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Tetrahedron
Tetrahedron 60 (2004) 1235–1246

Asymmetric synthesis of spiro 2-pyrrolidin-5-ones, 2-piperidin-6-ones and 1-isoindolin-3-ones. Part 1: *N*-Acyliminium ion cyclisations with an internal arene nucleophile

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Received 23 July 2003; revised 20 October 2003; accepted 24 October 2003

Abstract—A series of chiral non-racemic 5,5- and 5,6-bicyclic lactams is prepared from (*R*)-phenylglycinol. These are isomerised on treatment with aluminium trichloride in 1,2-dichloroethane to give spiro lactams in high yield and >3:1 diastereoselectivity. From four structures determined by X-ray crystallography, it follows that spiro indenes are formed preferentially with retention of configuration at the spiro carbon atom and spiro naphthalenes with inversion.

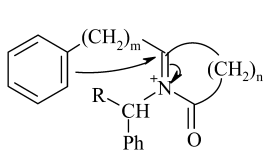
1. Introduction

Spiro lactam structures result from the intramolecular reaction of cyclic *N*-acyliminium ion intermediates with an alkene nucleophile tethered to the iminium carbon atom.[1–6] We have reported similar cyclisations, for example **1→4**, involving an arene nucleophile.[7] Two other examples are known in the context of a thiolium/*N*-acyliminium ion tandem cyclisation sequence.[8] Our first attempts to achieve diastereoselective cyclisation by the same route were unsuccessful, because the chiral *N*-1-phenylethyl group was too easily lost under the acidic conditions required for formation of the iminium ion **2**, and most of the cyclised product was racemic debenzylated spiro lactam **5**.[7] We describe herein[9] how this problem was overcome and diastereoselective spiro cyclisation of **3** achieved by the use of a chiral *N*-substituent derived from (*R*)-phenylglycinol.

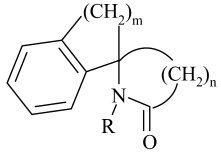
2. Results and discussion

2.1. Bicyclic lactam precursors

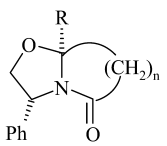
Bicyclic oxylactams based on structures **6** and **7** have been widely employed in asymmetric synthesis of tertiary and quaternary carbon centres;[10] in particular, the synthesis of pyrrolidines from **6** and piperidines from **7**,[11,12] and similarly of 3-substituted isoindolinones from **8**.[13] Similar bicyclic lactams incorporating the requisite ω-arylalkyl substituent at the ring junction position are appropriate precursors for generation of *N*-acyliminium ions **3** and cyclisation to spiro lactams.[14] Indeed, the same methodology has been employed before with alkene nucleophiles (as in Scheme 1),[5] but without any diastereoselection for configuration at the resulting spiro carbon atom. Accordingly, we prepared a series of bicyclic lactams starting from ketoacids **9**–**12** by condensation with (*R*)-phenylglycinol or, for **17**, with (*S*)-valinol.



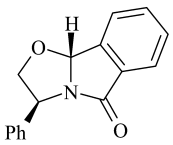
1 R = H
2 R = Me
3 R = CH_2OH



4 R = CH_2Ph
5 R = H



6 *n* = 2
7 *n* = 3



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Keywords: Diastereoselective; *N*-Acyliminium ions; Spiro lactams.
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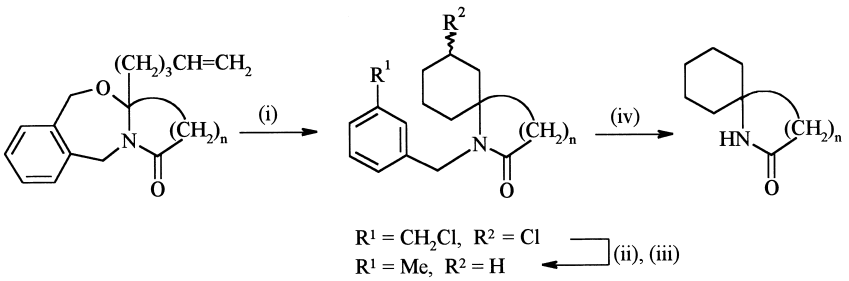
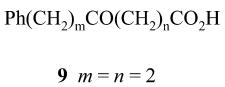
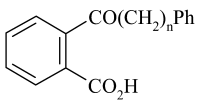
doi:10.1016/j.tet.2003.10.128



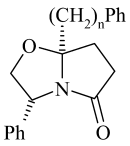
Scheme 1. *Reagents*: (i) $TiCl_4$, DCM, 20 °C (ii) H_2/Pd-C, EtOH; (iii) Bu_3SnH, AIBN; (iv) Na, NH_3, EtOH, −78 °C.



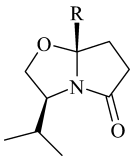
9 $m=n=2$
10 $m=3$, $n=2$
11 $m=2$, $n=3$
12 $m=n=3$



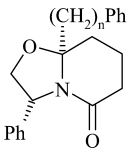
13 $n=2$
14 $n=3$



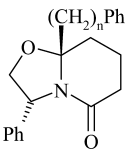
15 $n=2$
16 $n=3$



17 R = $(CH_2)_2Ph$
18 R = Me



19a $n=2$
20a $n=3$



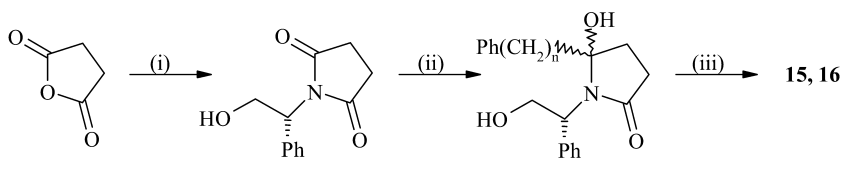
19b $n=2$
20b $n=3$

Bicyclic lactams **15**–**17** were obtained in 52–75% yields, in each case as a single diastereoisomer with the substituent at the ring junction 7a-position *cis* to phenyl (or isopropyl) at the 3-position. This assignment of stereochemistry follows numerous precedents in Meyers's work,[10,11] and the folded shape of the 5,5-fused bicyclic system would be severely strained by a 3-substituent on the inside (*endo*) face. Bicyclic lactams **15** and **16** were also obtained by the alternative route via imide **21** shown in Scheme 2, but in only ca. 21% overall yield from (*R*)-phenylglycinol. The first route from ketoacids represents more efficient use of phenylglycinol.

The 5,6-fused bicyclic lactams **19** and **20** were obtained in 72% yield as inseparable mixtures of two diastereoisomers in ca. 84:16 ratio (from ^{13}C NMR spectra), in accordance with literature precedents.[10,12] The major diastereoisomer is **19a** or **20a**, although the greater conformational flexibility of the 6-membered lactam ring (in comparison with that in **15** and **16**) can accommodate a 3-substituent on the *endo* face of the bicyclic system in the minor isomer **19b** or **20b**. The mixed stereochemistry at the 8a-position is of no consequence because the *N*-acyliminium ion intermediate in the ensuing cyclisation step is planar at this position and the diastereoselectivity of formation of the ultimate spiro lactam products does not depend upon the stereochemistry of the precursor bicyclic lactams.

The corresponding ketoacids **13** and **14** required for the preparation of tricyclic lactams **25** and **26** were made by Grignard addition to phthalic anhydride, but they were imperfectly purified by column chromatography, so the alternative route via the phthalimide **22** was preferable. Grignard addition to **22** afforded the 3-hydroxyisoindolinones **23** and **24** as single diastereoisomers after chromatography (Scheme 3). Our assignment of (*R*)-configuration to C-3 in these products is based on X-ray crystallographic results for the related adduct of 3-butenyl Grignard reagent and **22** described in the accompanying paper.[15] However, the C-3 stereochemistry in **23** and **24** is unimportant, because subsequent acid-catalysed steps involve intermediates in which this position becomes planar and give rise to end-products with either (*R*)- or (*S*)-configuration at this centre.

Treatment of **23** with trifluoroacetic acid (TFA) in dichloromethane (DCM) at 0 °C afforded a mixture of tricyclic lactam **25** and isomeric enamide **27**. Similarly, **24** afforded a mixture of **26** and **28**, which were separated by chromatography. It was noted that decreasing the quantity of TFA resulted in a higher ratio of **26**:**28**, although the highest yield (of both products) was obtained from **24** using a 10-fold excess of TFA (Table 1). Also, partial interconversion of **26** and **28**, and similarly of **25** and **27**, occurred in the presence of TFA in DCM. Tricyclic lactams **25** and **26** were obtained as single diastereoisomers, in which C-9b must have the (*S*)-configuration shown for the



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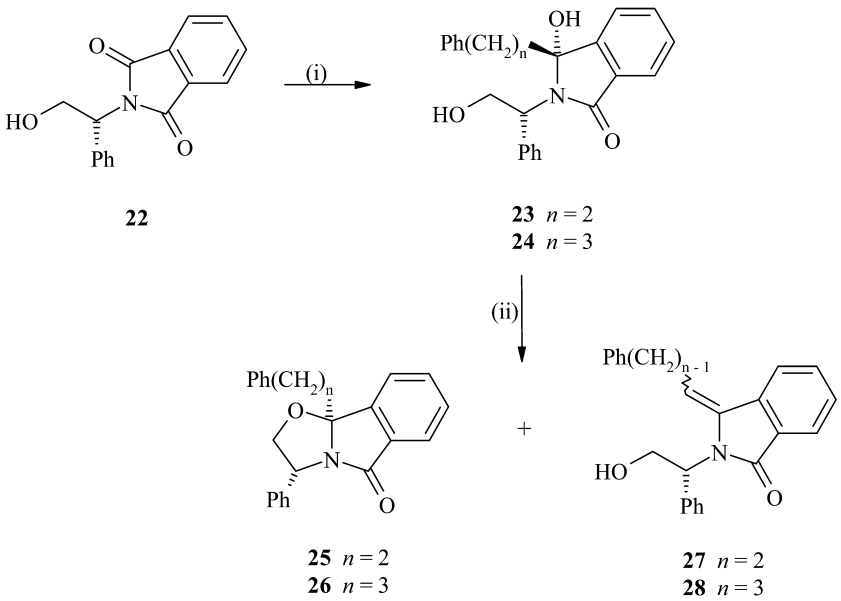
Scheme 2. *Reagents*: (i) (*R*)-$HOCH_2CH(Ph)NH_2$, PhMe, reflux; then Et_3N, reflux; (ii) $Ph(CH_2)_nMgBr$, THF, 0 °C; (iii) TFA, DCM, 0 °C.



Scheme 3. *Reagents*: (i) $Ph(CH_2)_nMgBr$, THF, 0 °C; (ii) TFA, DCM, 0 °C.

Table 1. Effect of TFA on product distribution, **26** and **28**

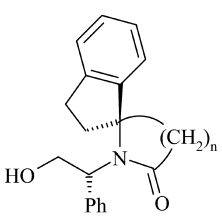
Mole ratio **24**:TFA	Yield **26** (%)	Yield **28** (%)	Total yield (%)	Ratio **26**:**28**
1:30	18.1	53.5	71.6	25:75
1:20	38.4	45.2	83.6	46:54
1:10	48.5	40.7	89.2	53:47
1:2	77.5	3.5	81.0	96:4
1:1	78.5	4.2	82.7	95:5

same reasons discussed previously and following the precedent of **8**.[13] Subsequent conversion into spiro lactams was pursued only with the lactams **25** and **26**, although in principle the enamides could also have been used as precursors for the same *N*-acyliminium ion intermediates and for spiro cyclisation.

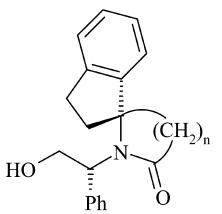
2.2. Cyclisation to spiro lactams

In our previous work, involving the synthesis of spiro lactams,[16] we have used TFA or polyphosphoric acid to achieve the spiro cyclisation step. However, when bicyclic lactam **15** was heated in TFA under reflux for 3 h, it was incompletely converted into a new product, subsequently identified as the spiro lactam **29a**, which was isolated in only 11% yield. On the other hand, treatment of **15** with aluminium trichloride in either dichloromethane or 1,2-dichloroethane (DCE) at room temperature or below resulted in high conversion into two diastereoisomeric spiro products **29a** and **b**, which were cleanly separated by column chromatography. The optimum conditions were found to be a 1:3 mole ratio of **15** to aluminium trichloride in DCE at −5 °C, from which **29a** and **b** were isolated in 93% yield and 78:22 ratio. This ratio appears to be the result of kinetic control, because the minor isomer survived treatment again with $AlCl_3$ in DCE and no interconversion to **29a** occurred. Both spiro products showed IR absorption for OH (absent in **15**) and ^{13}C NMR absorptions for the spiro carbon and for an additional unprotonated aromatic carbon in comparison with the spectra of **15**. The major isomer was more polar, eluting second in chromatography. Its structure was confirmed as **29a** by single crystal X-ray analysis.[9] The minor isomer is therefore **29b**.

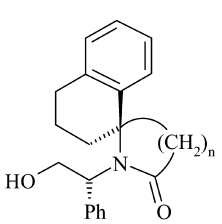
Bicyclic lactam **19** (in this case a mixture of **19a** and **b**) was unreactive under the same reaction conditions used for cyclisation of **15**. 6-Membered lactams such as **7** are also less reactive than 5-membered lactams **6** in metalation and alkylation reactions.[10] However, by using a 1:4 mole ratio of **19** and $AlCl_3$ in DCE at room temperature, cyclisation to the spiro lactams **30a** and **b** was achieved in 88% yield. The major isomer was again the slower running component in chromatography. Single crystal X-ray analysis confirmed the spiro structure with the relative configuration shown in Figure 1. As the side chain chiral centre is derived from (*R*)-phenylglycinol, the spiro carbon is (*S*)-configuration and the structure is as drawn in **30a**. This is entirely consistent with the formation of **29a** as the major product



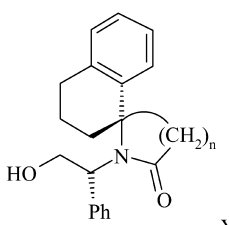
29a $n=2$
30a $n=3$



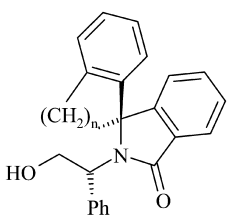
	Yield **a** + **b**	Ratio **a** : **b**
29b $n=2$	92.5%	78:22
30b $n=3$	88.5%	76:24



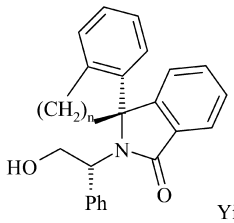
31a $n=2$
32a $n=3$



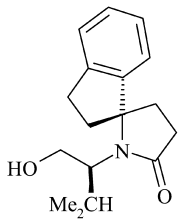
	Yield **a** + **b**	Ratio **a** : **b**
31b $n=2$	90%	20:80
32b $n=3$	99%	25:75



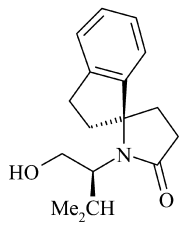
33a $n=2$
34a $n=3$



	Yield **a + b**	Ratio **a : b**
33b $n=2$	75%	57:43
34b $n=3$	75%	45:55



35a



	Yield **a + b**	Ratio **a : b**
35b	87%	74:26

from **15**; in both **29a** and **30a** the new bond to the spiro centre is formed by phenyl from the $Ph(CH_2)_n$ group replacing oxygen of the oxazolidine ring with retention of configuration.

For the corresponding spiro lactam products **31a** and **b** and **32a** and **b** obtained in the same way from bicyclic lactams **16** and **20**, respectively, the diastereoisomer ratio was about the same as before, between 3:1 and 4:1, but the major isomer was now the less polar component in each case. X-Ray diffraction by a single crystal of the major isomer from **20** proved the structure is **32b**.[9] The minor isomer is therefore **32a**, and the minor and major products from **16** are assigned the structures **31a** and **b**, respectively. Formation of the 6-membered carbocyclic ring in **31** and **32** has occurred prefentially with inversion of configuration at the spiro carbon in relation to that in the precursor bicyclic lactams **16** and **20**.

Although conformations in solution are not necessarily the same as those seen in the solid state, it is noteworthy that crystal structures of the less polar products **32b** and **35b** (vide infra) both show intramolecular hydrogen bonding, whereas crystal structures of the more polar products **29a** and **30a** are characterised by intermolecular hydrogen bonding. The chemical shift of the spiro carbon atom varied with the size of rings, in line with previous observations,[2] but the differences between the chemical shift values for diastereoisomeric pairs were always small and did not correlate reliably with the stereochemistry as deduced from comparisons of chromatographic behaviour (Table 2). On the other hand, comparisons of ^{1}H NMR spectra were informative in two respects. The position of the OH resonance differed in most cases by almost 1 ppm between diastereoisomeric pairs, with the resonance for the less polar (intramolecularly hydrogen bonded) compound being always at lower field. In the spectrum of one compound in each pair, which was always the less polar component and the one to which we have assigned stereochemistry involving retention of configuration in forming the spiro centre, signals for two aromatic hydrogens are deshielded, with a complex splitting pattern. These signals are assigned to (one each) *ortho* and *meta* hydrogens of the side chain phenyl group, which is consistent with the absence of corresponding signals in the spectra of either isomeric spiro lactam **35a** and **b** derived from (*S*)-valinol (vide infra).

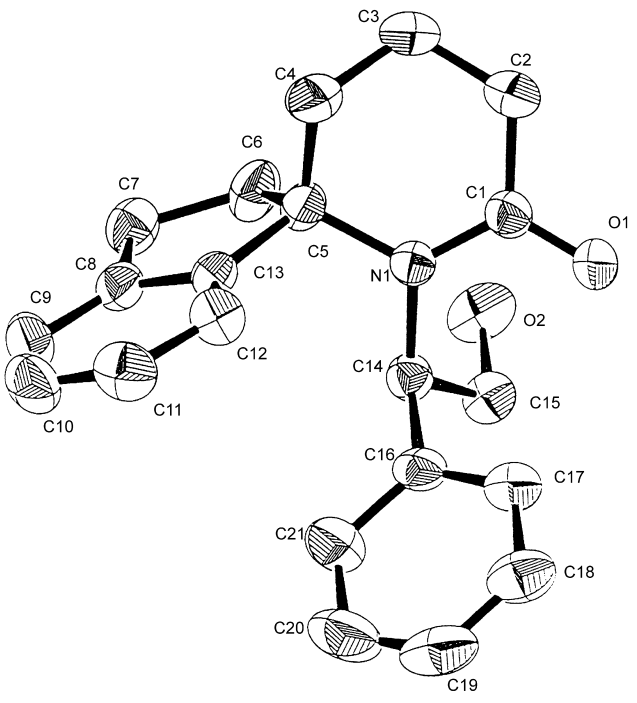


Figure 1. ORTEP drawing of the crystal structure of spiro lactam **30a** with crystallographic numbering scheme (hydrogen atoms omitted).

For spiro cyclisation of the phthalimide-derived tricyclic lactams **24** and **25**, the diastereoselectivity was low. Nevertheless, using comparisons of chromatographic behaviour between diastereoisomeric products, we are able to determine which product has which structure. The major product of the pair **33a** and **b** (with the 5,5-spiro ring system) was the more polar component and its structure is therefore **33a** (formed with retention of configuration at the spiro centre). Conversely, the major product of the pair **34a** and **b** (with the 6,5-spiro ring system) was the less polar component and its structure is therefore, **34b** (formed with inversion of configuration at the spiro carbon). These assignments are also consistent with differences between ^{1}H NMR spectra of diastereoisomeric product pairs in respect of both criteria (OH resonance and deshielded aromatic hydrogen resonances, see Table 2) discussed above.

Bicyclic lactams **6** react with nucleophiles at the 7a-position, with opening of the oxazolidine ring. The stereoselectivity of these reactions depends on several factors. Reduction of **6** (R=Pr, Bu, Ph, $PhCH_2$) by alane or by triethylsilane catalysed by $TiCl_4$ gives pyrrolidines **36** or pyrrolidinones **37** with high diastereoselectivity, the result of retention of configuration.[11] On the other hand, reaction of **6** (R=H) with allyltrimethylsilane in the presence of $TiCl_4$ gives predominantly **37** (R=allyl) by inversion of configuration; allylation of **6** (R=Me) gives a similar result, with inversion preferred over retention by a

Table 2. Comparisons between spiro lactam products

Compound	Ring size[a]	Relative polarity	Yield (%)	δ spiro C	δ OH	δ aryl H
29a	5,5	More	72.6	77.5	4.3	6.5–7.2
29b	5,5	Less	19.9	77.3	4.9	7.1–7.5
30a	6,5	More	67.3	74.7	4.1[b]	6.5–7.3
30b	6,5	Less	21.2	74.3	5.1	7.1–7.3
31a	5,6	More	18.3[c]	69.5	4.3[b]	6.4–7.3
31b	5,6	Less	72.1[c]	69.6	5.2	7.1–7.4
32a	6,6	More	24.9	66.2	4.2[b]	6.4–7.3
32b	6,6	Less	74.3	66.4	5.1	7.0–7.5
33a	5,5	More	43.0	78.4	4.4	6.1–7.8
33b	5,5	Less	32.0	78.4	5.0	6.8–8.0
34a	5,6	More	33.5	68.3	4.1	6.1–7.9
34b	5,6	Less	41.5	70.1	5.3	6.8–8.0
35a	5,5	More	64.2	76.2	4.5	7.3 (s)
35b	5,5	Less	22.4	76.2	5.0	7.3 (s)

[a] Lactam, carbocycle.
[b] OH signal overlapped by signals for C*H*C*H*$_2$OH between δ 3.9–4.4.
[c] Yields 19.8 and 78.4%, respectively, corrected for recovery of 8% unreacted **16**.

factor of 10.[11] However, this stereoselectivity is reversed by a bulkier 3-substituent; for example, for allylation of **18** the diastereoisomer ratio is 1:2 for pyrrolidinones formed by inversion or retention, respectively.

In the light of Meyers's results, we changed the 3-phenyl group in **15** for isopropyl in **17** to see what effect, if any, this might have on the diastereoselectivity of cyclisation to spiro lactams. Rearrangement of **17** catalysed by $AlCl_3$ afforded a 3:1 mixture of diastereoisomeric spiro lactams **35a** and **b**, in which the more polar (slower running) component was the major isomer **35a**. The crystal structure of the minor isomer **35b** was determined by X-ray analysis (Fig. 2), which shows the same intramolecular hydrogen bond and inversion of configuration at the spiro centre as in **32b**. In this system, in contrast to that studied by Meyers,[11] the change of 3-substituent has almost no effect on the diastereoselectivity. This may be attributable to the fact that, for the internal nucleophile involved in spiro cyclisation, the freedom of movement to approach the reaction centre is restricted. We have modelled the cyclisation step, assuming that the oxazolidine ring is opened to give an *N*-acyliminium ion intermediate **38**, in which the conformation of the *N*-substituent is ordered through the C=O group coordinating to aluminium. This confirms that cyclisation with retention of configuration to form a 5-membered ring is preferred, in agreement with our experimental findings, but the model does not indicate a clear preference for inversion vs. retention of configuration for formation of a 6-membered ring.

A further variation in the substitution pattern of the oxazolidine ring of the bicyclic lactam precursors led to an unexpected result. The bicyclic lactam **39** was prepared from (1*R*,2*S*)-norephedrine and keto acid **9**. (^{1}H and ^{13}C

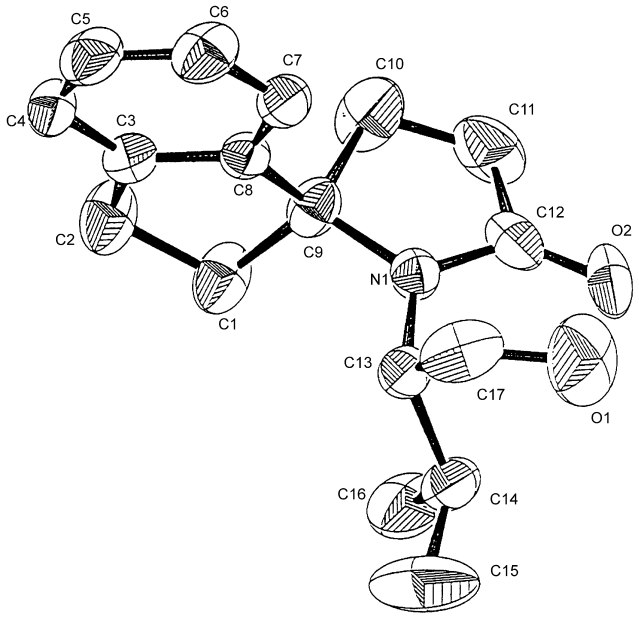
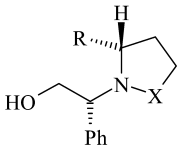
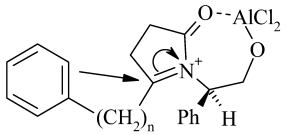


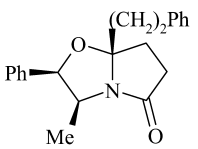
Figure 2. ORTEP drawing of the crystal structure of spiro lactam **35b** with crystallographic numbering scheme (hydrogen atoms omitted).



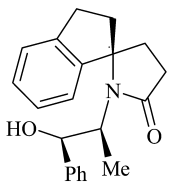
36 X = CH_2
37 X = C=O



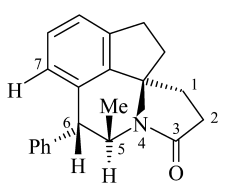
38



39



40



41

NMR spectra of **39** indicated the presence of 3% of the 7a-epimer.) We expected **39** to be cyclised to spiro lactam **40**, the major product being the result of retention of configuration as for all the other spiro indenes. However, the product obtained in 44% yield from treatment of **39** with $AlCl_3$ showed no IR or ^1H NMR absorption for an OH group, and the ^{13}C NMR spectrum included signals for four (instead of three) substituted aromatic carbons as well as for the quaternary spiro carbon. The tetracyclic structure **41** for this product is compatible with all the spectroscopic evidence. The spiro carbon must have the (*S*)-configuration (from **40**) and C-5 must have the (*S*)-configuration (from norephedrine), but the configuration at the benzylic position (C-6) is apparently inverted in the process of intramolecular Friedel–Crafts substitution in **40** catalysed by $AlCl_3$. A Dreiding model of structure **41** shows a conformationally rigid piperidine ring with the methyl group in a *pseudo*-axial position. With the phenyl group also *pseudo*-axial, the dihedral angle between bonds to H-5 and H-6 is ca. 60° and the bonds to H-6 and H-7 are nearly coplanar. This accounts for the small coupling constant (J=1.7 Hz) between H-5 and H-6 and for the strong NOE interactions observed between H-5 and H-6 and between H-6 and H-7.

In conclusion, our results demonstrate the efficient formation of a range of spiro lactams by intramolecular reaction of *N*-acyliminium ion intermediates with a tethered arene nucleophile. Stereochemistry, established by X-ray analysis of four spiro lactams, has been correlated with comparisons of chromatographic behaviour and spectroscopic properties between pairs of diastereoisomeric products. Although the diastereoselectivity is only ca. 3:1, diastereoisomeric products are cleanly separable. This paves the way towards the preparation of enantio-pure spiro lactams by removal of the side chain from nitrogen.[17]

3. Experimental

IR Spectra were recorded on Pye-Unicam SP3-200 or Perkin Elmer 1420 spectrophotometers; only those absorptions appropriate to recognise functional groups are reported. NMR Spectra were recorded at 90 MHz for ^1H (22.5 MHz for ^{13}C) on JEOL FX90Q or at 270 MHz for ^1H (67.5 MHz for ^{13}C) on JEOL FX270 or at 300 MHz for ^1H (75 MHz for ^{13}C) on Bruker MSL300 spectrometers for solutions in deuteriochloroform (unless otherwise stated) with tetramethylsilane as internal standard. Assignments of ^{13}C NMR signals were assisted by use of DEPT spectra. In ^{13}C NMR spectra lines enclosed in | | are assigned to the minor diastereoisomer of a pair. Mass spectra were obtained by electron impact at 70 eV on a VG Autospec spectrometer; high resolution spectra were obtained in EI mode or in CI mode using ammonia. Chromatographic separations were performed on MN-silica (230–400 mesh). THF and diethyl ether were dried before use. Light petroleum refers to the fraction bp 40–60 °C (unless otherwise stated). DCM refers to dichloromethane and DCE to 1,2-dichloroethane.

3.1. General procedure for keto acids 9–12

The Grignard reagent freshly prepared in THF was added slowly to the acid anhydride in THF with stirring, which was continued for 3 h. The mixture was poured into dilute sulfuric acid and extracted with ether. The ether extract was extracted with saturated aqueous $NaHCO_3$. The aqueous layer was reacidifed with dilute sulfuric acid and extracted with chloroform. The chloroform extract was dried with $MgSO_4$, filtered, and the solvent evaporated. The residue was purified by chromatography on silica. 6-Phenyl-4-oxohexanoic acid **9** thereby obtained from 2-phenylethyl magnesium bromide and succinic anhydride; mp 88–89 °C (from toluene–light petroleum) (lit.[18] 89 °C). 7-Phenyl-4-oxoheptanoic acid **10** from 3-phenylpropyl magnesium bromide and succinic anhydride, 7-phenyl-5-oxoheptanoic acid **11** from 2-phenylethyl magnesium bromide and glutaric anhydride, and 8-phenyl-5-oxooctanoic acid **12** from 3-phenylpropyl magnesium bromide and glutaric anhydride were all oils, with IR, ^1H NMR and mass spectra consistent with the structures assigned.

3.2. General procedure for bicyclic lactams obtained via keto acids

Equimolar quantities of the appropriate keto acid and (*R*)-(−)-phenylglycinol were dissolved in toluene and heated under reflux for 22–24 h in a Dean–Stark apparatus for azeotropic removal of water. The solution was cooled and toluene removed by evaporation in vacuo. The residue was chromatographed on silica, from which the bicyclic lactam product was eluted with ethyl acetate–chloroform (1:4 v/v).

3.2.1. (3*R*,7a*S*)-3-Phenyl-7a-(2-phenylethyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5-one 15. The title compound was obtained from keto acid **9** (0.38 g) and (*R*)-phenylglycinol (0.25 g), yield 0.433 g (76.5%), mp 113–114 °C (from toluene–light petroleum); HREIMS found M^+ 307.1574. $C_{20}H_{21}NO_2$ requires M 307.1572; IR ν_{max}/cm^{-1} ($CHCl_3$) 1710 (C=O); ^1H NMR (270 MHz) δ 1.83–2.07 (2H, m, CH_2), 2.22 (1H, dt, J=13.5, 10.1 Hz), 2.35–2.47 (1H, m), 2.57–2.73 (3H, m, CH_2 and H-3), 2.87 (1H, dt, J=17.3, 9.9 Hz), 4.12 (1H, dd, J=7.1, 8.7 Hz), 4.66 (1H, t, J=8.5 Hz), 5.22 (1H, t, J=7.6 Hz) and 7.03–7.37 (10H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 30.4 (CH_2), 31.0 (CH_2), 33.2 (CH_2), 38.2 (CH_2), 57.6 (CH), 72.7 (CH_2), 102.3 (C-7a), 125.5 (2×CH), 126.1 (CH), 127.4 (CH), 128.2 (2×CH), 128.5 (2×CH), 128.7 (2×CH), 139.9 (C), 140.9 (C) and 179.2 (C=O); MS m/z 307 (M^+, 2%), 277, (1), 248 (1) and 202 ($M-(CH_2)_2Ph$, 100).

3.2.2. (3*R*,7a*S*)-3-Phenyl-7a-(3-phenylpropyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5-one 16. The title compound was obtained from keto acid **10** (0.50 g) and (*R*)-phenylglycinol (0.25 g), yield 0.312 g (54%), viscous oil; HREIMS found M^+ 321.1729. $C_{21}H_{23}NO_2$ requires M 321.1729; IR ν_{max}/cm^{-1} ($CHCl_3$) 1710 (C=O); ^1H NMR (90 MHz) δ 1.66–1.85 (4H, m, 2×CH_2), 2.00–2.88 (6H, m, 3×CH_2), 3.99 (1H, dd, J=7.1, 8.6 Hz, H-3), 4.55 (1H, t, J=8.4 Hz), 5.15 (1H, apparent t, J=7.7 Hz) and 7.02–7.35 (10H, m aryl H); ^{13}C NMR (22.5 MHz) δ 25.7 (CH_2), 30.8 (CH_2), 33.2 (CH_2), 35.6 (CH_2), 35.8 (CH_2), 57.5 (CH), 72.6 (CH_2), 102.4 (C-7a), 125.5 (2×CH), 125.9 (CH), 127.3 (CH), 128.3 (3×CH), 128.6 (2×CH), 140.0 (C), 141.6 (C) and 179.8 (C=O); MS m/z 321 (M^+, <1%), 264 (1), 230 (1), 217 (7), 202 ($M-(CH_2)_3Ph$, 100) and 91 (47).

3.2.3. (3*R*,7a*S*)-3-(1-Methylethyl)-7a-(2-phenylethyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5-one 17. The title compound was obtained from keto acid **9** (0.51 g) and (*S*)-valinol (0.255 g), yield 0.377 g (56%), viscous oil; HREIMS found M^+ 273.1730. $C_{17}H_{23}NO_2$ requires *M* 273.1729; IR ν_{max}/cm^{-1} ($CHCl_3$) 1710 (C═O); ^1H NMR (270 MHz) δ 0.88 (3H, d, *J*=6.6 Hz, CH_3), 1.08 (3H, d, *J*=6.6 Hz, CH_3), 1.63 (1H, m), 1.90–2.81 (8H, m, 4×CH_2), 3.63 (1H, dt, *J*=7.1, 10.6 Hz, H-3), 3.81 (1H, dd, *J*=6.6, 8.9 Hz), 4.22 (1H, apparent t, *J*=8.6 Hz) and 6.88–7.46 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 18.9 (CH_3), 20.8 (CH_3), 30.6 (CH_2), 30.7 (CH_2), 33.0 (CH_2), 34.0 (CH), 39.0 (CH_2), 61.7 (CH), 70.9 (CH_2), 101.8 (C-7a), 126.1 (CH), 128.1 (2×CH), 128.5 (2×CH), 141.0 (C) and 179.4 (C═O); MS *m*/*z* 273 (M^+, 1%), 230 (1), 217 (1), 188 (2), 174 (24), 168 (M−$(CH_2)_2$Ph 100), 100 (16) and 91 (24).

3.2.4. (3*R*,7a*S*)- and (3*R*,7a*R*)-3-Phenyl-8a-(2-phenylethyl)-2,3,6,7,8,8a-hexahydrooxazolo[3,2-*a*]pyridin-5(5*H*)-one 19a and b. The title compounds were obtained from keto acid **11** (0.82 g) and (*R*)-phenylglycinol (0.50 g), yield 0.84 g (71.5%), viscous oil; diastereoisomer ratio 80:20 of **19a**:**19b** from ^{13}C NMR spectrum; ^1H NMR (90 MHz) δ 1.50–2.80 (10H, m, 5×CH_2), 3.90 (1H, apparent t, *J*=8.4 Hz, H-3), 4.52 (1H, apparent t, *J*=8.6 Hz), 5.37 (1H, apparent t, *J*=8.4 Hz) and 7.09–7.42 (10H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 16.8 (CH_2), |17.0 (CH_2)|, |30.0 (CH_2)|, 30.5 (CH_2), 30.7 (CH_2), 31.1 (CH_2), |36.3 (CH_2)|, 36.5 (CH_2), 58.8 (CH), |59.1 (CH)|, 69.5 (CH_2), |71.4 (CH_2)|, |95.0 (C-8a)|, 95.8 (C-8a), 125.5 (2×CH), 126.1 (CH), 126.3 (CH), 127.2 (CH), 127.4 (CH), 128.2 (2×CH), 128.6 (3×CH), 139.8 (C), 141.1 (C), |141.7 (C)|, |167.5 (C═O)| and 170.0 (C═O); MS *m*/*z* 321 (M^+, <1%), 251 (8), 216 (M−$(CH_2)_2$Ph, 100) and 120 (24).

3.2.5. (3*R*,7a*S*)- and (3*R*,7a*R*)-3-Phenyl-8a-(3-phenylpropyl)-2,3,6,7,8,8a-hexahydrooxazolo[3,2-*a*]pyridin-5(5*H*)-one 20a and b. The title compounds were obtained from keto acid **12** (0.80 g) and (*R*)-phenylglycinol (0.47 g), yield 0.82 g (71.5%), viscous oil; diastereoisomer ratio 83:17 of **20a**:**20b** from ^{13}C NMR spectrum; ^1H NMR (90 MHz) δ 1.36–1.90 (6H, m, 3×CH_2), 2.05–2.73 (6H, m, 3×CH_2), 3.67 (1H, dd, *J*=8.0, 8.9 Hz, H-3), 4.39 (1H, apparent t, *J*=8.6 Hz), 5.30 (1H, apparent t, *J*=7.7 Hz) and 7.10–7.35 (10H, m, aryl H); ^{13}C NMR (22.5 MHz) δ |14.2 (CH_2)|, 16.5 (CH_2), 25.5 (CH_2), |29.7 (CH_2)|, |30.2 (CH_2)|, 30.6 (CH_2), 30.7 (CH_2), |33.4 (CH_2)|, 33.8 (CH_2), 35.3 (CH_2), 58.2 (CH), |58.7 (CH)|, 69.0 (CH_2), |70.9 (CH_2)|, |94.9 (C-8a)|, 95.6 (C-8a), 125.4 (2×CH), 125.6 (CH), |125.8 (CH)|, 126.1 (2×CH), |127.1 (CH)|, 127.9 (CH), 128.1 (3×CH), 128.3 (2×CH), 139.8 (C), 141.4 (C), |167.1 (C═O)| and 169.5 (C═O); MS *m*/*z* 335 (M^+, 1%), 264 (1), 216 (M−$(CH_2)_3$Ph, 100) and 120 (20).

3.2.6. (2*R*,3*S*,7a*R*)-3-Methyl-2-phenyl-7a-(2-phenylethyl)-2,3,7,7a-tetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one 39. The title compound was obtained from keto acid **9** (0.53 g) and (*1R,2S*)-norephedrine (0.39 g), yield 0.42 g (50%), viscous oil; IR ν_{max}/cm^{-1} ($CHCl_3$) 1715 (C═O); ^1H NMR (270 MHz) δ 0.85 (3H, d, *J*=7.3 Hz, CHCH_3), 2.04–3.03 (8H, m, 4×CH_2), 4.50 (1H, m, C*H*CH_3), 5.03 (1H, d, *J*=5.6 Hz, C*H*Ph) and 7.20–7.44 (10H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 15.6 (CH_3), 30.4 (CH_2), 32.6 (CH_2), 33.2 (CH_2), 40.8 (CH_2), 55.2 (CH), 82.0 (CH), 100.6 (C-7a), 126.1 (2×CH), 127.8 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.6 (CH), 136.5 (C), 141.3 (C) and 178.6 (C═O); MS *m*/*z* 321 (M^+, <1%), 303 (<1), 232 (<1), 215 (100), 186 (10), 124 (65), 117 (15) and 91 (30). Additional lines in the ^1H NMR spectrum due to *ca* 4% of the 7a-epimer δ 1.02 (3H, d, *J*=6.9 Hz, CHCH_3), 4.10 (1H, m, C*H*CH_3) and 5.46 (1H, d, *J*=7.6 Hz, C*H*Ph).

3.3. (*R*)-*N*-(2-Hydroxy-1-phenylethyl)-succinimide 21 and -phthalimide 22

The succinimide **21** was prepared following the literature procedure for the (*S*)-enantiomer,[19] but using (*R*)-phenylglycinol; yield 59% of a viscous oil, ^1H NMR spectrum in agreement with lit.[19] The phthalimide **22** was prepared from phthalic anhydride (0.27 g) and (*R*)-phenylglycinol (0.25 g), which were mixed and heated at 140–150 °C for 4 h. The mixture was cooled and dissolved in chloroform (40 mL), then extracted successively with dilute sulfuric acid (1 M, 2×20 mL), aqueous sodium bicarbonate (2×20 mL) and water (2×20 mL), dried ($MgSO_4$), and the solvent evaporated in vacuo. The residue was chromatographed on silica from which ethyl acetate–chloroform (1:4 v/v) eluted the phthalimide **22** (0.49 g, 100%), mp 64–66 °C (toluene–light petroleum); HREIMS found MH^+ 268.0980. $C_{16}H_{14}NO_3$ requires 268.0974; ^1H and ^{13}C NMR and mass spectra in agreement with those reported for **22**, which was obtained previously as an oil.[20]

3.4. Bicyclic/tricyclic lactams obtained via imides

An excess of the Grignard reagent freshly prepared from 2-phenylethyl bromide (1.1 g) and magnesium (0.15 g) in THF was added to the succinimide **21** (0.44 g) in THF with stirring. After aqueous work up and extraction of the product into ether, which was dried ($MgSO_4$) and evaporated, the crude hydroxy lactam was redissolved in DCM (10 mL) and added dropwise to TFA (1.6 mL) in DCM (25 mL) cooled at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 1 h before addition of saturated aqueous ammonium chloride (100 mL) and extraction with chloroform (2×20 mL). The extract was dried ($MgSO_4$) and the chloroform evaporated in vacuo. The residue was chromatographed on silica, eluting with ethyl acetate–chloroform (1:4 v/v) to afford the bicyclic lactam **15** (0.24 g, 21% based on (*R*)-phenylglycinol), identical with the sample obtained above. In the same way starting from 3-phenylpropyl bromide and succinimide **21**, the bicyclic lactam **16** was obtained (20% based on (*R*)-phenylglycinol), identical with the sample obtained via keto acid **10**.

3.4.1. 2-(2-Hydroxy-1(*R*)-phenylethyl)-3(*R*)-hydroxy-3-(2-phenylethyl)-2,3-dihydroisoindol-1(1*H*)-one 23. The Grignard reagent was prepared from 2-phenylethyl bromide (1.50 g) and magnesium (0.20 g) in THF and added rapidly with stirring to phthalimide **22** (0.49 g) in THF (20 mL) at 0 °C. After evaporation of the solvent, the crude product was chromatographed on silica, eluting with ethyl acetate–chloroform (1:4 v/v) to give the lactam **23** (0.40, 59%) as a viscous oil; HREIMS found M^+ 373.1678. $C_{24}H_{23}NO_3$ requires *M* 373.1678; ^1H NMR (270 MHz) δ 1.57 (2H,

apparent quint, J=12.6, 5.1 Hz, CH_2), 1.94 (1H, td, J=13.8, 4.8 Hz), 2.14 (1H, td, J=12.6, 7.6 Hz), 3.69 (1H, dd, J=10.5, 3.8 Hz, CHPh), 4.59–4.80 (2H, m, CH_2OH), 5.42 (1H, s, OH), 6.31 (2H, m, aryl H), 7.01 (2H, m, aryl H) and 7.30–7.60 (10H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 29.8 (CH_2), 38.5 (CH_2), 58.8 (CH), 62.8 (CH_2), 91.9 (C-3), 121.7 (CH), 123.2 (CH), 125.7 (CH), 128.0 (5×CH), 128.6 (2×CH), 128.8 (2× CH), 129.5 (CH), 131.5 (C), 132.7 (CH), 138.9 (C), 140.5 (C), 146.4 (C) and 168.9 (C=O); MS m/z 373 (M^+, 10%), 355 (13), 342 (21), 250 (16), 237 (18), 130 (10), 106 (36), 91 (100) and 77 (14).

3.4.2. 2-(2-Hydroxy-1(*R*)-phenylethyl)-3(*R*)-hydroxy-3-(3-phenylpropyl)-2,3-dihydroisoindol-1(1*H*)-one 24. The title compound was obtained in the same way starting from 3-phenylpropyl bromide (1.48 g), magnesium (0.18 g) and phthalimide **22** (0.52 g); yield 0.45 g (65%) of a viscous oil; HREIMS found MH^+ 388.1915. $C_{25}H_{26}NO_3$ requires 388.1913; ^{1}H NMR (270 MHz) δ 0.55–0.72 (2H, m, CH_2), 1.22–2.05 (4H, m, 2×CH_2), 3.75 (1H, dd, J=10.6, 4.0 Hz, CHPh), 4.22 br (1H, s, OH), 4.61 (1H, dd, J=10.2, 4.3 Hz), 4.75 Br (1H, apparent t, J=10.6 Hz) overlapping 4.80 (1H, s, OH), 6.64 (2H, dd, J=5.6, 2.0 Hz, H-4 and H-7), 7.02–7.14 (3H, m, aryl H), 7.27–7.41 (5H, m, aryl H) and 7.46–7.55 (4H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 25.7 (CH_2), 35.4 (CH_2), 36.3 (CH_2), 59.0 (CH), 63.2 (CH_2), 92.3 (C-3), 122.0 (CH), 123.4 (CH), 125.9 (CH), 128.2 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.7 (2×CH), 129.0 (2×CH), 129.7 (CH), 131.6 (C), 132.8 (CH), 139.0 (C), 141.7 (C), 146.7 (C) and 169.1 (C=O); MS m/z 388 (MH^+, 75%), 370 (9), 340 (100), 278 (10), 250 (25), 106 (27) and 91 (13).

3.4.3. (*R*)-3-Phenyl-(*S*)-9b-(2-phenylethyl)-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-5-one 25 and 2-[(*R*)-(2-hydroxy-1-phenylethyl)]-3-(2-phenylethylidene)-2,3-dihydroisoindol-1(1*H*)-one 27. Hydroxy lactam **23** (0.18 g) in dry DCM (5 mL) was added slowly with stirring to TFA (0.11 g) in DCM cooled to 0 °C. The solution was stirred for 1 h as it warmed to room temperature, then poured into saturated aqueous sodium bicarbonate. The organic phase was separated and the aqueous layer reextracted with chloroform (2×10 mL). The extracts were combined, dried ($MgSO_4$), and the solvent evaporated. The residue was chromatographed on silica, eluting with ethyl acetate–chloroform (1:4 v/v). Lactam **25** (135 mg, 74%) was obtained as a viscous oil; HREIMS found M^+ 373.1682. $C_{24}H_{23}NO_3$ requires M 373.1678; ^{1}H NMR (270 MHz) δ 1.53 and 1.62 (each 1H, overlapping dt, J=12.4, 5.3 Hz, CH_2), 1.94 and 2.14 (each 1H, distorted dt, J=12.4, 5.3 Hz, CH_2), 2.53 br (1H, s, OH), 3.69 and 4.62 (each 1H, dd, J=9.0, 4.0 Hz, CH_2OH) overlapping 4.75 br (1H, t, J=9.0 Hz, CHPh), 5.43 (1H, s, OH), 6.28–6.32 (2H, m, aryl H), 7.00–7.03 (3H, m, aryl H), 7.31–7.39 (4H, m, aryl H) and 7.47–7.60 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 29.8 (CH_2), 38.5 (CH_2), 58.8 (CH), 62.8 (CH_2), 91.9 (C-3), 121.0 (CH), 123.2 (CH), 125.7 (CH), 128.0 (5×CH), 128.6 (2×CH), 128.8 (2×CH), 129.5 (CH), 131.5 (C), 132.7 (CH), 138.9 (C), 140.5 (C), 146.4 (C) and 168.9 (C=O); MS m/z 373 (M^+, <1%), 342 (M−CH_2OH, 21), 250 (16), 237 (18), 130 (10), 106 (36), 91 (100) and 77 (13). Later fractions eluted from the column afforded the enamide **27** (9 mg, 5%) as a white solid, mp 158–159 °C (from toluene–light petroleum); HREIMS found M^+ 355.1581. $C_{24}H_{21}NO_2$ requires M 355.1572; ^{1}H NMR (270 MHz) δ 3.86 and 3.94 (each 1H, overlapping dd, J=17.0, 7.8 Hz, CH_2OH), 4.18–4.32 (2H, m, CH_2Ph), 4.48–4.59 (1H, br, OH), 5.25 (1H, dd, J=3.7, 7.8 Hz, alkene CHCH$_2$), 5.60 (t, J=7.8 Hz, alkane CHCH$_2$), 6.99 (1H, dd, J=7.3, 1.6 Hz, aryl H), 7.15–7.35 (7H, m, aryl H), 7.48 (2H, m, aryl H), 7.79 (1H, d, J=7.3 Hz, aryl H) and 7.94 (1H, dd, J=6.6, 1.5 Hz, aryl H); ^{13}C NMR (67.5 MHz) δ 33.2 (CH_2), 61.0 (CH), 64.0 (CH_2), 113.2 (CH), 123.2 (CH), 123.7 (CH), 126.5 (CH), 126.7 (2×CH), 127.6 (CH), 128.0 (2×CH), 128.6 (2×CH), 128.8 (2×CH), 129.0 (CH), 130.1 (C), 132.4 (CH), 135.3 (C), 135.9 (C), 137.7 (C), 139.2 (C) and 168.2 (C=O); MS m/z 355 (M^+, 4%), 324 (M−CH_2OH, 27), 264 (15), 246 (14), 236 (19), 234 (22), 232 (27), 189 (12), 165 (12), 130 (30), 103 (30), 91 (100) and 77 (30).

3.4.4. (*R*)-3-Phenyl-(*S*)-9b-(3-phenylpropyl)-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-5-one 26 and 2-[(*R*)-(2-hydroxy-1-phenylethyl)]-3-(3-phenylpropylidene)-2,3-dihydroisoindol-1(1*H*)-one 28. These were prepared in the same way starting from hydroxy lactam **24** (0.36 g) treated with TFA (0.21 g) in DCM, followed by work up and chromatography. Lactam **26** (266 mg, 77%); white solid, mp 107–108 °C (toluene–light petroleum); HREIMS found MH^+ 388.1915. $C_{25}H_{26}NO_3$ requires 388.1913; ^{1}H NMR (270 MHz) δ 0.58–0.75 (2H, m, CH_2), 1.65–2.05 (4H, m, 2×CH_2), 3.75 and 4.61 (each 1H, dd, J=10.6, 4.0 Hz, CH_2OH), 4.22 br (1H, s, OH), 4.75 br (1H, t, J=10.6 Hz, CHPh) overlapping 4.80 (1H, s, OH), 6.63 (2H, dd, J=7.5, 1.8 Hz, H-4 and H-7), 7.02–7.14 (2H, m, aryl H), 7.27–7.40 (5H, m, aryl H) and 7.46–7.54 (5H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 25.7 (CH_2), 35.4 (CH_2), 36.3 (CH_2), 59.0 (CH), 63.2 (CH_2), 92.3 (C-3), 122.0 (CH), 123.4 (CH), 125.9 (CH), 128.2 (CH), 128.3 (2×CH), 128.4 (2×CH), 128.7 (2×CH), 129.0 (2×CH), 129.7 (CH), 131.6 (C), 132.8 (CH), 139.0 (C), 141.7 (C), 146.7 (C) and 169.1 (C=O); MS m/z 388 (MH^+, 75%), 370 (M−OH, 100), 340 (10), 278 (10), 250 (M−$(CH_2)_3$Ph, 25), 106 (27) and 91 (13). Enamide **28** (12 mg, 7%) obtained from later fractions; white solid, mp 117–121 °C (toluene–light petroleum); HREIMS found M^+ 369.1730. $C_{25}H_{23}NO_2$ requires M 369.1729; ^{1}H NMR (270 MHz) δ 1.25 (1H, m), 1.60 (1H, m), 2.01 (1H, m), 2.79 (2H, m), 4.19–4.48 (2H, m), 5.12–5.48 (2H, m) and 6.65–7.92 (14H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 29.1 (CH_2), 35.7 (CH_2), 61.0 (CH), 64.1 (CH_2), 114.1 (CH), 123.2 (CH), 123.6 (CH), 126.2 (CH), 126.7 (2×CH), 127.6 (CH), 128.4 (CH), 128.5 (CH), 128.7 (3×CH), 130.0 (C), 132.3 (CH), 135.3 (C), 137.7 (C), 140.6 (C) and 168.1 (C=O); MS m/z 369 (M^+, 5%), 338 (7), 278 (6), 250 (10), 158 (100), 103 (12) and 91 (32).

3.5. General procedure for cyclisation to spiro lactams with aluminium trichloride

The hydroxy lactam precursor dissolved in DCE was added dropwise with stirring to aluminium trichloride (typically 3–4 mol eq) in DCE at the temperature stated. An orange–brown colour developed. The mixture was stirred for 3–4 h or until analysis by tlc showed disappearance of the starting material; it was then poured onto ice, acidified by addition of dilute sulfuric acid (1 M) and extracted twice with

chloroform. The combined extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was chromatographed on silica and the products eluted with ethyl acetate–chloroform (1:4 v/v).

3.5.1. (*R*,*R*)- and (*R*,*S*)-1′-(2-Hydroxy-1-phenylethyl)-2,3-dihydrospiro[indene-1,2′-pyrrolidin]-5′-ones 29a and b. The title compound were obtained from bicyclic lactam **15** (0.31 g) and aluminium trichloride (0.40 g) in DCE at −5 °C. Elution of the column gave first unreacted **15** (3 mg, 1%), followed by the(*R*,*S*)-spiro lactam **29b** (61 mg, 20%), mp 172–173 °C (from toluene–light petroleum); found: C, 77.68; H, 6.64; N, 4.29. $C_{20}H_{21}NO_2$ requires C, 78.14; H, 6.88; N, 4.56%; IR ν_{max}/cm^{-1} ($CHCl_3$) 3340 (O–H) and 1655 (C═O); ^1H NMR (90 MHz) δ 1.86–2.04 (2H, m, CH_2), 2.09–2.37 (2H, m, CH_2), 2.62–2.85 (4H, m, 2×CH_2), 4.04 (3H, m, CH_2CH), 4.88 (1H, br s, OH) and 7.10–7.52 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 29.2 (CH_2), 30.6 (CH_2), 35.0 (CH_2), 36.7 (CH_2), 61.1 (CH), 65.8 (CH_2), 77.3 (C), 122.9 (CH), 125.4 (CH), 127.3 (2×CH), 127.6 (CH), 128.5 (2×CH), 128.7 (CH), 139.0 (C), 142.9 (C), 144.4 (C) and 177.5 (C═O); MS *m*/*z* M^+ absent, 289 (M−H_2O, 1), 277 (M−CH_2O, 100), 276 (61), 188 (19), 143 (34) and 106 (67). Further elution of the column afforded the (*R*,*R*)-spiro lactam **29a** (223 mg, 73%), mp 195–196 °C (toluene–light petroleum); IR ν_{max}/cm^{-1} ($CHCl_3$) 3350 br (O–H) and 1652 (C═O); ^1H NMR (90 MHz) δ 2.06–2.46 (4H, m, 2×CH_2), 2.53–2.78 (2H, m, CH_2), 2.87–3.12 (2H, m, CH_2), 3.74–4.10 (3H, m, CH_2CH), 4.33 (1H, br t, OH), 6.45 (1H, d, *J*=7.9 Hz, *o*-ArH), 6.71–6.89 (1H, m, *m*-ArH) and 7.02–7.16 (7H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 29.4 (CH_2), 31.0 (CH_2), 35.0 (CH_2), 35.7 (CH_2), 61.8 (CH), 65.3 (CH_2), 77.5 (C), 124.6 (CH), 124.7 (CH), 126.4 (CH), 127.2 (CH), 127.9 (2×CH), 128.1 (2×CH), 128.5 (CH), 139.1 (C), 142.9 (C), 143.1 (C) and 177.1 (C═O); MS *m*/*z* M^+absent, 289 (M−H_2O, 1), 277 (M−CH_2O, 100), 276 (86), 188 (30), 143 (43), 128 (33) and 106 (97).

3.5.2. (*R*,*R*)- and (*R*,*S*)-1′-(2-Hydroxy-1-phenylethyl)-2,3-dihydrospiro[indene-1,2′-piperidin]-6′-ones 30a and b. The title compound were obtained from the bicyclic lactam **19** (0.33 g) and aluminium trichloride (0.54 g) in DCE at room temperature. Elution of the column gave first the (*R*,*R*)-spiro lactam **30b** (70 mg, 21%), semi-solid; HREIMS found M^+ 321.1721. $C_{21}H_{23}NO_2$ requires *M* 321.1729; ^1H NMR (90 MHz) δ 1.78–2.37 (6H, m, 3×CH_2), 2.62–2.90 (4H, m, 2×CH_2), 3.95–4.30 (3H, m, CH_2CH), 5.11 (1H, br s, OH) and 7.08–7.33 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 17.8 (CH_2), 29.0 (CH_2), 33.9 (CH_2), 35.8 (CH_2), 36.8 (CH_2), 63.7 (CH), 65.8 (CH_2), 74.8 (C), 123.3 (CH), 125.6 (CH), 126.7 (CH), 126.9 (2×CH), 127.3 (CH), 128.2 (2×CH), 128.6 (CH), 137.9 (C), 141.9 (C), 145.7 (C) and 173.4 (C═O). This was followed by the (*R*,*S*)-spiro lactam **30a** (220 mg, 67%), mp 173–174 °C (toluene–light petroleum); found: C, 78.16; H, 7.14; N, 4.19. $C_{21}H_{23}NO_2$ requires C, 78.47; H, 7.21; N, 4.36%; IR ν_{max}/cm^{-1} ($CHCl_3$) 3360 br (O–H) and 1710 (C═O); ^1H NMR (270 MHz) δ 1.23–3.06 (10H, m, 5×CH_2), 3.67 (1H, dd, *J*=7.4, 12.6 Hz, C*H*CH_2), 3.82–3.97 (1H, m,) and 4.06–4.23 (1H, m, CHCH_2), 6.48 (1H, d, *J*=7.2 Hz, *o*-ArH), 6.62 (1H, t, *J*=7.2 Hz, *m*-ArH) and 6.90–7.33 (7H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 17.7 (CH_2), 29.0 (CH_2), 33.9 (CH_2), 35.8 (CH_2), 36.8 (CH_2), 63.7 (CH), 65.8 (CH_2), 74.8 (C), 123.2 (CH), 125.6 (CH), 126.6 (CH), 126.9 (2×CH), 127.3 (CH), 128.2 (2×CH), 128.5 (CH), 137.9 (C), 141.8 (C), 145.6 (C) and 173.4 (C═O); MS *m*/*z* 321 (M^+, <1%), 303 (M−H_2O, 2), 291 (M−CH_2O, 45), 202 (32), 185 (50), 143 (36) and 106 (100).

3.5.3. (*R*,*R*)- and (*R*,*S*)-1′-(2-Hydroxy-1-phenylethyl)-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-pyrrolidin]-5′-ones 31a and b. The title compound were obtained from the bicyclic lactam **16** (325 mg) and aluminium trichloride (0.40 g) in DCE at −5 °C. Elution of the column gave first unreacted starting material **16** (26 mg, 8%), then the (*R*,*S*)-spiro lactam **31b** (234 mg, 72%), mp 176–177 °C (toluene–light petroleum); found: C, 77.93; H, 7.12; N, 4.20. $C_{21}H_{23}NO_2$ requires C, 78.47; H, 7.21; N, 4.36%; HREIMS found M^+ 321.1733. $C_{21}H_{23}NO_2$ requires *M* 321.1729; IR ν_{max}/cm^{-1} ($CHCl_3$) 3320 br (O–H) and 1655 (C═O); ^1H NMR (90 MHz) δ 1.50–1.87 (4H, m, 2×CH_2), 2.13–2.34 (2H, m, CH_2), 2.58–2.80 (4H, m, 2×CH_2), 3.79–4.25 (3H, m, CH_2CH), 5.12–5.27 (1H, m, exchangeable, OH) and 7.10–7.35 (9H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 20.1 (CH_2), 29.3 (CH_2), 29.9 (CH_2), 35.0 (CH_2), 36.6 (CH_2), 61.7 (CH), 65.8 (CH_2), 69.6 (C), 126.1 (CH), 126.8 (CH), 127.2 (CH), 127.3 (2×CH), 127.6 (CH), 128.4 (2×CH), 129.7 (CH), 138.2 (C), 139.2 (C), 139.6 (C) and 177.9 (C═O); MS *m*/*z* 321 (M^+, <1%), 291 (M−CH_2O, 67), 202 (18), 185 (22), 143 (20), 129 (22) and 106 (100). Later fractions afforded the (*R*,*R*)-spiro lactam **31a** (59 mg, 18%), mp 235–236 °C (toluene–light petroleum); IR ν_{max}/cm^{-1} ($CHCl_3$) 3360 br (O–H) and 1655 (C═O); ^1H NMR (90 MHz) ($CHCl_3$-*d*+MeOH-d_4) δ 1.72–2.92 (10H, m, 5×CH_2), 3.77–3.99 (2H, m, CH_2CH), 4.28 (1H, br, OH) overlapping 4.30 (1H, dd, *J*=8.2, 12.6 Hz, CH_2C*H*), 6.44–6.72 (2H, m, aryl H) and 6.87–7.29 (7H, m, aryl H); ^{13}C NMR (22.5 MHz) ($CHCl_3$-*d*+MeOH-d_4) δ 20.9 (CH_2), 29.8 (CH_2), 30.5 (CH_2), 32.7 (CH_2), 36.6 (CH_2), 62.5 (CH), 65.0 (CH_2), 69.6 (C), 125.6 (CH), 127.3 (2×CH), 128.0 (2×CH), 128.6 (3×CH), 129.2 (CH), 137.3 (C), 138.5 (C), 139.1 (C) and 177.7 (C═O); MS *m*/*z* 321 (M^+, <1%), 303 (M−H_2O, 1), 291 (M−CH_2O, 41), 202 (16), 185 (20) and 106 (100).

3.5.4. (*R*,*R*)- and (*R*,*S*)-1′-(2-Hydroxy-1-phenylethyl)-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-piperidin]-6′-ones 32a and b. The title compound were obtained from the bicyclic lactam **20** (0.35 g) and aluminium trichloride (0.52 g) in DCE at room temperature. Elution of the column afforded first the (*R*,*S*)-spiro lactam **32b** (260 mg, 74%), mp 113–115 °C (toluene–light petroleum); HREIMS found M^+ 335.1873. $C_{22}H_{25}NO_2$ requires *M* 335.1885; IR ν_{max}/cm^{-1} ($CHCl_3$) 3380 br (O–H) and 1720 (C═O); ^1H NMR (270 MHz) δ 1.67–2.06 (7H, m) and 2.19–2.29 (1H, m, 4×ring CH_2), 2.66–2.82 (4H, m, 2×ring CH_2), 3.80–3.95 (2H, m, CHCH_2OH), 4.17 br (1H, d, *J*=5.1 Hz, C*H*CH_2), 5.08 (1H, dd, *J*=9.8, 2.8 Hz, CH_2O*H*) and 7.09–7.37 (9H, m, aryl H); after shaking the sample with D_2O the OH signal at δ 5.08 disappeared, the signal at δ 4.17 was unchanged, and the signal for CH_2OH simplified to δ 3.84 (1H, dd, *J*=19.0, 5.1 Hz) and 3.91 (1H, dd, *J*=19.0, 1.9 Hz); ^{13}C NMR (22.5 MHz) δ 17.1 (CH_2), 20.5 (CH_2), 29.4 (CH_2), 33.3 (CH_2), 33.8 (CH_2), 38.3 (CH_2), 64.6 (CH), 65.4 (CH_2), 66.4 (C), 126.4 (CH), 126.9 (2×CH), 127.4 (CH), 127.6 (CH), 128.1 (2×CH), 129.4 (CH), 138.1 (C), 138.5 (C), 139.9 (C)

and 173.6 (C═O); MS *m/z* 335 (M^+, <1%), 317 (M−H_2O, 5), 305 (M−CH_2O, 37), 216 (16), 199 (16), 157 (18), 129 (26), 106 (100) and 91 (18). This was followed by the (*R*,*R*)-spiro lactam **32a** (87 mg, 25%), mp 98–100 °C (toluene–light petroleum). Anal. found C, 78.47; H, 7.63; N, 3.84. $C_{22}H_{25}NO_2$ requires C, 78.77; H, 7.51; N, 4.18%; IR ν_{max}/cm^{-1} ($CHCl_3$) 3360 br (O–H) and 1680 (C═O); ^{1}H NMR (90 MHz) δ 1.62–2.38 (8H, m, 4×CH_2), 2.54–2.98 (4H, m, 2×CH_2), 3.86–4.41 (4H, m, CH_2CH and OH) and 6.35–7.30 (8H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 17.4 (CH_2), 20.9 (CH_2), 29.9 (CH_2), 33.3 (CH_2), 33.6 (CH_2), 37.7 (CH_2), 66.1 (C), 66.8 (CH), 125.2 (CH), 126.4 (CH), 126.9 (CH), 127.5 (2×CH), 128.5 (3×CH), 129.2 (CH), 137.5 (C), 138.2 (C), 139.1 (C) and 173.5 (C═O); MS *m/z* 335 (M^+, <1%), 305 (M−CH_2O, 32), 216 (17), 199 (19), 129 (20) and 106 (100).

3.5.5. (*R*,*R*)- and (*R*,*S*)-2′-(2-Hydroxy-1-phenylethyl)-2,3,2′,3′-tetrahydrospiro[indene-1,1′-isoindol]-3′-ones 33a and b. The title compound were obtained from the tricyclic lactam **25** (0.17 g) and aluminium trichloride (0.19 g) in DCE at 0 °C. Elution of the column afforded first the (*R*,*R*)-spiro lactam **33b** (55 mg, 32%) as a viscous oil; HRCIMS found MH^+ 356.1651. $C_{24}H_{22}NO_2$ requires 356.1651; ^{1}H NMR (90 MHz) δ 2.27 (2H, t, *J*=7.2 Hz, CH_2), 2.97–3.18 (2H, m, CH_2), 3.95–4.25 (3H, m, C*H*C*H*$_2$OH), 4.98 br (1H, t, OH), 6.82 (1H, d, *J*=6.8 Hz, *o*-ArH), 7.02–7.13 (1H, m, *m*-ArH), 7.19–7.52 (10H, m, aryl H) and 7.88–7.98 (1H, m, aryl H); ^{13}C NMR (22.5 MHz) δ 30.6 (CH_2), 35.4 (CH_2), 61.0 (CH), 66.0 (CH_2), 78.4 (C), 121.8 (CH), 123.6 (CH), 123.8 (CH), 125.5 (CH), 127.2 (2×CH), 127.4 (CH), 127.8 (CH), 128.4 (CH), 128.6 (2×CH), 129.4 (CH), 130.1 (C), 132.7 (CH), 138.9 (C), 141.4 (C), 144.3 (C), 151.3 (C) and 170.2 (C═O); MS *m/z* 356 (MH^+, <1%), 325 (M−CH_2O, 46), 234 (26), 219 (100), 189 (16), 165 (12) and 106 (13). This was followed by the (*R*,*S*)-spiro lactam **33a** (74 mg, 43%); white solid, mp 143–145 °C (toluene–light petroleum); HRCIMS found MH^+ 356.1653. $C_{24}H_{22}NO_2$ requires 356.1651; ^{1}H NMR (270 MHz) δ 2.67 (1H, ddd, *J*=14.7, 9.4. 6.6 Hz) and 2.87 (1H, ddd, *J*=14.7, 8.9, 4.3 Hz, CH_2-2), 3.20–3.45 (2H, m, CH_2-3), 4.00 (1H, dd, *J*=11.5, 4.3 Hz) and 4.22 (1H, dd, *J*=8.3, 4.3 Hz, C*H*$_2$OH), 4.35 br (1H, s, OH), 4.68 br (1H, t, *J*=10.6 Hz, CHPh), 6.12 (1H, d, *J*=7.6 Hz, *o*-ArH), 6.63 (1H, t, *J*=7.6 Hz, *m*-ArH), 7.01–7.13 (3H, m, aryl H), 7.25–7.44 (7H, m, aryl H) and 7.77 (1H, d, *J*=7.6 Hz, aryl H); ^{13}C NMR (67.5 MHz) δ 31.4 (CH_2), 36.9 (CH_2), 62.4 (CH), 64.7 (CH_2), 78.4 (C), 122.2 (CH), 123.5 (CH), 125.1 (CH), 125.7 (CH), 127.1 (CH), 127.5 (CH), 128.2 (2×CH), 128.3 (2×CH), 128.5 (CH), 129.2 (CH), 131.4 (C), 132.7 (CH), 139.2 (C), 140.9 (C), 144.5 (C), 151.7 (C) and 169.6 (C═O); MS *m/z* 356 (M^+, <1%), 325 (M−CH_2O, 41), 324 (37), 219 (100), 191 (14), 189 (16), 165 (11) and 106 (14).

3.5.6. (*R*,*R*)- and (*R*,*S*)-2′-(2-Hydroxy-1-phenylethyl)-1,2,3,4,2′,3′-hexahydrospiro[naphthalene-1,1′-isoindol]-3′-ones 34a and b. The title compound were obtained from the tricyclic lactam **26** (164 mg) and aluminium trichloride (0.18 g) in DCE at 0 °C for 5 h. Elution of the column afforded first the (*R*,*R*)-spiro lactam **34b** (68 mg, 41.5%); white solid, mp 155–157 °C; HRCIMS found MH^+ 370.1802. $C_{25}H_{24}NO_2$ requires 370.1807; ^{1}H NMR (270 MHz) δ 1.68–2.35 (4H, m, 2×CH_2), 2.84?2.89 (2H, m, CH_2), 4.03–4.12 (2H, m, C*H*$_2$CH), 4.29 (1H, dd, *J*=5.5, 2.2 Hz, CHPh), 5.30 br (1H, s, OH), 6.77 (1H, d, *J*=7.9 Hz, aryl H), 6.99–7.10 (1H, m, aryl H), 7.18–7.33 (2H, m, aryl H), 7.43–7.50 (8H, m, aryl H) and 7.94–7.97 (1H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 20.4 (CH_2), 29.3 (CH_2), 34.6 (CH_2), 61.6 (CH), 66.2 (CH_2), 70.1 (C), 122.8 (CH), 123.9 (CH), 126.1 (CH), 127.2 (CH), 127.3 (2×CH), 127.4 (CH), 128.1 (CH), 128.2 (CH), 128.5 (2×CH), 129.8 (CH and C), 132.4 (CH), 133.7 (C), 139.0 (C), 139.2 (C), 153.3 (C) and 170.8 (C═O); MS *m/z* 369 (M^+, <1%), 339 (M−CH_2O, 100), 338 (M−CH_2OH, 42), 250 (11), 234 (38), 233 (76), 215 (35), 106 (17) and 91 (16). Further elution gave the (*R*,*S*)-spiro lactam **34a** (55 mg, 33.5%) as a viscous oil; HREIMS found MH^+ 370.1804. $C_{25}H_{24}NO_2$ requires 370.1807; ^{1}H NMR (270 MHz) δ 1.95–2.02 (1H, m) and 2.50–2.62 (1H, ddd, *J*=13.5, 10.6, 5.6 Hz, CH_2-2), 2.12–2.28 (2H, m, CH_2), 2.91–3.07 (2H, m, CH_2), 4.06 br (1H, s, OH) overlapping 4.12 (1H, dd, *J*=11.6, 4.6 Hz) and 4.31 (1H, dd, *J*=7.6, 4.6 Hz, C*H*$_2$OH), 4.55–4.62 (1H, m, CHPh), 6.11 (1H, dd, *J*=7.9, 1.0 Hz, *o*-ArH), 6.37 (1H, t, *J*=6.9 Hz, *m*-ArH) and 6.92 (1H, dd, *J*=7.6, 1.3 Hz, aryl H), 7.05–7.17 (7H, m, aryl H), 7.35–7.41 (2H, m, aryl H) and 7.81–7.85 (1H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 20.0 (CH_2), 28.6 (CH_2), 33.9 (CH_2), 61.0 (CH), 63.8 (CH_2), 68.3 (C), 121.2 (CH), 122.5 (CH), 124.6 (CH), 126.2 (CH), 126.5 (CH), 126.8 (2×CH), 126.9 (CH), 127.7 (2×CH), 128.6 (CH), 129.3 (C), 131.0 (CH), 131.3 (C), 137.7 (C), 152.6 (C) and 169.0 (C═O); MS *m/z* 369 (M^+, <1%), 351 (M−H_2O, 2), 339 (M−CH_2O, 100), 338 (M−CH_2OH, 72), 250 (8), 233 (77), 215 (55), 202 (34), 178 (16), 106 (25), 91 (37) and 77 (21).

3.5.7. (*S*,*S*)- and (*S*,*R*)-1′-(1-Hydroxy-3-methylbut-2-yl)-2,3-dihydrospiro[indene-1,2′-pyrrolidin]-5′-ones 35a and b. The title compound were obtained from the bicyclic lactam **17** (0.33 g) and aluminium trichloride (0.50 g) in DCE at −5 °C. Chromatography of the crude product afforded first the (*S*,*R*)-spiro lactam **35b** (74 mg, 22.4%); white solid, mp 142–143 °C; HREIMS found M^+ 273.1731. $C_{17}H_{23}NO_2$ requires *M* 273.1729; ^{1}H NMR (90 MHz) δ 0.98 (6H, d, *J*=6.6 Hz, 2×CH_3), 1.98–3.08 (9H, m, 4×CH_2 and CH), 3.60–3.70 br (2H, m, C*H*$_2$OH), 4.98 br (1H, s, OH) and 7.29 (4H, s, aryl H); ^{13}C NMR (22.5 MHz) δ 20.2 (CH_3), 20.9 (CH_3), 24.9 (CH), 29.5 (CH_2), 29.9 (CH_2), 35.1 (CH), 37.8 (CH_2), 62.4 (CH), 65.1 (CH_2), 76.2 (C), 123.0 (CH), 125.3 (CH), 127.2 (CH), 128.7 (CH), 142.2 (C), 144.8 (C) and 177.9 (C═O); MS *m/z* 273 (M^+, 7%), 255 (M−H_2O, 3), 242 (M−CH_2OH, 68), 188 (23), 171 (47), 143 (55), 128 (100), 115 (41) and 72 (72). Further elution gave the (*S*,*S*)-spiro lactam **35a** (212 mg, 64%); white solid, mp 125–126 °C (toluene–light petroleum). Anal. found C, 74.63; H, 8.62; N, 4.99. $C_{17}H_{23}NO_2$ requires C, 74.69; H, 8.48; N, 5.13%; ^{1}H NMR (90 MHz) δ 0.59 (3H, d, *J*=6.6 Hz, CH_3), 0.81 (3H, d, *J*=6.6 Hz, CH_3), 2.05–3.02 (9H, m, 4×CH_2 and CH), 3.78–4.10 br (2H, m, C*H*$_2$OH), 4.53 br (1H, s, OH) and 7.30 (4H, s, aryl H); ^{13}C NMR (22.5 MHz) δ 20.1 (CH_3), 20.9 (CH_3), 25.7 (CH), 30.0 (CH_2), 30.7 (CH_2), 35.0 (CH), 38.6 (CH_2), 62.6 (CH), 76.2 (C), 125.0 (CH), 125.2 (CH), 126.8 (CH), 129.2 (CH), 142.5 (C), 144.5 (C) and 176.9 (C═O); MS *m/z* 273 (M^+, 6), 255 (M−H_2O, 6), 242 (M−CH_2OH, 86), 230 (5), 188 (40), 171 (49), 143 (68), 128 (53), 115 (28), 72 (100) and 60 (27).

3.5.8. 5-Methyl-6-phenyl-1,2,5,6,10,11-hexahydrocyclopenta[*kl*]pyrrolo[2,1-*a*]isoquinolin-3(3*H*)-one 41. The title compound was obtained from the bicyclic lactam **39** (0.30 g) and aluminium trichloride (0.40 g) in DCE at 0 °C. Chromatography afforded the tetracyclic lactam **41** (125 mg, 44%) as a viscous oil; HREIMS found M^+ 303.1631. $C_{21}H_{21}NO$ requires *M* 303.1623; IR ν_{max}/cm^{-1} ($CHCl_3$) 1720 (C=O); ^1H NMR (270 MHz) δ 0.97 (3H, d, *J*=7.0 Hz, CH_3), 1.46–1.59 (1H, m), 1.89 (1H, dd) overlapping 1.92–2.00 (1H, m), 2.17 (1H, dd, *J*=11.5, 7.0 Hz), 2.36 (1H, dd, *J*=11.2, 5.6 Hz), 2.49 (1H, ddd, *J*=16.5, 12.8, 7.0 Hz), 2.75 (1H, dd, *J*=15.5, 7.3 Hz), 3.11 (1H, ddd, *J*=15.5, 11.4, 5.6 Hz), 4.02 (1H, s, H-6), 5.20 (1H, dq, *J*=7.0, 1.7 Hz, CH_3CH), 7.04 (1H, d, *J*=6.6 Hz, H-7 or H-9) and 7.16–7.31 (7H, m, aryl H); ^{13}C NMR (67.5 MHz) δ 19.5 (CH_3), 30.0 (CH_2), 31.5 (CH_2), 32.9 (CH_2), 42.3 (CH_2), 50.5 (CH), 51.8 (CH), 68.4 (C-11a), 123.7 (CH), 126.6 (CH), 127.8 (CH), 128.0 (2×CH), 128.2 (CH), 128.5 (2×CH), 132.9 (C), 140.8 (C), 142.3 (C), 142.6 (C) and 177.6 (C=O); MS *m/z* 303 (M^+, 100%), 288 ($M-CH_3$, 7), 260 (13), 232 (11), 203 (18), 128 (16) and 91 (14).

3.6. Crystallographic structure determinations

X-Ray analysis of **30a** and **35b** were carried out on a Rigaku AFC6S four-circle diffractometer with graphite-monochromated Mo Kα radiation, λ=0.710 70 at 20 °C. The structures were solved by direct methods using SHELX-76 and refined on F^2 using SHELXL. Crystal structures of **29a** and **32b** have been reported previously.[9]

3.6.1. Crystal data for 30a.[21] $C_{21}H_{23}NO_2$, *M*=321.40. The crystal size was 0.50×0.50×0.40 mm; orthorhombic, space group $P2_12_12_1$, with unit cell *a*=10.969(3), *b*=15.196(3), *c*=10.266(2) Å, *V*=1711.2(7) Å^3, *Z*=4, D_c=1.248 g cm^{-1}. 2672 reflections were collected in the range $5<2\theta<50°$, of which 2378 were independent (R_{int} 0.0161). Full matrix least squares refinement on F^2 with 219 parameters for 2378 reflections with $I>2\sigma I$ gave final values of R_1=0.0301 and wR_2=0.0721.

3.6.2. Crystal data for 35b.[21] $C_{17}H_{23}NO_2$, *M*=273.36. The crystal size was 0.50×0.30×0.20 mm; orthorhombic, space group $P2_12_12_1$, with unit cell *a*=11.915(1), *b*=18.256(4), *c*=6.915(3) Å, *V*=1504.1(7) Å^3, *Z*=4, D_c=1.207 g cm^{-1}. 3103 reflections were collected in the range $5<2\theta<50°$, of which 2651 were independent (R_{int} 0.0152). Full matrix least squares refinement on F^2 with 182 parameters for 2650 reflections with $I>2\sigma I$ gave final values of R_1=0.0425 and wR_2=0.1041.

Acknowledgements

Grateful acknowledgement is made of an ORS award to A. A. B.

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