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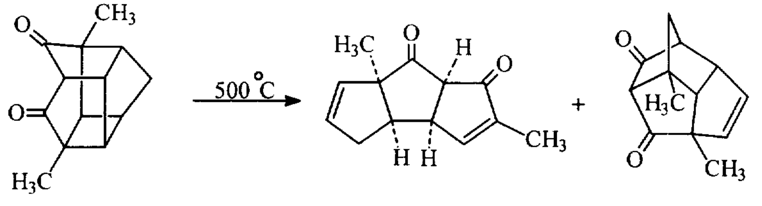
Synthesis of Novel Tetracyclo[6.3.0.0^{2,6}.0^{3,10}]undecane and Tetracyclo[6.4.0.0^{2,6}.0^{3,10}]dodecane Derivatives.

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

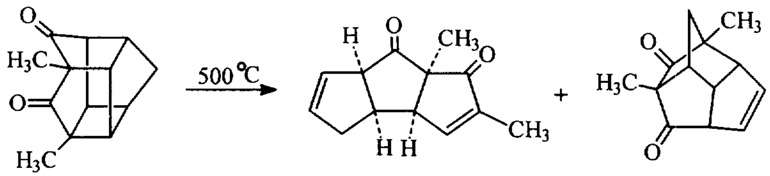
[a]Department of Chemistry, Potchefstroom University for CHE, Potchefstroom 2520, South Africa.
[b]Department of Chemistry, University of Pretoria, Pretoria 0001, South Africa.

Abstract: 4,6-Dimethyl-tetracyclo[6.3.0.0^{2,6}. 0^{3,10}]undecane-5,9-dione has been synthesised from 8,11-dimethyl-pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-1-ol by chromium trioxide oxidation. In the same fashion tetracyclo[6.4.0.0^{2,6}.0^{3,10}]dodecane-5,9-dione was obtained from pentacyclo[6.4.0.0^{2,6}.0^{5,9}.0^{4,12}] dodecan-2-ol. The synthesis of a 4,6-cyclised homologue is also discussed.

It was previously shown[1] that flash vacuum pyrolysis of 1,8-dimethyl- and 1,10-dimethyl-pentacyclo[6.3.0.0.^{2,6}.0^{3,10}.0^{4,8}]undecane-9,11-diones **1** and **4** affords the corresponding *cis, syn ,cis*-tricyclo [6.3.0.0^{2,6}]undecanes **2** and **5** respectively along with novel tetracyclic rearranged products **3** and **6**. It was also shown[2] that the tricyclic dione **7** on storage and on contact with acid establishes equilibrium with its trans-skeletal aldol cyclisation product **8**. A near quantitative formation of the tetracyclic methyl ether **9** was achieved by treatment of **7** with methanol in the presence of p-toluenesulphonic acid[2].

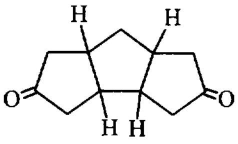


1 **2** **3 (25%)**



4 **5** **6 (55%)**

Compounds with carbon frameworks as displayed in **3**, **6**, **8** and **9** offer interesting synthetic possibilities which urged us to investigate the synthesis of other homologues. The D_3-trishomocubane carbon framework **10** is a potential precursor for the formation of tetracyclo[6.3.0.0^{2,6}.0^{3,10}]undecane derivatives. Cleavage of the C_1-C_2-bond in **10** should produce the desired novel carbon skeleton.



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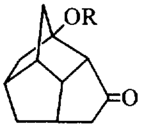
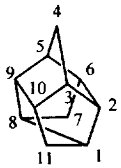


8, R = H

9, R = CH₃



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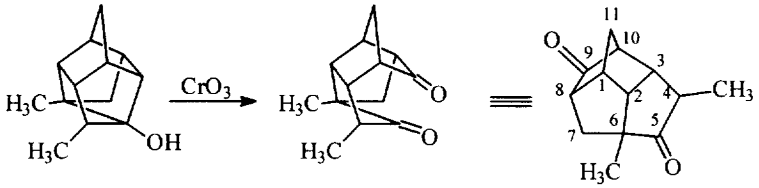


11 **12**

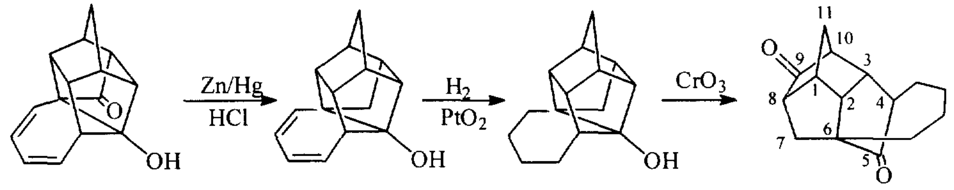
The hydroxy derivative **11** is readily obtainable[2,3] from 1,3-cyclopentadiene and 2,3-dimethyl-1,4-benzoquinone in four high yielding steps. We found that treatment of **11** with chromium trioxide in acetic acid resulted in selective oxidative cleavage of the C_1-C_2-bond to produce **12** in 80% yield.

The electron impact induced (EI) mass spectrum of **12** exhibits a molecular ion at m/z 204. An elemental analysis supported a molecular formula of $C_{13}H_{16}O_2$. The infrared spectrum of **12** displays a strong carbonyl group absorption band at 1735 cm^{-1} and no O-H stretching vibration absorptions associated with hydroxyl groups. Confirmative evidence for the correctness of the allocated structure of **12** was obtained from a ^1H and ^{13}C n.m.r. study.

The ^1H n.m.r. spectra of compounds such as **12** are very complex. In addition to geminal and vicinal proton-proton couplings, long-range (over more than three bonds) proton-proton interactions are also operative resulting in fairly broad unresolved resonances. The 300 MHz ^1H n.m.r. spectrum of **12** (DMSO-d_6) shows signals for two methyl groups. The singlet at δ_H 1.09 can be associated with the protons of the methyl group bonded to C-6 whereas the doublet registered at δ_H 1.01 (J=7.7 Hz) can be attributed to the protons of the methyl group on C-4. Clearly the C_1-C_2 bond in **11** suffered oxidative cleavage to produce **12** and the C_1-C_8 and C_1-C_{11} bonds of **11** stayed intact. The methylene protons on C-11 of **12** are registered as an AB part of a spin system and appear as two doublets centered around δ_H 1.77 (J=10.7 Hz) and δ_H 1.95 (J=10.7 Hz). The methylene protons on C-7 (δ_H 1.63) exhibit a geminal coupling constant ($J_{a,b}$=9.1 Hz) characteristic of those observed for normal five membered rings. Only one of these methylene protons couples significantly to other protons, probably to H-8. A proton-proton chemical shift correlation 2D (COSY) n.m.r.-experiment[4] indeed confirmed interaction only with the proton resonance at δ_H 2.34 (H-8) whereas the methylene proton resonances of H-11a and H-11b show distinct cross peaks with the proton resonances registered at δ_H 2.51 and δ_H 3.05 (H-10 and H-1). Cross peaks are also observed between the resonances of H-8 and H-1 confirming the assignment of the latter. The assignments of the rest of the resonance signals in the ^1H n.m.r. spectrum of **12** followed from the correlations observed between the methyl proton resonances at δ_H 1.01 and the resonances at δ_H 1.96 (H-4) and the correlation between the latter and the resonances at δ_H 2.99 (H-3).

The ^{13}C n.m.r. spectrum of **12** exhibits resonance signals of two carbonyl carbon atoms, one quaternary, two methyl, two methylene and six methine carbon atoms. The assignments of the different ^{13}C n.m.r. signals to certain nuclei were made from a heteronuclear chemical shift correlation 2D (HETCOR) experiment[5] from the assigned ^1H n.m.r. spectrum and are given in the experimental section.

Oxidative cleavage of the C_1-C_2 bond in compounds containing the D_3-trishomocubane carbon framework (**10**) as a possible route to tetracyclo-undecane derivatives was further demonstrated by the chromium trioxide oxidation of **15** whereby **16** was obtained in 70% yield. The tertiary alcohol **15** was obtained from a Clemmensen reduction of **13**[6] followed by catalytic reduction of **14** with platinum dioxide as catalyst. Chromium trioxide oxidation of **14** produced a complex mixture of oxidation products which persuaded us to convert **14** to **15**.

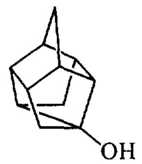


13 **14** **15** **16**

An elemental analysis of **16** is supportive of a molecular formula of $C_{15}H_{18}O_2$ which was confirmed by a mass spectrum showing a molecular ion at m/z 230. The infrared spectrum exhibits a strong carbonylic absorption band at 1738 cm^{-1}. The ^{13}C n.m.r. spectrum also supports the proposed structure of **15** and exhibits resonances of two carbonylic carbon atoms, one quaternary, six methine and six methylene carbon atoms.

The 300 MHz ^1H n.m.r. spectrum of **16** exhibits a complex signal pattern for four methylene protons between δ_H 1.29 and δ_H 1.67. A COSY-2D experiment showed interactions between the resonances around δ_H 1.64 and the resonance signals registered at δ_H 2.45. No other interactions from the spin system of the four methylene proton resonances with methine protons are registered, confirming that the resonance at δ_H 2.45 could be assigned with confidence to H-4 (arbitrary numbering for reference purposes only). The methylene protons of C-7 and C-11 are both registered as AB spin systems and appear as double doublets at δ_H 1.74 and δ_H 1.85 ($J_{a,b}$=11.5 Hz) for H-7 and at δ_H 1.50 and δ_H 2.44 ($J_{a,b}$=12.7 Hz) for H-11. The assignments of the ^1H resonance signals to certain nuclei were made from the COSY experiment starting from the assigned resonance of H-4. Assignments of the ^{13}C resonance signals were made from a HETCOR experiment and are given in the experimental section.

Unsubstituted D_3-trishomocuban-1-ol (**17**) is not known. However, the tertiary alcohol **18**[3,7,8] is a suitable substrate to demonstrate whether α-substitution (**11** and **15**) has an influence on the chromium trioxide oxidation of D_3-trishomocuban-1-ol derivatives.



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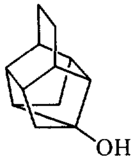

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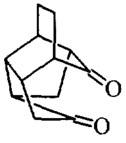

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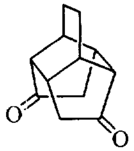
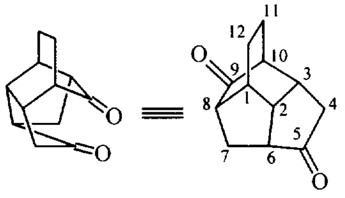


20

Treatment of **18** with chromium trioxide in acetic acid produced the diketone **19** in 75% yield. The symmetric diketone **20** could not be isolated from the reaction mixture indicating that only one of the bonds of the quaternary carbon atom suffered oxidative cleavage.

The infrared spectrum of **19** shows carbonylic absorptions at 1735 and 1715 cm^{-1}. An elemental analysis supported a molecular formula of $C_{12}H_{14}O_2$ which corresponds with the mass spectrum which exhibits a molecular ion at m/z 190. The 500 MHz ^1H and 125 MHz ^{13}C spectra of **19** clearly show its asymmetric character (Table 1).



19 **19**

Table 1 ^1H and ^{13}C n.m.r. data[a] of **19**

Carbon / proton	δ_H (ppm)[b]	J (Hz)	δ_C (ppm)[b,c]	^1J (Hz)
1	2.277 q(br)		38.78 D	135.6
2	2.959 q	7.30	41.16 D	134.7
3	2.594 t	9.14	34.34 D	137.2
4a	2.516 dd	18.58 ($J_{a,b}$), 1.75	42.91 T	130.4
b	1.997 d(br)			
5			221.14 S*	
6	2.688 dd	11.38, 7.29	49.29 D	137.2
7a	2.156 ddd	13.41 ($J_{a,b}$), 11.99, 6.62	33.47 T	136.2
b	1.651 d(br)			
8	2.498m		52.02 D	138.0
9			217.60 S*	
10	2.102m		48.28 D	141.1
11	1.947		17.47 T**	133.7
12	1.808	ABCD spin system[d]	25.35 T**	130.8

[a] 500MHz for ^1H and 125MHz 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, q = quartet and m = multiplet.

[c] Values marked * or ** are mutually interchangeable.

[d] ABCD part of an ABCDXY spin system with the resonances at δ_H 1.949 integrating for one proton and those at δ_H 1.808 for three protons.

The ^{13}C spectrum exhibits resonance signals at δ_C 217.60 and δ_C 221.14 of two different carbonyl carbon atoms of which the chemical shifts are characteristic for ketonic groups in five or six membered rings.

The ^{13}C spectrum also shows signals for four methylene and six methine carbon atoms. The ^{1}H n.m.r. spectrum shows the presence of an ABCD spin system that must be attributed to the CH_2CH_2-group. The geminal (^{1}H, ^{1}H) coupling constants of the two remaining methylene groups are 13.41 Hz and 18.58 Hz. The one methylene group (^{2}J=18.58 Hz) must be next to one of the carbonyl groups while the other methylene group (^{2}J=13.41 Hz) must be more than one bond removed from the carbonyl groups. All these features can only be accommodated by the proposed structure of **19**.

The coupling pattern between the different protons as shown by a COSY-2D experiment further support the structure of **19**. The proton H-7a couples, in addition to H-7b, with big couplings to the protons resonating at δ_H 2.498 (H-8) and δ_H 2.688 (H-6). Correlation peaks are also observed between H-8 and the resonances at δ_H 2.277 (H-1). The latter resonances exhibit cross correlation peaks with the ABCD spin system. The resonance at δ_H 2.959 (H-2) exhibit, however, only a correlation with the resonance at δ_H 2.277 (H-1). Very weak correlations are observed between H-2 and H-6 and H-3. Selective irradiation at δ_H 2.959 in a conventional (^{1}H, ^{1}H) decoupled experiment proved that H-2 couples mainly with the protons resonating at δ_H 2.277 (H-1), δ_H 2.688 (H-6) and δ_H 2.594 (H-3). The assignments of the ^{13}C resonance signals were made from a HETCOR experiment from the assigned ^{1}H n.m.r. spectrum and are given in Table 1.

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EXPERIMENTAL

Infrared spectra were recorded on a Nicolet Magna-IR Series II system 550 spectrophotometer. EI mass spectra were obtained at 70eV on a VG7070-E mass spectrometer. 300 MHz n.m.r. spectra were recorded on a Varian Gemini-300 spectrometer and 500MHz spectra on a Brucker WM500. Melting points are uncorrected.

4,6-Dimethyl-tetracyclo[6.3.0.$0^{2,6}$.$0^{3,10}$]undecane-5,9-dione (**12**)
Chromium trioxide (0.3g, 3mmol) was added in 0.1g (1mmol) portions with 3h intervals to a well stirred solution of **11** (0.19g, 1mmol) in 90% acetic acid (10ml) at room temperature. The reaction mixture was stirred for 48h, diluted with water and the product continuously extracted with dichloromethane and purified by medium pressure flash chromatography[9] with silica gel (E. Merck, Kieselgel 60; 230-400 mesh) as stationary phase and a 1:1 petroleum ether (40-60°C)-ethyl acetate mixture as eluant to yield **12** (0.165g, m.p.38°C).
IR (CsI-disc) : ν_{max} 2960, 2935, 2870, 1735, 1450, 1375, 1245, 1080, 1005, 980 and 950 cm^{-1}; **EI MS:** m/z 204 (M^{+}). Calc. for $C_{13}H_{16}O_2$: C, 76.47; H, 7.84%. Found: C, 76.45; H, 7.81% ^{13}**C**-n.m.r. ($CDCl_3$, 75 MHz) δ_C 225.62 (S, C-5), 218.11 (S, C-9), 55.19 (S, C-6), 52.88 (D, C-8), 52.40 (D, C-10), 50.50 (D, C-2), 45.59 (D, C-1), 44.03 (D, C-3), 42.92 (D, C-4), 42.16 (T, C-7), 34.27 (T, C-11), 22.89 (Q, 6-CH_3) and 16.87 (Q, 4-CH_3). ^{1}**H**-n.m.r. ($CDCl_3$, 300 MHz): δ_H 3.05 (H-1), 2.99 (H-3), 2.69 (H-2), 2.51 (H-10), 2.34 (H-8), 1.96 (H-4), 1.95 (d, J=10.7 Hz, H-11a), 1.77 (d, J=10.7 Hz, H-11b), 1.67 (d, J=5.1Hz, H-7, 1xH), 1.63 (d, J=9.1Hz, H-7, 1xH), 1.09 (6-CH_3), 1.01 (d, J=7.7Hz, 4-CH_3).

Clemmensen reduction of **13**
A mixture of **13** (0.452g, 2mmol), dichloromethane (7ml), hydrochloric acid (10ml, 6mol dm^{-3}) and water (15ml) was stirred at room temperature. Amalgamated zinc (6g) was added to the reaction mixture in four 1.5g portions with 3h intervals. After 36h the reaction mixture was filtered and the residue washed with dichloromethane to remove all the organic materials. Dichloromethane extraction followed by steam distillation of the extract yielded **14** (0,31g, m.p.43°C)
IR (KBr-disc) : ν_{max} 3410 (br), 3010, 2960, 2870, 1285, 1253, 1237, 1130, 1080, 1048 and 720 cm^{-1}; **EI MS:** m/z 212 (M^{+}). ^{13}**C**-n.m.r. ($CDCl_3$, 75 MHz) : δ_C 132.63 (D), 132.07 (D), 125.84 (D), 125.25 (D), 80.50 (S, C-OH), 59.00 (S), 57.35 (D), 53.76 (D), 50.95 (D), 50.85 (D), 49.82 (D), 47.05 (D), 46.11 (D) 38.05 (T) and 32.79 (T). ^{1}**H**-n.m.r. ($CDCl_3$, 300 MHz): δ_H 5.67-5.83 (m, 4xH), 2.42 (d. J=6.9 Hz, 1xH), 2.11-2.28 (m, 6xH), 1.93 (d, J=10.2 Hz,½xCH_2), 1.47 (d, J=10.2 Hz, ,½xCH_2), 1.31 (d, J=10.3 Hz, ½xCH_2), 1.06 (d, J=10.3 Hz, ½xCH_2) and 1.83 (OH).

Catalytic reduction of **14**

A solution of **14** (0.424g, 2mmol) in absolute methanol (35ml) was hydrogenated with preactivated platinum dioxide as catalyst (0.1g) until no more hydrogen was absorbed (15h). The reaction mixture was filtered to remove the catalyst and the filtrate concentrated under reduced pressure to produce **15** (0.35g, m.p. 74°C) as colourless crystals.

IR (KBr-disc): ν_{max} 3358 (OH), 2958, 2912, 2888, 1455, 1390, 1350, 1307, 1245, 1210, 1163, 1130, 1102, 1077, 1028 and 998 cm^{-1}. **EI MS**: m/z 216 (M$^+$). ^{13}**C** n.m.r. ($CDCl_3$, 75 MHz): δ_C 90.53 (S, C-OH), 57.02 (S), 54.67 (D), 49.14 (D), 48.79 (D), 47.69 (D), 47.63 (D), 46.92 (D), 45.19 (D), 40.65 (T), 34.85 (T), 31.05 (T), 29.08 (T), 27.42 (T) and 24.43 (T). ^{1}**H**-n.m.r. ($CDCl_3$, 300 MHz): δ_H 2.14-2.16 (m, 2xH), 2.02 (t, J=3.9 Hz, 1xH), 1.71-1.91 (m, 6xH), 1.47-1.68 (m, 6xH), 1.26-1.37 (m, 2xH) and 1.18-1.24 (m, 2xH).

Chromium trioxide oxidation of **15**

0.216g (1mmol) of **15** was treated with chromium trioxide (0.3g, 3mmol) as described before to yield **16** (0.16g, m.p. 80°C) as colourless crystals.

IR (KBr-disc) : ν_{max} 2930, 2850, 1738, 1445, 1280, 1220, 1160, 1120, 1080, 1020, 980 and 925 cm^{-1}; **EI MS:** m/z 230 (M$^+$). Calc. for $C_{15}H_{18}O_2$: C, 78.26; H, 7.83%. Found: C, 78.23; H, 7.81%. ^{13}**C**-n.m.r. ($CDCl_3$, 75 MHz) : δ_C 222.22 (S, C-5 or C-9), 218.99 (S, C-9 or C-5), 60.51 (S, C-6), 54.23 (D, C-10), 53.26 (D, C-1), 50.68 (D, C-8), 50.51 (D, C-4), 45.79 (D, C-3), 45.63 (D, C-2), 38.34 (T, C-11), 35.46 (T, C-7), 31.10 (T, CH_2), 30.37 (T, CH_2) 25.76 (T, CH_2) and 23.87 (T, CH_2). ^{1}**H**-n.m.r. ($CDCl_3$, 300 MHz): δ_H 2.86 (H-8), 2.83 (H-2), 2.47 (H-10), 2.45 (H-4), 2.22 (H-3), 2.19 (H-1), 2.14 (d, J=12.7 Hz, H-11a), 1.85 (d, J=11.5 Hz, H-7a), 1.74 (d, J=11.5Hz, H-7b), 1.50 (d, J=12.7Hz, H-11b) and 1.67-1.29 (m, 4xCH_2).

Tetracyclo[6.4.0.$0^{2,6}$*.*$0^{3,10}$*]dodecane-5,9-dione* (**19**)

1.76g (1mmol) of **18** was treated with chromium trioxide and the product **19** (1.45g, m.p. 95°C) isolated as described before.

IR (KBr-disc) : ν_{max} 2950, 2905, 1735, 1715, 1480, 1460, 1415, 1255, 1245, 1190, 1005, 940 and 925 cm^{-1}; **EI MS:** m/z 190 (M$^+$). Calc. for $C_{12}H_{14}O_2$: C, 75.79; H, 7.36%. Found: C, 75.75; H, 7.35%. 125 MHz ^{13}C and 500 MHz ^{1}H n.m.r. data given in Table 1.

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