THE SYNTHESIS OF TRIQUINACENE VIA THE WEISS REACTION.[1]

Steven H. Bertz

AT&T Bell Laboratories
Murray Hill, New Jersey 07974

and

G. Lannoye and J. M. Cook*
Department of Chemistry
University of Wisconsin-Milwaukee
Milwaukee, Wisconsin   53201

Summary: A short, simple preparation of triquinacene 1 is based on four key steps: the Weiss reaction, high-yield monoalkylation of the resulting bicyclo[3.3.0] system, aldol cyclization of aldehyde 6 and HMPA-mediated dehydration of triol 8.

Although the first synthesis of triquinacene 1 was published in 1964 by Woodward, et al.,[2] a number of research groups have recently reported new syntheses.[3] Much of the renewed interest in 1 has been stimulated by attempts to convert it into the highly strained acepentalene.[4]   Our initial route to 1 via the Weiss reaction[1] involved the monoalkylation of the highly symmetrical cis-bicyclo[3.3.0]octane-3,7-dione which could at best be accomplished in only 45% yield. A number of chemists have reported difficulties in the selective destruction of the symmetry of the cis-bicyclo[3.3.0]octane-3,7-dione system.[5] Since the alkylation step was crucial to the success of the synthesis of 1 from glyoxal and 2 (Scheme I), as well as many other targets, we have studied ways to solve this problem. Recently, a high yield method for the symmetrical 2,6-dialkylation of the 2,4,6,8-tetraester derivative of cis-bicyclo-[3.3.0]octane-3,7-dione was developed in our laboratories.[6] During the course of this work, a method to monoalkylate the tetraester was discovered, which has permitted the synthesis of 1 via the Weiss reaction to be accomplished much more efficiently.

Scheme I

1

3a, R = Me
3b, R = t-Bu

SEVERAL STEPS

1. BASE
2. NEUTRAL.

2a, R = Me
2b, R = t-Bu
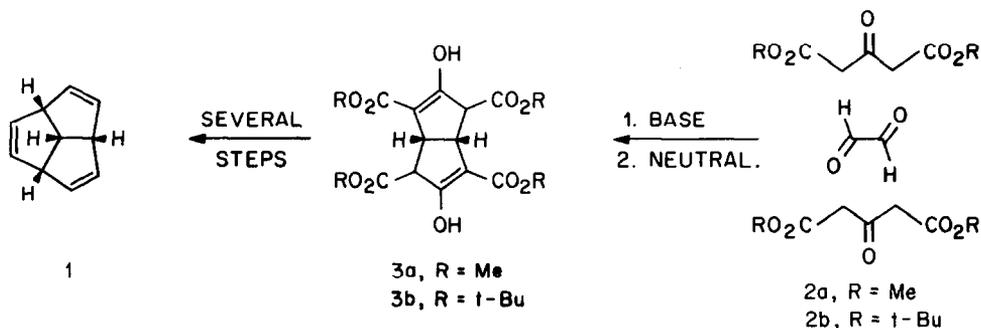
The cis-bicyclo[3.3.0]octane-3,7-dione system would appear to be an ideal starting material for the preparation of **1**.   Indeed, it contains 8 of the 10 carbon atoms necessary for construction of the carbon skeleton of **1**, and the 3,7-oxo groups in the diquinane framework are suitably disposed for annelation of the third ring and conversion to two of the double bonds present in **1**.   Equally important, tetraester derivatives **3** are available on greater than two hundred gram scale from the reaction of glyoxal with 3-oxoglutarates, **2**.[7]

Outlined in Scheme II is the improved route to **1** which employs the bulky t-butyl ester groups of **3b** in order to obtain high yields of monoalkylated product.   Glyoxal was reacted with di-t-butyl 3-oxoglutarate **2b** in an alkaline medium to provide the bisenol **3b**.[7],[8]   The bisenol nature of compounds such as **3** has been demonstrated by Camps[9] for the ethyl ester and by Bertz et al. for **3a**.[8]   In order to block two of the four potential sites of alkylation in **3b**, the bisenol ether **4** was prepared in virtually quantitative yield by stirring **3b** with diazomethane.   Stirring **4** with 2.3 equivalents of KH at room temperature followed by allyl iodide at -58°C provided the desired monoalkylated cis-bicyclo[3.3.0]octane-3,7-dione **5**, after hydrolysis and decarboxylation, in 90% overall yield from **3b**.   The mono-allyl derivative **5** was isolated as a mixture of stereoisomers accompanied by less than 2% of dialkylated material.   When cis-bicyclo[3.3.0]octane-3,7-dione was treated with 2.2 equivalents of lithium diisopropylamide, followed by addition of 3 equivalents of allyl iodide at -60°C, at best a 45% yield of **5** was obtained.

Scheme II

4

5

6

7

8
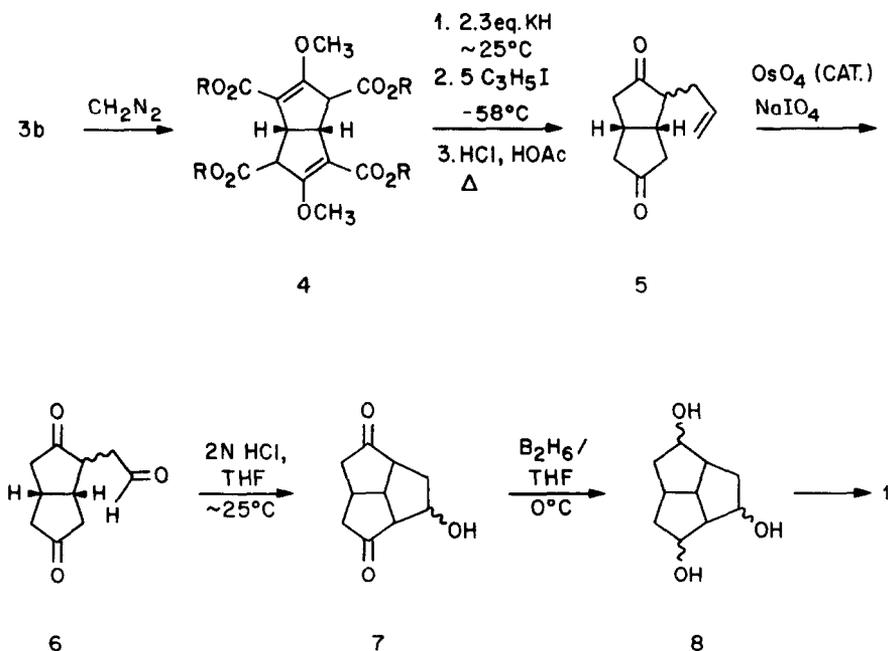
The mono-allyl derivative **5** was isolated as a mixture of <u>endo</u> and <u>exo</u> stereoisomers, with the seemingly less desirable <u>exo</u> isomer predominating by 3:1(^{13}C-NMR, suppressed NOE). The double bond of **5** was cleaved in 90% yield by $OsO_4/NaIO_4$,[10] providing the mixture of aldehydes **6**, which was subjected to aldol cyclization. Although the initial equilibrium concentrations of <u>endo</u> **6a** and <u>exo</u> **6b** (1:3) favored the <u>exo</u> isomer **6b**, which cannot cyclize, a 92% yield of **7** can be obtained by running the reaction under equilibrating conditions (2N HCl/THF). Once the aldol reaction of **6a** has taken place, the new carbon-carbon bond is very stable and reversion of β-hydroxyketone **7** back into **6** does not readily occur. Apparently, the equilibration is slow, as the reaction takes several days to go to completion.

Reduction of the two carbonyl groups present in **7** under basic conditions ($NaBH_4$, CH_3OH) resulted in the retroaldol reaction to **6** followed by reduction of the three carbonyl groups of the ring-opened product. In contrast, reduction with B_2H_6,[11] a Lewis acid, resulted in formation of the desired triol **8**, isolated as a mixture of stereoisomers in 92% yield. Formation of aldehyde **6**, cyclization to aldol **7**, and reduction to the triol **8** were all carried out in better than 90% yield.

In agreement with a report by Monson[12] and recent work from our laboratory,[13] the triol **8** was heated in refluxing HMPA (coldfinger condenser, -78°C) to furnish an 80% yield of **1** accompanied by 8% of isotriquinacene.[14] Triquinane triol **8** was also converted (mesyl chloride, py) into the trimesylate, and the three mesylate groups were then eliminated according to the alumina procedure of Deslongchamps[15] to provide **1** (80%) accompanied by less than 2% of isotriquinacene. The spectral and physical properties of **1** prepared by our route from **2** and **3** were identical to those reported in the literature.[2,3]

The benefits of our improved route are summarized below. All of the steps outlined in Scheme II can be run on better than fifty gram scales, and the yields in all but the last reaction are better than 90%. Since the starting <u>cis</u>-bicyclo[3.3.0]octane-3,7-diones **3** can be prepared on large scale (>200g) via the Weiss reaction, it is felt that this route will become useful for the preparation of multigram quantities of **1**. Moreover, the compounds are extremely easy to handle and often need little purification before proceeding to the next step. The monoalkylation of the tetraester **4** is a significant improvement over the alkylation of <u>cis</u>-bicyclo[3.3.0]octane-3,7-dione,[5] and should make its derivatives even more useful in other areas of synthesis.[16] Furthermore, the aldol condensation **6** to **7** is noteworthy, for it clearly demonstrates that the unfavorable equilibrium between **6a** and **6b** can be overcome. The HMPA-mediated dehydration permits the elimination of three molecules of water from the triol **8** in one step.

Substitution of other 1,2-dicarbonyl compounds for glyoxal (Scheme I) in this sequence should also lead to the corresponding substituted triquinacene derivatives. In addition, our approach to **1** may be extended to the preparation of strained tetraquinenes[4] related to **1** as well as other polyquinenes.

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