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Chiral [2:2]Paracyclophanes.1. : Synthesis and Characterisation of Unique Homochiral Amino-Acids derived from [2:2]Paracyclophane

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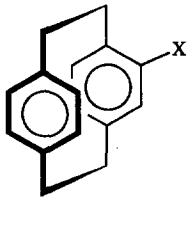
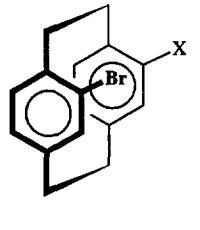
Abstract The synthesis and characterisation of unique, homochiral amino-acids derived from linearly chiral [2:2]paracyclophane derivatives is described.

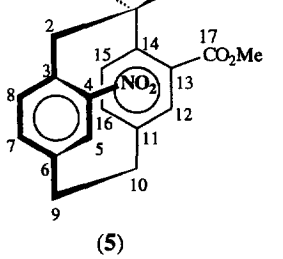
Substituted [2:2]paracyclophanes (**1**) (Figure 1) are molecules that are linearly chiral[1], chemically stable[2] and racemise only at temperatures above 180°C at which the system dissociates to *p*-quinone methides.[3] As such they have great potential as chiral reagents, chiral auxiliaries and chiral catalysts. This potential is greatly enhanced in that the readily resolvable acid (**2**)[4] and related esters and ketones undergo regioselective bromination in the 'ψ-geminal' position to give (**4**).[5] The close proximity of the two functional groups in (**4**) allows for the synthesis of a wide variety of compounds, some with interacting functional groups useful for chiral catalysis, others with one functional group subject to 'tuned' steric hindrance from the adjacent group. So far only three examples of the use of [2:2]paracyclophane (2.2PC) derivatives in chiral synthesis have been reported.[6, 7, 8] One[6] incorporates the 2.2PC derivative within the substrate, one[7] uses a 2.2PC unit as a chiral auxiliary and the third uses a derivative as a chiral catalyst.[8] For the last two years we have investigated a series of 2.2PC phenols[9], amines[10] and boron[11] derivatives as chiral auxiliaries and reagents. We now report on the preparation and characterisation of homochiral amino-acids which are unique in that their chirality depends solely on the chirality of the 2.2PC unit. Such amino-acids will affect the topology and lipophilicity of any peptide chains into which they are incorporated.



(**1**); (**2**), X = CO_2H
(**3**), X = CO_2Me



(**4**)

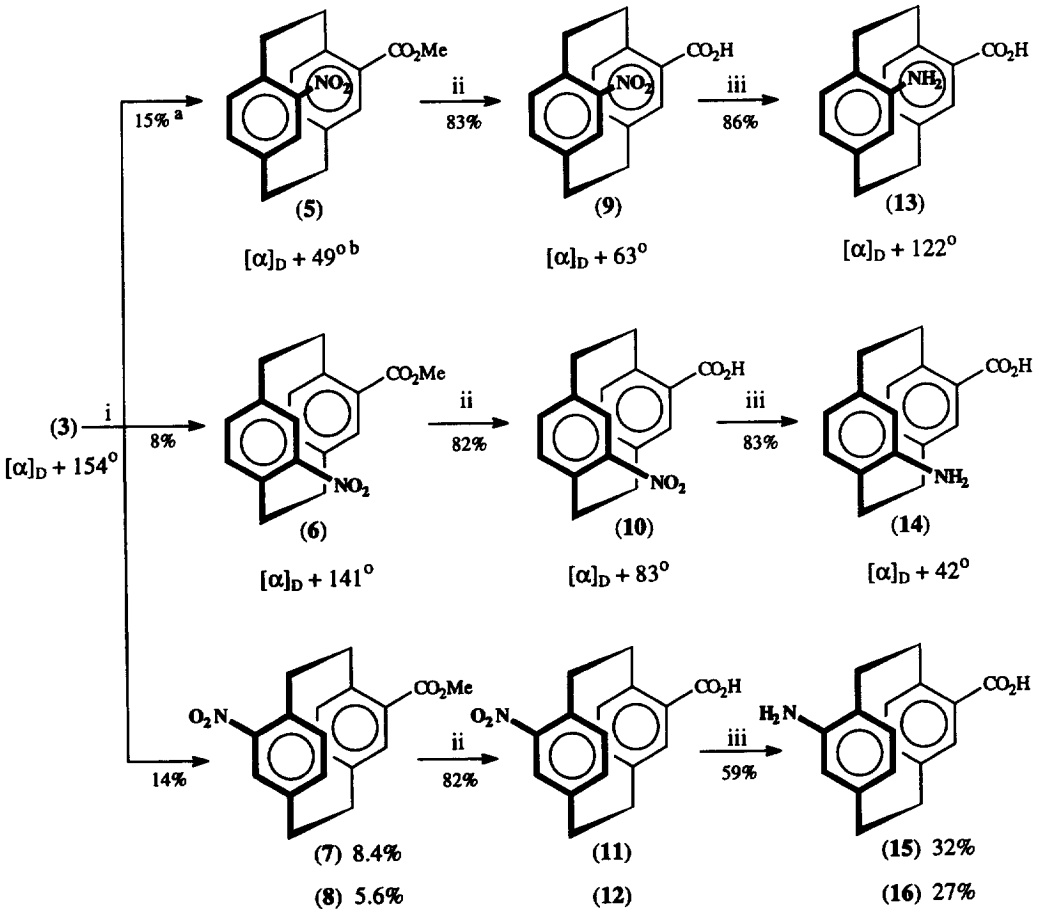


(**5**)

Figure 1

Methylation of (S)-(+)-(2) (> 99% e.e.)[13, 14] gives (S)-(+)-(3). The nitration of (3) was not regiospecific but gave a mixture of mono-nitrated compounds in 37% overall yield. Separation gave pure (R)-(+)-4-nitro-13-carbomethoxy[2:2]paracyclophane (5) of ≥ 98% e.e. and (R)-(+)-5-nitro-13-carbomethoxy[2:2]paracyclophane (6) of ≥ 99% e.e. We were unable to separate (7) or (8) or any of the derived compounds shown in Scheme 1, and the yields of (7), (11) and (15) are based on difference spectra. The spectra were however, so clear that unequivocal structures could be assigned to these compounds.

Saponification of the nitro-esters gave the corresponding acids (9), (10), (11) and (12) which were catalytically reduced to the target amino-acids, (13), (14), (15) and (16) (Scheme 1).



i) HNO_3/H_2SO_4. ii)KOH/EtOH, Δ. iii) H_2/Pd-C

a) All yields are of isolated products. b) All rotations were taken at 25 °C at defined concentrations

Scheme 1

Complete structural assignments will be given in a full paper, but briefly the process used was as follows.

(*a*) The mass spectra and the couplings of the aromatic protons in the 400 MHz ^{1}H nmr spectra were used to prove that the two substituents were on different aromatic rings.

(*b*) By using appropriate mono-substituted 2.2PC derivatives we have tabulated the direct and through-space effects of a variety of substituents on the chemical shifts of both aliphatic and aromatic protons, in an extension of earlier work by Cram.[12] We have done the same for the ^{13}C nmr data.

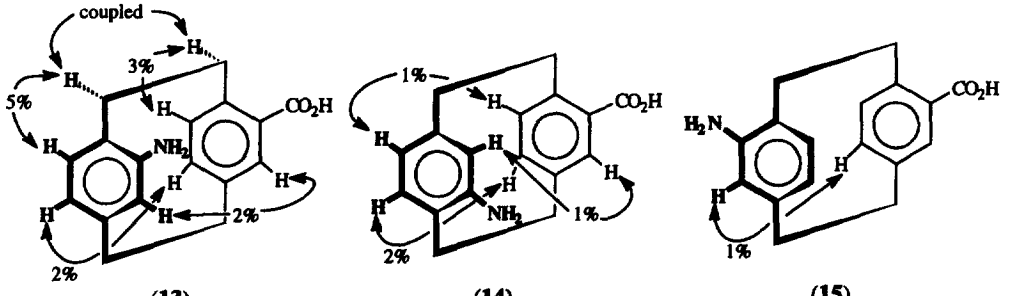
We find that nitro, carboxyl and carbomethoxyl groups have little effect on the chemical shifts of protons on the adjacent ring but have major effects on the closest aliphatic protons (*e.g.* H-1a and H-2a of (**5**)), as well as on the *ortho*- and *para*-protons. Decoupling experiments can show whether the shifted aliphatic protons are coupled or not and so define whether both substituents are in the 'top' half of the molecule or whether one is in the 'top' and one in the 'bottom' half.

The most useful effect for us was that there was a downfield shift of 0.70 ppm by an amino group on a ψ-geminal proton (H-13) and an upfield shift of 1.11 ppm on the *ortho*-proton (H-5) relative to 2.2PC at 6.38 ppm. The signals for H-13 (if present) and H-5 are well clear of the signals due to the other aromatic protons, the assignments of which are then readily accessible by decoupling experiments.

Thus one of the amino-acids had *no* protons shifted downfield and so was unequivocally defined as 4-amino-13-carboxy[2:2]paracyclophane (**13**). Another had a proton at δ 7.99 as a doublet (J = 2 Hz). This extremely low field signal reflects the combined effect of a transannular amino group together with the *ortho* effect of a carboxyl group and shows that structure (**14**), 5-amino-13-carboxy[2:2]paracyclophane had to be assigned to this product. In the mixture of products (**15**) and (**16**), the major product had an aromatic proton as a doublet (J = 8 Hz) at δ 6.98, the result of a ψ-geminal amino group and a *meta*-carboxyl group. The major product therefore was 8-amino-13-carboxy[2:2]paracyclophane, (**15**).

The ^{13}C nmr were less helpful in structure assignment as transannular effects could not be mapped. However the functional group shifts are larger and were in full accord with the structures assigned.

(*c*) The n.O.e. spectra were investigated and were in close agreement with our assignments (Figure 2).



(**13**) (**14**) (**15**)

Figure 2

(*d*) Although many of our products were crystalline, in nearly every case the crystals were either 'feathery' or twinned. However we were able to obtain a suitable crystal of (**5**), the X-ray analysis of which confirmed the given structure (Figure 3). This result showed that the arguments used previously were indeed well founded. The crystal used was of a single enantiomer and the absolute configuration was also in accord with our expectations based on *indirect* assignments of absolute configuration to (**2**).[13, 14]

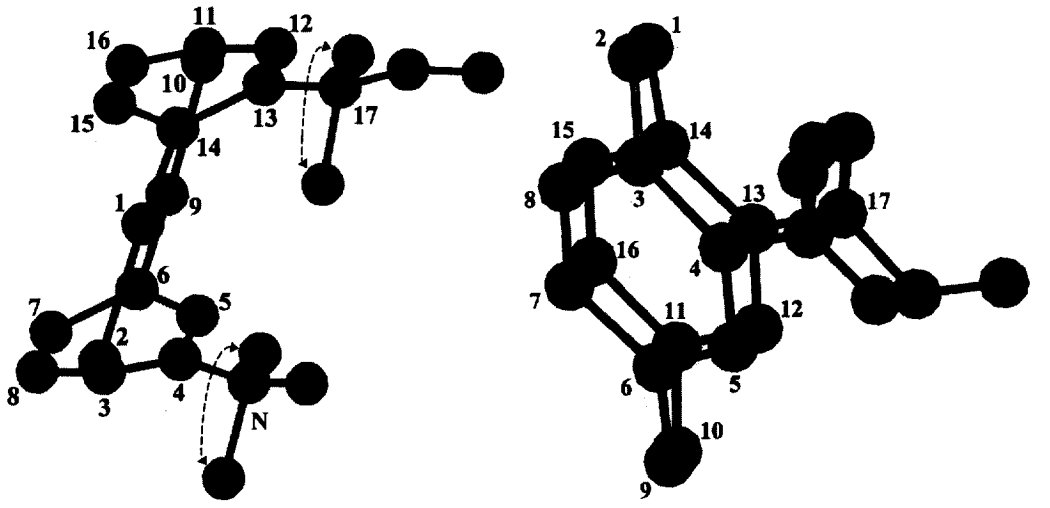


Figure 3

A rational synthesis that makes either enantiomer of (**13**) readily available will be reported separately. When built into a peptide chain (**13**) should lead to the equivalent of a β-turn and to the possibility of synthesising rigidly defined β-sheet structures.

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