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Complementary kinetic and thermodynamic resolution of a chiral biaryl axis

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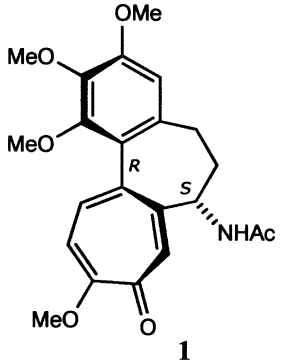
Abstract—The condensation of 2′-formylbiphenyl-2-carboxylic acid **4** with (*S*)-valinol proceeds under kinetic control to give a major product, (4b*R*,7*S*,a*S*)-6,7-dihydro-7-isopropyldibenz[*c*,*e*]oxazolo[3,2-*a*]azepin-9(4b*H*)-one **6a** (84%), in which the biaryl axis has the (*S*)-configuration. Heating **6a** at 140°C with a catalytic amount of acid gives rise to an equilibrium dominated by the diastereoisomeric (4b*S*,7*S*)-lactam **6b** (**6a**:**6b** ratio 27:73), in which the biaryl unit has the (*R*)-configuration. The structures of both lactams were established by X-ray crystallography; no other diastereoisomers were obtained.

Whereas the degree of control that can be exerted over the configuration of stereogenic atoms in a synthetic sequence has reached high levels, methods for the stereoselective generation of axial chirality have been emerging more slowly.[1] In the case of biaryls, the significance of axial chirality rose steeply with the observation of configuration-dependent biological activity, e.g. the ability of analogues of the alkaloid colchicine **1** to bind to the protein tubulin, which is dependent on their helicity,[2] and the widespread use of 1,1′-binaphthyls such as BINOL **2** as auxiliaries in asymmetric synthesis.[3] Our interest in these areas prompted us to evaluate the potential of configurationally-restrained biaryls for use in various contexts, and we herein describe two complementary routes to a potentially versatile fused lactam system **3**[4] in which chirality is efficiently relayed between the stereogenic centres and the biaryl axis.[5]

The polycyclic system was easily assembled by heating the aldehyde-acid **4**, available in two steps from diphenic anhydride,[6] with (*S*)-valinol **5** under dehydrating conditions,[7] which gave a mixture of two isomeric lactams **6**, as indicated by 300 MHz ^{1}H NMR spec-



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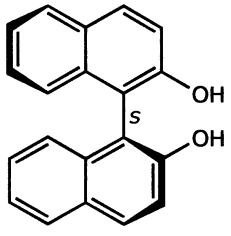

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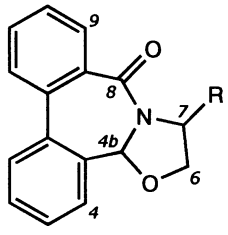

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Keywords: biaryl; fused lactam; axial chirality; kinetic resolution; chiral auxiliary; valinol.
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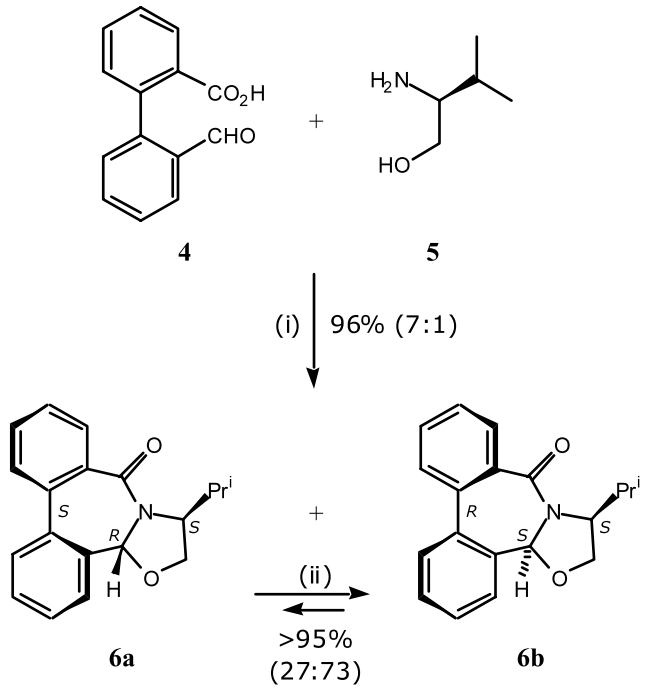
troscopy and TLC (Scheme 1).[8] The characterising features of the NMR spectrum of the mixture were two singlets at δ 5.89 and 5.72 ppm, which were assigned to the respective H-4b (methine) signals of the major and minor products (ratio $\geq$6:1). Chromatography afforded the major product **6a** (84%), mp 121–123°C (EtOAc), whose relative stereochemistry was confirmed as (4b*R*,7*S*,a*S*) by X-ray crystallography (Fig. 1).[9] A second product, mp 114–115°C (petroleum, bp 60–80°C), was also analysed by X-ray crystallography and identified as the (4b*S*,7*S*,a*R*)-diastereoisomer **6b** (12%) (Fig. 2).[10] The lactams **6a** and **6b** have highly twisted



Scheme 1. *Reagents and conditions*: (i) toluene, Dean–Stark apparatus, reflux, 32 h; (ii) *p*-TsOH (0.4 equiv.), d_8-toluene, sealed tube, 140°C, 3 days.

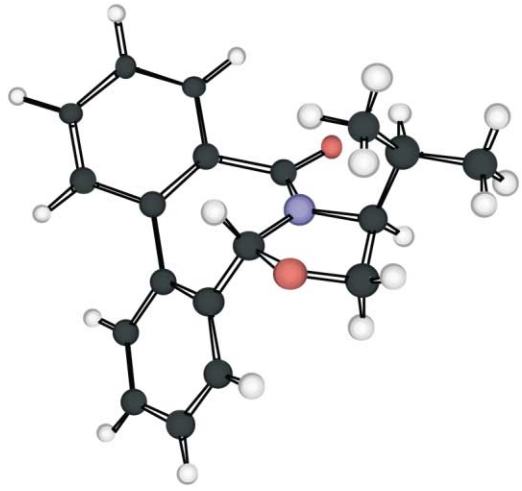


Figure 1. Structure of the lactam (4b*R*,7*S*,a*S*)-**6a** generated with *Chem3D* using X-ray data.

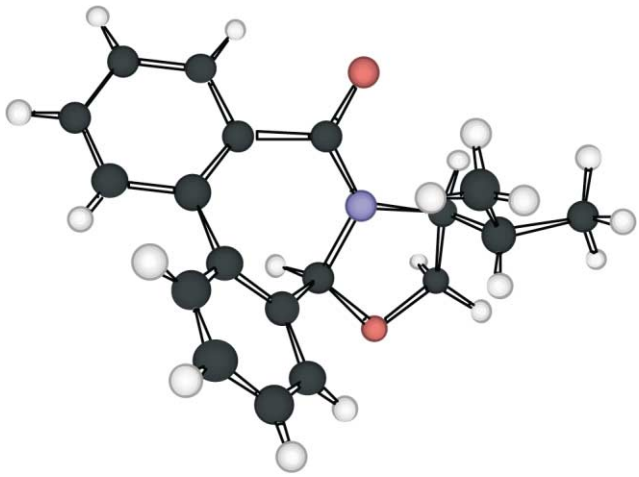
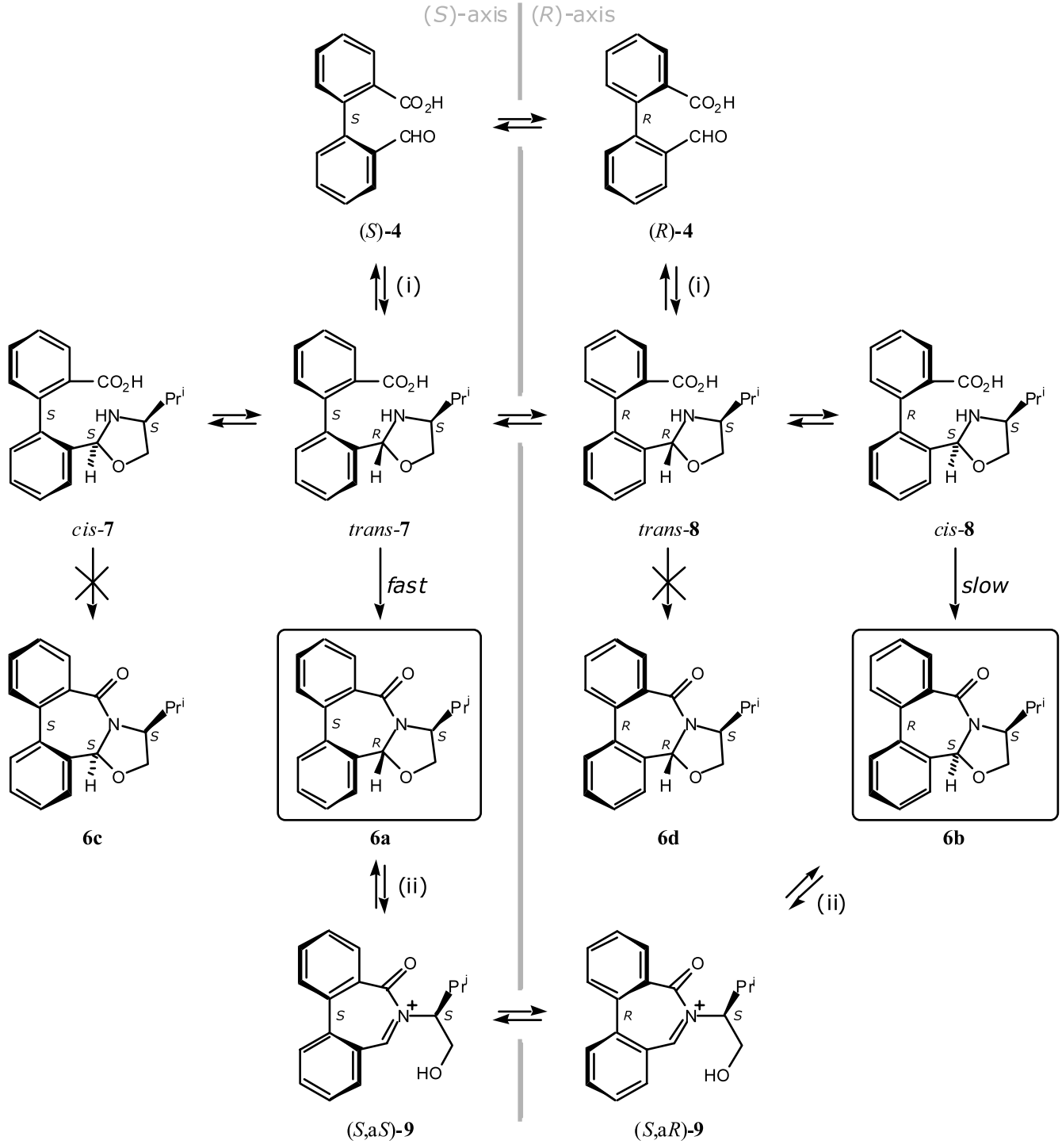


Figure 2. Structure of the lactam (4b*S*,7*S*,a*R*)-**6b** generated with *Chem3D* using X-ray data.

frameworks, the aromatic rings of each biaryl unit being 40–45° from coplanarity, and the respective carbonyls being −36° and +33° out of the plane of the adjacent aromatic ring.

Molecular modelling of **6a** and **6b** led to the conclusion that the latter might be the less strained of the two,[11] and equilibration experiments were therefore carried out. A solution of **6a** in deuterioacetonitrile containing *p*-toluenesulfonic acid (0.4 equiv.) was heated at 55°C and monitored by ^{1}H NMR spectroscopy. The slow formation of an equilibrium mixture of **6a** and **6b** was observed (ratio 35:65 after 33 days), and the first-order rate constant for the forward reaction (**6a**→**6b**) under these conditions was calculated to be 7×10^{-7} s^{-1}. For preparative purposes the equilibration was more conveniently carried out in toluene at 140°C, the final **6a**:**6b** ratio being 27:73 (by ^{1}H NMR spectroscopy) after 3 days (Scheme 1). No other products were evident, and no reaction was observed when **6a** was heated in acid-free toluene at 140°C for 7 days.

The formation of **6a** and **6b** as described above is presumed to involve the sequence of events depicted in Scheme 2. The condensation of **4** with (*S*)-valinol **5** leads to an equilibrium involving an iminoalcohol and the derived oxazolidines **7** and **8**. Acylation of such mixtures generally gives high yields of *N*-acyl-2,4-*cis*-oxazolidines, consistent with a kinetically controlled reaction favouring the least hindered transition state.[12] Under dehydration conditions, *trans*-**7** can readily cyclise to the lactam **6a**, but the cyclisation of *cis*-**8** to the lactam **6b** involves a more congested transition state and is consequently slower. Direct cyclisations of *cis*-**7** and *trans*-**8** do not occur because the lactams **6c** and **6d** are prohibitively strained.[11] Protonation of the lactam **6a** leads to the reversible formation of an acyliminium species **9**, which on heating can undergo rotation about the biaryl axis. The resulting equilibrium is dominated by the slightly less strained lactam **6b**.



Scheme 2. *Reagents*: (i) (*S*)-valinol **5**, dehydration; (ii) catalytic acid, heat.

The first step in Scheme 1 amounts to the dynamic kinetic resolution of the aldehyde-acid **4**, the biaryl unit of the lactam **6a** being made available for further manipulation in a single configuration. On the basis of Scheme 2 it is expected that this resolution process will be non-dynamic for a conformationally stable analogue of **4**, i.e. one with additional *ortho* substituents, because the pathways involving the oxazolidines **7** and **8** will be mutually exclusive. Nevertheless, given the ready availability of diverse enantiopure aminoalcohols, a broad range of functional[7] lactams **3** with unusual chiral topology should be accessible by this route. The scope of the second (equilibration) process will depend on the conformational flexibility of acyliminium species such as **9** when the biaryl unit has additional *ortho* substituents.[13] Experiments designed to explore these and other issues involving the lactams **3** are in progress and will be described in due course.

Acknowledgements

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8. New compounds gave satisfactory spectroscopic and analytical data. Selected data for **6a**: Colourless crystals, mp 121–123°C (EtOAc); $[\alpha]_D^{23}$ −183±7 (*c* 1.9, $CHCl_3$); ν_{max} (film)/cm^{-1} 1639; δ_H (300 MHz, $CDCl_3$) 0.94 (3H, d, *J* 7, Me_A), 0.97 (3H, d, *J* 7, Me_B), 2.69 (1H, dq, *J* 3.5 and 7, C*H*Me_2), 4.27 (3H, br s, 6-H_2, 7-H), 5.89 (1H, s, 4b-H), 7.39–7.59 (7H, m, Ar*H*), 7.95 (1H, dd, *J* 1.5 and 7.5, 9-H); (300 MHz, d_8-toluene) 0.73 (3H, d, *J* 7, Me), 0.83 (3H, d, *J* 7, Me), 2.81 (1H, dq, *J* 3.5 and 7, C*H*Me_2), 3.72 (1H, dd, *J* 6.5 and 9, 6-H), 3.80 (1H, dd, *J* 1.5 and 9, 6-H), 3.99 (1H, overlapping ddd, *J* 1.5, 6.5 and 9, 7-H), 5.62 (1H, s, 4b-H), 7.06–7.21 (6H, m, Ar*H*), 7.37–7.42 (1H, m, Ar*H*), 8.10 (1H, dd, *J* 1.5 and 7, 9-H); δ_C (75 MHz, $CDCl_3$) 16.5 (Me_A), 19.8 (Me_B), 28.0 (*C*HMe_2), 61.9 (7-C), 67.2 (6-C), 86.6 (4b-C), 122.3, 128.4 (two signals), 129.2, 129.4, 130.0, 130.2 and 131.4 (Ar*C*H), 135.7, 136.2, 136.6 and 139.0 (quaternary Ar*C*), 164.5 (8-C); R_f (hexane–ethyl acetate, 4:1) 0.30. Selected data for **6b**: Colourless crystals, mp 114–115°C (petroleum, bp 60–80°C); $[\alpha]_D^{27}$ +148±5 (*c* 2.25, $CHCl_3$); ν_{max} (film)/cm^{-1} 1639; δ_H (300 MHz, $CDCl_3$) 0.77 (6H, d, *J* 7, 2×Me), 2.08 (1H, apparent sextet, *J* 7, C*H*Me_2), 4.09–4.16 (1H, m, 6-H), 4.26–4.33 (2H, m, 6-H and 7-H), 5.72 (1H, s, 4b-H), 7.40–7.52 (3H, m, Ar*H*), 7.54–7.59 (3H, m, Ar*H*), 7.63–7.67 (1H, m, Ar*H*), 8.11 (1H, dd, *J* 1 and 8, 9-H); δ_C (75 MHz, $CDCl_3$) 18.7 (Me), 19.7 (Me), 30.7 (*C*HMe_2), 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 (Ar*C*H), 134.1, 136.2, 137.6 and 139.3 (quaternary Ar*C*), 165.4 (8-C); R_f (hexane–ethyl acetate, 4:1) 0.28.
9. *Crystal data* for **6a**: Colourless crystals from EtOAc: $C_{19}H_{19}NO_2$, $M=293.36$, monoclinic, $a=22.2220(6)$, $b=6.9665(2)$, $c=12.0229(4)$ Å, $\beta=121.135(2)°$, $U=1593.15(8)$ $Å^{-3}$, $T=293(2)$ K, space group *C* 2, $Z=4$, $D_{calcd}=1.223$ Mg m^{-3}, λ (Mo-K_α)=0.71073 Å, $\mu=0.079$ mm^{-1}, 14070 reflections measured, 3510 unique ($R_{int}=0.0414$) which were used in all calculations. The final $wR(F^2)$ was 0.0895 (all data). Crystallographic data (excluding structure factors) for compound **6a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 200172. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
10. *Crystal data* for **6b**: Colourless crystals from petroleum, bp 60–80°C: $C_{19}H_{19}NO_2$, $M=293.36$, monoclinic, $a=17.5383(7)$, $b=8.0426(3)$, $c=11.0989(6)$ Å, $\beta=104.339(2)°$, $U=1516.77(12)$ $Å^{-3}$, $T=150(2)$ K, space group *C* 1 2 1, $Z=4$, $D_{calcd}=1.285$ Mg m^{-3}, λ (Mo-K_α)=0.71073 Å, $\mu=0.083$ mm^{-1}, 12550 reflections measured, 3375 unique ($R_{int}=0.0551$) which were used in all calculations. The final $wR(F^2)$ was 0.0951 (all data). The isopropyl side-chain is disordered over two sites in the ratio 64:36. Figure 2 shows the major of the two rotamers. Crystallographic data (excluding structure factors) for compound **6b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 200173. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
11. The structures **6a–d** were generated in *Quantum CAChe 4.5* (Fujitsu) and their geometries optimised using semi-empirical methods (*CONFLEX* and *Mechanics* applications, augmented MM3 force field). The minimised total steric energies (kcal/mol) were: **6b**, 23.4; **6a**, 25.2; **6c**, 41.4; **6d**, 44.1. The main contributor to the difference in total steric energy between **6a** and **6c** was dihedral strain (+13.6).
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