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Spirobicyclic diamines. Part 3: Synthesis and metal complexation of proline-derived [4.4]-spirodiamines

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Abstract—The syntheses of racemic and homochiral [4.4]-spirolactams, starting from L-proline, in good yields are described. Reduction of the lactam carbonyl group of spirolactams, containing chiral substituents on the lactam nitrogen, with lithium aluminium hydride, gives a series of homochiral [4.4]-spirodiamines. The crystal structure of one of these spirodiamines on complexation with zinc chloride was obtained. Interestingly it showed a hydrogen-bonded dimeric structure, where the monomers are diastereoisomeric diamines.
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1. Introduction

Diamines, especially vicinal diamines, are of interest because of their ability to strongly bind metal ions leading to Lewis acid complexes, which have found use as catalysts in a wide range of organic syntheses.[1] Many of the well known diamines, such as ethylenediamine (**1**, Fig. 1), are acyclic and are very flexible in nature. The introduction of constraints into such structures is a well studied method for reducing this conformational flexibility giving molecules with a more defined 3D structure [e.g., *trans*-1,2-diaminocyclohexane (**2**)[2] is a constrained version of ethylenediamine]. In some cases this has been used in biologically active molecules to either increase the affinity of the molecule for its target (cyclic versus acyclic peptides),[3] or to make the molecules more metabolically stable, which can lead to improved bioavailability.[4] The naturally occurring polycyclic diamine (−)-sparteine (**3**) has found use as a chiral ligand in a number

of applications in asymmetric synthesis.[5] Another method of constraint, which has been used is to introduce a spirofusion of two rings, which forces the nitrogen atoms into a mutually orthogonal relationship (**4**, Fig. 1).

There are currently a large number of methods for the synthesis of spirocyclic compounds and they can also be easily formed in a stereocontrolled manner.[6] Freidinger was the first to incorporate a lactam constraint in the backbone of a peptide in order to rigidify the peptide tertiary structure into a more defined conformation.[7] One of the most common methods for the synthesis of lactams is the cyclisation of an amino group (primary or secondary) onto a carboxylic ester, with concomitant loss of an alcohol. The overall efficiency of the cyclisation is dependant on the size of the ring being formed, the nature of the amino substituent in the case of a secondary amine, any substituents on the resulting ring and the structure of the alkyl moiety of the ester group. Many of the reactions take place spontaneously at ambient temperature, while others require heating in a suitable solvent.[8]

L-Proline-derived spirolactams have, in particular, been studied for their use in constraining peptides with L-proline residues to mimic the β-turn, a very important component of peptide secondary structure. Depending on their final use spirolactams are synthesised either as racemic mixtures or as single enantiomers. In most cases these syntheses start from L-proline, which must then be alkylated in the α-position. Full control of the stereochemistry can easily be achieved using Seebach's 'self-reproduction of chirality' methodology,[9] whereas the racemic compounds simply require alkylation of the enolate of a suitably protected proline molecule, which, after a series of further functional group manipulations, gives cyclisation precursors.
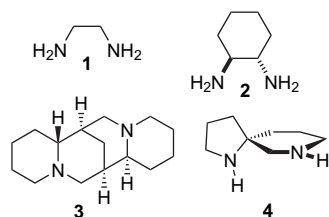

Figure 1. Structure of ethylenediamine **1**; *trans*-1,2-diaminocyclohexane **2**; (−)-sparteine **3** and 1,7-diazaspiro[4.5]decane **4**.

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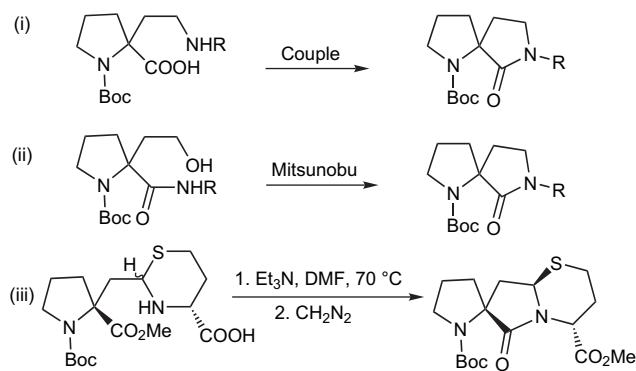
Figure 2. Cyclisation methods for proline-derived spirolactams.[8,10,11]

A number of different strategies have also been used for the critical final cyclisation step to form the spirobicyclic lactam ring. These include (i) intramolecular amide coupling, with a coupling agent (e.g., DCC or EDC), of tethered secondary amines with the deprotected proline carboxylic acid group;[10] (ii) cyclisation of proline carboxylic amides onto a primary alcohol under Mitsunobu conditions[11] and (iii) thermal cyclisation of a tethered secondary amine onto a proline carboxylic ester in DMF at 70 °C, although the yield of the latter reaction was very low (27%), with only one diastereoisomer cyclising and the side chain carboxylic acid subsequently being converted to the methyl ester by treatment with diazomethane (Fig. 2).[12]

2. Results and discussion

As part of a programme of research to synthesise both racemic and homochiral spirocycles, the synthesis of proline-derived [4.4]-spirolactams[13,15] and their conversion to spirodiamines were of interest.

The variety of different cyclisation methods used, along with their wide ranging yields, prompted us to study one of the methods, the thermal cyclisation reaction, in more detail in order to investigate whether it was a viable method for the synthesis of a range of proline-derived [4.4]-spirolactams. This necessitated the synthesis of secondary amines for subsequent cyclisation onto a carboxylic ester (Scheme 1).[13]
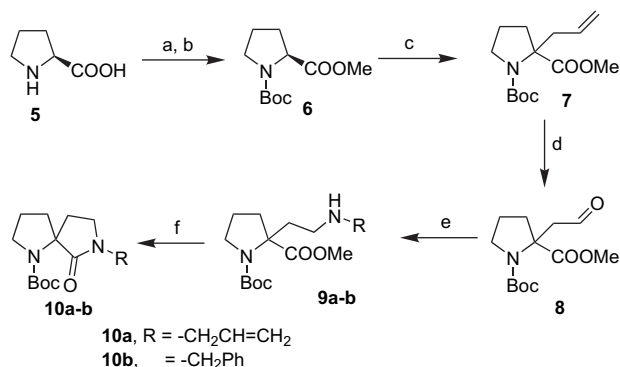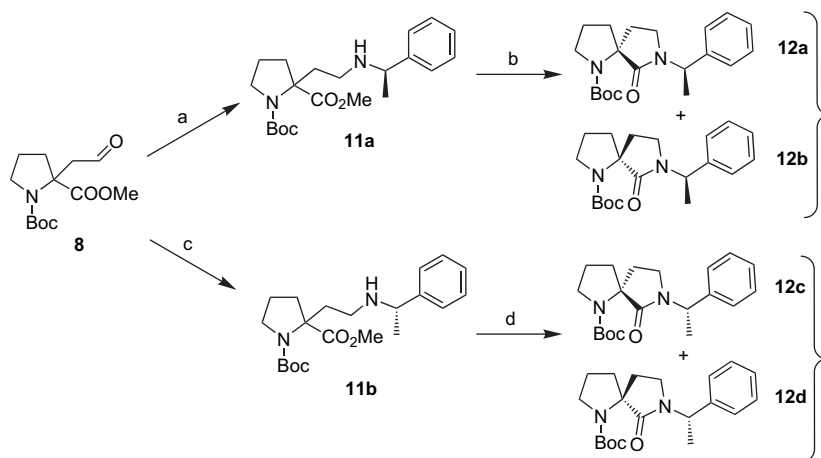

Scheme 1. Reagents and conditions: (a) SOCl$_2$, MeOH, reflux, 94%; (b) (Boc)$_2$O, DMAP, Et$_3$N, DCM, rt, 74%; (c) (i) LiHMDS, THF, −78 °C, (ii) allyl bromide, rt, 80%; (d) OsO$_4$/NaIO$_4$, THF/H$_2$O (4:1), rt, 74%; (e) (i) RNH$_2$, EtOH, (ii) NaBH$_4$, rt; (f) toluene, reflux, 60–88%.

The required secondary amines (**9a–c**) would be obtained by reductive amination of the racemic aldehyde **8**, so the efficient synthesis of this aldehyde was critical to the overall success of this method, as a generalised route to spirolactams. Compound **8** was prepared in four steps from L-proline by Boc protection of the nitrogen of the methyl ester of L-proline, which was obtained quantitatively from L-proline by treatment with SOCl$_2$ in methanol. The α-allyl group was efficiently introduced in 80% yield.[14] Oxidative cleavage of the alkene using OsO$_4$/NaIO$_4$ gave the aldehyde **8** in a 74% yield.[10e] It was necessary to efficiently purify the aldehyde by column chromatography to free it from any traces of osmium by-products, as failure to do so led to major reductions in the yield of the subsequent reductive amination and cyclisation reactions, with a large amount of decomposition occurring. Reductive amination of **8** with allylamine, gave the required secondary amine spirolactam precursor **9a**. Following the method of Johnson,[11a] thermal cyclisation of **9a** in DMF at 70 °C gave the spirolactam **10a** in a 99% yield, though the work-up was lengthy. Cyclisation in refluxing toluene gave **10a** in a 66% yield, with a simpler work-up procedure. When benzylamine was used in place of allylamine, using the same reaction cyclisation conditions, the N-benzyl substituted spirolactam (**10a**) was obtained in a higher yield of 75%.

Extension of this methodology using chiral α-substituted amines would give pairs of diastereoisomeric spirolactams.[15] Reductive amination of aldehyde **8** with either (R)- or (S)-α-methylbenzylamine gave spirolactams **11a** and **11b** (Scheme 2). Prolonged stirring of solutions of these compounds in refluxing toluene gave no indication of any cyclisation. In a similar cyclisation reaction of a secondary amine, where alanine methyl ester was used in the reductive amination step, Auberson et al. were able to successfully achieve cyclisation in yields of >90%, by stirring at reflux temperature in xylenes for 2 h.[16] Stirring solutions of amino ester **11a** or **11b** in refluxing xylenes, even for extended periods of time, gave no indication of any cyclisation reaction occurring.

Treatment of toluene solutions of **11a** or **11b** with sodium amide (50% solution in toluene) at reflux temperature gave the desired spirolactams **12a–d** (as pairs of diastereoisomers in 1:1 ratios), isolated in yields of 30 and 51%, from aldehyde **8**. HPLC analysis of each diastereoisomer showed a high degree of purity (all greater than 98.8% pure). The only impurity identified, in each case, was the diastereoisomeric product produced in the reaction.

It was not possible to obtain crystals suitable for X-ray analysis of any of the four diastereoisomers **12a–d**. Although the stereochemistry of the α-methyl benzyl substituent was known from the choice of the starting homochiral amine the absolute stereochemistry of the spirocentre in each case was not known. Molecular modelling[17] was used to give minimised energy conformations of the SR and RR diastereoisomeric pair (**12a** and **12b**). It was immediately evident from the minimised structures (Fig. 3) that in the SR diastereoisomer the hydrogens of the Boc protecting group and the meta hydrogens of the phenyl group were close in space (closest distance of 2.67 Å), whereas in the RR isomer the Boc and phenyl groups were a large distance

Scheme 2. Reagents and conditions: (a) (i) (*R*)-1-phenylethylamine, MgSO$_4$, MeOH, (ii) NaBH$_4$, rt; (b) NaNH$_2$ in toluene, reflux, 30% from **8**; (c) (i) (*S*)-1-phenylethylamine, MgSO$_4$, MeOH, (ii) NaBH$_4$, rt; (d) NaNH$_2$ in toluene, reflux, 51% from **8**.
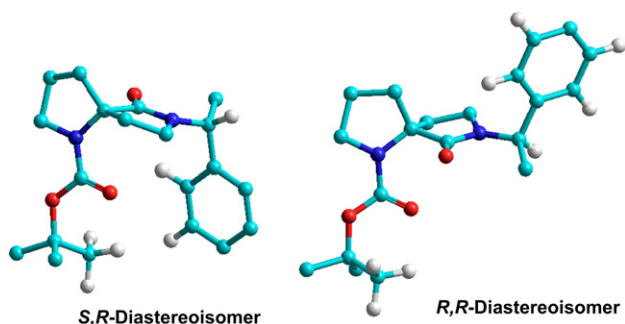

Figure 3. Energy minimised conformations of **12a** (*S*,*R*) and **12b** (*R*,*R*).[17]

apart. It was therefore expected that NOE NMR experiments would be able to distinguish between the two diastereoisomers. Irradiation of the signal for the hydrogens of the Boc group of the diastereoisomer assigned as *SR* showed an NOE to the phenyl hydrogens, whilst no similar NOE was observed in the case of the *RR* diastereoisomer, though this is not conclusive proof of the absolute stereochemistry of the spirocentre.

The homochiral diamines derived from the spirolactams **12a**–**d** were obtained when the *N*-Boc protecting group was cleanly removed from each spirolactam to give the free amino spirolactams **13a**–**d**, and the reduction of the lactams was then examined. The optimal condition found for successful reduction was the use of 20 M equiv of lithium aluminium hydride in THF (Scheme 3), which gave the diamines **14a**–**d** in acceptable isolated yields (43–56%).

One of our interests is in the use of these diamines as ligands for metal ions, thus giving chiral complexes, which may have potential as novel chiral catalysts in asymmetric transformations. The first step was to examine whether the amines bound to a metal ion. No complexation was observed when ethanolic solutions of the amines were treated with copper(II) acetate. Zinc(II) was then chosen as it is diamagnetic, making studies of complexation also possible by NMR spectroscopy. When ethanolic solutions of amines **14a**–**d** were refluxed with 1.5 M equiv of ZnCl$_2$ and the solutions were left standing at room temperature, the solutions containing amines **14a** and **14b** each gave one small single crystal (**15a** and **15b**) suitable for X-ray analysis. The surprise result
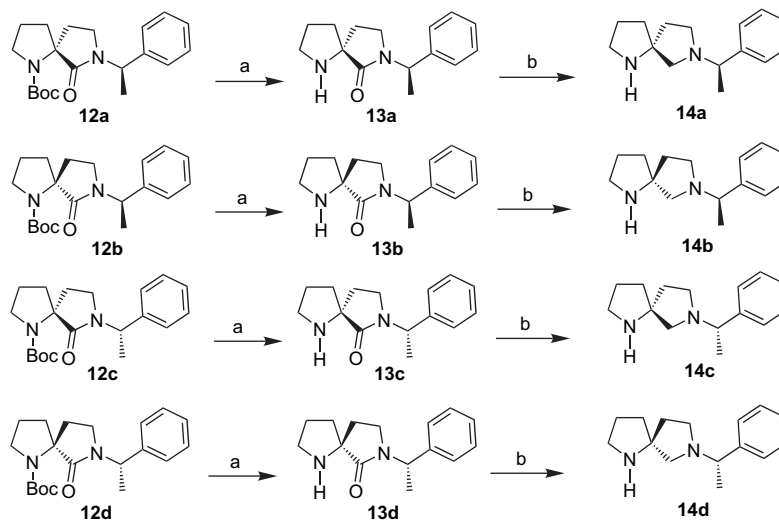
Scheme 3. Reagents and conditions: (a) (i) 50% TFA in DCM, (ii) 3 M KOH; (b) LiAlH$_4$, THF, rt.

**Table 1**. Selected bond lengths (Å) and angles (°) for **15a**

Bond	Bond lengths	Angle	Bond angles
Zn(1A)–N(1A)	2.067(5)	N(1A)–Zn(1A)–N(2A)	84.4(2)
Zn(1A)–N(2A)	2.104(6)	N(1A)–Zn(1A)–Cl(1A)	113.11(16)
Zn(1A)–Cl(1A)	2.213(2)	N(2A)–Zn(1A)–Cl(1A)	117.00(16)
Zn(1A)–Cl(2A)	2.2191(18)	N(1A)–Zn(1A)–Cl(2A)	108.42(17)
Zn(1B)–N(1B)	2.049(5)	N(2A)–Zn(1A)–Cl(2A)	107.20(16)
Zn(1B)–N(2B)	2.117(5)	Cl(1A)–Zn(1A)–Cl(2A)	120.71(7)
Zn(1B)–Cl(2B)	2.2118(19)	N(1B)–Zn(1B)–N(2B)	84.4(2)
Zn(1B)–Cl(1B)	2.213(2)	N(1B)–Zn(1B)–Cl(2B)	109.46(16)
		N(2B)–Zn(1B)–Cl(2B)	111.39(17)
		N(1B)–Zn(1B)–Cl(1B)	110.69(17)
		N(2B)–Zn(1B)–Cl(1B)	116.31(17)
		Cl(2B)–Zn(1B)–Cl(1B)	119.11(7)

from these studies was that the X-ray crystal structures of the zinc complexes **15a** and **15b** were identical (Fig. 3).

Close examination of the X-ray structures shows that a 1:1 dimeric complex had formed where each spirodiamine accommodates one zinc metal. The asymmetric unit of the crystal contains two independent molecules linked to a hydrogen-bonded dimer. Each zinc atom occupies a pseudo-tetrahedral geometry, where it is complexed to the two nitrogens of the spirocycle and to two chlorine atoms. The N–Zn–N angle is 84.4(2)° in both molecules of the dimer, and the Cl–Zn–Cl angle is 120.71(7)° in one molecule while it is 119.11(7)° in the other. The dimer is then formed by two intermolecular hydrogen bonds via one of the chlorine atoms and an amine N–H. The nitrogen to chlorine distances for the two hydrogen bonds are 3.355(6) and 3.372(6) Å. The important bond lengths and angles are shown in Table 1. The formation of a dimer may not be in itself unusual, but the most intriguing aspect of the crystal structure is that the two spirodiamines that make up the dimer are diastereoisomeric. This result was certainly not anticipated as purification of each precursor amine (**14a–d**) was carried out very carefully. HPLC analysis showed that there was only a very small amount of the corresponding diastereoisomer present in the 'purified' amines. In the case of **14a** it was shown to be 98.7% pure with 1.2% of **14b** being present. Therefore on complexation with zinc chloride the vast majority of

complexed diamine **14a** remained in solution with only a small amount crystallising out with the opposite diastereoisomeric diamine 'impurity' **14b**. Also by HPLC analysis amine **14b** was found to be 99.3% pure, contaminated with only 0.7% of the diastereoisomer **14a**. Again on complexation with zinc chloride the same result was obtained as before.

Thus the ability of the chiral spirodiamines to complex a selected metal ion has been demonstrated. Mukaiyama has studied the asymmetric catalysis of the aldol reaction (Mukaiyama aldol) using diamines derived from L-proline, which are complexed to tin(II) triflate, as asymmetric-catalysts (Fig. 4).[18] Using molecular modelling,[17] when the proline-derived diamine **16** was bound to zinc chloride and was minimised, the N–N distance was calculated to be 2.77 Å. From the crystal structure of complex **15a** it is observed that the N–N distances are 2.797 and 2.798 Å. Thus these distances compare very favourably with the calculated value for the Mukaiyama ligand **16**, above (Fig. 5).[17,18] This leads us to believe that the spirodiamines **14a–d** have the potential to be used as ligands for Sn^{2+}, with the resulting complexes being used as catalysts in the asymmetric Mukaiyama aldol reaction. It is also envisaged that the spirodiamines will complex other metal ions, and thus have applications in metal catalysed asymmetric synthetic reactions. It is also envisaged that the homochiral spirolactams **13a–d** will have
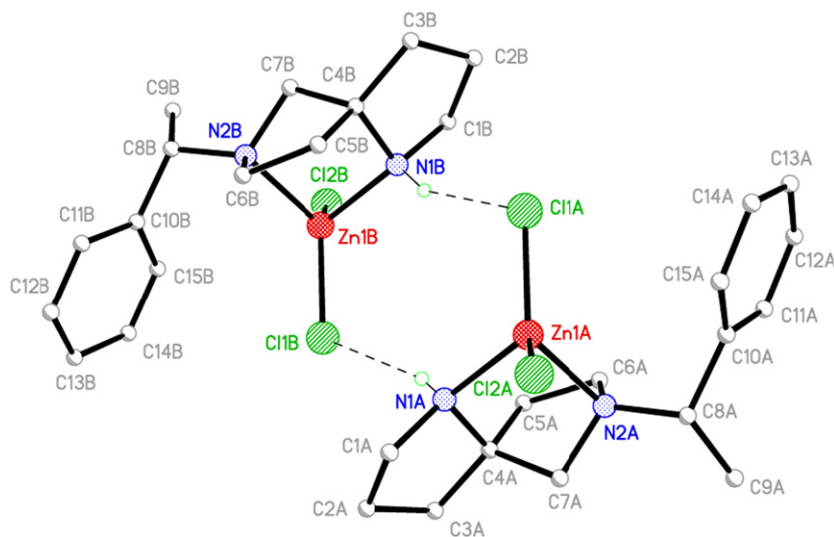
Figure 4. X-ray crystal structure of spirodiamine–ZnCl$_2$ complex **15a**.
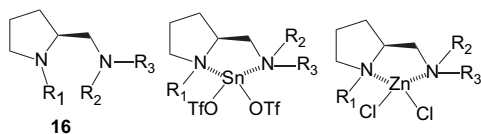
Figure 5. Mukaiyama's diamines **16**, complexed to Sn(OTf)$_2$[17] and ZnCl$_2$.

applications as novel organocatalysts. All of these studies are currently being undertaken.

3. Conclusions

In conclusion, a series of homochiral spirolactams derived from L-proline have been prepared. These spirolactams were reduced to spirodiamines using lithium aluminium hydride as reductant, and the diamines formed complexes with zinc chloride. The X-ray crystal structure of one of these complexes showed an unusual dimeric form where the two spirodiamines present were diastereoisomeric. The properties of these spirodiamines are currently being further elucidated and their potential as ligands for metals to act as catalysts in asymmetric synthesis is currently being undertaken. The results of these studies will be reported in due course.

4. Experimental

4.1. General

Allylbromide was purified by passing it through a plug of activity III basic alumina. TLC was performed on Merck silica gel 60F$_{254}$ plates and column chromatography was performed on Aldrich silica gel, 70–230 mesh, 60 Å. ^{1}H and ^{13}C NMR (δ ppm; *J* Hz) spectra were recorded on a Jeol JNM-LA300 FTNMR spectrometer using CDCl$_3$ solutions with Me$_4$Si as internal reference, unless otherwise indicated, with resolutions of 0.18 Hz and 0.01 ppm, respectively. CHCl$_3$ was used to remove last traces of ethyl acetate from some samples. The last trace of CHCl$_3$ persisted even after prolonged heating in vacuo and in these cases was visible in NMR spectra and microanalysis. Infrared spectra (cm^{-1}) were recorded as KBr discs or liquid films between NaCl plates using a Nicolet Impact 410 FTIR. Melting points were obtained on a Bibby Stuart Scientific SMP1 melting point apparatus and are uncorrected. Microanalyses were carried out at the Microanalytical Laboratory of University College Dublin. Mass spectra were obtained in the Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin. X-ray crystal structures were obtained in the Chemistry Department, Loughborough University, Loughborough, UK. HPLC analysis were carried out using methods on a Shimadzu HPLC system Class-VP, incorporating a LC-10AD pump, SPD-M10AVP Diode Array Detector, Auto-injector SIJ-10A with a system controller SCL-10A VP. Polarimetry was carried out at Dublin City University (DCU), using a Perkin–Elmer 343 with cell path-length of 100 mm at 20 °C.

4.1.1. *N*-Boc-L-proline methyl ester (6).[14] Compound **6** was prepared from L-proline by the method of Confalone.[14]

Microanalysis: Found C, 57.51; H, 8.60; N, 5.88. Calculated for C$_{11}$H$_{19}$NO$_4$: C, 57.60; H, 8.34; N, 6.10.

4.1.2. (±)-α-Allyl *N*-Boc-proline methyl ester (7).[14] Compound **7** was prepared from **6** by the method of Confalone,[14] except a 1 M solution of LiHMDS in tetrahydrofuran, instead of hexane, was used as the base. Microanalysis: Found C, 62.29; H, 8.80; N, 4.95. Calculated for C$_{14}$H$_{23}$NO$_4$: C, 62.43; H, 8.61; N, 5.20.

4.1.3. (±)-α-Formylmethyl *N*-Boc-proline methyl ester (8).[10e] Compound **8** was prepared from **7** by the method of Johnson.[10e] Microanalysis: Found C, 53.59; H, 7.60; N, 4.22. Calculated for C$_{14}$H$_{23}$NO$_4$ (0.33 CHCl$_3$): C, 53.43; H, 7.40; N, 4.67.

4.1.4. (±)-7-Allyl-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylic acid *tert*-butyl ester (10a). *Method A*: to a stirred solution of **8** (0.10 g, 0.35 mmol) in ethanol (3 ml) under nitrogen was added dropwise allylamine (0.030 ml, 0.35 mmol) over 10 min at ambient temperature, and the solution was stirred for 2 h. Sodium borohydride (0.020 g, 0.42 mmol) was added in small portions over 5 min and the resulting solution was stirred at ambient temperature for 48 h. Water (30 ml) was added and the mixture was extracted with ethyl acetate (3×15 ml), and the combined organic layers were washed with brine (2×15 ml), dried over MgSO$_4$ and concentrated in vacuo. The residue was dissolved in DMF (5 ml) under nitrogen, to which triethylamine (0.050 ml, 0.35 mmol) was added. The solution was stirred at 70 °C for 24 h, poured into water (50 ml) and extracted with ethyl acetate (3×20 ml). The combined organic layers were washed with 10% citric acid solution (2×20 ml), water (4×20 ml) and brine (2×20 ml), dried over MgSO$_4$ and concentrated in vacuo giving **10a** as an oil (0.092 g, 99%). R_f 0.21, 40% ethyl acetate/hexane. IR (thin film)/cm^{-1} 2986, 1682, 1388, 901. ^{1}H NMR (two rotamers present) δ 5.81–5.66 (m, 1H, olefin CH), 5.26–5.16 (m, 2H, olefin CH$_2$), 4.13–4.01 (m, 1H, allyl CH$_2$), 3.85–3.67 (m, 1H, allyl CH$_2$), 3.57–3.47 (m, 2H, pyrrolidine α-CH$_2$), 3.41–3.14 (m, 2H, lactam γ-CH$_2$), 2.70–2.41 (m, 2H, lactam β-CH$_2$), 2.12–1.80 (m, 4H, pyrrolidine β- and γ-CH$_2$), 1.44 and 1.42 (2×s, 9H, *tert*-butyl). ^{13}C NMR δ 174.24 and 174.20 (lactam carbonyl), 154.0 and 153.6 (Boc carbonyl), 136.6 and 136.2 (olefin CH), 118.6, 117.9 (olefin CH$_2$), 80.0 and 79.5 (*tert*-butyl C$_q$), 67.0 and 66.7 (spiro C$_q$), 48.0 and 47.7 (allyl CH$_2$), 46.1 (pyrrolidine δ-CH$_2$), 43.1 and 42.7 (lactam γ-CH$_2$), 37.6 and 37.1 (lactam β-CH$_2$), 31.0 and 30.2 (pyrrolidine β-CH$_2$), 28.6 (*tert*-butyl CH$_3$), 23.4 and 22.7 (pyrrolidine γ-CH$_2$). Microanalysis: Found C, 57.81; H, 7.98; N, 8.60. Calculated for C$_{15}$H$_{24}$N$_2$O$_3$ (0.5 CHCl$_3$): C, 57.76; H, 7.66; N, 8.69.

Method B: to a stirred solution of allylamine (0.37 ml, 4.9 mmol) in dry methanol (7 ml) was added a solution of **8** (1.20 g, 4.4 mmol) in dry methanol (1.5 ml). Magnesium sulfate (0.316 g, 2.6 mmol) was added to the solution after 3 h and the solution was then stirred for a further 2 h. The reaction was cooled to −4 °C and NaBH$_4$ (0.294 g, 7.8 mmol) was added portionwise. The reaction was quenched after 1 h with a saturated solution of NaHCO$_3$ (5 ml) and water (5 ml). The mixture was extracted with ethyl acetate (3×30 ml) then dried over MgSO$_4$ and concentrated in vacuo. The resulting

oil was stirred at reflux temperature in toluene (15 ml) for 16 h. After cooling to ambient temperature the solution was concentrated in vacuo giving an oil, which was purified on silica gel in 10% ethyl acetate/hexane to give a pale yellow oil (0.685 g, 60%). For analysis see method A.

4.1.5. (±)-7-Benzyl-6-oxo-1,7-diazaspiro[4.4]nonane-1-carboxylic acid *tert*-butyl ester (10b). *Method A*: compound **10b** was prepared by a similar method to that used for **10a** (method A) using benzylamine giving a pale yellow oil (88% yield). R_f 0.12, 40% ethyl acetate/hexane. IR (thin film)/cm^{-1}: 3000, 2950, 1700, 1680. ^{1}H NMR (two rotamers present) δ 7.35–7.22 (m, 5H, aromatic), 4.90 (d, 1H, $J=$ 14.7 Hz, benzyl CH$_2$), 4.72 (d, 1H, $J=$14.4 Hz, benzyl CH$_2$), 4.28 (d, 1H, $J=$15 Hz, benzyl CH$_2$), 3.97 (d, 1H, $J=$14.5 Hz, benzyl CH$_2$), 3.62–3.42 (m, 2H, pyrrolidine α-CH$_2$), 3.34–3.03 (m, 2H, lactam γ-CH$_2$), 2.66–2.39 (m, 1H, lactam β-CH$_2$), 2.21–2.08 (m, 1H, lactam β-CH$_2$), 2.06–1.95 (m, 2H, pyrrolidine β-CH$_2$), 1.89–1.76 (m, 2H, pyrrolidine γ-CH$_2$), 1.46 and 1.39 (2×s, 9H, *tert*-butyl). ^{13}C NMR (two rotamers present) δ 174.5 and 174.4 (lactam carbonyl), 153.5 and 153.4 (Boc carbonyl), 136.6 (*ipso* aromatic), 128.7, 128.4 and 128.3 (aromatic CH), 80.0 and 79.5 (*tert*-butyl C$_q$), 67.0 and 66.9 (spiro C$_q$), 48.0 and 47.8 (benzyl CH$_2$), 47.5 and 47.4 (lactam γ-CH$_2$), 42.9 and 42.7 (pyrrolidine δ-CH$_2$), 37.8 and 37.1 (lactam β-CH$_2$), 30.9 and 30.8 (pyrrolidine β-CH$_2$), 28.5 (*tert*-butyl CH$_3$), 23.4 and 22.8 (pyrrolidine γ-CH$_2$). Microanalysis: Found C, 62.55; H, 7.39; N, 7.14. Calculated for C$_{15}$H$_{24}$N$_2$O$_3$ (0.5 CHCl$_3$): C, 62.73; H, 7.42; N, 7.50.

Method B: compound **10b** was prepared by a similar method to that used for **10a** (method B) giving a pale yellow oil (1.46 g, 75%) after purification on silica gel in 15% ethyl acetate/hexane. For analysis see method A.

4.1.6. (5S)- and (5R)-6-Oxo-7-((1′R)-phenylethyl)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid *tert*-butyl esters (12a and 12b). To a stirred solution of (R)-(+)-1-phenylethyl amine (1.29 ml, 10.1 mmol) in dry methanol (6 ml) was added a solution of aldehyde **8** (2.5 g, 9.22 mmol) in dry methanol (2 ml). After 1 h of stirring at ambient temperature, magnesium sulfate (0.66 g, 5.5 mmol) was added to the solution and stirring was continued for 4 h. The reaction was cooled to −4 °C and NaBH$_4$ (0.56 g, 15 mmol) was added portionwise over 10 min. The reaction was quenched after 1 h at ambient temperature with a saturated solution of NaHCO$_3$ (7 ml) and water (3 ml). The aqueous layer was extracted with ethyl acetate (3×30 ml), dried over MgSO$_4$ and concentrated in vacuo to give a yellow oil (2.10 g). The resulting oil was stirred at reflux temperature for 24 h in toluene (20 ml) in the presence of 50% sodium amide (suspension) in toluene (0.20 ml, 5.2 mmol). After cooling to ambient temperature the solution was quenched with H$_2$O (4 ml) and extracted with ethyl acetate (3×20 ml). The combined organics were then concentrated in vacuo to give a colourless oil (0.909 g, 30%), which was purified by flash column chromatography on silica gel in 10% ethyl acetate/hexane resulting in **12a** (0.491 g, 54%) as a white solid. R_f 0.78 (60% ethyl acetate/hexane). Mp 92–96 °C. IR (KBr)/cm^{-1} 3031, 2976, 1702, 1682, 1361. ^{1}H NMR (two rotamers present) δ 7.35–7.25 (m, 5H, aromatic), 5.77–5.49 (m, 1H, α-CH), 3.58–3.44 (m, 2H, pyrrolidine α-CH$_2$), 3.42–3.23

(m, 1H, lactam γ-CH$_2$), 2.79–2.67 (m, 1H, lactam γ-CH$_2$), 2.61–2.37 (m, 1H, lactam β-CH$_2$), 2.13–1.66 (m, 5H, pyrrolidine β- and γ-CH$_2$, and lactam β-CH$_2$), 1.58 and 1.56 (2×d, 3H, $J=$9.87 Hz, α-CH$_3$), 1.48 and 1.46 (2×s, 9H, *tert*-butyl CH$_3$). ^{13}C NMR δ (two rotamers present) 174.1 (C=O, lactam), 153.5 (C=O, Boc), 140.4 (*ipso* aromatic), 128.4 (*meta*), 127.6 (*ortho*), 127.1 (*para*), 80.0 and 79.4 (*tert*-butyl C$_q$), 67.3 (spiro C$_q$), 49.6 and 49.2 (α-CH), 48.1 and 47.8 (pyrrolidine α-CH$_2$), 38.6 and 37.9 (CH$_2$, lactam γ-CH$_2$), 36.9 and 36.6 (CH$_2$, pyrrolidine γ-CH$_2$), 30.4 and 29.9 (lactam β-CH$_2$), 28.5 and 28.4 (*tert*-butyl CH$_3$), 23.3 and 22.4 (CH$_2$, pyrrolidine β-CH$_2$), 15.6 and 15.5 (α-CH$_3$). Microanalysis: Found C, 69.87; H, 8.49; N, 7.86. Calculated for C$_{20}$H$_{28}$N$_2$O$_3$: C, 69.74; H, 8.16; N, 8.13.

Compound **12b** was obtained as a white solid. R_f 0.68 (60% ethyl acetate/hexane). Mp 128–132 °C. IR (KBr)/cm^{-1} 3032, 2975, 1700, 1685, 1360. ^{1}H NMR (two rotamers present) δ 7.45–7.22 (m, 5H, aromatic), 5.48 (q, 0.5H, $J=$ 7.14 Hz, α-CH), 5.38 (q, 0.5H, $J=$7.14 Hz, α-CH), 3.61–3.48 (m, 2H, pyrrolidine α-CH$_2$), 3.19–3.03 (m, 2H, lactam γ-CH$_2$), 2.58–2.37 (2×m, 1H, lactam β-CH$_2$), 2.17–1.76 (m, 5H, pyrrolidine β- and γ-CH$_2$, and lactam β-CH$_2$), 1.50 and 1.48 (2×d, 3H, $J=$14.28 Hz, α-CH$_3$), 1.46 and 1.26 (2×s, 9H, *tert*-butyl CH$_3$). ^{13}C NMR (two rotamers present) δ 174.4 and 174.2 (C=O, lactam), 153.5 (C=O, Boc), 140.1 (*ipso* aromatic), 127.64 (*meta*), 127.61 (*ortho*), 127.5 (*para*), 80.3 and 79.5 (spiro C$_q$), 67.5 and 67.4 (*tert*-butyl C$_q$), 50.9 and 49.5 (α-CH), 48.6 and 48.2 (CH$_2$, pyrrolidine α-CH$_2$), 38.9 and 38.7 (CH$_2$, lactam γ-CH$_2$), 37.5 and 37.1 (CH$_2$, pyrrolidine γ-CH$_2$), 30.4 and 30.1 (CH$_2$, lactam β-CH$_2$), 28.8 and 28.5 (CH$_3$, *tert*-butyl CH$_3$), 23.6 and 22.6 (CH$_2$, pyrrolidine β-CH$_2$), 16.6 and 16.4 (CH$_3$, α-CH$_3$). Microanalysis: Found C, 70.38; H, 8.65; N, 7.53. Calculated for C$_{20}$H$_{28}$N$_2$O$_3$: C, 69.74; H, 8.16; N, 8.13.

4.1.7. (5R)- and (5S)-6-Oxo-7-((1′S)-phenylethyl)-1,7-diazaspiro[4.4]nonane-1-carboxylic acid *tert*-butyl esters (12c and 12d). Compound **12c** was prepared by a similar method to the preparation of **12a** and **12b** using (S)-(−)-1-phenylethyl amine in 51% yield. Compound **12c** was obtained as a white solid. Analytical data were the same as **12b**. Microanalysis: Found C, 69.68; H, 8.14; N, 8.05. Calculated for C$_{20}$H$_{28}$N$_2$O$_3$: C, 69.74; H, 8.16; N, 8.13.

Compound **12d** was obtained as a white solid. Analytical data were the same as **12a**. Microanalysis: Found C, 69.49; H, 8.14; N, 7.89. Calculated for C$_{20}$H$_{28}$N$_2$O$_3$: C, 69.74; H, 8.16; N, 8.13.

4.1.8. (5S)-6-Oxo-7-((1′R)-phenylethyl)-1,7-diazaspiro-[4.4]nonane (13a). To a stirred solution of **12a** (0.270 g, 0.78 mmol) in DCM (2.7 ml) was added TFA (2.7 ml) and the resulting solution was stirred for 2 h at ambient temperature. The solution was basified to pH 10 with aqueous 3 M KOH solution, and extracted with chloroform (2×30 ml). The combined organic layers were washed with brine (2×20 ml), dried over MgSO$_4$ and concentrated in vacuo giving a yellow oil (0.169 g, 89%). R_f 0.24 (10% methanol/ethyl acetate). $[\alpha]_D^{20}$ +9616.6 (*c* 0.0180, methanol). IR (thin film)/cm^{-1} 3329, 2972, 2876, 1682. ^{1}H NMR δ 7.36–7.26 (m, 5H, aromatic), 5.50–5.46 (q, 1H, $J=$6.93 Hz, α-CH), 3.29–3.20 (m, 2H, pyrrolidine α-CH$_2$), 2.98–2.90

and 2.84–2.76 (2×m, 2H, lactam γ-CH₂), 2.06 (br s, 1H, N–H), 2.01–1.74 (m, 6H, pyrrolidine β- and γ-CH₂, and lactam β-CH₂), 1.55 (d, 3H, J=7.14 Hz, α-CH₃). ^{13}C NMR δ 176.74 (C=O, lactam), 140.0 (*ipso* aromatic), 128.5 (*meta*), 127.5 (*ortho*), 126.9 (*para*), 67.9 (spiro C$_q$), 49.4 (α-CH), 47.5 (lactam γ-CH₂), 39.0 (pyrrolidine α-CH₂), 35.2 (CH₂, pyrrolidine γ-CH₂), 34.8 (lactam β-CH₂), 26.1 (pyrrolidine γ-CH₂), 16.0 (α-CH₃).

4.1.9. (5*R*)-6-Oxo-7-((1′*R*)-phenylethyl)-1,7-diazaspiro-[4.4]nonane (13b).

Compound **13b** was prepared from **12b**, by the method used for **12a**. Yield 73%, as a light yellow oil. R_f 0.26 (10% methanol/ethyl acetate). $[\alpha]_D^{20}$ +13211.3 (*c* 0.0246, methanol). IR (thin film)/cm^{-1} 3484, 2970, 2876, 1682. ^{1}H NMR δ 7.36–7.26 (m, 5H, aromatic), 5.46–5.39 (q, 1H, J=7.14 Hz, α-CH), 3.34–3.15 (m, 2H, pyrrolidine α-CH₂), 3.08–2.94 (2×m, 2H, lactam γ-CH₂), 2.77 (br s, 1H, N–H), 2.04–1.73 (m, 6H, pyrrolidine β- and γ-CH₂, and lactam β-CH₂), 1.55 (d, 3H, J=7.14 Hz, α-CH₃). ^{13}C NMR δ 175.9 (C=O, lactam), 139.0 (*ipso* aromatic), 128.6 (*meta*), 127.5 (*ortho*), 126.9 (*para*), 68.1 (spiro C$_q$), 49.6 (CH, α-CH), 47.2 (lactam γ-CH₂), 39.1 (pyrrolidine α-CH₂), 35.1 (pyrrolidine γ-CH₂), 34.2 (lactam β-CH₂), 25.7 (CH₂, pyrrolidine γ-CH₂), 16.3 (CH₃, α-CH₃).

4.1.10. (5*R*)-6-Oxo-7-((1′*S*)-phenylethyl)-1,7-diazaspiro-[4.4]nonane (13c).

Compound **13c** was prepared from **12c**, by the method used for **12a**. Yield 76%, as a light yellow oil. Analytical data were the same as **13a**.

4.1.11. (5*S*)-6-Oxo-7-((1′*S*)-phenylethyl)-1,7-diazaspiro-[4.4]nonane (13d).

Compound **13d** was prepared from **12d**, by the method used for **13a**. Yield 80%, as a light yellow oil. Analytical data were the same as **13b**.

4.1.12. (5*S*)-7-((1′*R*)-Phenylethyl)-1,7-diazaspiro[4.4]-nonane (14a).

To a stirring solution of lithium aluminium hydride 1 M solution in THF (14.8 ml, 14.8 mmol) in dry THF (5 ml) at −20 °C under nitrogen, was added a **13a** (0.179 g, 0.74 mmol) in dry THF (1 ml) and the solution was allowed to warm to ambient temperature and stirred for 48 h. To the reaction mixture, saturated sodium chloride solution and 50% sodium hydroxide solution were added alternately (each time adding three drops), until no hydride was left (i.e., until the solution did not vigorously react). The solution was then filtered, and the precipitate was washed thoroughly with chloroform (3×20 ml). The combined washings were dried over K₂CO₃ and concentrated in vacuo giving a yellow oil, which was purified on preparative TLC on silica gel in 40% methanol/chloroform to give a pale yellow oil (0.090 g, 53%). R_f 0.12 (40% methanol/chloroform). $[\alpha]_D^{20}$ +4736.8 (*c* 0.019, methanol). IR (thin film)/cm^{-1} 3354, 2970, 2776. [Note: pyrrolidine ring derived from lactam is labelled pyrrolidine B and other is pyrrolidine A.] ^{1}H NMR δ 7.34–7.21 (m, 5H, aromatic), 3.24 (q, 1H, J=6.6 Hz, α-CH), 3.01–2.88 (m, 3H, pyrrolidine B δ-CH₂ and pyrrolidine A α-CH₂), 2.62–2.54 (m, 2H, pyrrolidine B δ-CH₂ and pyrrolidine B α-CH₂), 2.37 (d, 1H, J=9.33 Hz, pyrrolidine B α-CH₂), 1.89–1.68 (m, 6H, pyrrolidine B γ-CH₂, pyrrolidine A β-CH₂ and pyrrolidine A γ-CH₂), 1.35 (d, 3H, J=6.6 Hz, α-CH₃). ^{13}C NMR δ 145.43 (*ipso* aromatic), 128.2 (*meta*), 127.0 (*ortho*), 126.7 (*para*), 68.21 (spiro C$_q$), 65.5 (α-CH), 64.8

(pyrrolidine B α-CH₂), 52.0 (pyrrolidine B δ-CH₂), 45.2 (pyrrolidine A α-CH₂), 38.2 (pyrrolidine A γ-CH₂), 37.8 (pyrrolidine B γ-CH₂), 24.7 (pyrrolidine A β-CH₂), 23.6 (CH₃, α-CH₃). Mass spectrum *m/z* [M+H] 231.1857 (calculated for C₁₅H₂₃N₂ 231.1861).

4.1.13. (5*R*)-7-((1′*R*)-Phenylethyl)-1,7-diazaspiro[4.4]-nonane (14b).

Compound **14b** was prepared from **13b**, by the method used for **14a**. Yield 46%, as a pale yellow oil. R_f 0.12 (40% methanol/chloroform). $[\alpha]_D^{20}$ +3928.5 (*c* 0.021, methanol). IR (thin film)/cm^{-1} 3359, 2970, 2776. ^{1}H NMR δ 7.35–7.21 (m, 5H, aromatic), 3.27 (q, 1H, J=6.6 Hz, α-CH), 3.03–2.84 (m, 3H, pyrrolidine B δ-CH₂ and pyrrolidine A α-CH₂), 2.52 (d, 1H, J=9.5 Hz, pyrrolidine B α-CH₂), 2.40 (d, 1H, J=9.5 Hz, pyrrolidine B α-CH₂), 2.4–2.36 (m, 1H, pyrrolidine B δ-CH₂), 1.94–1.74 (m, 6H, pyrrolidine B γ-CH₂, pyrrolidine A β-CH₂ and pyrrolidine A γ-CH₂), 1.35 (d, 3H, J=6.6 Hz, α-CH₃). ^{13}C NMR δ 145.35 (*ipso* aromatic), 128.2 (*meta*), 127.1 (*ortho*), 126.7 (*para*), 68.4 (spiro C$_q$), 65.3 (α-CH), 64.3 (pyrrolidine B α-CH₂), 51.7 (pyrrolidine B δ-CH₂), 45.0 (pyrrolidine A α-CH₂), 37.9 (pyrrolidine A γ-CH₂), 37.1 (pyrrolidine B γ-CH₂), 24.3 (pyrrolidine A β-CH₂), 22.8 (α-CH₃). Mass spectrum *m/z* [M+H] 231.1858 (calculated for C₁₅H₂₃N₂ 231.1861).

4.1.14. (5*R*)-7-((1′*S*)-Phenylethyl)-1,7-diazaspiro[4.4]-nonane (14c).

Compound **14c** was prepared from **13c**, by the method used for **14a**. Yield 48%, as a pale yellow oil. Analytical data were the same as **14a**. Mass spectrum *m/z* [M+H] 231.1864 (calculated for C₁₅H₂₃N₂ 231.1861).

4.1.15. (5*S*)-7-((1′*S*)-Phenylethyl)-1,7-diazaspiro[4.4]-nonane (14d).

Compound **14d** was prepared from **13d**, by the method used for **14a**. Yield 43%, as a pale yellow oil. Analytical data were the same as **14b**. Mass spectrum *m/z* [M+H] 231.1871 (calculated for C₁₅H₂₃N₂ 231.1861).

4.2. X-ray crystallography

Suitable crystals of **15a** and **15b** for X-ray study were obtained from ethanol solutions. The data were collected at 150(2) K on a Bruker APEX CCD diffractometer. The structure was solved by direct methods and refined on F^2 using all the reflections.[19] All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model.

Compound **15a**. *Crystal data*: C₁₅H₂₂Cl₂N₂Zn, M=366.62, triclinic, a=7.288(3), b=10.862(5), c=11.169(5) Å, α=90.304(6)°, β=103.671(5)°, γ=95.005(6)°, U=855.5(7) Å^3, space group *P*1, Z=2, μ(Mo Kα)=1.740 mm^{-1}; 6662 data (5905 unique, R_{int}=0.0261) were measured in the range 1.88<θ<25.99°. $R_1(I$>$2\sigma(I))$=0.0376 and wR_2 (all data)=0.0986. Goodness of fit on F^2=1.004. CCDC No. 641381.

4.3. Molecular modelling

The energy of the conformations of **12a** and **12b** were minimised using the MM$^+$ molecular mechanics force field in HYPERCHEM 7.5.

4.4. Supplementary data

Acknowledgements

References and notes

1. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2581–2627.
2. Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3197.
3. Samanen, J.; Wilson, G.; Smith, P.; Lee, C.-P.; Bondinell, W.; Ku, T.; Rhodes, G.; Nichols, A. *J. Pharm. Pharmacol.* **1996**, *48*, 119–135.
4. For example: Burgess, K.; Ho, K.-K.; Pettitt, B. *J. Am. Chem. Soc.* **1995**, *117*, 54–65.
5. Schultz, T. *Synlett* **2003**, 901–902 and references cited therein.
6. Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007–9071.
7. (a) Freidinger, R.; Veber, D.; Perlow, D.; Brooks, J.; Saperstein, R. *Science* **1980**, *210*, 656–658; (b) Freidinger, R.; Perlow, D.; Veber, D. *J. Org. Chem.* **1982**, *47*, 104–109.
8. A number of examples are given and the list is far from exhaustive: (a) See Ref. 7b; (b) Mueller, R.; Revesz, L. *Tetrahedron Lett.* **1994**, *35*, 4091–4092; (c) Reddy, P.; Hsiang, B.; Latifi, T.; Hill, M.; Woodward, K.; Rothman, S.; Ferrendelli, J.; Covey, D. *J. Med. Chem.* **1996**, *39*, 1898–1906; (d) Batey, R.; Mackay, D. *Tetrahedron Lett.* **2000**, *41*, 9935–9938; (e) Vitry, C.; Vasse, J.-L.; Dupas, G.; Levacher; Queguiner, G.; Bourguignon, J. *Tetrahedron* **2001**, *57*, 3087–3098; (f) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345–8349; (g) Herrero, S.; Garcia-Lopez, M.; Latorre, M.; Cenarruzabeitia, E.; Del Rio, J.; Herranz, R. *J. Org. Chem.* **2002**, *67*, 3866–3873.
9. Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.
10. (a) Castelhano, A.; Witter, D. Patent No. US 6638941B1, 2003; *Chem. Abstr.* **2003**, *139*, 345905; (b) Montserrat Fernandez, M.; Diez, A.; Rubiralta, M.; Montenegro, E.; Casamitjana, N. *J. Org. Chem.* **2002**, *67*, 7587–7599; (c) Millet, R.; Goosens, L.; Bertrand-Caumont, K.; Goosens, J.-F.; Houssin, R.; Henichart, J.-P. *J. Pharm. Pharmacol.* **2001**, *53*, 929–934; (d) Millet, R.; Goosens, L.; Bertrand-Caumont, K.; Houssin, R.; Rigo, B.; Goosens, J.-F.; Henichart, J.-P. *Lett. Pept. Sci.* **2001**, *7*, 269–279; (e) Khalil, E.; Ojala, W.; Pradhan, A.; Nair, V.; Gleason, W.; Mishra, R.; Johnson, R. *J. Med. Chem.* **1999**, *42*, 628–637; (f) Witter, D.; Famiglietti, S.; Cambier, J.; Castelhano, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3137–3142; (g) Genin, M.; Gleason, W.; Johnson, R. *J. Org. Chem.* **1993**, *58*, 860–866; (h) Ward, P.; Ewan, G.; Jordan, C.; Ireland, S.; Hagan, R.; Brown, J. *J. Med. Chem.* **1990**, *33*, 1848–1851.
11. (a) Genin, M.; Ojala, W.; Gleason, W.; Johnson, R. *J. Org. Chem.* **1993**, *58*, 2334–2337; (b) See Ref. 10f; (c) Hinds, M.; Welsh, J.; Brennand, D.; Fisher, J.; Glennie, M.; Richards, N.; Turner, D.; Robinson, J. *J. Med. Chem.* **1991**, *34*, 1777–1789.
12. Ács, M.; Fogassy, E.; Faigl, F. *Tetrahedron* **1985**, *41*, 2465–2470.
13. Kelleher, F.; Kelly, S. *Tetrahedron Lett.* **2006**, *47*, 3005–3008.
14. Confalone, P.; Huie, E.; Ko, S.; Cole, G. *J. Org. Chem.* **1988**, *53*, 482–487.
15. Kelleher, F.; Kelly, S. *Tetrahedron Lett.* **2006**, *47*, 5247–5250.
16. Auberson, Y.; Glatthar, R.; Salter, R.; Simic, O.; Tintelnot-Blomley, M. Patent No. WO2005/035535 A1, 2005; *Chem. Abstr.* **2005**, *142*, 411343.
17. *HYPERCHEM Release 7.5*; Hypercube: Gainesville, FL, 2003.
18. Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59–76.
19. Sheldrick, G. M. *SHELXTL Version 6.12*; Bruker AXS: Madison, WI, 2001.