Tetrahedron Vol. 37, No. 25, pp. 4521 to 4542, 1981
Printed in Great Britain.

0040-4020/81/254521-22$02.00/0

GENERAL APPROACH FOR THE SYNTHESIS OF POLYQUINANES. FACILE GENERATION OF MOLECULAR COMPLEXITY VIA REACTION OF 1,2-DICARBONYL COMPOUNDS WITH DIMETHYL 3-KETOGLUTARATE

R. MITSCHKA, J. OEHLDRICH, K. TAKAHASHI and J. M. COOK*
Department of Chemistry, University of Wisconsin–Milwaukee, Milwaukee, WI 53201, U.S.A.

U. WEISS*
Laboratory of Chemical Physics, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, Bethesda, MD 20205, U.S.A.

and

J. V. SILVERTON
National Heart, Lung and Blood Institute, Bethesda, MD 20205, U.S.A.

(*Received in U.S.A.* 3 *April* 1981)

Abstract—The condensation of dimethyl 3-ketoglutarate **1** with 1,2-dicarbonyl compounds provides access to the polyquinane derivatives tricyclo[6.3.0.$0^{1,5}$]undecane - 3,7,9 - trione **27**, tricyclo[3.3.3.$0^{1,5}$]undecane **31**; tetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$] - tridecane - 2,6,8,12 - tetraone **41**; tetracyclo[6.6.0.$0^{1,5}$.$0^{8,12}$]tetradecane - 2,7,9,14 - tetraone **44**; and the tetracyclo[5.5.1.$0^{10,13}$]tridecane triones **5b** and **6b**. The unique structure of staurane tetraone **41** has resulted in spontaneous resolution of the two antipodes on crystallization from DMF. In addition, examination of the crystal structures of tetraones **41** and **44**, in terms of strain energy, coupled with the steric accessibility of the β-diketone functionality contained in **41** and **44** have been employed to explain why tetraone **44** and trione **27** undergo a retro-Claisen reaction (CH_3OH) more rapidly than staurane tetraone **41**.

The synthesis, physical properties and chemical reactivity of di- and polycyclic condensed ring systems composed of cyclohexane units have long been the object of intense study. In contrast, relatively little attention has been paid until recently to the analogous cyclopentanoid systems. Yet questions related to conformation, chemical behaviour, and perhaps pharmacological action of such compounds definitely deserve investigation. In addition, substances with carbon skeletons derived entirely, or in part, from di- and tricyclopentanoid systems have been found in nature; discovery of many additional compounds of this type may be confidently expected.

We have been involved for some time[1a,b] in the development of a general method for the preparation of polyquinanes, and some of the systems of interest for the initial phases of this investigation are depicted in Fig. 1. Our synthetic strategy was based on the earlier observation[2] that two molecules of dimethyl 3-ketoglutarate **1** reacted with one molecule of glyoxal **2** in aqueous acidic solution to provide modest and somewhat erratic yields of tetramethyl *cis* - bicyclo[3.3.0]octane - 3,7 - dione - 2,4,6,8 - tetracarboxylate **3**,[3] a substance which had been obtained previously by a much more involved procedure.[4] Acid-catalyzed hydrolysis, followed by spontaneous decarboxylation of the resulting β-ketoacids gave *cis* - bicyclo[3,3,0]octane - 3,7 - dione **4**. The reaction of **1** with 1,2-dicarbonyl compounds other than **2** established[2] the generality of the process. For example, pyruvaldehyde and biacetyl gave the 1-monomethyl and 1,5-dimethyl analogs of **3**, respectively, while alicyclic 1,2-diones provided the corresponding [n.3.3] propellane derivatives.

In a synthetic (not electronic) sense, the generation of two five-membered rings from reaction of **1** and **2** parallels the generation of two six-membered rings in the Diels–Alder reaction, as illustrated at the bottom of Scheme 1. Consequently this facile production, albeit in low yield (15%), of two polyquinane rings from aliphatic precursors led us to investigate this condensation under a variety of conditions in order to explore the synthetic potential of this process.

Several other β-ketoesters were produced from **1** and **2** which contributed to the complex nature of this process; these compounds **5a**,[5] **6a**,[6] **7a**,[7] **8a**,[8] and **9a**[8] are illustrated in Scheme 2. The endocyclic and exocyclic triketones **5a**[5] and **6a**,[6] respectively, are members of the polyquinane series represented by structure F (see Fig. 1). The structures of the polycyclic products **5a–7a**, as well as their corresponding hydrolysis products **5b–7b**, have been confirmed by spectroscopy[5–8] and in some cases by X-ray analysis.[5,7] In addition, the structures of the trione **8b** and the cage compound **9b** have been reported in an elegant piece of work by Bertz.[8]

Careful examination of structures **5a–8a** in a retrosynthetic sense, provided the first clue to the low yield of **3** in the earlier work for many of the β-ketoesters **5a–8a** appeared to be reaction products of **1** and **2** with **3**.[9] Apparently, dimethyl β-ketoglutarate **1** and glyoxal **2** were present in equilibria with intermediates in the reaction medium which eventually led to the numerous products shown in Scheme 2.

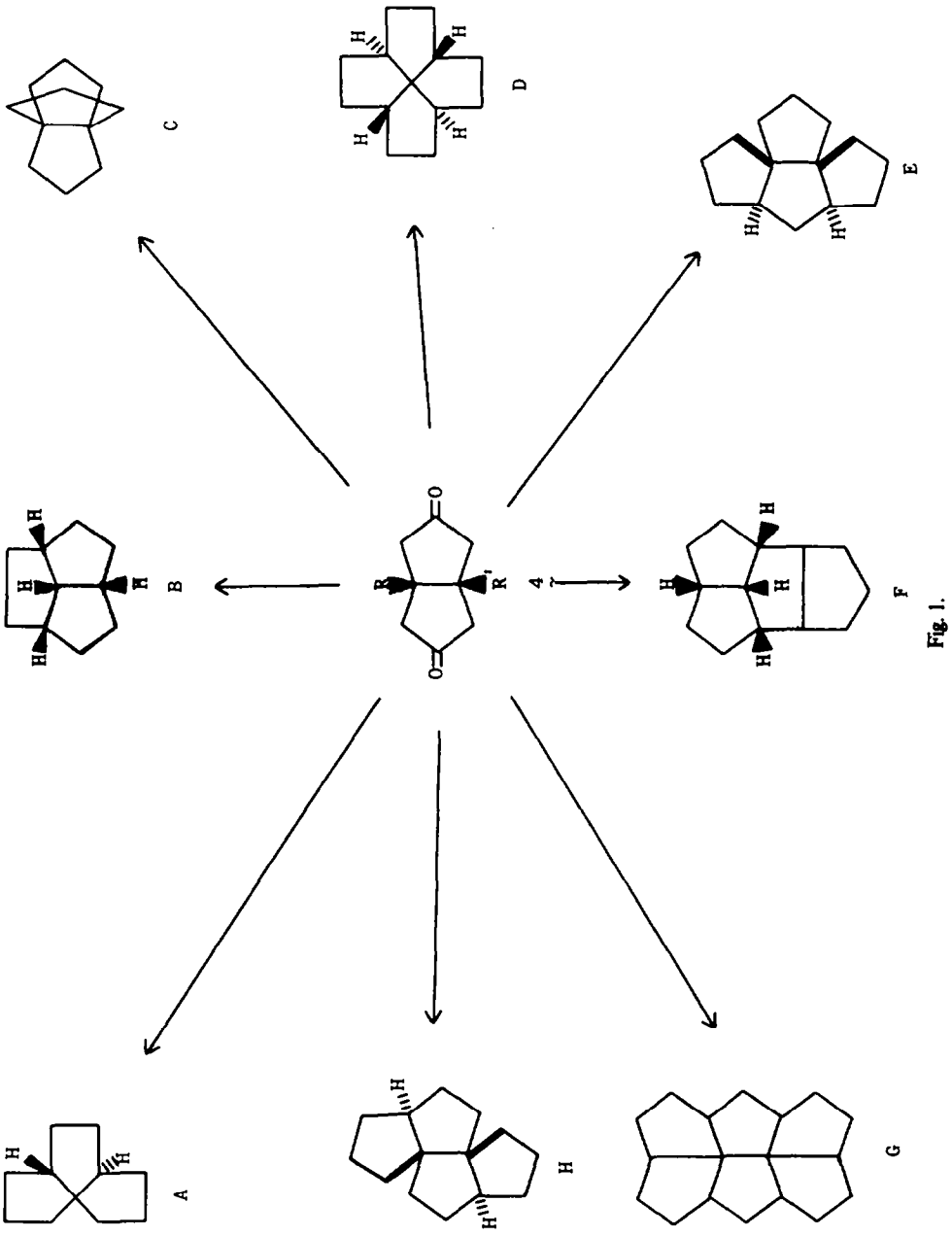
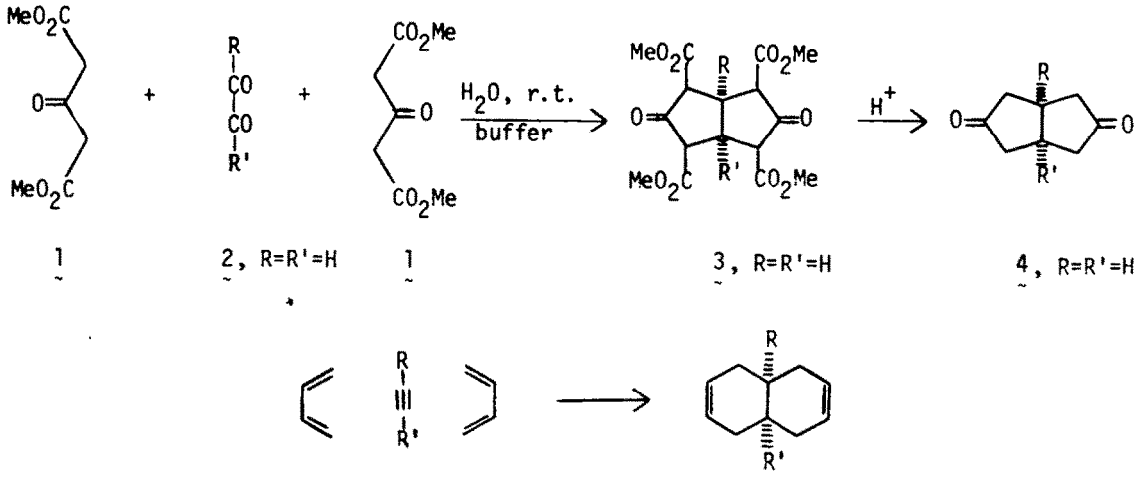
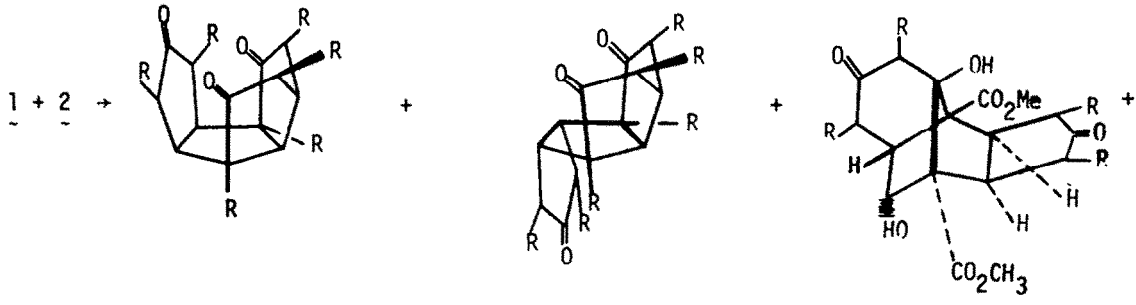


Fig. 1.



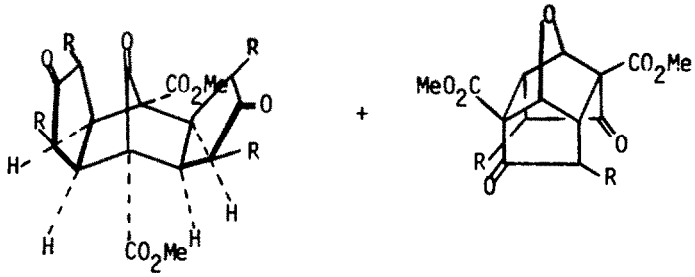
1 2, R=R'=H 1 3, R=R'=H 4, R=R'=H

Scheme 1.



5a, R=CO_2CH_3 6a, R=CO_2CH_3 7a, R=CO_2CH_3

5b, R=H 6b, R=H 7b, R=H

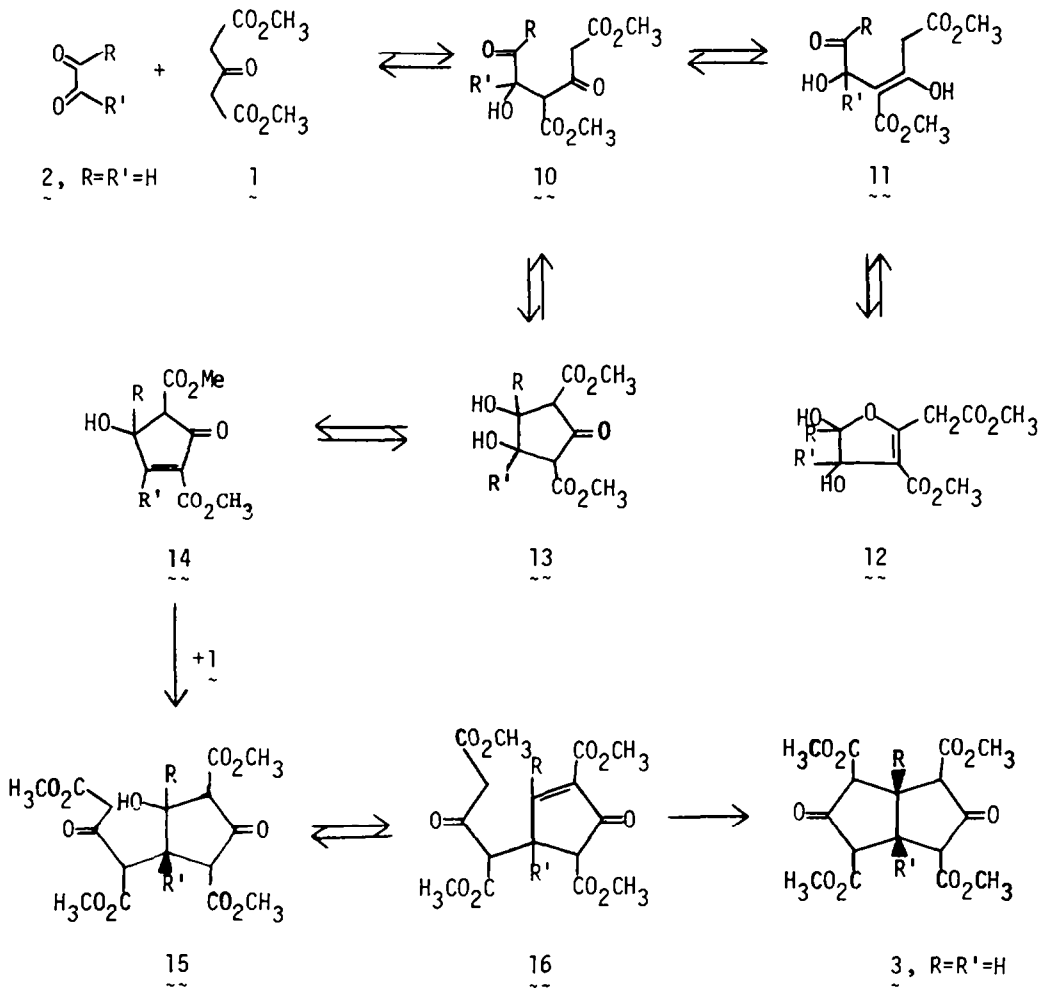


8a, CO_2Me 9a, R=CO_2CH_3

8b, R=H 9b, R=H

Scheme 2.

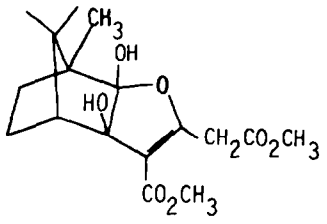
In an attempt to improve the yield of the desired bicyclo[3.3.0]octane system in the condensation it was decided to explore the mechanism of this sequence to determine what parameters had a direct effect on the formation of **3**. The mechanism initially proposed[9] centered on the aldol condensation of one molecule of glyoxal (or equivalent) with one molecule of dimethyl 3-ketoglutarate to generate the β-hydroxy-ketone **10**. This hydroxy-ketone could then undergo a second aldol reaction to provide **13** followed by loss of a molecule of water to generate the key intermediate **14**, a 4 - hydroxycyclopent - 2 - enolone. This material **14** would



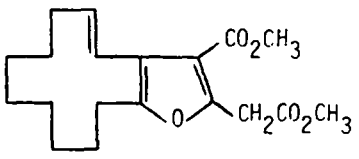
Scheme 3.

not be expected[10] to lose another molecule of water since this would generate a high-energy cyclopentadienone; however, the quite reactive enone system of **14** would be an ideal Michael acceptor. Addition of a second molecule of **1** to the enone **14** followed by the series of steps outlined in Scheme 3 (**14**→**15**→**16**) would provide **3**.

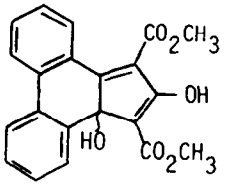
Much time and effort has been spent in our laboratory in an attempt to isolate intermediates in this sequence, especially the 1:1 adduct similar in structure to the 4-hydroxycyclopentenolone **14**. In the earlier work,[2,9] when 1,2-diones such as glyoxal, biacetyl, pyruvaldehyde, cyclohexane - 1,2 - dione, etc. were reacted with **1**, no 1:1 adducts were either isolated or trapped. Use of a hindered 1,2-dione, however, such as camphorquinone, which could not add a second molecule of **1**, did provide a 1:1 adduct. This compound was shown to be a dihydroxydihydrofuran **17** rather than a 4 - hydroxycyclo - pentenolone. Moreover drastically different reaction conditions provided the furan (from cyclododecanedione and **1**, pTsA, Δ) **18**;[11] again a molecule which could be derived from a dihydroxydihydrofuran. The isolation of furans **17** and **18** coupled with the lability of **17**[9] toward retro-aldol reactions, led us to modify our initial mechanistic hypothesis to include equilibration between the dihydroxyfuran **12** and the β-hydroxy ketone **10** *via* the enol **11**, as depicted in Scheme 3. It now became apparent that compounds such as **11** and **12** might well be present during the reaction sequence, as well as the other products depicted in Scheme 2. Efforts to isolate a β-hydroxycyclopentenolone were eventually rewarded when 1,2-diones such as benzil and phenanthrenequinone were stirred with **1**; however, the condensation did not take place until strongly alkaline conditions were employed, and hydroxycyclopentenolones such as **19**[12] do not add another mole of **1** to the enone.[13] Even stronger evidence has been forthcoming recently for the origin of intermediates such as **14** in the condensation. Careful examination of the structure of the cage compound **9b**[8] clearly indicated this molecule can be derived by an intermolecular condensation between two molecules of **14**; furthermore, our efforts to trap a 1:1 intermediate in the alicyclic area have recently resulted in the characterization of the crystalline 4-hydroxycyclopentenolone **21**[14] (from bis-cyclohexyldiketone). The preparation of furans **17** and **18** and enones **19** and **21**,



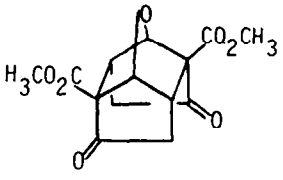
17



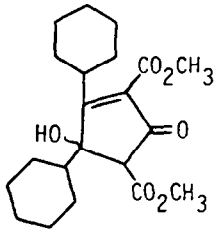
18



19



9b



21

Scheme 4.

coupled with the isolation of **9b** from the original reaction of **1** with **2**, serve to corroborate the mechanistic scheme proposed earlier,[9] as outlined in Scheme 3.

Based on the findings presented above an extensive investigation of the reaction of **1** with **2** under a variety of conditions (principally in aqueous buffer) has been carried out.[6,8,9,15a] In fact, when **1** and **2** were reacted in alkaline medium[8,15a] only the desired tetramethyl *cis* - bicyclo - [3.3.0]octane - 3,7 - dione - 2,4,6,8 - tetracarboxylate **3** was produced which provides for the first time facile entry into the parent ring system. It is important to mention that in alkaline solution (pH = 8.3 or $CH_3OH/NaOH$)[8,15a] none of the byproducts illustrated in Scheme 2 were observed by tlc, in contrast to the condensation in acidic medium. Recent evidence[15b] suggests the mechanism, in the case of glyoxal, in alkaline media may be slightly different than that which occurs at acidic pH.

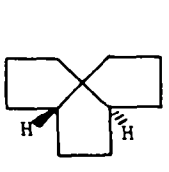
One further point needs to be made regarding the condensation described in the preceding pages with regard to its potential as a synthetic method: The sequence **1** plus **2** has the merit of complete stereospecificity; it leads to derivatives of *cis* - bicyclo[3.3.0] - octane in every case investigated to date. The configuration of the parent compound **4** was first demonstrated by Wanzlick[16] through conversion to the known *cis* - bicyclo[3.3.0]octane.[17] Since this hydrocarbon had been shown by Barrett and Linstead[18] to be more stable, thermodynamically, than its *trans*-stereoisomer by 6–7 kcal/mol, this stereospecificity is not surprising. The mild conditions under which the condensation of **1** with **2** occurs take definite advantage of this thermodynamic preference for the *cis*-isomer. In fact, the same *cis* configuration has been demonstrated for the ring-junctures of all compounds discussed in this paper wherever evidence is available[5,7,19]; generally data have been obtained by X-ray crystallography (see Fig. 2).[5,7,19]

Armed with the realization that condensation of **1** and **2** was stereospecific, and that conditions could be designed to facilitate synthesis of the simplest member **4** of the class in high yield,[8,15a] we studied the synthesis of a number of ring systems A–H, illustrated in Fig. 1. Although studies directed toward construction of all the structures in Fig. 1 are in progress, only the successful entry into ring systems A, C, D, F and H will be described here, while the conversion of these molecules to the parent hydrocarbons will remain a topic for future reports.

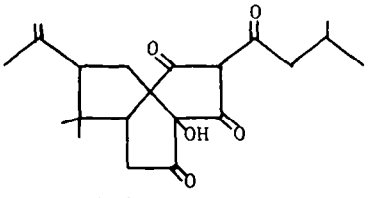
RESULTS

System A. Tricyclo[6.3.0.0^{1,5}]undecane-3,7,9-trione **27**

Initial efforts directed toward construction of ring systems depicted in Fig. 1 centered on the synthesis of the tricyclic trione **27** (System A), as illustrated in Scheme 5. This arrangement of three fused, five-membered rings is present in isocomene,[20a] tricyclodehydroisohumulone, a



A

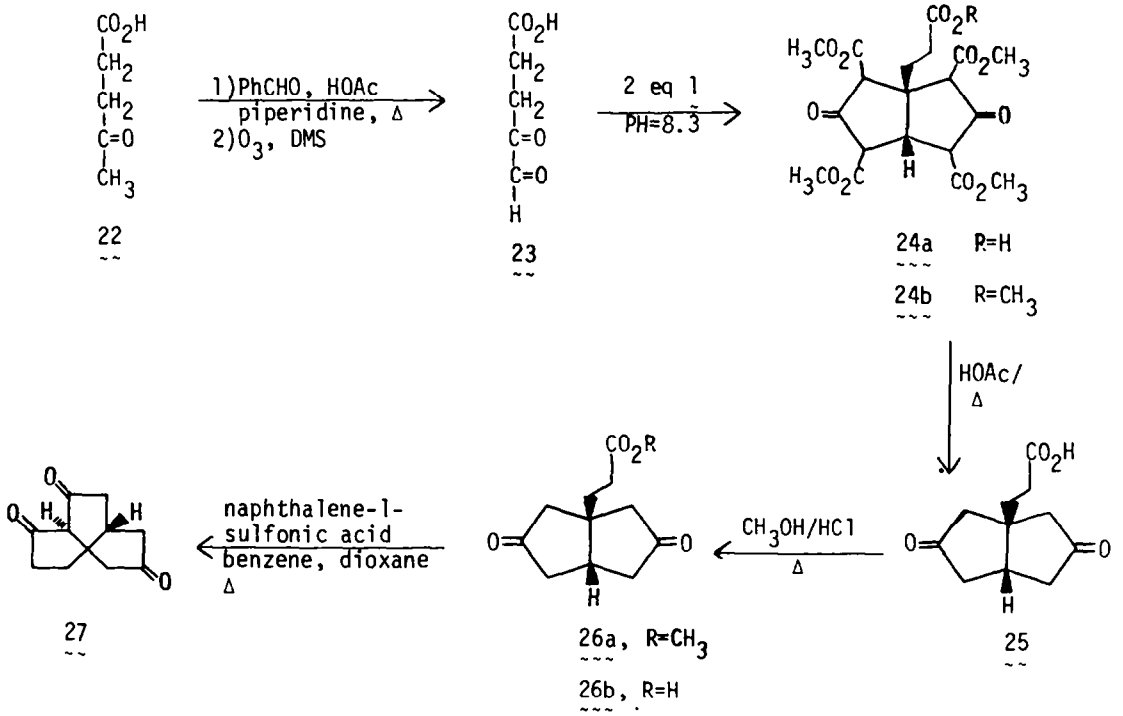


tricyclodehydroisohumulone

constituent of beer,[20b] and this system also comprises a portion of the structure of retigeranic acid.[21] The 1,2-dioxo derivative **23** required for synthesis of the trione **27** had been prepared earlier by Wolff from 3,5 - dibromolevulinic acid.[22] It was, however, found more convenient to convert levulinic acid to the 5-benzylidene derivative, according to the method of Zaheer,[23] followed by ozonolytic cleavage[24] of the newly generated benzylidene double bond. This sequence provided 4,5-dioxopentanoic acid **23** in very good overall yield from

22. The dioxo monoacid **23** was subsequently stirred at room temp with two equivalents of **1** in citrate-phosphate buffer (pH = 5.6) to generate a 70% yield of the 1-substituted bicyclo[3.3.0]octanedione tetracarbocylate **24a**. This is an extremely facile and productive manner in which to build up molecular complexity in the polyquinane area, as pointed out earlier.[1b] Moreover when the same reaction was performed in alkaline medium (bicarbonate solution, pH = 8.3) an 80% yield of the desired *cis* - bicyclo[3.3.0]octane system **24a** was realized. This is in agreement with the improved yields of the parent system **3** when prepared at alkaline pH.[8,15a] The tetra-ester **24a** was converted to the penta-ester **24b** (CH_3OH, HCl) in quantitative fashion, while hydrolysis of **24a** gave the key 1,3'-propanoic acid - *cis* - bicyclo[3.3.0] - octane - 3,7 - dione **25**. The NMR, IR and mass spectra of these compounds were in complete agreement with the assigned structures (see Experimental).

third ring may have formed but had undergone nucleophilic ring-opening during the workup. In a somewhat similar β-diketone, *cis* - bicyclo[3.3.0]octane - 2,8 - dione, Eaton had observed rapid ring opening on treatment with aqueous base.[25] It was decided, therefore, to employ conditions for the cyclization which completely excluded nucleophiles from the reaction medium. This would prohibit the retro-Claisen reaction from competing effectively with formation of the desired trione **27**. Previously Loewenthal and Neuwirth[26] had reported the successful cyclization of α-ketoacids, via the enol, catalyzed by a sulfonic acid. This method appeared very attractive since the nucleophilic byproduct (water) could be continuously removed by azeotropic distillation. This approach was found to be quite successful; heating the monoacid **26b** in benzene–dioxane solution in the presence of a catalytic amount of naphthalene - 1 - sulfonic acid furnished a good yield of crystalline tricyclo[6.3.0.0^{1,5}]undecane - 3,7,9 - trione **27**; no attempts to



Scheme 5.

Many efforts were made to form the third 5-membered ring of the desired system (A). Initially, the penta-ester **24b** was treated with sodium methoxide in dry methanol; however, only starting material was recovered. This was not surprising, since the tricyclic trione prepared from the penta-ester **24b** would be devoid of a hydrogen atom at the newly formed β-diketone ring juncture, and therefore could not form a stable enolate. This would permit the attack of methoxide anion on the β-diketone in a retro-Claisen fashion to regenerate **24b** instead of the desired trione. In an analogous fashion the mono-ester **26a** was treated with bases under a variety of conditions ($NaOCH_3$, CH_3OH; $NaOCH_3$, benzene; NaH, THF); however, these procedures always returned **26a**.

Since starting material was recovered continually from the base-catalyzed sequence, it occurred to us that the maximize this yield have been made to date. The trione was purified by column chromatography on silica gel (benzene/ethyl acetate, gradient elution). During and after the chromatography the trione **27** must be kept away from nucleophilic solvents for the β-diketone bond undergoes a retro-Claisen reaction on stirring of **27** in methanol (see below). Analogously, the trione is regiospecifically transformed to the monoacid **26b** when treated with aqueous bicarbonate.

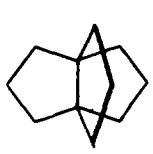
The structure proof for **27** was relatively straightforward and based primarily on spectroscopy. The IR spectrum of **27** contained bands at 1760.8 and 1734.8 cm^{-1}, while a weak band at 1707 cm^{-1} was indicative of the small amount of enol present in this β-diketone system. These bands are similar to those of the β-triketone, *cis,syn,cis* - tricyclo[6.3.0.0^{3,7}]undecane - 2,4,11 - trione,

reported by Eaton.[25] Further proof for the assignment was obtained on examination of the ^{13}C-NMR spectra of the monoacid **26b** and the triketone **27** (see Experimental). In the carbon spectrum of **26b** the signal for the carboxylic acid carbon appeared at 177.7 ppm; however, on conversion of this compound to **27**, this resonance line disappeared and a new signal was observed at 206.5 ppm. This observation is in complete agreement with the formation of the third 5-membered ring; the other signals were consistent in number and chemical shift for a structure with the symmetry (C_s) of **27**.

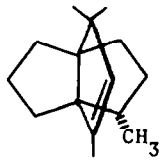
No direct evidence on the stereochemistry of ring systems in compounds **24–27** is available other than carbon NMR data; we formulate them as *cis*-compounds on the basis of the preferred thermodynamic stability of the *cis* - bicyclo[3.3.0]octane system alluded to earlier.[18] Furthermore, X-ray crystallographic analysis of the *endo*-stereoisomer **5b** (Scheme 2) of the tetracyclic triketone obtained from **1** and glyoxal indicated *cis* stereochemistry at all ring junctions.[5] The tricyclo[6.3.0.$0^{1,5}$]undecane system present in the pentacyclic sesterterpene, retigeranic acid,[21] has also been shown to have this *cis*-stereochemistry. While a few other syntheses of tricyclo[6.3.0.$0^{1,5}$]undecane systems have appeared over the last several years,[26] to the authors' knowledge the five-step synthesis described in Scheme 5 is the shortest, most direct route to a simple system such as **27**. The lability of the trione **27** toward aqueous base, and the regiospecific retro-Claisen ring opening of **27** in the presence of methanol will be discussed below.

System C. Tricyclo[3.3.3.$0^{1,5}$]*undecane*

Another system chosen as a target for synthesis can be formally recognized as the [3.3.3]propellane **31** (C, Fig. 1). Although this symmetrical structure was interesting on its own merit, the fact that this hydrocarbon comprises the skeleton of the natural sesquiterpene modhephene[29] provided further impetus for construction of



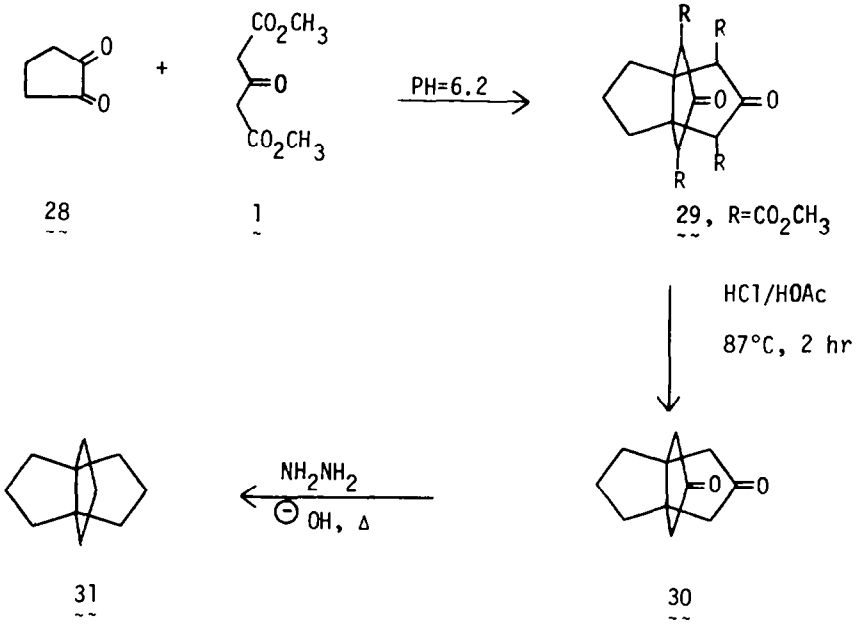
C



modhephene

such a system. The ability to generate rather intricate polycyclopentanoid hydrocarbons again by way of the condensation of 1,2-diones with **1** can be amply illustrated by the three-step synthesis of the [3.3.3]-propellane (see Scheme 6).

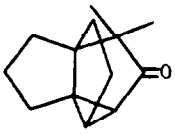
Cyclopentane - 1,2 - diones are somewhat labile in aqueous acidic or basic media;[30a,b] consequently the condensation of cyclopentane - 1,2 - dione **28** with **1** in acidic buffer (pH = 5.6) provided initially[2] only 20–40% yields of the [3.3.3]propellane tetramethyltetracarboxylate **29**, moreover, yields were decidedly lower at pH = 8.3. The corresponding condensation with cyclohexane - 1,2 - dione had been carried out in better than 80% yield [2,31] which suggested that the lability of the dione **28** lies at the root of the problem. The tetracarboxylate **29**, on hydrolysis, was converted to the propellane dione **30** which was subsequently subjected to Wolff–Kishner reduction to generate the [3.3.3]propellane **31** (C, Fig. 1). Several improvements in the sequence need to be mentioned. The yields of the 1:2 adduct **29** have been increased by addition (small portions) of the dione **28** to an excess of glutarate **1** at pH = 6.6 which circumvents the lability of said dione. In addition, the temperature of the medium during conversion of **29** to **30** was found to be a critical factor; for if this temperature was maintained at or near 87° the yields of **30** were observed to range from 87–90% (see Experimental for details). Finally, the starting dione **28**, previously prepared in poor yield by the acyloin method,[32] can now be obtained readily by the



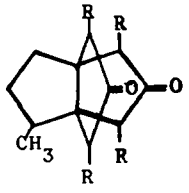
Scheme 6.

oxidative cleavage of 2-cyclopentylidene cyclopentanone developed in our laboratories.[33] The sequence of transformations outlined in Scheme 6 has also been employed to synthesize the [4.3.3], [6.3.3] and [10.3.3]propellanes.[31]

By use of the technology outlined in Scheme 6, the [3.3.3]-propellane derivatives **32** and **33** have been prepared.[34] The cyclopropyl ketone **32** is available in seven steps from **28** while 2 - methyl - 6,8,9,11 - tetramethyl tetracarboxylate **33** was obtained in one step from reaction of **1** with 3 - methyl - 1,2 - cyclopentanedione. The chemistry of these latter two systems will be reported elsewhere.[34]



32

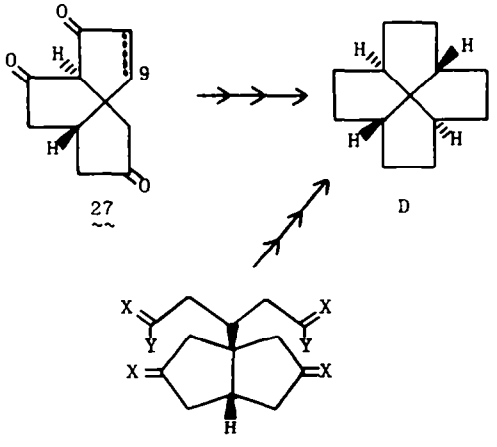


33, R = CO_2CH_3

System D. Tetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$]*tridecane* - 2,6,8, 12 - *tetraone* ("*staurane tetraone*")

In the previous syntheses described here, the emphasis was placed on construction of polyquinane ring systems composed of three fused five-membered rings; however, the concept of a "general approach" dictates that the method must be capable of extension to more complex systems. To further explore the potential of the reaction of 1,2 - dicarbonyl compounds with dimethyl 3-ketoglutarate **1** the tetracyclic system designated D was chosen as the next carbocycle for study. Not only was a considerable amount of interest generated in D because of the high degree of symmetry (D_{2d} point group) inherent in the molecule, but a suitably functionalized compound related to D might provide entry into molecules which house a planar tetracoordinate carbon atom.[35] In addition, when work in this area began no report of a carbocyclic molecule related to D had appeared; therefore, the condensation of 1,2-dicarbonyl compounds with **1** might provide the first access to this ring system.

Retrosynthetic analysis of the structure of D clearly



27 D

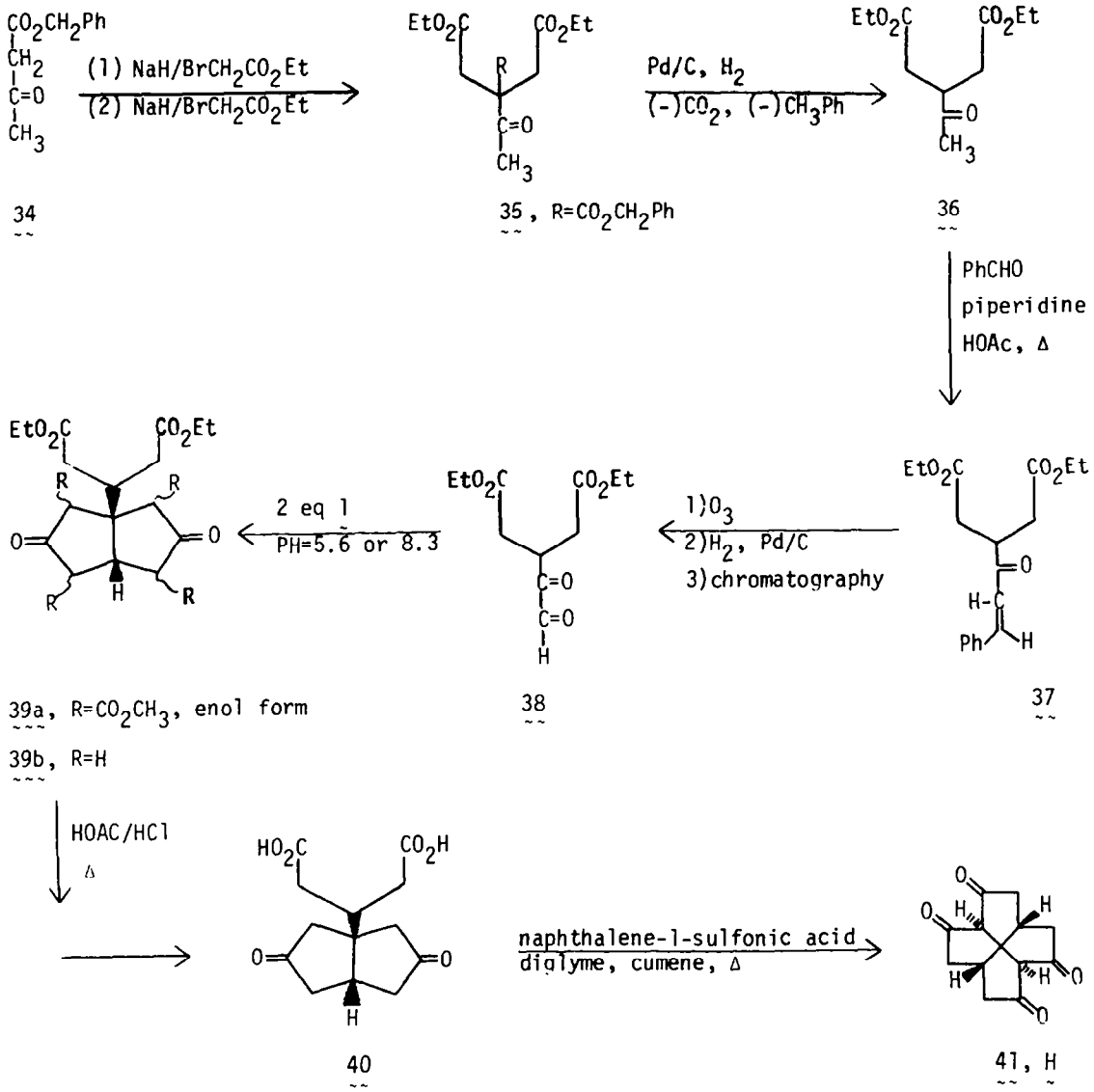
40, X=O, Y=leaving group

delineated two possible routes of attack for entry into such a system. The most obvious was the conversion of the previously prepared trione **27** to the carbocycle; however, the susceptibility of **27** to ring opening reactions (see above) militated against this approach in favor of a pathway which would take advantage of the D_{2d} symmetry of the molecule. The immediate goal was therefore preparation of the *cis* - bicyclo[3.3.0]octane - 3,7 - dione derivative **40** in the hope that the functional groups(=X) which remained would be capable of manipulation to the tetracyclic system.

The synthesis of tetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$]tridecane - 2,6,8,12 - tetraone **41** is outlined in Scheme 7. The readily available benzyl acetoacetate was chosen as the starting material; two successive alkylations with sodium hydride–ethyl bromoacetate[36] provided better than 70% overall yield of the symmetrical triester **35**. Catalytic removal of the benzyl function permitted generation of a β-keto acid intermediate which spontaneously lost carbon dioxide to furnish the desired diester **36** (93%).[37] This step was a vast improvement over the conversion of the triester **35** to the diester **36** by way of an hydrolysis/esterification sequence initially employed in our laboratory, since the hydrogenolysis route provided a very clean, distillable diester **36**. Previously several attempts under Knoevenagel–Schmidt conditions had been made to convert the methyl ketone function of the triester **35** to a benzylidene derivative[37] but these were unsuccessful presumably because the ketone function of **35** was too hindered for facile formation of an enamine with piperidine. Treatment of the diester **36** with benzaldehyde, however, under identical conditions furnished excellent yields of the desired benzylidene adduct **37**.[38] The benzylidene derivative **37** was then treated with ozone, followed by decomposition of the ozonide with dimethysulfide[24] which gave ethyl 3 - carbethoxymethyl - 4,5 - dioxopentanoate **38**, after chromatography, in 80% yield. If the ozonide was destroyed by catalytic hydrogenation (Pd/C) the yield of **38** was nearly identical; however, the chromatography was much easier to perform in the latter case.

With the preparation of the 1,2-dicarbonyl compound **38** well in hand, the stage was now set for the first of two critical steps required for preparation of the tetracyclic tetraketone **41**. Dissolution of two equivalents of dimethyl 3-ketoglutarate **1** in bicarbonate solution (pH = 8.3), followed by addition of one equivalent of the dicarbonyl compound **38** provided, after several days, a 51% yield of the desired 1:2 adduct, tetramethyl - 1,3' - diethylglutarate - *cis* - bicyclo[3.3.0]octane - 3,7 - dione - 2,4,6,8 - tetracarboxylate **39a** (see Experimental for important details). When the reaction was repeated in citrate–phosphate buffer (pH 5.6–6.0)[39] the yield of hexa-ester **39a** was 42%. It is believed the lower yield of **39a**, as compared to the results obtained during synthesis of **24a** (see Scheme 5) is due to steric congestion in the transition state during formation of **39a**. This steric congestion is extremely important for it begins to define the limits of the condensation of dicarbonyl compounds with **1**; data to support this hypothesis will be presented below. Hydrolysis and decarboxylation of the hexa-ester **39a** smoothly provided the diketo–diacid **40** (76%) alluded to earlier as the key intermediate for the construction of ring-system D.

Attention was now turned to the conversion of the diketo–diacid **40** to the desired tetracyclic system **41**. From the very beginning it had seemed desirable to



34 35, R=CO_2CH_2Ph 36

39a, R=CO_2CH_3, enol form 38 37

39b, R=H

40 41, H

Scheme 7.

effect the conversion of the bicyclic ketone **40** to the tetracyclic tetraone **41**, by way of two simultaneous acid-catalyzed cyclizations. Moreover, the mass spectrum (indirect inlet, electron impact) of the diacid **40** contained the base peak at a mass value consistent with the parent peak of **41**, while direct inlet, chemical ionization mass spectroscopy showed the parent peak of **40** as the most intense signal in the spectrum. To take advantage of this phenomenon, several high-vacuum pyrolysis reactions of **40** were carried out; however, only mixtures of compounds and products of carbonization were observed in each case. Heating the diacid **40** in benzene–dioxane solution in the presence of a catalytic amount of naphthalene - 1 - sulfonic acid, according to the earlier work of Oehldrich,[1a] also provided only complex mixtures of decomposition material. It was decided a more rapid reaction under more dilute, more acidic conditions might facilitate the intramolecular nature of the acid-catalyzed cyclization, while decreasing the formation of byproducts. In accordance with this hypothesis, the diacid **40** (0.6 g) was stirred for four days with naphthalene - 1 - sulfonic acid (0.5 g) in refluxing cumene-diglyme (2:1) which resulted in the precipitation of the tetraone **41** (78% yield) as a light grey microcrystalline powder; this material was the sole component of the crystalline solid isolated from the sequence. This constitutes the first synthesis of a carbocyclic molecule in which four 5-membered rings are attached to the same central carbon atom. The cross-like shape of the structural formula of **41** prompted us to propose[1b] the name "staurane" (from Greek stauros, cross) for the hypothetical parent hydrocarbon D. To the best of our knowledge only one other derivative of the staurane system is known and this was reported by Keese[40] in 1979.

The structure proof for staurane - 2,6,8,12 - tetraone **41** was initially based entirely on spectroscopic data[1b] some of which will be discussed below. Tetraketone **41** (m.p. 288°) is remarkably insoluble in common organic solvents with the exception of pyridine, dimethylformamide, and dimethylsulfoxide and, in fact, it was purified by sublimation (190°, 0.02 mm) or by crystallization from

dimethylformamide. Although the proton NMR of such a symmetrical molecule is nearly first order [δ (pyridine-d_5) 2.51 (2H, d, J = 6.5 Hz), 2.59 (2H, d, J = 6.5 Hz), 2.87 (2H, d, J = 8.4 Hz), 2.95 (2H, d, J = 8.4 Hz), 3.07 (2H, sextet), and 4.05 (2H, s)] the burden of proof for the assigned structure rested with the carbon NMR spectra. Since each quadrant of **41** (C_{2v} symmetry) was identical to its nearest neighbor, the five line carbon spectrum [δ (CD_3CN), 39.5 (d), 46.1 (t), 64.3 (s), 67.4 (d) and 208.0 (s)] was sufficient evidence to conclude that the structure was correct as proposed. Furthermore, the exact mass of **41** [M^+, calc. for $C_{13}H_{12}O_4$, 232.0736, found 232.0739], established by high-resolution mass spectrometry, was in agreement with the proposed structure. The tetraketone **41** is somewhat more strained than the triketone **27**, as evidenced by examination of both Dreiding models and the IR spectra of the two species; the spectrum in the case of the tetraone contained distinct bands at 1769.5 (m), 1736. (s), 1710. (s) and 1679.2 (sh) cm^{-1} while the bands found in the spectrum of **27** [1760.8, 1734.8 and 1707.8 (w)] were similar, but at lower wave numbers.

The spectroscopic findings reported above on **41** are consistent with the symmetry (C_{2v}) expected from examination of its structure. Surprisingly, however, X-ray crystallographic analysis obtained recently on the molecule (see Fig. 3) clearly indicates that this symmetry does not exist in the crystal, but that the four cyclopentanone rings assume two different conformations. The molecule, therefore, has an approximate two-fold axis as the only element of symmetry. As a consequence, **41** exists in the crystal in the form of *d* or *l*-antipodes, and each crystal is made up exclusively of molecules of one antipode. If well-developed crystals of the tetraone become available the compound might be resolved in the way Pasteur in 1848 performed the first resolution of a racemate. It is doubtful, however, whether the optical activity of **41** would survive in solution.

Although several reactions have been carried out in order to convert **41** to staurane (D), most of these will be presented elsewhere;[41] however, one critical observation needs to be discussed. When the trione **27** was stirred in methanol at room temp the compound was regiospecifically transformed into the monoester **26a** within a few hours as indicated in Scheme 8; however, the staurane system **41** remained intact even while stirred in methanol for 24 hr (see Scheme 8). The relatively low reactivity of **41** compared to the lability of **27** was not due to the insolubility of the former, since a mixture of methanol, **41**, and pyridine at room temp was also without action, however, if the tetraone was stirred in refluxing methanol for a period of 16–24 hr, the diester derivative of **39b** was produced in quantitative yield. Both β-diketone bonds in **27** and **41** had undergone fission in a regiospecific sense. Moreover, attempts to observe the formation of the trione monoester failed which further indicated that triones such as **27** undergo cleavage (retro-Claisen) of the β-diketone bond much more rapidly than the staurane system **41**.

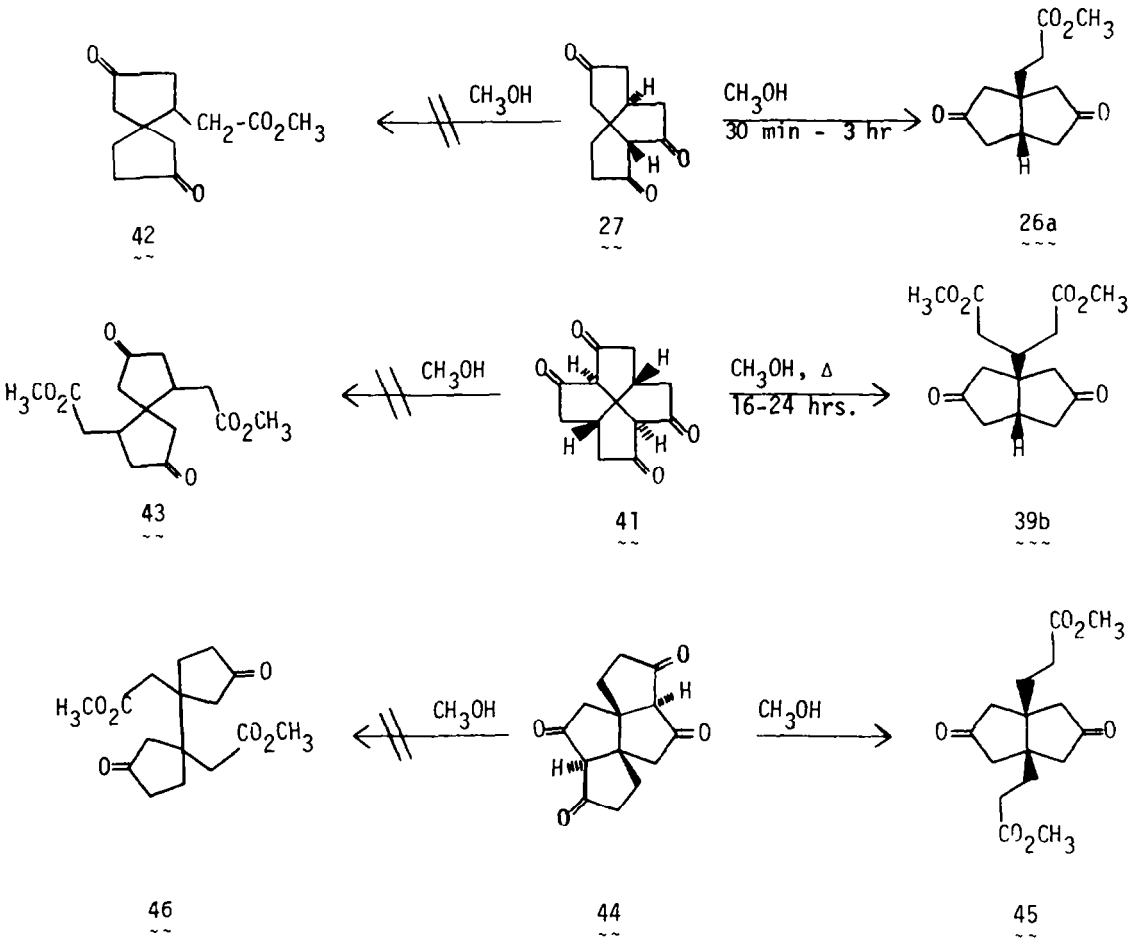
Since the future conversion of staurane tetraone to the parent hydrocarbon D will rely heavily on the stability, or lack thereof, of the β-diketone moieties, the relatively low reactivity of the tetraone **41** intrigued us. Three possible explanations for this reactivity pattern have emerged to date: (1) there must be orbital overlap of the β-diketone bond which breaks with the remaining carbonyl. This may be poor in the case of **41**; (2) the higher degree of symmetry in **41** (C_{2v}) may permit the strain energy to be more evenly spread over the entire molecule as compared to the less symmetrical **27** (C_s). This fact may be reflected in differences in torsional strain, angle strain, and bond lengths contained in the two molecules; (3) the approach of the nucleophile toward **41** may be hindered for some reason in the case of **41**, whereas this same steric restriction may not operate during the ring opening of trione **27**. The IR data previously discussed clearly indicated that the staurane system **41** contained more strain energy than **27**; however, torsion angles, bond angles, etc. were necessary from X-ray crystallographic data (see below) before one of these hypotheses could be selected over another. If, however, symmetry and torsion angles did play a role in the stability of **41**, a molecule related to **27** and **41** with symmetry properties between these two molecules might be of interest *vis a vis* the reaction with methanol. The tetraketone **44** (Schemes 8 and 9) was just such a molecule. The preparation and reactions of this tetracyclic[6.6.0.0^{1,5}.0^{8,12}]tetradecane system are described in the next section.

System H. Tetracyclo[6.6.0.0^{1,5}.0^{8,12}]*tetradecane* - 2,7,9, 14-*tetraone*

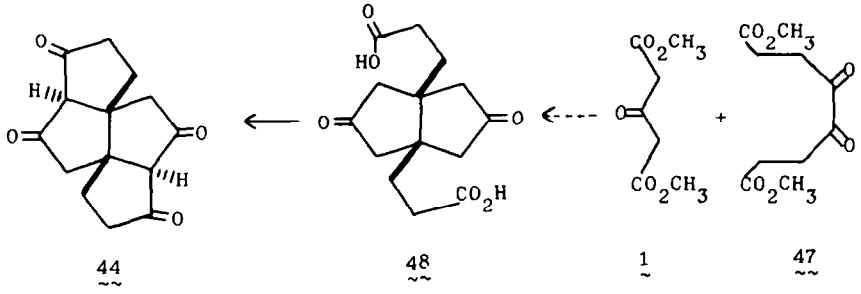
Interest in the tetracyclo[6.6.0.0^{1,5}.0^{8,12}] tetradecane system represented by structure H (Fig. 1) was not solely due to its unique molecular structure but was also stimulated by the desire to study, as mentioned above, the facile retro-Claisen reaction of a tetraone (C_2) such as **44** (see Scheme 8). Examination of the structure of **44**, in a retro-synthetic sense, indicated that a dioxodiester **47** might serve as a precursor to **44** via the 1:2 adduct **48**; however, this sequence was abandoned, since it suffers from two serious drawbacks. In the previous section it had been shown that the dioxodiester **38** reacted with **1** to furnish the 1:2 adduct of type **39a** at best in only 51% yield, principally due to steric congestion in the transition state. In addition, the repulsion between propionic acid groups (*cis*-disposed) in the intermediate leading to **48** was considered a problem in the high-yield preparation of such a molecule. Both of these difficulties, however, were surmounted by judicious choice of an alicyclic (rather than aliphatic) starting dione which decreased the steric interactions in formation of the 1:2 adduct, while assuring the desired *cis*-stereochemistry in the product.

In this vein, the two C_3-groups destined to become the two cyclopentane rings attached centrosymmetrically to the *cis* - bicyclo[3.3.0]octane - 3,7 - dione system of **44** were housed in the cyclooctene ring of the intermediate [6.3.3]propellene **50**. Immobilized in this fashion the two C-3 units were less likely to interfere with formation of the 1:2 adduct. This approach was indeed successful since the 1:2 adduct **50** was obtained in very high yield (86%); its further conversion into **44** was uneventful.

The readily available diene, cycloocta - 1,5 - diene was converted to the 1,2-dicarbonyl compound **49** by the method (H_2O_2) of Yates.[42] Reaction of **49** with two equivalents of dimethyl 3-ketoglutarate produced the crystalline tetramethyl[6.3.3]propellene tetracarboxylate **50** in better than 85% yield. Hydrolysis in the usual manner gave the [6.3.3]propellene dione **51** in 92% yield. This dione was converted in modest yield (18–25%) to the diketo diacid **45a** by treatment with ozone; however, stirring the propellene **51** with osmium tetroxide followed by chromium VI oxidation of the resulting diol furnished the diacid **45** in 60% overall yield. When the diacid **45**



Scheme 8.



Scheme 9.

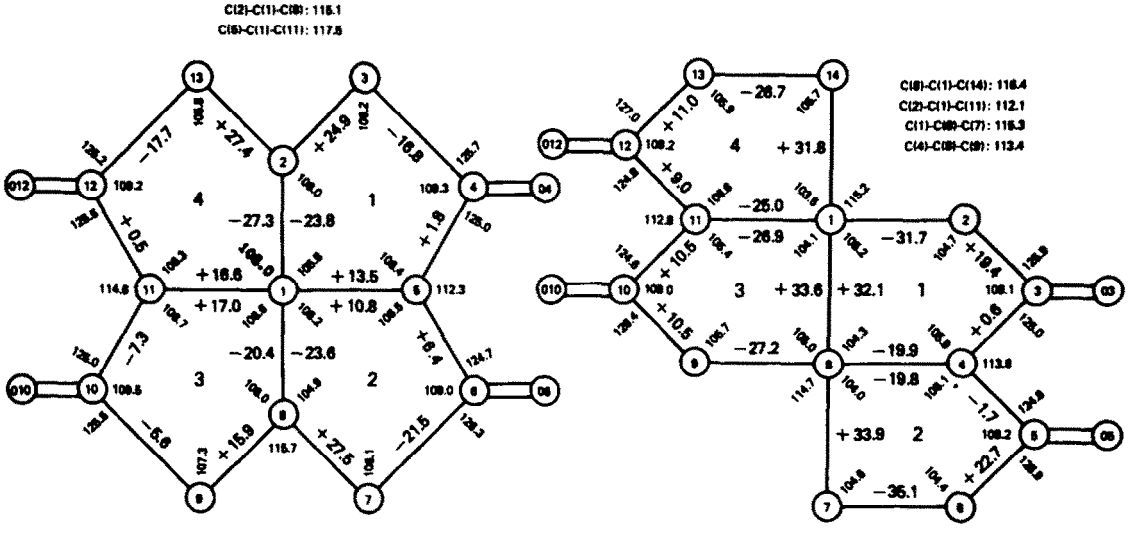
was heated with a catalytic amount of naphthalene - 1 - sulfonic acid in refluxing cumene–diglyme extensive decomposition occurred. To circumvent this problem the diacid **45** was heated with an equivalent amount of naphthalene - 1 - sulfonic acid in refluxing benzene–dioxane solution for several days which resulted in the precipitation of an off-white solid (47%). Addition of a small amount of naphthalene - 1 - sulfonic acid to the mother-liquors followed by heating for several days gave another 13% of the tetraone **44** (total yield, 60%).

Since the formation of the diketo diacid occurred via the propellene **51**, the diacid **45** was formed in stereospecific fashion; moreover the production of tetraone **44** occurred in a regiospecific fashion. The strain present in a system such as **52** with three contiguous sp^2 centers, when combined with the nonbonded interactions between methylene hydrogens (rings B and D) militate against formation of any of the alternative tetraone **52** in the reaction medium. The physical properties of the tetracyclo[6.6.0.$0^{1,5}$.$0^{8,12}$]tetraone **44** are quite similar to

those of the previously prepared staurane tetraone **41**. For instance, the tetraketone **44** was insoluble in most organic solvents with the exception of dimethylformamide and dimethylsulfoxide. Crystallization of the material from either of the latter solvents provided beautiful white crystals of m.p. 309°. The assignment of structure **44** to this high-melting solid was initially based on data obtained from carbon-13 NMR [δ ($DMSO_{d6}$), 27.65 (t), 38.95 (t), 47.55 (t), 53.47 (s), 69.46 (d), 206.07 (s), 207.29 (s)] and IR spectroscopy [(KBr) 1759.9 (s) and 1710.7 (w) cm^{-1}]. Additional support for the structural assignment was obtained from high-resolution mass spectroscopy [(M^+) calc. for $C_{14}H_{14}O_4$, 246.0891; found, 246.0887].[28] Examination of the structure of the two possible tetraones **44** and **52** clearly established that a seven line spectrum (two carbonyl resonance lines) should result from the carbon NMR of **44**, while that of tetraketone **52** should contain eight lines (three carbonyl signals). Experimentally only seven lines were observed in the carbon spectrum of **44**. Furthermore the two carbonyl signals were found at 206 and 207 ppm, respectively, in agreement with the chemical shift found for the β-diketone carbons in staurane tetraone (208 ppm). Subsequent to our initial report of the synthesis of **44**,[28] we have had occasion to subject this material to single crystal X-ray analysis; the data illustrated in Fig. 4 completely confirm our assignment.

Earlier it was mentioned that the trione **27** (C_s symmetry) underwent a retro-Claisen reaction much more rapidly than staurane tetraone **41** (C_{2v} symmetry). This was illustrated in Fig. 7. Because tetraone **44** (C_2) was intermediate in symmetry properties between **27** and staurane tetraketone **41**, it was decided to subject it to treatment with methanol. In fact, as predicted,[28] the tetraone **44** underwent complete ring opening at a rate intermediate between **27** and **41**; moreover, the only diester observed by tlc and isolated was the symmetrical diester **45b**. Although initially it was felt that the torsional strain in the less reactive staurane tetraone would be less than in tetracyclo[6.6.0.$0^{1,5}$.$0^{8,12}$] **44**, comparison of the torsion angles and torsional strain between the systems **41** and **44** clearly indicated that the strain is greater in the staurane **41** (see Fig. 2). This observation was important for both the IR and X-ray data agree, based on strain arguments, that **41** is the more strained of the two systems in agreement with our previous conclusions based solely on Dreiding models.[28]

Close examination of molecular models of **27**, **41** and **44** has provided the first insight into both the regiospecificity and rate of retro-Claisen reaction in these three molecules. Both **27** and **44** have one thing in common: there is a path of attack open from the convex face of one of the β-diketone carbonyl moieties. Attack of methanol on either **27** or **44** [at an angle of 109.3° as regards the carbonyl plane in keeping with Baldwin's rules, J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976)] to provide a regioisomer other than that already illustrated in Scheme 8 (**26a** or **45** respectively) would require attack on one of the carbonyls from the concave face of the molecule. Since it had already been established that **41** was more strained than **27** or **44** (IR and X-ray data) we turned to the model of staurane



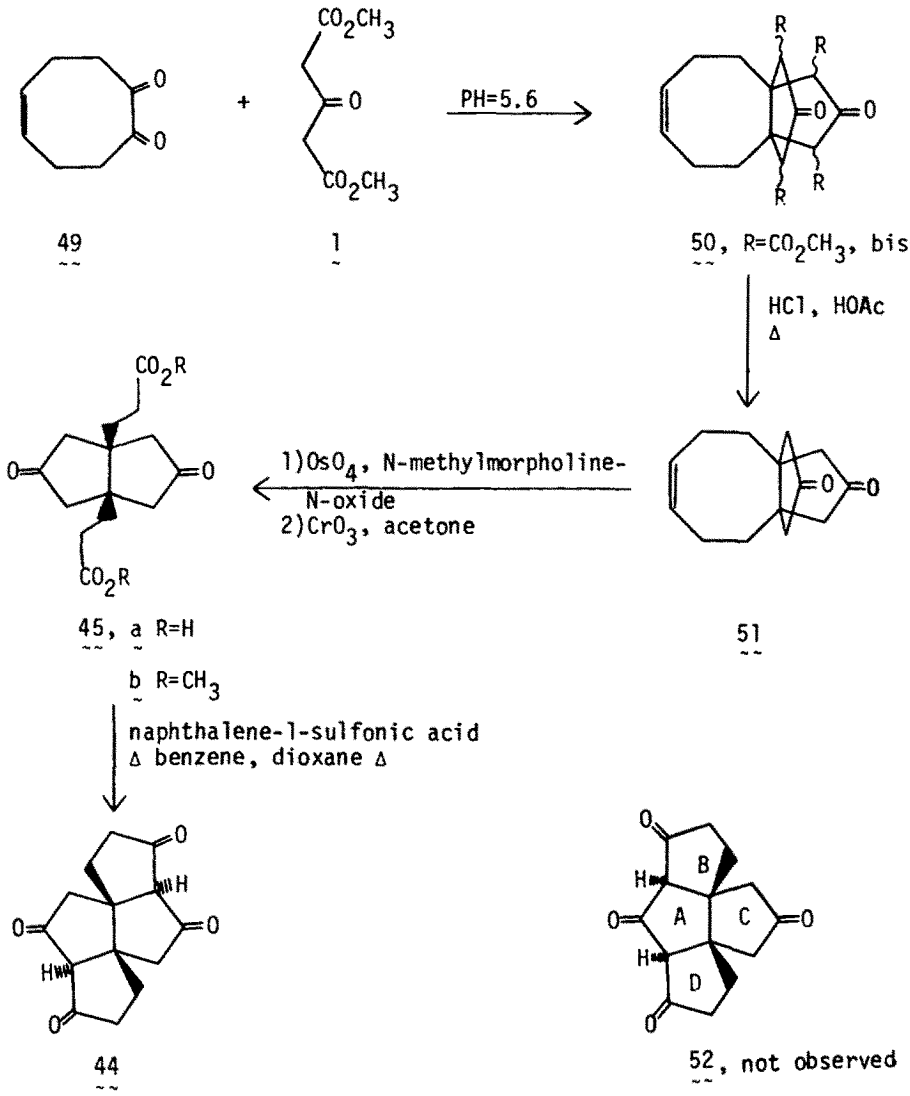
	1	2	3	4
Φm	25.7	27.8	20.4	28.8
Δ	27.5	8.9	5.0	33.8

41

	1	2	3	4
Φm	33.5	36.3	33.5	31.9
Δ	34.5	30.4	0.2	4.2

44

Fig. 2. Torsion angles, bond angles and conformational parameters for **41** and **44**. Comparison with Figs. 3 and 4 indicates the very close similarity of all the various classes of bond lengths and angles. The parameters ϕ_m (maximum torsion angle) and Δ (pseudo-rotation angle) follow C. Altona, H. J. Geise and C. Romers, *Tetrahedron* 24, 13 (1968). Δ would be zero for an ideal half-chair conformation and 36° for an ideal envelope. The flattening of the rings and possible concomitant torsional strain is clearly indicated by the lower ϕ_m values for **41**. The dihedral angles between a π orbital on a carbonyl carbon atom and the diketone bond β to the atom, e.g. atom 4 and bond 5–6 in **41**, are as follows: **41**: Atoms 4, 6, 10, 12: 33°, 39°, 42°, 36°; **44**: Atoms 3, 5, 10, 12: 35°, 36°, 42°, 28°.



49 + 1 → 50, R=CO_2CH_3, bisenol form

50 → 51

51 → 45, a R=H; b R=CH_3

45 → 44

51 → 52, not observed

Scheme 10.

tetraone to support or refute this hypothesis. The very nature of the staurane system lies at the heart of this inertness, since **41** has no free convex face. Because of the unique molecular structure of **41**, each β-diketone carbonyl has a concave as well as a convex face. Moreover, as soon as one of the β-diketone bonds of **41** is broken, the trione which results can undergo attack and ring opening in a regiospecific fashion analogous to the opening of trione **27**. In conclusion, the decreased rate of ring opening, and complete regiospecificity of the retro-Claisen reaction in staurane tetraketone **41** rests solely on the steric accessibility of the β-diketone carbonyl groups to attack. The X-ray data, torsion angles and torsional strain parameters for both **41** and **44** are illustrated in Fig. 2. Ortep drawings of the molecules are represented in Figs. 3 and 4.

System G. endo - Tetracyclo[5.5.1.$0^{2,6}$.$0^{10,13}$]*tridecanetrione* **5b** *and exo - tetracyclo*[5.5.1.$0^{2,6}$.$0^{10,13}$]*tridecanetrione* **6b**

The formation of the endocyclic and exocyclic tetracyclotridecane triones **5b** and **6b**, respectively, has been reported earlier.[5,6] These molecules resulted from the condensation of **1** with **2** at acidic pH, as outlined in Scheme 11, followed by hydrolysis and decarboxylation of the β-ketoester functions. Surprisingly it was found in the initial work at NIH[5,6] and confirmed both at the University of Wisconsin–Milwaukee and at Harvard,[8] that of the two stereoisomers **5a** and **6a** the latter trione is formed to a lesser extent than the former, even though there is some crowding and consequent distortion in **5b** as established by X-ray crystallography.[5] No X-ray data are available for **6b**, but its structure and a study of Dreiding models indicate little reason to assume existence of undue strain or crowding. The reasons for the preponderance of **5a** over **6a** in the reaction have been elegantly determined by Bertz.[8] The synthesis of the endocyclic and exocyclic triketones **5b** and **6b** provided the first entry into System G.

Future Work

Systems E and G. The construction of several other polyquinane systems is under active investigation in our laboratory. These include System E which makes up the

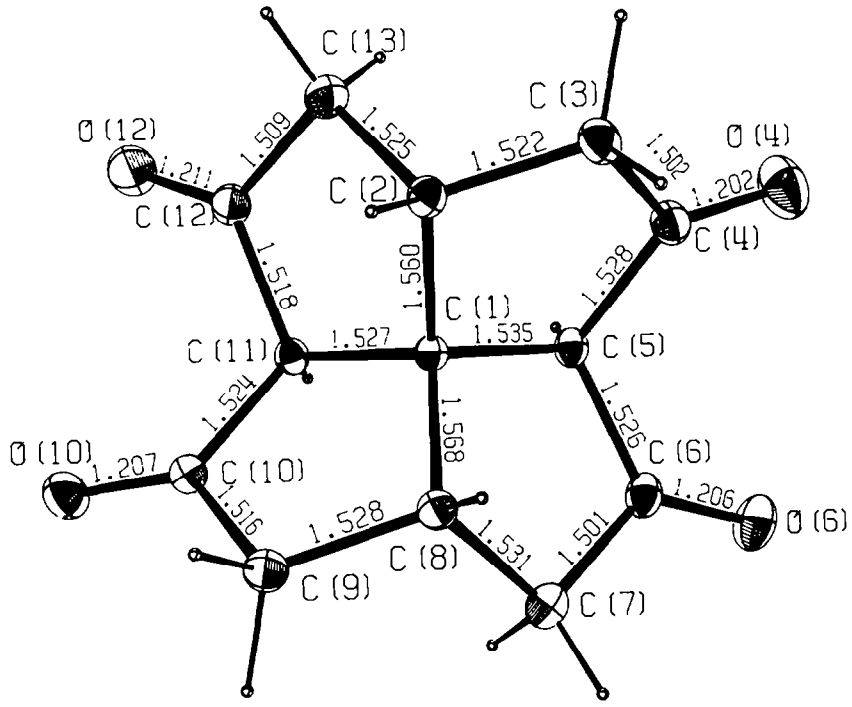


Fig. 3. Bond lengths and crystal conformation of **41** (ORTEP drawing: C, K. Johnson, Report ORNL-379A, Oak Ridge National Laboratory, TE, 1965). Reported bond lengths for this compound and also for **44** have esd.s < 0.003 Å.

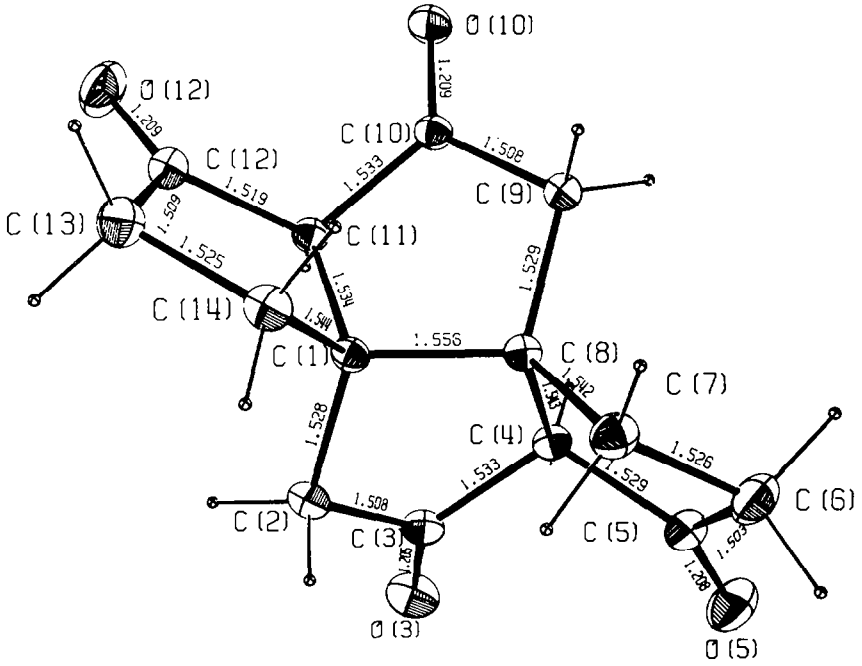
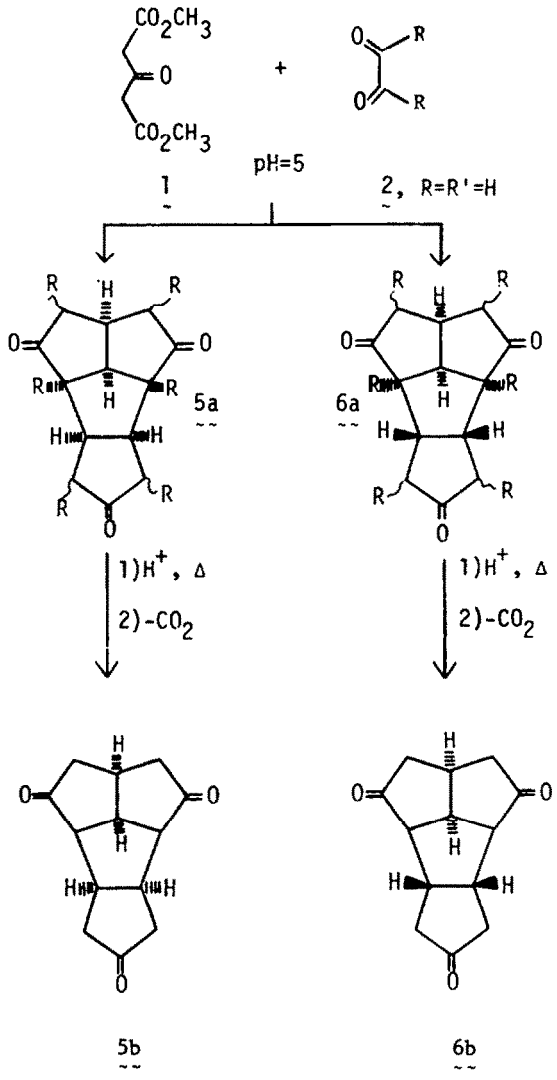


Fig. 4. Bond lengths and crystal conformation of **44** (ORTEP drawing).

skeleton of the transannular cyclization product of ophioboline D[43] (Scheme 12), and System G, a more complex polyquinane system composed of six fused five-membered rings (Fig. 1). The strategy for construction of **54** will be relatively straightforward. The diketo diacid **45**, already in hand, will be converted to the monoketone **53** which can only cyclize to **54** (System E).

In regard to System G (Fig. 1), recent results from our laboratory are quite exciting and are outlined in Scheme 13. The cyclopentene 4-carboxylic acid **55** has been

glyoxal **56**,[44] and the same acid has been converted to the *bis*-cyclopentenyl diketone **59**.[45] Furthermore, in a previous section it had been reported that the low yield of 1:2 adduct **39a** (staurane series, Scheme 7) had been obtained due to steric congestion in the transition state. Indirect proof for this hypothesis has now been obtained, in a chemical sense, since the glyoxal **56** with both side chains tied back reacted with **1** to provide the 1:2 adduct **57** in greater than 85% yield. This yield has not been maximized, but is expected to be elevated to 90% in the near future. Hydrolysis and decarboxylation would then provide **58**, a new *cis* - bicyclo[3.3.0] system which could be converted into staurane tetraketone **41** in a simpler fashion than previously reported.[1b] From the same approach our efforts will now turn toward conversion of the *bis*-cyclopentenyl diketone **59** to the 1:2 adduct **60**. Hydrolysis and decarboxylation, followed by transformation (OsO_4/CrO_3) of the resulting dione **61** to the tetraacid should provide a diketo tetraacid. This tetraacid, upon four simultaneous acid-catalyzed cyclizations would furnish entry into System G. Some precedent for this approach does exist in the ready conversion of the glyoxal **56** to the 1:2 adduct **57**. Much work in this area is in progress at the moment and needs to be completed.

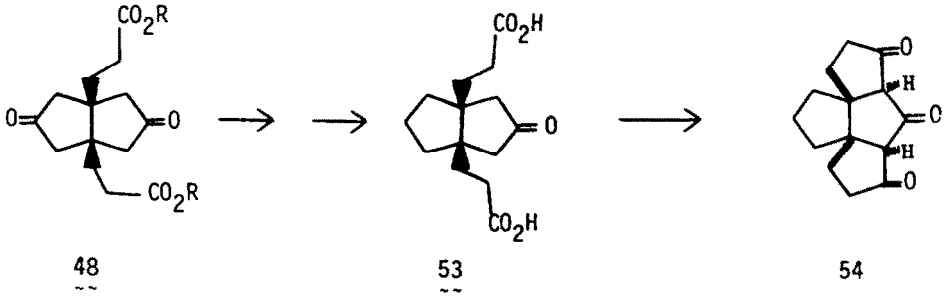


Scheme 11.

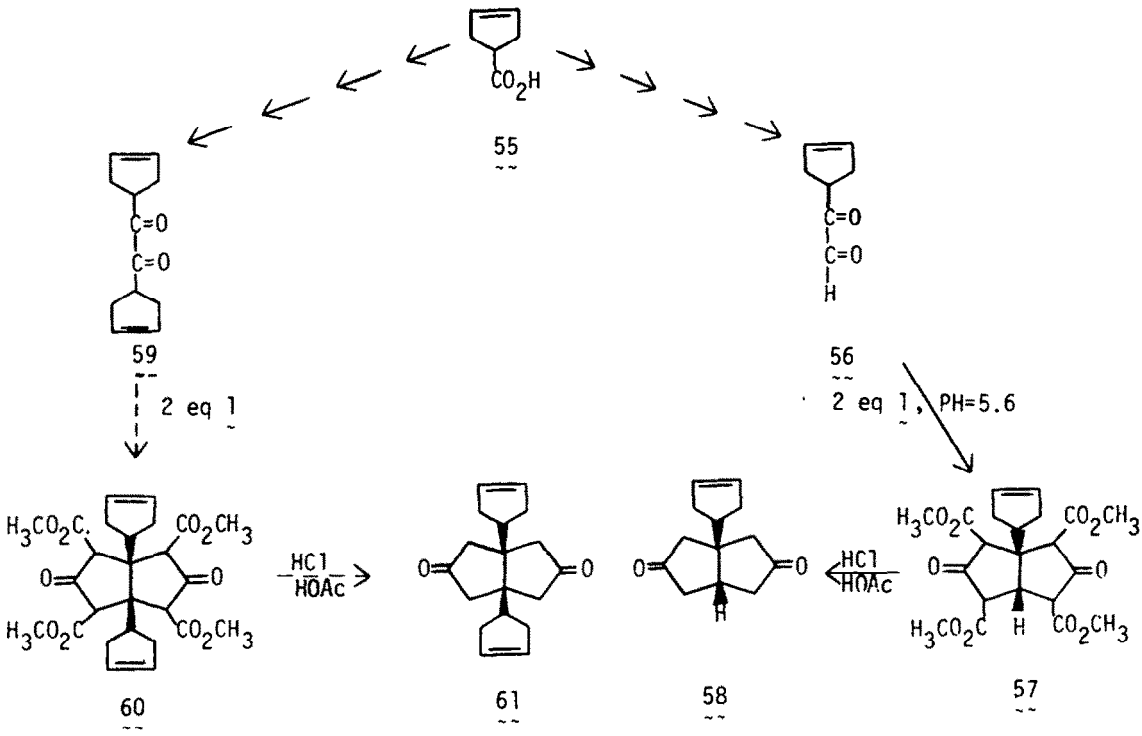
CONCLUSION

Recent interest in polyquinane ring systems has been well-documented[46-48] and a number of them have been synthesized including triquinacene,[49] peristylane,[50] C_{16}-hexaquinacene,[51] and dimethyldodecahedrane.[52] In addition, the discovery of natural compounds[53] with ring systems derived, in part or entirely, of cyclopentanoid rings has stimulated additional interest in this area of research, furthermore some of these compounds have been synthesized.[54] In none of the work reported to date has a simpler method been developed for rapid generation of molecular complexity[55] over a variety of different polyquinane ring systems, than the condensation of 1,2-dicarbonyl compounds **1** with dimethyl 3-ketoglutarate **2**. The facile preparation of **4** (R=R'=H, Fig. 1)[8,15a] and entry into systems A, C, D, F and H provide ample evidence of the versatility of this synthetic method. This method, moreover, has been recently employed by Coates[56] and Paquette[57] for the synthesis of gymnomitrol and by Nicolaou for preparation of the important molecule, carboprostacycline.[58] In addition, Dauben has recently employed this technology for the key step in the synthesis of isocomene.[59]

Much work remains to be done in the context of the present investigation, including conversion of the various β-diketones to the parent hydrocarbons, and completion of the synthesis of Systems B, E and G (Fig. 1). Since the reaction of **1** with **2** to generate substituted *cis* - bicyclo[3.3.0]octane - 3,7 - diones can be carried out successfully under very mild conditions (room temp, aqueous solution), this synthetic method should be applicable for construction of a variety of polyquinanes,



Scheme 12.



Scheme 13.

including natural products. We plan, in the future, to examine such possibilities and to explore the chemistry of compounds illustrated in Fig. 1 in greater detail.

EXPERIMENTAL

Microanalyses were preformed on an F and M Scientific Corporation Carbon, Hydrogen, Nitrogen Analyzer Model 185; some analyses were also carried out at the National Institutes of Health, Bethesda, Maryland. M.ps were taken on a Thomas Hoover m.p. apparatus and are uncorrected.

Nuclear magnetic resonance spectra were recorded on a Varian T-60 or Jeol FX-90 spectrometer while carbon-13 spectra were taken on Varian CFT-20 and XL-100 instruments. IR spectra were recorded on a Beckman Aculab-1 spectrophotometer while FT-IR were taken on a Nicolet MX-1 instrument. The low-resolution mass spectra were run on an Hitachi RMU-6, Finnegan 1015 or Hewlett–Packard 5859 mass spectrometer, while high-resolution spectra were recorded on an AEI-MS-902 mass spectrometer.

Analytical tlc plates used were E. Merck Brinkmann UV active silica gel on plastic. The spray reagent was composed of 2,4-dinitrophenylhydrazine, ethanol and sulfuric acid. The citrate/phosphate buffer (pH = 5.6) was prepared by dissolving disodium hydrogen phosphate heptahydrate (11.67 g) and citric acid (3.68 g) in tap water (900 ml). If the starting dione was not soluble in the aqueous buffer, methanol was added to the medium until the 1,2-dicarbonyl compound dissolved, then buffer was added again (drop by drop) until the solution became slightly turbid. The addition of methanol, of course, altered the pH of the solution. Even though buffer (pH 5.6) was employed in some reactions, the pH recorded varied between 5.6 and 6.6 due to the addition of different amounts of methanol to the medium. This will be discussed, where pertinent, below. The bicarbonate solution (pH 8.3) was generated by dissolving sodium bicarbonate (1.40 g) in water (100 ml). In many cases the 1:2 adduct (bicyclooctane-diones) precipitated from the reaction medium; however, at alkaline pH it was necessary to acidify the solution in order to bring about the precipitation of the desired 1:2 adducts. During this process ice was added to the reaction medium and to the acidic solution employed for acidification. This simple process prevented yield loss *via* premature hydrolysis of the β-ketoester functions. It was difficult at times to separate dimethyl 3-ketoglutarate **1** from the 1:2 adducts; it became desirable, therefore, to design conditions which led to precipitation of the desired adduct, thus avoiding a tiresome chromatography. In general, hydrolysis of the 1:2 adduct to provide the bicyclo[3.3.0]octane - 3,7 - dione was quite facile; however, this process provides much better yields of the 3,7 - dione if all of the glutarate **1** has been removed *before* the hydrolysis.

Levulinic acid, benzaldehyde, benzyl acetoacetate, dimethyl 3-ketoglutarate, ethyl bromoacetate, diethyl succinate, cycloocta - 1,5 - diene, piperidine, glyoxal, cyclopentylidene - 2 - cyclopentanone and naphthalene - 1 - sulfonic acid (80%, 20% naphthalene - 2 - sulfonic acid) were purchased from Aldrich Chemical Co., Inc. The palladium on carbon catalyst was obtained from Pfaltz and Bauer, Inc.

δ-Benzylidene levulinic acid

Levulinic acid (**22**, 29.0 g, 0.25 mol) and benzaldehyde (26.5, 0.25 mol) were dissolved in dry benzene (200 ml). Acetic acid (30 ml, glacial) and dry piperidine (10 ml) were also added to the mixture. This solution was then refluxed for 72 hr and the water collected in a Dean–Stark trap. After the solution was cooled, water (100 ml) was added. The aqueous layer was then extracted with ether (3 × 150 ml); the combined extracts were washed with water and dried (Na_2SO_4). Removal of solvent at reduced pressure afforded 38.6 g (75.7%) of white crystalline δ-benzylidenelevulinic acid: m.p. 124–126° (lit.[22,23] m.p. 124–125°); IR (KBr 1700 (s) and 1660 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.64–3.14 (4H, 4 unequal singlets), 6.67 (1H, d, J = 16 Hz), 7.36 (5H, m), 7.46 (1H, d, J = 16 Hz). One of the peaks of the AB doublet overlaps with the edge of the doublet at δ 7.36. Mass spectrum: *m/e* 204 (M^+).

Chromatography of the mother liquors from the crystallization above provided an additional six grams of δ-benzylidene levulinic acid.

Preparation of 4,5-*dioxopentanoic acid* (**23**)

δ-Benzylidene levulinic acid (20.0 g, 0.098 mol) was dissolved in dry methanol (300 ml) and cooled to −70° in an acetone/dry-ice bath. Ozone was passed through the solution until the excess ozone caused the solution to acquire a slight bluish color. The solution was allowed to warm to −10°. When the temperature reached −10°, dimethylsulfide (8.44 g, 0.136 mol) was added; the temperature was maintained at −10° for 1 hr after addition of methylsulfide. After 1 hr the temperature was permitted to rise to 0° and maintained for 1 hr. At the end of the 1 hr period the solution was allowed to come to room temp and maintained for 1 hr. The solvent was removed under reduced pressure; the residue was dissolved in water (200 ml) and extracted with ether (5 × 100 ml) to remove the dimethylsulfoxide. The water was then removed under reduced pressure to provide **23** (13.9 g, 95.9%) as an oil, which was obtained as the monohydrate: IR (neat) 3500–3000 (broad, OH) and 1725 cm^{-1}; NMR (pyridine-d_5) δ 2.18 (4H, s), 7.36 (2H, s, *gem*-diol of aldehyde). A small amount of this monohydrate was purified by chromatography for microanalysis. The remainder of the material was used directly in the next reaction. (Found: C, 40.58; H, 4.65. Calc. for $C_5H_8O_5$ C, 40.82; H, 4.80%).

Preparation of tetramethyl 1,3′ - *propanoic acid bicyclo*[3.3.0]*octane* - 3,7 - *dione* 2,4,6,8 - *tetracarboxylate* (**24a**) *at pH* 6.8

Dimethyl 3-ketoglutarate (**1**, 69.6 g, 0.40 mol) was dissolved in citrate/phosphate buffer (600 ml, pH 5.6); 4,5-dioxopentanoic acid (**23**, 26.00 g, 0.176 mol) was then added in one portion. The solution was stirred for several days at room temp until tlc indicated the absence of **23**, and then extracted with chloroform (5 × 250 ml). The combined extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. The oily residue was dissolved in methanol and allowed to crystallize. The crystals were filtered from the solution and dried, yielding 50.3 g (64.8%) of a white crystalline solid (**24a**, m.p. 154–156°); IR (KBr) 3500–3100 (broad OH), 1740 (s), 1725 (s) and 1705 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.31 (4H, q), 3.66 (14H, m), 9.57 (3H, broad singlet); mass spectrum *m/e* 442 (5, M^+), 410 (13), 378 (22), 368 (17), 346 (22), 335 (30), 334 (100), 306 (22), 305 (22), 304 (11), 303 (24), 302 (91), 280 (30). (Found: C, 51.56; H, 4.98. Calc. for $C_{19}H_{22}O_{12}$: C, 51.59; H, 5.01%.)

Preparation of tetramethyl 1 - (2′ - *carboxyethyl*) *bicyclo*[3.3.0]*octane* - 3,7 - *dione* - 2,4,6,8 - *tetracarboxylate* (**24a**) *at pH* 8.3

Dimethyl 3-ketoglutarate (**1**, 5.22 g, 0.030 mol) was dissolved in aqueous sodium bicarbonate buffer (100 ml), after which 4,5-dioxopentanoic acid (**23**, 0.015 mol) was added to the solution in one portion. This mixture was stirred for 72 hr, acidified to pH = 1 with ice-cold 6 *M* H_2SO_4 and extracted with chloroform (3 × 100 ml). The combined extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The oil was dissolved in methanol and allowed to crystallize. White crystals were isolated of **24a** (5.3 g, 79.9%), which were identical with those obtained at acidic pH described in the previous experiment.

Hydrolysis and decarboxylation of **24a** *to provide* 1 - (2′ - *carboxyethyl*) *bicyclo*[3.3.0]*octane* - 3,7 - *dione* (**25**)

The bicyclo[3.3.0]octane - 3,7 - dione derivative (**26a**, 100 mg, ate (**24a**, 10.04 g, 0.023 mol) was dissolved in a mixture of concentrated hydrochloric acid (50 ml), glacial acetic acid (80 ml) and water (10 ml), after which the mixture was refluxed for 6 hr. The solution was cooled and extracted with chloroform (4 × 100 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate to provide (**25**, 3.20 g) white crystals (67%): m.p. 101–102°, IR (KBr) 3500–2800 (broad OH), 1730 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.31 (12H, m), 6.67 (2H, s, D_2O exchangeable); mass spectrum *m/e* 210 (36 M^+), 195 (12), 194 (16), 193 (13), 191 (12), 169 (12), 168 (24), 167 (100), 153 (13), 152 (13), 151 (11), 150 (27), 149 (57), 141 (20), 137 (44), 127 (12), 125 (20), 124 (12), 123 (28), 122 (12), 121 (12), 119 (12), 113 (32). An additional 500 mg of the monoacid **25** were obtained from the mother liquors after chromatography (silica gel, ethyl acetate–methanol). (Found: C, 62.84; H, 7.07. Calc. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71%.)

Preparation of tetramethyl 1 - (2′ - *methoxycarbonylethyl*) *bicyclo*[3.3.0]*octane* - 3,7 - *dione* 2,4,6,8 - *tetracarboxylate* (**24b**)

The bicyclo[3.3.0]octane - 3,7 - dione - 2,4,6,8 - tetracarboxylate (**24a**, 1.00 g, 2.26 mmol) was dissolved in methanolic hydrogen chloride (10 ml), The solution was stirred for 24 hr. The precipitate which formed was filtered from the solution and dried. The ester (0.95 g, 92%) which was isolated was a white crystalline solid (**24b**): m.p. 109–111°; IR 1735, 1680 cm^{-1}; NMR ($CDCl_3$) δ 2.31 (4H, q), 3.70 (18H, m); mass spectrum *m/e* 456 (10, M^+), 425 (19), 424 (38), 393 (50), 392 (100), 361 (42), 360 (73), 338 (39), 333 (27), 332 (23), 329 (19), 328 (35), 318 (23), 306 (81), 301 (31), 245 (65). (Found: C, 52.49; H, 5.27. Calc. for $C_{20}H_{24}O_{12}$: C, 52.63; H, 5.30%.)

Attempted preparation of tetramethyl tricyclo[6.3.0.$0^{1,5}$]*undeca* - 3,7,9 - *trione* 2,4,6,8 - *tetracarboxylate*

The bicyclo[3.3.0]octane - 3,7 - dione - 2,4,6,8 - tetracarboxylate (**24b**, 49.5 mg, 0.11 mmol) was dissolved in dry methanol (5 ml) to which sodium methoxide (5.92 mg, 0.11 mmol) was added; the mixture was stirred for 11 hr. It was then heated to reflux for the last 5 hr. The solution was neutralized with cold hydrochloric acid (0.2 *N*) and extracted with chloroform (4 × 20 ml). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Only starting material **24b** (43.0 mg) was recovered from this sequence.

Attempted preparation of tricyclo[6.3.0.$0^{1,5}$]*undeca* - 3,7,9 - *trione* (**27**)

The bicyclo[3.3.0]octane - 3,7 - dione derivative (**26a**, 100 mg, 0.476 mmol) was dissolved in dry benzene (5 ml) and sodium methoxide was added (64 mg, 1.19 mmol). The solution was refluxed for 24 hr. Only starting material (**26a**) and compounds of high molecular weight were isolated.

Tricyclo[6.3.0.$0^{1,5}$]*undeca* - 3,7,9 - *trione* (**27**)

The propanoic acid bicyclo[3.3.0]octane - 3,7 - dione (**25**, 250 mg, 1.19 mmol) was dissolved in a solution of dry benzene (15 ml) and dry dioxane (5 ml). Naphthalene - 1 - sulfonic acid (25 mg) was added and the solution which resulted was heated to reflux for five days. A Dean–Stark moisture trap was employed to remove water which formed during the process. The mixture was then cooled and the solvent removed under reduced pressure. The brown solid (250 mg) which remained was composed of **25** and the trione **27**. This solid was chromatographed on a column of silica gel (benzene/ethyl acetate, gradient elution) to provide a 60% yield of the desired trione **27** (137 mg) as a white crystalline solid: m.p. 142–143° (benzene); FT-IR (KBr) 1760.8 (s), 1734.8 (s) and 1707 cm^{-1} (weak); NMR ($CDCl_3$) δ 1.82–3.72 (12H, m); carbon NMR δ ($CDCl_3$) 215.5, 206.3, 68.45, 53.21, 48.53, 44.72, 43.74, 39.93, 38.66 and 32.52. Mass spectrum *m/e* 192 (M^+, 100), 181 (11), 167 (11), 164 (27), 155 (19), 150 (14), 149 (33), 137 (16), 136 (19), 135 (16), 123 (10), 109 (10), 108 (16), 107 (19). In Ref. [1a] we reported that **27** was crystallized from methanol; however, this was in error. The solvent of crystallization was benzene, although **27** can also be purified by sublimation. (Found: C, 68.56; H, 6.20. Calc. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29%.)

Although attempts to maximize the yield of this sequence have not been made, it is believed that simply heating the reaction mixture for a longer period of time should provide additional quantities of **27**.

Reaction of tricyclo[6.3.0.$0^{1,5}$]*undeca* - 3,7,9 - *trione* (**27**) *with methanol and sodium methoxide*

Tricyclo[6.3.0.$0^{1,5}$]undeca - 3,7,9 - trione (**27**, 5.0 mg, 0.026 mmol) was added to a sodium methoxide/methanol solution

(10%, 2.0 ml) and stirred. The reaction was monitored by thin-layer chromatography. After 10 min, no spot corresponding to starting material was observed. A new spot had developed with an R_f value and NMR spectrum identical with that of methyl-1,3' propionate bicyclo[3.3.0]octane - 3,7 - dione **26** ($CDCl_3$) δ 1.70–3.10 (13H, m), 3.74 (3H, s); IR ($CDCl_3$) 1731 cm^{-1} prepared by an unambiguous route.

Reaction of tricyclo[6.3.0.0^{1,5}]*undeca - 3,7 - trione* (**27**) *with methanol*

Tricyclo[6.3.0.0^{1,5}]undeca - 3,7,9 - trione (**27**, 5 mg) was dissolved in methanol (2 ml) and stirred. The reaction was monitored by thin-layer chromatography. After 10 min, no change in the starting material was seen. The reaction was monitored at 30 min intervals and after 50 min a new spot of higher R_f had developed. After 3 hr no starting material remained and the new compound had an R_f value identical with that of methyl - 1,3' - propionate bicyclo[3.3.0]octane - 3,7 - dione **26**. No further isolation or characterization was done. Methanol which had not been previously dried was employed in this experiment.

Preparation of tetramethyl tricyclo[3.3.3.0^{1,5}]*undecane - 3,7 - dione - 2,4,6,8 - tetracarboxylate* (**29**)

Dimethyl 3-ketoglutarate (**1**, 163.5 g, 0.94 mol) was dissolved in citrate–phosphate buffer (3000 ml, pH 6.6) and the resulting mixture was allowed to stir overnight until all of **1** had dissolved. At this point cyclopentane - 1,2 - dione[33] (**28**, 46 g, 0.47 mol) was added to the solution at room temp in four-gram portions over a two-week period. The white precipitate which formed was filtered from the reaction medium and crystallized from methanol to provide **29** in 40% yield: m.p. 150–152° [(CH_3OH, lit.[2] 149–150°)]. Extraction of the aqueous layer (from above) with chloroform gave a mixture of **1** and **29**. This material was chromatographed and provided additional (10%) quantities of tetracarboxylate **29**. The low yield of this sequence is due to the lability of cyclopentane - 1,2 - dione **28** when brought in contact with acidic or basic media. The yield was much lower when the reaction was carried out at pH 8.3 and, in fact, the decomposition of **28** can be easily monitored by tlc. The aqueous buffer was prepared by dissolution of dibasic sodium phosphate (327.6 ml, 0.2 *M*) and citric acid (122.4 ml, 0.1 *M*) in tap water (2550 ml).

Tricyclo[3.3.3.0^{1,5}]*undeca-3,7-dione* **30**

The tetracarboxylate **29** (120 g, 0.29 mol) was slurried in glacial acetic acid (400 ml) and aqueous hydrochloric acid (600 ml of 10%). The mixture was brought within 15 to 20 min to 87° and then stirred at this temperature for 8 hr. Within the first 50 min of heating, the white suspension had changed to a homogeneous pale yellow solution. After the 8 hr period the solution was either allowed to stand overnight or cooled to 0° and neutralized immediately (whichever was convenient). Chloroform or methylene chloride (1200 ml) and ice were added to the acidic solution after which potassium carbonate (aqueous, saturated) was dropped in carefully until the mixture was slightly alkaline. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 × 800 ml). The combined extracts were washed with brine and dried (Na_2SO_4). The drying agent was filtered from the mixture and the solvent removed under reduced pressure to provide a yellow solid. This solid was washed with cold ether to provide **30** as a white crystalline solid (48 g, 92%): m.p. 225–226°; IR (KBr) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (6H, s) and 2.50 (8H, s). This material was identical in all respects with the propellanedione **30** reported earlier.[2,31]

If the hydrolysis was carried out at 70°, the yield dropped to less than 40%. Rapid heating and maintenance of the temperature at 87° are critical for the high-yield preparation of **30**. This material was converted to the [3.3.3]propellane *via* Wolff Kishner reduction according to the procedure of Alder, as described in Ref. [31].

Preparation of ethyl 3-carboxybenzyllevulinate

Benzyl acetoacetate (**34**, 19.2 g, 0.10 mol) was added dropwise to a slurry of NaH (2.64 g, 0.11 mol) in dry benzene (60 ml). The mixture was stirred until no further evolution of hydrogen gas was observed ($\approx$ 40 min). The solution was then heated to 60° and ethyl bromoacetate (25.1 g, 0.15 mol) was added dropwise over a period of 10 min. The reaction mixture was subsequently brought to reflux and heating continued for 16 hr (NaBr precipitated from the solution). The mixture was cooled to room temp, and water (15 ml) was slowly added. The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was distilled under vacuum and the fraction boiling at 115–117° (0.08 mm Hg) was collected to furnish ethyl 3-carboxybenzyllevulinate (22.3 g, 81.1%) as a water-white liquid: IR (neat) 2980 (CH), 1740 (s), shoulder 1730, and 1150 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3H, t, J = 7 Hz), 2.20 (3H, s), 2.81 (2H, d, J = 6 Hz), 3.05 (1H, t, J = 6 Hz), 4.05 (2H, quartet, J = 7 Hz), 5.10 (2H, s), 7.30 (5H, s). Mass spectrum *m/e* 278 (M^+, 1), 259 (35), 230 (22), 214 (68), 185 (59), 170 (37), 108 (87), 91 (100). (Found: C, 64.80; H, 6.31. Calc. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.47%.)

Recombination and redistillation of the other fractions from this distillation provided another three grams of product.

Diethyl 3 - acetyl - 3 - carboxybenzylglutarate (**35**)

Ethyl 3 - carboxybenzyllevulinate (20.0 g, 0.71 mol) was added to a slurry of NaH (1.0 g, 0.079 mol) in dry benzene (50 ml) as described above. Ethyl bromoacetate (19.8 g, 1.2 mol) was added dropwise and the reaction was carried out in the manner previously described. The fraction boiling at 135–138° (0.06 mm Hg) was collected to furnish **35** (20.2 g, 78.1%) as a water-white liquid: IR (neat) 2980 (s), 1730 (C=O), 1150 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (6H, t, J = 7 Hz), 2.20 (3H, s), 3.15 (4H, s), 4.05 (4H, quartet, J = 7 Hz), 5.10 (2H, s), 7.30 (5H, s). Mass spectrum *m/e* 364 (15, M^+), 346 (17), 322 (25), 260 (95), 237 (100), 230 (34), 202 (78), 196 (27), 185 (36), 140 (52), 91 (85). Recombination and distillation of the other fractions provided another 10% of **35**. (Found: C, 62.61; H, 6.63. Calc. for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64%.)

Diethyl 3-acetylglutarate (**36**)

Diethyl 3 - acetyl - 3 - carboxybenzyllevulinate (**35**, 20.0 g, 0.055 mol) was dissolved in methanol (200 ml), palladium on carbon (1.10 g, 5%) catalyst was added, and the mixture was shaken at 55 psi (H_2 gas) for 8 hr. The catalyst was removed by filtration and the solution concentrated under vacuum. The residue was distilled under vacuum and the fraction boiling at 95–96° (0.1 mm Hg) was collected to furnish **36** (11.8 g, 93%) as a water-white liquid: IR (neat) 2989 (s, CH), 1730 (C=O) shoulder 1710 (C=O) and 1150 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7 Hz), 2.15 (3H, s), 2.55 (4H, d of d, J = 6 Hz), 3.35 (1H, quintet, J = 6 Hz), 4.20 (4H, quartet, J = 7 Hz). Mass spectrum *m/e* 230 (5, M^+), 215 (17), 188 (100), 186 (98), 157 (78), 142 (65), 139 (72), 114 (96), 97 (52), 85 (41). (Found: C, 57.36; H, 7.91. Calc. for $C_{11}H_{18}O_5$: C, 57.42; H, 7.88%.)

Ethyl 3 - carbethoxymethyl - 5 - benzylidenelevulinate (**37**)

Diethyl 3-acetylglutarate (**36**, 20.0 g, 0.083 mol) was dissolved in dry benzene (100 ml). Benzaldehyde (15.0 g, 0.14 mol), piperidine (5 ml) and glacial acetic acid (15 ml) were added and the mixture was heated to reflux with a Dean–Stark trap to remove water. Heating was continued until no more water was obtained (approximately 135 hr). The reaction mixture was cooled, and the solvent removed under reduced pressure. Water (50 ml) was added and the solution extracted with chloroform (3 × 100 ml). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (benzene–ethyl acetate, gradient elution) to provide **37** (22.6 g, 81%) as a red–brown oil: IR (neat) 2960 (s, CH), 1735 (C=O), 1685, 1655, 1605, and 1150 (br, C–O) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (6H, t, J = 7 Hz), 2.65 (4H, d of d, J = 6 Hz), 3.75 (1H, quintet, J = 5 Hz), 4.15 (4H, quartet, J = 7 Hz), 6.80 (1H, d, J = 16 Hz), 7.45 (5H, complex multiplet), 7.75 (1H, d, J = 16 Hz). Part of the quintet at δ 3.75 overlapped with the quartet at δ 4.15. One of the peaks of the AB doublet overlapped with the complex pattern at δ 7.45. Mass spectrum *m/e* 318 (41, M^+), 290 (17), 273 (21), 257 (27), 244 (57), 230 (62), 215 (31), 199 (6), 185 (16), 141 (100). (Found: C, 67.69; H, 7.03. Calc. for $C_{18}H_{22}O_5$: C, 67.92; H, 6.91%.)

Ethyl 3 - *carbethoxymethyl* - 4,5 - *dioxopentanoate* (**38**)

Ethyl 3 - carboethoxymethyl - 1,5 - benzylidenelevulinate (**37**, 16.0 g, 0.050 mol) was dissolved in dry methanol (175 ml) and cooled to −70° in a dry-ice acetone bath. Ozone was bubbled through the solution until a slight blue color developed (approximately 30 min). The reaction vessel was flushed with oxygen for 5 min and then allowed to warm to 0° over a period of 1 hr. Palladium on carbon (0.50 g, 5%) was added to the mixture which was shaken for 8 hr at atmospheric pressure with hydrogen gas. The solvent was removed under reduced pressure, and the residue chromatographed on silica gel (benzene–ethyl acetate, gradient elution) to give **38** (10.5 g, 80%) as the *gem*-diol: IR (neat) 3680–3120 (OH), 2980 (s), 1730 (br, C=O); NMR ($CDCl_3$) δ 1.30 (6H, t, J = 7 Hz), 2.75 (4H, d of d, J = 6 Hz), 3.70 (1H, quintet, J = 6 Hz), 4.10 (4H, quartet, J = 7 Hz), 7.25 (2H, s, gem diol).[60] Mass spectrum *m/e* 244 (M^+). (Found: C, 50.30; H, 6.59. Calc. for $C_{11}H_{18}O_7$: C, 50.38; H, 6.87%.)

Tetramethyl 1 - {*bis*(*ethoxycarbonylmethyl*)*methyl*} *bicyclo*[3.3.0]*octane* - 3,7 - *dione* 2,4,6,8 - *tetracarboxylate* (**39a**)

Dimethyl 3-ketoglutarate (**1**, 10.0 g, 0.057 mol) was added to an aqueous sodium bicarbonate solution (180 ml, pH 8.3) and the mixture stirred for 10 min. Ethyl 3 - carbethoxymethyl - 4,5 - dioxopentanoate (**38**, 5.1 g, 0.021 mol) was added, and the mixture was stirred at room temp for 7 days. Upon acidification to pH 6.8 with cold hydrochloric acid (1 *N*), crystals of **39a** precipitated from the solution and were collected by filtration. The filtrate was extracted with chloroform (3 × 150 ml) dried (Na_2SO_4) and concentrated under vacuum. The residue was chromatographed on silica gel (benzene–ethyl acetate, gradient elution) to give 11.0 g of an oil which was dissolved in hot methanol and left to crystallize overnight. The total yield of crystals of **39a** was 5.90 g (51%): m.p. 135–137° (from methanol); IR (KBr) 3500–2950, 1740–1610 (br ester and enol absorptions); NMR ($CDCl_3$) δ 1.25 (6H, t, J = 7 Hz), 2.50 (5H, multiplet), 3.80 (16H, 4 × OCH_3 groups overlapping with two other protons), 4.05 (4H, q, J = 7 Hz) and δ 9.57 (1H, broad enol, D_2O exchange). Mass spectrum *m/e* 556 (27, M^+), 524 (36), 492 (91), 460 (63). In order to obtain a second crop of **39a**, it was sometimes necessary to chromatograph the mother liquors over silica gel. (Found: C, 53.95; H, 5.74. Calc. for $C_{25}H_{32}O_{14}$: C, 54.06; H, 5.74%.)

Preparation of tetramethyl - 1 - {*bis*(*ethoxycarbonylmethyl*) - *methyl*} *bicyclo*[3.3.0]*octane* - 3,7 - *dione* 2,4,6,8 - *tetracar* - *boxylate* (**39a**) *in citrate/phosphate buffer*

Dimethyl 3-ketoglutarate (**1**, 10.0 g, 0.057 mol) was added to a citrate/phosphate buffer system (100 ml, pH 5.6) and stirred for 10 min. Ethyl 4,5 - dioxo - 3 - carbethoxymethylpentanoate (**38**, 5.1 g, 0.021 mol) was then added at room temp with stirring. Since **38** was not completely soluble in the buffer, methanol was added until the solution clarified. Additional amounts of the citrate/phosphate buffer solution were subsequently added until the solution became slightly turbid; stirring was continued for 2 weeks. Since no precipitate formed during this process the reaction mixture was extracted with chloroform (3 × 150 ml); the chloroform extracts were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on silica gel (benzene–ethyl acetate, gradient elution) to yield an oil (13.5 g) which was dissolved in hot methanol and allowed to crystallize. A white crystalline solid (**39a**, 5.0 g, 42.1%) was obtained which was identical in all respects with **39a** reported in the previous experiment.

Preparation of tetramethyl 2 - *carboxymethyl* - 2 - *hydroxy* - 4 - *oxo* - 6 - *phenyl* - 1,3,5 - *cyclohexanetricarboxylic acid ester*[61]

Dimethyl 3-ketoglutarate (11.0 g, 0.063 mol) was added to aqueous bicarbonate buffer (200 ml, pH 8.3) and stirred for 10 min. Benzaldehyde (3.5 g, 0.032 mol) was added to this solution and the reaction stirred for 2 days. The reaction mixture was filtered and the precipitate washed with cold methanol to give 13.1 g (95.3%) of a white crystalline powder identical in all respects with the title compound: m.p. 187–188°; IR (KBr) 3540 (OH), 2960 (s, CH), 1730 (br, C=O) and 1150 cm^{-1}; NMR (DMSO–d_6) δ 2.65 (2H, d of d, J = 17 Hz), 3.40 (13H, multiplet), 3.90 (1H, t, J = 12 Hz), 4.40 (1H, d, J = 12 Hz), 5.38 (1H, s), 7.23 (5H, s). Mass spectrum C.I. (NH_3) *m/e* 454 ($M^+ + 18$, 100), 437 ($M^+ + 1$, 100), 436 ($M^+ + 10$). The spectral data are identical with those of an authentic sample of the ester prepared by the method of W. Hänsel and R. Haller, *Arch. Pharm.* **303**, 334 (1970). (Found: C, 57.51; H, 5.60. Calc. for $C_{21}H_{24}O_{10}$: C, 57.79; H, 5.50%.)

1 - {*Bis*(*carboxymethyl*)*methyl*} *bicyclo*[3.3.0]*octane* - 3,7 - *dione* (**40**)

The tetramethyl bicyclo[3.3.0]octane - 3,7 - dione - 2,4,6,8 - tetracarboxylate (**39a**, 4.0 g, 0.007 mol) was added to a solution of concentrated hydrochloric acid (16 ml), glacial acetic acid (28 ml), and water (3 ml). The mixture wqs refluxed until CO_2 evolution ceased, (approximately 8 hr). The solution was cooled and extracted with chloroform (4 × 50 ml). The combined extracts were dried (Na_2SO_4) and concentrated under vacuum. Toluene (200 ml aliquots) was added to the oil and removed under reduced pressure until the acetic acid had been flashed from the residue. The solid which remained was boiled in ethyl acetate and allowed to cool. A white crystalline solid was filtered from the solution to provide **40** (1.5 g, 76.5%): m.p. 180–185° (EtOAc); IR (KBr) 3500–2800 (br), 1730, 1710 and 1400 cm^{-1}; NMR (Me_2SO–d_6) δ 2.40 (14H, m), 12.0 (2H, br singlet). Mass spectrum *m/e* 268 (2, M^+), 250 (26), 232 (100), 206 (47), 204 (45), 190 (62), 162 (78). (Found: C, 58.16; H, 6.01. Calc. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01%.)

Tetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$]*tridecane*-2,6,8,12-*tetraketone* (**41**)

The bicyclo[3.3.0]octane - 3,7 - dione derivative (**40**, 0.60 mg, 2.3 mmol) was added to a solution of cumene (45 ml), diglyme (21 ml) and naphthalene - 1 - sulfonic acid (0.5 g, 2.0 mmol), and the mixture refluxed for 4 days. The reaction was cooled and the solid which had precipitated filtered from the medium to provide **41** (0.40 mg, 78% yield) as a grey microcrystalline solid. Sublimation (190°, 0.02 mm Hg) gave a white microcrystalline solid: m.p. 288° [dec], recrystallized from DMF; IR (FT, KBr) 2960, 1769.5 (m), 1737 (s), 1710 (s) and 1697 (w) cm^{-1}; NMR–^1H (pyridine–d_5) δ 2.51 (2H, d, J = 6.5 Hz), 2.59 (2H, d, J = 6.5 Hz), 2.87 (2H, d, J = 8.4 Hz), 2.95 (2H, d, J = 8.4 Hz), 3.08 (2H, sextet) and 4.05 (2H, s)]; NMR–^{13}C (from TMS) δ (Me_2SO–d_6) 37.5, 44.8, 62.5, 65.8, 207.0 ppm (proton decoupled spectrum). Mass spectrum 232 (100, M^+), 204 (4), 190 (13), 170 (5), 163 (20), 162 (33), 161 (16), 149 (5), 148 (7), 147 (6), 137 (12), 136 (34), 135 (21), 134 (25), 122 (18), 121 (17), 120 (15), 105 (18), 94 (12), 91 (22); chemical ionization (NH_3), *m/e* 240 (100, $M^+ + 18$), in NO, *m/e* 262 (100, $M^+ + 30$). High resolution mass spectrum *m/e* 232.0739 (95, M^+), 204.0768 (65), 190.0640 (80), 162.0689 (90). (Found: C, 67.78; H, 5.37. Calc. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.24%.)

Since the mother liquors from the above filtration contained only diacid **40** and naphthalene - 1 - sulfonic acid, it is believed the yield of this conversion can be increased above the 85% level although no attempt has been made as yet to do this.

Reaction of tetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$]*trideca* - 2,6,8,12 - *tetrake* - *tone* (**41**) *with methanol*

Tetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$]tridecane - 2,5,6,12 - tetraketone (**41**, 5.0 mg, 0.021 mmol) was added to methanol (2 ml) and stirred. The reaction was monitored by tlc at 30 min intervals. After stirring for 8 hr no new spots could be seen. The reaction was heated to reflux and after 16 hr all of the starting material had disappeared and a new spot of higher R_f could be seen. The new spot had an R_f value identical with that of dimethyl 1,3'-glutarate bicyclo[3.3.0]octane - 3,7 - dione (**39b**) prepared by an alternate route [IR ($CDCl_3$), 1740 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.60–3.20 (multiplet) and 3.64 (3H, s)]. No further purification or isolation was done. The methanol employed in this experiment was not previously dried.

This reaction was repeated at room temp after the ketone **41** had been dissolved in pyridine. Addition of methanol followed by stirring at room temp for 6 hr again led to isolation only of starting material **41**.

Tetramethyl tricyclo[6.3.3.0^{1,5}]*undeca - 11 - ene - 3,7 - dione 2,4,6,8 - tetracarboxylate* (**50**)

Cyclooct - 5 - ene - 1,2 - dione **49** (6.5 g, 0.047 mol) prepared by the method of Yates[42] was added to aqueous citrate–phosphate buffer (100 ml, pH 5.6) and dimethyl 3-ketoglutarate **1** (16.39 g, 0.094 mol) was added to the mixture at room temp. In order to obtain a homogeneous solution, methanol (100 ml) was then added to the reaction and the liquid was stirred at room temp for two days. A white solid precipitate was collected by vacuum filtration and washed with methanol to provide **50** (18.1 g; 0.2 g additional material was obtained from the mother liquors, total yield, 86.3%): m.p. 177–179°; IR (KBr) 1740 and 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.95–2.90 (8H, m), 3.60 and 3.75 (14H, two singlets overlapping with two other protons, 4× OCH_3), 5.65 (2H, m). Mass spectrum *m/e* 474 (M^+). (Found: C, 60.45; H, 5.38. Calc. for $C_{24}H_{26}O_{10}$: C, 60.75; H, 5.48%.)

Tricyclo[6.3.3.0^{1,5}]*undec-11-ene-3,7-dione* (**51**)

The tetraester **50** (4.5 g) was slurried in a solution composed of aqueous hydrochloric acid [75 ml, 10% (v/v)] and glacial acetic acid (40 ml). The mixture was brought to reflux, and held there until all of the solid had dissolved and no further evolution of carbon dioxide was observed. The solution was cooled in an ice bath, chloroform (200 ml) was added and cold (ice) aqueous sodium carbonate solution was dripped in until the solution became slightly alkaline (ph 8). The organic layer was separated and the aqueous layer which remained was extracted with chloroform (3×50 ml). The combined extracts were dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The oily residue (2.1 g) was purified by chromatography on alumina (chloroform) to provide a 90% yield of **51** as an off-white solid: m.p. 75–77°; IR (KBr) 1738 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (4H, m), 2.40 (4H, m), 2.45 (4H, s), 2.55 (4H, s), and 5.60 (2H, t, distorted); carbon-^{13}NMR ($CDCl_3$) δ 25.0 (t), 34.51 (t), 48.82 (s), 51.93 (t, intense signal), 128.61 (d) and 215.72 (s, C=O). Masss spectrum (C.I., CH_4), 219 (M^+ + 1, 100). (Found: C, 77.00; H, 8.00. Calc. for $C_{14}H_{18}O_2$: C, 77.06; H, 8.25%.)

Preparation of 11,12 - *dihydroxytricyclo* [[6.3.3.0^{1,5}]*undecane - 3,7 - dione*

The diketone **51** (7.74 g, 0.036 mol) dissolved in tetrahydrofuran (15 ml) was added dropwise to a solution [which contained N - methylmorpholine - N - oxide (5.5 g, 0.041 mol), osmium tetroxide (0.037 g, 0.16 mmol), t-butanol (65 ml), tetrahydrofuran and water (7 ml)] maintained at 0° (ice bath). The addition required 30 min. The liquid was then allowed to warm to room temp, at which time it was monitored by tlc. After 4 hr tlc indicated the absence of starting material after which the mixture was filtered through celite to remove the catalyst. The solvent was removed from the filtrate under reduced pressure and the residue was taken up in ethyl acetate (150 ml). The organic layer was washed with dilute hydrochloric acid [10% (v/v)], separated and the aqueous layer was extracted with chloroform (3× 150 ml). The aqueous layer was further extracted with ethyl acetate on a continuous extractor. The combined extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to provide the desired 11,12 - dihydroxytricyclo[6.3.3.0^{1,5}]undecane - 3,7 - dione (5.8 g, 64% yield). Continuous extraction of the filtrate provided another 15% of the desired diol as an oil; IR (neat) 3465 (broad OH) and 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (8H, m), 2.40 (8H, s), 3.9 (2H, m), 4.30 (2H, broad s, disappeared on addition of D_2O to sample). Mass spectrum *m/e* 252 (M^+).

This material was used directly in the next experiment.

Preparation of diketo diacid (**45a**)

The dihydroxydione (5.8 g, 0.023 mol) obtained from the previous experiment was dissolved in acetone (360 ml) and cooled in an ice bath. Jones' reagent [14.0 g of CrO_3, 12 ml of conc H_2SO_4 diluted to 100 ml with H_2O] was added dropwise at 0° until the solution developed a permanent orange–brown color at which time the solution was stirred for an additional 30 min (0°). After this, ethyl acetate (360 ml) and water (360 ml) were added followed by addition of sodium bisulfite until the ethyl acetate layer became clear. The mixture was then concentrated under reduced pressure to remove the acetone, followed by several extractions with ethyl acetate (4 × 500 ml). The organic layer was dried (Na_2SO_4), while the aqueous layer was subjected to continuous extraction (ethyl acetate) for several days. The combined organic layers were concentrated under reduced pressure to provide the diacid **45a** (3.9 g, 60% yield). The yield could be increased (15%) by continuous extraction of the aqueous layer with ethyl acetate over longer periods of time. The diacid (**45a**) was purified by heating in ethyl acetate to provide a white crystalline solid: m.p. 220°; IR (KBr) 3100–2800, 1740, and 1710 cm^{-1}; NMR (DMSO–d_6) δ 1.50–2.00 (4H, m), 2.05–2.60 (4H, m), 2.40 (8H, s) and 10.5 (2H, broad singlet); carbon-13 NMR (DMSO–d_6) 29.37, 30.78, 48.14, 49.33, 175.61 and 218.08 ppm. Mass spectrum *m/e* 282 (M^+). (Found: C, 59.37; H, 6.25. Calc. for $C_{14}H_{18}O_6$: C, 59.57; H, 6.38%.)

Tetracyclo[6.6.0.0^{1,5}.0^{8,12}]*tetradecane - 2,7,9,14 - tetraone* (**44**)

Naphthalene-1-sulfonic acid (0.69 g, 0.0028 mol) was added to a solution of benzene (70 ml) and dioxane (25 ml) and the mixture heated to reflux for 24 hr; water was removed *via* a Dean–Stark trap. The diacid **45a** (0.8 g, 0.0028 mol) was then added, and the Dean–Stark trap replaced by a fresh trap containing dry benzene (10 ml). The reaction mixture was subsequently refluxed for eight days; the precipitate which formed was filtered from the solution to provide **44** (0.32 g, 47% yield) as an off-white solid. Additional quantities (15%) of **44** were obtained by adding naphthalene - 1 - sulfonic acid (50 mg) to the filtrate and heating the mixture to reflux for six additional days. The combined solids were crystallized from DMSO: m.p. 309°; IR (FT, KBr) 1759.9 (s) and 1710.7 (w) cm^{-1}; NMR (DMSO–d_6) δ 2.20 (2H, m), 2.35 (4H, m), 2.50 (2H, m), 2.90 (4H, s), 3.20 (2H, s, β-diketone proton); carbon-13 NMR (DMSO–d_6) 27.65 (t), 38.95 (t), 47.55 (t), 53.47 (s), 69.47 (d), 206.07 (s), 207.29 (s). (Found: C, 68.00; H, 5.60. Calc. for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69%.)

Treatment of **44** *with methanol*

The tetraketone (**44**, 100 mg) was added to methanol (20 ml), and the mixture left to stir at room temp. Tlc (silica gel, ethyl acetate/benzene) indicated the presence of a new compound after several hours. The starting material had disappeared after stirring for 10 hr and the new compound was found to be identical in all respects with **45b** [IR (KBr) 1745 and 1728 (sh) cm^{-1}; NMR ($CDCl_3$) δ 1.60–2.50 (8H, m), 2.40 (8H, s), 3.70 (6H,s, 2OCH_3). Mass spectrum (C.I., CH_4) 311 (M + 1, 100%)] prepared by an unambiguous route. The methanol employed in this sequence was not previously dried. The diester produced was shown to be **45b**; however, both the diacid **45a** and a monoester/monoacid were also present in the reaction. The ketone **44** did not open up readily to **45b** in the presence of dry methanol; therefore, it is presumed the water present in the methanol lead regiospecifically to the diacid or the monoester/monoacid and these materials catalyzed the regiospecific addition of methanol to **44** to furnish diester **45b**: m.p. 145–6° (CH_3OH). The tetraketone **44** was converted to **45b** in only 7 hr when stirred in methanol at 55°.

1,5 - *Dimethyl* 2,4,6,8 - *tetramethoxycarbonylbicyclo*[3.3.0]*octane - 3,7 - dione* (**4**, R=R'=CH_3)

Dimethyl 3-ketoglutarate (70 g, 0.40 mol) was dissolved in 400 ml of a freshly prepared solution of sodium hydrogen carbonate (5.6 g, pH 8.3). Biacetyl (17.2 g, 0.20 mol) was added to the solution in one portion and the resulting mixture was stirred at room temp for 24 hr, during which time white crystals separate. The solid was collected by suction filtration and dried in vacuum to give 67–68 g, m.p. 158–160° (lit.[2] 144–6°, sublimed). The filtrate was cooled in an ice bath, acidified to pH 5 (pHydrion paper) with dilute HCl, and extracted with three 100 ml portions of chloroform. The combined organic layers are washed with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to yield an additional 2–3 g (87–89% total). Recrystallization from hot methanol gives 66–67 g (83–84%), m.p. 159–160°. (Found: C, 54.45; H, 5.30. Calc. for $C_{18}H_{22}O_{10}$: C, 54.28; H, 5.53%.)

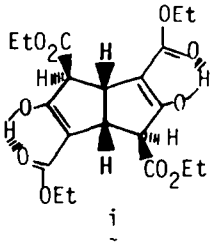
Acknowledgement—This work was generously supported by grants from the Petroleum Research Foundation (12052-ACI) and the National Science Foundation (CHE-7910302). We wish to thank Dr. Peter Roller for high-resolution mass spectrometry and Dr. Robert Highet for the high-resolution NMR spectra. We are also grateful to Mr. Frank Laib and Mr. Noel Whittaker for the low-resolution mass spectra. This work could not have been accomplished without the able help of many students including Robert Weber, Daisy Yang-Lan, Jay Wrobel, Winston Han, Mahendra Deshpande, Robert Dovi, Dave Wichman and Drs. Gawish and Avasthi; we will always be grateful for their enthusiasm, energy and persistence. We wish to thank Dr. Steven Bertz (Bell Laboratories) for sharing his work on a "New Theory of Molecular Complexity,"[55] prior to publication, and Dr. Alfred Bader for his continued interest in this work. Finally, we wish to acknowledge Ms. Gail Boviall and Ms. Delphine Welch for their fine technical assistance.

REFERENCES

[1a]J. Oehldrich, J. M. Cook and U. Weiss, *Tetrahedron Letters* 4549 (1976); [b]R. Mitschka, J. M. Cook and U. Weiss, *J. Am. Chem. Soc.* **100**, 3973 (1978).

[2]U. Weiss and J. M. Edwards, *Tetrahedron Letters* 4885 (1968).

[3]Here, and elsewhere in this paper, β-keto esters such as **3** are written in the keto form for easy correlation with the ketones resulting from hydrolysis and decarboxylation (e.g. **4**). In reality, tetraethyl *cis* - bicyclo[3.3.0]octane 3,7 - dione - 2,4,6,8 - tetracarboxylate has been shown to exist in solution as the bis-enol tautomer **i** [P. Camps, *Tetrahedron Letters* 4067 (1974)].



i

[4a]G. Vossen, Dissertation, Bonn, 1910; [b]P. Yates, E. S. Hand and G. B. French, *J. Am. Chem. Soc.* **82**, 6347 (1960); see also S. Tanaka, *Ibid.* **80**, 5264 (1958).

[5a]J. M. Edwards, I. H. Qureshi, U. Weiss, T. Akiyama and J. V. Silverton, *J. Org. Chem.* **38**, 2919 (1973); [b]T. Akiyama and J. V. Silverton, *Acta. Crystallographica* **B31**, 2336 (1975).

[6]K. C. Rice, N. E. Sharpless, U. Weiss and R. J. Highet, *Tetrahedron Letters* 3763 (1975).

[7]K. C. Rice, U. Weiss, T. Akiyama, R. J. Highet, T. Lee and J. V. Silverton, *Ibid.* 3767 (1975).

[8]S. H. Bertz, Ph.D. Thesis, Harvard University, 1978. S. Bertz, A. Gawish, U. Weiss and J. M. Cook, *Org. Syn.* submitted.

[9]S. Yang-Lan, M. Mueller-Johnson, J. Oehldrich, D. Wichman, U. Weiss and J. M. Cook, *J. Org. Chem.* **41**, 4053 (1976).

[10]C. F. H. Allen, *Chem. Rev.* **37**, 209 (1945).

[11]O. Campos and J. M. Cook, *J. Heterocyclic Chem.* **14**, 711 (1977).

[12]F. B. Japp and G. D. Lander, *J. Chem. Soc.* **71**, 139 (1897); S. Yang and J. M. Cook, *J. Org. Chem.* **41**, 1903 (1976).

[13]D. Wichman, J. Oehldrich and J. M. Cook, unpublished results.

[14]K. Avasthi, M. N. Deshpande, Wen-Ching Han, U. Weiss and J. M. Cook, *Tetrahedron Letters*, **22**, 3475 (1981).

[15a]J. Oehldrich, M. S. Thesis, University of Wisconsin–Milwaukee (1976); [b]S. H. Bertz, W. O. Adams and J. V. Silverton, *J. Org. Chem.* **46**, 2828 (1981).

[16]H. W. Wanzlick, *Chem. Ber.* **86**, 269 (1953).

[17]R. P. Linstead and E. M. Meade, *J. Chem. Soc.* 935 (1934).

[18]J. W. Barrett and R. P. Linstead, *Ibid.* 611 (1936).

[19]W. C. Han, K. Takahashi, R. Mitschka, U. Weiss, J. M. Cook and J. V. Silverton, *J. Am. Chem. Soc.*, submitted.

[20a]L. H. Zalkow, R. N. Harris III, D. Van Derveer and J. A. Bertrand, *J. Chem. Soc. Chem. Commun.* 457 (1977); [b]J. A. Elvidge, D. R. J. Laws, J. D. McGuinness, A. M. Davis and P. V. R. Shannon, *J. Chem. Soc. Perkin I* 1250 (1979); [c]F. Bohlmann and J. Jakupovic, *Phytochemistry* **19**, 259 (1980); F. Bohlmann, N. Le Van and J. Pickardt, *Chem. Ber.* **110**, 3777 (1977).

[21]K. Kaneda, R. Takahashi, Y. Iitaka and S. Shibata, *Tetrahedron Letters* 4609 (1972).

[22]L. Wolff, *Justus Liebigs Ann.* **260**, 79 (1890).

[23]S. Zaheer, I. Kacker and N. Rao, *Chem. Ber.* **89**, 351 (1956).

[24]J. Pappas, W. Keaveney, E. Gancher and M. Berger, *Tetrahedron Letters* 4273 (1966).

[25]P. E. Eaton, G. Giordano, G. Schloemer and U. Vogel, *J. Org. Chem.* **41**, 2238 (1976).

[26]H. Loewenthal and Z. Neuwirth, *Ibid.* **32**, 517 (1967).

[27]Y. Ohfune, H. Shirahama and T. Matsumoto, *Tetrahedron Letters* 2869 (1976); R. L. Cargill and J. W. Crawford, *J. Org. Chem.* **35**, 356 (1970); R. L. Cargill and A. M. Foster, *Ibid.* **35**, 1971 (1970); W. G. Dauben, *Ibid.* **42**, 3787 (1977).

[28]A. Gawish, R. Mitschka, U. Weiss and J. M. Cook, *Tetrahedron Letters* **22**, 211 (1981).

[29]L. H. Zalkow, R. N. Harris III and D. Van Derveer, *J. Chem. Soc. Chem. Commun.* 420 (1978); F. Bohlmann and J. Jakupovic, *Phytochemistry* **19**, 259 (1980); F. Bohlmann, C. Zdero, R. Bohlmann, R. M. King and H. Robinson, *Ibid.* **19**, 579 (1980).

[30a]J. Strating, S. Reiffers and H. Wynberg, *Synthesis* 211 (1971); [b]J. Wrobel and J. M. Cook, unpublished work.

[31]R. W. Weber and J. M. Cook, *Can. J. Chem.* **56**, 189 (1978).

[32]J. J. Bloomfield, D. C. Owsley and J. M. Nelke, *Organic Reactions* (Edited by W. G. Dauben), Vol. 23, p. 309. Wiley, New York (1976).

[33]J. Wrobel and J. M. Cook, *Synthetic Commun.* **10**, 333 (1980).

[34]K. Takahashi, B. Dovi, U. Weiss, S. Bertz and J. M. Cook, unpublished results.

[35]R. Hoffmann, *Pure and Appl. Chem.* **28**, 181 (1971).

[36]M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson and E. A. Bowler, *J. Am. Chem. Soc.* **72**, 3704 (1950).

[37]R. K. Mitschka, M. S. Thesis, University of Wisconsin–Milwaukee, Milwaukee, Wisconsin (1978).

[38]A detailed study of this type of conversion has been carried out recently in our laboratory. The base, pyrrolidine, which is smaller in size than piperidine, has been found to be more effective in the formation of such enones. This work will be presented elsewhere [M. Deshpande, W. Han and J. M. Cook, manuscript in preparation].

[39]In all of these condensation reactions with **1**, tap water was used to prepare the aqueous buffer. The metal ions in tap water seemed to be significant: Keese has found the condensation is far less effective in distilled water. R. Keese, private communication.

[40]R. Keese, A. Pfenninger and A. Roesle, *Helv. Chim. Acta* **62**, 326 (1979).

[41]K. Takahashi, J. M. Cook and U. Weiss, unpublished results.

[42]P. Yates, E. G. Lewars and P. H. McCabe, *Can. J. Chem.* **50**, 1548 (1972).

[43]S. Nozoe and A. Itai, *Chem. Commun.* 872 (1971).

[44]M. Deshpade, W. Han, U. Weiss and J. M. Cook, unpublished results.

[45]K. Avasthi, U. Weiss and J. M. Cook, unpublished results.

[46]L. A. Paquette, *Topics in Current Chemistry* **79**, 41 (1979).

[47]P. E. Eaton, *Tetrahedron* **35**, 2189 (1979).

[48]I. T. Jacobson, Ph.D. Thesis, University of Lund (1973).

[49a]R. B. Woodward, T. Fukunaga and R. C. Kelly, *J. Am. Chem. Soc.* **86**, 3162 (1964); [b]M. J. Wyvratt and L. A. Paquette, *Tetrahedron Letters* 2433 (1974); [c]C. Mercier, P. Soucy, W. Rosen and P. Deslongchamps, *Synth. Commun.* **3**, 161 (1973); P. Deslongchamps, U. Cheriyan, Y. Lambert, J.-C. Mercier, L. Ruest, R. Russo and P. Soucy, *Can. J. Chem.* **56**, 1687 (1978).

[50]P. E. Eaton, R. H. Mueller, G. R. Carlson, D. A. Cullison, G. F. Cooper, T. C. Chou and E.-P. Krebs, *J. Am. Chem. Soc.* **99**, 2751 (1977).

[51]L. A. Paquette, R. A. Snow, J. L. Muthard and T. Cynkowski, *Ibid.* **100**, 1600 (1978).

[52]L. A. Paquette, D. W. Balogh, R. Usha, D. Kountz and G. G. Christoph, *Science* **211**, 575 (1981).

[53]A number of natural products have been isolated with ring systems composed entirely, or in part, of polyquinane units; however, these are too numerous to mention here. This list will be presented at a later date, more appropriately included in a review.

[54]Isocomene: L. A. Paquette and Y. K. Han, *J. Org. Chem.* **44**, 4014 (1977); W. Oppolzer, W. Battig and T. Hudlicky, *Helv. Chim. Acta.* **62**, 1493 (1979); M. C. Pirrung, *J. Am. Chem. Soc.* **101**, 7130 (1979). Modhephene: A. B. Smith III and P. J. Jervis, *Abstracts of Papers*, 179th National Meeting of the American Chemical Society, Houston, Texas; American Chemical Society, Washington, D.C. (1980); ORGN 63: M. Karpf and S. Dreiding, *Tetrahedron Letters* **21**, 4569 (1980); A. B. Smith III and P. J. Jerris, *J. Am. Chem. Soc.* **103**, 194 (1981); H. Schostorez and L. A. Paquette, *Ibid.* **103**, 722 (1981). Hirsutic acid: H. Hashimoto, K. Tsuzuki, F. Sakan, H. Shirahama and T. Matsumoto, *Tetrahedron Letters* 3745 (1974); P. T. Lansbury, N. Y. Wang and J. E. Rhodes, *Ibid.* 2053 (1972); K. Hayano, Y. Ohfune, H. Shirahama and T. Matsumoto, *Ibid.* 1991 (1978). B. M. Trost, C. D. Shuey, F. J. Dinnino and S. S. McElvain, *J. Am. Chem. Soc.* **101**, 1284 (1979). Hirsutene: K. Tatsuta, K. Akimoto and M. Kinoshita, *J. Am. Chem. Soc.*, **101**, 6116 (1979); A. E. Greene, *Tetrahedron Letters* **21**, 3059 (1980). T. Hudlicky, F. J. Koszyk, T. M. Kutchan and J. P. Sheth, *J. Org. Chem.* **45**, 5020 (1980). Coriolin: K. Tatsuta, K. Akimoto and M. Kinoshita, *J. Antibiot.* **23**, 100 (1980); S. Danishefsky, R. Zamboni, M. Kahn and S. J. Etheredge, *J. Am. Chem. Soc.* **102**, 2097 (1980).

[55]S. H. Bertz, *A new theory of molecular complexity*, presented at the Second Chemical Congress of the North American Continent, Las Vegas, Nevada, August 24–29, 1980, Abstract No. ORGN-50; S. H. Bertz, *J. Am. Chem. Soc.*, **103**, 3599 (1981).

[56]R. M. Coates, S. K. Shah and R. W. Mason, *J. Am. Chem. Soc.* **101**, 6765 (1979).

[57]Y.-K. Han and L. A. Paquette, *J. Org. Chem.* **44**, 3731 (1979).

[58]K. C. Nicolaou, W. J. Sipio, R. L. Magolda, S. Seitz and W. E. Barnette, *J. Chem. Soc., Chem. Commun* 1067 (1978); M. Shibasaki, J. Ueda and S. Ikegami, *Tetrahedron Letters* 433 (1979).

[59]W. G. Dauben and D. M. Walker, *J. Org. Chem.* **46**, 1103 (1981).

[60]B. I. Ionin and B. A. Ershov, *NMR Spectroscopy in Organic Chemistry*. Plenum Press, New York (1970).

[61]During the preparation of the 1,2-dicarbonyl compound **38**, benzaldehyde was formed as a byproduct. This must be carefully removed from the dione **38** since **1** also reacts with benzaldehyde to provide tetramethyl 2 - carboxymethyl - 2 - hydroxy - 4 - oxo - 6 - phenyl - 1,3,5 - cyclohexane tricarboxylic acid ester. An authentic sample of the ester was prepared according to the method of Hänsel [W. Hänsel and R. Haller, *Arch. Pharm.* **303**, 334 (1970)].