Kinetic and thermodynamic control of axial chirality in biaryl-derived fused oxazolidine lactams exploiting a centre-axis relay of unit efficiency

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The condensation of a 2-substituted-2-aminoethanol with methyl 2'-formylbiphenyl-2-carboxylate produces only two of the four possible axially chiral 6,7-dihydrodibenz[c,e]oxazolo[3,2-a]azepin-9(4bH)-ones (fused oxazolidine lactams), with kinetically controlled diastereoisomer ratios of up to 96 : 4. Within each lactam product the central chirality of the oxazolidine-fused benzylic position C(4b) is relayed to the biaryl axis with unit efficiency, the mis-matching of these stereogenic elements being prohibited due to strain, as predicted by molecular mechanics calculations. Diastereoisomeric lactam pairs can be equilibrated by heating with acid, and under these thermodynamic conditions reversed diastereoisomer ratios of up to 26 : 74 are observed.

Introduction

The control of axial chirality in biaryls has been a focus of much attention in recent years as these materials became prominent in synthetic, materials and supramolecular chemistry, and prompted the development of new methods for their enantioselective (atroposelective) synthesis.¹ The key component of chiral biaryls, a stereogenic axis, is also biologically significant, there being a large number of compounds whose physiological properties depend on their axial configuration. These include not only fixed-axis biaryls such as (aR)-gossypol, an oral anti-spermatogenic agent,² but also many flexible systems exemplified by N-acetylcolchinol methyl ether (NCME) 1, an antimitotic agent whose (aR)-form binds strongly to tubulin³ and whose (aR)- and (aS)-forms equilibrate in solution (ratio 3:1 in chloroform-d).⁴ These properties of 1 serve to illustrate the phenomenon of dynamic axial chirality which, in appropriate circumstances, can be manipulated (e.g. inverted) to useful effect without breaking bonds.⁵ The sense of the axial chirality in NCME 1 depends on the configuration of the benzylic stereocentre, where the acetamido substituent prefers a pseudo-equatorial orientation, and the three-atom bridge effectively operates as a mechanical centre-axis chirality relay. The degree of axial chirality in biaryls, i.e. the aryl-aryl dihedral angle, can also be controlled using suitable designs of multi-atom bridge.6,7

The interplay between benzylic central chirality and axis configuration, as illustrated above, is a recurrent theme in atroposelective biaryl synthesis,¹ and our interest in this area led us to investigate the potential of [7,5]-fused lactams based on 6,7-dihydrodibenz[c,e]oxazolo[3,2-a]azepin-9-one **2** as conformationally restrained biaryls. Although the ring system in **2** is analogous to the [5,5]- and [6,5]-fused lactams introduced and exploited so productively by Meyers and co-workers,⁸ the biaryl lactams described in our preliminary publication⁹ were the first of their



type. However, the heterocyclic nucleus was already known in the form of 3^{10} and 4,¹¹ and another series of lactams based on **2** was subsequently described by Levacher and co-workers.^{12,13} We report herein the details of our initial study, in which we identify complementary kinetic and thermodynamic routes to biaryl lactams of the form **2**, and from which we conclude that a chirality relay of unit efficiency links the biaryl axis and C(4b) in such systems.

Results and discussion

The starting materials for our study were prepared from commercial diphenic anhydride **5** using the two sequences shown in Scheme 1. Heating the anhydride **5** with hydrazine hydrate gave the hydrazide 6,¹⁴ which could be cleaved to the acid-aldehyde **7** using periodic acid;¹⁵ the ozonolysis of phenanthrene offers an alternative route to **7**.¹⁶ The corresponding ester **9** was prepared by opening the anhydride **5** with methanol, followed by reduction to the known ester-alcohol **8** using borane-methyl sulfide.¹⁷ The oxidation of **8** to **9** with manganese(IV) oxide has been described,¹⁸ but in our hands this reaction sometimes gave significant amounts

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Scheme 1 Preparation of biaryl starting materials 7 and 9.

of the lactone 10, a result which we ascribe to the variable activity of the manganese reagent. Fortunately the oxidation of 8 under Swern conditions¹⁹ afforded the ester-aldehyde 9 cleanly and in good yield.

The polycyclic nucleus of **2** was first assembled by heating the acid-aldehyde **7** with (*S*)-valinol **11a** under dehydrating conditions, which gave a mixture of two products as indicated by ¹H NMR spectroscopy and TLC (Scheme 2 and Table 1). The characterising features of the NMR spectrum of the mixture were two singlets at δ 5.91 and 5.73 ppm, which were assigned to the respective H(4b) signals of the major and minor products (ratio >5 : 1). Chromatography afforded the crystalline lactams **12a** (84%) and

 Table 1
 Condensation of the biaryls 7 and 9 with aminoalcohols 11



Scheme 2 Condensation of the biaryls 7 and 9 with aminoalcohols 11.

13a (12%), which were identified as the respective (aS,4bR,7S) and (aR,4bS,7S) diastereoisomers by X-ray crystallography.⁹ These lactams have highly twisted frameworks, with the aromatic rings of each biaryl unit 40-45° from coplanarity and the respective carbonyls 36° and 33° out of the plane of the adjacent aromatic ring. The reactions of 7 with other commercial amino alcohols 11b-f also gave two lactams 12 and 13, each pair distinguishable through the characteristic H(4b) signals in their ¹H NMR spectra (Table 2 and Table 3), but the yields and diastereoselectivity of the process were at best moderate, leading to some isolation problems. The situation was improved using the ester-aldehyde 9, whose condensation with valinol 11a in toluene gave the lactam 12a with a d.e. of 92% (entry 7). To shorten reaction times, other condensations of 9 were carried out under more forcing conditions (155 °C, 3 d) which provided convenient access to the lactams 12 except in the case of tert-leucinol 11f (entry 12). An alternative route to the phenylglycinol-derived lactam 12b which proceeds at lower temperature, based on the activation of 7 with Mukaiyama's salt, was developed by the Levacher group.13

In principle, the condensation of **7** or **9** with an amino alcohol **11** could provide up to four diastereoisomeric lactams, and in order to rationalise the results in Table 1, in particular the absence of **14** and **15** from the product mixtures, the core structures **16** and **17** and the related systems **18–21** were analysed using molecular mechanics

Entry	Biaryl	Series	R	Method ^a	Products (yield (%)) ^b	Ratio ^e	
1	7	a	\mathbf{Pr}^{i}	А	12a (84), 13a (12)	84:16	
2	7	b	Ph	A	12b + 13b (75)	70:30	
3	7	c	Bn	A	12c + 13c (54)	62:38	
4	7	d	Me	A	12d + 13d (59)	56:44	
5	7	e	CH ₂ OBn	А	12e + 13e(61)	50:50	
6	7	f	Bu ^t	А	12f + 13f(55)	64:36	
7	9	a	\mathbf{Pr}^{i}	A^d	12a + 13a (71)	96:4	
8	9	b	Ph	В	12b (88)	91:9	
9	9	c	Bn	B	12c (83), 13c (6)	92:8	
10	9	d	Me	B	12d (72), 13d (10 ^{e})	85:15	
11	9	e	CH ₂ OBn	B	$12e(74)$ $13e(23^{e})$	87.13	
12	0	f	Ru ^t	B	_f		

^{*a*} Method A: toluene, Dean–Stark, reflux, 36 h. Method B: xylene, bath temp. 155 °C, 72 h. ^{*b*} Isolated yields after chromatography. ^{*c*} Estimated from the ¹H NMR spectrum of the product mixture. ^{*d*} Reflux maintained for 7 d. ^{*c*} Not obtained pure. ^{*f*} No products observed.

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Table 2 ¹H NMR data (δ values and multiplicity) for 'kinetic' lactams 12^{*a*}

۳ 0,	H ^B _β

) m			
Lactam	R	H-4b	ArH	Н-6а	Н-6β	Н-7	Other signals
1 2a	\Pr'	5.91 (s)	7.40–7.60 (7 H, m) 7.96 (1 H, dd, J 1.5, 7.5)		4.29 (3 H, br s) –		2.62–2.78 (1 H, m) 0.99 (3 H, d, <i>J</i> 7.0) 0.05 (3 H, d, <i>J</i> 7.0)
12b	Ph	6.23 (s)	7.29–7.34 (1 H, m) 7.36–7.42 (4 H, m) 7.44–7.53 (3 H, m) 7.55–7.65 (4 H, m)	4.68 (dd, J 6.0, 8.5)	4.28 (d, <i>J</i> 8.5)	5.35 (d, <i>J</i> 6.0)	See ArH
12c	Bn	5.86 (s)	7.20 (1 H, dd, J 1.2, 8.0) 7.21-7.34 (5 H) 7.39-7.62 (7 H) 8.06 (1 H, AA, 71 5, 7.8)	4.20 (2 H, d, J	/ 3.0)	4.56 (tdd, J 3.0, 3.0, 9.8)	3.48 (1 H, dd, <i>J</i> 3.0, 13.0) 2.91 (1 H, dd, <i>J</i> 9.8, 13.0)
12d	Me	5.95 (s)	8.00 (1 11, 00, 7 1.3, 7.6) 7.40–7.75 (7 H, m) 8.01 (1 H, dA, 7 1 2, 7 7)	$4.40 (\mathrm{dd}, J 6.0, 8.4)$	4.04 (d, J 8.4)	4.46 (dq, J 6.0, 6.0)	1.50 (3 H, d, J 6.3)
12e	CH ₂ OBn	5.90 (s)	0.01 (11.1, ud., 7.12, 7.7) 7.26–7.37 (5 H, m) 7.43–7.61 (7 H, m) 7.97 (1 H, dd, J 1.0, 7.5)	4.35 (dd, J 5.8, 8.8)	4.48 (d, J 8.8)	4.50-4.57 (m)	4.65 (1 H, d, J 11.8, OCHPh) 4.57 (1 H, d, J 11.8, OCHPh) 4.00 (1 H, dd, J 3.3, 8.8, CHOBn) 2.23 (1 H, - 1.00, CHODEn)
12f	Bu'	5.93 (s)	7.40–7.70 (7 H, m) 7.79 (1 H, dd, <i>J</i> 1.0, 7.5)	4.19 (dd, J 5.9, 9.0)	4.30 (d, <i>J</i> 9.0)	4.39 (d, <i>J</i> 5.9)	2.05 (1 ft, 1, 7 0.0, CITODII) 1.05 (9 H, s)
^a All spectra we	the run in CDCl3	at 400 MHz exce	ept 12e, which was run at 300 N	AHz; J values are quoted i	n Hz.		

					H ^R H ^R		
Lactam	R	H-4b	ArH	Η-6α	Н-6β	Н-7	Other signals
13a	\mathbf{Pr}^{i}	5.73 (s)	7.40–7.68 (7 H, m)	4.14 (dd, <i>J</i> 6.1, 8.7)	4.27-4.34 ((2 H, m)	2.09 (1 H, dq, J 7.0, 7.0) 0.781 (3 H, d, J 7.0) 0 776 (3 H d J 7.0)
13b	Ph	5.98 (s)	7.0–7.7 (12 H, m) 8 12 (1 H d 78 0)	4.60 (dd, J 6.6, 8.5)	4.40 (dd, J 3.7, 8.5)	5.47 (dd, J 3.7, 6.6)	see ArH
13c	Bn	5.77 (s)	7.15-7.30 (5 H, m) 7.44-7.72 (7 H, m) 8.10(1 H, d. 7 8.0)	4.10 (dd, J 6.0, 8.8)	4.26 (dd, J 1.9, 8.8)	4.63-4.69 (m)	3.17 (1 H, dd, J 4, 13.5) 2.61 (1 H, dd, J 10, 13.5)
13d	Me	5.74 (s)	7.40-7.75 (7 H, m) 8.08 (1 H, d, 78.0)	4.31 (dd, J 6.0, 8.4)	4.14 (dd, <i>J</i> 2.4, 8.4)	4.55 (ddq, J 2.4, 6.0, 6.4)	1.27 (3 H, d, J 6.3)
13e	CH ₂ OBn	5.75 (s)	7.22–7.38 (5 H) 7.21–7.57 (7 H) 8.09 (1 H, br d, <i>J</i> 7.5)	4.18 (dd, J 5.8, 8.7)	4.48 (d, J 8.7)	4.63-4.70 (m)	4.50 (1 H, d, <i>J</i> 11.9, OC <i>H</i> Ph) 4.43 (1 H, d, <i>J</i> 11.9, OC <i>H</i> Ph) 3.57 (1 H, dd, <i>J</i> 4.2, 9.2, C <i>H</i> OBn) 3.55 (1 H, dd, <i>J</i> 4.2, 9.2, C <i>H</i> OBn)
13f	Bu ^ć	5.68 s	7.40–7.70 (7 H, m) 8.21 (1 H, d, <i>J</i> 8.0)	4.04 (dd, J 6.4, 9.0)	4.39 (d, <i>J</i> 9.0)	4.34 (d, <i>J</i> 6.4)	э. ээ (н п, ц, <i>у э. г., СП</i> ОВП) 0.88 (9 Н, s)
" All spectra	were run in CDC	l ₃ at 400 MHz i	in CDCl ₃ except 13e, which was	s run at 300 MHz; J values	s are quoted in Hz.		

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Table 3 ¹H NMR data (δ values and multiplicity) for 'thermodynamic' lactams **13**

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techniques (Fig. 1). Minimum energy conformations were located for both 16 and 17 (Fig. 2), and the steric energy of 17 was calculated to exceed that of 16 by more than 100 kJ mol⁻¹. This is a compelling difference, especially when considered in conjunction with the estimated 80 kJ mol^{-1} by which the axial torsion barrier in a simple three-atom bridged biaryl can be raised by $o_{,o'-}$ dimethylation.²⁰ It can be concluded that the diastereoisomers 14 and 15 based on the mis-matched system 17 are effectively disallowed by strain, with major contributions from excessive bending and torsion (eclipsing). The structure 17 is also subject to a loss of amide resonance due to the pyramidalisation of the nitrogen,²¹ which is manifested inter alia by the O(9)-C(9)-N(8)-C(7) dihedral angle (39.6°) and the reduced sum of the bond angles at the nitrogen atom (352.6°). Some insight into the uniqueness of the relationship between 16 and 17, which feature a threeatom bridge containing two trigonal atoms, is provided by the analyses of 18-21. In 18 and 19 the carbon atoms of the bridge are tetrahedral while the nitrogen is pyramidal, and the two structures would not appear to be differentiated on the basis of strain. However, in 20 and 21 the presence of one trigonal atom in the bridge is sufficient to bring about a matched/mis-matched centreaxis relationship in favour of 20, based on steric strain. Examples of this relay are discussed later.

A proposed mechanism for the formation of the lactams 12 and 13 is shown in Scheme 3. The initial step is the formation of an imine species 22 which can equilibrate with the respective *trans*- and *cis*-oxazolidines 23 and 24. In analogous systems such equilibria are dominated by the ring-opened forms (*cf.* 22),²² but intermolecular *N*-acylation is kinetically selective for the *cis*-2,4disubstituted oxazolidine form (*cf.* 24) in which one face of the heterocyclic ring is unhindered.²³ In contrast, the intramolecular *N*-acylation which gives lactam 12 can proceed most favourably through the arrangement depicted in (a*S*)-23, in which the groups R and X are apart, whereas in the alternative (a*R*)-24 leading to 13 these groups are close. The higher selectivity observed using the ester-aldehyde 9 and its failure to react with the bulky *tert*-leucinol 11f (Table 1, entry 12) are consistent with this mechanistic picture.

A second series of molecular mechanics calculations was carried out on the lactams 12 and 13, and the results (Table 4) indicate that the minor product 13 is the thermodynamically more stable isomer of each pair. On the basis of precedents²⁴ it was anticipated that the interconversion of 12 and 13 might be induced by treatment with acid, and the results of a study of this equilibration process are shown in Table 5.

Table 4 Minimised steric energies" and equilibrium compositions for lactams 12 and 13

	Minimised energies/k	l steric J mol ⁻¹				
Series	12	13	$\Delta G/\mathrm{kJ}~\mathrm{mol}^{-1}$	12:13 at 25 °C		
a	127.624	124.729	2.894	23.7:76.3		
b	129.012	127.606	1.406	36.2:63.8		
c	136.075	132.697	3.378	20.4:79.6		
d	108.918	107.626	1.292	37.3:62.7		
e	183.423	176.621	6.802	6.0:94.0		
f	146.698	142.445	4.253	15.2:84.8		

" Calculated using MacroModel 8.0 (MM3 force field).



Fig. 1 Energy-minimised conformations of the fused dibenzazepines 16-21 and their steric energies, calculated using MacroModel 8.0 (MM3 force field).



Fig. 2 Potential energy plots of the C(1)–C(13b)–C(13a)–C(13) biaryl dihedral angle (modulus) in lactams 16 and 17 in the region of their steric energy minima, calculated using MacroModel 8.0 (MM3 force field).

In an initial experiment (entry 1), the valinol-derived lactam 12a in acetonitrile- d_3 was heated to 55 °C in the presence of a catalytic amount of p-toluenesulfonic acid, and the solution was monitored by ¹H NMR spectroscopy. The equilibration process was slow under these conditions, but the equilibration proceeded with the expected first-order kinetics (Fig. 3). The reaction was stopped after 33 d, after which time the ratio 12a:13a was converging on a value of 1:2, thus confirming the greater thermodynamic stability of the diastereoisomer 13a and that the overall lactam-forming sequence (Scheme 3) was kinetically controlled.

For convenience, many of the equilibrations shown in Table 5 were carried out at higher temperatures using an excess of trifluoroacetic acid (TFA), and two blanks (entries 3 and 6) confirmed the requirement for acid. It is noteworthy that in all cases the isomer distribution favoured the lactam 13, as predicted by calculation. In some cases the calculated and observed isomer ratios were quite close, but the largest discrepancy (entry 10) serves as a reminder of the approximations made in assembling the results in Table 4: the steric energy-minimised structure of 13e incorporated π -stacking between the benzyl and biaryl components that would be negated by aromatic solvents.

The mechanism for acid-induced equilibration is presumed to involve the protonation of the lactam 12 followed by ring-opening to the acyliminium species 26, which can isomerise to 27 and recyclise to 28, providing access to 13 (Scheme 4). The ratedetermining step is likely to be the ring-opening of 25, in which the C(4b)–O(5) bond is fixed with poor alignment for elimination.

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ble 5	Acid-induced equ	ilibration of	the biaryl lac	tams 12 and 1 .	3				
Entry	Starting lactam	R	Solvent	Added acid	Temperature $T/^{\circ}C^{a}$	Time/d	Products	Observed ratio ^b	Calculated ratio
1	12a	\mathbf{Pr}^{i}	$MeCN-d_3$	p-TsOH	55	33 ^d	12a + 13a	36:64	26:74
2	12a	\mathbf{Pr}^{i}	Toluene- d_8	<i>p</i> -TsOH	140	3	12a + 13a	27:73	30:70
3	12a	\mathbf{Pr}^{i}	Toluene- d_8	None	140	7	12a	_	30:70
4	12a	\mathbf{Pr}^{i}	Toluene- d_8	CF ₃ CO ₂ H	100	7	12a + 13a	29:71	28:72
5	12b	Ph	Toluene- d_8	CF ₃ CO ₂ H	100	7	12b + 13b	45:55	39:61
6	12b	Ph	Xylene	None	150	2	12b	_	40:60
7	12c	Bn	Toluene- d_8	CF_3CO_2H	100	7	12c + 13c	36:64	27:73
8	12c	Bn	HCO_2H	None	100	3^d	12c + 13c	43:57	27:73
9	12d/13d ^e	Me	Toluene- d_8	CF_3CO_2H	100	7	12d + 13d	34:66	40:60
10	12e/13e ^f	CH ₂ OBn	Xylene	CF_3CO_2H	150	3	12e + 13e	30:70	13:87
11	12f/13f ^g	$\mathbf{B}\mathbf{u}^{t}$	Toluene	CF_3CO_2H	100	7	12f + 13f	26:74	21:79

" Bath temperature. " Estimated from the 'H NMR spectrum of the product mixture." Predicted equilibrium composition at T °C based on calculated steric energies (Table 4). ^d Stopped before completion. ^e Starting ratio 56: 44. ^f Starting ratio 50: 50. ^g Starting ratio 64: 36.



Scheme 3 Proposed mechanism for the formation of 12 and 13.





Scheme 4 Proposed mechanism for the acid-catalysed equilibration of 12 and 13.

Fig. 3 The progress of the equilibration of lactams **12a** and **13a** in CD₃CN at 55 °C. The fitted curve for [**12a**] corresponds to an observed rate constant $(k_1 + k_{-1})$ of 1.1×10^{-6} s⁻¹ and an equilibrium ratio of 1 : 2.

This can be seen in the crystal structure of **12a**, in which the dihedral angles C(4)–C(4a)–C(4b)–O(5) and C(9)–N(8)–C(4b)–O(5) are 3.7° and 177.2° respectively, *i.e.* the oxazolidine C–O bond is essentially orthogonal to both the aromatic and amide π -systems (Fig. 4). The protonated oxygen therefore receives little assistance from either when operating as a leaving group. The isomer **13a** is similarly situated, the corresponding dihedral angles being 2.0° and 165.4° .



Fig. 4 Dihedral angles affecting O(5) from the X-ray crystal structure of **12a**.⁹

The results of this study confirm that a mobile biaryl axis can be restrained in a predictable and fixed configuration by incorporation within a fused oxazolidine lactam of the type developed and used extensively in synthesis by Meyers et al.8 The most prominent feature of such lactams, illustrated by the properties of 12a-f and 13a-f, is the effectiveness of the mechanical link between the benzylic position C(4b) and the biaryl axis, through which stereochemical information is relayed with complete fidelity. Related chirality relays are present in the chemical literature, one such example being the cyclisation of the iminium species 29 which, on the basis of analogy with 20/21, presumably gave (\pm) -30, although this was not specified.²⁵ Other reactions of this type were reported by Hilt et al.,26 who confirmed the cyclisation of (\pm) -31 to (\pm) -32 using X-ray crystallography. Only one other, non-crystalline, diastereoisomer was isolated from this reaction (d.r. 8:1) but its configuration remained unspecified. Again, by analogy with 20/21 the minor diastereoisomer was probably (\pm) -33, as the alternative axis-centre permutation would be disfavoured due to strain.



The most intriguing illustration of benzylic centre-axis complementarity is the observation by Zavada and co-workers that the zinc bromide-induced elimination of cyanide ion from the fixedaxis biaryl **34** produces only **35**, indicating that only the axial cyano group is expelled.²⁷ Moreover, the reverse reaction, in which **35** undergoes the addition of cyanide ion, is also completely selective, regenerating **34** in the absence of stereoisomers. The centre-axis stereochemical relay thus operates in both directions, with the configuration of the axis dictating the orbital alignment of the imine moiety in **35**.

Conclusions

The formation of biaryl-fused lactams **12** *via* the mechanism shown in Scheme 3 amounts to the dynamic kinetic resolution of **7** or **9**, whose flexible biaryl axis is converged to a single configuration in the form of the derived lactam **12**. The overall sequence involves the relay of chirality from the auxiliary amino alcohol **11** to the benzylic fusion position, C(4b), which proceeds with kinetic selectivity (up to 92% d.e.) originating in the faster cyclisation of (a*S*)-**23** as compared to (a*R*)-**24**. The alternative cyclisations of **23** through an (*R*)-configured axis to give **14**, and of **24** through an (*S*)-configured axis to give **15**, are prohibited by strain, which is manifested in the lactams **12** and **13** as a chirality relay of unit efficiency between C(4b) and the biaryl axis. The diastereoisomeric pairs in each lactam series can be interconverted by heating with acid, leading to equilibrium mixtures in which **13** generally predominates by *ca.* **3** : **1**.

Given the established advantages of amino alcohols as chiral auxiliaries, based on their ready availability in enantiopure form and the methods by which they can be installed, exploited and disconnected,⁸ biaryl-fused oxazolidine lactams of the forms **12**

and 13 could be useful in a variety roles that require robust, conformationally defined chiral frameworks. Experiments designed to explore the chemistry of these lactams, with particular emphasis on processes that allow the retention of the induced axial chirality after disconnection of the oxazolidine ring, are in progress and will be reported in due course.

Experimental

Melting points were determined using a Kofler hot-stage or an Electrothermal apparatus and are uncorrected. IR spectra were recorded for neat thin films on NaCl plates, using Perkin-Elmer 1710FT or Nicolet Nexus 670/870 spectrometers. NMR spectra were measured on Bruker DPX200, AC300 and Advance 400 instruments for solutions in deuteriochloroform, unless otherwise indicated; resonances were assigned with the aid of COSY, HMBC, HMQC and DEPT spectra where appropriate. Low-resolution mass spectra were measured on a Micromass LCT instrument using a Waters 2790 separations module with electrospray (ES⁺) ionisation and TOF fragment detection. High-resolution mass spectra were recorded on ThermoFinnigan MAT95XP or Kratos Concept S1 instruments. Data for most of the peaks of intensity <20% of that of the base peak are omitted. Elemental analyses were carried out by the UMIST and University of Manchester microanalytical services. Optical rotations were measured at 589 nm using an AA-100 polarimeter (Optical Activity Ltd). The sealed tubes used in equilibration experiments were screw-capped and made from thick-walled glass (Aldrich Z18106-4).

Starting materials and solvents were routinely purified by conventional techniques²⁸ and most reactions were carried out under nitrogen or argon. Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 on aluminium plates containing a 254 nm fluorescent indicator. The chromatograms were visualised by the use of UV light or the following developing agents: ethanolic vanillin or potassium permanganate. Unless otherwise indicated, preparative (column) chromatography was carried out using the flash technique²⁹ on 60H silica gel (Merck 9385). Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to a light petroleum fraction, b.p. 40–60 °C, unless otherwise stated. 'Ether' refers to diethyl ether. 'Xylene' refers to anhydrous *o*-xylene (Aldrich 294780).

2'-(Hydrazinocarbonyl)biphenyl-2-carboxylic acid 614

To a solution of hydrazine monohydrate (4.0 mL, 82.5 mmol) in water (4 mL) at 0 °C was added diphenic anhydride **5** (8.00 g, 35.7 mmol) over a period of 5 min with vigorous stirring and then the mixture was heated to 90 °C for 1 h. The reaction was cooled and poured into water (50 mL). The solution was acidified with conc. HCl to pH 2 with vigorous stirring until a gummy brown solid began to form. Chilling and scratching gave a fine white precipitate. Filtration and crystallisation (EtOH) gave the monohydrazide **6** (8.70 g, 95%) as a colourless solid, m.p. 182.5–183 °C (Found: C, 65.4; H, 5.0; N, 10.6. $C_{14}H_{12}N_2O_3$ requires C, 65.62; H, 4.72; N, 10.93%); v_{max}/cm^{-1} 3269, 3165; δ_H (300 MHz, CDCl₃) 7.76 (1 H, dd, *J* 1.5, 7.5 Hz, ArH), 7.52–7.38 (5 H, m, ArH), 7.14–7.09 (3 H, m, ArH); δ_C (100 MHz, CDCl₃) 127.4,

127.6, 129.3, 129.6, 130.3, 130.6, 130.9, 132.3, 134.3, 140.4, 140.9, 168.2, 169.1; *m/z* 279 ([M + Na]⁺, 25%), 257 ([M + H]⁺, 18), 239 (100); *R*_f 0.20 (EtOAc–EtOH, 3 : 2).

2'-Formylbiphenyl-2-carboxylic acid 715

To a cooled solution (0 °C) of periodic acid (as H₅IO₆, 1.54 g, 6.8 mmol) in water (36 mL) and aq. ammonium hydroxide (8% w/w, 14 mL) was added the hydrazide 6 (1.0 g, 3.9 mmol) dissolved in aq. ammonium hydroxide (8% w/w, 7 mL) with vigorous stirring, keeping the temperature below 5 °C. The mixture was stirred at 5 °C for 5 min and then at room temperature for 15 min. Conc. sulfuric acid (ca. 6 mL) was added, producing a gummy brown solid, which was dissolved in dichloromethane (30 mL). The layers were separated, the aqueous layer was extracted with dichloromethane $(3 \times 30 \text{ mL})$, and the combined organic phase was dried over MgSO₄ and evaporated. Chromatography of the residual brown oil (80 g SiO2, EtOAc-dichloromethane 1:4) and crystallisation from EtOAc gave the title compound 7 (440 mg, 50%) as a white solid, m.p. 134–136 °C [lit.¹⁶ 134–135 °C (MeOH– water)] (Found: C, 74.1; H, 4.6. C₁₄H₁₀O₃ requires C, 74.33; H, 4.46%; v_{max} /cm⁻¹ 3064, 2843, 1728, 1689, 1596, 1402, 1274, 1200, 757; δ_H (300 MHz, CDCl₃) 10.30 (1 H, s, OH), 9.78 (1 H, s, CHO), 8.11 (1 H, dd, J 1.4, 7.9 Hz, ArH), 7.99 (1 H, dd, J 1.5, 7.5 Hz, ArH), 7.62-7.48 (4 H, m, ArH), 7.30 (1 H, dd, J 1.2, 7.5 Hz, ArH), 7.23 (1 H, dd, J 1.1, 7.5 Hz, ArH); $\delta_{\rm C}$ (75 MHz, CDCl₃) 128.0, 128.3, 128.6, 129.6, 130.4, 131.5, 132.3, 132.7, 133.6, 134.1, 140.6, $145.2, 172.2, 192.1; m/z 290 ([M + 2Na + H_2O]^+, 100\%), 249 ([M + 100\%)$ Na]⁺, 30), 209 (6), 181 (50); R_f 0.20 (EtOAc-dichloromethane, 1:4).

Methyl 2'-hydroxymethylbiphenyl-2-carboxylate 8

A stirred suspension of diphenic anhydride 5 (3.52 g, 15.7 mmol) in MeOH (50 mL) was heated to reflux for 3.3 h. The resulting solution was concentrated in vacuo to yield a dark oil. To a stirred solution of this oil in THF (100 mL) at 0 °C was added dropwise a solution of borane-dimethylsulfide in THF (2 M, 14.1 mL, 28.2 mmol) and the resulting solution was allowed to warm to room temperature over 23.5 h. The mixture was cautiously quenched with MeOH (10 mL) and the volatiles removed in vacuo. The residue was diluted with EtOAc (100 mL) and washed with saturated aqueous NaHCO₃ (2 \times 50 mL). The organic phase was dried, filtered, concentrated in vacuo and purified by chromatography (EtOAc-hexane, 1 : 3), which gave the title compound 8 (2.56 g, 67% over two steps) as a colourless oil; $\delta_{\rm H}$ (300 MHz, CDCl₃) 7.94 (1 H, dd, J 0.8, 7.5 Hz, 6-H), 7.58–7.22 (6 H, m, ArH), 7.06 (1 H, d, J 6.8 Hz, 3'-H), 4.44 (1 H, d, J 12.1 Hz, CHH'OH), 4.38 (1 H, d, J 12.1 Hz, CHH'OH), 3.67 (3 H, s, OCH₃), 1.94 (1 H, s, OH) (in accord with published data¹⁷); $R_{\rm f}$ 0.23 (EtOAc-hexane, 3 : 7).

Methyl 2'-formylbiphenyl-2-carboxylate 9

Method A (ref. 18). To a stirred solution of the ester-alcohol 8 (2.56 g, 10.6 mmol) in dichloromethane (200 mL) was added MnO_2 (80% pure; 10.82 g, 0.10 mol) and the resulting suspension was heated under reflux for 3 h. The reaction mixture was cooled to room temperature, filtered through Celite and concentrated *in vacuo* to yield a mixture (*ca.* 1 : 1) of 9 and 10 (2.36 g) as a colourless

oil. Chromatography (EtOAc–hexane, 15 : 85) gave a sample of the ester-aldehyde **9** (484 mg, 19%) as a colourless oil; $\delta_{\rm H}$ (300 MHz, CDCl₃) 9.81 (1 H, s, CHO), 8.06 (1 H, d, *J* 7.0 Hz, ArH), 8.02 (1 H, d, *J* 7.9 Hz, ArH), 7.64–7.50 (4 H, m, ArH), 7.30 (1 H, d, *J* 7.5 Hz, ArH), 7.26 (1 H, d, *J* 8.7 Hz, ArH), 3.63 (3 H, s, OMe); $v_{\rm max}/\rm cm^{-1}$ 3062, 2951, 2842, 2751, 1728, 1696, 1596, 1435, 1258, 1196, 1129, 1086, 761, 668; $R_{\rm f}$ 0.52 (EtOAc–hexane, 3 : 7). Further elution of the column yielded a mixed fraction (1.45 g, 61%) followed by 7*H*-dibenzo[*c*,*e*]oxepin-5-one **10** (425 mg, 19%) as white crystals, m.p. 132–135 °C [lit.³⁰ 132–134 °C (sublimed)]; $\delta_{\rm H}$ (300 MHz, CDCl₃) 7.98 (1 H, d, *J* 7.9 Hz, ArH), 7.70–7.40 (7 H, m, Ar*H*), 5.03 (2 H, br d, *J* 15.5 Hz, 7-H₂) (in accord with published data³¹); $v_{\rm max}/\rm cm^{-1}$ 3069, 1716 (C=O), 1600, 1449, 1379, 1277, 1226, 1111, 1091, 1048, 1011, 765, 740; $R_{\rm f}$ 0.42 (EtOAc–hexane, 3 : 7).

Method B. A solution of DMSO (0.51 mL, 561 mg, 7.2 mmol, 1.3 eq.) in dichloromethane (3 mL) was added to a 2 M solution of oxalyl dichloride (3 mL, 6.0 mmol) in dichloromethane (20 mL) at -78 °C and stirred for 30 min. The ester-alcohol 8 (1.33 g, 5.5 mmol) in dichloromethane (5 mL) was added and the reaction mixture stirred for a further 30 min at -78 °C. Triethylamine (2 mL, 1.45 g, 14.3 mmol) was added and the reaction mixture was allowed to warm to room temperature while stirring for 3 h. The mixture was quenched with aq. ammonium chloride (2 M, 20 mL), extracted with dichloromethane (3 × 30 ml), dried (Na₂SO₄) and concentrated, giving the ester-aldehyde 9 as a pale yellow oil (1.20 g, 91%), identical (TLC, ¹H NMR) to material obtained using Method A above.

Formation of biaryl lactams (Table 1)

Method A. From the acid-aldehyde 7 in toluene: A solution of 2'-formylbiphenyl-2-carboxylic acid 7 and the appropriate aminoalcohol **11** (1.4–1.5 mol. equiv.) in toluene was heated under reflux in a Dean–Stark apparatus for 36 h. The solution was cooled, evaporated *in vacuo* and the residue was analysed by ¹H NMR spectroscopy to determine the diastereoisomer ratio (see Table 2 and Table 3 for ¹H NMR data). The products were isolated by chromatography over silica gel.

Method B. From the ester-aldehyde **9** in xylene: A solution of methyl 2'-formylbiphenyl-2-carboxylate **9** and the appropriate aminoalcohol **11** (1.4–1.5 mol. equiv.) in xylene was heated at 155 °C (bath temp.) for 3 d. The solution was cooled, evaporated *in vacuo* and the residue was analysed by ¹H NMR spectroscopy to determine the diastereoisomer ratio. The products were isolated by chromatography over silica gel.

(a*S*,4b*R*,7*S*)-6,7-Dihydro-7-isopropyldibenz[*c*,*e*]oxazolo[3,2*a*]azepin-9(4b*H*)-one 12a and (a*R*,4b*S*,7*S*)-6,7-dihydro-7isopropyldibenz[*c*,*e*]oxazolo[3,2-*a*]azepin-9(4b*H*)-one 13a

Method A. The acid-aldehyde 7 (280 mg, 1.24 mmol) and (*S*)-valinol **11a** (180 mg, 1.74 mmol) in toluene (16 mL) was heated under reflux in a Dean–Stark apparatus under Ar for 36 h. TLC indicated complete conversion, the reaction was cooled and the solvent removed *in vacuo*. The residue was partially purified by chromatography over silica gel (80 g SiO₂, EtOAc–hexane 1 : 5 as eluant), which gave the *title compound* **12a** (210 mg, 58%) as colourless crystals, m.p. 121–123 °C (EtOAc) (Found: C, 77.7; H,

6.8; N, 5.0. C₁₉H₁₉NO₂ requires C, 77.79; H, 6.53; N, 4.77%); [a]²³_D $-183 \pm 7 (c \ 1.9, \text{CHCl}_3); v_{\text{max}}/\text{cm}^{-1} \ 3068, 2959, 2885, 1639, 1600,$ 1449, 1406, 1289, 1216, 1173, 1080, 854; $\delta_{\rm C}$ (75 MHz, CDCl₃) 16.5 (Me_A), 19.8 (Me_B), 28.0 (CHMe₂), 61.9 (7-C), 67.2 (6-C), 86.6 (4b-C), 122.3, 128.4 (two), 129.2, 129.4, 130.0, 130.2 and 131.4 (ArCH), 135.7, 136.2, 136.6 and 139.0 (quaternary ArC), 164.5 $(8-C); m/z 609 ([2M + Na]^+, 100\%), 357 (79), 294 ([M + H]^+, 82);$ $R_{\rm f}$ 0.30 (EtOAc-hexane, 1:4). Mixed fractions were condensed to give an oil (139 mg, 38%) which was purified by preparative TLC $[20 \times 20 \times 0.02 \text{ cm} (\text{Merck } 1.05583); \text{multiple elution with EtOAc-}$ hexane 1 : 6], giving 12a (95 mg, 26%) and the title compound 13a (42 mg, 11.5%), m.p. 114–115 °C (petroleum, b.p. 60–80 °C) (Found: C, 78.0; H, 6.8; N, 5.0. C₁₉H₁₉NO₂ requires C, 77.79; H, 6.53; N, 4.77%); $[a]_{D}^{27}$ +148 ± 5 (c 2.25, CHCl₃); v_{max}/cm^{-1} 3064, 2959, 2874, 1639, 1596, 1445, 1402, 1344, 1169, 1080, 994, 963, 858, 742, 703; $\delta_{\rm C}$ (75 MHz, CDCl₃) 18.7 (Me), 19.7 (Me), 30.7 (CHMe₂), 63.0 (7-C), 69.5 (6-C), 86.1 (4b-C), 122.5, 128.3, 128.4, 129.1, 129.7, 130.3, 130.7 and 131.8 (ArCH), 134.1, 136.2, 137.6 and 139.3 (quaternary ArC), 165.4 (8-C); m/z 609 ([2M + Na]⁺, 100%), 357 (88), 294 ([M + H]⁺, 81); $R_{\rm f}$ 0.28 (EtOAc-hexane, 1:4).

From ester 9. Heating the ester-aldehyde 9 (230 mg, 0.96 mmol) and (S)-valinol 11a (148 mg, 1.43 mmol) in toluene (15 mL) under reflux (bath temp. 120 °C) for 7 d gave the mixed lactams 12a and 13a (total 200 mg, 71%, ratio 96 : 4).

(aS,4bR,7S)-6,7-Dihydro-7-phenyldibenz[c,e]oxazolo[3,2-a]azepin-9(4bH)-one 12b and (aR,4bS,7S)-6,7-dihydro-7-phenyldibenz[c,e]oxazolo[3,2-a]azepin-9(4bH)-one 13b

Method A. Heating the acid-aldehyde 7 (296 mg, 1.31 mmol) and the amino alcohol **11b** (270 mg, 1.97 mmol) in toluene (15 mL) under reflux (bath temp. 120 °C) for 36 h gave the mixed lactams **12b** and **13b** (total 320 mg, 75%, ratio 70 : 30).

Method B. Heating the ester-aldehyde 9 (100 mg, 0.42 mmol) and (S)-phenylglycinol 11b (86 mg, 0.63 mmol) in xylene (5 mL) at 155 °C (bath temp.) for 3 d followed by removal of the solvent in vacuo gave a mixture of isomeric lactams (ratio 91 : 9). Chromatography (EtOAc-hexane, 1:4) gave the title compound 12b (120 mg, 88%) as colourless needles, m.p. 143–145 °C (MeOH) (lit.¹³ 138–140 °C); $[a]_{D}^{28}$ -86 ± 8 (c 0.26, CHCl₃); v_{max} /cm⁻¹ 3662, 3471, 3269, 3067, 3021, 2948, 2889, 1638, 1452, 1398, 1339, 1277, 1211, 1157, 904, 737; $\delta_{\rm C}$ (100 MHz, CDCl₃) 60.2 (6-C), 74.0 (7-C), 86.6 (4b-C), 121.8, 126.3 (two), 127.8, 128.2 (two), 128.8 (two), 129.1, 129.4, 130.0, 130.2 and 131.4 (ArCH), 134.8, 136.2, 136.4, 138.3 and 140.8 (quaternary ArC), 163.7 (8-C); m/z 677 ([2M + Na]⁺, 49), 510 (53), 391 ([M + 2Na + H_2O]⁺, 58), 355 (100), 350 ([M + Na]⁺, 82), 329 (76), 235 (73), 207 (38) (Found: M + Na, 350.1145; $C_{22}H_{17}O_2$ NNa requires 350.1152); $R_f 0.25$ (EtOAc– hexane, 3 : 7).

(a*S*,4b*R*,7*S*)-6,7-Dihydro-7-(phenylmethyl)dibenz[*c*,*e*]oxazolo[3,2*a*]azepin-9(4b*H*)-one 12c and (a*R*,4b*S*,7*S*)-6,7-dihydro-7-(phenylmethyl)dibenz[*c*,*e*]oxazolo[3,2-*a*]azepin-9(4b*H*)-one 13c

Method A. Heating the acid-aldehyde 7 (260 mg, 1.15 mmol) and (*S*)-phenylalaninol **11c** (260 mg, 1.72 mmol) in toluene (15 mL) under reflux (bath temp. $120 \,^{\circ}$ C) for 36 h gave the mixed

lactams **12c** and **13c** (total 210 mg, 54%), ratio 62 : 38 by ¹H NMR spectroscopy.

Method B. Heating the ester-aldehyde 9 (110 mg, 0.46 mmol) and (S)-phenylalaninol 11c (104 mg, 0.69 mmol) in xylene (5 mL) at 155 °C (bath temp.) for 3 d followed by removal of the solvent in vacuo gave a mixture of isomeric lactams (ratio 92 : 8). Chromatography (EtOAc-hexane, 15:85) gave the title compound 12c (129 mg, 83%) as a colourless solid, m.p. 84-84.5 °C (dichloromethane) (Found: C, 80.75; H, 5.67; N, 4.03. $C_{23}H_{19}NO_2$ requires C, 80.92; H, 5.61; N, 4.10%); $[a]_{D}^{26} - 226 \pm 9$ $(c 1.0, \text{CHCl}_3); v_{\text{max}}/\text{cm}^{-1}$ 3069, 2927, 1638, 1447, 1406, 750; δ_{C} (100 MHz, CDCl₃) 37.0 (PhCH₂), 58.2 (7-C), 69.4 (6-C), 86.0 (4b-C), 121.7, 126.7, 128.13, 128.15, 128.7 (two), 128.9, 129.4, 129.6 (two), 129.9, 130.0 and 131.3 (ArCH), 134.8, 136.1, 136.2, 137.9 and 138.4 (quaternary ArC), 163.9 (8-C); m/z 705 ([2M + Na]⁺, 46%, $405([M + 2Na + H_2O]^+, 69)$, $364([M + Na]^+, 100)$, $342([M + Ma]^+, 100)$, $342([M + Ma]^+$ H]⁺, 82) (Found: M, 341.1416; C₂₃H₁₉O₂N requires 341.1410); R_f 0.38 (EtOAc-hexane, 3:7). Further elution of the column yielded a mixed fraction (11 mg, 7%) and the *title compound* **13c** (9 mg, 6%) as a colourless oil; v_{max}/cm^{-1} 2913, 2844, 1642, 1448, 1081; $\delta_{\rm C}$ (100 MHz, CDCl₃) 38.5 (CH₂Ph), 58.5 (7-C), 70.5 (6-C), 85.8 (4b-C), 121.9, 126.7, 128.2, 128.4, 128.7 (two), 128.9, 129.5 (two), 129.6, 129.8, 130.2 and 131.5 (ArCH), 133.9, 135.9, 137.2, 137.8 and 139.4 (quaternary ArC), 164.2 (8-C); m/z 705 ([2M + Na]⁺, 11%), $405 ([M + 2Na + H_2O]^+, 47)$, $364 ([M + Na]^+, 96)$, $342 ([M + Na]^+, 96)$, 342 ([M + NaH]⁺, 100) (Found: M, 341.1412; $C_{23}H_{19}O_2N$ requires 341.1410); R_f 0.31 (EtOAc-hexane, 3:7).

(aS,4bR,7S)-6,7-Dihydro-7-methyldibenz[c,e]oxazolo[3,2-a]azepin-9(4bH)-one 12d and (aR,4bS,7S)-6,7-dihydro-7-methyldibenz[c,e]oxazolo[3,2-a]azepin-9(4bH)-one 13d

Method A. Heating the acid-aldehyde 7 (290 mg, 1.28 mmol) and (S)-2-amino-1-propanol 11d (144 mg, 1.92 mmol) in toluene (15 mL) under reflux (bath temp. 120 °C) for 36 h gave the mixed lactams 12d and 13d (total 200 mg, 59%), ratio 56 : 44 by ¹H NMR spectroscopy.

Method B. Heating the ester-aldehyde 9 (95 mg, 0.40 mmol) and (S)-2-amino-1-propanol 11d (45 mg, 0.60 mmol) in xylene (5 mL) at 155 °C (bath temp.) for 3 d followed by removal of the solvent *in vacuo* gave a mixture of isomeric lactams (ratio 85 : 15). Chromatography (EtOAc-hexane, 15:85) gave the title compound **12d** (76 mg, 72%) as a colourless oil; $[a]_{D}^{29} - 143 \pm 7 (c \ 3.6, \text{CHCl}_{3});$ $v_{\rm max}/{\rm cm}^{-1}$ 3065, 2975, 2887, 1638, 1451, 1410, 1217, 940, 912, 748, 730; δ_c (100 MHz, CDCl₃) 18.3 (Me), 52.7 (7-C), 72.8 (6-C), 85.7 (4b-C), 121.7, 128.1 (two), 128.9, 129.4, 129.9, 130.0 and 131.1 (ArCH), 134.9, 136.17, 136.20 and 138.5 (quaternary ArC), 163.7 (8-C); m/z 266 ([M + H]⁺, 100%) (Found: M + H, 266.1165; $C_{17}H_{16}O_2N$ requires 266.1176); R_f 0.20 (EtOAc-hexane, 3 : 7). Further elution of the column yielded a mixed fraction (17 mg, 16%) and a fraction enriched in the minor isomer 13d (10 mg, 10%, ca. 80% d.e. by ¹H NMR spectroscopy) as a colourless oil; $v_{\rm max}/{\rm cm}^{-1}$ 2964, 2923, 2912, 2841, 1632, 1463, 1407, 1094, 741; $\delta_{\rm C}$ (75 MHz, CDCl₃) 19.1 (Me), 52.9 (7-C), 73.7 (6-C), 85.7 (4b-C), 121.7, 128.2, 128.3, 128.9, 129.7, 129.8, 130.2 and 131.5 (ArCH), 134.1, 135.9, 137.1 and 139.8 (quaternary ArC), 163.6 (8-C); m/z 266 ([M + H]⁺, 100%) (Found: M + H, 266.1181; C₁₇H₁₆O₂N requires 266.1176); R_f 0.14 (EtOAc-hexane, 3 : 7).

(aS,4bR,7S)-7-Phenylmethoxymethyl-6,7-dihydrodibenz-[c,e]oxazolo[3,2-a]azepin-9(4bH)-one 12e and (aR,4bS,7S)-7phenylmethoxymethyl-6,7-dihydrodibenz[c,e]oxazolo-[3,2-a]azepin-9(4bH)-one 13e

Method A. Heating the acid-aldehyde 7 (100 mg, 0.44 mmol) (*R*)-2-amino-3-benzyloxy-1-propanol **11e** (120 and mg. 0.66 mmol) in toluene (15 mL) under reflux (bath temp. 120 °C) for 36 h gave the mixed lactams 12e and 13e (total 100 mg, 61%), ratio 1 : 1 by ¹H NMR spectroscopy.

Method B. Heating the ester-aldehyde 9 (79 mg, 0.33 mmol) and (R)-2-amino-3-benzyloxy-1-propanol 11e (89 mg, 0.49 mmol) in xylene (5 mL) at 155 °C (bath temp.) for 3 d followed by removal of the solvent in vacuo gave a mixture of isomeric lactams (ratio 87:13). Chromatography (EtOAc-hexane, 15:85) gave the title compound 12e (90 mg, 74%) as a colourless gum; $[a]_{D}^{29}$ -96 \pm 7 (c 4.1, CHCl₃); v_{max}/cm⁻¹ 3063, 2950, 2885, 1640, 1451, 1409, 1214, 1097, 920, 748, 737; $\delta_{\rm C}$ (100 MHz, CDCl₃) 56.0 (7-C), 67.7 (CH₂), 69.2 (CH₂), 73.5 (CH₂), 86.0 (4b-C), 121.9, 127.8 (three), 128.1, 128.2, 128.5 (two), 129.0, 129.4, 130.0 and 130.1 (ArCH), 134.5, 136.2 (two), 138.1 and 138.4 (quaternary ArC), 164.2 (8-C); *m*/*z* 394 ([M + Na]⁺, 100%), 372 ([M + H]⁺, 47) (Found: M + Na, 394.1421; C₂₄H₂₁O₃NNa requires 394.1414); R_f 0.29 (EtOAchexane, 3 : 7). Further elution of the column yielded a mixed fraction (28 mg, 23%, ratio 12e: 13e 1: 1.6) R_f 0.29 + 0.21 (EtOAchexane, 3 : 7).

(aS,4bR,7S)-7-tert-Butyl-6,7-dihydrodibenz[c,e]oxazolo[3,2alazepin-9(4bH)-one 12f and (aR,4bS,7S)-7-tert-Butyl-6,7dihydrodibenz[c,e]oxazolo[3,2-a]azepin-9(4bH)-one 13f

Method A. Heating the acid-aldehyde 7 (280 mg, 1.24 mmol) and (S)-tert-leucinol 11f (216 mg, 1.84 mmol) in toluene (15 mL) under reflux (bath temp. 120 °C) for 36 h gave the mixed lactams 12f and 13f (total 210 mg, 55%), ratio 64 : 36 by ¹H NMR spectroscopy, as a colourless gum; $v_{\text{max}}/\text{cm}^{-1}$ 3067, 2966, 2873, 2244, 1650, 1452, 1394, 1219, 1153, 1083, 912, 741; m/z 308 ([M + H]+, 100%).

Method B. Heating the ester-aldehyde 9 (230 mg, 0.96 mmol) and the amino alcohol 11f (168 mg, 1.43 mmol) in xylene (15 mL) at 155 °C (bath temp.) for 3 d gave no lactams by ¹H NMR spectroscopy.

Molecular mechanics calculations (Table 4, Fig. 1 and Fig. 2)

Minimised steric energy (MSE) values for the lactams 12, 13 (Table 4), and 16-21 (Fig. 1) were calculated on a PC running Linux (Fedora Core 3) with MacroModel v. 8.0 (Maestro v. 5.0 interface) using the MM3 force field and Monte Carlo conformational search (csearch) method (1000 iterations). The standard minimisation parameters were: no solvent; PRCG method; convergence on gradient; max. number of iterations 3000; convergence threshold 0.0200. The procedure returned multiple repeats of the same global MSE in each case. The difference, ΔG , for each pair of structures 12 and 13 was converted into the equilibrium populations indicated in Table 4 using the equation $\Delta G = -RT \ln K$ (where $R = 8.31451 \text{ J K}^{-1} \text{ mol}^{-1}$). The dihedral driving (drive) plots shown in Fig. 2 were acquired by locating the energy-minimised structure for 16 using csearch as described

above, and then disconnecting the oxazolidine ring at C(4b). The identities of H(4b) and O(5) were exchanged and the oxazolidine ring was then reconnected. A constraint (force constant 100, range $\pm 10^{\circ}$) was imposed on the (S)-configured biaryl torsion angle (42.5°) and the structure was subjected to a new *csearch* operation. The torsional constraint was removed from the resulting structure, ent-17, whose steric energy was then minimised (mini) once more. MSE values for 18-21 were calculated similarly. The structures 16 and ent-17 were each subjected to a drive analysis of the dihedral angle C(1)-C(13b)-C(13a)-C(13) in the region of the respective minima (interval 0.1°), which provided the data for the plots in Fig. 2. The calculated MSE values $(kJ mol^{-1})$ were: 16, 103.95; 17, 214.47; 18, 118.87; 19, 118.28; 20, 27.67; 21, 55.44.

Acid-induced equilibration of lactams (Table 5)

Except for entry 1, all temperatures are those of oil baths and are approximate (±5 °C).

Entry 1. A solution of the lactam 12a (11.2 mg, 0.038 mmol) and p-toluenesulfonic acid hydrate (2.6 mg, 0.014 mmol) in CD_3CN (6 mL) was heated at 55 \pm 2 °C (bath) for a total of 33 d, during which time samples were periodically removed for analysis by ¹H NMR spectroscopy. The integrals for the respective H(4b) signals were used to monitor the change in the diastereoisomer ratio [13a]/[12a]. The data used to plot Fig. 3 are listed in Table 6.

Table 6 Data used to plot Fig. 3

12a (%)	Time/h	
100.0	0.0	
98.1	9.0	
96.8	15.0	
77.6	107.0	
65.2	184.5	
58.6	250.5	
46.4	419.5	
43.8	493.0	
40.2	611.0	
38.2	688.0	
36.7	758.5	
36.0	805.5	

For the equilibration of A and B via first-order processes, the change in concentration of A is related to the respective forward and reverse rate constants k_1 and k_{-1} using the expression

$$\frac{\mathbf{d}[\mathbf{A}]}{\mathbf{d}t} = -k_1[\mathbf{A}] + k_{-1}[\mathbf{B}]$$
(1)

and the equilibration process is represented by the integrated rate equation, eqn (2).

$$[\mathbf{A}]_{t} = [\mathbf{A}]_{\infty} + ([\mathbf{A}]_{0} - [\mathbf{A}]_{\infty}) e^{-(k_{1}+k_{-1})t}$$
(2)

The value of k_{-1} corresponds to k_1/K , where K is the value of **[B]**/**[A]** at equilibrium.

Fig. 3 was plotted using the observed isomer ratios listed in Table 6. The calculated exponential decay curve for [12a] was generated using eqn (2) with the variables $[12a]_{\infty}$, $\{[12a]_0 - [12a]_{\infty}\}$ and $(k_1 + k_{-1})$ optimised by minimising the sum of the R^2 values for each data point. The data yielded the following parameters (errors approximate, based on $\pm 2\%$ accuracy in NMR integrals): $k_1 = 7.3 \times 10^{-7} \text{ s}^{-1} (\pm 0.3 \times 10^{-7})$

 $\begin{aligned} k_{-1} &= 3.7 \times 10^{-7} \, \mathrm{s}^{-1} \, (\pm \, 0.3 \times 10^{-7}) \\ [\mathbf{A}]_{\infty} &= 34\% \, (\pm 2\%) \\ [\mathbf{A}]_0 - [\mathbf{A}]_{\infty} &= 67\% \, (\pm 2\%) \end{aligned}$

Entry 2. A solution of the lactam **12a** (8.2 mg, 0.028 mmol) and *p*-toluenesulfonic acid hydrate (2.0 mg, 0.011 mmol) in toluene- d_8 (0.6 mL) was heated in a sealed tube at 140 °C for 3 d, during which time the mixture was periodically analysed by ¹H NMR spectroscopy. The estimated equilibrium ratio **12a** : **13a** was 27 : 73.

Entry 3. A solution of the lactam 12a (11.2 mg, 0.038 mmol) in toluene- d_8 (0.6 mL) was heated in a sealed tube at 140 °C for 7 d, after which time the ¹H NMR spectrum indicated that 12a remained intact. No other products were evident.

Entry 4. A sample of the lactam 12a (20 mg, 0.07 mmol) in toluene- d_8 (0.5 mL) in an NMR tube was treated with a solution of TFA in toluene- d_8 (6.7 M, 0.1 mL, 0.67 mmol). The stoppered tube was sealed in a screw-capped thick-walled glass tube and heated at 100 °C for 7 d. The equilibration, monitored by ¹H NMR spectroscopy, stabilised with an estimated 12a:13a ratio of 29 : 71.

Entry 5. A sample of the lactam 12b (20 mg, 0.06 mmol) in toluene- d_8 (0.5 mL) in an NMR tube was treated with a solution of TFA in toluene- d_8 (6.7 M, 0.1 mL, 0.67 mmol). The stoppered tube was sealed in a screw-capped thick-walled glass tube and heated at 100 °C for 7 d. The equilibration, monitored by ¹H NMR spectroscopy, stabilised with an estimated 12b:13b ratio of 45 : 55.

Entry 6. A sample of the lactam 12b (50 mg) in xylene (10 mL) was sealed in a screw-capped thick-walled glass tube and heated at 150 °C for 2 d. Evaporation of the solvent and analysis of the residue by ¹H NMR spectroscopy indicated that no equilibration had occurred.

Entry 7. A sample of the lactam 12c (20 mg, 0.06 mmol) in toluene- d_8 (0.5 mL) in an NMR tube was treated with a solution of TFA in toluene- d_8 (6.7 M, 0.1 mL, 0.67 mmol). The stoppered tube was sealed in a screw-capped thick-walled glass tube and heated at 100 °C for 7 d. The equilibration, monitored by ¹H NMR spectroscopy, stabilised with an estimated 12c:13c ratio of 36 : 64.

Entry 8. A sample of the lactam 12c (20 mg, 0.06 mmol) in formic acid (4 mL) was sealed in a screw-capped thick-walled glass tube and heated at 100 °C for 3 d. Evaporation of the solvent and analysis of the residue by ¹H NMR spectroscopy gave an estimated 12c:13c ratio of 43 : 57.

Entry 9. A mixture of the lactams 12d and 13d (ratio *ca.* 56 : 44; 20 mg, 0.075 mmol) in toluene- d_8 (0.5 mL) in an NMR tube was treated with a solution of TFA in toluene- d_8 (6.7 M, 0.1 mL, 0.67 mmol). The stoppered tube was sealed in a screw-capped thick-walled glass tube and heated at 100 °C for 7 d. The equilibration, monitored by ¹H NMR spectroscopy, stabilised with an estimated 12d:13d ratio of 34 : 66.

Entry 10. A mixture of the lactams **12e** and **13e** (ratio *ca.* 50 : 50; 50 mg, 0.16 mmol) and TFA (0.2 mL, 2.7 mmol) in xylene (10 mL) was sealed in a screw-capped thick-walled glass tube and

heated at 150 °C for 3 d. The equilibration, monitored by ¹H NMR spectroscopy, stabilised with an estimated **12e:13e** ratio of 30 : 70.

Entry 11. A mixture of the lactams 12f and 13f (ratio *ca.* 64 : 36; 20 mg, 0.065 mmol) in toluene- d_8 (0.5 mL) in an NMR tube was treated with a solution of TFA in toluene- d_8 (6.7 M, 0.1 mL, 0.67 mmol). The stoppered tube was sealed in a screw-capped thick-walled glass tube and heated at 100 °C for 7 d. The equilibration, monitored by ¹H NMR spectroscopy, stabilised with an estimated 12f:13f ratio of 26 : 74.

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