Research Article

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NMR elucidation of a novel (*S*)-pentacyclo-undecane bis-(4-phenyloxazoline) ligand and related derivatives

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The NMR elucidation of a novel ligand (*S*)-pentacyclo-undecane bis-(4-phenyloxazoline) and related pentacyclo-undecane (PCU) derivatives is reported. Two-dimensional NMR proved to be a powerful technique in overcoming the difficulties associated with the elucidation of these compounds when only one-dimensional NMR data is utilized. A chiral substituent was introduced to both 'arms' of the PCU skeleton to produce derivatives 1–3. These derivatives display C_1 symmetry with all thecage atoms being nonequivalent. Owing to overlapping of peaks in the ^{1}H spectra, identification of these diastereomeric protons was very difficult. The ^{13}C spectra gave rise to clear splitting of the nonequivalent carbons. This is unusual compared to similar PCU derivatives with chiral substituents as splitting of all the diastereomeric cage carbons has not yet been reported. Nuclear Overhauser enhancement spectroscopy (NOESY) correlations of derivatives 1–3 confirm the different conformations of the molecule in which the side 'arms' occupy different orientations with respect to cage moiety.

Supporting information may be found in the online version of this article.

Keywords: NMR; ^{1}H NMR; ^{13}C NMR; 2D NMR; PCU; chiral ligands

Introduction

Organic chemists have explored the chemistry of pentacyclo-undecane (PCU) cage compounds for many years.[1–3] The effect of the unique cage geometry on chemical reactivity and the behavior of the rest of the molecules has been extensively studied.[1,3] The difficulties associated with the NMR elucidation of these compounds have been highlighted by many authors.[4–7] Broad unresolved overlapping resonances as a result of through-space effects, geminal and vicinal proton–proton coupling and long-range proton–proton interactions make the assignments of cage ^{1}H spectra quite challenging. The 2D NMR technique has been used as an invaluable tool to overcome these difficulties. Our group has been actively involved in the elucidation of the PCU-derived cage compounds.[7–11] A branch of our research interests involves the chemistry of the PCU cage and the attachment of chiral ligands to the cage for applications in asymmetric catalysis.[12,13] As a result, the NMR elucidation of four PCU derivatives **1–4** was recently investigated. Ligand **3** is currently being tested as a catalyst in the asymmetric Diels–Alder reaction of cyclopentadiene and 3-acryloyl-2-oxazolidinone.[14] The novel compounds **1** and **2** are precursors of ligand **3**. Derivative **4** is the precursor of ligand **5** and the full NMR elucidation of **4** is reported below. The elucidation of ligand **5** was not achieved because of its instability and only the ^{1}H and ^{13}C NMR spectra were recorded (Fig. 1).

The PCU dione **6** was converted to the 3,5-diallyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane **7** as described previously.[15,16] This diene **7** is an intermediate in the synthesis of all the derivatives **1–5** being investigated. Ozonolysis of **7** followed by an oxidative workup using formic acid and hydrogen peroxide afforded the PCU diacid **8**.[15] To avoid competing reactions due to the free hydroxyl group on the amino alcohol, it was decided to protect the alcohol by using *tert*-butyldimethylsilyl (TBDMSi) chloride to give (*S*) *tert*-butyldimethylsilyl 2-amino-3-phenylpronoate **9.**[17] This protecting group is known to be hydroxyl group selective in the presence of a primary amine. An *N*,*N*-dicyclohexylcarbodiimide (DDC) promoted condensation of the PCU diacid **8** with **9** afforded the protected PCU bis-amide **1** which was purified using column chromatography.[18] The PCU bis-amino alcohol **2** was obtained by deprotection of **1** with tetra-*N*-butylammonium fluoride (TBAF) and purification was again achieved using column chromatography.[17] Cyclization was achieved by the chlorination of **2** using thionyl chloride to give the PCU bis-chloride **10**, followed by treatment with aqueous sodium hydroxide[14,19] to yield the novel ligand PCU bis-(4-phenyloxazoline) **3**, which was isolated by column chromatography in 80% yield from the PCU bis-amino alcohol **2** (Scheme 1).

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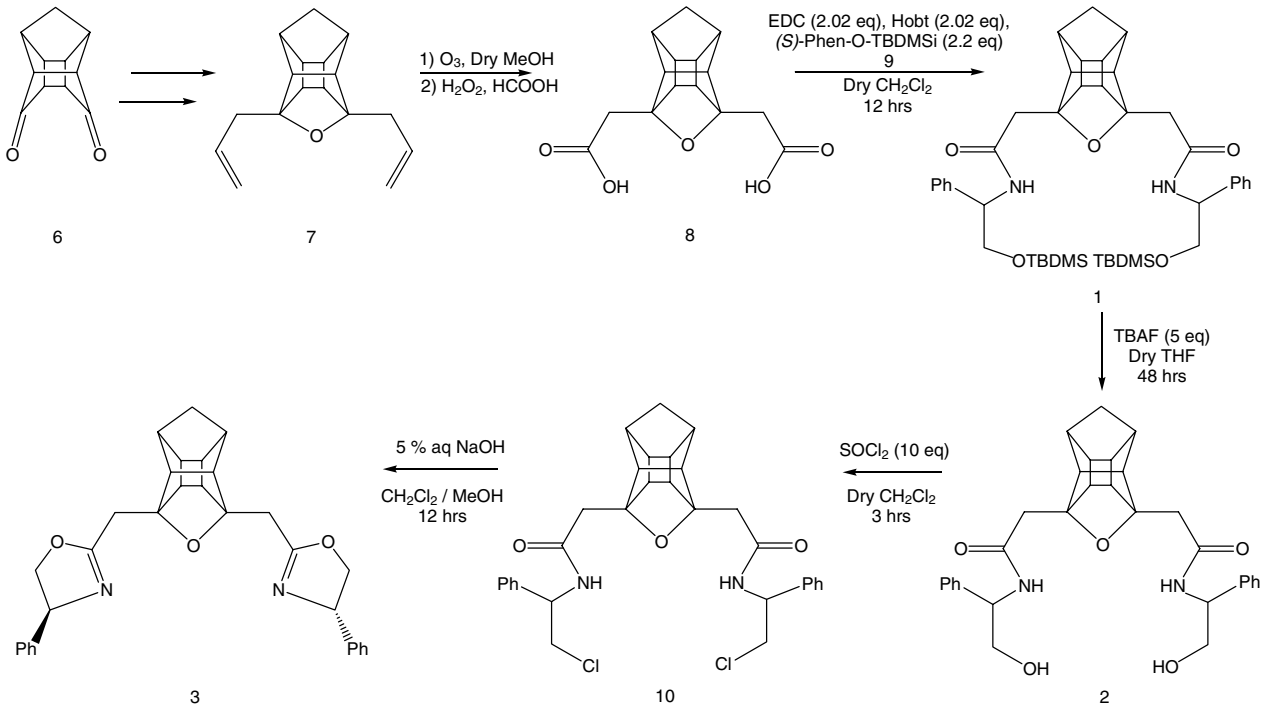
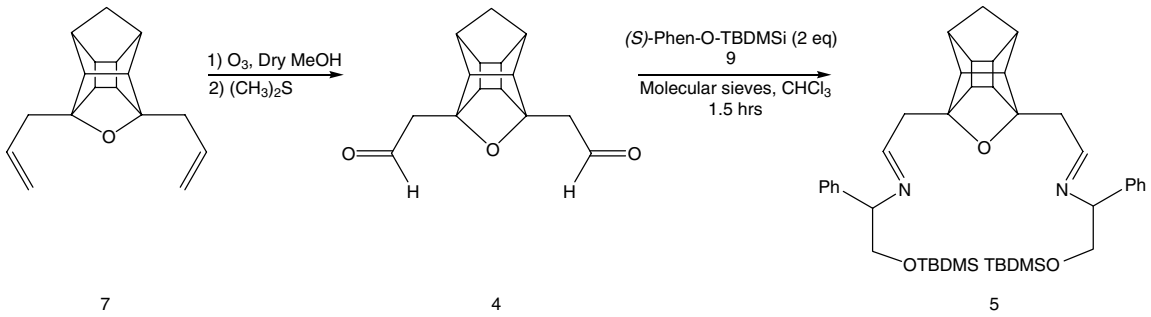


Scheme 1. Synthesis of novel compounds **1**–**3**.



Scheme 2. Synthesis of novel compounds **4** and **5**.

Ozonolysis of **7** followed by a reductive workup using dimethyl sulfide, afforded the novel PCU dialdehyde **4**. A Schiff base reaction of **4** with **9** in the presence of molecular sieves afforded the PCU diimine **5** (Scheme 2).

Results and Discussion

Note that the left half of the PCU skeleton in **1**–**3** is the mirror image of the right half, with the result that the chiral side arms induce a diastereomeric character to the cage skeleton. Owing to overlapping in the ^{1}H spectra, identification of the nonequivalent protons was very difficult. However, the ^{13}C spectra gave rise to clear splitting of the carbon atoms (C-1–C-11) and (C1′–C-8′) on the cage and 'side arms' of **1,** respectively. This is unprecedented compared to analogous PCU derivatives reported before, as splitting of only the diastereomeric carbons closest to the new chiral center is usually observed.[7–11] The nature of this effect was investigated and is discussed below.

In the ^{1}H spectrum of **1**, the characteristic methylene protons (H-4) register as doublets at 1.65 (H-4a) and 1.98 ppm (H-4b) with a coupling constant of 10.5 Hz.[7–11] Owing to major overlapping of protons, only the coupling constant of H-4 could be calculated. Also, from the ^{1}H spectrum protons H-3′ and H-4′ at 5.21 and 4.05 ppm were assigned, respectively, from their literature values.[17,20] In addition, the silyl protons were assigned based on integration, 0.0 (H-10′ = 12 H′s) and 0.9 ppm (H-11′ = 18 H′s). Recording the ^{13}C spectra in attach proton test (APT) mode assisted in distinguishing the quaternary and methylene carbons from the methine and methyl carbons. On the basis of heteronuclear single quantum coherence (HSQC) spectrum of **1,** the carbons corresponding to H-4′ and H-4 were identified. By elimination, the methylene signal at 3.0 ppm was assigned to C-1′ and its correlation to the doublet at 2.56 ppm was assigned to H-1′. H-1′ also displays a COSY and Nuclear Overhauser Enhancement Spectroscopy (NOESY) interaction with the overlapping cage methine signals at 2.87 ppm. The position of H-1′ was also confirmed with HMBC correlations with the cage skeleton (see below).

The quaternary carbons were assigned as follows: C-9′ at 18.2 ppm was assigned because of its HMBC correlation to the methyl protons attached to the silyl atom; C-5′ at 140 ppm was assigned based on its correlations to H-3′ and H-4′ and

Magnetic Resonance in Chemistry

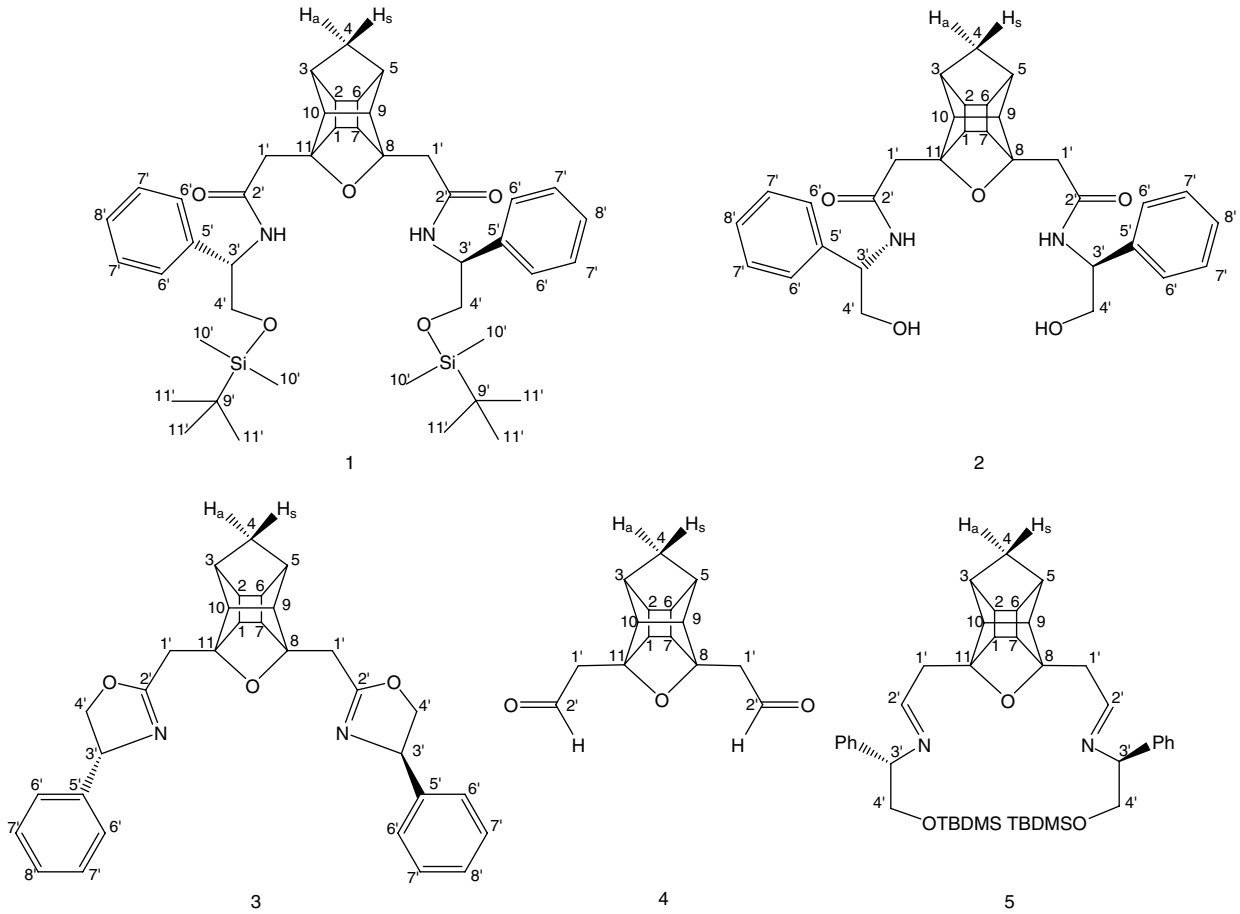


Figure 1. PCU derivatives **1**–**5**.

C-2′ at 169 ppm, which is characteristic of an amide carbonyl carbon; it also has HMBC correlations with H-3′, H-1′ and some of the aromatic protons (7.36–7.52 ppm). Through elimination, the set of quaternary carbons at 94.2 ppm was assigned to the diastereomeric C-8 and C-11 carbons.

All the cage carbon signals display splitting as a result of the diastereomeric effect (induced by the chiral side arms). The nature of this effect is confirmed due to the absence of any splitting of the nonchiral (nondiastereomeric) methylene signal of H-4. In addition, high-temperature NMR experiments of **1** at 60, 120 and 150 °C revealed the cage carbon signals of C-1/7, C-9/10 and C-8/11 remained split throughout the temperature ramp. This confirmed the diastereomeric effect experienced by these carbon atoms.

The proton signal appearing at 2.56 ppm displays a HMBC correlation to a cage carbon signal at 44.1 ppm, and a COSY and NOESY correlation to the H-4. Therefore, it could either be assigned to H-2/6 or H-3/5. However, this HMBC correlation also corresponds to a carbon sharing a correlation with H-1′, thus eliminating H-2/6. Therefore, the signal at 44.1 ppm was assigned to H-3/5. Signals at 58.0 ppm share HMBC correlations to H-4, H-1′, H-3/5 and the overlapping cage protons. The possibility of this signal being C-1/7 was ruled out as C-1/7 cannot correlate to H-4 and these carbon signals were subsequently assigned to C-9/10. The remaining cage carbon signals at 47.0 and 41.4 ppm were assigned to C-1/7 and C-2/6 respectively based on the HMBC and NOESY spectra.

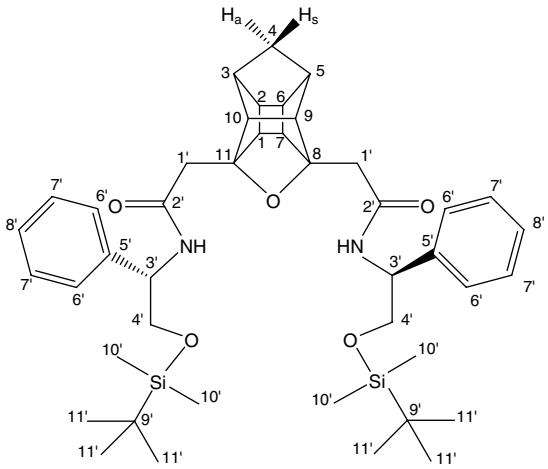
In view of the above stated assignments, the overlapping of cage methine protons at 2.87 ppm may be assumed to result from H1/7, H2/6 and H9/10. Interestingly, the aromatic protons (7.36–7.52 ppm) show NOESY interactions with H-1′, H1/7, H2/6, H9/10 and H-3/5. The silyl methyl protons H-10′ and H-11′ display NOESY interactions with H-1′, H1/7, H2/6 and H9/10.

This observation suggests a conformation of **1** in which one of the 'arms' is perhaps positioned in front and the other at the back of the cage moiety. From the high-temperature experiments, the split carbon signals on the side arm (C-1′–C-8′) at room temperature gradually became a single peak as the temperature was increased (60, 120 and 150 °C) indicating that these carbon atoms experienced splitting due to a conformational effect. When the heteroatoms on the side arms are positioned in close proximity to the cage, it induces a through-space deshielding effect resulting in nonequivalence of atoms on the cage and that of the 'arm' similar to observations in previous reports of related chiral PCU ligands.[9,11]

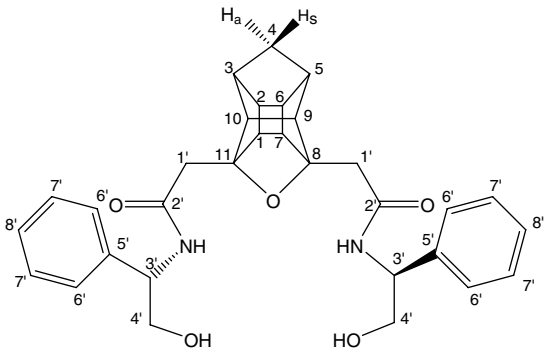
The infrared (IR) spectrum of **1** displays a sharp N–H absorption at 3312 cm^{-1}, and methyl absorptions at 2949 and 2929 cm^{-1}; the absorption at 1646 cm^{-1} confirms the presence of the amide bond. The mass spectrum of **1** exhibits the correct molecular ion peak at *m*/*z* 741.4118 ($[M + H]^+$). The assignments of all signals for **1** are reported in Table 1.

The same methodology was used to elucidate **2**. C-8/11, C-2′ and C-4′ carbon signals in **2** do not display splitting as in the case of the derivative **1**. A possible explanation could be the absence of the bulky TBDMSi group in **2;** hence, the conformational effect in which

Table 1. NMR data of PCU derivatives **1** and **2**[a,b]



1



2

Atom no.	Derivative **1**		Derivative **2**	
	^{1}H (ppm)	^{13}C (ppm)	^{1}H (ppm)	^{13}C ppm
1/7	2.87 m	48.83/47.82	2.73 m	48.63/48.01
2/6	2.87 m	41.50/41.44	2.73 m	41.54/41.39
3/5	2.56 m	44.28/44.19	2.45 s	44.12/44.00
4a	1.65[c] d	43.35	1.55[c] d	43.48
4s	1.98[c] d	43.35	1.90[c] d	43.48
8/11	–	94.21/94.16	–	94.14
9/10	2.87 m	59.11/58.06	2.73 m	59.05/58.40
1′	3.06 m	39.91/39.89	2.82 m	39.49/39.47
2′	–	169.2/169.1	–	170.1
3′	5.21 s	54.64/54.60	5.02 s	55.23/55.17
4′	4.05 m	66.60/66.11	3.73 m	65.90
5′	–	140.36/140.30	–	139.33/139.32
6′	7.52 m	126.92/126.91	7.43 m	126.6
7′	7.43 m	128.52/128.32	7.29 m	128.6
8′	7.36 m	127.24/127.27	7.23 m	127.6
9′	–	18.26		
10′	0.98 s	−5.600		
11′	0.00 s	25.83		

[a] Solvent $CDCl_3$.
[b] 400 MHz for ^{1}H and 100 MHz for ^{13}C.
[c] Coupling constant = 10.5 Hz.

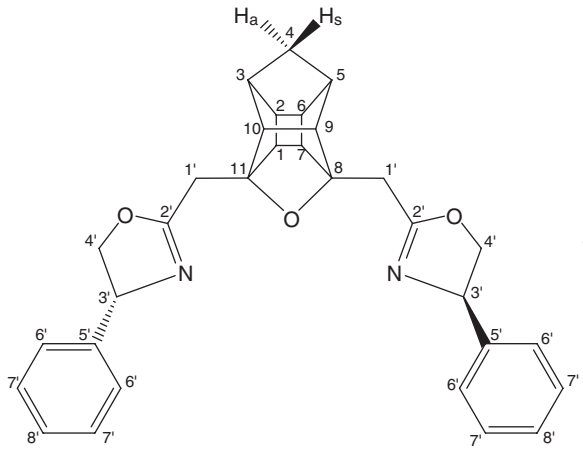
one of the 'arms' is closer to a different part of the cage moiety is less pronounced. From the IR spectrum, the presence of the alcohol group was confirmed by the broad band at 3288 cm^{-1} and as was the case with **1,** the presence of the amide bond absorption was still present at 1641 cm^{-1}. Presence of the expected molecular ion peak of *m*/*z* 513.2396 ($[M + H]^+$) in the mass spectrum confirmed the structure of compound **2**. The detailed NMR assignments are presented in Table 1.

The elucidation of the PCU bis-(4-phenyloxazoline) **3** followed a similar approach as mentioned above. The ^{1}H spectrum of **3** differs from its precursors in that all the cage protons appear as clear signals and H-4′ is split into two separate doublet of doublets. From the ^{13}C spectrum, the absence of the carbonyl carbon signal at 170 ppm and presence of the characteristic imine carbon signal at 165 ppm were indicative that cyclization was achieved. Also, C-3′ displays a distinct downfield shift as a result of the adjacent imine bond. HMBC correlations of C-2′ with protons H-3′ and H-4′ confirm the formation of the oxazoline ring. The aromatic protons (7.21–7.38 ppm) show a NOESY interaction with H-2/6. Similar to **1,** this observation indicates the different conformations of **3** in which the 'arms' exist as different conformations with respect to the cage moiety. A weak, but observable COSY correlation between H-3′ and H-1′ is observed which is unusual as these protons are more than three bonds apart (in fact, they are four bonds apart).

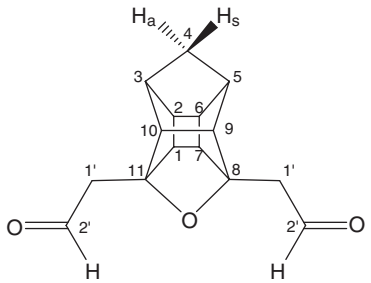
The IR spectrum of **3** displays the characteristic imine absorption band at 1663 cm^{-1} and aromatic ether absorption band at 1217 cm^{-1}. Also, as expected, disappearance of the amide bond absorptions was observed. The mass spectrum of **3** displays the correct molecular ion peak at *m*/*z* 477.2147 ($[M+H]^+$). The detailed assignments are presented in Table 2.

Magnetic Resonance in Chemistry

Table 2. NMR data for PCU derivative **3** and **4**[a,b]



3



4

Atom no.	Derivative **3**		Derivative **4**	
	^{1}H ppm	^{13}C ppm	^{1}H ppm	^{13}C ppm
1/7	2.82 s	48.67/48.58	2.68 m	48.57
2/6	2.64 s	41.86/41.84	2.71 m	41.62
3/5	2.41 s	44.64/44.61	2.50 s	44.16
4a	1.51[c] d	43.55	1.59[c] d	43.45
4s	1.90[c] d	43.55	1.93[c] d	43.45
8/11	–	93.71/93.69	–	92.77
9/10	2.75 s	59.26/59.16	2.64 m	59.21
1′	2.98 s	32.11/32.96	2.85 s	45.99
2′	–	165.9/165.8	9.77 s	200.5
3′	5.18 t	69.66/69.61	–	–
4′	4.61/4.08[d] dd	74.76/74.69	–	–
5′	–	142.3	–	–
6′	7.34 m	126.5	–	–
7′	7.28 m	128.8		
8′	7.24 m	126.5		

[a] Solvent $CDCl_3$.
[b] 400 MHz for ^{1}H and 100 MHz for ^{13}C.
[c] Coupling constant = 10.5 Hz.
[d] Coupling constant = 9.5 Hz.

Derivative **4** is a *meso* compound making all the atoms except the methylene group hydrogens at C-4 equivalent. Once again, the elucidation followed a similar approach as presented above. From the ^{1}H spectrum, the signal at 9.7 ppm was characteristic of an aldehyde proton. In addition, only the proton signals H-4, H-3/5 and H-1′ appear as separate signals while the remaining cage protons display overlapping (2.5–2.8 ppm). On the basis of the *meso* nature of the molecule, the ^{13}C spectrum was somewhat simplified and overlapping of the equivalent carbons occur. Six distinct carbon signals were observed for derivative **4** as against 11 carbon signals which were observed for the chiral derivatives **1–3**. From the HSQC, HMBC, NOESY and COSY spectra, the overlapping proton signals were distinguished and all the assignments were verified.

The IR spectrum displays the characteristic aldehyde absorption band at 1719 cm^{-1} and the mass spectrum displays the correct molecular ion peak at *m*/z 242.1248 ($[M + H]^{+}$). The detailed assignments are presented in Table 2.

Conclusion

The NMR elucidation of the novel ligand (*S*)-pentacyclo-undecane bis-(4-phenyloxazoline) **3**, two of its precursors **1–2** and the PCU dialdehyde **4** was successfully achieved. 2D NMR techniques were required to identify the NMR signals for the PCU derivatives **1–3** that display C_1 symmetry with all the cage atoms being nonequivalent. The ^{13}C spectra of these derivatives gave rise to clear splitting of the nonequivalent carbons, with the exception of C-9′, C-10′, C-11′ in **1**; C-8/11, C-2′, C-4′, C-6′, C-7′, C-8′ in **2** and C-6′, C-7′, C-8′ in **3**. NOESY correlations of derivatives **1–3** indicate conformational differences with respect to the side arms. The heteroatoms on the side arm induce a through-space deshielding effect resulting in nonequivalence of atoms on the cage skeleton and that of the side 'arm'. Even though the cage carbons become diastereomeric with respect to the chiral side arms, the same level of nonequivalence by related chiral cage ligands has not yet been reported. As expected, the *meso* PCU dialdehyde **4** gave rise to six

distinct carbon signals as compared to the chiral derivatives **1–3** which gave rise to 11 carbon signals.

Experimental

All synthetic experiments were conducted under an atmosphere of nitrogen, unless otherwise indicated. All the solvents were distilled over the appropriate desiccant. NMR spectra were recorded on a Bruker AVANCE III 400 MHz instrument using ~50 mg of sample per 0.5 ml of $CDCl_3$. IR spectra were obtained on a Perkin Elmer Spectrum 100 instrument with an attenuated total reflectance (ATR) attachment. Optical rotations were carried out on a Perkin Elmer 341 polarimeter. All melting points are uncorrected. Column chromatography was carried out using silica gel 60. Electron spray mass spectra were carried out on a Waters LCT Premier time-of-flight (TOF) mass spectrometer.

The chemical shifts were referenced to the solvent peak 7.24 ppm for $CDCl_3$ at ambient temperature. The ^{1}H NMR spectrum was recorded at 400.222 MHz (spectral width, 8223.685 Hz; acquisition time, 1.992 s; pulse width, 9 μs; scans, 16; relaxation delay, 1.0 s). The ^{13}C NMR spectrum was recorded at 100.635 MHz (spectral width, 24038.461 Hz; acquisition time, 1.363 s; pulse width, 13.801 μs; scans, 2400; relaxation delay, 2.00 s). The 2D experimental data parameters were as follows: 90° pulse width, 9 μs for all the spectra; spectral width for ^{1}H, 822.68 for **1–4**; spectral width for ^{13}C, 24038.46 for **1–4**; number of data points per spectrum, 2048, (COSY) for **1–4**, 2048, (NOESY) for **1–4**, 4096, (HMBC) for **1–4**, 1024 (HSQC) for **1–4**; number of time-incremented spectra, 128 (COSY) for **1–4**, 256, (NOESY) for **1–4**, 128, (HMBC) for **1–4**, 256 (HSQC) for **1–4**; relaxation delay, 1.38 s (COSY) for **2** and **3**, 1.39 s (COSY) for **1**, 1.44 s (COSY) for **4**, 1.98 s (NOESY) for **2** and **3**, 1.96 s (NOESY) for **1**, 2.01 s (NOESY) for **4**, 1.31, 1.25, 1.30, 1.41 s (HMBC) for **1–4** respectively, 1.45, 1.43, 1.45, 1.47 s (HSQC) for **1–4** respectively; spectra acquired in phase-sensitive mode, **1–4** (NOESY and HSQC); spectra acquired in absolute value mode, **1–4** (COSY and HMBC); gradients used for **1–4** (COSY, HSQC and HMBC). All NMR spectra are available as Supporting Information.

5,5-Dicarboxymethyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{5,10}.0^{5,9}.0^{8,11}]dodecane 8

A solution of the diene **7** (5.0 g, 20.3 mmol) in dry methanol (150 ml) was cooled to −78 °C via application of an external dry-ice–acetone bath and then was purged with nitrogen for 20 min. Ozone was bubbled into the mixture until a blue-purple color persisted, thereby indicating the presence of excess ozone and completion of the reaction. Excess ozone was flushed from the reaction vessel with a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to yield the ozonide. Hydrogen peroxide (50 ml, 30%) was added dropwise to a stirred, ice-bath-cooled mixture of the ozonide and formic acid (50 ml, 80%). The resulting mixture was stirred at ambient temperature for 1 h and then gently refluxed for 12 h. The reaction mixture was allowed to cool gradually to ambient temperature during which time the product precipitated out of solution. Pure **8** (4.7 g, 82%) was thereby obtained as a colorless microcrystalline solid: ^{1}H NMR (DMSO, δ) : 1.45 (AB, J_{AB} = 10 Hz, 1H),1.83 (AB, J_{AB} = 10 Hz, 1H), 2.36–2.80 (m, 12H), 12.15 (br s, 2H); (DMSO)^{13}C NMR δ: 37.94 (t), 41.27 (d), 42.81 (t), 44.04 (d), 47.91 (d), 58.55 (d), 92.56 (s) and 171.40 (s).

(*S*)-*tert*-Butyldimethylsilyl 2-amino-3-phenylpronoate 9

(*S*)-Phenylglycine methyl ester (1.0 g, 4.9 mmol) was added to a stirred solution of lithium aluminum hydride (0.4 g, 9.8 mmol) in dry tetrahydrofuran (THF) (150 ml) at ambient temperature. Thereafter, the solution was refluxed for 1.5 h. The reaction mixture was then allowed to cool after which an equal volume of diethyl ether was added. The reaction mixture was quenched with saturated aqueous Na_2SO_4 solution. It was filtered and the solvent was removed *in vacuo* to yield pure amino alcohol as yellow crystals (0.6 g, 88%). To a solution of the amino alcohol (3.0 g, 21.7 mmol) in dry CH_2Cl_2 (150 ml) were added at room temperature Et_3N (6.3 ml, 44.5 mmol) and 4-Dimethylaminopyridine (DMAP) (0.5 g, 4.09 mmol). The solution was cooled to 0 °C and TBDMSiCl (3.4 g, 27.7 mmol) in CH_2Cl_2 (20 ml) was added. The solution was stirred for further 48 h at room temperature and then H_2O (30 ml) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (CH_2Cl_2/MeOH, 95 : 5) to afford product **9** (4.5 g, 83%) as a yellow oil. ^{1}H NMR ($CDCl_3$, δ): 0.04 (6H, s), 0.91 (9H, s), 1.85 (NH, br s), 3.50 (1H, dd CH_2O), 3.72 (1H, dd, CH_2O), 4.07 (1H, dd, *CH*Ph), 7.40–7.23 (5H, m); ^{13}C NMR ($CDCl_3$, δ): −5.41 (CH_3), 18.3 (CH_3), 25.9(*C*(CH_3)$_3$), 57.6 (CHPh), 69.5 (CH_2O), 126.9, 127.2, 128.2, 142.6 (aromatic)[17,20].

PCU bis-amide 1

To a stirred solution of **8** (2.0 g, 7.25 mmol) in dry CH_2Cl_2 (150 ml), *N*-Hydroxybenzotriazole (2.0 g, 14.6 mmol) and then *N*,*N*-Dicyclohexylcarbodiimide (3.0 g, 14.6 mmol) were added. This mixture was allowed to stir for 15 min until a clear homogenous solution was obtained. Thereafter, a mixture of **9** (4.5 g, 18.0 mmol) and Et_3N (4.0 ml, 28.9 mmol) in 50 ml dry CH_2Cl_2 was added and the resulting mixture was stirred at ambient temperature for a further 12 h. The reaction mixture was then filtered and H_2O added to the filtrate. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (Hexane/EtOAc, 50 : 50) to afford compound **1** (4.8 g, 90%) as a yellow solid. $[\alpha]^{20}_D$ − 11.35 (*c*1, CH_2Cl_2). IR ν_{max}: 3312 (s), 1646 (vs), 1112 (vs) and 776 cm^{-1} (vs). mp 126–130 °C. High resolution mass spectrum (HRMS) calcd for $C_{43}H_{60}N_2O_5Si_2$ ([M + H]$^+$), 741.4119; found, 741.4118.

PCU bis-amino alcohol 2

The PCU bis-amide **1** (5.5 g, 7.41 mmol) was dissolved in dry THF (200 ml) and TBAF (29.6 ml, 1 M in THF) was added. The mixture was stirred for 48 h at ambient temperature. Brine was added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The resulting residue was purified by column chromatography (EtOAc/MeOH, 95 : 5) to afford the deprotected alcohol **2** (3.0 g, 76%) as a pale yellow solid. $[\alpha]^{20}_D$ + 32.45 (*c*1, CH_2Cl_2). IR ν_{max}: 3288 (br), 1641 (vs), 1039 (s) and 706 cm^{-1}(vs). mp 50–60 °C. HRMS: calculated for $C_{31}H_{32}N_2O_5$ ([M + H]$^+$), 513.2389; found, 513.2396.

PCU bis-(4-phenyloxazoline) 3

To a stirred solution of **2** (1.0 g, 1.88 mmol) in dry CH_2Cl_2 (100 ml), $SOCl_2$ (2.7 ml, 37.5 mmol) was added. The solution was stirred at

ambient temperature for 3 h. The resulting mixture was poured into H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and the solvent removed *in vacuo* to yield a brown residue of the PCU bis-chloride **10** which was used without further purification. The residue was treated with NaOH (1 g in 20 ml H_2O) in a MeOH (50 ml)/CH_2Cl_2 (30 ml) solution at ambient temperature for 12 h. The organic solvents were evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvents removed *in vacuo*. The resulting residue was purified by column chromatography (100% EtOAc) to afford the PCU bis-(4-phenyloxazoline) **3** (0.72 g, 80%) as a yellow oil. $[\alpha]^{20}_D - 57.24$ (*c* 0.85, $(CH_3)_2CHOH$). IR ν_{max}: 2964 (w), 1663 (s), 984 (s) and 700 cm^{-1} (vs). HRMS: calculated for $C_{31}H_{28}N_2O_3$ ($[M + H]^+$), 477.2178; found, 477.2174.

PCU dialdehyde 4

A solution of the diene **7** (5.0 g, 20.3 mmol) in dry methanol (150 ml) was cooled to −78 °C via application of an external dry-ice–acetone bath and then was purged with nitrogen for 20 min. Ozone was bubbled into the mixture until a blue-purple color persisted, thereby indicating the presence of excess ozone and completion of reaction. The excess ozone was flushed from the reaction vessel with a stream of nitrogen. The reaction mixture was then transferred to a round bottom flask and $(CH_3)_2S$ (6.4 ml, 83.2 mmol) was added and stirred for 12 h at ambient temperature. The solvents were evaporated *in vacuo* and the residue was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The resulting residue was purified by column chromatography (Hexane/EtOAc, 70 : 30) to afford the PCU dialdehyde **4** (0.49 g, 49%) as a yellow oil. IR ν_{max}: 2958 (s) 1719 (vs), 1075 (s) and 527 cm^{-1} (w). HRMS: calculated for $C_{43}H_{60}N_2O_5Si_2$ ($[M + H]^+$), 242.1247; found, 242.1248.

PCU diimine 5

PCU dialdehyde **4** (0.05 g, 0.20 mmol) was dissolved in 5 ml dry $CHCl_3$ and **9** (0.10 g, 0.40 mmol) was added along with 4 Å molecular sieves. The reaction mixture was left to stand without stirring for 1.5 h. The reaction mixture was filtered and the solvent removed *in vacuo* to afford the PCU diimine **5** (0.14 g, 100%) as a brown oil. ^{1}H NMR ($CDCl_3$, δ) : 1.01 (AB, J_{AB} = 10 Hz, 1H), 1.52 (AB, J_{AB} = 10 Hz, 1H), 2.13–2.62 (m), 3.3–3.8(m); 4.15 (H-3′), 4.05 (H-4′) and 7.2–7.4 (aromatic). ($CDCl3$)^{13}C NMR δ: 48.1 (C-1/7), 41.5 (C-2/6), 44.1 (C-3/5), 43.5 (C-4), 94.1 (C-8/11), 59.1 (C9/10), 38.4 (C-1′), 162.5 (C-2′), 58.5 (C-3′), 68.0 (C-4′), 140.1 (C-5′), 126–130 (C-6′, C-7′, C-8′), 18.1 (C-9′), −4.2 (C-10′) and 26.0 (C-11′).

Supporting information

Supporting information may be found in the online version of this article.

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References

[1] AP. Marchand, *Chem. Rev.* **1989**, *89*, 1011.
[2] G. W. Griffin, A. P. Marchand, *Chem. Rev.* **1989**, *89*, 997.
[3] A. Marchand, , *Advances in Theoretically Interesting Molecules*. JAI press: USA vol. 1, **1989**, 357.
[4] D. H. Cadd, W. J. Feast, A. M. Kenwright, J. M. Say, *Magn. Reson. Chem.* **1993**, *31*, 801.
[5] G. A. Craze, I. J. Watt, *J. Chem. Soc., Perkin Trans. 2* **1981**, 2175.
[6] F. J. C. Martins, G. H. Coetzee, L. Fourie, H. J. Venter, A. M. Viljoen, P. L. Wessels, *Magn. Reson. Chem.* **1993**, *31*, 578.
[7] T. Govender, H. G. Kruger, T. Raasch, *Struct. Chem.* **2005**, *16*, 129.
[8] H. G. Kruger, R. Ramdhani, *S. Afr. J. Chem.* **2006**, *59*, 71.
[9] H. G. Kruger, R. Ramdhani, *Magn. Reson. Chem.* **2006**, *44*, 1058.
[10] H. G. Kruger, P. S. Mdluli, *Struct. Chem.* **2006**, *17*, 121.
[11] G. A. Boyle, H. G. Kruger, G. E. M. Maguire, A. Singh, *Struct. Chem.* **2007**, *18*, 633.
[12] G. A. Boyle, T. Govender, H. G. Kruger, G. E. M. Maguire, *Tetrahedron: Asymmetry* **2004**, *15*, 3775.
[13] G. A. Boyle, T. Govender, H. G. Kruger, G. E. M. Maguire, *Tetrahedron: Asymmetry* **2004**, *15*, 2661.
[14] S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada, D. P. Curran, *J. Am. Chem. Soc.* **1998**, *120*, 3074.
[15] T. Govender, H. K. Hariprakasha, H. G. Kruger, A. P. Marchand, *Tetrahedron: Asymmetry* **2003**, *14*, 1553.
[16] A. P. Marchand, Z. L. Huang, Z. B. Chen, H. K. Hariprakasha, I. N. N. Namboothiri, J. S. Brodbelt, M. L. Reyzer, *J. Heterocycl. Chem.* **2001**, *38*, 1361.
[17] S. Kaden, H. U. Reissig, *Org. Lett.* **2006**, *8*, 4763.
[18] N. Sewald, H.-D. Jakubke, *Peptides: Chemistry and Biology*, Wiley-VCH Verlag Gmbtt: Weinheim, Reprint **2005**.
[19] G. Desimoni, G. Faita, K. A. Jorgensen, *Chem. Rev.* **2006**, *106*, 3561.
[20] N. Cabedo, I. Andreu, M. C. R. DeArellano, A. Chagraoui, A. Serrano, A. Bermejo, P. Protais, D. Cortes, *J. Med. Chem.* **2001**, *44*, 1794.

