Asymmetric Synthesis of Spiro 2-Pyrrolidin-5-ones and 2-Piperidin-6-ones

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Bicyclic lactams **14–17** are isomerised on treatment with aluminium trichloride in 1,2-dichloroethane to give spiro lactams in high yield and >3 : 1 diastereoselectivity; from the structures of **19a** and **22b** determined by X-ray crystallography, it follows that the indenes **19** and **21** are formed preferentially with retention of configuration at the spiro carbon atom and the naphthalenes **20** and **22** with inversion.

Bicyclic lactams incorporating β-amino alcohols as chiral auxiliary have been employed in various ways in asymmetric synthesis of tertiary and quaternary carbon centres.[1] The stereoselective conversion of bicyclic lactams **1** into 5-substituted 2-pyrrolidinones and pyrrolidines (Scheme 1)[2] suggested to us a new asymmetric approach to the synthesis of spiro lactams based on *N*-acyliminium ion chemistry.

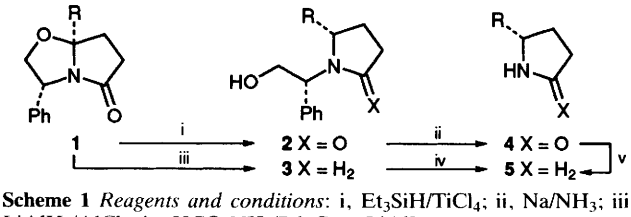
We have already seen *N*-acyliminium ion cyclisations involving an aromatic ring as π-nucleophile attached by a tether of variable length to the iminium carbon atom.[3] But this method applied to the chiral precursors **6** and **7** gave racemic spiro lactams **8** and **9**, respectively, as the major products through loss of the benzylic group. Therefore, we investigated the possibility of spiro cyclisations of fused oxazolidines **14–17** in which the bridgehead substituent R = $(CH_2)_mPh$ (m = 2 or 3) provides the π-nucleophile for intramolecular reaction with an *N*-acyliminium ion intermediate.

The 4-oxo acid **10** was heated with (*R*)-phenylglycinol to give a single product **14a**, in which the 3-phenyl and 7*a*-(3-phenylpropyl) substituents are *cis*, both on the convex face of the 5,5 bicyclic system, in line with the stereochemistry of related compounds.[1,2] The bicyclic lactam **14a** rearranged on treatment with aluminium trichloride to give a mixture of diasteroisomeric spiro lactams **19a,b**: the reaction was optimised with a 3 : 1 mole ratio of $AlCl_3$ and **14a** in 1,2-dichloroethane at −5 °C to give the results shown in Table 1. The products were separated chromatographically and the stereochemistry assigned by X-ray crystallography of the major diastereoisomer **19a** (Fig. 1),† which shows retention of configuration at the spiro carbon centre. This is the same stereochemical result as that observed for reductive ring-opening of the oxazolidine ring in **1** (Scheme 1).[2]

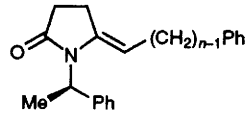
The homologous 4-oxo acid **11** similarly afforded the bicyclic lactam **15a**, which on treatment with aluminium trichloride gave a similar mixture of diastereoisomeric spiro lactams **20a,b**. However, in this case the minor product is the more polar (lower R_f value), whereas in the previous case the major product **19a** was more polar than the minor product **19b**. This and other evidence, in particular the crystal structure of another spiro naphthalene **22b** (Fig. 2), leads us to the surprising conclusion that the major product from **15a** is, in fact, **20b** in which the spiro centre has been formed with inversion of configuration at C-7*a* in structure **15a**.

The 5-oxo acids **12** and **13** reacted with (*R*)-phenylglycinol to give mixtures of diastereoisomeric bicyclic lactams **16a,b** and **17a,b**, respectively. These mixtures (*ca* 84 : 16 ratio from the ^{13}C NMR spectra) were inseparable on a silica column. The major component in each case is the *cis* diastereoisomer, **16a** and **17a**, by analogy with stereochemical assignments to related compounds by Meyers *et al.*[1] However, it is noteworthy that the condensation of (*R*)-phenylglycinol with methyl 5-oxopentanoate gives the opposite stereochemical result, although the product **18b** (25% yield) is equilibrated to a 86 : 14 mixture of **18a,b** on treatment with acid.[4]

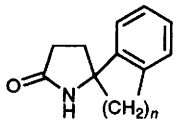
Isomerisation of **17a,b** on treatment with aluminium trichloride in 1,2-dichloroethane at room temperature afforded a mixture of spiro lactams **22a,b**, which was separated by



Scheme 1 *Reagents and conditions*: i, $Et_3SiH/TiCl_4$; ii, Na/NH_3; iii, $LiAlH_4/AlCl_3$; iv, HCO_2NH_4/Pd–C; v, $LiAlH_4$



6 n = 2
7 n = 3



8 n = 2
9 n = 3

$Ph(CH_2)_mCO(CH_2)_nCO_2H$
10 $m = n = 2$
11 $m = 3, n = 2$
12 $m = 2, n = 3$
13 $m = n = 3$

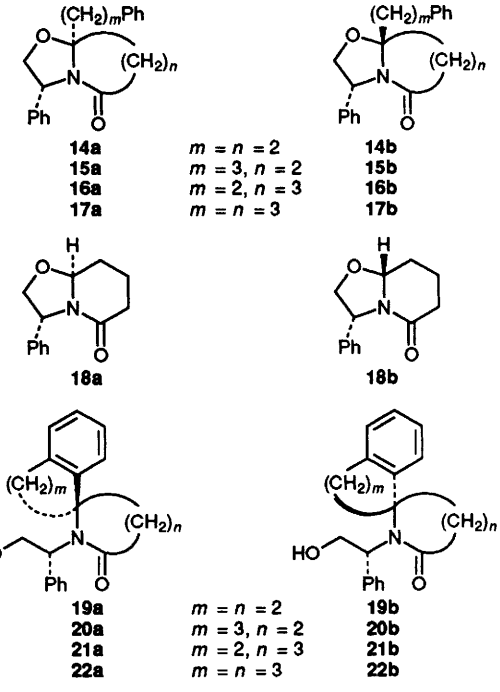


Table 1 Bicyclic oxazolidines and spiro lactams

Oxo acid	Oxazolidine	Spiro lactams	Ring size[a]	Ratio **a** : **b**
10	**14a** 77%	**19a,b** 93%	5,5	3.6 : 1
11	**15a** 54%	**20a,b** 90%	5,6	1 : 3.9
12	**16a,b** 72%	**21a,b** 88%	6,5	3.2 : 1
13	**17a,b** 72%	**22a,b** 99%	6,6	1 : 3.0

[a] Ring size is lactam, carbocycle.

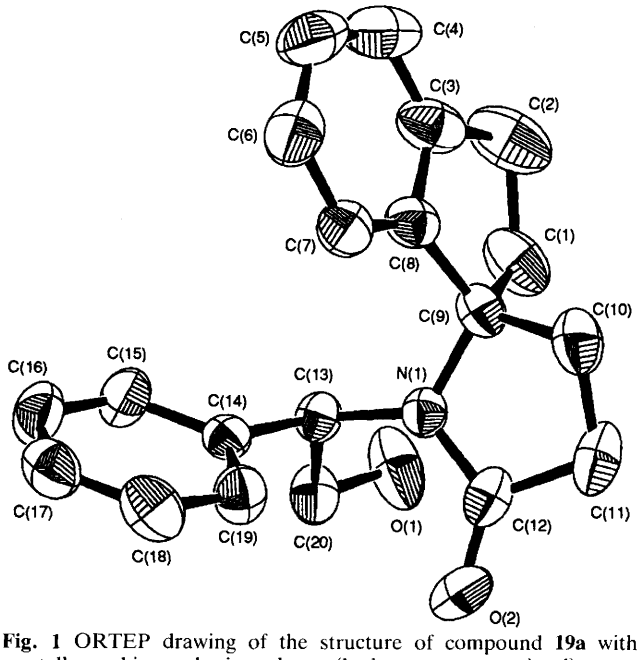


Fig. 1 ORTEP drawing of the structure of compound **19a** with crystallographic numbering scheme (hydrogen atoms omitted)

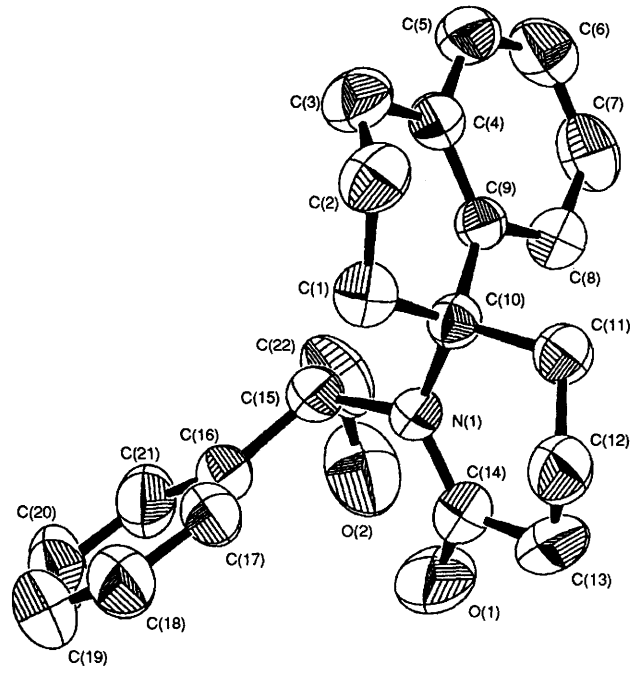


Fig. 2 ORTEP drawing of the structure of compound **22b** with crystallographic numbering scheme (hydrogen atoms omitted)

chromatography. The major diastereoisomer was the less polar component (eluted first) and its structure **22b** confirmed by X-ray crystallography,† which shows the spiro stereogenic centre has the (*S*)-configuration (Fig. 2). Analogous spiro lactams **21a,b** were obtained in the same way from **16a,b**, but in this case the major diastereoisomer was the more polar and it is therefore assigned the (*R,R*)-configuration **21a**, as for the other spiro indene **19a**. These results are summarised in Table 1.

Our results show that it is possible to access spiro lactams with a range of ring sizes by this approach, and to separate diastereoisomeric products **19–22**. The usual reductive methods for debenzylation are inappropriate for removal of the α-hydroxymethylbenzyl group from nitrogen in **19–22** because of the likelihood of opening the lactam ring. However, an alternative method of debenzylation in two steps used in a similar situation by Meyers *et al.* gave **5** (R = Ph, 51% yield) from **3** (R = Ph).[2] This will allow the further conversion of single diastereoisomers of **19–22** into single enantiomers of the corresponding 1-aza spirans.

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Footnote

† *Crystal Data* for spiro compound **19a**. $C_{20}H_{21}NO_2$, M = 307.4, monoclinic, space group $P2_1$, a = 9.0974(9), b = 9.8532(11), c = 9.8766(10) Å, β = 108.101(8)°, U = 841.5(1) Å^3, Z = 2, D_c = 1.213 g cm^{-3}, $F(000)$ = 328, μ(Mo-Kα) = 0.78 cm^{-1}, crystal size 0.7 × 0.6 × 0.6 mm.

For spiro compound **22b**. $C_{22}H_{25}NO_2$, M = 335.4, orthorhombic, space group $P2_12_12_1$, a = 10.486(3), b = 18.490(5), c = 9.459(3) Å, U = 1833.9(8) Å^3, Z = 4, D_c = 1.215 g cm^{-3}, $F(000)$ = 720, μ(Mo-Kα) = 0.77 cm^{-1}, crystal size 1.0 × 0.6 × 0.5 mm.

Intensity data were collected at 293 K on a Rigaku four-circle diffractometer with graphite-monochromated Mo-Kα X-radiation, λ = 0.7107 Å. Equivalent reflections were merged and only Lorentz and polarisation corrections were applied. The structures were solved by direct methods using SHELX-76 and refined on F^2 using SHELXL. Full-matrix least-squares refinement of 208 parameters for 1577 independent reflections [$I \geqslant \sigma(I)$] in the range $2.66 < \theta < 25°$ gave R_F = 0.0373 and wR_I = 0.0937 [R_F = 0.0327 on $I \geqslant 2\sigma(I)$ data] for structure **19a**. Similar refinement of 226 parameters for 1858 independent reflections [$I \geqslant \sigma(I)$] in the range $3 < \theta < 25°$ gave final values of R_F = 0.0738 and wR_I = 0.2184 [R_F = 0.0408 on $I \geqslant 2\sigma(I)$ data] for structure **22b**. The absolute configuration at the spiro centre in each compound [(*R*) in **19a**, (*S*) in **22b**] was established relative to the known absolute configuration of the (*R*)-phenylglycinol moiety. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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