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Chiral [2.2]paracyclophanes — III. The preparation of unique homochiral amino-acids derived from [2.2]paracyclophane[1] †

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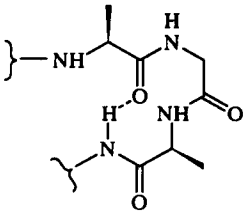
Abstract: The synthesis and characterisation are described of homochiral (+)-4-carboxy-13-amino-[2.2]paracyclophane and (+)-4-carboxy-12-amino-[2.2]paracyclophane, which are unique, linearly chiral amino-acids which may act as β-turn mimics. © 1997 Elsevier Science Ltd. All rights reserved.

The ability to control the steric and electronic relationships of portions of peptide chains is a serious challenge of continuing interest due to the wide ranging and varying biological activities of peptides.[2] The number of native and modified peptides used as drugs, both as agonists and antagonists is rapidly increasing,[3] although their frequent instability to enzymes and poor membrane permeability have led to native peptides being used mainly as lead pharmacophores for the design of peptidomimetics possibly with good chemical and metabolic stability, bioavailability, receptor selectivity and affinity and with few side effects.

The β-turn, **1**, is a structural motif common to many biologically active peptides and to molecular recognition segments of proteins (for example, extracellular matrix peptides involved in cell recognition) as well as to transformations associated with platelet aggregation.[4] Hence many attempts have been made to replace the β-turn by some kind of rigid template from which peptide chains of known initial steric relationship can be grown. Compounds **2**,[5] **3**,[6] **4**,[7] and **5**[8] represent such frameworks.



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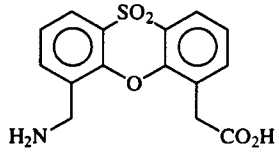

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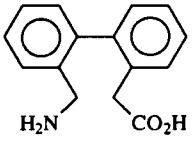

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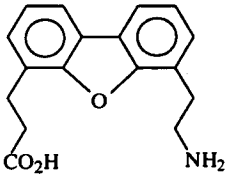

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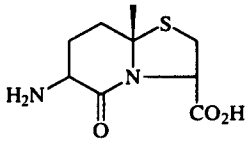

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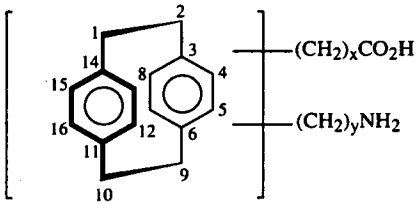

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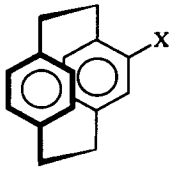

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Compounds **2**, **3** and **4** all have rigid, achiral, lipophilic frameworks from which two peptide chains can be grown from adjacent benzene rings. Compound **5** differs from these in that the framework is

† Dedicated to Professor H. C. Brown in recognition of his leadership and friendship.

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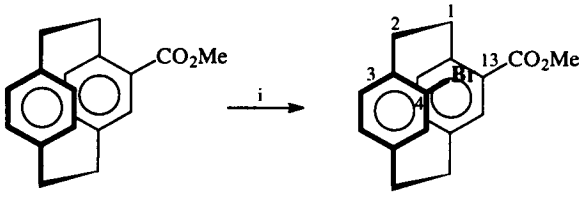
itself a chiral, bicyclic peptide which is presumably hydrophilic. Compound **5** has only been used in a micro-synthesis and its chemical stability is unreported. It may also be susceptible to enzymic degradation and racemisation.

[2.2]Paracyclophanes are molecules in which two benzene rings are held rigidly and closely face to face.[7] So constrained is the system that the benzene rings are deformed into shallow boats[10] with the *para*-positions *ca* 12° out of plane and with a strain energy of 129.8 kJ mol^{-1} mainly associated with the distortion of the benzene rings.[9] A slight concertina movement of the two benzene rings towards and away from each other occurs, as well as a simultaneous twisting of up to 6° of the benzene rings from their normal axis. The molecule is effectively rigid due to the inability of one benzene ring to rotate independently of the other and hence all mono-substituted [2.2]paracyclophane (22PC) derivatives are linearly chiral,[11] as well as many di-substituted compounds. In order for racemisation to occur, a bridge C–C bond must be broken and this does not occur below *ca* 180°C.[12]

Despite the slight distortion of the benzene rings the system is chemically stable and undergoes most of the usual benzenoid reactions as well as some peculiar to the 22PC system. Among the latter is electrophilic substitution at C-13 (φ-geminal) of 22PC derivatives substituted with electron withdrawing groups such as COR, CO_2Me, NO_2, SO_2Ph.[13] An important example is shown in Eq. 1.



(1)

8 **9**

i, Br_2/Fe, 93%

The acid **7a** (**7**, X=CO_2H) is readily produced from commercially available [2.2]paracyclophane and it is easily resolved.[14] The (+)-isomer of **7a** is converted to (+)-**8** from which (−)-**9** is produced. We have recently carried out an X-ray determination of (−)-**9** showing that it is the (*R*)-isomer, as shown in Eq. 1.[15] The (+)-isomer of **8** is therefore the (*S*)-isomer shown. These assignments are in accord with those made by less direct methods.[14,16–18] This helps also to highlight an important advantage to the use of 22PC derivatives. Not only may they be homochiral but *the geometrical relationships of any substituents directly attached are unequivocally defined.*

It therefore seemed that the 22PC system was an ideal substrate on which to build a set of amino-acids **6** in which both substituents could be on one ring or on different rings. This approach has something in common with those leading to **2**, **3** and **4** but it is unique in that the phenyl rings are in a chiral framework and the substituents are not in the same plane.

We therefore set out to prepare some examples of amino-acids **6** with x=y=0, in the first instance.[1] In particular we aimed at homochiral 4-amino-13-carboxy-[2.2]paracyclophane, **15**, starting with the (+)-(*S*)-ester, **8** (>99.9% e.e.). Of course both enantiomers of **8** were available to us. Before embarking on the synthesis we carried out preliminary MOPAC calculations[19] of the conformations of simple peptides derived from **15**. These showed that, due to the close proximity of the amino and carboxyl groups, the chain was squeezed so that there was no hydrogen bonding between the second carbonyl and amide NH groups. After this, however, there was regular hydrogen bonding and the residues strongly resemble a β-sheet, the overall geometry being controlled by the 22PC moiety (Figure 1).

By analogy with the bromination of **8** we hoped that its nitration would be selective to give the 13-CO_2Me, 4-NO_2 isomer **10** in good yield. However mono-nitration of 22PC itself to give 4-nitro-22PC is known not to proceed in high yields[13,20] and in our hands only 15% could be obtained. In

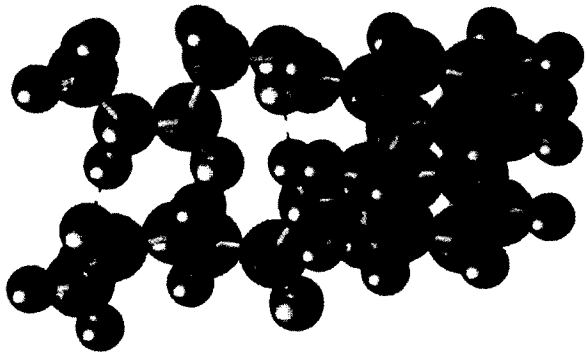
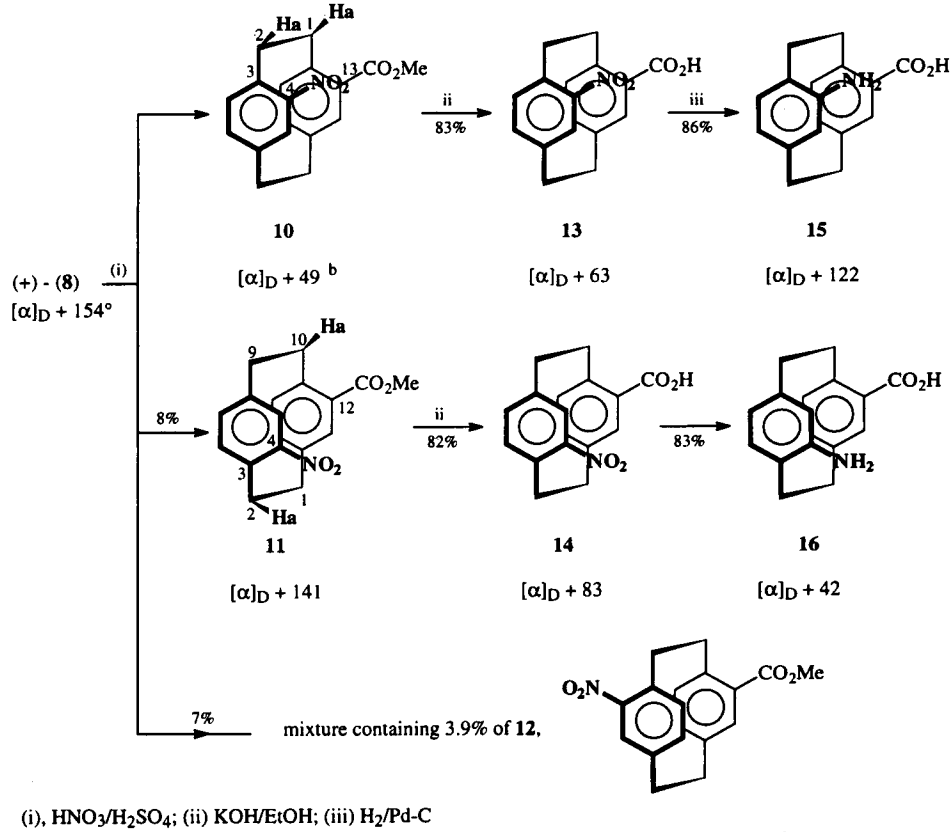


Figure 1.

the event, nitration of (+)-(**8**) gave only 25% of a mixture of mono-nitro esters, with no great degree of regioselectivity (Scheme 1).



(i), HNO_3/H_2SO_4; (ii) KOH/EtOH; (iii) H_2/Pd-C
(a) All yields are of isolated products. (b) All rotations taken at 25°C at defined concentrations.

Scheme 1.

Despite the use of many nitrating agents, including N_2O_5, we were unable to improve the yield or selectivity of the nitration. Compounds **10** and **11** were readily separated as pure compounds by column chromatography, each with an e.e of >99.9%. However compound **12**, whilst shown to be

Table 1. Substituent effects in 4-monosubstituted [2.2]paracyclophanes

Substituent	*H-2a*	*H-5*	*H-7*	*H-8*	*H-12*	*H-13*	*H-15*	*H-16*
CO_2Me	+1.00	+0.65	+0.34	+0.07	-	-	-	-
CO_2H	+1.25	+0.82	+0.24	+0.10	+0.06	+0.06	-	-
NO_2	+0.82	+0.77	+0.49	+0.30	+0.18	+0.18	+0.06	+0.06
NH_2	-	-1.11	-0.36	-0.22	+0.10	+0.70	+0.10	+0.10

Table 2. Predicted and experimental ^1H NMR signals for compounds **10**, **13** and **15**

Substance	*H-1a*	*H-2a*	*H-5*	*H-7*	*H-8*	*H-12*	*H-15*	*H-16*
Compound 10								
Predicted	4.07	3.89	7.25	6.97	6.78	7.31	6.61	6.88
Found	**4.1-4.3**	**3.9-4.1**	**7.15**	**6.75**	**6.66**	**7.23**	**6.64**	**6.71**
Compound 13								
Predicted	4.32	3.89	7.31	6.97	6.78	7.48	6.64	6.78
Found	**4.16-4.21**	**3.97-4.1**	**7.23**	**6.88**	**6.79**	**7.19**	**6.73**	**6.80**
Compound 15								
Predicted	4.32		5.53	6.13	6.26	7.40	6.68	6.82
Found	**4.32**		**5.58**	**6.22**	**6.36**	**7.40**	**6.48**	**6.62**

present in 3.9% overall yield by ^1H NMR studies, could not be isolated from another isomer of unknown constitution. Unfortunately, this was true also of the derived nitro-acid and amino-acid mix, so that **12** and its derivatives were never obtained pure.

Saponification of **10** and **11** to **13** and **14**, respectively, were unexceptional, as were the reductions to yield amino-acids **15** and **16**. These are *unique* amino-acids which owe their chirality *entirely* to the linearly chiral [2.2]paracyclophane unit.

The characterisation of the products was relatively easy and used the following routes.

(1) The multiplicities of the proton signals in the ^1H NMR spectra clearly indicated whether the substituents were on one ring or two. In each case the latter was found.

(2) Many years ago[21] the positions of substituents in the [2.2]paracyclophane nucleus were arrived at by ^1H NMR spectra analysis, essentially by plotting the shifts of single substituents and assuming that these are additive for the disubstituted compounds. We have followed this method, greatly extending the range of substituents and using coupling constraints to assign particular protons. In the present context, the substituents of interest are CO_2Me, CO_2H, NO_2 and NH_2. The aromatic protons of [2.2]paracyclophane itself give a signal at δ 6.48 and the aliphatic protons at 3.07. All substituent shifts are given relative to these signals and are shown in Table 1.

Applying these data to compounds **10–16** (the numbering used has the carbon bearing the nitrogen substituent at C-4) gave the results shown in Tables 2 and 3.

Agreement is excellent and is backed by the multiplicities of all signals. Another important point

Table 3. Predicted and experimental ^{1}H NMR signals for compounds **11**, **14**, **16**

Substance	*H-2a*	*H-10a*	*H-5*	*H-7*	*H-8*	*H-13*	*H-15*	*H-16*
Compound 11								
Predicted	3.89	4.07	7.25	6.97	6.78	7.31	6.88	6.61
Found	**3.9-4.2**		**7.24**	**6.83**	**6.63**	**7.19**	**6.75**	**6.61**
Compound 14								
Predicted	3.89	4.32	7.25	6.97	6.78	7.48	6.78	6.64
Found	**3.90**	**4.0-4.2**	**7.24**	**6.95**	**6.74**	**7.20**	**6.84**	**6.68**
Compound 16								
Predicted	-	4.32	5.37	6.12	6.26	8.00	6.82	6.68
Found	-	**3.9-4.1**	**5.47**	**6.10**	**6.24**	**7.79**	**6.63**	**6.56**

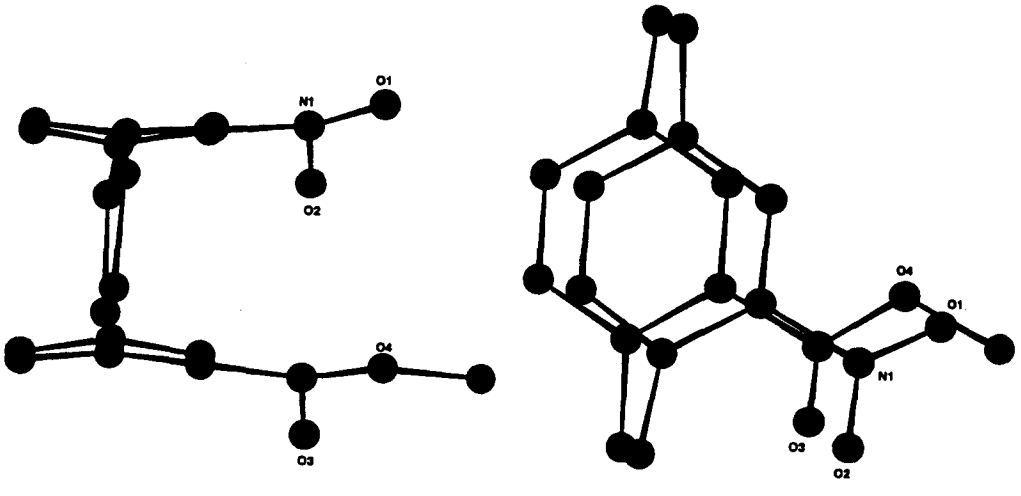


Figure 2.

is that in one series the bridged protons that are moved downfield (H-1a and H-2a) are coupled but in the other they are not (H-2a, H-10a). Additional evidence came from NOE effects.[18]

In this series, it proved very difficult to obtain crystals suitable for X-ray analysis. However crystals of (±)-**10** were finally obtained and analysed, the results being given in two projections in Figure 2.[22]

Conclusion

The homochiral unique amino-acids, (+)-4-amino-13-carboxy-[2.2]paracyclophane **15** and the isomeric (+)-4-amino-12-carboxy-[2.2]paracyclophane **16** have been prepared and characterised. These amino-acids are unique in that they are linearly chiral and may act as β-turn peptidomimetics. We are currently essaying more rational syntheses of **15** which will be reported separately.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a WM 250 Bruker instrument at 250.1 MHz and 62.9 MHz respectively. DEPT/135 spectra were also obtained on this instrument. NMR spectra were recorded in $CDCl_3$ unless otherwise stated and are reported relative to tetramethylsilane (δ=0). J values

are quoted in Hz. IR spectra were recorded on a Perkin–Elmer 1420 ratio recording spectrometer and a UNICAM SP 1050 spectrometer as KBr discs unless otherwise stated and absorptions are given in cm^{-1}. UV–vis spectra were recorded on a Phillips PV 8720 UV–vis scanning spectrophotometer with absorption maxima reported in nm along with $\log_{10} \varepsilon$. Mass spectra were obtained using a VG MASSLAB 12-250 quadrupole instrument using alternating chemical/electron impact ionisation (ACE) conditions. Accurate masses were recorded on a ZAB-E VG analytical reverse geometry magnetic instrument.

All solvents were purified by standard methods.[23] Chromatographic separations were carried out under medium pressure on silica gel (230–400 mesh).

Nitration of S-(+)-4-carbomethoxy-[2.2]paracyclophane **8**

Compound **8** (0.88 g, 3.31 mmol) was dissolved in CH_2Cl_2 (60 ml), and the solution divided equally between four 50 ml round-bottomed flasks, each containing water (5 ml). The flasks were partially submerged in an ultrasound bath and the mixture emulsified by exposure to ultrasound for 30 min.

A pre-mixed solution of conc. H_2SO_4 and conc. HNO_3 (1:1 by volume) was added to the sonicated reaction mixture at *ca* 1 drop/minute until no starting material could be detected by TLC. During the reaction, the initially colourless solution gradually became orange. Continuous monitoring showed the production of a wide range of products, including three fast-running fractions. At no time was a clean reaction mixture produced.

The reaction mixture was washed with water (10 ml) and the organic layer was separated, washed with saturated Na_2CO_3, dried over $MgSO_4$, filtered and evaporated. Chromatography on silica gel using light petroleum:CH_2Cl_2 as an eluent gave three fractions: (i) 72 mg (7%) of a mixture of two isomers containing **12** (3.9% overall); (ii) 154 mg (15%), R_F=0.34, shown to be pure **10**; and (iii) 82 mg (8%), R_F=0.45, shown to be pure **11**.

*4-Nitro-13-carbomethoxy-[2.2]paracyclophane, **10***, R_F 0.34 (CH_2Cl_2), m.p. 122–127°C (*ex* CH_2Cl_2) had the following characteristics. δ_H 7.23 (1H, d, J=1.8, H-5), 7.15 (1H, d, J=1.9, H-12), 6.75 (1H, dd, J=8, 1.8, H-7), 6.71 (1H, dd, J=8, 1.9, H-16), 6.66 (1H, d, J=8, H-8), 6.64 (1H, d, J=8, H-15), 4.3–4.1 (1H, m, H-1a), 4.1–3.9 (H-2a), 3.84 (3H, s, OCH_3), 3.2–3.0 (6H, m, H-1b, H-2b, H-9, H-10). δ_C 167.0 q (C=O), 149.2 q (C-4), 141.8 q, 141.6 q (C-6, C-14), 139.5 q (C-11), 137.71, 137.70 q (C-16, C-13), 136.1 (C-7), 134.2 (C-8), 130.2 q (C-3), 129.3 (C-5), 128.0, 123.7 (C-12, C-15), 51.9 (OCH_3), 34.56, 34.47, 34.39, 33.59 (C-1, 2, 9, 10). ν_{max}, 1770 (C=O), 1520, 1350 (N=O). λ_{max} (EtOH), 218 (4.44), 324 (3.49). m/z 311 (8, M^+), 280 (45), 162 (100), 149 (7), 133 (17), 119 (76), 104 (62), 91 (40). Found, M^+ 311.1158, $C_{18}H_{17}NO_4$ requires 311.1158. $[\alpha]_D$ +49 (c 0.53 in $CHCl_3$).

*4-Nitro-12-carbomethoxy-[2.2]paracyclophane, **11***, R_F 0.45 (CH_2Cl_2), m.p. 93.2–94.4°C, had the following characteristics. δ_H, 7.24 (1H, d, J=1.9, H-5), 7.19 (1H, d, J=2, H-13), 6.83 (1H, dd, J=8, 1.9, H-7), 6.75 (1H, dd, J=8, 1.9, H-15), 6.63 (1H, d, J=8, H-8), 6.61 (1H, d, J=8), H-16), 4.2–3.9 (2H, m, H-2a, 10a), 3.8 (s, OCH_3), 3.4–3.0 (4H, m), 3.0–2.7 (2H, m). ν_{max} 1730 (C=O), 1530, 1350 (N=O). λ_{max} (EtOH) 203.5 (4.54), 218 (4.44), 324 (3.49). m/z, 311 (69, M^+), 280 (15), 162 (100), 149 (10), 147 (52), 119 (50), 104 (58), 96 (30). Found, M^+ 311.1158, $C_{18}H_{17}NO_4$ requires 311.1158. $[\alpha]_D$ +141 (c 0.14 in $CHCl_3$).

*General method for the conversion of the nitro-esters **10** and **11** into the nitro-acids **13** and **14***

The nitro-ester (100 mg, 0.32 mmol) was added to EtOH (8 ml) containing KOH (103 mg, 1.8 mmol) and the reaction mixture heated under reflux for 8 h. At this stage all the nitro-ester had vanished and therefore the solvent was removed and the product was dissolved in water (10 ml). The solution was first extracted with CH_2Cl_2 and then the aqueous layer was acidified with conc. HCl and extracted with CH_2Cl_2. The organic extract was dried ($MgSO_4$), filtered and evaporated to give the required nitro-acids, essentially pure. From **10**, 79.26 mg (82%) of **13** were obtained. From **11**, 80.23 mg (83%) of **14** were obtained.

*4-Nitro-13-carboxy-[2.2]paracyclophane, **13***, R_F 0.45 (ether:petroleum ether=7:4), had the follow-

ing characteristics. δ_H (d_4-MeOH), 7.23 (1H, d, J=1.8, H=5), 7.19 (1H, d, J=2, H-12), 6.88 (1H, dd, J=8, 1.9, H-7), 6.80 (1H, dd, J=8, 2, H-16), 6.79 (1H, d, J=8, H-8), 6.73 (1H, d, J=8, H-15), 4.2–4.16 (1H, H-1a), 4.11–3.97 (1H, H-2a), 3.3–2.8 (6H, H-1b, 2b, 9, 10). δ_C 172.0 (C=O), 144, 142, 139.1, 138.5, 137.6, 137.4, 135.4, 128.8, 35.37, 35.23, 35.18, 34.44. ν_{max} 3500–2500 (COOH), 1680 (C=O), 1340 (NO_2). λ_{max} (EtOH), 250 (4.37), 312 (3.91). m/z (CI), 315 ($M+NH_4^+$, 100), 297 (5, M^+), 149 (12), 148 (80), 133 (23), 119 (100), 104 (25), 91 (74). Found, $M+NH_4^+$=315.1358, $C_{17}H_{19}N_2O_4$ requires 315.1345. $[\alpha]_D$ +63 (c 0.15 in $CHCl_3$).

4-Nitro-12-carboxy-[2.2]paracyclophane, ***14****,* R_F 0.18 (CH_2Cl_2:MeOH=10:1), had the following characteristics. δ_H (d_4-MeOH), 7.24 (1H, d, J=2, H-5), 7.20 (1H, d, J=2, H-13), 6.95 (1H, dd, J=8, 1.8, H-7), 6.84 (1H, dd, J=8, 2, H-15), 6.74 (1H, d, J=8, H-8), 6.68 (1H, d, J=8, H-16), 4.2–4.0 (m, H-10a), 3.90 (1H, dt, J=16.7, 12.4, 9, H-2a), 3.3–2.8 (6H, m, H-1, 2b, 9, 10b). δ_C 170.0 q, 150.0 q, 144.0 q, 143.7 q, 143.6 q, 141.15 q, 139.05, 137.5, 137.3, 133.2, 132.4 q, 130.1, 128.4. ν_{max}, 3500–2000 (OH) 1680 (C=O), 1519 (NO_2) 1341 (NO_2). λ_{max} (EtOH) 216.8 (4.30), 304.0 (3.26), m/z 297 (4, M^+), 280 (24), 250 (12), 148 (100), 104 (24), 91 (84). Found, M^+ 297.1001, $C_7H_{15}NO_4$ requires 297.1001. $[\alpha]_D$ +83 (c 0.165 in $CHCl_3$).

General procedure for the reduction of nitro-acids ***13*** *and* ***14*** *to* ***15*** *and* ***16***

The nitro-acid (81 mg, 0.27 mmol) was dissolved in MeOH (15 ml) and 10% Pd–C (22 mg) was added. The mixture was placed in a Parr apparatus which was flushed with hydrogen and then shaken at 40 psi at room temperature for 24 h, after which no starting material was left (TLC). The mixture was filtered through Celite, evaporated and the required amino-acid was isolated by purification on a chromatotron using CH_2Cl_2:MeOH (10:1). The yield of **15** is 60.5 (83%). The yield of **16** is 62.6 mg (86%).

4-Amino-13-carboxy-[2.2]paracyclophane ***15****,* R_F 0.50 (CH_2Cl_2:MeOH=8:1) has the following characteristics. δ_H (d_4-MeOH), 7.20 (1H, d, J=1.8, H-12), 6.54 (1H, dd, J=8, 1.7, H-16), 6.35 (1H, d, J=8, H-15), 6.32 (1H, d, J=8, H-8), 6.12 (1H, dd, J=8, 1.7, H-7), 5.56 (1H, d, J=1.5, H-5), 4.39 (1H, ddd, J=5, 10, 13, H-1a), 3.21 (1H, ddd, J=2, 10, 13, H-2a), 3.1–2.8 (5H, m, H-2b, 9, 10), 2.7 (1H, ddd, J=5, 11, 14, H-2b with 5% NOE with H-8) δ_C 179.5 q (C=O), 148.2 q (C-4), 141.7 q, 141.6 q (C-6, C-14), 139.4 q (C-11), 136.8 q (C-13), 135.78, 135.72, 135.3, 135.2 (C-8, C-12, C-15, C-16), 126.2 (C-3), 124.1 (C-5), 123.5 (C-7), 35.81, 35.63, 32.7, 32.4 (C-1, C-2, C-9, C-10). ν_{max} 3500–2500 (OH, NH_2), 1650 (ArCO), 1625, 1597 (Ar). λ_{max} (EtOH) 241 (4.27), 321 (3.55). m/z 268 (32, $M+H^+$), 250 (78), 249 (5), 221 (16), 149 (33), 119 (58), 91 (100). Found, MH^+ 268.1338, $C_{17}H_{18}NO_2$ requires 268.1338. $[\alpha]_D$ +122 (c 0.225 in MeOH).

4-Amino-12-carboxy-[2.2]paracyclophane ***16****,* R_F 0.46 (CH_2Cl_2:MeOH=10:1), had the following characteristics. δ_H (d_4-MeOH), 7.79 (1H, d, J=1.8, H-13), 6.63 (1H, d, J=8, H-16), 6.56 (1H, dd, J=8, 1.5, H-15), 6.24 (1H, d, J=8, H-8), 6.10 (1H, dd, J=8, 1.5, H-7), 5.47 (1H, d, J=1.5, H=5), 4.10–3.90 (1H, m, H-10a), 3.30–2.50 (7H, H-1, 2, 9, 10b). δ_C 171.3 q (C=O), 147.0 q (C-4), 142.7 q (C-6), 142.4 q (C-11), 140.7 q (C-14), 138.6 q (C-12), 137.9 (C-15), 136.5 (C-13), 136.2, 130.7 (C-8, C-16), 125.4 q (C-3), 122.9 (C-5), 121.8 (C-7), 36.63, 35.22 (C-2, C-10), 32.96, 32.94 (C-1, C-9). ν_{max}, 3600–2600 (NH_2, COOH), 1680 (ArCO). λ_{max} (EtOH) 211.2 (4.55), 301 (3.91). m/z 267 (M^+, 53), 148 (17), 119 (100), 104 (14), 91 (61). Found for M^+, 267.1259, $C_{17}H_{17}O_2N$ requires 267.1259. $[\alpha_D]$ +42 (c 0.2 in MeOH).

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