H.G. Kruger and R. Ramdhani,
S. Afr. J. Chem., 2006, **59**, 71–74,
<http://journals.sabinet.co.za/sajchem/>.

NMR Analysis of Some Pentacycloundecanedione Derivatives

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Received 22 December 2005; revised 17 May 2006; accepted 5 June 2006.

ABSTRACT

The complete NMR elucidation of four pentacycloundecanedione (PCUdione) derivatives is described. Major proton shifts occur when additions are performed on the carbonyl carbons. Some of the carbon signals are also transposed. Despite the fact that the signals of the methine protons on the cage skeleton experience major overlapping, complete assignment of all the protons is possible through 2D NMR experiments. Nuclear Overhauser Effect Spectroscopy (NOESY) interaction between the two non-equivalent bridge protons and protons on the cage skeleton proved to be a very convenient handle to elucidate the structures of the PCU compounds. A density functional theory (DFT) optimization [B3LYP/6-31+G(d)] of two possible ketal conformations was used to assist with the elucidation of the asymmetric ketal structure.

KEYWORDS

NMR elucidation, pentacycloundecane, 2D NMR.

1. Introduction

The chemistry of pentacycloundecanedione (PCUdione) derivatives, including trishomocubane derivatives, has been well studied[1–3] and some fundamental research has been performed by a number of South African scientists. The *South African Journal of Chemistry* also has a proud history of cage chemistry publications.[4,5] To date, one of these papers by Oliver and Dekker[4e] has been cited 37 times. South African authors have also contributed considerably towards utilizing NMR spectroscopy as a tool to determine the structures of these cage compounds.[4d,5e,6,7]. As part of a programme to utilize NMR spectroscopy as a crucial tool for the structure elucidation of PCU derivatives, the NMR elucidation of four PCU derivatives (**1–4**) was recently explored.

Although many authors have commented on the difficulty of NMR elucidation of these cage compounds,[1,6j,7b,8] the readily available routine 2D experiments have largely assisted in overcoming these former difficulties.

Cookson's dione **1**[9,10] was first reported in 1964. In 1993 Cadd *et al.*[7b] published the NMR assignment of the PCU dione **1** by analogy after studying a PCU derivative. The dione **1** is used as starting material for the other three derivatives (**2–4**) and the conversions will be described below. The *endo-endo* diol **3**[11,12] is an intermediate for the diol **4**[13,14] which is used in the synthesis of various crown ethers[13,15–17] and macrocycles.[11,18]

2. Experimental

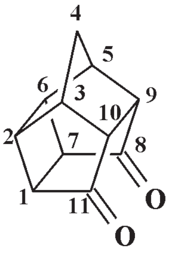
The four products were synthesized using methods from the literature as indicated in the text and the experimental details are available as supplementary material. The NMR data are summarized in Table 1. The 1H, 13C and 2D NMR spectra were recorded on a Varian Unity Inova 400 MHz spectrometer using approximately 50 mg of sample per 0.5 mL solvent. The technical NMR details for the 2D experiments were the same as those reported before.[7c]

3. Results and Discussion

The pentacycloundecanedione **1** is a meso compound, which simplifies the NMR spectrum since all atoms, except the methylene group hydrogens at C-4, exist as pairs. In the proton NMR spectrum the methylene protons are registered as an AB spin system at 2.03 and 1.89 ppm. A relatively complex pattern between 2.68 and 3.15 ppm, which integrates to eight protons represents the eight methine protons.

The signals of the geminal PCU bridge methylene protons (H-4) are registered as doublets at 1.86 (H-4a) and 2.03 ppm (H-4s) with a coupling constant of 11.4 Hz.

The most convenient tool to elucidate the structure of the dione **1** is the Nuclear Overhauser Effect Spectroscopy (NOESY) spectrum. H-4a and H-4s interact with H-3/H-5 (2.91 ppm). H-3/H-5 interact with two other protons (2.68 and 3.15 ppm), which are most probably H-2/H-6 and H-9/H-10. Both these sets of protons should interact with H-3/H-5 and possibly with H-4a



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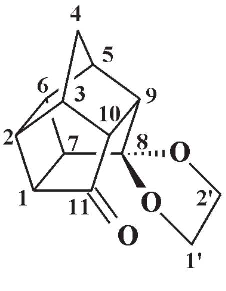

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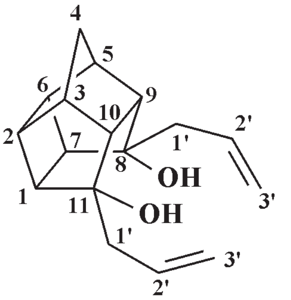

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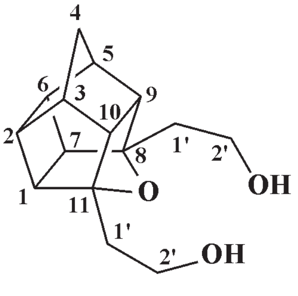

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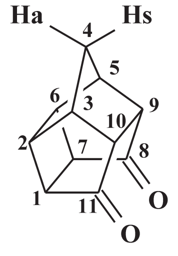

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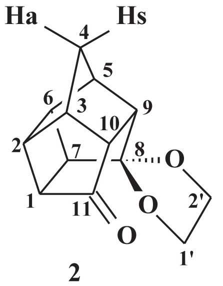

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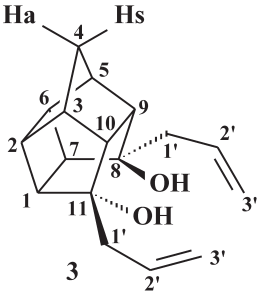

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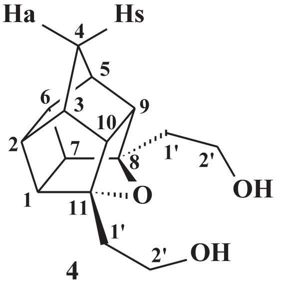

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Table 1 NMR data[a] of the four PCUdione derivatives.

	Dione **1**			Alkene Diol **3**			Diol **4**				**Ketal 2**		
Atom	δ_H^b /ppm	J /Hz	δ_c^b /ppm	δ_H^b /ppm	J /Hz	δ_c^b /ppm	δ_H^b /ppm	J /Hz	δ_c^b /ppm	Atom	δ_H^b /ppm	J /Hz	δ_c^b /ppm
1/7	2.79		43.8	2.44		42.8	2.61		47.6	1	2.63		42.3
2/6	3.15		38.7	2.45		40.0	3.75		41.4	2	2.94		41.5
3/5	2.91		44.6	2.36		44.0	2.41		44.1	3	2.80		45.8
4_a	1.86	11.4	40.5	1.07	10.8	33.9	1.52	10.4	43.5	4a	1.56	11.0	38.7
4_s	2.03	11.4		1.50	10.8		1.88	10.4		4s	1.85	11.0	
8	–		212.1	–		72.2	–		96.4	5	2.58		42.9
9/10	2.68		54.7	2.15		49.1	2.57		58.2	6	2.78		36.3
11	–		212.1	–		77.2	–		96.4	7	2.55		41.3
1′	–		–	1.97–2.24		44.0	2.0		34.2	8	–		215.4
2′	–		–	5.90		133.8	3.75		60.1	9	2.43		50.7
3′a	–		–	5.01	8.0, 2.6	117.9	–			10	2.47		53.0
3′b	–		–	5.11	8.0, 2.6		–			11	–		113.9
OH	–		–	5.30		–	12.15			$1'_A$	3.90	c	65.1
										$1'_X$	3.83	c	
										$2'_A$	3.90	c	
										$2'_X$	3.90	c	64.5

[a] 400 MHz for ^1H and 100 MHz for ^{13}C.
[b] Solvent $CDCl_3$.
[c] Owing to overlap of these proton signals, the respective coupling constants could not be determined.

or H-4s. Only H-2/H-6 should interact with one more set of protons, namely H-1/H-7. Through elimination it is clear that H-2/H-6 should register at 3.15 ppm and H-1/H-7 at 2.79 ppm. H-9/H-10 are therefore assigned to 2.68 ppm. The position of H-4a and H-4s can also be verified from the NOESY spectrum. H-4s (2.03 ppm) interacts with H-9/H-10 (2.68 ppm) and H-4a (1.89 ppm) with H-2/H-6 (3.15 ppm). The rest of the signals were verified utilizing the Heteronuclear Single-Quantum Correlation (HSQC), Correlation Spectroscopy (COSY) and Heteronuclear Multiple Bond Coherence (HMBC) spectra and the assignments are summarized in Table 1.

The assignments for the dione **1** correspond well with those deduced by Cadd *et al.*[7b] The conversion[4d] of the dione **1** to the ketal **2** is presented in Fig. 1.

The asymmetric keto-ketal (**2**) was elucidated next. Carbons C-1′ and C-2′ were assigned to the downfield signals at 64.5 and 65.7 ppm as they are directly attached to oxygen atoms. H-1′ and H-2′ resonate between 3.90 and 3.83 ppm and should be an AA′XX′ or ABXY system. It is not yet possible to distinguish between these two diastereotopic methylene groups.

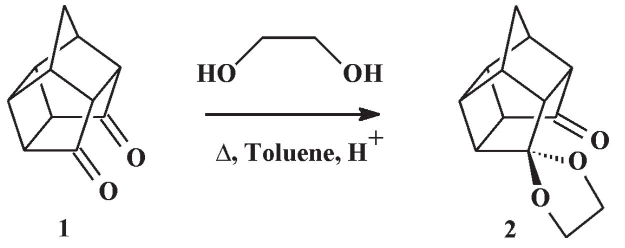
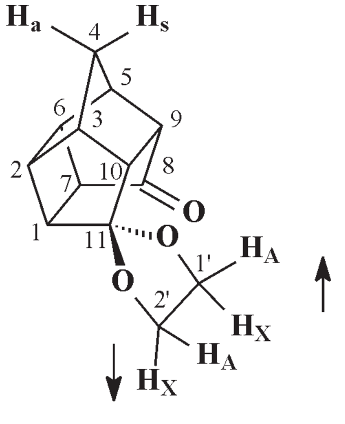


Figure 1 Monoprotection of the dione.[4d]



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From the HSQC spectrum it is clear that the protons attached to one carbon (64.5 ppm) experience a larger non-equivalence shift (3.83 and 3.90 ppm) than the other protons (3.90 ppm). It is likely that protons on C-1′ experience through-space deshielding[7c] from the oxygen on C-8, causing the larger difference in chemical shift between $H-1'_A$ and $H-1'_X$. Unfortunately, the proton signals at H-2′ also overlap at 3.90 ppm, making it difficult to determine the different coupling constants.

The NOESY spectrum of the ketal shows correlation between

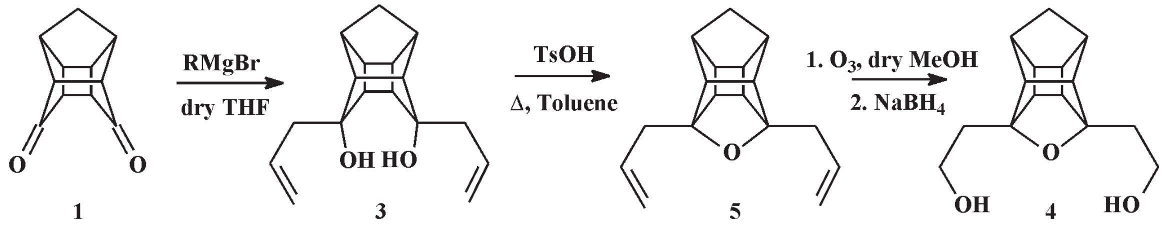


Figure 2 Synthesis of the diols **3** and **4**.

the two methylene groups (3.83 and 3.90 ppm) and two methine protons on the cage (2.63 and 2.46 ppm), respectively.

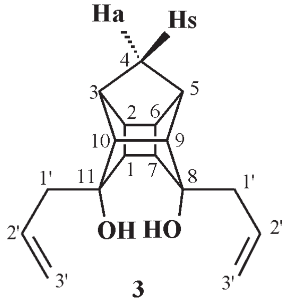
A high level DFT optimization [B3LYP/6-31+G(d)] of the ketal indicated two possible conformations for the ketal group. The ketal group is twisted with either C1′ up and C-2′ down (conformation 1), or C-1′ down and C-2′ up (conformation 2). The Cartesian coordinates of the optimized structures are provided as supplementary material. Both conformations were optimized and it turned out that conformation 1 is 0.4 kJ mol^{-1} lower in energy. As this energy difference is small, both conformations should exist in solution. Closer inspection of the DFT-optimized structure of conformation 1 indicated that proton H-2′$_X$ is in close proximity to H-1 (2.8Å) and H$_A$-1′ to H-10 (3.2Å). Conformation 2 exhibits close proximity between H-2′$_A$ to H-10 (3.2Å) and H-1′$_X$ to H-1 (2.9Å). The NOESY interactions should therefore correspond to H-1′$_A$ and H-2′$_A$ (3.90 ppm) with H-10 (2.47 ppm); and H-1′$_X$ (3.83 ppm) and H-2′$_X$ (3.90 ppm) with H-1 (2.63 ppm).

Another convenient NMR handle to solve the structure of the ketal **2** is to use the NOESY correlations between H-4a (1.56 ppm) and H-3/H-5 as well as H-2; between H-4s (1.85 ppm) and H-3/H-5 as well as H-9/H-10. Interaction with H-3/H-5 (2.78 and 2.58 ppm) is the common factor and the positions of H-2 (2.94 ppm) and H-9/H-10 (2.43 and 2.46 ppm) are therefore apparent. At this stage distinction between H-3 and H-5, as well as between H-9 and H-10, is still required. The position of H-3 (2.80 ppm) can be determined from the NOESY interaction with H-2 (2.94 ppm) and H-10 (2.47 ppm); and H-9 (2.43 ppm) with H-10. H-5 (2.58 ppm) was assigned through elimination since the position of H-3 (2.80 ppm) is now known. The position of H-5 was also confirmed through COESY correlation with H-9 (2.43 ppm). The positions of the corresponding carbon signals were obtained from the HSQC spectrum.

The next convenient tool to be used is the HMBC spectrum of the ketal. H-2 (2.94 ppm) correlates with C-10 (53.0 ppm). Both H-3 (2.80 ppm) and H-6 (2.78 ppm) correlate with C-9 (50.7 ppm). H-3 correlates with C-1 (42.3 ppm) and C-6 (36.3 ppm). H-6 (2.78 ppm) correlates with C-1. The last remaining proton, H-7 (2.55 ppm), was also assigned through interaction with C-9 (50.7 ppm). The rest of the carbon signals were assigned using the HSQC spectrum. The NMR assignments are summarized in Table 1.

The synthesis of **3** and **4** is shown in Fig. 2. Treatment of the dione **1** with excess Grignard reagent (Mg + allylbromide) produced the alkene diol **3**. Dehydration of the diol **3** under Dean-Stark conditions produced the diene **5**.[11–13] Ozonolysis with a reductive work-up produced the diol **4**.[14]

The diene-diol **3** is a meso compound as the nucleophilic attack from the Grignard reaction[4a] occurs from the *exo*-face of the carbonyl carbon. The integration values of the proton spectrum can be used to assign: H-4a (1.07 ppm) and H-4s (1.50 ppm); H-3′ (5.01 and 5.11 ppm; J = 8.0 and 2.6 Hz); H-2′ (5.90 ppm) and OH (5.30 ppm, exchange with D$_2$O). Some of the cage methine proton signals at 2.15 ppm partially overlap with that of H-1′ (1.97–2.24 ppm).



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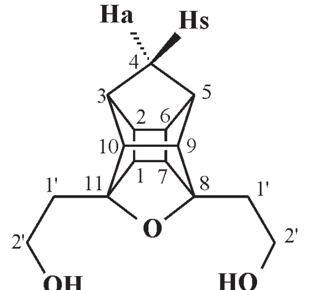
The NOESY handle is used to correlate H-4s (1.50 ppm) with H-3/H5 and H-2/H-6; H-4a (1.07 ppm) with H-3/H-5 and H-9/H-10. The interaction with H-3/H-5 (2.36 ppm) is the common factor and the positions for H-2/H-6 (2.45 ppm) and H-9/H-10 (2.15 ppm) are apparent. NOESY correlations between OH (5.30 ppm) and H-1/H-7 (2.44 ppm) as well as H-9/H10 (2.15 ppm) confirm these positions. Interestingly, H-2′ (5.90 ppm) shows NOESY correlation with H-9/H-10 (strongest at 2.15 ppm), H-1′ (1.97–2.24 ppm), H-1/H-7 (2.44 ppm) and H-3/H-5 (2.36 ppm). The positions of the carbon signals were obtained from the HSQC spectrum. Note that C-1′ overlaps with C-3/C-5. The details of all NMR assignments are provided in Table 1.

The same methodology was used to solve the NMR spectra for the diol **4**. Through elimination of NOESY interaction between H-4a, H-4s with H-3/H-5, H-2/H-6 and H-9/H-10 the positions of these proton signals were assigned.



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The HMBC spectrum is useful to determine the interaction between H-1′ and C-1/C-7 as well with C-9/C-10. Distinction between C-1/C-7 and C-9/C-10 is possible through HMBC correlation of H-4a and C-9/C-10 but not possible with C-1/C-7. The rest of the signals were verified utilizing the HSQC, COSY and HMBC spectra and the assignments are summarized in Table 1.

The methine NMR signals of the dione **1**, the diene-diol **3**, and the diol **4** appear similar, however the methine proton signals for **3** and **4** are more crowded. Protons H-1/H-7 and H-3/H-5 are interchanged for **1** and **3**. The same happens when **1** and **4** are compared; protons H-9/H-10 are shifted downfield and also exchange positions with H-3/H-5. The carbon signals are also shuffled. Between **1** and **3** only the order of C-2/C-6 and C-4 is changed. Between **1** and **4** the order of C-3/C-5 and C-1/C-7 is changed. The ketal **2** is unsymmetrical and cannot really be compared with the other three structures.

4. Conclusion

The complete NMR elucidation of four classic pentacycloundecanedione derivatives was achieved. Even though these molecules are used by most researchers in the field as crucial starting materials for various other derivatives, the NMR assignments of these derivatives have never been elucidated before. Earlier authors have commented on the difficulty of NMR elucidation of cage compounds due to severe overlapping of the proton signals. Owing to advances in NMR technology, the complete assignment of the NMR signals of these molecules can now be made with modern 2D experiments. A DFT optimization of two ketal conformations was used to account for the NOESY interactions observed for the asymmetric PCU ketal.

5. Supplementary Material

All the NMR spectra as well as the experimental details are available as supplementary material. The Cartesian coordinates of the two ketal (**2**) conformations are also provided as supplementary material.

Acknowledgements

This work was supported by grants from the National Research Foundation (South Africa), GUN 2046819, and the University of KwaZulu-Natal.

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