Tetrahedron Letters,Vol.26,No.19,pp 2275-2278,1985 0040-4039/85 $3.00 + .00
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GENERAL APPROACH FOR THE SYNTHESIS OF POLYQUINENES VIA THE WEISS REACTION. PREPARATION OF THE CHIRAL TETRACYCLO [6.6.0.$0^{1,5}$.$0^{8,12}$]TETRADECANE-3,6,10,13,-TETRAENE

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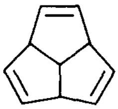
Summary: The aldol approach to construct the tetracyclic polyquinane skeleton of 12, followed by hydroboration and the HMPA mediated dehydration of four hydroxyl groups has resulted in the facile synthesis of the chiral polyquinene, tetracyclo[6.6.0.$0^{1,5}$.$0^{8,12}$]-tetradecane-3,6,10,13-tetraene 2. This method completely avoids the troublesome fragmentation reactions earlier encountered when the strained tetraone 9 was reacted with nucleophilic reagents.

Strained alkenes have been of interest to chemists since the beginning of this century.[1] This attention has been extended recently to compounds which contain unsaturated five-membered rings[2-5] termed "polyquinenes" in the present work.

During research concerned with the preparation of 1, 2 and 3, it became apparent that the Weiss reaction[6-8] provides one of the most rapid entries into unsaturated cyclopentanoid compounds. This occurs because the condensation leads to cis-bicyclo[3.3.0]octanediones with the 3,7-dioxo functionality in the diquinane framework suitably disposed for further functionalization. This has been demonstrated by our recent synthesis of triquinacene 1.[9]



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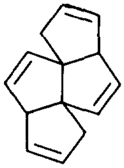

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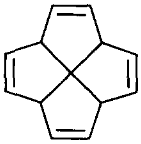

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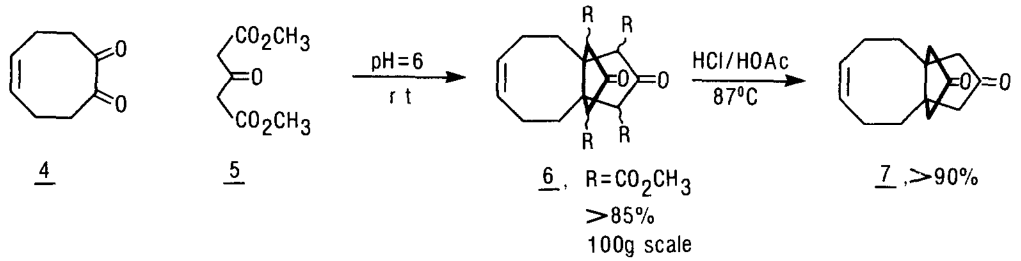
The present paper deals with the synthesis of the interesting chiral tetraene 2, while research is in progress in regard to preparation of 3.[5, 10, 11]

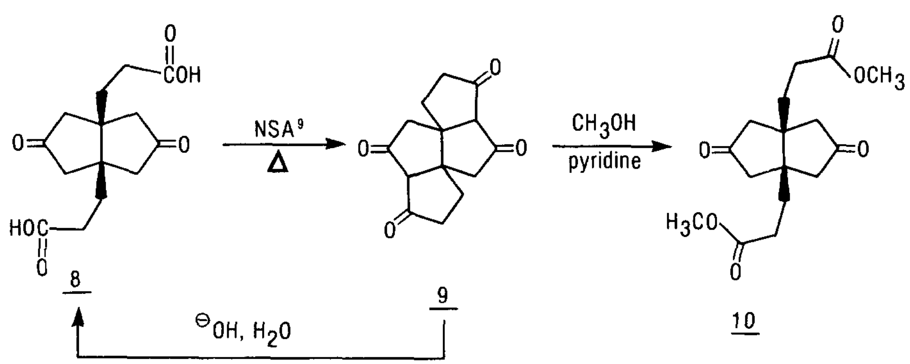
It was reported[8] earlier that the Weiss reaction between 4 and 5 gave 6 which on treatment with acid provided the propellenedione 7, as illustrated in Scheme I.

Scheme I



Oxidative cleavage of the double bond of 7 followed by acid catalyzed cyclization of 8 then generated the tetraketone 9.[8] Although this tetraone 9 appeared ideal for our purposes in regard to hydride attack on the carbonyl groups, treatment of this material with methanol in pyridine gave 10, the product of a retro-Claisen reaction.[12] In addition, stirring 9 in the presence of other nucleophiles, such as aqueous base, returned the starting 8 in regiospecific fashion *via* a retro-aldol reaction.

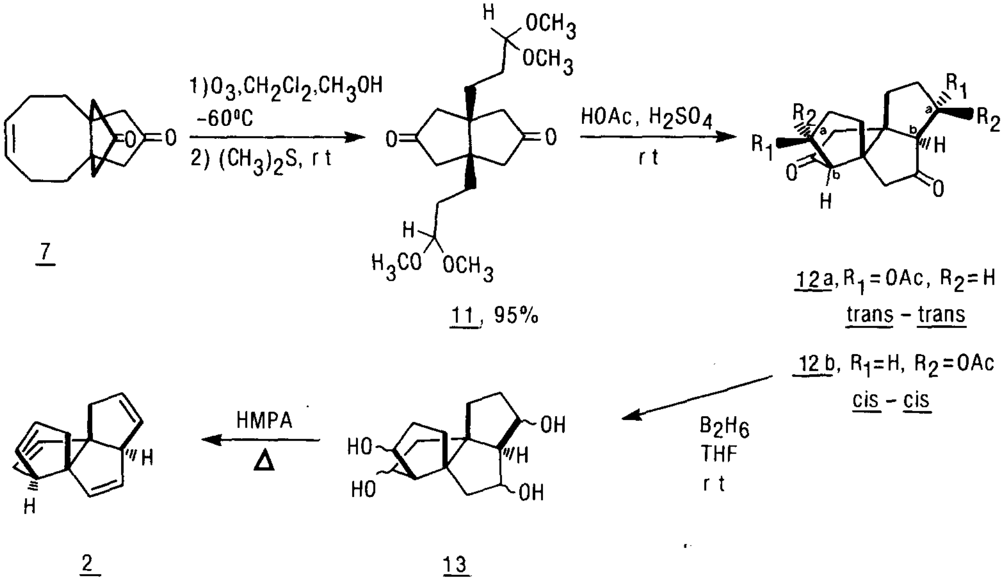
Scheme II



Examination of the conversion of 9 into either 8 or 10 clearly indicated that attack of a nucleophile on the carbonyl groups of 9 would generate a tetrahedral intermediate. This species could then collapse to an sp^2 carbon by fragmentation of the carbon-carbon bond located in the strained β-diketone system. To avoid the labile β-dicarbonyl groups of 9, the oxidation states of the two carboxylic acid carbons of 8 were lowered to those of the corresponding aldehydes. If cyclization were successful with a β-ketoaldehyde, then the β-hydroxy ketone could be trapped and the retro-aldol reaction completely avoided. As outlined in Scheme III, the execution of this approach occurred in decidedly simple fashion. Oxidation of the [6.3.3] propellene dione 7, available in one hundred gram quantities, with ozone followed by reductive work-up with dimethylsulfide gave a 95% yield of the bisacetal 11.[13] The protected dialdehyde was then stirred in acetic acid in the presence of a trace of concentrated sulfuric acid.[10] This acidic medium not only catalyzed the desired aldol condensation but also trapped the intermediate β-hydroxy ketones as the β-acetoxy derivatives 12a and 12b consequently prohibiting the retro-aldol reaction. The two diacetates 12a (*trans*-*trans*)[14] and 12b (*cis*-*cis*)[15] were obtained as a mixture of diastereomers in greater than 75% yield. Examination of the crude reaction mixture by carbon-13 NMR with suppressed NOE indicated that the two isomers 12a and 12b were present in the ratio of 1:3. Both 12a and 12b were shown to behave nearly identically under the conditions of CI mass spectroscopy with ions appearing at m/e 335 (P+1), 275 (-HOAc) and 215 (-2HOAc).

While the elemental analyses, 250 mHz proton and carbon NMR spectra were in agreement with the structures, as represented, it was necessary to employ 2-dimensional correlated (COSY) NMR spectroscopy to assign the structures unequivocally. In addition, examination of the proton spectrum of 12a in deuteriobenzene indicated that the coupling constant between proton $\underline{H}_a$ attached to the acetate bearing carbon and the proton at the ring juncture ($\underline{H}_b$) was very small (J = 2 Hz) while the coupling constant between $\underline{H}_a$ and $\underline{H}_b$ of 12b was 9 Hz. Based on the ^1H, ^{13}C and 2D NMR experiments it was proposed that 12a and 12b differed only in the stereochemistry at the site of the acetate functionality. In keeping with the Karplus[16] variation of the three bond coupling constant the first isomer has been determined to possess the C-O acetate bonds trans to the carbon bonds bearing the carbonyl group. The *cis*-*cis* isomer (12b) contains the two acetate groups, therefore, in the opposite configuration with respect to that of 12a. The mixture of acetates was then subjected to reaction with diborane. Reduction of the carbonyl groups followed by reductive cleavage of the acetate functionality provided, as expected, a mixture of tetrols represented by structure 13. At this point, it was decided to subject the mixture of tetrols to dehydration by simply heating in HMPA,[17] although at least one of the isomers had been purified to homogeneity. The product of this sequence, the desired tetraene 2,[18] was extracted from the HMPA with pentane and the material purified by chromatography on silica gel. While the mass spectrum, proton NMR and IR were in complete agreement with structure 2, the carbon spectrum was definitive. The carbon NMR spectrum

Scheme III



contained only seven lines in agreement with the C_2 symmetry of the molecule, moreover, these signals appeared at chemical shifts [40.08(t), 62.31(d), 67.11(s), 128.88(d), 130.08(d), 134.23(d) and 139.11(d)] consistent with the assignment. Conversion of 13 into 2 serves also to verify the structures of 12a, 12b and 13 since rearrangements are not expected to occur when HMPA is employed as the dehydrating agent.[17] More importantly, the successful execution of the aldol approach with the subsequent conversion of 13 into 2 without ring fragmentation serves to further support the versatility of the Weiss reaction for the preparation of gram quantities of strained polyquinenes and polyquinanes. The interesting properties of the tetraene 2 with regard to chirality and reactions with electrophiles including transition metal cations will be reported in due course.

Acknowledgement:

We thank the National Science Foundation (CHE-7910302) for generous financial support and Professor Eaton for his interest in this work.

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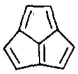
11. Polyquinenes i - iv are also of interest in this area.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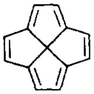
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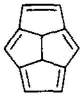
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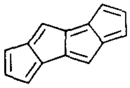
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13. 11: mp 110-111°C; ir (KBr) 1740 cm^{-1}; ^{13}C NMR (250 mHz, $CDCl_3$) 28.51(t), 28.86(t), 48.18(q), 49.18(s), 53.04(t), 104.32(d), 215.48(s); Mass spectrum (EI, 15 eV) 342(2.1), 310(1.1), 278(75.1), 246(100), 214(13).
14. 12a (trans-trans) mp 180-181°C; ir (KBr) 1741 cm^{-1}; ^{13}C NMR ($CDCl_3$) 20.81(q), 32.10(t), 33.41(t), 49.33(t), 54.92(s), 66.07(d), 78.69(d), 169.72(s), 214.60(s).
15. 12b (cis-cis) mp 162-163°C; ir (KBr) 1742 cm^{-1}; ^{13}C NMR (250 mHz, $CDCl_3$) 20.85(q), 32.51(t), 34.07(t), 52.28(t), 55.45(s), 62.01(d), 76.44(d), 169.69(s), 211.54(s).
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18. 2: oil; ir (neat) 3047, 2930 cm^{-1}; ^{1}H NMR (250 mHz, $CDCl_3$)δ; 2.15-2.35 (m,CH_2,4H) 3.40 (quintet, CH,2H) 5.50-5.70 (m,4H); ^{13}C NMR ($CDCl_3$) 40.08(t), 62.31(d), 67.11(s), 128.88(d), 130.08(d), 134.23(d), 139.11(d); Mass spectrum (EI, 15 eV), 182(59), 167(100), 149(58), 125(58).

(Received in USA 14 January 1985)