{C}H_2CH_2CH_2NMe$), 23.7 ($CH_2\underline{C}H_2CH_2NMe$); *m/z* (CI) 155 ($M+H^+$); HRMS: Found: $M+H^+$, 155.1541. $C_9H_{19}N_2$ requires 155.1548.

2,7-Di-*t*-butylcarboxy-2,7-diazaspiro[4.4]nonane (28)

Spirodiamine **2**[1b] (688 mg; 5.46 mmol) was dissolved in EtOH (35 mL), cooled to 0-5°C and 0.5M aq. NaOH (4.3 mL) and solution of Boc_2O (2.51 g; 2.1 eq) in EtOH (15 mL) were added while stirring. The mixture was stirred overnight at room temperature, concentrated in vacuo and worked up in DCM/water. The organic layer was dried with $MgSO_4$, concentrated and chromatographed on silica gel (DCM-MeOH 19:1) to give biscarbamate **28 (**1.78 g 100%) as a white solid. δ_H (400 MHz, $CDCl_3$) 3.50-3.15 (8H, m, $C\underline{H}_2NBoc$), 1.90-1.70 (4H, m, $C\underline{H}_2CH_2NBoc$), 1.45 (18H, s, $C(CH)_3)_3$); ^{13}C NMR specrutm was poorly resolved due to amide resonance; *m/z* (CI) 327 ($M+H^+$); HRMS: Found: $M+H^+$, 327.2277. $C_{17}H_{31}N_2O_4$ requires 327.2284.

2-*t*-Butylcarboxy-2,7-diazaspiro[4.4]nonane (29)

Biscarbamate **28** (1.78 g; 5.46 mmol) was dissolved in DCM (140 mL), cooled to 0-5°C and a solution of TFA (2.3 mL; 5 eq) in DCM (40 mL) was added dropwise while stirring. The mixture was stirred overnight at room temp. TLC still showed a significant amount of starting material. Further TFA (0.5 mL) was added and the mixture was stirred for another 24 h at room temp. An excess of saturated aq. $NaHCO_3$ were added CAREFULLY and the layers were separated. The aqueous (and basic) phase was extracted five times with DCM and the combined extracts were concentrated in vacuo and chromatographed on silica gel (EtOH- aq NH_3 9:1) to give the monoBoc product **29** (307 mg; 25%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) 4.68 (1H, br s, NH), 3.40-3.30 (2H, m, $CH_2C\underline{H}_2NBoc$), 3.25-3.15 (2H, m, $C\underline{H}_2NBoc$), 3.15-3.05 (2H, m, $C\underline{H}_2NH$), 2.95-2.80 (2H, m, $CH_2C\underline{H}_2NH$), 1.90-1.70 (4H, m, $C\underline{H}_2CH_2NBoc$, $C\underline{H}_2CH_2NH$), 1.45 (9H, s, $C(CH)_3)_3$); δ_C (100.5 MHz, $CDCl_3$) 79.5 ($\underline{C}(CH)_3)_3$), 51.5, 45.8, 36.0, 28.6 ($C(\underline{C}H)_3)_3$) (remaining signals were poorly resolved due to amide resonance); *m/z* (CI) 227 ($M+H^+$); HRMS: Found: $M+H^+$, 227.1758. $C_{12}H_{23}N_2O_2$ requires 227.1760.

2,8-Di-*t*-Butylcarboxy-2,8-diazaspiro[5.5]undecane (30)

Spirodiamine **4**[1b] (331 mg; 2.15 mmol) was dissolved in EtOH (15 mL). The solution was cooled to 0-5°C and 0.5M aq. NaOH (1.7 mL) and a solution of Boc_2O (0.99 g; 4.46 mmol) in EtOH (7 mL) were added while stirring. The mixture was stirred overnight at room temp., concentrated in vacuo and worked up in DCM/water. The organic layer was dried with $MgSO_4$, concentrated and chromatographed on silica gel (DCM-MeOH 19:1) to give biscarbamate **30** (754 mg; 99%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.60-2.85 (8H, m,

$C\underline{H}_2NBoc$), 1.60-1.20 (8H, m, $C\underline{H}_2C\underline{H}_2CH_2NBoc$), 1.43 (18H, s, $C(CH)_3)_3$). This product was not characterized further.

2-*t*-Butylcarboxy-2,8-diazaspiro[5.5]undecane (31)

Biscarbamate **30** (662 mg; 1.89 mmol) was dissolved in DCM (50 mL) and cooled to 0-5^{o}C. To the stirred mixture was added dropwise a solution of TFA (0.8 mL; 5 eq) in CH_2Cl_2 (15 mL) and the mixture was stirred overnight at room temp. TLC (EtOH-NH_3aq 50:1) showed mainly the mono-Boc product (R_f 0.35) and some di-Boc starting material (R_f 0.8). The reaction was quenched with saturated aq. $NaHCO_3$, the aqueous layer was extracted twice with DCM. The combined organic extracts were dried with Na_2SO_4, concentrated in vacuo and chromatographed on silica gel (EtOH- aq. NH_3 50:1) to give the mono-Boc product **31** (233 mg; 49%) and the di-Boc starting material **38** (281 mg) which was resubmitted to the deprotection conditions. Following a second cycle, monocarbamate **31** (323 mg, 68% in total) was isolated as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.65-2.95 (8H, m, $C\underline{H}_2NH$, $C\underline{H}_2NBoc$), 1.65-1.10 (8H, m, $C\underline{H}_2C\underline{H}_2CH_2NH$, $C\underline{H}_2C\underline{H}_2CH_2NBoc$), 1.41 (9H, s, $C(CH)_3)_3$); *m/z* (CI) 255 ($M+H^+$); HRMS: Found: $M+H^+$, 255.2068. $C_{14}H_{27}N_2O_2$ requires 255.2067.

Ethyl 3,3-dicyano-1,4-butanedicarboxylate (32)

Ethyl 3,3-dicyanopropanoate[35] (0.5 g; 3.29 mmol) was dissolved in dry dioxan (2.5 mL) (cooled in ice-water bath, but avoiding dioxan freezing) and Triton B (40% soln. in MeOH; 0.06 mL; 0.04 eq) was added dropwise. The mixture was stirred at room temp. for 15 min., slightly cooled in ice-water bath and ethyl acrylate (0.36 mL; 3.3 mmol) was added dropwise. The mixture was stirred overnight at room temperature, then neutralised with 1M HCl and worked up in DCM/water. The organic layer was dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (hexane:AcOEt 3:1) to give **32** (736 mg; 89%) as a colourless oil. δ_H (270 MHz, $CDCl_3$) 4.21 (2H, q, *J* 7.2, $OC\underline{H}_2CH_3$), 4.18 (2H, q, *J* 7.2, $OC\underline{H}_2CH_3$), 2.99 (2H, s, $C\underline{H}_2COOEt$), 2.74 (2H, t, *J* 8.0, $CH_2C\underline{H}_2COOEt$), 2.39 (2H, t, *J* 8.0, $C\underline{H}_2CH_2COOEt$), 1.31 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 1.27 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$); δ_C (100.5 MHz, $CDCl_3$) 170.5, 166.2 ($\underline{C}OOEt$), 114.2 (CN), 62.5 ($O\underline{C}H_2CH_3$), 61.5 ($O\underline{C}H_2CH_3$), 41.0 ($\underline{C}H_2COOEt$), 33.2 ($\underline{C}H_2CH_2COOEt$), 32.5 (C 4^o), 30.3 ($CH_2\underline{C}H_2COOEt$), 14.2 ($OCH_2\underline{C}H_3$), 14.0 ($OCH_2\underline{C}H_3$); *m/z* (CI) 253 ($M+H^+$); HRMS: Found: $M+H^+$, 253.1188. $C_{12}H_{17}N_2O_4$ requires 253.1188.

2,7-Diazaspiro[4.5]decane-1,3,6,8-tetraone (33)

A stirred solution of **32** (3.65 g; 14.5 mmol) in glacial AcOH (9 mL) was cooled to 0-5^{o}C and concentrated H_2SO_4 (1 mL) was added dropwise. The mixture was heated in reflux for 30 min. and allowed to cool to room temperature at which point a white solid crystallised. After cooling to 0-5^{o}C for 1.5 h, th solid was filtered off, washed with ice-cold water and dried in vacuo in the presence of P_2O_5 until constant weight to give **33** (1.77 g; 62%) which was used in the next step without further purification. mp 223-225^{o}C. IR (neat): ν 3201, 1717, 1693, 1651; δ_H (400 MHz, DMSO-D_6) 11.61 (1H, s, NH), 11.19 (1H, s, NH), 3.04 (1H, d, *J* 18.1, C$\underline{H}_2$CONH), 2.80-2.70 (1H, m, $CH_2C\underline{H}_2CONH$), 2.73 (1H, d, *J* 18.1, C$\underline{H}_2$CONH), 2.60-2.50 (1H, m, $CH_2C\underline{H}_2CONH$), 2.32 (1H, ddd, *J* 13.5, 7.0, 5.0 C$\underline{H}_2CH_2CONH$), 2.15 (1H, ddd, *J* 13.5, 9.0, 5.5 C$\underline{H}_2CH_2CONH$); δ_C (100.5 MHz, DMSO-D_6) 177.9, 177.1, 173.2, 172.3 (CONH), 52.3 (C 4^{o}), 40.2 ($\underline{C}H_2CONH$), 29.0 ($\underline{C}H_2CH_2CONH$), 26.3 ($CH_2\underline{C}H_2CONH$); *m/z* (CI) 197 ($M+H^+$); HRMS: Found: $M+H^+$, 197.0562. $C_8H_9N_2O_4$ requires 197.0562.

2,7-Diazaspiro[4.5]decane (7)

Bisimide **33** (1.7 g; 8.67 mmol) was suspended in dry THF (30 mL) in 0-5^{o}C under N_2 and 1M solution of $LiAlH_4$ in THF (40 mL; 40 mmol) was added dropwise. The ice bath was removed and the mixture was heated in reflux for 2 days under N_2. It was cooled to 0-5^{o}C, diluted with THF (10 mL) and the following were slowly added dropwise in 0-5^{o}C: water (1.8 mL), 15% NaOHaq (1.8 mL) and water (5.5 mL). The resulting slurry was filtered through Celite, the solids were washed with THF (250 mL) and the combined filtrates were concentrated in vacuo to give a yellow oil which was distilled under vacuum (bp 70^{o}C at 1.0 mmHg) to give the product **7** (580 mg; 48%) as a colourless oil. δ_H (400 MHz, CD_3OD) 2.88, 2.86 (2H, 2d, *J* 7.1, C$\underline{H}_2$NH 5-membered), 2.74 (1H, d, *J* 11.4, C$\underline{H}_2$NH), 2.74-2.65 (2H, m, $CH_2C\underline{H}_2NH$), 2.65-2.58 (2H, m, $CH_2CH_2C\underline{H}_2NH$), 2.57 (1H, d, *J* 11.4, C$\underline{H}_2$NH 6-membered), 1.72-1.45 (6H, m, $CH_2C\underline{H}_2CH_2NH$, $C\underline{H}_2CH_2CH_2NH$, C$\underline{H}_2CH_2NH$); δ_C (100.5 MHz, CD_3OD) 56.1 (), 54.6 ($\underline{C}H_2NH$), 45.6 ($CH_2CH_2\underline{C}H_2NH$), 45.2 ($CH_2\underline{C}H_2NH$), 42.5 (C 4^{o}), 36.8 ($\underline{C}H_2CH_2NH$), 35.1 ($\underline{C}H_2CH_2CH_2NH$), 23.8 ($CH_2\underline{C}H_2CH_2NH$); *m/z* (CI) 141 ($M+H^+$); HRMS: Found: $M+H^+$, 141.1385. $C_8H_{17}N_2$ requires 141.1392.

N-Arylation of spirodiamine scaffolds.

General procedure. 8-Methyl-2-(6-chloropyridin-3-yl)-2,8-diazaspiro[5.5]undecane (39)

(The same procedure was used when P(i-Bu$NCH_2CH_2)_3$N was employed as ligand.)

$Pd_2(dba)_3$ (11 mg; 0.012 mmol; 2% mol based on 2-chloro-5-iodopyridine) and Xantphos (21 mg; 0.036 mmol; 6% mol, or equivalent amount of P(i-Bu$NCH_2CH_2)_3$N) were dissolved in

dry toluene (3 mL) and stirred under N_2 at room temp. After 10 min. Bu^{t}ONa (85 mg; 0.89 mmol), 2-chloro-5-iodopyridine (187 mg; 0.77 mmol; 1.3 eq), N-methylspirodiamine **3** (100 mg; 0.60 mmol) and fresh dry toluene (3 mL) were added and the mixture was heated in reflux overnight under N_2. It was cooled to room temp. and worked up in ether/brine. The organic layer was dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (DCM:MeOH:aq. NH_3 360:40:1) to give the N-arylated adduct **39** (130 mg; 78%) as a pale oil which solidified when cooled. δ_H (400 MHz, $CDCl_3$) 7.99 (1H, d, *J* 3.8, H-12), 7.21 (1H, dd, *J* 10.4, 3.8, H-14), 7.11 (1H, d, *J* 10.4, H-15), 3.30-3.15 (2H, m, H-1, H-3), 3.10-2.95 (2H, m, H-1', H-3'), 2.60-2.50 (1H, m, H-9), 2.43 (1H, d, *J* 10.5, H-7), 2.21 (3H, s, CH_3), 2.20-2.05 (1H, m, H-9'), 2.00 (1H, d, *J* 10.5, H-7'), 1.75-1.45 (6H, m, H-4, H-4', H-5, H-10, H-10', H-11), 1.40-1.30 (1H, m, H-5'), 1.25-1.10 (1H, m, H-11'); δ_C (75.5 MHz, $CDCl_3$) 147.1 (C-16), 139.9 (C-13), 137.5 (C-12), 126.1 (C-14), 123.7 (C-15), 63.7 (C-7), 57.6 (C-1), 56.9 (C-9), 49.2 (C-3), 46.9 (CH_3), 34.4 (C-6), 34.2 (C-5), 33.0 (C-11), 21.9 (C-10), 21.2 (C-4); *m/z* (CI) 280 ($M+H^+$); HRMS: Found: $M+H^+$, 280.1758. $C_{15}H_{23}{}^{35}ClN_3$ requires 280.1755.

Data for other N-arylated spirodiamines.

36: pale brown oil.δ_H (300 MHz, $CDCl_3$) 7.65 (1H, d, *J* 3.1, H-10), 7.09 (1H, d, *J* 8.8, H-13), 6.76 (1H, dd, *J* 8.8, 3.1, H-12), 3.40-3.25 (3H, m, H-1, H-1', H-3), 3.20 (1H, d, *J* 8.8, H-3'), 2.72 (1H, ddd, *J* 9.3, 7.7, 6.2, H-8), 2.62 (1H, d, *J* 9.6, H-6), 2.62-2.54 (1H, m, H-8'), 2.49 (1H, d, *J* 9.6, H-6'), 2.38 (3H, s, CH_3), 2.12-1.95 (2H, m, H-4, H-4'), 1.95-1.80 (2H, m, H-9, H-9'); δ_C (75.5 MHz, $CDCl_3$) 142.8 (C-14), 137.4 (C-11), 132.8 (C-10), 123.8 (C-12), 120.9 (C-13), 66.9 (C-6), 59.7 (C-1), 56.0 (C-8), 48.9 (C-5), 47.2 (C-3), 42.3 (CH_3), 37.7 (C-4), 36.7 (C-9); *m/z* (CI) 252 ($M+H^+$); HRMS: Found: $M+H^+$, 252.1266. $C_{13}H_{19}{}^{35}ClN_3$ requires 252.1262.

37: colourless solid mp 120-125 ^{o}C (DCM/hexane). δ_H (300 MHz, $CDCl_3$) 7.59 (1H, d, *J* 2.7, H-10), 7.04 (1H, d, *J* 8.8, H-13), 6.70 (1H, dd, *J* 8.8, 2.7, H-12), 3.48-3.18 (6H, m, H-3, H-3', H-6, H-6', H-8, H-8'), 3.18 (1H, d, *J* 9.3, H-1), 3.11 (1H, d, *J* 9.3, H-1'), 2.04-1.75 (4H, m, H-4, H-4', H-9, H-9'), 1.39 (9H, s, $C(CH_3)_3$); δ_C (75.5 MHz, $CDCl_3$) 154.5 (CO), 142.5 (C-14), 137.6 (C-11), 132.8 (C-10), 123.8 (C-12), 121.0 (C-13), 79.5 ($\underline{C}(CH_3)_3$), 56.7 (C-1), 55.4, 54.8 (C-6), 48.8, 48.0 (C-5), 46.9 (C-3), 45.1, 44.8 (C-8), 35.4 (C-4), 34.8, 34.6 (C-9), 28.4 ($C(\underline{C}H_3)_3$); *m/z* (CI) 337 (M^+); HRMS: Found: M^+, 337.1556. $C_{17}H_{24}{}^{35}ClN_3O_2$ requires 337.1557.

40: δ_H (400 MHz, $CDCl_3$) 7.97 (1H, m, H-12), 7.17-7.07 (2H, m, H-14, H-15), 3.65-2.70 (8H, m, H-1, H-1', H-3, H-3', H-7, H-7', H-9, H-9'), 1.90-1.20 (17H, m, H-4, H-4', H-5, H-5', H-10, H-10', H-11, H-11', $C(CH_3)_3$); δ_C (100.5 MHz, $CDCl_3$) 155.0 (C-16), 148.0 (CO), 147.3 (C-13), 140.8 (C-12), 138.1 (C-14), 123.7 (C-15), 80.5 ($\underline{C}(CH_3)_3$), 57.5, 51.0, 49.7, 45.0, 34.5, 34.1, 32.5, 28.4 ($C(\underline{C}H_3)_3$), 21.3, 21.1, spectrum of poor quality due to amide resonance; *m/z* (CI) 365 (M^+); HRMS: Found: M^+, 365.1872. $C_{19}H_{28}{}^{35}ClN_3O_2$ requires 365.1870.

42: δ_H (400 MHz, $CDCl_3$) 7.97 (1H, d, *J* 3.2, H-11), 7.16 (1H, dd, *J* 8.8, 3.2, H-13), 7.09 (1H, d, *J* 8.8, H-14), 3.12 (1H, ddd, *J* 11.7, 6.0, 4.5, H-3), 3.05 (1H, d, *J* 11.7, H-1), 2.98 (1H, ddd, *J* 11.7, 7.8, 3.9, H-3'), 2.87 (1H, d, *J* 11.7, H-1'), 2.71 (1H, ddd, *J* 8.8, 7.9, 4.9, H-9), 2.63 (1H, d, *J* 9.3, H-7), 2.39 (1H, ddd, *J* 8.8, 7.9, 7.6, H-9'), 2.30 (3H, s, CH_3), 2.15 (1H, d, *J* 9.3, H-7'), 1.77-1.44 (6H, m, H-4, H-4', H-5, H-5', H-10, H-10'); δ_C (100.5 MHz, $CDCl_3$) 147.1 (C-15), 140.7 (C-12), 137.8 (C-11), 126.4 (C-13), 123.7 (C-14), 66.8 (C-7), 60.2 (C-1), 55.8 (C-9), 49.0 (C-3), 42.7 (C-6), 42.4 (CH_3), 36.7 (C-10), 36.0 (C-5), 23.1 (C-4); *m/z* (CI) 266 ($M+H^+$); HRMS: Found: $M+H^+$, 266.1422. $C_{14}H_{21}{}^{35}Cl\ N_3$ requires 266.1419.

43: δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, *J* 2.9, H-11), 7.08 (1H, d, *J* 8.8, H-14), 6.77 (1H, dd, *J* 8.8, 2.9, H-13), 3.38-3.22 (3H, m, H-1, H-3, H-3'), 3.09 (1H, d, *J* 9.3, H-1'), 2.60-2.45 (1H, m, H-8), 2.36 (1H, d, *J* 11.5, H-6), 2.31-2.05 (2H, m, H-6', H-8'), 2.25 (3H, s, CH_3), 2.02-1.90 (1H, m, H-4), 1.87-1.76 (1H, m, H-4'), 1.74-1.60 (2H, m, H-9, H-9'), 1.60-1.48 (1H, m, H-10), 1.44-1.32 (1H, m, H-10'); δ_C (75.5 MHz, $CDCl_3$) 142.9 (C-15), 137.2 (C-12), 132.8 (C-11), 123.7 (C-13), 121.1 (C-14), 64.5 (C-6), 57.0 (C-1), 56.1 (C-8), 46.7 (CH_3), 46.1 (C-3), 42.5 (C-5), 35.8 (C-4), 33.5 (C-10), 23.3 (C-9); *m/z* (CI) 266 ($M+H^+$); HRMS: Found: $M+H^+$, 266.1418. $C_{14}H_{21}{}^{35}ClN_3$ requires 266.1424.

Deprotection of N-arylated adduct **40**.

N-Boc adduct **40** (170 mg; 0.47 mmol) was dissolved in DCM (15 mL), cooled to 0-5^{o}C and TFA (0.4 mL; 4.6 mmol) was added dropwise. The mixture was stirred overnight at room temperature and worked up in DCM/sat. $NaHCO_3$. The organic layer was dried with $MgSO_4$, concentrated in vacuo and chromatographed on silica gel (EtOH:NH_3aq 30:1) to give spiroamine **41** (105 mg; 85%) as a pale yellow oil. δ_H (300 MHz, CD_3OD) 7.99 (1H, dd, *J* 3.2, 0.5, H-12), 7.41 (1H, dd, *J* 8.8, 3.2, H-14), 7.22 (1H, dd, *J* 8.8, 0.5, H-15), 3.22-3.12 (2H,

m, H-3, H-3), 3.10 (1H, d, *J* 12.4, H-1), 3.04 (1H, d, *J* 12.4, H-1'), 2.88-2.65 (2H, m, H-9, H-9'), 2.74 (1H, d, *J* 12.9, H-7), 2.63 (1H, d, *J* 12.9, H-7'), 1.80-1.62 (3H, m, H-4, H-4', H-11), 1.62-1.49 (3H, m, H-5, H-10, H-10'), 1.46-1.33 (2H, m, H-5', H-11'); δ_C (75.5 MHz, CD_3OD) 149.1 (C-16), 140.7 (C-13), 138.2 (C-12), 128.1 (C-14), 125.2 (C-15), 58.1 (C-1), 54.6 (C-7), 50.5 (C-3), 47.6 (C-9), 34.5 (C-5), 34.2 (C-11), 34.0 (C-6), 22.8 (C-10), 22.0 (C-4); *m/z* (CI) 266 ($M+H^+$); HRMS: Found: $M+H^+$, 266.1421. $C_{14}H_{21}{}^{35}ClN_3$ requires 266.1419.

38: pale yellow oil. δ_H (400 MHz, CD_3OD) 7.61 (1H, d, *J* 2.9, H-10), 7.19 (1H, d, *J* 8.8, H-13), 6.99 (1H, dd, *J* 8.8, 2.9, H-12), 3.42-3.35 (2H, m, H-3, H-3'), 3.29 (1H, d, *J* 9.3, H-1), 3.23 (1H, d, *J* 9.3, H-1'), 3.15-3.05 (2H, m, H-8, H-8'), 2.97 (1H, d, *J* 11.2, H-6), 2.92 (1H, d, *J* 11.2, H-6'), 2.12-1.99 (2H, m, H-4, H-4'), 1.97-1.83 (2H, m, H-9, H-9'); δ_C (100.5 MHz, CD_3OD) 143.3 (C-14), 136.5 (C-11), 131.9 (C-10), 123.9 (C-12), 121.8 (C-13), 57.0 (C-1), 55.2 (C-6), 49.4 (C-5), 46.8 (C-3), 45.3 (C-8), 35.9 (C-9), 35.3 (C-4); *m/z* (CI) 238 ($M+H^+$); HRMS: Found: $M+H^+$, 238.1103. $C_{12}H_{17}{}^{35}ClN_3$ requires 238.1111.

References and notes.

1. (a) While specific examples are cited here, a good deal of work relevant to the topic of this paper is contained within the patent literature. Where defined, we have made every effort to cite relevant patents but, and because of the scope of the claims and compounds made often inherent in a patent, it is difficult to do this consistently and comprehensively. (b) Culbertson, T. P.; Sanchez, J. P.; Gambino, L.; Sesnie, J. A. *J. Med. Chem.* **1990,** *33*, 2270-2275.

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(effectively) in removal of acrylate, the result of which is a slowing of the desired Michael addition reaction.

33. Interestingly, reactions involving **16** and **17** to give **19** did not produce a bisamide adduct analogous to e.g. **10** (Scheme 2) or **24** (Scheme 5). In these other cases, bisamide formation preceded six-membered ring imide formation, but in the case of **19**, it is presumably the involvment of a more favoured five-membered ring that promotes imide generation. This does not, however, exclude bisamides as intermediates in the conversion of **16** and **17** to **19**.

    An X-ray diffraction experiments on imide **19** was carried out at 173K on a Bruker SMART diffractometer using Mo-K_α radiation (λ = 0.71073 Å). Data collections were performed using a CCD area detector from a single crystal mounted on a glass fibre. Intensities were integrated (Bruker-AXS SAINT , Madison, Wisconsin) from several series of exposures measuring 0.3° in ω or ϕ. Absorption corrections were based on equivalent reflections using SADABS (Sheldrick, G. M. SADABS V2.03, University of Göttingen, Germany). The structure was solved using SHELXS and refined against all F_o^2 data with hydrogen atoms riding in calculated positions using SHELXL, except for that on N2, which was found in the difference map and its position allowed to refine freely (Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112-122). The crystal data are of poor quality owing to a crystal with multiple domains which could not be resolved. This has resulted in high R-values and large residual peaks in the difference map. ***Crystal structure and refinement data:*** habit block; Size/mm 0.50×0.25×0.10; Empirical Formula $C_9H_{12}N_2O_3$; M 196.21; Crystal system monoclinic; Space group $P2_1/n$; a/Å 12.242(3); b/Å 5.8833(15); c/Å 13.701(3); α/° 90.00; β/° 115.126(4); γ/° 90.00; V/Å^3 893.4(4); Z 4; μ/mm^{-1} 0.111; T/K 173; $\theta_{min,max}$ 1.87,27.54; Completeness 0.988 to θ = 27.54°; Reflections total/independent 8719/2045; R_{int} 0.0545; Final $R1$ and $wR2$ 0.1299, 0.4245; Largest peak, hole/eÅ^{-3} 1.233, -0.596; ρ_{calc}/g cm^{-3} 1.459; Flack parameter n/a.

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36. The observed lack of selectivity for mono-Boc protection is not surprising given the comparable environments of the two secondary amine sites. What is less clear is the exact distribution of the possible products as separation (and characterisation) of the mono protected isomers was problematic.

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