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Synthesis and X-ray crystallographic analysis of chiral pyridyl substituted carbocyclic molecular clefts

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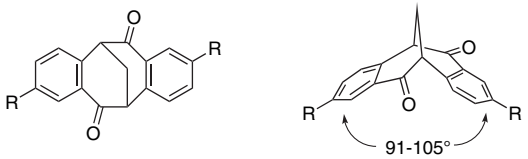
Abstract—Ditopic symmetrical bis(pyridyl) ligands incorporating the chiral dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione cleft have been synthesised and characterised by NMR spectroscopy, mass spectrometry and X-ray crystallography. The ligands, which incorporate pyridyl groups directly connected to the carbocyclic cleft core or via alkyne or phenyl linkers were accessed from palladium-catalysed coupling reactions of 2,8-dibromodibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione. X-ray crystal analyses show the interplanar angles between the two cleft aromatic rings in these molecules, which range from 97.80(3) to 109.80(4)°.

1. Introduction

Oligopyridines are widely studied as ligands and building blocks in coordination and supramolecular chemistries today.[1] Most prevalent are those where the heteroaromatic units are directly connected to each other via a carbon–carbon single bond, examples include bipyridines, terpyridines and phenanthrolines. Oligopyridines of the types described are characterised by their rigid structure. In recent years, the incorporation of semi-rigid and flexible oligopyridines in supramolecular systems has also been the subject of intensive study. Typically, their structures contain a flexible alkyl bridging unit between the pyridyl groups.[2] The versatility of oligopyridines as ligands is reflected in many elegant syntheses of architecturally fascinating supramolecular structures, ranging from discrete species such as polygons,[3] catenanes,[4] rotaxanes,[5] single[6] and double-stranded helices[7] to extended systems, which include grids[8] and wires.[9]

Recently, the dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione framework has been identified as a versatile supramolecular building block,[10–12] and the applications and potential of this system in supramolecular chemistry have been reviewed recently.[13] These molecular clefts can be considered as analogues of Tröger's base but contain a carbocyclic core that may be elaborated to introduce additional molecular recognition groups via the ketone functional groups. A key feature of the dibenzobicyclo[*b*,*f*][3.3.1]-nona-5a,6a-diene-6,12-dione **1**[14] is its angular or cleft-like framework that is imposed by the bicyclononane skeleton. Apart from its well-defined geometry, the cleft possesses an element of chirality as well as functional handles that allow access to new structural motifs with the potential for chiral molecular recognition processes. Thus, the carbonyl groups can be transformed to hydroxyls or oximes by reaction with lithium aluminium hydride and hydroxylamine, respectively.[10,12,14] The ready access to the bisarylbromide derivative **2** also allows entry into aryl and alkynyl-substituted clefts through metal catalysed cross-coupling reactions.[11]



1 R = H
2 R = Br

In the course of our studies towards the assembly of chiral metallomacrocycles of nanoscale dimensions, we required the efficient synthesis of bispyridyl derivatives of the clefts **L1**, **L2** and **L3** in which the distance between the pyridyl units was systematically varied. In addition, given that substituents may influence the size of the cleft angle,[11,12] X-ray crystallographic analyses were undertaken to provide measurements of the cleft angle in order to gauge the likely outcome of metal complexation and self-assembly studies.

Keywords: Molecular clefts; Supramolecular chemistry; Metal complexation; Suzuki cross-coupling; Sonogashira cross-coupling; X-ray analysis.
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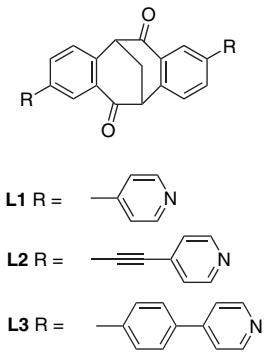


2. Results and discussion

2.1. Synthesis

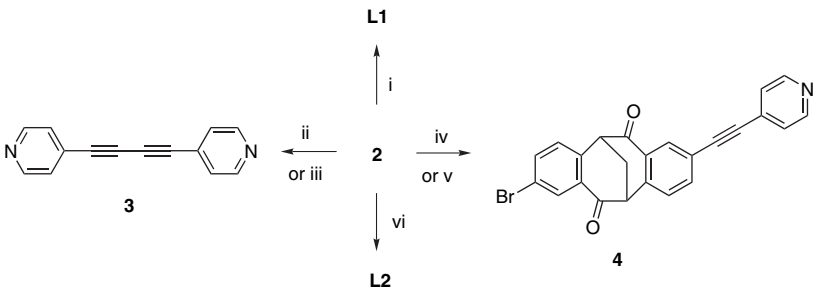
The target ligands **L1**, **L2** and **L3** are pyridyl, acetylenylpyridyl and *p*-(4′-pyridyl)phenyl derivatives of the parent molecular cleft **1**. While there have been numerous recent reports and reviews on catalysts and conditions to effect metal catalysed couplings,[15,16] the application of these methods to heterocycles is frequently limited and deactivation of the metal catalyst by heterocycles requires careful optimisation of reaction conditions.[17]

Ligand **L1** was prepared by the direct coupling of the dibromo cleft **2** with (4-pyridyl)boronic acid pinacol ester under the catalysis of $PdCl_2(PPh_3)_2$ (Scheme 1). The synthesis of the ligand **L2** from the dibromo cleft **2** and 4-ethynylpyridine was first attempted using the protocol developed for appending alkynyl units to the peripheral arms of the cleft (Scheme 1).[11] Thus, dibromo cleft **2** was treated with 4-ethynylpyridine hydrochloride, $PdCl_2(PPh_3)_2$ and CuI in neat triethylamine, that is, the standard Sonogashira conditions.[16] However, these conditions afforded only the homocoupled product, (4,4′-dipyridyl)butadiene **3**. Use of the more active $Pd(PPh_3)_4$ catalyst under similar conditions led to the same result. Further optimisation of the reaction by the use of $Pd(PPh_3)_4$–CuI as the catalytic system and the use of organic solvents showed that in contrast to most successful Sonogashira reactions that are performed using an amine base, the choice of solvent was critical to the success of the reaction. While the use of THF and MeCN resulted in formation of the monocoupled cleft **4** in 30% and 43% yield, respectively, the desired ligand **L2** was obtained in 83% yield with the use of DMF (Scheme 1).

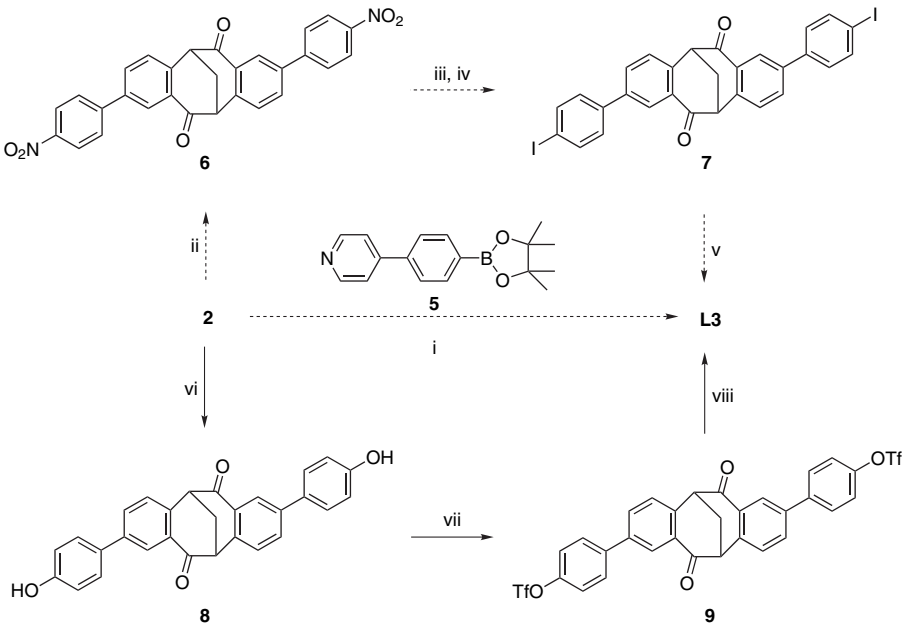
Ligand **L3** contains two new biaryl bonds and hence is accessible via a number of different routes (Scheme 2). The first route investigated used Suzuki coupling of the diaryl boronic ester **5** to the dibromo cleft **2**. The synthesis of the diaryl boronic ester **5** has not been reported previously, and required initial preparation of the corresponding aryliodide **11** (Scheme 3). Aniline **10**,[18] was converted to the iodide **11** according to the literature report.[19] However, in our hands, the literature yields could not be reproduced, and careful temperature control and the use of sodium nitrite/HBF_4 were required to furnish the diaryliodide **11** in only moderate yield of 44%. The diazotization step required slow addition of an aqueous solution of $NaNO_2$ (over 1.5 h) with the internal temperature of the reaction mixture being maintained at no higher than −40 °C. Iodination was effected with addition of KI also at −40 °C and allowing the reaction mixture to warm slowly to rt. Purification of the crude diaryliodide **11** according to the literature procedure by recrystallisation from hot toluene was unsuccessful due to the apparent insolubility of **11**. All attempts to convert the crude diaryliodide **11** to the boronic ester **5** were unsuccessful upon treatment with $PdCl_2(dppf)\cdot CH_2Cl_2$, bis(pinacolato)diborane and KOAc in dioxane or DMSO (Scheme 3).[20]

The alternative strategy to ligand **L3** involved initial attachment of a *para*-substituted boronic ester to the cleft followed by introduction of the pyridyl groups (Scheme 2). The first key step involved the coupling of the dibromo cleft **2** with 4-nitrophenylboronic acid. The nitro groups serve as functional handles enabling conversion of adduct **6** to the diiodide **7**, the latter being a suitable coupling partner for the subsequent Suzuki reaction with (4-pyridyl)boronic acid pinacol ester. This route failed as reaction of cleft **2** with 4-nitrophenylboronic acid under $PdCl_2(PPh_3)_2$ catalysis resulted predominantly in the monocoupled product **13** under forcing conditions and long reaction times. Hence the corresponding iodide **12** was prepared via the Sandmeyer reaction of the diamino cleft **15** (Scheme 4).[11] While the rate of the reaction improved by the use of the iodide **12** in place of the bromide **2**, the monocoupled product **14** was the major product due to its poor solubility, which resulted in precipitation during the reaction (Scheme 5). Changing the solvent and conditions was unsuccessful, and while minor amounts of the bisnitro product **6** were formed, the extremely low solubility of this product in all common organic solvents precluded efficient purification.

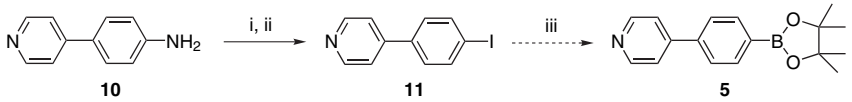
To avoid these problems, the alternative approach involved preparation of the more soluble bisphenol **8** via Suzuki



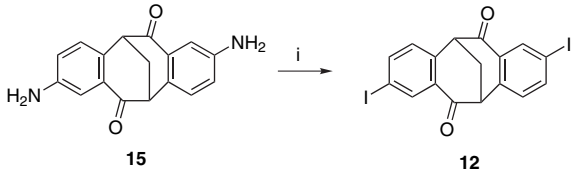
Scheme 1. *Reagents and conditions*: i. $PdCl_2(PPh_3)_2$, Na_2CO_3, (4-pyridyl)boronic acid pinacol ester, DME–H_2O; ii. $PdCl_2(PPh_3)_2$, CuI, Et_3N; iii. $Pd(PPh_3)_4$, CuI, Et_3N, THF; iv. $Pd(PPh_3)_4$, CuI, Et_3N, MeCN; v. $Pd(PPh_3)_4$, CuI, Et_3N, DMF.



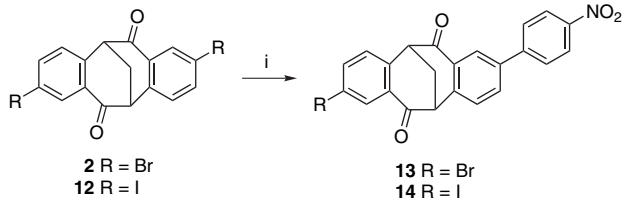
Scheme 2. *Reagents and conditions*: i. $PdCl_2(PPh_3)_2$, Na_2CO_3, DME–H_2O; ii. 4-nitrophenylboronic acid, $PdCl_2(PPh_3)_2$, Na_2CO_3, DME–H_2O; iii. Fe/CH_3CO_2H; iv. $NaNO_2$, H_2SO_4, KI; v. (4-pyridyl)boronic acid pinacol ester, $PdCl_2(PPh_3)_2$, Na_2CO_3, DME–H_2O; vi. 4-(hydroxy)boronic acid pinacol ester, $PdCl_2(PPh_3)_2$, Na_2CO_3, DME–H_2O; vii. Tf_2O, pyridine, CH_2Cl_2; viii. (4-pyridyl)boronic acid pinacol ester, $Pd(PPh_3)_4$, Na_2CO_3, DME–H_2O.



Scheme 3. *Reagents and conditions*: i. $NaNO_2$, 40% aq HBF_4, EtOH, −40 °C; ii. KI, −40 °C to rt; iii. bis(pinacolato)diborane, $PdCl_2(dppf)\cdot CH_2Cl_2$, KOAc, dioxane or DMSO.



Scheme 4. *Reagents and conditions*: i. H_2SO_4, $NaNO_2$, KI.



Scheme 5. *Reagents and conditions*: i. $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$, Na_2CO_3, 4-nitrophenylboromic acid, DME–H_2O.

reaction of the dibromo cleft **2** and (4-hydroxyphenyl)boronic acid pinacol ester, catalysed by $PdCl_2(PPh_3)_2$ (Scheme 2). In contrast to attempted preparation of **6**, the bisphenol **8** was formed in good yield and exhibited good solubility thus avoiding the problems encountered with the nitro compound. Bisphenol **8** was treated with triflic anhydride and pyridine to afford the corresponding bistriflate **9** as a suitable coupling partner for Suzuki reactions. However, under standard Suzuki reaction conditions,[21] treatment of (4-pyridyl)-boronic acid pinacol ester with bistriflate **9** in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ (2.5 mol %), K_3PO_4 and KBr in dioxane gave no reaction. The use of more forcing conditions (increased catalyst loading, use of the more active $Pd(PPh_3)_4$ catalyst and prolonged reaction time) also resulted in no reaction. The failure of this reaction is most likely because of the precipitation of palladium black at the reaction onset, which results from the side reaction of the triflate with the triphenylphosphine ligand to afford phosphonium salts.[21,22] Accordingly, application of the methodology of Fu et al.[23] for coupling of aryl triflates and boronic acids was investigated. Following the reported optimal conditions, there was no reaction at rt using $Pd(OAc)_2$ and PCy_3 in DMF, and the successful synthesis of ligand **L3** required the use of $Pd(PPh_3)_4$ and sodium carbonate in DME–H_2O with heating. Purification of **L3** required chromatography, followed by recrystallisation from MeOH and trifluoroacetic acid.

2.2. X-ray crystallography

Single crystals of racemic **L1**, **L2** and **L3** suitable for X-ray diffraction analysis were obtained by recrystallisation from MeOH. Crystallographic details and pertinent metric details are summarised in Tables 1–3, and ORTEP depictions are provided in Figures 1 and 2. The crystal structure of ligand **L1** includes a water solvate molecule that forms a hydrogen bond with **L1**. The crystal structure of **L2** contains a disordered methanol solvate molecule, whilst the solid state

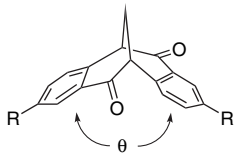
Table 1. Single crystal X-ray diffraction details for ligands **L1**, **L2** and **L3**

Compound	**L1**	**L2**	**L3**
Formula	$C_{27}H_{20}N_2O_3$	$C_{32}H_{22}N_2O_3$	$C_{39}H_{26}N_2O_2$
Crystal system	Orthorhombic	Monoclinic	Triclinic
Molecular weight	420.45	482.52	554.62
Size (mm^3)	0.31×0.27×0.26	0.33×0.17×0.15	0.31×0.26×0.10
Space group	*P*ccn(#56)	$P2_1/c$(#14)	$P\bar{1}$(#2)
a (Å)	17.3760(6)	7.499(6)	11.7599(10)
b (Å)	10.6974(4)	27.08(2)	15.3672(14)
c (Å)	10.8602(3)	12.224(10)	16.5565(14)
α (°)	—	—	95.6950(10)
β (°)	—	104.336(13)	107.2570(10)
γ (°)	—	—	97.1050(10)
V ($Å^3$)	2018.67(12)	2405(3)	2806.1(4)
D_{calcd} ($g\,cm^{-3}$)	1.383	1.333	1.313
Z	4	4	4
μ(Mo Kα) (mm^{-1})	0.091	0.086	0.081
$T(SADABS)_{min,max}$	0.891, 0.977	0.733, 1.000	—
$2\theta_{max}$ (°)	70.00	57	61
hkl range	−28 28, −17 17, −14 17	−10 9, −34 34, −16 16	−16 16, −22 21, −23 23
N	40,515	22,452	48,618
N_{ind} (R_{merge})	4405(0.025)	5603(0.078)	17,155(0.070)
N_{obs} [$I>2\sigma(I)$]	3505	3339	10,392
N_{var}	150	354	775
$R1(F)$,$wR2(F^2)$	0.0428, 0.1055	0.0560, 0.1287	0.0446, 0.0903
GoF (all)	1.270	1.401	1.148
ρ_{max} ($e\,Å^{-3}$)	−0.199, 0.463	−0.311, 0.306	−0.267, 0.385

Table 2. Selected bond lengths (Å) and angles (°) for ligands **L1**, **L2** and **L3**

Ligand **L1**			
O(1)–C(7)	1.2164(10)	C(5)–C(4)–C(10)–C(14)	25.88(12)
C(1)–C(8)–C(7)	108.78(7)	C(3)–C(4)–C(10)–C(11)	24.59(12)
Ligand **L2**			
O(1)–C(7)	1.228(2)	O(2)–C(15)	1.224(3)
C(7)–C(8)–C(9)	107.51(16)	C(1)–C(16)–C(15)	108.01(16)
Ligand **L3**			
O(1)–C(7)	1.2167(13)	O(3)–C(46)	1.2148(13)
O(2)–C(15)	1.2174(14)	O(4)–C(54)	1.2173(14)
C(7)–C(8)–C(9)	108.75(9)	C(46)–C(47)–C(48)	108.84(9)
C(1)–C(16)–C(15)	107.28(10)	C(40)–C(55)–C(54)	108.02(10)
C(5)–C(4)–C(18)–C(23)	−142.45(12)	C(44)–C(43)–C(57)–C(62)	−141.28(12)
C(11)–C(12)–C(29)–C(34)	34.17(17)	C(50)–C(51)–C(68)–C(69)	144.00(12)
C(22)–C(21)–C(24)–C(25)	46.43(17)	C(61)–C(60)–C(63)–C(64)	50.40(17)
C(33)–C(32)–C(35)–C(39)	38.33(18)	C(70)–C(71)–C(74)–C(78)	−34.18(17)

Table 3. Cleft angle θ and nitrogen–nitrogen separations for **L1**, **L2** and **L3**



Compound	Interplanar 'cleft' angle θ (°)	Distance between nitrogen atoms (Å)
L1	97.80(3)	13.57(1)
L2	102.47(8)	17.55(1)
L3[a]	103.30(4), 109.80(4)	21.35(1), 21.40(1)

[a] The asymmetric unit contains two independent molecules.

structure of ligand **L3** contains two crystallographically independent molecules.

The dihedral angle formed by the least square planes of the two opposing phenyl rings immediately attached to the bridgehead superstructure, provides a simple measure of the intramolecular cleft angle. Previous analyses of 2,8-disubstituted dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione clefts have suggested substituent effects on cleft angles, with angles of 100–104° observed for clefts substituted with electron-donating aryl groups.[11] The cleft angles for **L1**, **L2** and **L3** (two independent molecules) are 97.80(3), 102.47(8), 103.30(4) and 109.80(4)°, respectively (Table 3). The single crystal structures indicate that the linker units of **L1**, **L2** and **L3** affect the overall shape of the oligopyridine clefts, though it is not clear if this reflects packing influences or electronic effects. The significantly different cleft angles found in the two independent molecules of **L3** suggest that packing influences are most likely to be the cause of the cleft angle variation, though we have not yet identified any particular causal contacts. The cleft angle of 109.80(4)° observed in the second molecule of **L3** is much like that which would be expected of an sp^3 carbon based geometry, suggesting perhaps that this molecule is actually least affected by packing influences. Paradoxically,

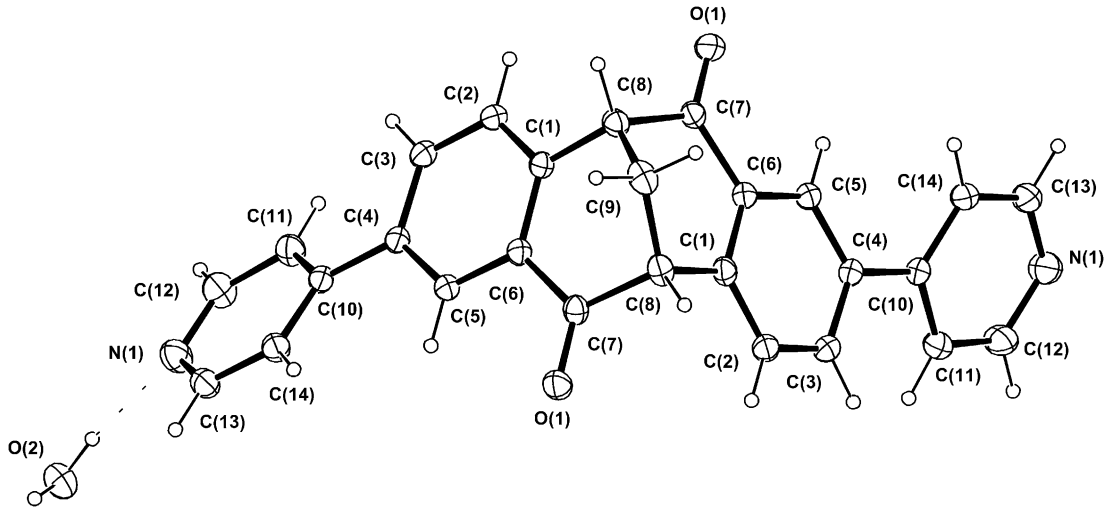


Figure 1. ORTEP depiction of structures of **L1** showing 50% displacement ellipsoids and the hydrogen bonding interaction with the solvate water molecule.

the **L3** intramolecular nitrogen–nitrogen distances are much the same at 21.35(1) and 21.40(1) (Å) (Table 3), and there is no obvious explanation for this contrast to the differing cleft angles found in the two molecules of **L3**.

The molecules of **L1** and **L3** pack with the apex of one molecule effectively nestling into the cleft of another, as suggested in Figure 2. In contrast, the stacking of molecules in the structure of **L2** is interleaved with the terminal residue of neighbouring molecules, as shown in Figure 3. The cleft angle of **L2** is between those of **L1** and **L3**, suggesting, in contrast to early observations that this packing difference does seem to influence the cleft angle. The solid state cleft angle of any particular molecule appears to be the outcome of subtle differences in packing and electronic influences, with no reliable systematic trend yet evident.

2.3. Metal complexation studies

Preliminary metal complexation studies of the racemic ligand **L1** with palladium(II) have been performed. Thus, a solution of $[Pd(ONO_2)_2(en)]$ in H_2O (16.7 mM) was treated with a solution of racemic ligand **L1** in MeOH (16.7 mM) at ambient temperature. ESI–MS analysis of the crude reaction mixture was consistent with the formation of the [2+2] metallomacrocycle and peaks at 631 $[M-2NO_3]^{2+}$, 508 $[M-4NO_3+7MeOH]^{4+}$, 380 $[M-4NO_3+3MeOH]^{4+}$ and 284 $[M-4NO_3]^{4+}$ were detected. Due to the chirality of

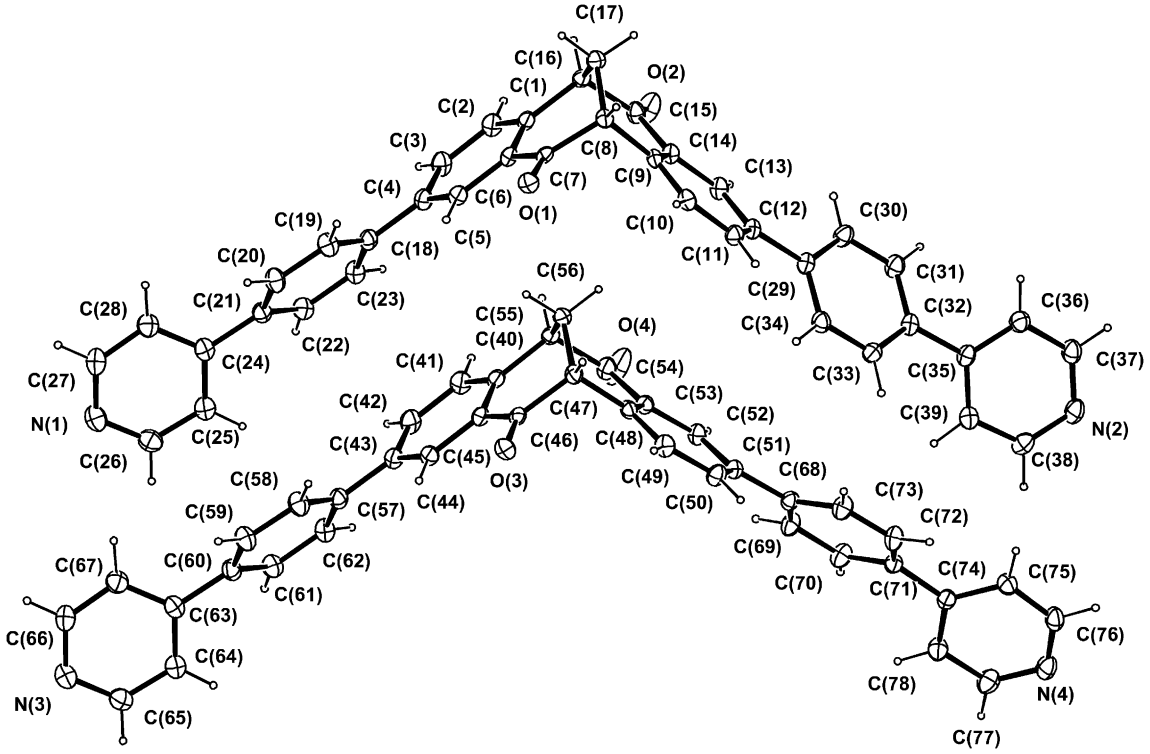


Figure 2. ORTEP depiction of structures of **L3** showing 50% displacement ellipsoids.

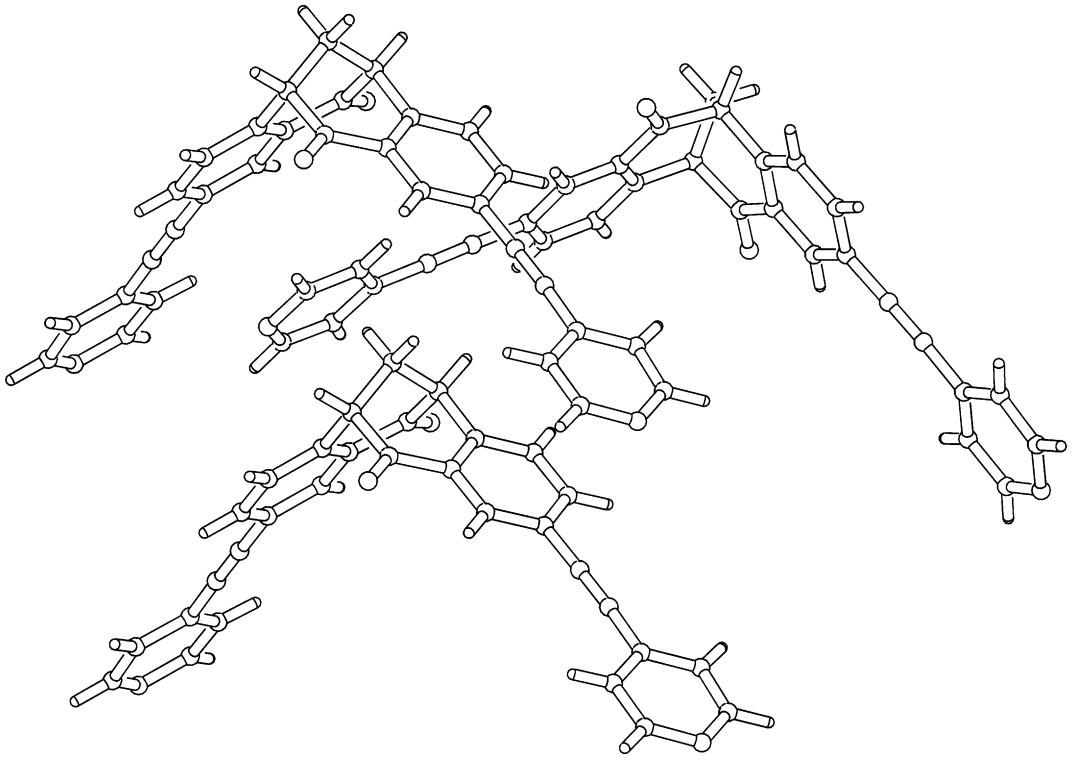


Figure 3. Ball and stick depiction of **L2** showing the interleaving of the molecules.

the ligand **L1**, the formation of stereoisomers is possible. In contrast to studies with bipyridyl clefts and zinc(II) [$Zn(OTf)_2$] where enantiomeric ligand–ligand recognition occurred,[24] the ^{1}H NMR spectrum of **L1** and Pd contained multiple signals consistent with formation of several complexes. Full characterisation of these complexes therefore requires studies with the pure enantiomers, which are accessible from optically pure **2**.[11]

Analogous results were obtained upon treatment of ligands **L2** and **L3** with [$Pd(ONO_2)_2$en]. These reactions were performed at more dilute concentrations due to the poor solubility of ligands **L2** and **L3** relative to **L1** in MeOH. ESI-MS analysis of the reaction mixtures was consistent with the formation of the corresponding [2+2] metallomacrocycles. In the case of **L2**, peaks were detected at *m*/*z* 616 $[M-4NO_3+4MeOH+10H_2O]^{4+}$ and 557 $[M-4NO_3+5MeOH+5H_2O]^{4+}$ while for **L3** peaks at *m*/*z* 833 $[M-2NO_3+MeOH+H_2O]^{2+}$, 720 $\{2[M-4NO_3]^{4+}\}$, 660 $[M-4NO_3+6MeOH+6H_2O]^{4+}$.

3. Conclusions

The new dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione molecular clefts incorporating pyridyl, ethynylpyridyl and *p*-(4′-pyridyl)phenyl groups were prepared via Pd and Pd–CuI catalysed cross-coupling methodologies. The choice of solvent was critical in mediating the cross-coupling reactions, with polar solvents such as DME–H_2O and DMF being required to facilitate these reactions. X-ray crystallographic analyses of the clefts confirm previous studies, which have shown that the substituents on the aryl rings affect the dimensions, and packing motifs, of the cleft in the solid state. Preliminary metal complexation studies have confirmed that under appropriate conditions the ditopic symmetrical bis(pyridyl) ligands can be used in the assembly of chiral [2+2] metallomacrocycles. The incorporation of these ligands into the design of chiral metallomacrocycles of nanoscale dimensions is currently under investigation in these laboratories.

4. Experimental

4.1. General experimental procedures

Melting points were measured on a Reichardt hot-stage and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 K on Bruker DPX200 and Bruker DPX300 NMR spectrometers. Low and high resolution mass spectra (EI) were obtained on a Kratos MS902 spectrometer at 70 eV. Values of *m*/*z* are quoted with intensities expressed as percentages of the base peak in parentheses. Infrared spectra were recorded on a Shimadzu FTIR-8400S spectrometer. Single crystal X-ray analyses were performed on either an APEXII-FR591 diffractometer or a Bruker SMART 1000 CCD diffractometer. $PdCl_2(PPh_3)_2$ and 4-ethynylpyridine hydrochloride were purchased from Sigma-Aldrich. (4-Pyridine)boronic acid pinacol ester and (4-hydroxyphenyl)boronic acid pinacol ester were sourced from Boron Molecular Pty Ltd. 4-Pyridylboronic acid was purchased from Alfa Asar. $Pd(PPh_3)_4$[25] and (±)-2,8-dibromodibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione were synthesised according to literature procedures.[11]

4.1.1. (±)-2,8-Dipyridyldibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione L1. To a mixture of dibromo dione **2** (200 mg, 0.492 mmol), (4-pyridine)boronic acid pinacol ester (202 mg, 0.986 mmol), Na_2CO_3 (312 mg, 2.96 mmol) and $PdCl_2(PPh_3)_2$ (70 mg, 20 mol %) at rt were added

DME (10 mL) and H_2O (2 mL). The mixture was degassed and purged with nitrogen (six cycles), then heated at 85 °C under an atmosphere of nitrogen for three days. After cooling to rt, the solvents were removed in vacuo. The resulting residue was taken up in EtOAc (30 mL) and washed with H_2O (20 mL). The aqueous phase was separated and extracted with EtOAc (3×30 mL). The organic solutions were combined and washed with brine (30 mL), then dried (Na_2SO_4) and concentrated to dryness. Flash chromatography of the tan residue on silica, eluting with MeOH/hexane (1:99 to 1.5:98.5) afforded **L1** as a off-white solid [R_f 0.13; MeOH/hexane (1:99)] (154 mg, 78%); mp 114–116 °C; IR (KBr) 1688, 1682 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.08 (t, J=3.0 Hz, 2H), 4.15 (t, J=3.0 Hz, 2H), 7.47 (d, J=5.4 Hz, 2H), 7.63 (d, J=8.1 Hz, 2H), 7.82 (d, J=8.1, 2.0 Hz, 2H), 8.27 (d, J=2.0 Hz, 2H), 8.67 (br s, 2H); δ_C (300 MHz, $CDCl_3$) 31.9, 48.5, 121.5, 126.8, 129.5, 129.9, 132.8, 140.4, 149.4, 193.5; UV λ_{max} (MeOH) 374 (sh) (481), 356 (sh) (1307), 338 (1782), 324 (1883), 306 (2241), 274 (3123), 270 (3126); *m/z* (EI, %) 402 (M^+, 100), 385 (24), 374 (28), 357 (13), 332 (9), 331 (2), 296 (6), 280 (2), 266 (5), 239 (2), 207 (1), 201 (4), 167 (3), 152 (2), 132 (1), 89 (1), 79 (1), 52 (2). Found: $M^{\bullet+}$, 402.1369. $C_{27}H_{18}N_2O_2$ requires $M^{\bullet+}$, 402.1368. Crystals suitable for X-ray diffraction were obtained by recrystallisation from MeOH.

4.1.2. (±)-2,8-(4-Bromo-4′-ethynylpyridyl)dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione 4. Triethylamine (1.0 mL, 7.25×10^{-3} mol) was added to a mixture of the dibromo cleft **2** (20.0 mg, 4.83×10^{-5} mol) and 4-ethynylpyridine hydrochloride (101 mg, 7.25×10^{-4} mol) in dry THF (4 mL) at rt. Under a steady stream of nitrogen, $Pd(PPh_3)_4$ (3 mg, 5 mol %) and CuI (0.5 mg, 5 mol %) were quickly added. The dark reaction mixture was evacuated and purged with nitrogen (3× freeze-pump-thaw cycles), then heated at 50 °C in the dark under an atmosphere of nitrogen for 50 h. After cooling to rt, the dark mixture was filtered, the solids washed with EtOAc (15 mL) and MeOH (15 mL). The filtrate was evaporated in vacuo and the resulting residue was taken up in EtOAc (30 mL). After washing with aq $NaHCO_3$ (30 mL), the layers were separated and the aqueous solution was extracted with EtOAc (3×30 mL). The organic solutions were combined and washed with aq $NaHCO_3$ (2×30 mL) and brine (30 mL), then dried (Na_2SO_4) and evaporated under reduced pressure. Flash column chromatography of the resultant brown residue on silica, eluting with MeOH/CH_2Cl_2 (1.5:98.5) afforded the cleft **4** (5.5 mg, 20%) as a white solid [R_f 0.31; MeOH/CH_2Cl_2 (1.5:98.5)]; mp>300 °C; IR (KBr) 1688, 1645, 1589, 1454, 1402 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 3.01 (t, J= 2.9 Hz, 2H), 4.04 (br m, 1H), 4.09 (br m, 1H), 7.37 (d, J= 8.2 Hz, 1H), 7.57 (dd, J=8.0, 2.2 Hz, 1H), 7.67 (dd, J=7.9, 1.8 Hz, 1H), 7.73 (d, J=8.2 Hz, 1H), 7.88 (d, J=6.5 Hz, 2H), 8.10 (dd, J=1.8 Hz, 1H), 8.21 (dd, J=2.1 Hz 1H), 8.71 (d, J=6.4 Hz, 2H); *m/z* (EI, %) 429 ($M^{\bullet+}$, 100), 399 (33), 385 (26), 358 (45), 348 (41), 320 (62), 291 (36), 263 (28), 261 (9), 213 (12), 163 (11), 149 (29), 131 (18), 126 (14), 85 (18), 71 (28); Found: $M^{\bullet+}$ 427.0213. $C_{24}H_{14}BrN_1O_2$ requires $M^{\bullet+}$, 427.0208.

4.1.3. (±)-2,8-Bis(4-ethynylpyridyl)dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione L2. Triethylamine (1.0 mL, 7.25×10^{-3} mol) was added to a mixture of the dibromo cleft **2** (20.0 mg, 4.83×10^{-5} mol) and 4-ethynylpyridine hydrochloride (40.0 mg, 2.90×10^{-4} mol) in dry DMF (5 mL) at rt. Under a steady stream of nitrogen, $Pd(PPh_3)_4$ (3 mg, 5 mol %) and CuI (0.5 mg, 5 mol %) were quickly added. The dark brown reaction mixture was evacuated and purged with nitrogen (3× freeze-pump-thaw cycles) then heated at 80 °C in the dark under an atmosphere of nitrogen for three days. After the cooling to rt, the reaction mixture was taken up in EtOAc (30 mL) and washed with H_2O (30 mL). The layers were separated and the aqueous solution was extracted with EtOAc (5×20 mL). The organic solutions were combined and washed with H_2O (4×30 mL) and brine (30 mL), then dried (Na_2SO_4) and evaporated under reduced pressure. Flash column chromatography of the resulting brown residue on silica, eluting with a gradient of MeOH/CH_2Cl_2 (1.5:98.5 to 4:96) afforded ligand **L2** (18 mg, 83%) as a white solid [R_f 0.31; MeOH/CH_2Cl_2 (4:96)]; mp>300 °C; IR (KBr) 2231, 2210, 1686, 1589 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 3.04 (t, J=2.8 Hz, 2H), 4.10 (t, J=2.8 Hz, 2H), 7.45 (d, J=6.2 Hz, 4H), 7.52 (d, J=8.0 Hz, 2H), 7.79 (dd, J=8.0, 1.9 Hz, 2H), 8.17 (s, 2H), 8.62 (d, J= 6.2 Hz, 4H); δ_C (300 MHz, $CDCl_3$) 31.7, 48.6, 88.4, 92.1, 123.3, 125.6, 129.0, 129.3, 130.8, 131.9, 137.2, 140.2, 149.9, 192.8; *m/z* (EI, %) 450 ($M^{\bullet+}$, 100), 422 (29), 421 (25), 405 (19), 380 (10); Found: $M^{\bullet+}$ 450.1360. $C_{31}H_{18}N_2O_2$ requires $M^{\bullet+}$, 450.1368. Crystals suitable for X-ray diffraction were obtained by recrystallisation from MeOH.

4.1.4. (±)-2,8-Di(4-hydroxyphenyl)dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione 8. To a mixture of dibromo cleft **2** (100 mg, 0.249 mmol), (4-hydroxyphenol) boronic acid pinacol ester (110 mg, 0.500 mmol), Na_2CO_3 (80.0 mg, 0.755 mmol) and $PdCl_2(PPh_3)_2$ (3.5 mg, 20 mol %) were added DME (5 mL) and H_2O (1 mL). The mixture was degassed and purged with nitrogen (six cycles), then heated at 85 °C under an atmosphere of nitrogen for 24 h. After cooling to rt and evaporation of solvent, the residue was taken up in EtOAc (30 mL) and washed with 3 M HCl (30 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×30 mL). The organic solutions were combined and washed with brine (30 mL), then dried (Na_2SO_4) and evaporated in vacuo. The resulting off-white solid was washed with cold Et_2O (30 mL) then dried under high vacuum to afford bisphenol **8** as an off-white solid (60 mg, 58%) [R_f 0.34; MeOH/hexane (1:9)]; mp>300 °C; IR (KBr) 3219 (br), 1670 cm^{-1}; δ_H (200 MHz, *d*-DMSO) 3.02 (br m, 2H), 4.07 (br m, 2H), 6.83 (d, J=8.6 Hz, 2H), 7.46 (d, J=8.6 Hz, 2H), 7.51 (d, J=8.1 Hz, 2H), 7.83 (dd, J=8.1, 2.0 Hz, 2H), 7.97 (d, J=2.0 Hz, 2H), 9.66 (br s, 2H); *m/z* (EI, %) 432 (M^+, 100), 419 (73), 404 (33), 388 (10), 362 (9), 327(8), 312 (10), 299 (14), 294 (15), 265 (22), 263 (11), 240 (11), 211 (43), 209 (34), 191 (9), 189 (12), 185 (22), 183 (15), 155 (21), 149 (41), 125 (18), 121 (23), 107 (23), 105 (95), 81 (48), 79 (64), 77 (69), 67 (48), 55 (54). Found: $M^{\bullet+}$, 432.1366. $C_{29}H_{20}O_4$ requires $M^{\bullet+}$, 432.1362.

4.1.5. (±)-2,8-Di(phenyl-4-trifluoromethanesulfonate) dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione 9. Pyridine (0.10 mL, 1.28×10^{-3} mol) was added to bisphenol **8** (115 mg, 2.66×10^{-4} mol) suspended in dry CH_2Cl_2 (17 mL) at rt under an atmosphere of nitrogen. The resultant

solution was cooled to 0 °C (ice bath) followed by addition of triflic anhydride (0.15 mL, 8.81×10^{-4} mol). After stirring at rt for 2 h, the reaction was quenched with aq $NaHCO_3$ (1 mL) and the mixture extracted into Et_2O (3×15 mL). The organic solution was washed with satd aq $CuSO_4$ (3×15 mL), H_2O (1×15 mL), and brine (1×15 mL), dried (Na_2SO_4) and concentrated in vacuo to afford crude bistriflate **9** as a yellow oil (183 mg, 99%) [R_f 0.93; MeOH/$CHCl_3$ (1:9)], which was used in the next reaction without further purification; δ_H (200 MHz, $CDCl_3$) 3.07 (t, J=2.6 Hz, 2H), 4.13 (t, J=2.6 Hz, 2H), 7.33 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.0 Hz, 2H), 7.60 (d, J=8.8 Hz, 2H), 7.74 (dd, J=8.0, 2.2 Hz, 2H), 8.18 (d, J=2.2 Hz, 2H).

4.1.6. (±)-2,8-Bis(4-phenylpyridyl)dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione L3. To a mixture of the bistriflate **9** (183 mg, 2.63×10^{-4} mol), 4-pyridinylboronic acid (100 mg, 8.13×10^{-4} mol) and sodium carbonate (140 mg, 1.32×10^{-3} mol) were added DME (20 mL) and H_2O (6 mL). The mixture was evacuated and purged with nitrogen (3× freeze-pump-thaw cycles) and heated at 85 °C in the dark under an atmosphere of nitrogen for 46 h. After cooling to rt, the mixture was taken up in CH_2Cl_2 (250 mL) and washed with H_2O (120 mL). The layers were separated and the organic layer was washed with aq Na_2CO_3 (2×50 mL). The aqueous solution was extracted with CH_2Cl_2 (100 mL); the organic solutions were combined then dried (Na_2SO_4) and evaporated in vacuo. Flash column chromatography of the residue on silica, eluting with MeOH/CH_2Cl_2 (3:97), followed by recrystallisation of the resulting white solid from MeOH and trifluoroacetic acid afforded ligand **L3** as colourless crystals (100 mg, 68%) [R_f 0.27; MeOH/CH_2Cl_2 (4:96)]; mp>300 °C; IR (KBr) 1683, 1653, 1558 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.10 (m, 2H), 4.15 (m, 2H), 7.55 (d, J=5.9 Hz, 4H), 7.63 (d, J=8.0 Hz, 2H), 7.72 (s, 8H), 7.83 (dd, J=8.0, 2.0 Hz, 2H), 8.29 (d, J=2.0 Hz, 2H), 8.69 (d, J=5.9 Hz, 4H); *m*/*z* (EI, %) 554 (M^+, 40), 553 (100), 526 (77), 277 (15), 242 (9), 228 (8), 165 (9), 156 (23), 149 (19), 105 (11), 95 (15), 91 (20), 77 (69), 79 (27), 67 (28), 55 (37). Found: $M^{\bullet+}$, 544.1991. $C_{39}H_{26}N_2O_2$ requires $M^{\bullet+}$, 554.1994. Crystals suitable for X-ray diffraction were obtained by recrystallisation from MeOH and trifluoroacetic acid.

4.1.7. Attempted preparation of (±)-2,8-bis(4-nitrophenyl)dibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione 6. Using the same protocol for the synthesis of cleft **L1**, the reaction of the dibromo cleft **2** (78 mg, 0.19 mmol), Na_2CO_3 (123 mg, 1.16 mmol), 4-nitrophenylboronic acid (74 mg, 0.44 mmol) and $PdCl_2(PPh_3)_2$ (30 mg, 43 μmol) followed by flash chromatography, eluting with EtOAc/hexane (3:1) afforded the crude monocoupled product **13** as a cream solid (55 mg, 64%) [R_f 0.65; EtOAc/hexane (2:1)]; δ_H (200 MHz) 3.05–3.02 (2H, m), 4.11–4.05 (2H, m), 7.81–7.58 (6H, m), 8.31–8.10 (4H, m); *m*/*z* (EI, %) 448.9 (MH^+, 97%), 446.9 (M^+, 100), 419.0 (33), 263.2 (32). Crude **13** was treated further with Na_2CO_3 (123 mg, 1.16 mmol), 4-nitrophenylboronic acid (74 mg, 0.44 mmol) and $PdCl_2(PPh_3)_2$ (30 mg, 43 μmol). ^1H NMR analysis of the resulting product indicated a complex mixture of products.

4.1.8. (±)-2,8-Diiododibenzobicyclo[*b*,*f*][3.3.1]nona-5a,6a-diene-6,12-dione 12. An aqueous solution (1 mL) of sodium nitrite (23 mg, 0.33 mmol) was added over 2 h to a stirred solution of cleft **15** (34 mg, 0.12 mmol) in water (1.5 mL) and concd H_2SO_4 (four drops) at 0 °C. After 30 min, an aqueous solution (1.5 mL) of KI (79.5 mg, 0.48 mmol) was slowly added. The reaction mixture was warmed to rt and left to stand for 40 min. The mixture was poured onto water (40 mL) and extracted with EtOAc (3×30 mL). The combined organic extracts were washed with 10% aq $Na_2S_2O_7$ (100 mL) and brine (100 mL), then dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the orange residue on silica, eluting with EtOAc/hexane (1:5) afforded the diiodide **12** as an off-white coloured solid (42.5 mg, 70%) [R_f 0.81 (CH_2Cl_2)]; mp 243.5–245.5 °C; IR (NaCl) 1683 cm^{-1}; δ_H (200 MHz) 2.96 (t, J=3.0 Hz, 2H), 3.96 (t, J=3.0 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 7.83 (dd, J=8.1, 2.0 Hz, 2H), 8.27 (d, J=2.0 Hz, 2H); *m*/*z* (ES^+, %) 500.8 ($M+H^+$, 18%), 499.8 (M^+, 100), 218.2 (41), 189.2 (36). Anal. Calcd for $C_{17}H_{10}I_2O_2$: (%) C 40.83, H 2.02. Found: C 41.07, H 2.12.

4.2. Metal complexation

A solution of ligand **L1** (10 mg, 2.49×10^{-5} mol) in MeOH (1.5 mL) was added dropwise to a solution of [$Pd(ONO_2)_2$(en)] (7.25 mg, 2.49×10^{-5} mol) in H_2O (1.5 mL) at 20 °C. The homogeneous solution was stirred at 20 °C for four days. The residue was redissolved in CD_3OD/D_2O (1:1) and analysed by ^1H NMR spectroscopy. The ^1H NMR spectrum contained multiple peaks consistent with the formation of a mixture of stereoisomers. Analysis by ESI mass spectrometry showed peaks consistent with the formation of the [2+2] macrocycle, *m*/*z* 631 $[M-2NO_3]^{2+}$, 508 $[M-4NO_3+7MeOH]^{4+}$, 380 $[M-4NO_3+3MeOH]^{4+}$ and 284 $[M-4NO_3]^{4+}$.

In an analogous fashion, methanolic solutions of ligand **L2** (4.49 mg, 1×10^{-5} mol; 1.2 mL) and ligand **L3** (5.54 mg, 1×10^{-5} mol; 3.3 mL) were independently treated with [$Pd(ONO_2)_2$(en)] (2.91 mg, 1×10^{-5} mol) in H_2O (1.2 mL). After stirring at 20 °C for 6 h, the crude reaction mixtures were analysed by ESI mass spectrometry. Peaks consistent with the formation of the [2+2] metallomacrocycles were observed as follows: for **L2**-containing macrocycle, *m*/*z* 833 $[M-2NO_3+MeOH+H_2O]^{2+}$, 720 $[M-4NO_3]^{4+}$, 661 $[M-4NO_3+6MeOH+6H_2O]^{4+}$; for **L3**-containing macrocycle, *m*/*z* 616 $[M-4(NO_3)]^{4+}$ and 557 $[M-4NO_3+5MeOH+5H_2O]^{4+}$.

4.3. X-ray diffraction

Data collections were undertaken at 150(2) K, graphite monochromated Mo Kα radiation (0.71073 Å). For **L1** and **L3**, an APEXII-Kappa-FR591 rotating anode diffractometer was used for the data collection, while for **L2**, a Bruker SMART 1000 sealed tube diffractometer was used. The diffraction data integration and reduction for **L1**, **L2** and **L3** were undertaken with SAINT and XPREP,[26] subsequent computations were carried out with the XTAL[27] and WinGX[28] graphical user interfaces. A multi-scan correction determined with SADABS[29] was applied to the data of **L1** and **L2**. There was no crystal decay during the data collections. The structures were solved by direct methods with SIR97[30] and extended and refined with SHELXL97.[31]

Anisotropic displacement parameters were refined for the non-hydrogen atoms. The asymmetric unit for **L1** contains half of the molecule located on a two fold axis passing through the bridgehead carbon site C(9), and there is also a water molecule residing on a two fold axis. In addition to the cleft molecule, the asymmetric unit for **L2** contains a methanol solvate disordered over two sites with occupancies refined and then fixed at 0.5. The asymmetric unit for **L3** contains two crystallographically independent molecules. ORTEP[32] depictions are provided in Figures 1 and 2.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited to the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 293459, 29360 and 293461. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk].

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