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Synthesis of 4-Oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]Dodecane-3-Carboxylic Acid

Frans J.C. Martins[a]*, Agatha M. Viljoen[a]*, Hendrik G. Kruger[a] and Philippus L. Wessels[b]

[a]Department of Chemistry, Potchefstroom University for CHE, Potchefstroom 2520, South Africa

[b]Department of Chemistry, University of Pretoria, Pretoria 0001, South Africa

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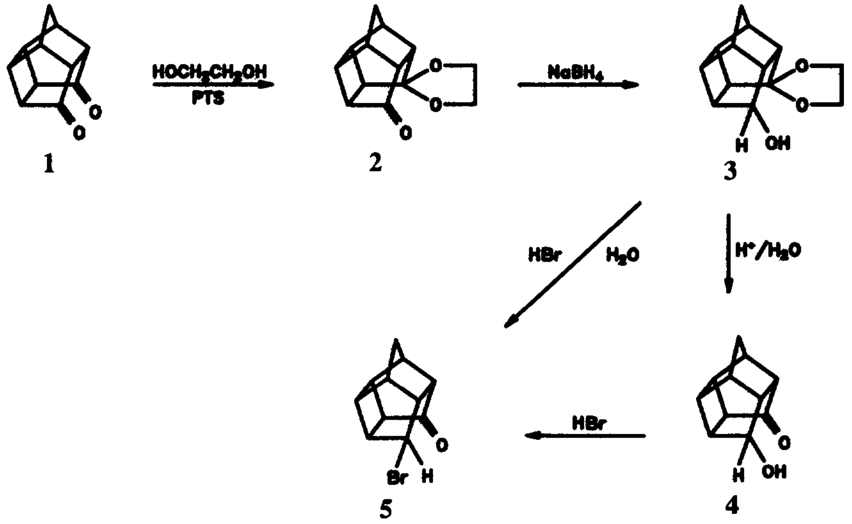
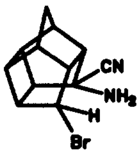
Abstract: *4-Oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane-3-carboxylic acid was obtained from hydrolysis of the cyano precurser which was synthesised by a Strecker reaction from exo-11-bromopentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-one. Endo-11-hydroxypentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8-one has not shown any reactivity towards Strecker reagents at room temperature. The structures of the title compound and corresponding cyano and ester derivatives were elucidated from an extensive ^{1}H and ^{13}C n.m.r. study.*

As part of a programme that is concerned with the synthesis and chemistry of amino acids with cage structures we have sought to synthesise novel unsymmetrical α-amino acids by utilising the bromo ketone **5** and the hydroxy ketone **4** as substrates in Strecker reactions. It was previously reported[1] that both **4** and **5** can be obtained in high yield from the readily available pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (**1**)[2] as outlined in the following scheme:



Reaction of **5** with a mixture of ammonium chloride, sodium cyanide and ammonium hydroxide failed to produce the expected aminonitrile **6** or the cyanohydrin **7**. Instead a compound was obtained in 80% yield of which the infrared spectrum exhibits no hydroxylic or amino group absorptions. A characteristic C-N stretching vibration absorption is registered at 2 246 cm^{-1}. An intense absorption peak at 982 cm^{-1} can be attributed to a C-O-C stretching vibration of a cyclic ether. The mass spectrum exhibits a molecular ion at m/z 185 suggesting **8** as a possible structure.



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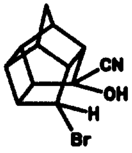

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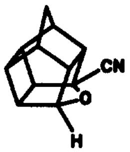

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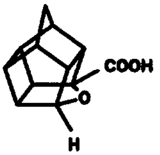
Hydrolysis of **8** with concentrated hydrochloric acid produced in quantitative yield the corresponding carboxylic acid of which the infrared spectrum shows a typical broad carboxylic absorption in the 3 330 - 2 830 cm^{-1} region and a corresponding carbonyl group absorption at 1 754 cm^{-1}. An electron impact induced (EI) mass spectrometrical analysis failed to produce a molecular ion. A fast atom bombardment (FAB) mass spectrometric analysis, using 3-nitrobenzyl alcohol as matrix, showed a pseudo molecular ion at m/z 205 ([M + H]$^+$). An elemental analysis is supportive of a molecular formula of $C_{12}H_{12}O_3$. Esterification with methanol and concentrated sulphuric acid produced an ester (**11**) of which the mass spectrum showed a molecular ion at m/z 218 (corresponding to $C_{13}H_{14}O_3$). On strength of the above data, as well as an extensive ^{1}H and ^{13}C n.m.r. investigation, structure **9** is proposed for the hydrolysis product of **8**.



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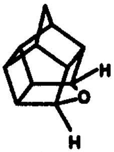

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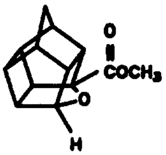

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The 500 MHz ^{1}H n.m.r. spectrum of **9** in $(CD_3)_2SO$ shows an AB spin system and five broad signals in the high field region. The peaks at δ 2.639 and δ 2.595 integrate for two and three protons respectively. From the 125 MHz ^{13}C n.m.r. data **9** consists of one methylene, nine methine, one aliphatic quaternary and one carbonyl carbon atom. The ^{13}C chemical shift and the directly bonded (C,H) coupling constant of the carbon atom resonating at δ 84.97 are characteristic of a carbon atom bearing an oxygen atom. From a HETCOR 2D-experiment the differenct ^{13}C resonances have been correlated with the observed proton resonances. The assignments of the different resonance signals in the ^{1}H and ^{13}C spectra of **9** to certain nuclei are given in Table 1. The assignment was verified by ^{13}C-^{1}H selective population inversion (SPI) experiments[3] which indicate the following:

(i) selective irradiation at δ 4.640 effected mainly the carbon resonance at δ 93.75. This proton must be three bonds from the affected carbon atom.

(ii) when a transition of 12-H_a or 12-H_s is selectively irradiated the carbon resonances at δ_C = 54.06 and 57.89 and δ_C = 41.76 and 40.64 are, respectively, mainly affected.

From the force field calculated three dimensional structure of **9**, obtained from the Alchemy programme[5], the dihedral angle between 5-H and C-3 is 180° whereas the dihedral angles between 12-H_a and C-2 and C-6 and between 12-H_s and C-8 and C-11 are all 170°. This explains the big vicinal (C,H) couplings observed for these nuclei.

Better resolved ^{1}H n.m.r. spectra and unambiguous correlations were observed in a COSY experiment when **9** was recorded in C_6D_6. (A 2 mg sample of **9** was dissolved in a drop op $(CD_3)_2SO$ and C_6D_6 added to obtain a 0.5 cm^3 solution). The ^{1}H chemical shifts and coupling constants observed in this solvent mixture are also collected in Table 1. The change in the ^{1}H chemical shifts can be explained by a complexation of benzene with the carbonyl group of **9**. ^{1}H detected heteronuclear multiple quantum coherence (HMQC) was used to correlate the ^{1}H resonances with the ^{13}C resonances using directly bonded (C,H) coupling constants. According to this experiment the ^{13}C chemical shifts of the different carbon atoms in **9** are similar in the two solvents. Using the calculated three dimensional structure of **9** all the expected ^{13}C-^{1}H correlations over three bonds were observed in a ^{1}H detected heteronuclear multiple bond connectivity (HMBC) experiment optimised for 10 Hz couplings. As vicinal (C,H) coupling constants are normally bigger than geminal (C,H) couplings, the correlation between protons and ^{13}C carbon atoms three bonds away, are normally observed.

Further support for the proposed structure is obtained when the n.m.r. data of **10**^{4} is compared with those observed for **9**. In **10** a vicinal (C,H) coupling of 9.6 Hz is observed between the proton and the carbon atom over the ether oxygen atom, compared to a coupling of 9.8 Hz between C-3 and the proton on C-5 in **9**. The ^{13}C chemical shifts of the carbon atoms C-5, C-6, C-7, C-8, C-9 and C-12 are also similar to those of **10**. (See footnote d of Table 1).

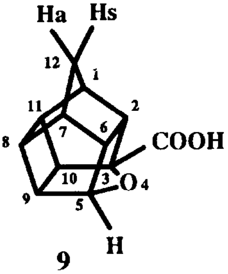

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Table 1 ^{1}H and ^{13}C n.m.r. data[a] of **9**

Carbon/ proton	δ_H^b(ppm)	δ_H^c(ppm)	J(Hz)	δ_C^b(ppm)	^{1}J(Hz)	$^{>1}$J(Hz)	$\delta\Delta^d$
1	2.390	2.633 td	4.9; 0.9	44.48 Dd	143.2	7.9	0.5
2	2.595^e	2.854 ddt	10 8, 4.5, 1 8	57.89 Dm	147.3		3.4
3				93.75 Sdd		9.8; 4.4	
5	4.640	4 619 t	5 0	84 97 Dd	158.9	3.8	-0.7
6	2.595^e	2 51^g		54.06 Dm	145.9		-0.4
7	2 266	2.036 td	4.8; 0.9	43.55 Dd	143.0	7.7	-0.5
8	2 485	2 252 qt	6 5, 1.7	40 64 Dm	146.8		-1.0
9	2 639^f	2 53^g		43.86 D(br)	150.4		0.2
10	2.639^f	2 925 ddt	8.0; 6.1; 1.7	47.86 D	150.5		4.2
11	2.595^e	2.55^g		41.76 Dm	146.8		0.2
12 s	1.790	1.667 dt(br)	10 5, 1 4	43.01 T	131.6		-0.9
a	1 398	1.299 dt	10.5; 1 6				
COOH	12.454			172.28 S			

[a] 500 MHz for ^{1}H and 125 MHz for ^{13}C.

[b] Solvent $(CD_3)_2SO$. Symbols in capital letters refer to patterns resulting from directly bonded protons and lower case letters to (C,H) couplings over more than one bond. S = singlet, D or d = doublet, T or t = triplet, q = quartet and m = multiplet.

[c] Solvent $C_6D_6/(CD_3)_2SO$ 50:1.

[d] δ(**9**) - δ(**10**).

[e] Overlapping resonances.

[f] Overlapping resonances.

[g] Resonances overlap. From COSY and HMQC experiments the individual resonance positions can be deduced.

The ^{13}C n.m.r. spectrum of **8** (Table 2) exhibits signals that can be associated with thirteen different carbon atoms. The cyano group carbon atom resonates at δ 118.77. The resonance at δ 83.25 can be assigned to the quaternary carbon atom C-3. The ^{13}C chemical shift and the directly bonded (C,H) coupling constant of the carbon atom resonating at δ 87.24, are characteristic of a carbon atom bearing an oxygen atom and can be associated with C-5. The methylene carbon atom C-12 resonates at δ 43.82. The resonance pattern of the remaining eight methine carbon resonances are very similar to those of **9**.

The 300 MHz ^1H n.m.r. spectrum of **8** in $CDCl_3$ exhibits a triplet at δ 4.888 (5-H), an AB spin system (methylene protons on C-12) and four broad signals centered at δ 2.48, δ 2.67, δ 2.83 and δ 3.05 and integrating for one, two, three and two protons respectively. The assignments of the different resonance signals in the ^1H and ^{13}C n.m.r. spectra of **8** were made from HETCOR and COSY experiments as well as comparison with corresponding n.m.r. data of **9** and **11** and are collected in Table 2.

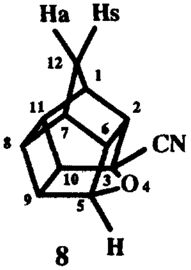

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Table 2 ^1H and ^{13}C n.m.r. data[a] of **8**

Carbon/ proton	δ_H^b(ppm)	J(Hz)	δ_C^b(ppm)	J(Hz)	$>^1J$(Hz)
1	2.699		44.25 Dd	142.9	7.8
2	3.020		60.66 Dm	146.2	
3			83.25 Sdd		9.6; 4.1
5	4.888 t	5.1	87.24 Dm	158.2	
6	2.83[c]		54.94 Dm	145.1	
7	2.480		43.98 Dd	143.4	7.6
8	2.717		41.17 Dm	146.0	
9	2.889		44.98 D	150.0	
10	3.054		50.39 D	149.8	
11	2.83[c]		42.09 Dm	146.4	
12 s	2.009 d	10.8	43.82 T	132.0	
a	1.630 d	10.8			
CN			118.7 S		

[a] 300 MHz for ^1H and 75 MHz for ^{13}C.

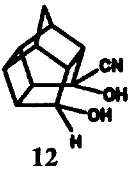
[b] Solvent $CDCl_3$. Symbols in capital letters refer to patterns resulting from directly bonded protons and lower case letters to (C,H) couplings over more than one bond. S = singlet, D or d = doublet, T or t = triplet and m = multiplet.

[c] Overlapping resonances.

The diagnostic value of the relatively big vicinal coupling between C-3 and the proton on C-5 in structures like **8**, **9**, **10** and **11** is clearly demonstrated by the coupling constants of 9.6, 9.8, 9.6 and 10.2 Hz respectively observed for these structurally related compounds.

It is clear that **8** is formed by means of a trans-annular cyclisation whereby the bromine atom is displaced by an internal nucleophilic reaction. Attempts to isolate 7 as a possible intermediate from the reaction mixture were unsuccessful.

The reaction of **4** under similar reaction conditions should follow a different course. Influence of the nearby *endo* orientated hydroxyl group can play a significant role in the reactivity of the carbonyl group towards nucleophilic addition reactions. However, the expected cyanohydrin **12** should be a thermodynamically stable compound compared to its homologues **13**[6] and **14**[7] which are readily synthesised from the dione **1**.



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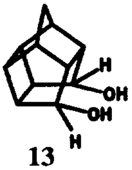

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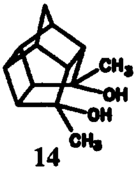

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Surprisingly no reaction occurred upon treatment of **4** with a mixture of ammonium chloride, sodium cyanide and ammonium hydroxide. Attempts to convert the ketal **2** to the corresponding cyanohydrin under Strecker reaction conditions, also failed. Clearly cyanohydrin formation on the carbonyl group is inhibited by the nearby *endo* orientated functional group.

EXPERIMENTAL

Infrared spectra (KBr-disc) were recorded on a Nicolet 5DX FT spectrophotometer. EI mass spectra were obtained at 70 eV on a VG 7070-E mass spectrometer. FAB mass spectra were obtained by bombardment with a 1 mA beam of 8 keV accelerated neutral xenon atoms produced by an Ion-Tech FAB gun. Melting points are uncorrected. N.m.r. spectra were recorded on a Brucker WM 500 FT and a Varian Gemini-300 spectrometer as indicated.

3-Cyano-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane (**8**)

A solution of **5** (1 g) in 15 cm^3 of a 1:2 diethyl ether-methanol mixture was slowly added to a cooled (<10°C) mixture of ammonium chloride (0.5 g), sodium cyanide (0.55 g), ammonium hydroxide (1.3 cm^3, 25%) and water (5 cm^3) over a period of 0.5 h. The reaction temperature was maintained below 10°C for a further 1.5 h while the reaction mixture was stirred, allowed to reach room temperature and stirred for an additional period of 8 h. The aqueous layer was saturated with sodium chloride and the product (**8**, 0.62 g, m.p. 117°C) extracted with diethyl ether and recrystallised from n-hexane.
ν_{max} 2 968, 2 869, 2 246, 1 311, 1 097, 1 023, 982, 933, 785 cm^{-1}. EI MS, m/z 185 (M$^+$), 157, 156, 131, 129, 116. Calc. for $C_{12}H_{11}NO$: C, 77.84; H, 5.95; N, 7.57%. Found: C, 77.82; H, 5.95; N, 7.56%.

4-Oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane-3-carboxylic acid (**9**)

A mixture of **8** (0.12 g) and concentrated hydrochloric acid (30 cm^3) was refluxed for 0.5 h, evaporated to dryness on a water bath and the product (**9**, 0.12 g, m.p. 150°C dec.) extracted with acetone and recrystallised from water containing a few drops of acetone
ν_{max} 3 330 - 2 830, 2 992, 2 976, 1 754, 1 729 (weak), 1 204, 1 081, 1 032, 991 cm^{-1}. EI MS, m/z 159 (M$^+$-COOH·). FAB MS, m/z 205 ([M + H]$^+$)(3-nitrobenzyl alcohol matrix). Calc. for $C_{12}H_{12}O_3$: C, 70.59; H, 5.88%. Found: C, 70.58; H, 5.85%.

4-Oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$ $0^{5,9}$ $0^{8,11}$]dodecane-3-methyl methanoate (**11**)

A solution of **9** (0.22 g) in absolute methanol (10 cm^3) containing concentrated sulphuric acid (0.2 cm^3) was refluxed for 0.5 h. The reaction mixture was poured into 50 cm^3 water and the product (**11**, 0.2 g, b.p. 155°C - 760 mm Hg) extracted with dichloromethane and purified by distillation.
ν_{max} 2 977, 2 869, 1 754, 1 442, 1 220, 1 089, 999, 786, 745 cm^{-1}. EI MS, m/z 218 (M$^+$). Calc. for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42%. Found: C, 71.55; H, 6,40%. ^{13}C n.m.r. [$(CD_3)_2SO$] δ_C 171.55 (S, C=O), 93.92 (Sdd, 10.2 Hz; 4.8 Hz, C-3), 85.28 (D, C-5), 58.13 (D, C-2), 54.18 (D, C-6), 51.74 (Q, CH_3), 48.09 (D, C-10), 44.58 (D, C-1), 44.01 (D, C-9), 43.64 (D, C-7), 43.16 (T, C-12), 41.83 (D, C-11), 40.74 (D, C-8). ^{1}H n.m.r.

[$(CD_3)_2SO$] δ_H 4.792 (t, 4.5 Hz, H-5), 3.669 (CH_3), 2.783 (H-10), 2.773 (H-9), 2.73 (H-6), 2.73 (H-2), 2.716 (H-11), 2.616 (H-8), 2.509 (H-1), 2.383 (H-7), 1.910 (d, 10.4 Hz; CH_2-H_s), 1.519 (d, 10.4 Hz; CH_2-H_a).

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