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A Simple Route to Cyclopentane Annulation

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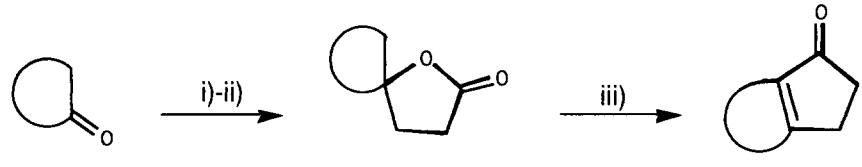
Abstract: We have developed a simple method for cyclopentane annulation using inexpensive reagents which is useful for the synthesis of polyquinane systems.

The development of novel methodologies for the construction of hetero- and carbocyclic ring systems has been a major goal in synthetic organic chemistry. Biologically active cyclopentanoid natural products and structurally intriguing polyquinanes have stimulated much research activity in recent years for the preparation of five membered ring compounds.[1]

In this communication, we describe a simple methodology for cyclopentane annulation which delivers various tetracyclic ring systems from the readily available bicyclic diones **3** and **6**. Our strategy for cyclopentane annulation is depicted in Scheme 1. The key step in this strategy is the generation of spiro-lactone without intermediates unlike the known methods for this purpose.[2-5] Moreover, the reagents used in this study are inexpensive.

Scheme 1

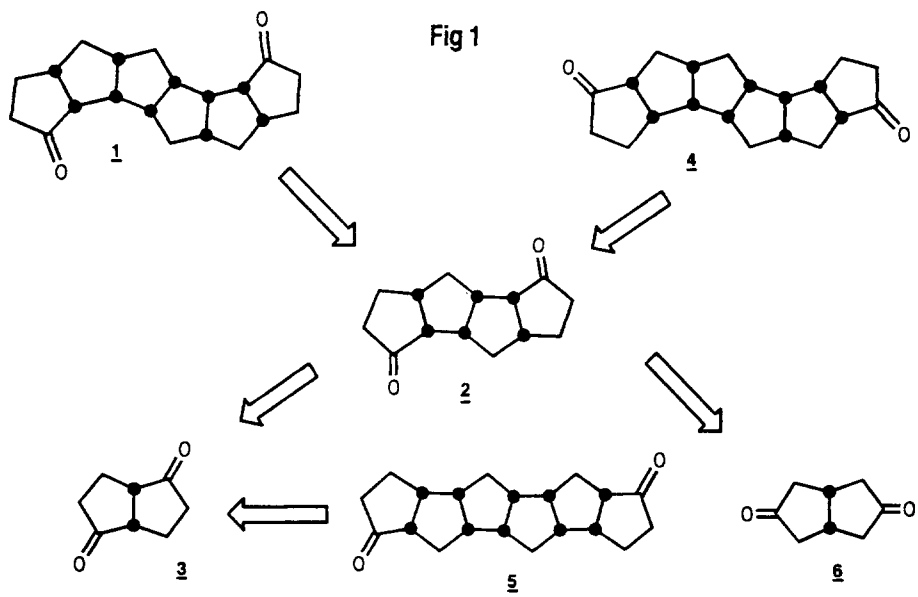


i) allylmagnesium bromide ii) oxidation iii) acid

In connection with dodecahedrane synthesis, McKervey and Vibuljan reported a novel and iterative approach to C20-hexaquinane derivative **1** starting from *cis*-bicyclo(3.3.0)octane-2,6-dione **3** *via* the intermediate **2**.[5] X-ray analysis of **1** revealed that it has an 'opened out' conformation due to severe intramolecular overcrowding of the keto group [C(1)-O] with the C(7')H2 moiety. Due to this reason hexaquinane **1** has limited use in dodecahedrane synthesis. A simultaneous 1,3 transposition of the carbonyl groups in **1** generates a new C20-hexaquinane system **4** where the above mentioned keto-methylene interactions are absent. Since the synthesis of **1** involves protective groups and a low overall yield (4.6%), we are interested in developing an alternate approach to the novel C20-hexaquinane **4**. Our

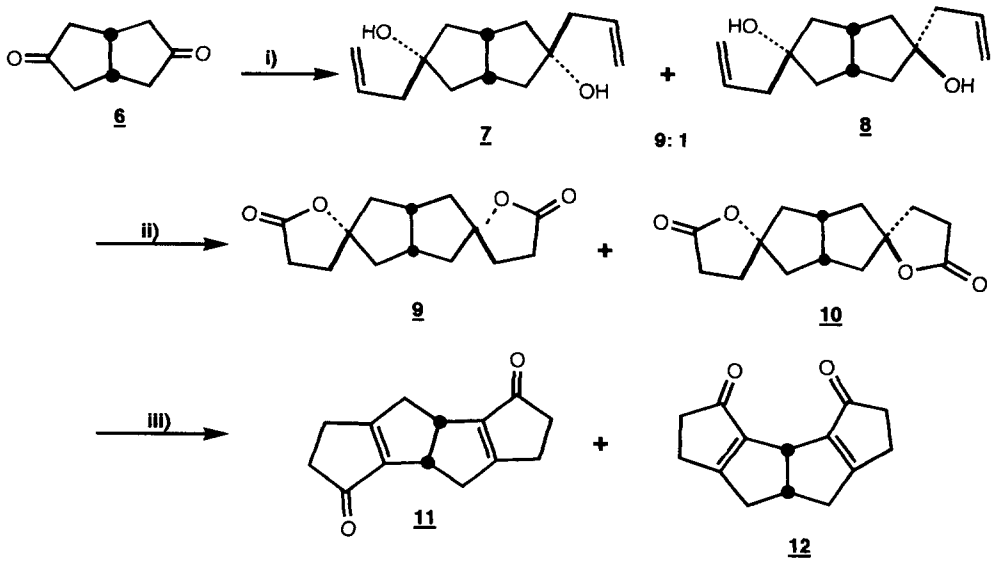
retrosynthetic analysis of this hexacyclic ketone involves tetracyclic intermediate **2**, which can be derived from readily available bicyclic dione **6** (Fig 1). Repetitive application of the present cyclopentane annulation strategy to dione **3** is expected to deliver a new C20-hexaquinane **5**.

Fig 1



The required bicyclic dione **6** was prepared in a three step sequence using Weiss-Cook reaction. This method involves the 2:1 condensation of dimethyl 1,3-acetonedicarboxylate with glyoxal under basic conditions.[6] Reaction of dione **6** with excess of allylmagnesium bromide gave the homoallylic alcohols **7** and **8** (9:1, 89%) (Scheme 2). The major compound **7**, m.p., 82-84°C and minor compound **8**, m.p., 104-106°C were isolated by column chromatography (silica gel). The structure of these isomeric alcohols has been deduced on the basis of NMR spectral data. The IR spectrum of the major compound indicated the presence of hydroxyl group at 3410 cm^{-1} and absence of carbonyl absorption. The ^1H NMR (300 MHz) spectrum exhibited the diagnostic feature of the allyl group [δ 5.08-5.15 (m, 4H); 5.8-5.96 (m, 2H)]. The major compound bears a C2 symmetry which is in agreement with the six-line ^{13}C NMR spectrum [δ 135.5, 118.5, 84.2, 47.2, 46.4, 42.6]. The unsymmetrical nature of the minor compound **8** was conformed by its 11 line ^{13}C NMR spectrum. The major compound was converted to symmetrical lactone **9**; [^{13}C NMR spectrum: δ 176.4, 94.1, 43.5, 38.7, 32.5, 28.9] by a hydroboration and oxidation sequence.[7] In the subsequent experiments the mixture of **7** and **8** were directly converted to the corresponding lactones **9** and **10** by one-pot operation (67% yield). The stereochemistry of the dilactone(s) (**9** and **10**) is of no consequence because the spiro centres would be destroyed in the next step to generate the tetracyclic enones. When the lactone mixture (**9** and **10**) was treated with 8% phosphorous pentoxide in methanesulfonic acid, tetracyclic enones (**11** and **12**) were formed

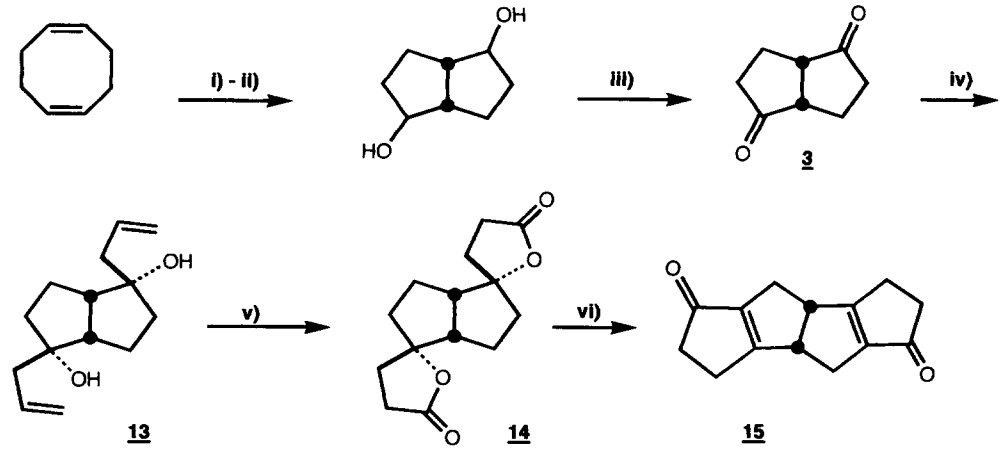
Scheme 2



6 7 8 9 10 11 12

i) Allyl bromide, Mg-ether/THF ii) $NaBH_4$, BF_3-Et_2O/THF ; Jones iii) MsOH, P_2O_5

Scheme 3



3 13 14 15

i) Pb $(OAc)_4$, $PdCl_2$, AcOH ii) KOH, MeOH iii) Jones iv) Allyl bromide, Mg-ether iv) $NaBH_4$, BF_3-Et_2O/THF ; Jones vi) MsOH, P_2O_5

in 2:1 ratio (combined yield 74%) [^{13}C NMR data, compound **11** : δ 203.7(s), 185.3(s), 149.1(s), 47.1(d), 41.0(t), 35.1(t), 25.5(t); compound **12** : δ 201.8, 185.4, 148.1, 51.9, 43.4, 40.8, 39.7, 25.5].

Along similar lines, *cis*-bicyclo(3.3.0)octane-2,6-dione **3**,[8] was converted to the tetracyclic enone **15** (Scheme 3). Reaction of **3** with allylmagnesium bromide gave homoallylic alcohol **13**,[9] which upon hydroboration and Jones oxidation gave the lactone **14**. Rearrangement of the dilactone **14** with methanesulfonic acid furnished tetracyclic enone **15**.[10] Utilization of **11**, **12**, and **15** towards the preparation of hexaquinanes **4** and **5** will be reported in due course of time.

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9. Only the major compound is shown in this scheme. ^{13}C NMR data of compound **13**: δ 134.8, 117.6, 79.5, 52.5, 43.7, 42.7, 20.5.
10. ^{13}C NMR data of compound **15** : δ 203.9, 186.2, 146.1, 52.6, 40.4, 27.4, 23.8.

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