# Synthesis of *Either* Enantiomer of *cis*-3-Aminocyclopentanecarboxylic Acid from *Both* Enantiomers of Racemic 2-Azabicyclo[2.2.1]hept-5-en-3-one

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(−)-2-Azabicyclo[2.2.1]hept-5-en-3-one (−)-**1** was converted into (−)-*cis*-3-aminocyclopentanecarboxylic acid (−)-**2** in two steps and into the enantiomeric amino-acid (+)-**2** in three steps.

Further to our recent work[1] on the whole-cell catalysed resolution of the carbocyclic nucleoside precursor (±)-2-azabicyclo[2.2.1]hept-5-en-3-one **1**, we have applied this resolution process to the production of intermediates for the synthesis of the important GABA agonist *cis*-3-aminocyclopentanecarboxylic acid **2**[2–4] in optically active form.

Enantiospecific hydrolysis of the lactam (±)-**1**[1] gave optically pure samples of the amino acid [*e.g.* (+)-**3**] and the lactam [*e.g.* (−)-**1**]. The amino acid (+)-**3** can be converted into the biologically active compound (+)-**2** by catalytic hydrogenation. The bicyclic compound (−)-**1** was converted into the lactam (−)-**4** by hydrogenation, then into the amino acid (−)-**2** by chemical hydrolysis, using procedures reported in the literature for the corresponding racemic compounds.[3,5]

We have also been able to convert the resolved lactam (−)-**1** into the opposite enantiomeric series to that obtained by simple hydrogenation, and hence into the same series as that derived from the amino acid (+)-**3**.

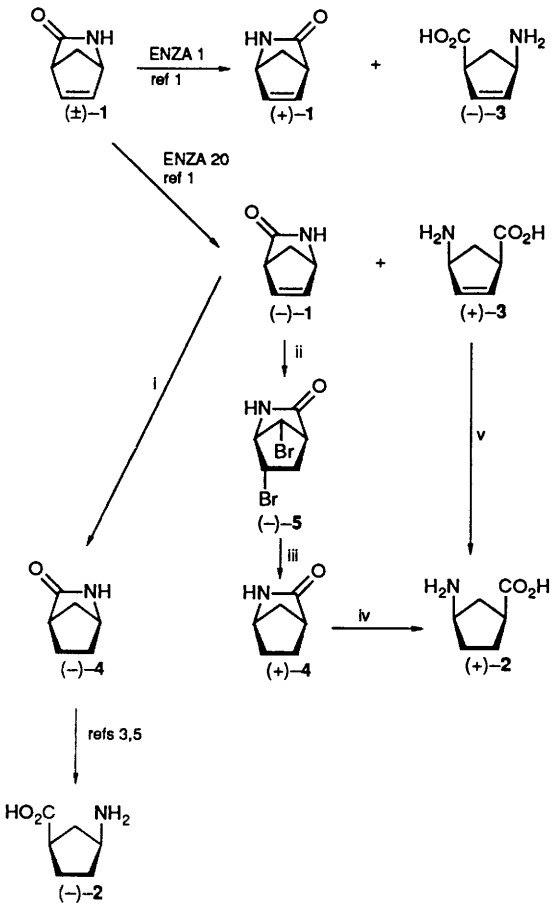
Thus treatment of the lactam (−)-**1** with bromine gave the adduct **5** which, through rearrangement of the bromonium ion intermediate,[6] has undergone a net 'inversion' of the carbocyclic skeleton. Reduction of the dibromo compound **5** with tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) gave the fully saturated lactam (+)-**4**, $[\alpha]_D$ +134°, of equal and opposite rotation to (−)-**4**, $[\alpha]_D$ −133°, obtained by hydrogenation of (−)-**1**.

Hydrolysis of (+)-**4** then gave (+)-**2**, identical with the material prepared by hydrogenation of (+)-**3** and to that described in the literature.[2]

Note that since it is possible to selectively hydrolyse either enantiomer of (±)-**1** depending on whether the biocatalyst ENZA-1 or ENZA-20 is chosen as the enantiospecific biocatalyst, it is possible to form either (+)- or (−)-**2** from both enantiomers of the racemic lactam, *i.e.* it is possible to set up enantioconvergent[7] syntheses of both (+)- and (−)-**2**. It is also noteworthy that the saturated γ-lactam (±)-**4** is unaffected by the abovementioned biocatalysts.

## Experimental

(+)-2-*Azabicyclo*[2.2.1]*heptan*-3-*one*.—Bromine (0.53 g) in dichloromethane (2 ml) was added dropwise to (−)-(2)-azabicyclo[2.2.1]hept-5-en-3-one (−)-**1** (0.36 g) in dichloromethane (4 ml) with stirring at room temp. After 15 min, methanol was added and the non-volatile compounds were adsorbed onto silica gel. Elution from the stationary phase using ethyl acetate gave (−)-6*endo*, 7*anti*-dibromo-2-azabicyclo[2.2.1]heptan-3-one (−)-**5** (0.7 g, 79%), m.p. 190–200 °C (decomp.). The lactam (−)-**5** (0.215 g) in toluene (2 ml) was refluxed under nitrogen with tributyltin hydride (0.815 g) and one crystal of AIBN for 5 h. Water (10 ml) was added and the mixture was washed with hexane (3 × 50 ml). The aqueous layer was extracted with dichloromethane (3 × 50 ml) and these organic fractions were dried and evaporated. The residue was chromatographed over




*Reagents and conditions:* i, $H_2$, Pd/C, EtOAc (94%); ii, $Br_2$, $CH_2Cl_2$ (79%); iii, $Bu_3SnH$, AIBN, $PhCH_3$, heat (87%); iv, HCl aq, heat (97%); v, $H_2$, Pd/C, AcOH (94%)

silica using ethyl acetate as eluent to give the title compound (0.077 g, 87%), m.p. 112–114 °C, $[\alpha]_D^{27}$ 134° (*c* 0.26, methanol).

(−)-2-*Azabicyclo*[2.2.1]*heptan*-3-*one*.—(−)-2-Azabicyclo-[2.2.1]-hept-5-en-3-one (−)-**1** (0.22 g) in ethyl acetate (3 ml) was added to a suspension of 10% palladium on carbon (13 mg) in ethyl acetate (4 ml) under an atmosphere of hydrogen. After 16 h the solution was filtered through Celite and the stationary phase was washed with ethyl acetate. Evaporation of the combined organic phases gave the title compound (0.21 g, 94%), m.p. 112–114 °C; $[\alpha]_D^{30}$ −133° (*c* 0.26, methanol).

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