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Oxazoline Mediated Routes to a Unique Amino-acid, 4-Amino-13-carboxy[2.2]paracyclophane, of Planar Chirality

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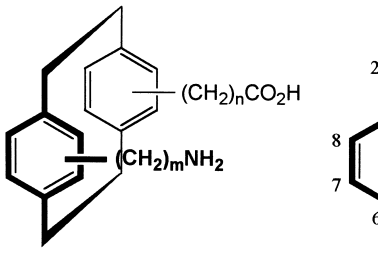
Abstract—Efficient syntheses leading to 4-amino-13-carboxy[2.2]paracyclophane and derivatives are described. Novel oxazolinyl[2.2]-paracyclophanes are used as intermediates and the oxazolinyl and amide groups are shown to be strong ψ-geminal directing groups. Compounds with potential as catalysts have been made.

As part of a programme directed to the investigation of uses of [2.2]paracyclophanes in chiral synthesis,[1,2,3] we are attempting to synthesise unique, homochiral amino-acids **1** which owe their chirality to the planar chirality[4] of unsymmetrical [2.2]paracyclophanes. We have succeeded in producing homochiral **2** and **3**[1,2] (**1**, n=m=0) from which our calculations indicate that conformationally constrained peptide chains with artificial β-sheet structures could be grown.[5,6] The [2.2]paracyclophane moiety would be acting as a rigid, lipophilic β-turn mimetic.[7,8,9]



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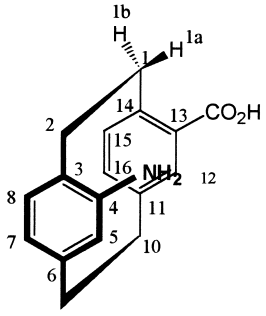

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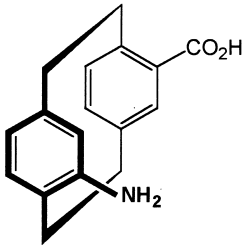

3

Our previous synthesis of **2** and **3** involved the nitration of homochiral, readily available 4-carbomethoxy[2.2]paracyclophane[2] followed by hydrolysis and reduction. The latter two steps both went in >80% yields but the nitration gave only 37% of mono-nitrated material from which 13-carbomethoxy-4-nitro[2.2]paracyclophane,[†] the precursor of **2**, was isolated in 15% yield and 12-carbomethoxy-4-nitro[2.2]paracyclophane, the precursor of **3** was isolated in 8% yield. This is in line with the nitration of [2.2]paracyclophane itself which, in our hands, gave only 12% of 4-nitro[2.2]paracyclophane.[10,11,18]

We therefore designed several approaches to **2**, one of which involving oxazolines is described below. We felt that oxazolines would be useful for the following reasons. The first is that **2** is ψ-geminally (4,13) disubstituted and therefore a ψ-geminal reaction must, at some stage, be carried out. ψ-Geminal directing groups are normally ester, carboxylic acid or ketone groups in which the carbonyl group can act as an intramolecular base to preferentially abstract a proton from C-13 of the carbocation complex involved in electrophilic bromination of the adjacent ring.[12] At some later stage in the synthesis we anticipated the use of organolithium or organomagnesium reagents and therefore the acid or ester group would have to be protected. An oxazoline ring seemed ideal for this purpose.[13] Moreover homochiral 4-carboxy[2.2]paracyclophane **4** is readily available[11,15–17] as is its methyl ester **5**, which we have already used in the synthesis of homochiral **2** and **3**.[2] Therefore any synthesis that proceeds through **4** or **5** must be considered as a potential chiral synthesis and this strongly influenced our approach. As a result we investigated Scheme 1, in which the required 4,13-substitution

Keywords: 4-amino-13-carboxy[2.2]paracyclophane; planar chirality; oxazolines; directing effects; potential catalysts.

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[†] All bifunctional [2.2]paracyclophane derivatives described in the Experimental and text are numbered as for **2**.

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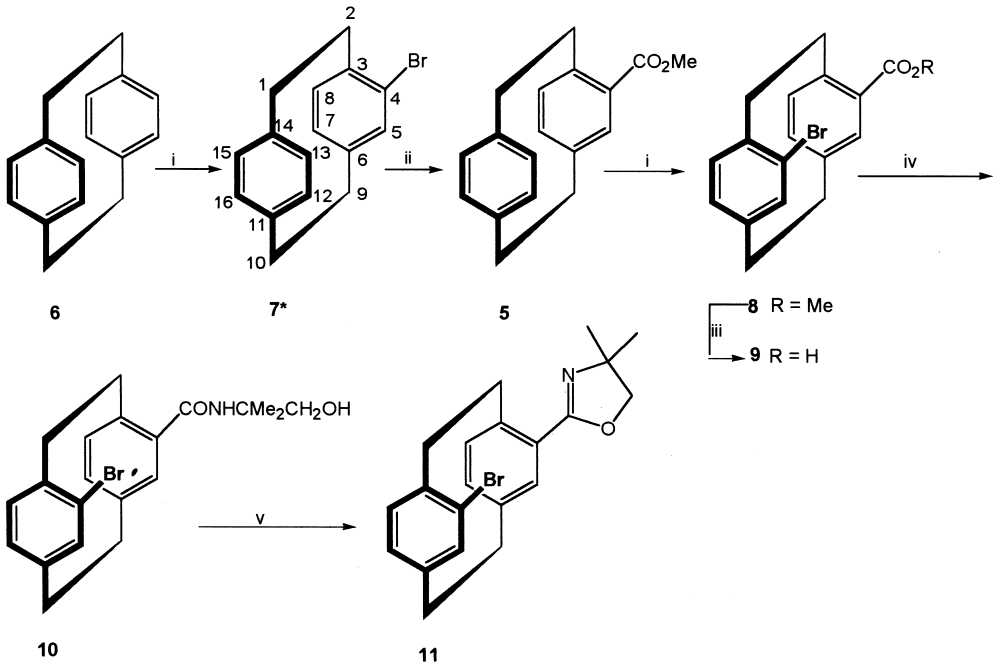
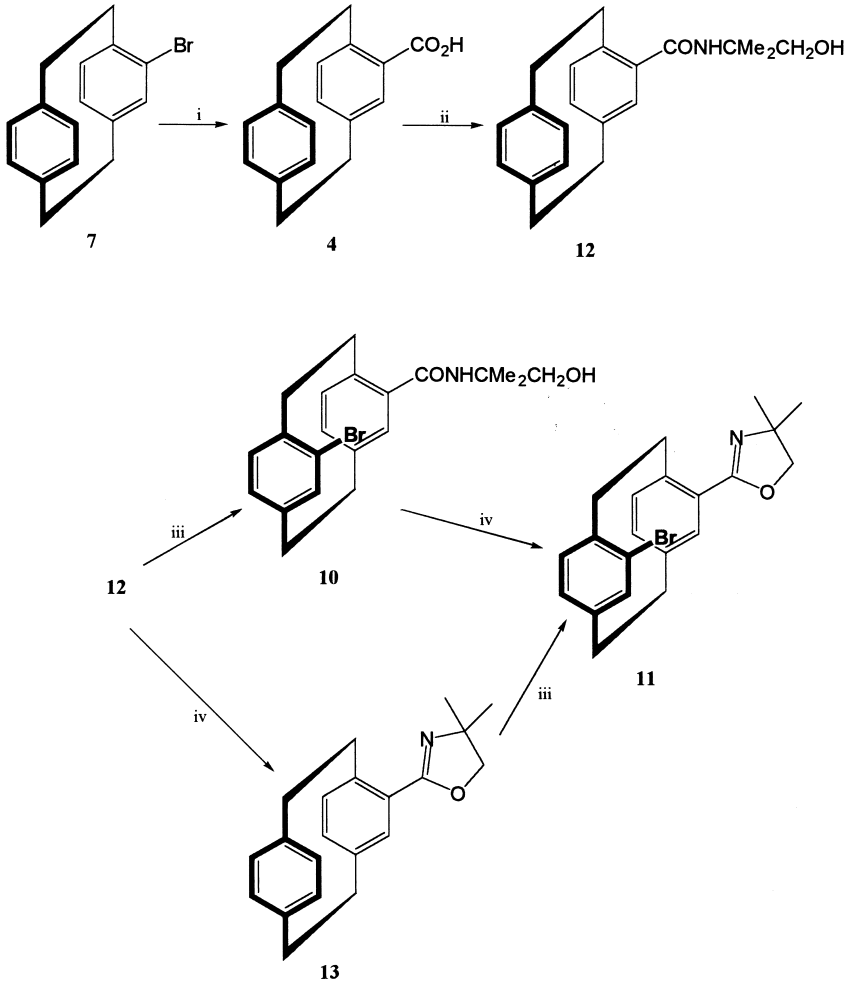
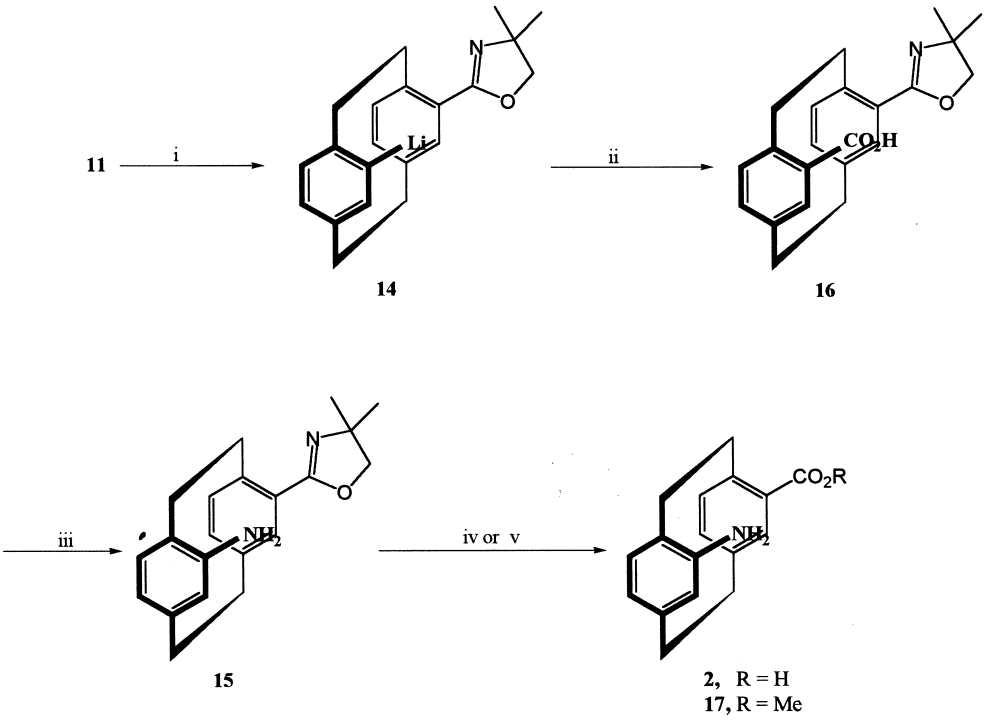


Scheme 1. Reagents i, Br_2/Fe, **6** to **7** (93%), **5** to **8** (87%); ii, Mg then $ClCO_2Me$ (80%), iii, aq. KOH (80%); iv, $SOCl_2$ then $NH_2CMe_2CH_2OH$ (69%); v, NEt_3/PPh_3/CCl_4 (97%). *This numbering is used for mono-substituted [2.2]paracyclophane derivatives.



Scheme 2. Reagents i, Mg then CO_2 (97%); ii, $SOCl_2$ then $NH_2CMe_2CH_2OH$ (94%); iii, Br_2/Fe **12** to **10** (100%), **13** to **11** (92%); iv, NEt_3/PPh_3/CCl_4, **10** to **11** (97%), **12** to **13** (95%).



Scheme 3. Reagents i, *n*BuLi, -78°C (100%), ii, CO_2 then aq. acid (100%); iii, (a) $SOCl_2$, (b) NaN_3/acetone (c) toluene, heat, (d) aq.KOH (58%); iv, 6 M HCl; (100%); v, conc. HCl then MeOH, heat (78%).

pattern is introduced by the known, high yield bromination of **5**.[12] For this initial investigation we used racemic compounds.

The bromination of **6** to **7** is known and direct conversion of **7** to **5** proceeded in excellent yield.[18] ψ-Geminal bromination to give **8** (87%) was followed by hydrolysis to give **9** (80%). The conversion of **9** to **10** was somewhat disappointing as, despite various attempts, it proceeded at best in 69% yield only. The overall yield from **6** to **10** was 36%.

The next step was the preparation of **11**, a key intermediate. We had originally intended to convert ester **8** directly to **11** but although we managed to quantitatively convert methyl benzoate to 2-phenyl-4,4-dimethyloxazoline using potassium hydroxide as base, the reaction failed on ester **8**. We therefore considered the conversion of **10** to **11**. We investigated a large number of methods[13] for this conversion but found that Bryce's method[14] gave the highest yield (97%). A convenient and cheaper alternative was the use of *cold* thionyl chloride which gave an excellent yield in the conversion of **12** to the corresponding oxazoline. Although **11** did become available by this process the overall yield was only 35% and we looked for alternatives.

On consideration it seemed reasonable that both amides and oxazolines could be ψ-geminal directing groups and, if so, this opened up the two routes shown in Scheme 2.

Compound **12** was produced in high yield from **4** and *on bromination gave a quantitative yield of the ψ-geminal product **10***. Cyclisation of **10** to **8** had already been shown to proceed in 97% yield (Scheme 1). By this route compound **11** is produced from the parent [2.2]paracyclophane **6** in 82% overall yield and **11** must now therefore be regarded as readily available.

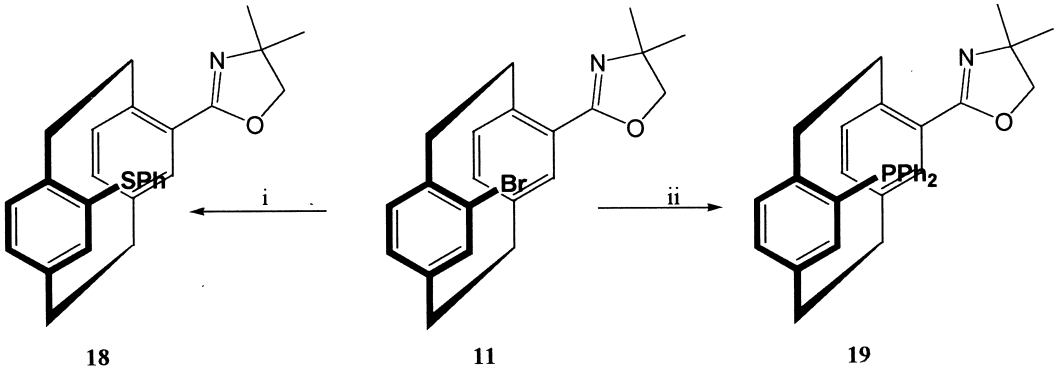
Alternatively **12** was converted to **13** in 92% yield and ***13** on bromination gave **11** in 95% yield*. By this route **11** was made from **5** in an overall yield of 74%.

Thus both amide and oxazolinyl groups are new ψ-geminal directing groups. Oxazolines **11** and **13** are the first 4-[2,2]paracyclophanyloxazolines.

As expected **11** yielded the lithio-derivative **14** in quantitative yield with no interference from the oxazoline ring (Scheme 3). We attempted to convert **14** directly to **15** by the method of Fringuelli[19] using *O*-methylhydroxylamine. However although on one occasion we obtained 60% of **15** the reaction was inconsistent and generally gave yields of $<$20%. We therefore converted **14** into the carboxylic acid **16** and used a Curtius process to consistently give **15** in 58% overall yield. Compound **15** is a most interesting masked form of **2** which is ready for peptide growth from the amine group. Treatment of **15** with 6 M HCl gave a quantitative yield of the required amino-acid **2**. The methyl ester **17** was also available directly from **15**.

*The target amino acid **2** is thus available from [2.2]paracyclophane in 48% overall yield.*

Oxazoline **11** is of great interest apart from its conversion to **2**. Scheme 4 shows its conversions (unoptimised) to two compounds, **18** and **19** with liganding groups held rigidly in close proximity. The possibilities of using **19** as a ligand in a variety of transition metal catalysed reactions are currently under investigation.



18 11 19

Scheme 4. Reagents i, *n*BuLi, −78°C, $PhSSO_2Ph$ (52%); ii, *n*BuLi, −78°C, $ClPPh_2$ (56%).

Experimental

General information

Melting points were determined using an Electrothermal digital melting point apparatus. Microanalyses were carried out at the University of Wales Cardiff. IR spectra were recorded on a Pye Unicam SP1050 spectrometer. ^{1}H NMR spectra were recorded on a Bruker 250WM spectrometer at 250 MHz or on a Bruker ARX400 spectrometer at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker ARX400 spectrometer at 100 MHz. All NMR spectra used tetramethylsilane as the internal standard and were run in $CDCl_3$ unless otherwise stated. *J* values are given in Hz. The mass spectra were obtained from a VG-12-250 low resolution quadrupole mass spectrometer, whilst accurate mass measurements were obtained from a ZAB-E, high resolution, double focussing mass spectrometer. UV spectra were recorded on a Philips PU8720 scanning spectrometer and reported in nm (ϵ). Thin layer chromatography (TLC) was carried out on Merck 5735 Kieselgel 60 F_{254} fluorescent plates. Flash chromatography was performed with silica gel (Merck Geduran SI 60 Art 11567).

Reactions carried out under an inert atmosphere refer to the use of argon or nitrogen. Ether, tetrahydrofuran (THF) and benzene were dried by being stirred overnight over calcium hydride, distilled and then distilled again from sodium wire and benzophenone. Dichloromethane, toluene, acetone and carbon tetrachloride were dried by distillation from calcium hydride after stirring overnight with CaH_2. Solutions of butyllithium in hexane and methyllithium in ether were obtained from Aldrich and were regularly estimated.[20] Low temperature baths were prepared by making a slurry of solid carbon dioxide with acetone (−78°C). All other reagents were purified by distillation, the pressure being reduced if the boiling point of the compound was greater than 110°C at atmospheric pressure.

Direct preparation of 4-carbomethoxy[2.2]paracyclophane 5[18,‡]

A dry, three-necked round bottomed flask fitted with a dry dropping funnel and condenser was charged with dry magnesium turnings (1.87 g, 76.82 mmol). A crystal of iodine was added and the turnings stirred and heated with a hot air gun for 1 h after which 4-bromo[2.2]paracyclophane **7** (20 g, 69.69 mmol) in THF (90 ml) was added slowly over 1 h and the mixture was then stirred for a further 4 h. The Grignard solution was cooled to 0°C and then added, using a double ended needle, to a stirred solution of methyl chloroformate (33 ml, 431.2 mmol) in THF (100 ml) also at 0°C and then stirred overnight at room temperature. The pale yellow mixture was concentrated and the residue was dissolved in dichloromethane and washed with brine. The organic layer was separated, dried ($MgSO_4$) filtered and concentrated. The pale yellow residue was purified by chromatography on silica (petroleum ether: CH_2Cl_2, 90:10 then 50:50) followed by crystallisation from CH_2Cl_2:Et_2O (20:80) to give **5**, (14.82 g, 80%) mp 135–137°C (lit.[21] 139–140°C). The ^{1}H and ^{13}C NMR mass spectrum and UV spectra were identical with a sample previously made[18] from the corresponding acid.

4-Bromo-*N*-(1-hydroxy-2-methyl-2-propyl)[2.2]paracyclophane-13-carboxamide 10. (i) Thionyl chloride (2 ml, 27.4 mmol) was added to **9** (1 g, 3 mmol) at room temperature and the mixture stirred at room temperature for 30 min and then at 60°C for 1.5 h. The cooled mixture was concentrated and then three portions of toluene were added sequentially, each being taken to dryness. The resulting solid was taken into dichloromethane (10 ml), cooled to 0°C and to the resulting solution was added a solution of 2-amino-2-methylpropan-1-ol (0.58 ml, 6 mmol) and triethylamine (0.84 ml, 6 mmol) in dichloromethane (10 ml) dropwise over 45 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. Dichloromethane (50 ml) was added and the solution washed with 4% aqueous $NaHCO_3$ (2×50 ml) and brine (50 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (silica, petroleum ether/ethyl acetate 60:40) gave **10** as a white solid (0.84 g, 69%) mp 169–170°C.

(ii) A solution of bromine (1.15 ml, 22.3 mmol) in dichloromethane (240 ml) was made up and 20 ml added to iron powder (0.12 g, 2.16 mmol) with exclusion of light. The mixture was stirred for 1 h and **12** (6 g, 18.6 mmol) in dichloromethane (360 ml) was added rapidly, with stirring. The resulting mixture was heated under reflux, the remainder of the bromine solution added dropwise over 2 h and

‡ We thank Mr H. Kidwell (University of Wales Swansea) who first introduced this procedure.

the solution heated under reflux for 18 h. The reaction mixture was cooled, washed with saturated aq. $NaHCO_3$ (2×500 ml) and brine (500 ml) and the organic layer dried ($MgSO_4$), filtered and concentrated to give almost pure **10** in quantitative yield. Purification by flash chromatography (silica, petroleum ether:ethyl acetate, 60:40) gave **10** as a white solid (7.07 g, 95%) mp 169–170°C. δ_H 1.36 (3H, s, CH_3), 1.46 (3H, s, CH_3), 2.87 (1H, ddd, J=6.5, 10.0, 13.5 Hz, H-2a), 3.07 (5H, m, H-1b, 9a, 9b, 10a, 10b), 3.56 (1H, ddd, J=2.0, 9.5, 13.5 Hz, H-2b), 3.68 (2H, d, J=5.5 Hz, CH_2OH), 3.94 (1H, ddd, 6.5, 9.5, 13.5 Hz, H-1a), 5.32 (1H, t, J=5.5 Hz, OH), 5.80 (1H, s, NH), 6.57 (5H, m, H-5, 8, 15, 16), 7.11 (1H, d, J=1.7 Hz, H-12). δ_C 24.4, 25.1 (2×CH_3), 31.8, 34.5, 34.9, 36.6 (C-1, 2, 9, 10), 56.6 (C(CH$_3$)$_2$), 71.1 (OCH$_2$), 126.9, 134.7, 137.7, 138.5, 139.2, 141.3 (C-3, 4, 6, 11, 13, 14), 130.8, 131.1, 133.0, 134.9, 135.8, 136.2 (C-5, 7, 8, 12, 15, 16), 168.4 (C=O). λ_{max} (CH_2Cl_2) 229.8 (16,242). ν_{max} (cm^{-1}) 1641 (CO), 2926 (OH), 3417 (NH). m/z (EI) 402, 404 (M^+, 30), 322 (22), 219 (29), 147 (100), 131 (22), 103 (20), 77 (18). HRMS Found: M=401.0990. $C_{21}H_{24}BrNO_2$ requires 401.0990.

4-Bromo-13-(4,4-dimethyloxazolin-2-yl)[2.2]paracyclophane 11. (i) To a solution of **10** (7 g, 17.41 mmol) in acetonitrile (400 ml) were added sequentially triethylamine (10.4 ml, 74.81 mmol), triphenylphosphine (16.15 g, 61.15 mmol) and carbon tetrachloride (15.6 ml, 161.4 mmol). The resultant mixture was stirred under argon at rt for 12 h. The solution was concentrated then diluted with dichloromethane (400 ml) and washed with brine (2×400 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography gave pure **11** (6.47 g, 97%) as a white solid mp 138–139°C.

(ii) ψ-Geminal bromination of **13** (0.5 g) was accomplished by the same method as that used to prepare **10**. Flash chromatography of the crude product on silica (petroleum ether:ethyl acetate, 80:20) as in (i) gave **11** as white crystals (0.54 g, 85%) mp 138–139°C *ex* petroleum ether:ethyl acetate 80:20. Found: C, 65.72; H, 5.73; N, 3.71%. $C_{21}H_{22}BrNO$ requires C, 65.63; H, 5.76; N, 3.64%. δ_H 1.34 (3H, s, CH_3), 1.41 (3H, s, CH_3), 2.88 (1H, ddd, J=4.9, 10.4, 13.3 Hz, H-2a), 2.97 (4H, m, H-9a, 9b, 10a, 10b), 3.03 (1H, ddd, J=3.4, 10.4, 13.4 Hz, H-1b), 3.51 (1H, ddd, J=3.4, 10.0, 13.4 Hz, H-2b), 4.09 (2H, 2×d, J=7.8 Hz, OCH_2), 4.46 (1H, ddd, J=4.9, 10.0, 13.4 Hz, H-1a), 6.50 (1H, d, J=7.8 Hz, H-15), 6.52 (2H, m, H-7, 8), 6.55 (1H, dd, J=1.9, 7.8 Hz, H-16), 6.62 (1H, br.s., H-5), 7.19 (1H, d, J=1.9 Hz, H-12); δ_H (C_6D_6) 1.2 (3H, s, CH_3), 1.36 (3H, s, CH_3), 2.60 (4H, m, H-9a, 9b, 10a, 10b), 2.69 (1H, ddd, J=3.9, 10.4, 13.5 Hz, H-2a), 2.83 (1H, ddd, J=4.3, 10.4, 13.2 Hz, H-1b), 3.66 (1H, ddd, J=4.3, 9.8, 13.5 Hz, H-2b), 3.76, 3.86 (2H, 2×d, J=7.8 Hz, OCH_2), 4.90 (1H, ddd, J=3.9, 9.8, 13.2 Hz, H-1a), 6.21 (4H, m, H-7, 8, 15, 16), 6.59 (1H, br.s., H-5), 7.40 (1H, br.s., H-12). δ_C, 28.0, 28.3 (2CH$_3$), 32.8, 34.4, 34.8, 35.6 (C-1, 2, 9, 10), 67.5 (C(CH$_3$)$_2$), 78.1 (OCH$_2$), 126.8, 127.0 (C-6, 11), 131.3, 131.3, 132.4, 134.7, 135.0, 136.0, 136.1 (C-5, 7, 8, 12, 15, 16), 138.4, 139.0, 140.4, 141.1 (C-3, 4, 13, 14), 161.9 (C=N). λ_{max} (CH_2Cl_2) 236.0 (13,167). ν_{max} (cm^{-1}) 1637 (C=N). m/z (CI) 384, 386 ($M+1^+$, 100), (EI) 383 and 385 (M^+, 10), 207 (100), 184 (8), 146 (15), 131 (10), 115 (5), 103 (20), 77 (23). HRMS Found: M=383.0885. $C_{21}H_{22}BrNO$ requires 383.0885.

4-Carboxy[2.2]paracyclophane 4.[16] A dry, three-necked flask fitted with a dropping funnel and a condenser was charged with some dry magnesium turnings (2.33 g, 95.84 mmol) and the turnings stirred under argon. After 1 h some crystals of iodine were added, the flask warmed with an air gun and stirring continued for ca. 4 min until some iodine sublimed. 4-Bromo[2.2]paracyclophane **7** (22.4 g, 78.74 mmol) in dry THF (150 ml) was added dropwise over 3 h to the activated magnesium with heating and stirring. The mixture was heated under reflux for 4 h, the solution cooled to room temperature and carbon dioxide, dried on $CaCl_2$, SiO_2, 5 Å molecular sieves, P_2O_5 and sulfuric acid was bubbled through for 18 h. The reaction mixture was acidified with 6 M HCl to pH 2.5, extracted with dichloromethane (4×150 ml), and then the combined organic extract was washed with aq. NaOH (4×175 ml, 12.5 M). The aqueous extract was acidified to pH 2.5 and gave a white precipitate that was extracted with dichloromethane, dried ($MgSO_4$), filtered and concentrated to give pure **4** (19.29 g, 97%) mp 214–215°C (lit.[21] 210–221°), *ex* AcOH. The product gave identical ^1H and ^{13}C NMR spectra with an authentic sample and also ran as one peak on coinjection (HPLC) with an authentic sample. δ_H 2.90 (1H, ddd, J=7.2, 10.0, 12.7 Hz, H-2b), 3.01 and 3.19 (6H, 2m, H-1a, 1b, 9a, 9b, 10a, 10b), 4.21 (1H, ddd, J=2.5, 8.8, 12.7 Hz, H-2a), 6.51, 6.59 (4H, m, H-12, 13, 15, 16), 6.58 (1H, d, J=7.8 Hz, H-8), 6.71 (1H, dd, J=1.9, 7.8 Hz, H-7), 7.29 (1H, d, J=1.9 Hz, H-5). δ_C 34.9, 35.1, 35.2, 36.3 (C-1, 2, 9, 10), 129.6 (C-3), 131.8, 132.3, 132.8, 133.1, 136.2, 136.4, 137.4 (C-5, 7, 8, 12, 13, 15, 16), 139.4, 140.0, 140.1 (C-6, 11, 14), 143.7 (C-4), 172.5 (CO$_2$H). λ_{max} (CH_2Cl_2) 229.9 (17,680). ν_{max} (cm^{-1}) 1685 (C=O), 2852, 2925 (Ar-H).

***N*-(1-Hydroxy-2-methyl-2-propyl)[2.2]paracyclophane-4-carboxamide 12.** Thionyl chloride (13.5 ml, 0.18 mol) was added to 4-carboxy[2.2]paracyclophane **4** (8 g, 0.032 mol) at room temperature and the mixture was brought to 60°C and stirred for 4 h. Most of the thionyl chloride was removed under reduced pressure and the last traces by azeotropic distillation with three portions of toluene. The resultant solid was dissolved in dichloromethane (60 ml) and cooled to 0°C. A cooled mixture of 2-amino-2-methylpropan-1-ol (6.06 ml, 0.0635 mol) and triethylamine (8.84 ml, 0.0635 mol) was added dropwise over 3 h. The resulting solution was allowed to warm to room temperature then stirred overnight. Dichloromethane (50 ml) was added and the reaction mixture washed with aq. $NaHCO_3$ (2×100 ml, 3.5%) and then brine (100 ml). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to give pure **12** (9.955 g, 97%), mp 149–150°C (*ex* petroleum ether:ethyl acetate, 1:1). Found: C, 78.01; H, 7.85; N, 4.20%. $C_{21}H_{25}NO_2$ requires C, 77.98; H, 7.79; N, 4.33%. δ_H 1.36 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.88 (1H, ddd, J=6.3, 9.8, 13.0 Hz, H-2b), 3.04 (6H, H-1a, 1b, 9a, 9b, 10a, 10b), 3.59 (1H, ddd, J=3.3, 9.2, 13.0 Hz, H-2a), 3.64 (2H, d, J=6.0 Hz, CH_2OH), 5.32 (1H, t, J=6.0 Hz, CH$_2$OH), 5.76 (1H, s, NH), 6.42 (1H, d, J=7.9 Hz, H-12), 6.46 (1H, d, J=7.8 Hz, H-8), 6.52 (2H, m, H-15, 16), 6.56 (1H, dd, J=1.8, 7.8 Hz, H-7), 6.64 (1H, d,

J=1.8 Hz, H-5), 6.76 (1H, d, J=7.9 Hz, H-13). δ_H (C_6D_6), 1.15 (3H, s, CH_3), 1.17 (3H, s, CH_3), 2.67 (1H, ddd, J=5.7, 10.3, 12.7 Hz, H-2b), 2.78 (4H, m, H-9a, 9b, 10a, 10b), 2.92 (1H, ddd, J=1.8, 10.3, 12.7 Hz, H-1a), 3.25 (1H, ddd, J=5.7, 10.2, 12.7 Hz, H-1b), 3.55 (2H, s, CH_2OH), 3.66 (1H, ddd, J=1.8, 10.2, 12.7 Hz, H-2a), 4.62 (1H, br.s., CH_2OH), 5.41 (1H, br.s., NH), 6.32 (5H, m, H-7, 8, 12, 15, 16), 6.62 (1H, br.s., H-5), 7.04 (1H, br.d., J=8.0 Hz, H-13). δ_C 24.5, 24.8 (2×CH_3), 34.9, 35.1, 35.3, 35.4 (C-1, 2, 9, 10), 56.4 ($C(CH_3)_2$), 71.0 (CH_2OH), 131.9, 132.4, 132.5, 132.6, 135.0, 136.0 (C-5, 7, 8, 12, 13, 15, 16), 135.4, 138.5, 139.2, 139.5, 140.3 (C-3, 4, 6, 11, 14) 170.1 (C=O). λ_{max} (CH_2Cl_2) 230.4 (14,035). ν_{max} (cm^{-1}) 1635, (C=0) 3392 (NH, OH). m/z (CI) 324 ($M+1^+$), (EI) 323 (M^+, 5), 306 (2), 252 (22), 235 (5), 219 (10), 147 (100), 104 (45). HRMS Found: M+H=324.1964. $C_{21}H_{26}NO_2$ requires 324.1964.

4-(4,4-Dimethyloxazolin-2-yl)[2.2]paracyclophane 13. (i) Cyclisation of **12** (2.4 g, 7.43 mmol) was accomplished by the same method as for the production of **11**. Purification of the crude product by flash chromatography on silica (eluent petroleum ether:ethyl acetate, 80:20) gave **13** as a white solid (2.5 g, 95%), mp 108–109°C from the eluent. Found: C, 82.53; H, 7.77; N, 4.55%. $C_{21}H_{23}NO$ requires C, 82.58; H, 7.59; N, 4.58%. δ_H 1.41 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.79 (1H, ddd, J=7.0, 10.1, 12.7 Hz, H-2b), 2.97–3.11 (6H, m, H-1a, 1b, 9a, 9b, 10a, 10b), 4.04 (1H, d, J=7.94 Hz, OCH), 4.06 (H, d, J= 7.94 Hz, OCH), 4.20 (1H, ddd, J=1.6, 9.8, 12.7 Hz, H-2a), 6.48–6.56 (6H, m, H-7, 8, 12, 13, 15, 16), 7.02 (1H, d, J=1.8 Hz, H-5). δ_H (C_6D_6) 1.21 (3H, s, CH_3), 1.27 (3H, s, CH_3), 2.68 (1H, ddd, J=7.2, 10.1, 12.5 Hz, H-2b), 2.80 (4H, m, H-9a, 9b, 10a, 10b), 3.06 (1H, ddd, J=1.2, 10.1, 12.7 Hz, H-1a), 3.22 (1H, ddd, J=7.2, 9.9, 12.7 Hz, H-1b), 3.60 (1H, d, J=7.9 Hz, OCH), 3.71 (1H, d, J=7.9 Hz, OCH), 4.60 (1H, ddd, J=1.2, 9.9, 12.5 Hz, H-2a), 6.26 (2H, m, H-7, 8), 6.33 (1H, dd, J=1.8, 7.8 Hz, H-15), 6.40 (1H, dd, J=1.7, 7.8 Hz, H-16), 6.50 (1H, dd, J=1.7, 7.8 Hz, H-12), 6.80 (1H, dd, J=1.8, 7.8 Hz, H-13), 7.30 (1H, br.s., H-5). δ_C 28.4 (CH_3), 28.5 (CH_3), 34.8, 35.0, 35.2, 36.0 (C-1, 2, 9, 10), 67.5 ($C(CH_3)_2$), 78.3 (OCH_2), 128.5 (C-3), 131.1, 132.2, 132.7, 133.0, 134.3, 134.6, 135.8 (C-5, 7, 8, 12, 13, 15, 16), 139.3, 139.4, 139.8 (C-6, 11, 14), 140.9 (C-4), 162.2 (C=N). λ_{max} (CH_2Cl_2) 230.4 (15,845). ν_{max} (cm^{-1}) 1638 (C=N), 2852–2926 (arom. C–H). m/z (CI) 306 ($M+1^+$), (EI) 305 (M^+, 39), 201 (100), 104 (30). HRMS Found: M=305.1780. $C_{21}H_{23}NO$ requires 305.1780.

(ii) Thionyl chloride (2 ml) was distilled from zinc into a dry round-bottomed flask containing **12** (0.2 g, 0.6191 mmol) and the mixture was stirred at room temperature for 4 h. The mixture was concentrated on a rotary evaporator and the residue dissolved in dichloromethane (30 ml) and stirred with 20% NaOH (25 ml). The organic layer was washed with brine (20 ml), separated, dried and concentrated to give a quantitative yield of *product* mp 107–108°C, that was 96% pure by HPLC. Crystallisation from petroleum ether:ethyl acetate (80:20) gave crystals mp 108–109°C identical in all respects with the product from (i).

4-Carboxy-13-(4,4-dimethyloxazolin-2-yl)[2.2]paracyclophane 16. Carboxylation of **11** (1 g, 2.6 mmol) was accomplished by the same method as used for the synthesis of **4**. In the work up acidification was controlled using enough 2N aq. HCl until the pH was 6.5. The aqueous mixture was then extracted with dichloromethane (4×100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated to give **16** (0.852 g, 94%), mp 180–181°C *ex* light petroleum:ethyl acetate, 60:40. Found: C, 75.56; H, 6.88; N, 3.98%. $C_{22}H_{23}NO_3$ requires C, 75.62; H, 6.63; N, 4.01%. δ_H 1.22 (3H, s, CH_3), 1.26 (3H, s, CH_3), 3.07 and 4.20 (8H as 2m, H-1a, 1b, 2a, 2b, 9a, 9b, 10a, 10b), 6.66, 6.67 (2H, 2d, J=7.7 Hz, H-8, 15), 6.74 (1H, dd, J=1.6, 7.7 Hz, H-7), 7.01 (1H, d, J=1.6 Hz, H-12), 7.37 (1H, d, J=1.6 Hz, H-5). δ_C 27.8, 28.1 (2CH_3), 34.2, 34.7, 35.0 (C-1, 2, 9, 10), 67.4 ($C(CH_3)_2$), 78.3 (OCH_2), 128.7, 128.8 (C-6, 11), 132.6 (C-12), 134.8 (C-5), 134.9, 135.5, 136.3, 137.2 (C-7, 8, 15, 16), 139.0, 139.7, 140.7, 144.0 (C-3, 6, 11, 14), 161.8 (C=N), 171.8 (C=O). λ_{max} (CH_2Cl_2) 245.5 (18, 552). ν_{max} (cm^{-1}) 1635 (C=N), 1681 (C=O), 3469 (CO_2H). m/z (CI) 350 (M+1), (EI) 349 (M^+, 32), 305 (50), 201 (100), 146 (23), 131 (20), 105 (41). HRMS Found: M=349.1678. $C_{22}H_{23}NO_3$ requires 349.1678.

4-Amino-13-(4,4-dimethyloxazolin-2-yl[2.2]paracyclophane 15. Acid **16** (0.352 g, 1.01 mmol) was stirred under argon with thionyl chloride (0.5 ml, 6.94 mmol) for 4 h at room temperature. The thionyl chloride was removed and the residue azeotroped with dry toluene (3×10 ml). The resulting acid chloride was dissolved in dry acetone (10 ml) and cooled to 0°C. A solution of sodium azide (0.437 g, 6.72 mmol) in acetone (5 ml) and water (7.5 ml) was made up and cooled to 0°C. The cooled acid chloride solution was then added to the stirred azide solution by cannula. The mixture was stirred overnight at room temperature then extracted with dichloromethane (4×50 ml). The combined organic layers were concentrated and the residue was dissolved in toluene (20 ml) and heated under reflux for 2 h. Aqueous KOH (10 ml 10% w/v) was added to the boiling toluene solution the mixture then being heated under reflux for a further 3 h. The mixture was concentrated and the residue was dissolved in dichloromethane (30 ml). The amine was extracted as a salt using HCl (3×50 ml, 2 M) and the acid solution was then treated with aqueous KOH to pH 9–10. The product was taken into dichloromethane (4×60 ml), the solution dried ($MgSO_4$), filtered and concentrated to give pure **15** (0.1918 g, 59%) mp 160–161°C. δ_H 1.30 (3H, s, CH_3), 1.31 (3H, s, CH_3), 2.64 (1H, ddd, J=6.4, 10.6, 16.4 Hz, H-2a), 2.88 (5H, m, 1b, 9a, 9b, 10a, 10b), 3.06 (1H, m, H-2b), 3.30 (2H, br, NH_2), 3.94 (1H, d, J=8.0 Hz, OCH), 4.00 (1H, d, J=8.0 Hz, OCH), 4.18 (1H, ddd, J=6.4, 9.4, 16.4 Hz, H-1a), 5.43 (1H, d, J=1.7 Hz, H-5), 6.01 (1H, dd, J=1.7, 7.7 Hz, H-7), 6.27 (1H, d, J=7.7 Hz, H-8), 6.31 (1H, d, J=7.7 Hz, H-15), 6.50 (1H, dd, J=1.9, 7.7 Hz, H-16), 7.06 (1H, d, J=1.9 Hz, H-12). δ_C 28.2 (2×CH_3), 30.9, 32.3 (C-1, 2) 34.6, 34.8 (C-9, 10), 67.4 ($C(CH_3)_2$), 78.5 (OCH_3), 121.4, 122.4 (C-5, 7), 132.2, 134.4 (C-8, 12, 15, 16), 124.2, 125.5 (C-3, 14), 138.3 (C-13), 140.0, 140.6 (C-6, 11), 146.5 (C-4), 163.4 (C=N). λ_{max} (CH_2Cl_2) 226 (19,192), 249 (12,808). ν_{max} (cm^{-1}) 3418, 3312 (N-H), 1624 (C=N). m/z (EI) 320 (M^+, 65), 201 (100), 119 (42). HRMS Found: M=320.18890. $C_{21}H_{24}N_2O$ requires 320.18885.

4-Amino-13-carboxy[2.2]paracyclophane 2.[2] Aqueous HCl (6 ml, 6 M) was added to a flask containing **15** (0.053 g, 0.1654 mmol). The mixture was heated under reflux for 24 h then cooled to room temperature and aq. NaOH (40%) was added dropwise to pH 3–5 until the amino-acid precipitated out. The sparingly soluble precipitate was taken into dichloromethane (5×20 ml), the solvent concentrated then pumped under high vacuum for 18 h to give pure (^{1}H NMR, ^{13}C NMR, HPLC) **2**, (0.0444 g, 100%) mp>289°C decomp. δ_H (CD_3OD) 2.78 (1H, ddd, *J*=5.0, 10.7, 15.3 Hz, H-2a), 2.89–3.02 (5H, m, H-9a, 9b, 10a, 10b, 1b), 3.07 (1H, m, H-2b), 4.17 (1H, ddd, *J*=5.0, 9.9, 15.3 Hz, H-1a), 5.65 (1H, d, *J*=1.7 Hz, H-5), 6.24 (1H, dd, *J*=1.7, 7.7 Hz, H-7), 6.40 (1H, d, *J*=7.7 Hz, H-8), 6.43 (1H, d, *J*=7.7 Hz, H-15), 6.67 (1H, dd, *J*=1.9, 7.7 Hz, H-16), 7.08 (1H, d, *J*=1.9 Hz, H-12). δ_C 32.2, 32.4, 35.4, 35.6 (CH_2), 123.7, 126.1, 129.5, 127.9, 131.3, 133.8, 136.2, 136.1, 137.0, 140.1, 141.8, 142.1, 174.1 (*C*=O). *m/z* (CI) 268 ($M+1^+$, 48) 226 (37), 224 (32). *m/z* (EI) 267 (M^+, 3), 148 (13), 119 (54), 118 (23), 92 (32), 91 (100). HRMS Found: M=267.1266. $C_{17}H_{17}NO_2$ requires 267.1266.

4-Amino-13-carbomethoxy[2.2]paracyclophane 17. The amine **15** (0.05 g, 0.156 mmol) was dissolved in toluene (2.5 ml) and aqueous HCl (2.5 ml, 12 M) was added and the stirred mixture was heated under reflux for 12 h. The mixture was cooled to room temperature and methanol (15 ml) was added. The reaction mixture was then heated under reflux for 24 h, cooled to room temperature and brought to pH 8–9 using 10% $NaHCO_3$. The toluene layer was concentrated to give pure **17** (0.0224 g, 78%) mp 180–181°C. δ_H 2.65 (1H, ddd, *J*=5.5, 10.7, 15.0 Hz, H-2a), 3.0–2.8 (5H, m, 1b, H-9a, 9b, 10a, 10b), 3.07 (1H, ddd, *J*=2.7, 9.7, 13.8 Hz, H-2b), 3.81 (3H, s, CO_2CH_3), 4.22 (1H, ddd, *J*=5.5, 9.7, 14.3 Hz, H-1a), 5.36 (1H, d, *J*=1.7 Hz, H-5), 6.10 (1H, dd, *J*=1.7, 7.7 Hz, H-7), 6.26 (1H, d, *J*=7.7 Hz, H-8), 6.34 (1H, d, *J*=7.8 Hz, H-15), 6.61 (1H, dd, *J*=1.9, 7.7 Hz, H-16), 7.17 (1H, d, *J*=1.9 Hz, H-12). δ_C 32.1, 30.1 (C-1, 2), 35.2, 35.1 (C-9, 10), 52.0 (CO_2CH_3), 122.7, 121.3 (C-5, 7), 124.4, 127.3 (C-3, 14), 136.7, 135.7, 135.2, 134.1 (C-8, 12, 15, 16), 141.9, 140.5, 138.6 (C-6, 11, 13), 145.9 (C-4), 168.9 (CO_2Me). λ_{max} (CH_2Cl_2) 227 (16,467), 247 (11,830). ν_{max} (cm^{-1}) 3439, 3350 (NH_2), 1693 (C=O). *m/z* (EI) 281 (M^+, 14), 162 (4), 119 (100). HRMS Found: M=281.1404. $C_{18}H_{19}NO_2$ requires 281.1416.

4-Phenylthio-13-(4,4-dimethyloxazolin-2-yl)[2.2]paracyclophane 18. Compound **11** (0.25 g, 0.651 mmol) was dissolved in dry ether (10 ml) with stirring under argon. The solution was cooled to −78°C and *n*-butyllithium (0.85 ml, 1.30 mmol) was added by syringe and the mixture stirred for 1.5 h during which it attained room temperature. *S*-Phenylbenzene thiosulfonate (0.35 g, 1.52 mmol) in ether (2.5 ml) was cooled to −30°C, and transferred by cannula to the previously made lithium derivative of **11** also at −30°C. The mixture was stirred for 5 min at −30°C and then for 5 h at rt, before the addition of ether (20 ml). The reaction mixture was washed with water (2×20 ml) and the organic layer dried ($MgSO_4$), filtered and concentrated. Purification by chromatography on silica (petroleum ether: ethyl acetate, 95:5) gave **18** as a pale yellow solid (0.14 g, 52%) mp 111–112°C (*ex* petroleum ether:ethyl acetate). Found: C, 78.50; H, 6.31; N, 3.58%. $C_{27}H_{27}SNO$ requires 78.41; H, 6.58; N, 3.38%. δ_H 1.43 (3H, s, CH_3), 1.52 (3H, s, CH_3), 2.79 (1H, ddd, *J*=4.5, 10.2, 13.6 Hz, H-2a), 3.01 (5H, m, H-1b, 9a, 9b, 10a, 10b), 3.43 (1H, ddd, *J*=4.0, 9.9, 13.6 Hz, H-2b), 4.11 (1H, d, *J*=7.8 Hz, OC*H*), 4.25 (1H, d, *J*=7.8 Hz, OC*H*), 4.45 (1H, ddd, *J*=4.5, 9.9, 13.5 Hz, H-1a), 6.66 (5H, m, H-5, 7, 8, 15, 16), 7.11 (6H, m, 5SAr*H*, H-12). δ_C 28.0 (CH_3), 28.4 (CH_3), 33.6, 34.2, 34.5, 34.8 (C-1, 2, 9, 10), 67.6 ($C(CH_3)_2$), 78.3 (OCH_2), 125.8, 128.2, 128.8, 132.6, 132.9, 134.9, 135.0, 136.0, 136.9 (C-5, 7, 8, 12, 15, 16 and C_6H_5), 129.0, 135.5, 137.9, 138.6, 140.2, 140.7, 142.4 (C-3, 4, 6, 11, 13, 14), 161.8 (*C*=N). λ_{max} (CH_2Cl_2) 231.5 (26,142). *m/z* (CI) 414 ($M+1^+$, 100), (EI) 413 (M^+, 20), 201 (100). HRMS Found: M=413.1813. $C_{27}H_{27}SNO$ requires 413.1830.

4-Diphenylphosphinyl)-13-(4,4-dimethyloxazolin-2-yl)-[2.2]paracyclophane 19. Pre-cooled *n*-butyllithium (0.6 ml, 2.65 M, 1.59 mmol) in ether was introduced with a syringe into a stirred solution of **11** (0.5 g, 1.30 mmol) in dry ether (20 ml) at −78°C under nitrogen. The mixture was allowed to reach room temperature and then cooled to −42°C and added by a cooled cannula to a well stirred solution of diphenylphosphinyl chloride (0.5 ml, 2.79 mmol) in ether (5 ml) at −42°C. The resulting mixture was allowed to warm to room temperature, stirred overnight and then concentrated almost to dryness. Dichloromethane (50 ml) was added and the solution washed with brine (50 ml). The organic fraction was dried, filtered and concentrated to give a yellow solid (1.112 g). Chromatography on a short column (silica matrix 60, 35–70 μ) using gradient elution (petroleum ether (100%) to petroleum ether:ethyl acetate (80:20)) gave two major fractions containing 4-(4,4-dimethyloxazolin-2-yl)[2.2]paracyclophane and the desired product. Further purification using a Chromatatron (silica gel 60 PF_{254}, petroleum ether:ether (90:10)) gave **19** (0.341 g, 54%) as white crystals mp 174–175°C. δ_H 1.48 (3H, s, CH_3), 1.59 (3H, s, CH_3), 2.90 (1H, m, H-2a), 3.11 (1H, ddd, *J*=4.0, 7.7, 12.2 Hz, H-1b), 3.43 (1H, m, H-2b), 4.21 (1H, d, *J*=7.6 Hz, OC*H*), 4.39 (1H, d, *J*=7.6 Hz, OC*H*), 4.56 (1H, ddd, *J*=2.6, 9.6, 12.2 Hz, H-1a), 5.88 (1H, dd, *J*=7.1, 1.4 Hz, H-5), 6.57 (2H, d, *J*=4.0 Hz), 6.65 (2H, s), 7.15 (1H, s), 7.33 (10H, m). δ_C ($CDCl_3$)[§] 27.76, 27.80, 28.5, 34.2, 34.4, 34.8, 34.9, 35.5, 67.6 (CMe_2), 78.1 (OCH_2), 127.1, 128.2, 128.3, 128.4, 128.5, 128.6, 132.3, 133.2, 133.5, 133.7, 134.5, 134.9, 135.1, 136.2, 137.1, 177.2, 137.8, 137.9, 138.8, 139.2, 139.4, 141.2, 143.6, 143.8, 162.0 (*C*=N). δ_P −4.981. λ_{max} (CH_2Cl_2) 227 (27,702), 267 (13,913). ν_{max} (cm^{-1}) 1639 (C=N). *m/z* (EI) 489 (M^+, 47%), 433 (42), 288 (100), 287 (44), 209 (68), 178 (64), 165 (37). HRMS Found: M=490.2293. $C_{33}H_{32}PNO$ requires 490.2300.

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§ The extra peaks in the ^{13}C NMR are due to restricted rotation phenomena as shown by variable temperature studies and by comparison with 4-diphenylphosphinyl[2.2]paracyclophane. These studies will be reported separately.

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