Complete NMR Elucidation of Two N-Protected Trishomocubane Hydantoins and the Ethyl Ester of the Corresponding Amino Acid

ARTICLE *in* STRUCTURAL CHEMISTRY · MARCH 2005

Impact Factor: 1.84 · DOI: 10.1007/s11224-005-2836-7

3 AUTHORS, INCLUDING:

Gert Kruger
University of KwaZulu-Natal
307 PUBLICATIONS **1,671** CITATIONS

SEE PROFILE

MAGNETIC RESONANCE IN CHEMISTRY
Magn. Reson. Chem. 2004; **42**: 617–623
Published online 11 May 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mrc.1397

Complete NMR elucidation of a novel trishomocubane hydantoin and its mono- and bis-*t*-Boc protected derivatives

Louis Fourie,[1] Thavendran Govender,[2] Humcha K. Hariprakasha,[3] Hendrik G. Kruger[2]* and Terrence Raasch[2]

[1] Department of Chemistry, Potchefstroom University, Potchefstroom 2520, South Africa
[2] Department of Chemistry, University of Kwazulu-Natal, Durban 4041, South Africa
[3] National Cancer Institute at Frederick, Frederick, Maryland 21702, USA

Received 15 September 2003; Revised 23 January 2004; Accepted 7 February 2004

The syntheses of a novel trishomocubane hydantoin and its mono- and bis-protected *t*-Boc derivatives are described. The less nucleophilic N-3′ nitrogen of the hydantoin ring is protected first when treated with di-*tert*-butyl dicarbonate (*t*-Boc anhydride), possibly owing to steric hindrance by the bulky trishomocubane cage skeleton. More basic conditions were required to form the bis-protected *t*-Boc hydantoin with the same reagent. The structures of these novel compounds were elucidated with 2D NMR techniques. The proton spectrum of the trishomocubane skeleton is complex owing to major overlap of proton signals. A high-level DFT calculation was used to determine some of the crucial interatomic positions, which assisted with the elucidation of the structures. The assignment of proton and carbon signals of the three structures is described and it differs significantly from each other and also from the trishomocubanol precursor. The bis-Boc hydantoin is required for a more facile hydrolysis to the corresponding trishomocubane amino acid at room temperature. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; trishomocubane; cage hydantoin; t-Boc protection

INTRODUCTION

Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (trishomocubane) was first reported by Eaton *et al*. in 1968, as a keto derivative.[1] Later, Underwood and Ramamoorthy were successful in synthesizing the underivatized $C_{11}H_{14}$ polycyclic hydrocarbon, for which they proposed the trivial name trishomocubane (**1**) (Fig. 1).[2]

Although NMR elucidation of the pentacycloundecane cage system has been well studied,[3–10] similar studies[11–13] on the intrinsically chiral[14] trishomocubane system have somehow been neglected. Here we report the synthesis and NMR characterizations of a trishomocubane hydantoin and its mono- and bis-protected *t*-Boc derivatives.

The synthesis of the cage hydantoin (see Fig. 2) was achieved[15] via a Bucherer–Bergs[16] conversion of trishomocubanone (**2**)[11,14,17,18] to its corresponding hydantoin (**3**). Base hydrolysis should yield the corresponding trishomocubane amino acid (**4**).[15] This method was previously successfully applied to adamantanone[19] and to pentacyclo-undecanone.[10]

As a result of the unique D_3 symmetry[14] of the trishomocubane cage skeleton, only two enantiomers of the hydantoin **3** are obtained as a racemate (see Fig. 3).

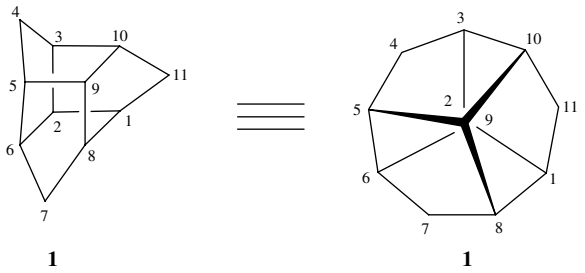
RESULTS AND DISCUSSION

The successful synthesis of the hydantoin is evident from the infrared spectrum, with the presence of two carbonyl absorption bands at 1766 and 1720 cm^{-1} and an N–H absorption band at 3314 cm^{-1}. The time-of-flight mass spectrum exhibits the correct molecular ion peak at m/z 231 [M + H$^+$].

Although a mixture of two enantiomers is obtained in the experiment, the NMR spectra of both are identical under achiral conditions. The numbering system of the novel hydantoin (see Fig. 3) and derivatives thereof was adopted from the numbering system used by Dekker *et al*.[11] for the NMR elucidation of trishomocubanol and trishomocubanone.

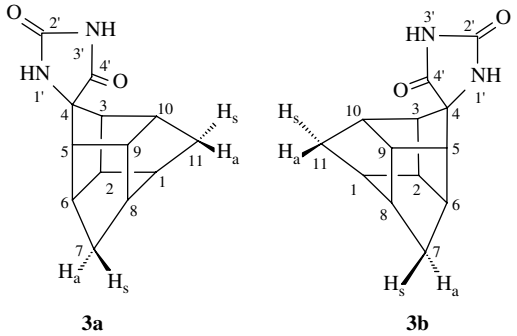
The presence of two D_2O exchangeable proton peaks at 7.88 and 10.54 ppm in the ^{1}H NMR spectrum is evidence of the amide (NH-1′) and imide (NH-3′) protons of the hydantoin ring, respectively. The ^{13}C NMR spectrum exhibits a characteristic[10] amide carbonyl signal (C-4′ at 177.50 ppm) and a urea carbonyl group (C-2′ at 157.05 ppm), the eight

*Correspondence to: Hendrik G. Kruger, Department of Chemistry, University of Kwazulu-Natal, Durban 4041, South Africa.
E-mail: kruger@ukzn.ac.za
Contract/grant sponsor: National Research Foundation Gun 2046819 (South Africa).
Contract/grant sponsor: University of Natal.
Contract/grant sponsor: National Computational Science Alliance (USA); Contract/grant number: CHE000031N.



1 **1**

Figure 1. The trishomocubane skeleton.



3a **3b**

Figure 3. Enantiomers of the trishomocubane hydantoin **3**.

methine carbons of the cage between 39.57 and 55.67 ppm and the presence of two methylene carbons at 32.95 and 33.49 ppm.

Two-dimensional NMR techniques were essential for the full elucidation of the trishomocubane hydantoin. C-4 of the cage is assigned to 73.48 ppm in the ^{13}C NMR spectrum owing to it being an integral part of the electron-withdrawing hydantoin ring system. This assignment is confirmed by the absence of heteronuclear single quantum coherence (HSQC) correlations and the presence of heteronuclear multiple bond coherence (HMBC) correlations with NH-1′ of the hydantoin ring. C-3 and C-5 are assigned as the next most downfield shifted carbons (54.82 and 55.67 ppm) owing to their direct attachment to the deshielded C-4 carbon. At this point it is essential to confirm other functional groups of the cage before it is possible to discriminate between the C-3 and C-5 carbons; it is possible to correlate their proton peaks to the region 1.90–1.98 ppm in the HSQC spectrum.

The positions of NH-1′ and the O-4′ oxygen with respect to the trishomocubane skeleton were determined next. This would assist with the elucidation of the rest of the cage skeleton. The positions of N-1′ and O-4′ were chosen as indicated in Fig. 3.

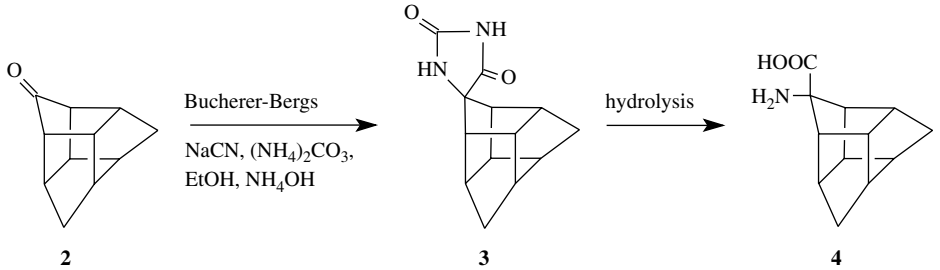
The positions of H-1′ and O-4′ with respect to the cage skeleton are confirmed from the NOESY spectrum of **3**. Correlations of NH-1′ are observed with four protons signals, which should be H-2, H-3, H-5 and H-6. Oxygen O-4′ is therefore pointing towards H-9 and H-10. The strongest NOESY interaction of NH-1′ should be with the nearest neighbouring proton (largest spot on the NOESY spectrum; correlation at 7.88 ppm with 2.45 ppm).

The extreme downfield-shifted methine proton at 2.84 ppm in the ^{1}H NMR spectrum is correlated with the carbon peak at 42.75 ppm in the HSQC spectrum. This proton peak (2.84 ppm) could potentially represent H-6 or H-10 owing to their close spatial proximity to the hydantoin ring. This assignment to either H-6 or H-10 is also evident from HMBC correlations with C-4. The downfield-shifted signal at 2.84 ppm is most likely the proton closest to the oxygen of the C-4′ carbonyl. The carbonyl oxygen of C-4′ could potentially interact through space with H-3, H-5, H-9 and H-10 and causes considerable deshielding to the nearest neighbouring protons. The closer the proton is to the carbonyl oxygen of C-10, the larger is the deshielding effect and, hence, the more the proton signal is moved downfield. By measuring the bond distances between the cage methine protons and the various functionalities of the hydantoin ring of a DFT-optimized[20] model of trishomocubane hydantoin, the proton signal at 2.84 ppm is correlated with H-10, the proton nearest (2.48 Å). A more detailed description of the computational information is presented in the experimental section; the optimised Cartesian coordinates of the hydantoin **3** are available as supporting material. The DFT-calculated interatomic distances are presented in Fig. 4.

Similar through-space deshielding as for H-10 was also observed[17] for the methine proton signal nearest to the oxygen in trishomocubanol. The proton closest to the hydantoin carbonyl oxygen in the PCU analogue[10] also experienced a large deshielding effect.

The assignment for H-6 is also assisted by the DFT-optimized structure of the hydantoin **3**. As mentioned above, NOESY interactions are distance dependent, and the nearest neighbouring proton should exhibit the largest NOESY spot (2.45 ppm correlation with 7.88 ppm) on the spectrum. The interatomic distances between NH-1′ and protons H-2, H-3, H-5 and H-6 are also presented in Fig. 4. It is clear that H-6 is situated the closest to NH-1′ (2.37 Å) and is therefore assigned to 2.45 ppm.

At this point, it is evident from the NOESY correlations of H-6 and H-10 with the relevant methylene functional groups of the cage that the peaks between 1.19–1.27 ppm and 1.36–1.39 ppm represent both H-7 and H-11 protons. A



2 **3** **4**

Figure 2. Bucherer–Bergs synthesis and hydantoin hydrolysis.

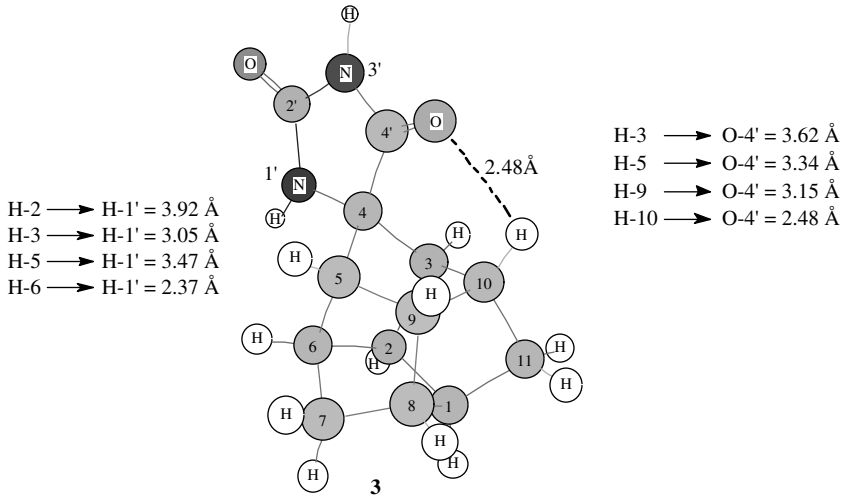


Figure 4. DFT-optimized structure of trishomocubane hydantoin[20].

more accurate assignment is presented below, but first it was important to assign the H-3 and H-5 protons of the cage. The H-3 methine proton is assigned to 1.97 ppm in the correlation spectroscopy (COSY) spectrum owing to correlations with H-10. This allows for assignment of H-5 to 1.91 ppm owing to a correlation with H-6 in the COSY spectrum. Discrimination between C-3 and C-5, which was not possible above, can now be made utilizing the HSQC spectrum. H-3 at 1.97 and H-5 at 1.91 ppm couple with C-3 at 55.67 and C-5 at 54.82 ppm, respectively.

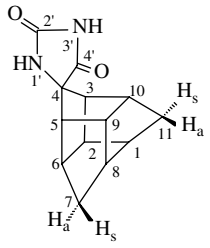
It is now possible to obtain a more accurate elucidation of the two methylene groups. The proton peaks at 1.19–1.22 ppm in the ^{1}H NMR spectrum were assigned to H-11s owing to NOESY correlations with H-3. The proton peaks 1.24–1.27 ppm were assigned to H-7s owing to NOESY correlations with H-5.

The H-2 methine proton is assigned to 2.18 ppm in the COSY spectrum owing to correlations with H-3 and H-6. This allows the assignment of H-1 to 2.10 ppm in the COSY spectrum owing to correlations with H-2 and H-11s. The H-9 methine proton is assigned to 2.13 ppm in the COSY spectrum owing to correlations with H-5 and H-10. This allows for the H-8 methine proton, which is the last unassigned methine proton of the cage, to be assigned to 2.10 ppm in the COSY spectrum. This assignment is confirmed by NOESY correlations of H-8 with both the H-7 and H-11 methylene protons.

Since H-7s has already been assigned, it is possible to assign H-7a to 1.36–1.39 ppm in the COSY spectrum owing to correlation with H-6. The previous assignment of H-11s also allows for the assignment of H-11a to 1.36–1.39 ppm in the COSY spectrum owing to correlation with H-10. These assignments are in agreement with the results obtained by Dekker *et al.*,[11] who reported that the methylene protons of trishomocubanol and trishomocubanone are significantly coupled to only one of the vicinal protons. They reported H-6—H-7a, H-10—H-11a, H-1—H-11s and H-8—H-7s couplings.

The rest of the carbon atoms are assigned through correlation with their established proton signals using the HSQC spectrum. A summary of the NMR data of the hydantoin **3** is presented in Table 1.

Table 1. NMR data for trishomocubane hydantoin (**3**)



Atom No.	^{1}H (ppm)	J (Hz)	^{13}C (ppm)
1	2.10		46.66
2	2.18		43.69
3	1.97		55.67
4			73.48
5	1.91		54.82
6	2.45		45.66
7a	1.36–1.39	10.2	32.95
7s	1.24–1.27	10.2	
8	2.10		47.10
9	2.13		42.20
10	2.84		42.75
11a	1.36–1.39	10.2	33.49
11s	1.19–1.22	10.2	
1′	7.88		
2′			157.05
3′	10.54		
4′			177.50

The normal base hydrolysis of the cage hydantoin requires elevated temperatures and pressures and produces average to poor yields of corresponding amino acids.[10,15,19] It was therefore decided to investigate the feasibility of a milder alternative method of hydantoin hydrolysis. Kubik *et al.*[21] modified a method that hydrolysed lactams and secondary amides[22] and developed an efficient, facile method for hydrolysis of α,α-disubstituted hydantoins. Kubik's

MRC

et al. This method involved Boc protection of the amide and imide nitrogens on the hydantoin ring followed by lithium hydroxide-aided hydrolysis at room temperature. Boc protection permits milder hydrolysis conditions owing to the carbonyl groups becoming more susceptible to nucleophilic attack and converts the nitrogens to better leaving groups, ensuring better amino acid yields.[21]

The method described by Kubik's *et al*. for bis-Boc addition to the hydantoin ring was applied to the trishomocubane hydantoin. It was clearly visible from the NMR data that the method only resulted in a monoprotected hydantoin (**5**) (Fig. 5). Addition also occurred, surprisingly, on the less nucleophilic imide nitrogen (N-3′). The imide nitrogen is positioned between two electron-withdrawing carbonyl functional groups. One would therefore expect this nitrogen to be far more electron-deficient than the corresponding amide nitrogen (N-1′). The attachment of the Boc group to N-3′ may have been forced owing to excessive steric hindrance from the bulky cage skeleton at NH-1′. This is easier to visualize if one considers that the preferred mechanism[23] of protection of amines with anhydrides involves a six-membered ring transition state where the leaving acetate serves as a base to remove the proton from the incoming nucleophile (—NH). A cyclic transition state at N-3′ which is perpendicular to the hydantoin ring should be exposed to less steric hindrance than a similar transition state[23] at NH-1′.

The structural elucidation of the trishomocubane hydantoin (**3**) was useful in elucidating the structure of **5** since a similar strategy was used to identify the various functional groups. It is possible to assign all the relevant carbons and protons of the cage and hydantoin ring system by following the logic described for the elucidation of the unprotected hydantoin. The complete NMR assignments are presented in the Experimental section. Confirmation of the position of the Boc group is, however, presented below.

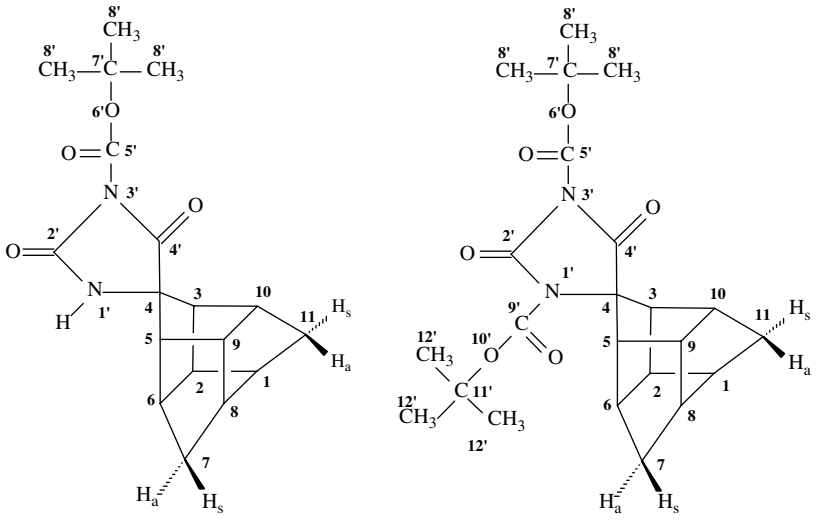
It is evident that the mono-Boc derivative (**5**) of the hydantoin had been synthesized with the appearance of three carbonyl peaks in the ^{13}C NMR spectrum and the expected molecular ion peak of m/z 331 [M + H$^+$] in the mass spectrum. The presence of a proton peak (1.56 ppm) in the ^{1}H NMR spectrum, which integrates to nine protons, could, therefore, be assigned to the three methyl groups (H-8′) of the Boc group. The absence of the imide proton (H-3′) at about 10 ppm and the presence of the amide proton (H-1′) at 6.40 ppm in the ^{1}H NMR spectrum is evidence of the Boc group attached to the imide nitrogen. The assignment of the H-1′ proton to 6.40 ppm in the ^{1}H NMR spectrum was later confirmed by a NOESY correlation with the H-6 methine proton of the cage. The C-7′ carbon of the Boc group was assigned to 85.31 ppm in the HMBC spectrum owing to a correlation with the H-8′ methyl protons.

In an attempt to add Boc functional groups to both the amide and imide nitrogens of the hydantoin ring, a method published by Wysong *et al*.[24] for derivatizing the hydantoin ring of α,α-disubstituted amino acids was applied to the hydantoin. The method is similar to the method by Kubik's *et al*., except that triethylamine was also added to the reaction mixture. The electrophilic nature of the base aided in activating the amide nitrogen (N-1′) for derivatization, enabling the bis-Boc derivative (**6**) to be successfully synthesized.

It was evident that **6** had been synthesized owing to the presence of four carbonyl groups present in the ^{13}C NMR spectrum. The absence of the amide and imide protons of the hydantoin ring at ~6 and ~10 ppm, respectively, in the ^{1}H NMR spectrum and the presence of the expected molecular ion peak of m/z 431 [M + H$^+$] in the mass spectrum further supported the presence of two Boc groups. The bis-Boc structure is further supported by the presence of two methyl peaks in the ^{1}H NMR spectrum, each of which integrates to the nine protons on the Boc functionality.

Due to the absence of the H-1′ proton, a different strategy was employed for elucidating the structure of **6** from that which is described for hydantoin (**3**) and the mono-Boc protected hydantoin (**5**).

The C-4 carbon of **6** is easily recognisable at 76.55 ppm in the HSQC spectrum as it displays no HSQC correlations. It is also expected to be the most downfield shifted cage carbon



5 **6**

Figure 5. Mono- and bis- protected *t*-Boc hydantoin.

owing to its direct attachment to the electron-withdrawing hydantoin ring. The next most downfield shifted carbons (54.03 and 58.15 ppm) are assigned to either C-3 or C-5 owing to their direct attachment to C-4. Through HSQC correlations their protons are located at either 2.16–2.17 or 2.52–2.53 ppm.

The next stage of elucidation relies on the previous assignments of the methylene (H-7a, H-7s, H-11a, H-11s) protons of the hydantoin (**3**) and mono-Boc hydantoin (**5**) and also the reported[11] couplings between H-6 (H-10) and H-7a (H-11a) and between H-1 (H-8) and H-11s (H-7s) of trishomocubanol and trishomocubanone. This allows the downfield-shifted proton peak at 3.12 ppm in the COSY spectrum to be assigned to the H-10 methine proton owing to correlations with the H-11a proton at 1.44–1.46 ppm. The H-6 (2.28 ppm), H-1 (2.09–2.13 ppm) and H-8 (2.14–2.15 ppm) methine protons are assigned owing to corresponding COSY correlations with H-7a (1.46–1.48 ppm), H-11s (1.27–1.30 ppm) and H-7s (1.30–1.33 ppm) protons, respectively.

H-2 is assigned to 2.38–2.40 ppm in the COSY spectrum owing to correlation with H-1. Similarily, the H-3 proton is assigned to 2.52–2.53 ppm in the COSY spectrum owing to correlation with H-2, which clarifies the uncertainty between H-3 and H-5 mentioned above. H-5 is assigned to 2.16–2.17 ppm, the other predicted shift mentioned above. The assignment of H-5 is confirmed by a visible COSY correlation with H-6. This allows the assignment of the last methine proton, H-9 of the cage, to 2.29 ppm owing to COSY and NOESY correlations with H-10.

The C-7 carbon is assigned to 33.02 ppm owing to HMBC correlations with H-5 and C-11 to 32.94 ppm owing to an HMBC correlation with C-2. The rest of the carbon atoms on the cage are assigned through correlation with their established proton signals using the HSQC spectrum.

The H-12′ protons of the Boc group are assigned to 1.53 ppm in the NOESY spectrum owing to through-space correlations with H-2 and H-6, therefore allowing the H-8′ Boc protons to be assigned to 1.55 ppm. This leads to the assignment of C-7′ to 86.11 ppm in the HMBC spectrum owing to correlation with H-8′. The HMBC correlation between H-12′ and the carbon peak at 84.95 ppm allows it to be assigned to C-11′. The C-4′ carbonyl is assigned to 169.58 ppm in the ^{13}C NMR spectrum and the C-2′ carbonyl is assigned to 145.74 ppm owing to more electron delocalization from N-1′ and N-3′ at C-2′. Based on the same analogy, C-5′ and C-9′ carbonyl groups could possibly be assigned to 149.67 and 149.03 ppm, respectively. The assignments for the bis-Boc protected hydantoin **6** are summarized in the Experimental section.

Comparison of the NMR data obtained in this study reveals that some of the ^{13}C signals are not consistent when the hydantoin is derivatized. For example, C-2, C-9 and C-10 of the Boc hydantoin **5** are reversed in terms of the carbon signals of the unprotected hydantoin **3**. The proton signals seem to be more consistent.

CONCLUSION

The complete NMR elucidation of the trishomocubane hydantoin (**3**), the mono-Boc hydantoin (**5**) and the bis-Boc hydantoin (**6**) was achieved using 2D NMR techniques. Interestingly, the less nucleophilic N-3′ nitrogen is more reactive towards *t*-Boc protection than the more nucleophilic N-1′ nitrogen, possibly owing to the larger steric hindrance exercised by the bulky trishomocubane skeleton at N-1′. The successful synthesis and elucidation of **6** open up the possibility of a more facile hydrolysis of the hydantoin **3** at room temperature to its corresponding amino acid.

EXPERIMENTAL

Infrared spectra (KBr disc) were recorded on a Nicolet 5DX FT spectrophotometer. Fast atom bombardment (FAB) mass spectra were obtained using a Micromass VG70-70E mass spectrometer equipped with an In Tech FAB gun. The samples were bombarded with xenon atoms (1 mA at 8 keV), with *m*-nitrobenzyl alcohol as the matrix. Electron ionization (EI) mass spectra (70 eV) were obtained using a Micromass Autospec-tof mass spectrometer. Elemental analyses were performed with a Leco CHNS 932 instrument. Melting-points are uncorrected. ^{1}H, ^{13}C and 2-D NMR spectra were recorded on a Varian Unity Inova-400 MHz spectrometer using ~50 mg of sample per 0.5 ml of solvent.

The chemical shifts were referenced to the solvent peak [2.50 ppm for $(CD_3)_2SO$ and 7.24 ppm for $CDCl_3$] at ambient temperature. The ^{1}H NMR spectrum was recorded at 399.945 MHz using solvent saturation (spectral width, 6000.6 Hz; acquisition time, 3.744 s; pulse width, 10 μs; scans, 16; relaxation delay, 1.5 s). The ^{13}C NMR spectrum was recorded at 100.577 MHz (spectral width, 26 999.7 Hz; acquisition time, 1.199 s; pulse width, 8.2 μs; scans, 48 000; relaxation delay, 1.00 s).

The 2D experimental parameters were as follows: 90° pulse width, 10 μs for all spectra; spectral width for ^{1}H, 4942.8, 3109.7, 3765.4 Hz for **3, 5** and **6**, respectively (NOESY, COSY, HSQC and HMBC); spectral width for ^{13}C, 18 357.0, 17 993.7 Hz (HSQC and HMBC) for **3**, 17 857.1, 17 853.2 Hz (HSQC and HMBC) for **5** and 16 590.6, 19 328.3 Hz (HSQC and HMBC) for **6**; number of data points per spectrum, 2048 (NOESY, COSY and HMBC), 1978 (HSQC) for **3**, 1024 (NOESY, COSY and HMBC), 1244 (HSQC) for **5** and 1506 (NOESY and HSQC), 1024 (COSY), 2048 (HMBC) for **6**; number of time-incremented spectra, 256 for all spectra; relaxation delay, 2.5 s (NOESY) for **3**–**6**; 1.5 s (HSQC and HMBC) for **3**–**5** and 1.5 s (COSY) for **5** and 1.0 s (COSY) for **3** and **6**; spectra acquired in phase-sensitive mode, **3**–**6** (NOESY and HSQC); spectra acquired in absolute value mode, **3**–**6** (COSY and HMBC); gradients used for **3**–**6** (NOESY, HSQC and HMBC).

Synthesis of trishomocubane hydantoin (3)[15,16]

A mixture of the monoketone (1.00 g, 6.25×10^{-3} mol), NaCN (1.00 g, 2.04×10^{-2} mol), $(NH_4)_2CO_3$ (2.00 g, 2.08×10^{-2} mol), ethanol (10 ml) and NH_4OH (15 ml) was sealed in a glass pressure vessel. This was sealed in a metal pressure vessel containing water. The reaction was placed in an oil-bath and heated at 60 °C for 2 h, 100 °C for 2 h and 120 °C overnight. The cooled reaction mixture was diluted with deionized water (100 ml) and extracted with ethyl acetate (150 ml). The solvent was removed *in vacuo* to yield the crude hydantion. The product was washed successively with acetone and diethyl ether, then recrystallized from tetrahydrofuran to yield pure hydantoin as a white solid (1.32 g, 92%), m.p. 325 °C. IR

(KBr), ν_{max} 3314, 2944, 1766, 1720, 1403 cm^{-1}. ^1H NMR [$(CD_3)_2SO$, 400 MHz], δ_H 1.19–1.22 (1H, H-11s, J = 10.2 Hz), 1.24–1.27 (1H, H-7s, J = 10.2 Hz), 1.36–1.39 (2H, H-7a, H-11a, J = 10.2 Hz), 1.91 (H-5), 1.97 (H-3), 2.10 (H-1, H-8), 2.13 (H-9), 2.18 (H-2), 2.45 (H-6), 2.84 (H-10), 7.88 (D_2O exchangeable H-1′), 10.54 (D_2O exchangeable H-3′). ^{13}C NMR [$(CD_3)_2SO$, 400 MHz], δ_C 32.95 (C-7), 33.49 (C-11), 42.20 (C-9), 42.75 (C-10), 43.69 (C-2), 45.66 (C-6), 46.66 (C-1), 47.10 (C-8), 54.82 (C-5), 55.67 (C-3), 73.48 (C-4), 157.05 (C-2′) and 177.50 (C-4′). FAB-MS $[M + H]^+$, m/z 231. Calc. for $C_{13}H_{14}N_2O_2$, C 67.81, H 6.13, N 12.17; found, C 67.66, H 6.01, N 12.21%.

Synthesis of mono-protected *t*-Boc hydantoin (5)[22]

A solution of trishomocubane hydantoin (0.50 g, 2.17×10^{-3} mol), di-*tert*-butyl dicarbonate (0.71 g, 3.26×10^{-3} mol) and 4-dimethylaminopyridine (DMAP) (3.00 mg, 2.17×10^{-5} mol) in dry THF (50 ml) was stirred under nitrogen gas for 24 h. The solution was concentrated *in vacuo* to yield the crude product. Purification was achieved through silica gel column chromatography (dichloromethane) to yield the product as a white powder (0.53 g, 74%), m.p. 206 °C. IR (KBr), ν_{max} 3220, 1770, 1712 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz), δ_H 1.26–1.29 (1H, H-11s, J = 10.4 Hz), 1.34–1.37 (1H, H-7s, J = 10.4 Hz), 1.46–1.49 (2H, H-7a, H-11a, J = 10.4 Hz), 1.56 (9H, H-8′), 2.08 (H-5), 2.09 (H-3), 2.18 (H-1), 2.19 (H-8), 2.27 (H-2), 2.33 (H-9), 2.39 (H-6), 2.95 (H-10), 6.40 (H-1′). ^{13}C NMR ($CDCl_3$, 400 MHz), δ_C 27.82 (C-8′), 32.80 (C-7), 33.16 (C-11), 41.98 (C-10), 42.78 (C-2), 43.20 (C-9), 45.32 (C-6), 46.69 (C-1), 46.76 (C-8), 55.12 (C-5), 56.08 (C-3), 71.78 (C-4), 85.31 (C-7′), 146.29 (C-2′), 152.20 (C-5′), 171.80 (C-4′). FAB-MS $[M + H]^+$, m/z 331. Anal. Calc. for $C_{18}H_{22}N_2O_4$, C 65.44, H 6.71, N 8.48; found, C 65.53, H 6.57, N 8.37%.

Synthesis of bis-protected *t*-Boc hydantoin (6)[24]

A solution of trishomocubane hydantoin (0.50 g, 2.17×10^{-3} mol), di-*tert*-butyl dicarbonate (1.19 g, 5.43×10^{-3} mol), 4-dimethylaminopyridine (DMAP) (1.3 mg, 1.09×10^{-4} mol) and triethylamine (0.35 ml, 2.60×10^{-3} mol) in dry THF (50 ml) was stirred under nitrogen gas for 24 h. The solution was concentrated *in vacuo* to yield the crude product. Purification was achieved through silica gel column chromatography (dichloromethane) to yield the product as a white powder (0.77 g, 98%), m.p. 227 °C. IR (KBr), ν_{max} 2965, 1771 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz), δ_H 1.27–1.30 (H-11s, J = 11.5 Hz), 1.30–1.33 (H-7s, J = 11.5 Hz), 1.44–1.46 (H-11a, J = 8.6 Hz), 1.46–1.48 (H-7a, J = 8.6 Hz), 1.53 (9H, H-12′), 1.55 (9H, H-8′), 2.09–2.13 (H-1), 2.14–2.15 (H-8), 2.16–2.17 (H-5), 2.28 (H-6), 2.29 (H-9), 2.38–2.40 (H-2), 2.52–2.53 (H-3), 3.12 (H-10). ^{13}C NMR ($CDCl_3$, 400 MHz), δ_C 27.52 (C-12′), 27.72 (C-8′), 32.94 (C-11), 33.02 (C-7), 41.94 (C-9), 42.91 (C-10), 45.27 (C-6), 45.93 (C-1), 46.11 (C-8), 46.23 (C-2), 54.03 (C-3), 58.15 (C-5), 76.55 (C-4), 84.95 (C-11′), 86.11 (C-7′), 145.74 (C-2′), 149.03 (C-9′), 149.67 (C-5′), 169.58 (C-4′). FAB-MS $[M + H]^+$, m/z 431. Anal. Calc. for $C_{23}H_{30}N_2O_6$, C 64.17, H 7.02, N 6.51; found, C 64.08, H 6.85, N 6.39%.

Details of the DFT-optimised structure for the hydantoin 3

The trishomocubane hydantoin was optimized by using Gaussian 98[20] utilizing density functional theory (DFT) at the B3LYP level of theory and the 6–31 + G(d) basis set. Diffuse functions are typically used for more accurate descriptions where π-electron delocalization is involved, while polarization functions remove some limitations of the basis set by expansion of the virtual space. Solvation effects were not considered in order to simplify the model.

Since the trishomocubane hydantoin is very rigid, conformational changes are almost completely absent, which enables a normal optimization algorithm to find the global minimum structure. The second-derivative analytical vibrational frequency calculation utilizing the same methodology employed in the location of stationary points showed no negative frequencies, indicating that the hydantoin structure is a minimum structure.

An interesting observation about the geometry of the hydantoin ring is that N-3′ is planar whereas N-1′ is forced to be non-planar by steric interactions between H-1′ and the nearby H-6.

Supplementary information

All the NMR spectra mentioned in the text are available as supplementary information. The Cartesian coordinates of the DFT-optimised structure of the hydantoin **3** are also provided as supplementary information.

Acknowledgements

This work was supported by grants from the National Research Foundation Gun 2046819 (South Africa), the University of Natal and the National Computational Science Alliance (USA) under grant number CHE000031N (NCSA SGI/CRAY Origin2000). The authors kindly acknowledge the contribution of Professors Frans J. C. Martins and Agatha M. Viljoen, Potchefstroom University, Potchefstroom 2520, South Africa, to the cage amino acid programme and for kindly allowing us to continue working in the field. We also thank Professor Alan P. Marchand, University of North Texas, Denton, TX, USA, for his generous intellectual and financial support during the first part[15] of the research, which was performed in his laboratory.

REFERENCES

1. Eaton PE, Cassar L, Hudson RA, Giordana C. Presented at the 155th Meeting of the American Chemical Society, San Francisco, April 1968.
2. Underwood GR, Ramamoorthy B. *Tetrahedron Lett.* 1970; 4125.
3. Dekker TG, Pachler KGR, Wessels PL, Dekker J, Dekker JJ, Fourie L. *Org. Magn. Reson.* 1978; **11**: 529.
4. Martins FJC, Fourie L, Venter HJ, Wessels PL. *Tetrahedron* 1990; **46**: 623.
5. Martins FJC, Viljoen AM, Coetzee M, Fourie L, Wessels PL. *Tetrahedron* 1991; **47**: 9215.
6. Cadd DH, Feast WJ, Kenwright AM, Say JM. *Magn. Reson. Chem.* 1993; **31**: 801.
7. Martins FJC, Viljoen AM, Kruger HG, Joubert JA. *Tetrahedron* 1993; **49**: 9573.
8. Martins FJC, Viljoen AM, Kruger HG, Wessels PL. *Tetrahedron* 1993; **49**: 6527.
9. Martins FJC, Viljoen AM, Kruger HG, Joubert JA, Wessels PL. *Tetrahedron* 1994; **50**: 10 783.
10. Martins FJC, Viljoen AM, Kruger HG, Fourie L, Roscher J, Joubert AJ, Wessels PL. *Tetrahedron* 2001; **57**: 1601.
11. Dekker TG, Oliver DW, Pachler KGR, Wessels PL, Woudenberg M. *Org Magn Reson.* 1981; **15**: 188.
12. Oliver DW, Dekker TG, Wessels PL. *Magn. Reson. Chem.* 1994; **32**: 330.
13. Schwartz M, Marchand AP, Wang KS, Reddy SP, Redda GM, Gadgil VR, Watson WH, Kashyap RP, Krawiec M. *J. Chem. Soc., Perkin Trans. 2* 1993; 1829.
14. Kent GJ, Godleski SA, Osawa E, Schleyer PvR. *J. Org. Chem.* 1977; **42**: 3852.
15. Govender T. *MSc Dissertation*, University of Natal, Durban, 2001.
16. Bucherer HT, Steiner W. *J. Prakt. Chem.* 1934; 291.
17. Dekker TG, Oliver DW. *S. Afr. J. Chem.* 1979; 45.
18. Eaton PE, Hudson RA, Giordano C. *J. Chem. Soc., Chem. Commun.* 1974; 978.
19. Nagasawa HT, Elberling JA, Shirota FN. *J. Med. Chem.* 1973; **16**: 823.
20. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Zakrzewski VG, Montgomery JA Jr, Stratmann RE, Burant JC, Dapprich S, Millam JM, Daniels AD, Kudin KN, Strain MC, Farkas O, Tomasi J, Barone V, Cossi M, Cammi R, Mennucci B, Pomelli C, Adamo C, Clifford S, Ochterski J, Petersson GA, Ayala PY, Cui Q, Morokuma K, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Cioslowski J, Ortiz JV, Baboul AG, Stefanov BB, Liu G, Liashenko A,

Piskorz P, Komaromi I, Gomperts R, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Andres JL, Gonzalez C, Head-Gordon M, Replogle ES, and Pople JA. *Gaussian 98, Revision A.9*, Gaussian: Pittsburgh, PA, 1998.
21. Kubik S, Meissner RS, Rebek J Jr. *Tetrahedron Lett.* 1994; **35**: 6635.
22. Flynn DA, Zelle RE, Grieco PA. *J. Org. Chem.* 1983; **48**: 2424.
23. Kruger HG. *Theochem* 2002; **577**: 281.
24. Wysong CL, Scott Yokum T, Morales GA, Gundry RL, McLaughlin ML, Hammer RP. *J. Org. Chem.* 1996; **61**: 7650.