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Full Paper

Synthesis of Two 2,2′-Bipyridine Containing Macrocycles for the Preparation of Interlocked Architectures*

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The synthesis and characterisation of two 28-membered, 2,2′-bipyridine-containing macrocycles in high yield is reported. The first imine-containing macrocycle was formed via a Williamson ether synthesis and showed no evidence of higher oligomer formation. Reduction of the imines with sodium borohydride produced the second macrocycle quantitatively.

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Introduction

The 2016 Nobel Prize for Chemistry was awarded to Sauvage, Stoddart, and Feringa for the design and synthesis of molecular machines.[1] Sauvage[2] and Stoddart,[3] in particular, have based their design strategies for these machines around the use of interlocked and topologically complex architectures such as catenanes and rotaxanes.[4] Building on their early work, Leigh and others have extended this approach producing a wide variety of increasingly complex molecules and machines[5] including rotors,[6] walkers,[7] peptide synthesisers,[8] ratchets,[9] and an extended series of knots and links.[10] Learning from the low yielding statistical approach to the first [2]catenane, which was isolated in 1×10^{-4}% yield over 50 years ago,[11] higher-yielding templated (pre-organised) designs have now been established; however, macrocyclisation reactions are generally still yield limiting.[12] In addition to high-dilution and/or syringe pump additions of reagents, several groups have also employed click reactions,[13] alkene-metathesis,[14] and coordination bonds[15] in order to enhance the yields of the target macrocyclic products. For example, Lindoy and colleagues[16] reported the quantitative formation a [2]catenane **1** in solution through the use of a reversible imine-condensation reaction and a copper(I) template. The macrocycle employed was designed to have more flexibility that the 1,10-phenanthroline-containing macrocycles employed by Sauvage.[17] In situ reduction with borohydride led to the isolation of the tetraamine-analogue **2** in more modest yield, which was characterised by X-ray crystallography. Treatment with potassium cyanide produced the metal-free [2]catenane. The individual non-interlocked 28-membered macrocyclic components of **1** and **2** (**3** and **4**, respectively) were not reported. These macrocycles, which contain a 2,2′-bipyridine unit would be useful components for the formation of a wide variety of interlocked architectures including further catenanes, rotaxanes, and molecular machines. The present study reports the preparation of macrocycle **3** in 82% yield and its quantitative reduction to macrocycle **4** on the NMR scale (Chart 1).

Results and Discussion

Lindoy and coworker's high-yielding synthetic strategy[16] to produce the [2]catenane **1** involved the pre-organisation of two diadelhyde-2,2′-bipyridine derivatives **5** around a copper(I) ion followed by a Schiff base condensation reaction (Scheme 1). The tetrahedral copper(I) template served to arrange the dialdehyde groups to promote the formation of the target [2]catenane rather than a non-interlocked [2+2] macrocyclic isomer, while the reversibility of the imine-formation reaction allowed for self-correction during the high-dilution reaction. Our first attempt to prepare **3** followed a similar approach (Scheme 2).

We prepared dialdehyde **5** following Lindoy and coworkers's method and added one equivalent of commercially available 1,6-diaminohexane in methanol. We monitored the reaction using a combination of ^{1}H NMR spectroscopy and

*Dedicated to Mrs Fay Lindoy on the occasion of Len's 80th birthday.

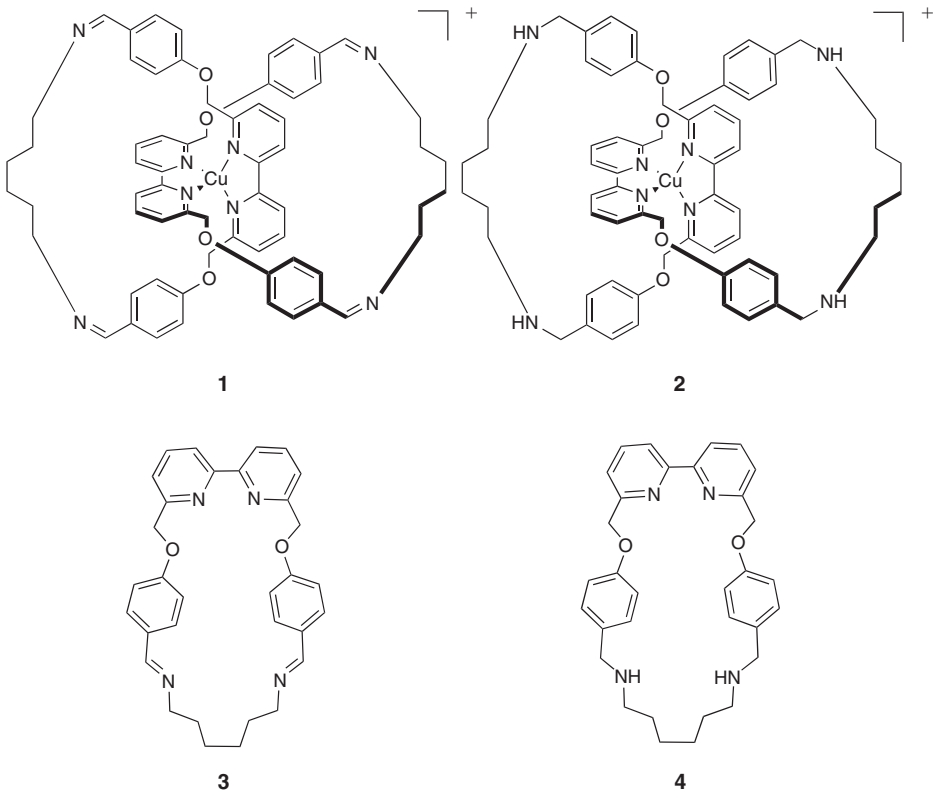
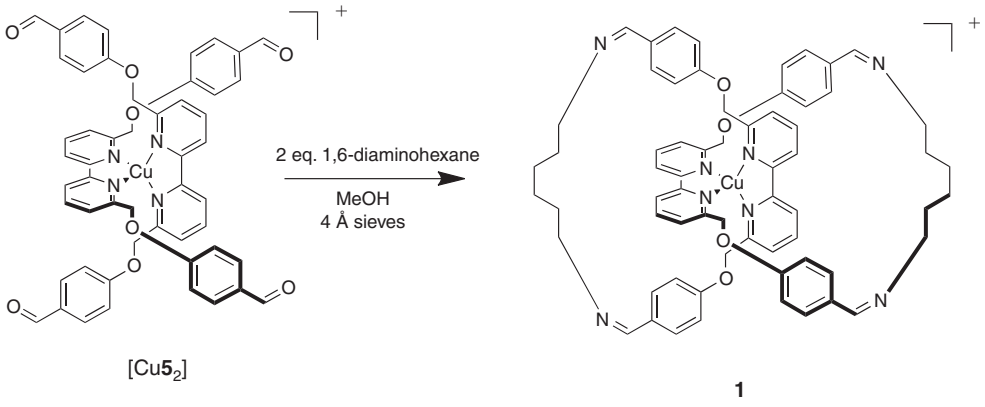


Chart 1.

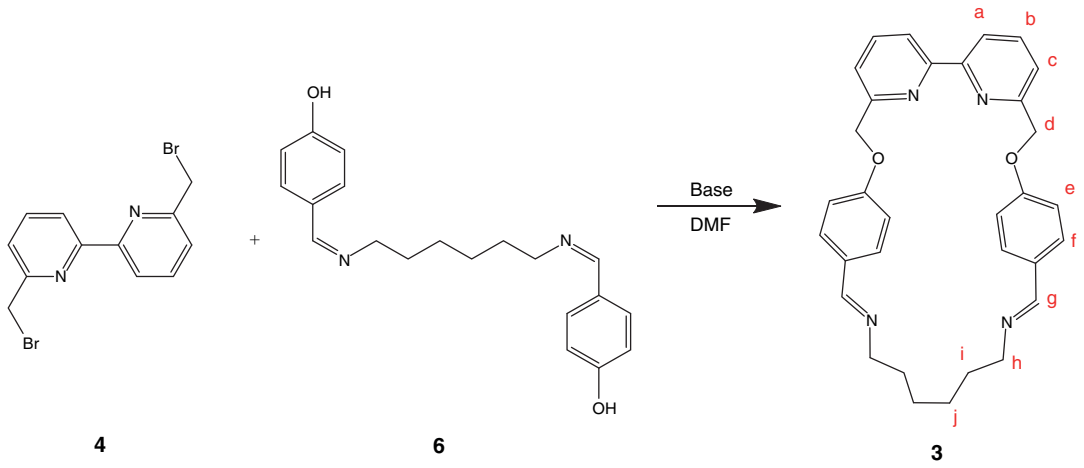


Scheme 1. Lindoy's synthetic route to [2]-catenane **1** via Cu^{I} templation and imine condensation.

electrospray ionisation mass spectrometry (ESI-MS). Even after 72 h of reflux no imine formation was observed. This reaction was performed numerous times with the addition of a variety of water sequestering agents (4 Å molecular sieves, magnesium sulfate, sodium sulfate) or catalytic amounts of acetic acid. In each case ^{1}H NMR spectroscopy and ESI-MS indicated only the dialdehyde and diamine starting materials were present.

We then explored the possibility of macrocyclisation via ether formation from the previously reported 6,6′-bis-(bromomethyl)-2,2′-bipyridine **4** and the corresponding diphenol **6** in the presence of base (Scheme 2). First we prepared **5** in 95 % yield from the Schiff base condensation of 4-hydroxybenzaldehyde and 1,6-diaminohexane. Compound **6** shows a characteristic ^{1}H NMR pattern with a sharp singlet corresponding to the imine proton at 8.14 ppm. We also successfully reduced the imine to the corresponding diamine-containing diphenol **7** by treatment with sodium borohydride.

The dropwise addition (over 12 h) of diphenol **6** to dibromide **4** under dilute conditions (0.1 mmoL) in *N,N*-dimethylformamide (DMF) in the presence of excess caesium carbonate followed by reflux for three days yielded the desired [1+1] macrocycle **3** in 82 % isolated yield after a sodium hydroxide work-up. High-resolution mass spectrometry (HR-MS) (Fig. S1, Supplementary Material) and ^{1}H NMR spectroscopy in $CDCl_3$ (Fig. 1) confirmed the formation of the desired product. The ^{1}H NMR spectrum of **3** in $CDCl_3$ produced a spectrum consisting of 10 signals, confirming the 2-fold symmetry of the macrocycle. The imine peak (H^{g} in Scheme 2) appears at 8.19 ppm. The breadth of the peaks suggests that intramolecular rotations are restricted to some extent, also consistent with a cyclised product.



Scheme 2. Preparation of macrocycle **3**.

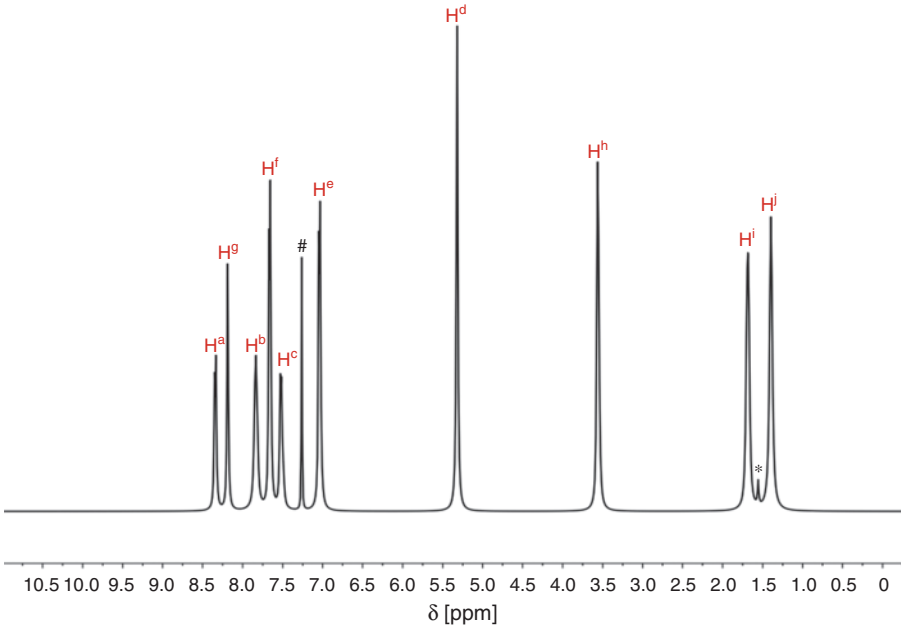


Fig. 1. The ^{1}H NMR spectrum of **3** (500 MHz, $CDCl_3$). Proton assignments correspond to the lettering shown in Scheme 2. Peaks marked with # correspond to residual $CHCl_3$ (7.26 ppm) and with * to residual water (1.5 ppm).

A ^{13}C NMR spectrum in $CDCl_3$ further supported the synthesis of macrocycle **3**. The dominant peak at *m/z* 505.26 in the HR-MS has a close match to the predicted isotropic distribution for $[M + H]^+$ (Fig. S1), while both low- and high-resolution mass spectra of the crude and purified products gave no evidence of the formation of higher oligomers or by-products (Fig. S2, Supplementary Material).

We then investigated the reduction of the imine groups of **3** to produce tetraamine **4** on the NMR scale. Treatment of **3** with two equivalents of $NaBH_4$ in methanol followed by filtration produced the desired product quantitatively. The ^{1}H NMR spectrum of the sample in $CDCl_3$ (Fig. 2) shows complete loss of the imine peak at 8.19 ppm (H^g in top of Fig. 2) and a new peak corresponding to the new methylene group at 3.33 ppm (H^g in bottom of Fig. 2). These peaks and their chemical shifts correspond closely to those of the previously reported [2] catenane, **2**.

Conclusions

We have successfully prepared two new 2,2′-bipyridine-containing macrocycles in high-yield. No-evidence for higher oligomer formation was observed during the macrocyclisation reaction. Future studies will investigate the metal-complexation properties of these ligands and their use in the formation of interlocked architectures.

Experimental

6,6′-Dimethyl-2,2′-bipyridine,[18] 6,6′-bis-(bromomethyl)-2,2′-bipyridine,[19] and 4,4′-(([2,2′-bipyridine]-6,6′-diylbis(methylene))bis(oxy))dibenzaldehyde[16] were synthesised and purified according to the literature methods. All other reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. DMF was dried and dispensed using an Innovative Technologies Pure Solv solvent

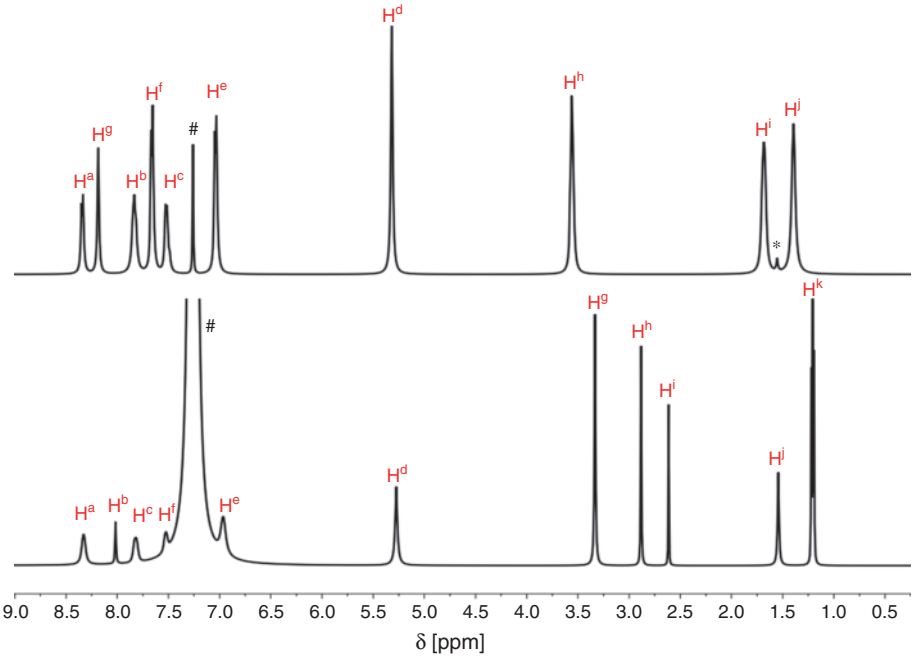


Fig. 2. ^{1}H NMR spectra of **3** (above) and the reduced macrocycle of **4** (below). The proton assignments correspond to the lettering shown in Scheme 2. Peaks marked with # correspond to residual $CHCl_3$ (7.26 ppm) and with * to residual water (1.5 ppm).

purification system, all other chemicals were used without purification. Bruker Avance 300 and 500 MHz spectrometers were used to collect NMR spectra. All manipulations were performed under an N_2 atmosphere. Elemental analyses were completed by The University of Queensland's School of Chemistry and Molecular Bioscience using a Thermo Scientific Flash 2000 Organic Elemental Analyser. All samples were dried under vacuum over P_2O_5 for a minimum of 12 h before elemental analysis submission. Mass spectrometry analyses were performed on either a Bruker MicrOTOF-Q 70 or an Applied Biosystems Voyager-DESTR instrument used for ESI-MS and matrix-assisted laser desorption–ionisation time-of-flight mass spectrometry (MALDI-TOF MS), respectively.

*Synthesis of 4,4′-(Hexane-1,6-diylbis(azaneylylidene))bis (methaneylylidine)diphenol (**6**) (Chart 2)*

4-Hydroxybenzaldehyde (2.0 g, 0.0164 mol) and 1,6-hexanediamine (0.95 g, 0.0082 mol) were dissolved in MeOH (100 mL) and the mixture stirred at 80°C for 16 h. The red solution was concentrated to 5 mL and a red solid was precipitated upon the addition of diethyl ether. The red solid was washed with diethyl ether (2 × 50 mL) and air-dried which afforded the pure imine product (2.51 g, 95 % yield). Anal. Calc. for $C_{20}H_{24}N_2O_2$: C 74.05, H 7.46, N 8.63. Found: C 73.90, H 7.77, N 8.58 %. δ_H (DMSO, 300 MHz, 300 K) 1.32 (m, br, 4H), 1.55 (m, br, 4H), 3.46 (t, *J* 6.75, 6.65, 4H), 6.76 (d, *J* 8.6, 4H, Ar-H), 7.51 (d, *J* 8.81, 4H, Ar-H), 8.14 (s, 2H). δ_C (DMSO, 125 MHz, 300 K) 27.0, 31.2, 60.7, 115.9, 127.9, 129.9, 160.2. *m/z* (ESI) 325 $(M+H)^+$.

*Synthesis of 4,4′-((Hexane-1,6-diylbis(azanediyl))bis (methylene))diphenol (**7**) (Chart 3)*

Compound **1** (250 mg, 0.772 mmol) and sodium borohydride (120 mg, 3.16 mmol) were dissolved in MeOH (50 mL) and stirred at room temperature for 16 h. The solvent was concentrated to 20 mL, excess diethyl ether was added, and a white solid precipitated. It was collected and washed with diethyl ether (2 × 50 mL) to produce **2** (yield 241 mg, 95 %). Anal. Calc. for

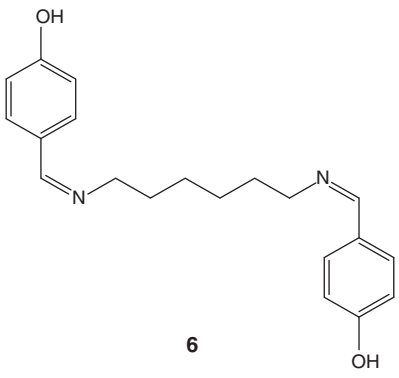


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Chart 2.

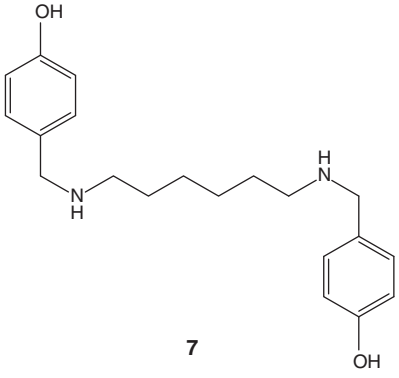

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Chart 3.

$C_{20}H_{28}N_2O_2$: C 73.14, H 8.59, N 8.53. Found: C 73.2, H 8.87, N 8.32 %. δ_H (DMSO, 300 MHz, 300 K) 1.22 (m, br, 4H), 1.35 (m, br, 4H), 2.42 (t, *J* 6.80, 6.60, 4H), 3.52 (s, 4H), 6.67 (d, *J* 8.10, 4H, Ar-H), 7.08 (d, *J* 7.86, 4H, Ar-H), 9.20 (s, 2H, Ar-OH). δ_H (DMSO, 125 MHz, 300 K) 27.4, 29.9, 49.1, 53.1, 115.2, 129.4, 131.6, 156.3. *m/z* (ESI) 329 $(M + H)^+$.

*Synthesis of Macrocycle **3** (Chart 4)*

Compound **1** (140 mg, 0.41 mmol) and caesium carbonate (550 mg, 1.64 mmol) were added to DMF (150 mL) and heated to 70°C. Compound **3** (135 mg, 0.42 mmol) dissolved in DMF (100 mL) was added dropwise over 12 h. The light brown mixture was stirred at 125°C for 3 days. After cooling, the solvent was concentrated to 20 mL and a fine solid precipitated upon the addition of diethyl ether. The brown solid was collected and suspended in NaOH (1 M, 10 mL) while stirring at 85°C for 15 min and the resulting solid collected to yield **3** as a light brown powder (yield 185 mg, 82 %). δ_H ($CDCl_3$, 500 MHz, 300 K) 1.39 (br m, 4H, H^J), 1.69 (br m, 4H, H^I), 3.56 (br m, 4H, H^H), 5.32 (s, 4H, H^D), 7.04 (d, 4H, *J* 8.03, H^E), 7.52 (d, 2H, *J* 7.22, H^C), 7.66 (m, 6H, *J* 8.03, H^F), 7.84 (m, 2H, *J* 7.22, 7.30, H^B), 8.19 (s, 2H, H^G), 8.35 (d, 2H, *J* 7.02, H^A). δ_C ($CDCl_3$, 125 MHz, 300 K) 27.3, 30.9, 61.6, 70.8, 114.9, 120.1, 121.3, 129.6, 137.7, 155.4, 156.4, 159.9, 160.3. *m/z* (ESI) 505.2 $(M + H)^+$.

*Preliminary Synthesis of Reduced Macrocycle **4** (Chart 5)*

The brown powder of **1** (10 mg, 0.02 mmol) was dissolved in MeOD, $NaBH_4$ added (1.5 mg, 0.04 mmol), and the mixture heated to 50°C for 3 h. The solvent was removed under vacuum and $CDCl_3$ was added and sonicated to aid in dissolving **4**. The precipitate was filtered and solvent removed to produce the light brown powder of **4**. δ_H ($CDCl_3$, 500 MHz, 300 K) 8.32 (d, 2H, H^A), 8.01 (s, 2H, H^B), 7.82 (d, 2H, H^C), 7.52 (d, 4H, H^F), 6.95 (d, 4H, H^E), 5.27 (s, 4H, H^D), 3.33 (s, 4H, H^G), 2.88 (s, 2H, H^H), 2.62 (s, 4H, H^I), 1.54 (s, 4H, H^J), 1.20 (t, 4H, H^K).

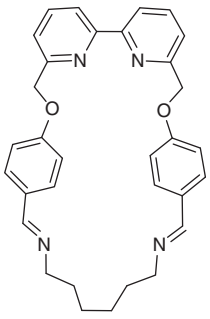

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Chart 4.

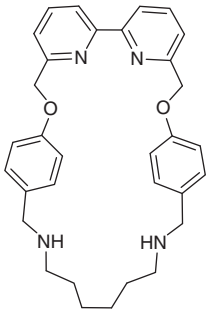

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Chart 5.

Crystallographic Data

The crystallographic data in CIF format has been deposited at the Cambridge Crystallographic Data Centre with CCDC 1519162–1519167. It is available free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1 EZ, UK; fax: (+44) 1223-336-033; or email: deposit@ccdc.cam.ac.uk.

Supplementary Material

PXRD patterns of the bulk phases and the patterns predicted from the single crystal experiments are available on the Journal's website.

Acknowledgements

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