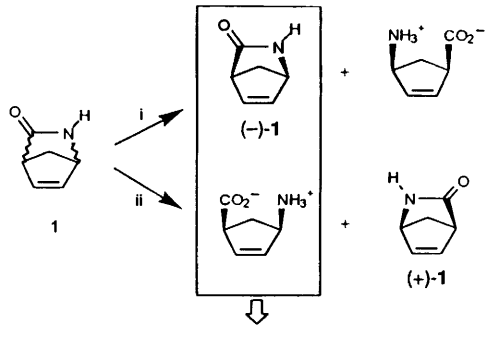
Conversion of one enantiomer of the carbocyclic nucleoside synthon 2-azabicyclo[2.2.1]hept-5-en-3-one into the other

Christopher F. Palmer and Raymond McCague
Chiroscience Ltd, Cambridge Science Park, Milton Road, Cambridge CB4 4WE, UK

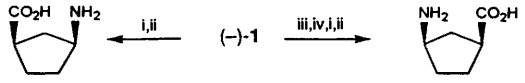
The lactam synthon 2-azabicyclo[2.2.1]hept-5-en-3-one was converted into its enantiomer by a 5-step sequence incorporating a skeletal rearrangement mediated by anchimeric assistance of the nitrogen atom; the route proceeded *via* a tosylate intermediate prone to racemization.

The bicyclic lactam, 2-azabicyclo[2.2.1]hept-5-en-3-one **1** is a versatile synthon for a variety of carbocyclic nucleosides.[1] Given that the required therapeutic activity of these nucleoside isosteres generally resides in one enantiomer having the natural nucleoside configuration, likewise the appropriate single-enantiomer of the bicyclic lactam synthon is required. We have reported the resolution of the lactam **1** by means of efficient enantiocomplementary enzymic resolutions whereby one enantiomer is specifically hydrolysed to the amino acid leaving the other as residual lactam (Scheme 1).[2,3] Thus, (−)-



Scheme 1 *Reagents:* i, whole cells from *Pseudomonas fluorescens*; ii, immobilized lactamase from *Aureobacterium sp.*

lactam remaining after a biotransformation with a strain of *Pseudomonas fluorescens* has been converted into the reverse transcriptase inhibitor (−)-carbovir. A particularly efficient transformation was with an isolated immobilized lactamase from a strain tentatively identified as an *Aureobacterium* species, on an aqueous solution of the lactam (200 g dm^{-3}) providing a clean product mixture from which the products are isolated with ease. In this case, the resulting (−)-amino acid from the transformation is appropriate for carbocyclic nucleosides of natural configuration and the downstream chemical steps for this are reported in the literature. As with any resolution, an issue is how to utilize the incorrect enantiomer, in this case the residual (+)-lactam, and we have considered whether it would be possible to effect an inversion of enantiomeric configuration so that all material would be converted into the same enantiomeric series. In this regard, it has been shown that such an inversion of configuration was possible by treatment with bromine followed by reduction to provide, from *either* enantiomer of **1**, an enantioconvergent route to *both* enantiomers of the GABA (γ-aminobutyric acid) agonist 4-aminocyclopentane-1-carboxylic acid (Scheme 2).[4] The key step is a skeletal rearrangement that takes place upon bromination with inversion of the configuration of the carbon skeleton.[5] However, as it stands, that approach does not leave

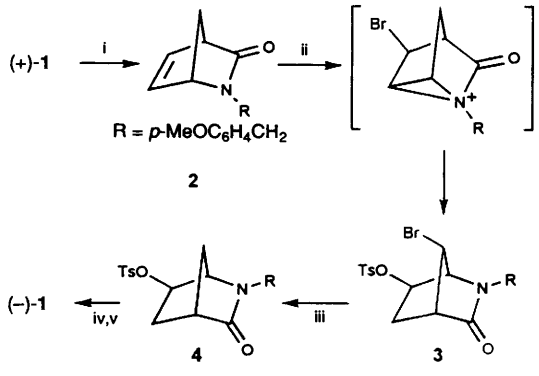


Scheme 2 *Reagents:* i, H_2, Pd/C, EtOH; ii, aq. HCl; iii, Br_2, CH_2Cl_2; iv, Bu_3SnH, toluene

the functionality in the cyclopentane ring necessary for synthetic elaboration.

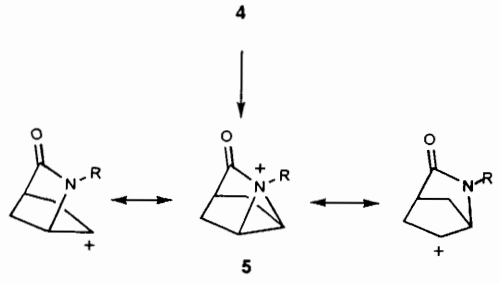
We now report the successful conversion of the (+)-enantiomer of the bicyclic lactam into the other and consider experimental conditions necessary to maintain the stereochemical control.

In principle, the objective of inverting the lactam configuration could be met simply by dibromination (with inversion of configuration), elimination with base to reinstate the olefin function, and finally reductive debromination of the remaining bridge bromine. Indeed, Snider[5] has shown the elimination step in the racemic series, but we find such elimination proceeds poorly. In any event, it was desirable to provide an intermediate with different C-6 and C-7 substituents to allow versatility in the synthesis and in this regard previous work[6] has shown that nucleophiles other than bromide can be used to trap the intermediate bromonium/aziridinium ion generated with either dibromodimethylhydantoin (DBDMH) or *N*-bromosuccinimide (NBS) on a suitably N-protected lactam. The *N*-4-methoxybenzyl lactam **2** was obtained in >95% yield from (+)-(**1**) by a phase-transfer method using solid potassium hydroxide and tetrabutylammonium bromide.[7] This particular protecting group, removable under oxidative conditions, was chosen since attempted reductive removal (Na/NH_3) of the simpler *N*-benzyl derivative of **1** resulted in cleavage of the nitrogen-bridgehead bond. With NBS and 4-methylbenzenesulfonic acid in dichloromethane, the N-protected lactam was converted into the tosylate **3** in 74% yield (Scheme 3).



Scheme 3 *Reagents:* i, *p*-methoxybenzyl chloride, base; ii, NBS, TsOH; iii, Bu_3SnH, AIBN, toluene; iv, $KOBu^t$–Me_2SO; v, ceric ammonium nitrate

Debromination of **3** with tributyltin hydride–azoisobutyronitrile (AIBN), followed by elimination of the tosylate with potassium *tert*-butoxide in dimethyl sulfoxide (yield generally < 45%), and deprotection (Scheme 3) provided the required (−)-lactam demonstrating, in principle, the overall inversion of the lactam in five synthetic steps. However, analysis by GC on a chiral column showed that the enantiomeric excess of 97% was less than that of the starting material (100% ee). Subsequent experiments revealed that the intermediate tosylate **4** was susceptible to racemization and this had taken place to a minor extent in the above conversion. Markedly, when the tosylate **4** was heated at 60 °C over 3 days in dimethyl sulfoxide prior to the elimination the azabicycloheptenone obtained was of only 6% ee. Such racemization is readily explained through the generation of the achiral aziridinium cation **5** by nitrogen-assisted solvolysis of the tosylate (Scheme 4). The cationic



Scheme 4

intermediate can alternatively be visualized as a pair of non-classical carbocation valance tautomers as typifies the chemistry of norbornane systems. Such an intermediate has been invoked by Mazzocchi *et al.*[8] to explain apparent retention of stereochemistry at C-6 in the displacement of a tosylate by a phenoxy group. Once formed, the achiral cation recombines with tosylate ion to reform racemic tosylate; we do not observe elimination of the tosylate to the olefin during the racemization conditions, so the direct loss of a proton from the intermediate does not seem to occur.

In order to prevent such racemization taking place, the elimination could be performed prior to the hydrodebromination. That way, even if the aziridinium carbocation does form, it will only recombine with tosylate to give a product with unaltered configuration, since the tosylate attacks the cation at the centre non-adjacent to the bromine. After hydrodebromination with either tributyltin hydride or tris(trimethylsilyl)silane in toluene at reflux, and deprotection, no trace of the (+)-enantiomer was detected in the product. However, once again, for reasons unknown, the elimination step gave only a rather poor yield (< 40%).

Subsequent work on the first route showed that the slight loss of enantiomeric excess had occurred not during the elimination but during the prior hydrodebromination, which was carried out in toluene at reflux (see above). Thus, recrystallization of the intermediate tosylate **4** resulted in the homochiral lactam (−)-**1** being obtained.

Overall, we have demonstrated the principle that the unwanted enantiomer from the biotransformation can be inverted enabling all the material from the biocatalytic resolution to be converged into one enantiomer. However, given the requirement for several steps using stoichiometric reagents and the low yield in the elimination step, it does not provide an economic process as it stands. Better could be to effect a racemization of the unwanted enantiomer of the product and then resubject it to the biotransformation, since in principle racemization, unlike inversion, could be catalytic. Given that we know that the tosylate **4** can be made to racemize, it was considered that if **4** can be formed from the olefin with 4-methylbenzenesulfonic acid then that would racemize. However, with tosic acid under a varity of conditions no such racemization takes place, only decomposition was observed which ties in with the lack of evidence for the reverse reaction, *i.e.*, direct elimination of tosylate **4** in the absence of strong base. Nonetheless, an effective catalytic racemization of the bicyclic lactam **1** remains a worthwhile pursuit.

Experimental

Inversion of protected (−)-2-azabicyclo[2.2.1]hept-5-en-3-one

A solution of 2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one **2** (10.3 g, 45.1 mmol) in dichloromethane (500 cm^3), containing 4-methylbenzenesulfonic acid (11.7 g, 62 mmol) was cooled to *ca.* −30 °C. *N*-Bromosuccinimide (10.4 g, 59 mmol) was added in small portions over 15 min and the resulting mixture allowed to warm to ambient temperature and stirred for 7 h. The reaction mixture was washed with 2 mol dm^{-3} HCl (3 × 100 cm^3), saturated aqueous $NaHCO_3$ (2 × 100 cm^3) and brine (100 cm^3) and finally dried (Na_2SO_4). After removal of the solvent the residue was subjected to chromatography (silica, 2:1 to 1:2 pentane–ethyl acetate) to give the dibromide (0.40 g, 2%) and the bromotosylate **3** (17.5 g, 81%; 16.1 g, 74% after recrystallization from ethyl acetate–pentane).

A solution of the bromotosylate (6.52 g, 14.0 mmol) and potassium *tert*-butoxide (1.71 g, 15.2 mmol) in dry dimethyl sulfoxide (15 cm^3) was stirred at 80 °C under nitrogen, further potassium *tert*-butoxide (1.67 g, 14.9 mmol) in dimethyl sulfoxide (5 cm^3) added after 18 h, and after a total of 21 h, the solution was diluted with ethyl acetate (200 cm^3), washed with water (3 × 20 cm^3) and dried (Na_2SO_4). The solvent was removed and the residue was subjected to chromatography (silica, 3:1 pentane–ethyl acetate) to give the bromoalkene (1.30 g, 31%).

A solution of the bromoalkene (0.87 g, 2.8 mmol), tributyltin hydride (1.2 cm^3, 4.45 mmol) and AIBN (20 mg) in toluene (20 cm^3) was heated at reflux under nitrogen for 2 h. The reaction mixture was cooled, diluted with acetonitrile (150 cm^3) and washed with pentane (4 × 25 cm^3). The solvent was removed and the residue was subjected to chromatography [silica, 2:1 diethyl ether–light petroleum (bp 40–60 °C)] gave 2-(4-methoxybenzyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (0.29 g, 44%, 1.26 mmol), which was dissolved in acetonitrile–water (15 cm^3; 3:1) at 0 °C. Ceric ammonium nitrate (0.77 g, 1.4 mmol) was added in small portions over 5 min. The solution was stirred at 0 °C for 30 min, when further ceric ammonium nitrate (0.67 g, 1.3 mmol) was added and the reaction stirred for a further 2 h. Ethyl acetate (50 cm^3) was added, the solution washed with water (2 × 5 cm^3) and dried (Na_2SO_4). The solvent was removed and the residue was subjected to chromatography (silica, diethyl ether) to give (−)-2-azabicyclo[2.2.1]hept-5-en-3-one (−)-**1** (0.036 g, 26%), 100% ee as determined by chiral GC on a Chrompak CP cyclodextrin B,2,3,6M19 column (50 m × 0.25 mm) at 25 psi† and 140 °C.

Acknowledgement

We thank Miss C. Ries for development of the chiral GC assay.

† 1 psi = 6.89 kPa.

References

1 N. Katagiri, M. Muto and C. Kaneko, *Tetrahedron Lett.*, 1989, **30**, 1645; N. Katagiri, M. Nomura, M. Muto and C. Kaneko, *Chem. Pharm. Bull.*, 1991, **39**, 1682; R. Vince and M. Hua, *J. Med. Chem.*,

1990, **33**, 17; J. Chen. M. Grim, C. Rock and K. Chan, *Tetrahedron Lett.*, 1989, **30**, 5543.
2 S. J. C. Taylor, A. G. Sutherland, C. Lee, R. Wisdom, S. Thomas, S. M. Roberts and C. T. Evans, *J. Chem. Soc., Chem. Commun.*, 1990, 1120.
3 S. J. C. Taylor, R. McCague, R. Wisdom, C. Lee, K. Dickson, G. Ruecroft, F. O'Brien, J. Littlechild, J. Bevan, S. M. Roberts and C. T. Evans, *Tetrahedron: Asymmetry*, 1993, **4**, 1117.
4 C. Evans, R. McCague, S. M. Roberts and A. G. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1991, 656.
5 W. C. Faith, C. A. Booth, B. M. Foxman and B. B. Snider, *J. Org. Chem.*, 1985, **50**, 1983.
6 C. F. Palmer, K. P. Parry and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1991, 484; C. F. Palmer, K. P. Parry, S. M. Roberts and V. Sik, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1021.
7 S. M. Roberts, personal communication.
8 P. H. Mazzocchi, H. L. Ammon, L. Liv, E. Colicelli, P. Ravi and E. Burrows, *J. Org. Chem.*, 1981, **46**, 4530.

Paper 5/00923E
Received 15*th February* 1995
Accepted 22*nd March* 1995