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Synthesis of two new hexaquinanes: advanced C_{20} precursors to dodecahedrane

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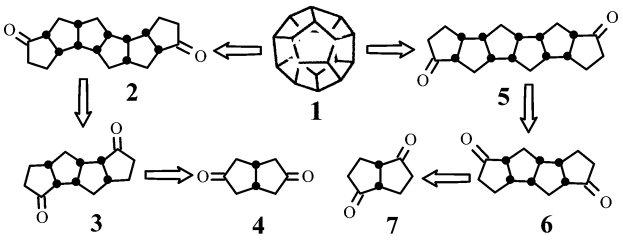
Abstract—A simple synthesis of hexaquinane diones **2** and **22** involving bench-top chemicals is reported. These two hexaquinanes are advanced C_{20} precursors to dodecahedrane **1** either by C–C bond formation reactions or by the isomerisation approach.

Several strategies for the synthesis of dodecahedrane **1** have been pursued over the last four decades due to its symmetrical nature and intricate properties.[1] In this regard, several intermediates have been synthesised and evaluated for their possible role as serviceable intermediates to dodecahedrane **1**. The target molecule **1**, however, yielded to synthetic pursuits initially in 1982[2] and much later in 1987[3] in an altogether different approach.

Based on a retrosynthetic analysis of **1**, two different C_2-symmetric C_{20}-hexaquinane diones **2** and **5** were identified as advanced precursors to dodecahedrane **1** (Scheme 1). A first stage towards dodecahedrane **1** would involve the conversion of the bicyclic diones **4** and **7** into the C_{14}-tetraquinanes **3** and **6** by a bis-cyclopentane annulation procedure involving both carbonyl groups.

However, the potential of the synthetic strategy shown in Scheme 1 depends on the application of the cyclopentane annulation procedure to the saturated C_{14}-tetraquinanes **3** and **6** to acquire the hexaquinanes **2** and **5**, respectively. In principle, catalytic hydrogenation of the bis-enone **8**, prepared from **4** as reported in the literature[4] may furnish three possible isomers with different stereochemistry at the ring junctions. The all *cis*,*syn* tetracyclic compound, the *cis*,*syn*,*cis*,*anti*,*cis* isomer and the *cis*,*anti*,*cis*,*anti*,*cis* isomer. However, the required isomer **3** may be obtained by purifying the catalyst prior to the reaction according to the procedure reported in the literature.[5] Hydrogenation of **8** in ethyl acetate using 10% palladium-on-carbon proceeded at 3 atm pressure with the exclusive formation of the known C_{14}-tetracyclic compound **3** (74%), reported earlier by McKervey involving protection–deprotection steps.[6] The spectroscopic properties of **3** are in complete agreement with the published data.[7] Apparently, the new annulation strategy developed here has considerable synthetic utility when compared to the procedures reported in the literature.[8]



Scheme 1.

In an iterative approach, the tetracyclic system **3** was successfully elaborated to a novel C_2-symmetric C_{20}-hexaquinane dione **2** as illustrated in Scheme 2. Reaction of the dione **3** with an excess of allylmagnesium bromide furnished the symmetrical and unsymmetrical allylic alcohols **9** and **10**, respectively, in the ratio 2:1 (78%). A hydroboration–oxidation sequence generated the bis-lactones **11** (81%) and **12** (77%). The crystal structure of **11** confirmed the all *cis–syn* fusion at the ring junctions.[9] The symmetrical and the unsymmetrical natures of the intermediates were confirmed on the basis of appropriate signals in the ^{13}C NMR spectra.

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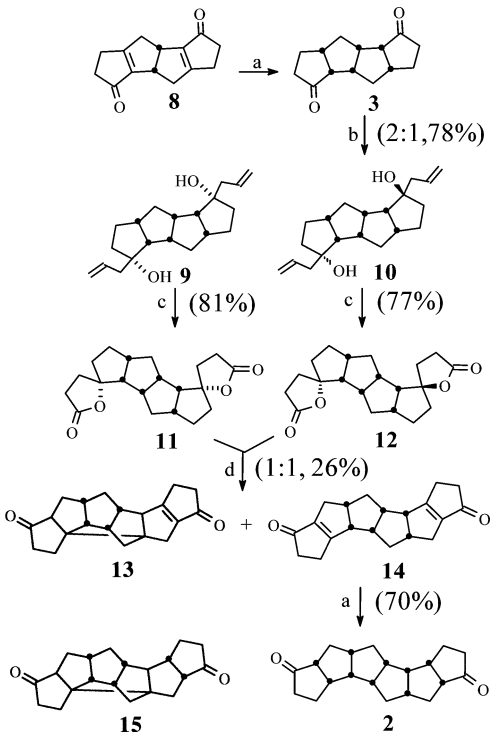
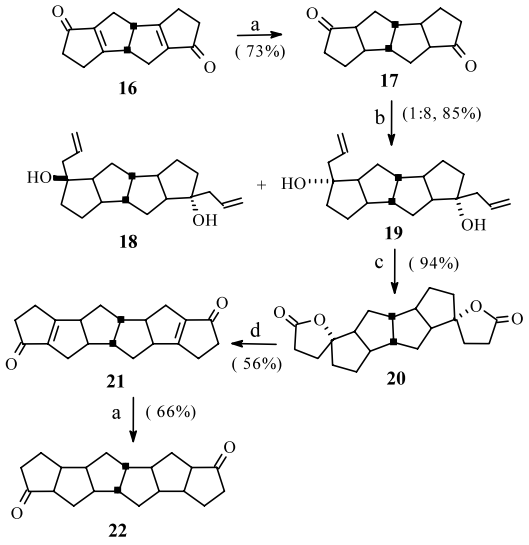


Scheme 2. *Reagents and conditions*: (a) 10% Pd/C, EtOAc, 3 atm; (b) allyl bromide, Mg-ether/THF; (c) (i) $NaBH_4$, $BF_3{\cdot}Et_2O$, (ii) Jones' oxidation; (d) methanesulphonic acid, P_2O_5.

Reaction of the bis-lactones **11** and **12** with P_2O_5 in methanesulphonic acid yielded the desired product **14** along with the unwanted isomer **13** in equal proportions (combined yield: 26%). The nature of the unwanted isomer **13** was not known until the molecular structure was confirmed by X-ray diffraction studies.[9] Catalytic hydrogenation of **13** and **14** at 3 atm pressure over 10% palladium-on-carbon furnished **15** (78%) and **2** (70%), respectively. The structure of the heptacyclic intermediate **15** was unequivocally established on the basis of X-ray diffraction studies.[9]

Attempts to acquire a single crystal of **2** for X-ray analysis has not been successful so far. The ^{13}C NMR data in combination with the earlier precedence for ring junction stereochemistry during the hydrogenation step has encouraged us to assign the structure for **2** as indicated in Scheme 2.

With the successful acquisition of **16** from **7**,[4] attempts focussed on the synthesis of another C_{20}-hexaquinane dione **5**. Catalytic hydrogenation of **16** over 10% palladium-on-carbon gave the *cis*,*anti*,*cis*,*anti*,*cis* isomer **17** (73%), exclusively, and the stereochemistry at the ring junctions was confirmed only after completing the synthesis of **22**, whose structure was confirmed by X-ray diffraction analysis (Scheme 3).[10] The stereochemical outcome during the catalytic hydrogenation can be explained on the basis of the stability of **17**, when compared to the all *cis*,*syn* isomer **6**.



Scheme 3. *Reagents and conditions*: (a) 10% Pd/C, EtOAc, 3 atm; (b) allyl bromide, Mg-ether/THF; (c) (i) $NaBH_4$, $BF_3{\cdot}Et_2O$, (ii) Jones' oxidation; (d) methanesulphonic acid, P_2O_5.

The second bis-annulation procedure was executed on the tetracyclic dione **17** in a similar manner. The addition of the Grignard reagent to **17** gave a mixture of **18** and **19** (1:8, 85%). Hydroboration–oxidation of **19** (94%) and then the rearrangement of **20** (56%) proceeded smoothly without complications. Catalytic hydrogenation of **21** furnished the C_{20}-hexaquinanedione **22** (66%) with the depicted stereochemistry at the ring junctions.[10]

The structure of **22** was established by X-ray crystallography (Fig. 1).[11] The crystal structure contains half a molecule per asymmetric unit. One half of the molecule is related to the other by twofold rotation. The packing is mainly stabilised by van der Waal's forces. In addition there are a few C–H···O intermolecular interactions. The hydrogen atoms at the ring junctions are *cis* fused.

In conclusion, two new C_{20}-hexaquinanes **2** and **22** have been prepared by an iterative cyclopentane annulation strategy from the bicyclic diones **4** and **7**. Compound **2**

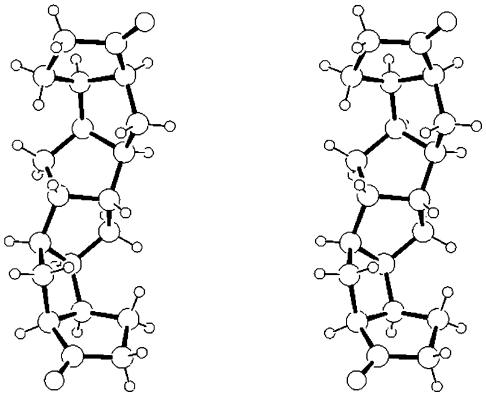


Figure 1. Stereoview of the hexaquinane dione **22**.

is an advanced precursor to dodecahedrane **1**, either by selective C–C bond formation reactions or by the isomerisation approach and **22** maybe a suitable precursor to **1** by the isomerisation approach.

Selected ^{13}C NMR spectral data

Compound **3**: δc (75 MHz, $CDCl_3$, CCl_4): 220.2, 52.7, 49.5, 44.2, 37.5, 34.7, 24.0.
Compound **9**: δc (75 MHz, $CDCl_3$, CCl_4): 134.5, 118.7, 81.9, 52.4, 50.8, 46.3, 45.5, 40.1, 36.6, 29.2.
Compound **10**: δc (75 MHz, $CDCl_3$, CCl_4): 134.46, 134.41, 118.8, 118.6, 81.8, 81.0, 55.2, 54.6, 49.4, 46.8, 46.7, 46.4, 44.9, 43.3, 40.7, 40.6, 39.9, 34.5, 31.1, 29.6.
Compound **11**: δc (75 MHz, $CDCl_3$, CCl_4): 177.2, 94.2, 52.3, 51.3, 44.0, 38.2, 36.1, 36.0, 28.7, 28.5.
Compound **12**: δc (75 MHz, $CDCl_3$, CCl_4): 176.1, 175.9, 94.6, 93.5, 56.2, 54.5, 49.7, 46.2, 44.0, 43.9, 39.7, 39.2, 35.3, 34.6, 32.9, 30.8, 29.3, 29.2, 29.0, 28.6.
Compound **13**: δc (75 MHz, $CDCl_3$, CCl_4): 222.8, 204.5, 189.0, 145.9, 65.6, 63.0, 61.0, 57.4, 52.7, 50.4, 43.7, 43.5, 43.4, 42.8, 42.7, 39.8, 36.9, 28.9, 25.6, 24.7.
Compound **14**: δc (75 MHz, $CDCl_3$, CCl_4): 204.5, 187.9, 146.6, 55.0, 47.7, 47.5, 40.8, 40.6, 31.7, 24.3.
Compound **15**: δc (75 MHz, $CDCl_3$, CCl_4): 223.0, 222.9, 63.6, 62.1, 60.8, 57.5, 52.4, 51.6, 51.5, 47.4, 47.2, 43.6, 43.5, 42.8, 42.6, 37.0, 35.4, 29.7, 28.8, 23.4.
Compound **2**: δc (75 MHz, $CDCl_3$, CCl_4): 221.3, 55.1, 53.2, 47.4, 46.7, 45.7, 39.2, 38.3, 33.7, 23.5.
Compound **17**: δc (75 MHz, $CDCl_3$, CCl_4): 220.6, 54.3, 51.3, 42.6, 38.7, 28.0, 22.5.
Compound **18**: δc (75 MHz, $CDCl_3$, CCl_4): 134.5, 118.7, 118.6, 81.3, 79.1, 56.5, 54.9, 52.1, 48.6, 46.7, 46.5, 45.9, 45.7, 42.0, 40.6, 31.6, 31.4, 27.4, 25.4.
Compound **19**: δc (75 MHz, $CDCl_3$, CCl_4): 134.7, 118.3, 79.5, 54.5, 51.5, 45.9, 45.3, 42.2, 26.0, 25.5.
Compound **20**: δc (75 MHz, $CDCl_3$, CCl_4): 176.9, 93.0, 54.6, 50.4, 41.9, 37.9, 33.5, 29.0, 28.4, 24.5.
Compound **21**: δc (75 MHz, $CDCl_3$, CCl_4): 204.2, 187.8, 147.0, 53.1, 51.9, 49.8, 40.7, 34.3, 25.4, 24.1.
Compound **22**: δc (75 MHz, $CDCl_3$, CCl_4): 222.2, 54.2, 54.1, 51.4, 47.8, 44.6, 38.9, 34.3, 33.8, 22.7.

Acknowledgements

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9. The crystal data are available at the Cambridge Crystallographic Data Centre (Deposition numbers: CCDC 163060 and 163061.
10. The crystal data are available at the Cambridge Crystallographic Data Centre (Deposition number: CCDC 162351).
11. Crystals of **22** ($C_{20}H_{26}O_2$) are monoclinic; $a=9.415(8)$, $b=10.739(2)$ and $c=15.332(1)$ Å, $\beta=92.49(1)°$, $V=1548(1)$ Å^3, $Z=4$, and $\mu=0.625$ mm^{-1}, $F(000)=648$; space group: $I2/a$. Final R indices [$I>2\sigma(I)$] $R_1=0.041$, $wR_2=0.144$.