Synthesis of Peristylane and the *acs*-(C_s)-C_{14}-Tetraquinane, C_{14}-Pentaquinane, and Norperistylane Systems

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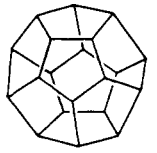
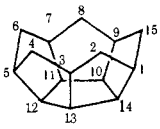
Abstract: The design and execution of the first synthesis of the $C_{15}H_{20}$, hexacyclic hydrocarbon peristylane (hexacyclo[7.5.1.$0^{3,13}$.$0^{5,12}$.$0^{7,11}$.$0^{10,14}$]pentadecane) are presented in full detail along with the preparation of a variety of peristylane derivatives. Intermediates in the synthetic scheme contain the *acs*-(C_s)-C_{14}-tetraquinane (tetracyclo[6.6.0.$0^{2,6}$.$0^{10,14}$]tetradecane), the C_{14}-pentaquinane (pentacyclo[6.6.0.$0^{2,6}$.$0^{3,13}$.$0^{10,14}$]tetradecane), and the norperistylane (hexacyclo[6.6.0.$0^{2,6}$.$0^{3,13}$.$0^{4,12}$.$0^{10,14}$]tetradecane) carbon skeletons, all novel systems described here fully for the first time. A new synthesis of β-(3-oxocyclopentyl)propionic acid, methyl ester is given along with the directions for its high yield conversion to *cis*-bicyclo[3.3.0]octane-2,8-dione. The first example of a hexacyclo[6.6.0.$0^{2,12}$.$0^{4,11}$.$0^{6,10}$.$0^{9,13}$]tetradecane is described. The proton and carbon magnetic resonance spectra of these compounds are given and discussed as appropriate. New examples of the synthetic utility of the reagents methanesulfonic acid–phosphorus pentoxide and ethyl 3-lithiopropyl acetaldehyde acetal are provided.

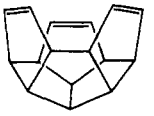
Dodecahedrane is a major synthetic challenge. A variety of imaginative plans have been advanced for the tactical synthesis of this molecule.[1] Each involves creation along the way of new ring systems simpler than dodecahedrane, but nonetheless interesting and challenging in their own right. Woodward's triquinacenes[1a] and Paquette's bivalvanes[1c] are notable examples from other laboratories. We are developing approaches to dodecahedrane from the peristylane (C_{15}-hexaquinane) and the C_{16}-hexaquinacene systems. This paper describes the synthesis of peristylane[1b] and its precursor ring systems, (C_s)-C_{14}-tetraquinane, C_{14}-pentaquinane, and norperistylane.[2]



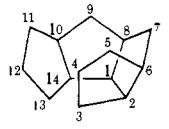
dodecahedrane



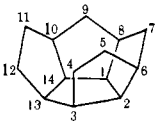
peristylane



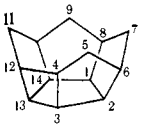
C_{16}-hexaquinacene



(C_s)-C_{14}-tetraquinane



C_{14}-pentaquinane



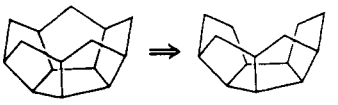
norperistylane

The frame of peristylane ($C_{15}H_{20}$) is made up of 15 carbon atoms joined together by 20 carbon–carbon bonds into six fused five-membered rings. The unsubstituted system has five mirror symmetry planes intersecting along a fivefold rotation axis. Peristylane is shaped rather like a bowl with a fluted rim. The hydrogens attached to the ten ring junction carbon atoms are cis to one another on the outside surface of the bowl. This stereochemical arrangement is certainly preferable to that of any "*epi*-peristylane", which would be considerably strained. The skeleton of peristylane is fairly rigid; movement is limited to breathing motions along the rim that bring alternate methylene groups toward one another. Additional bonding between any pair of peristylane atoms would lead to much more highly strained systems.

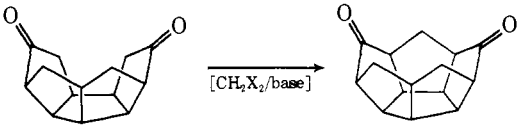
Two calculations of the heat of formation of peristylane have been made by Schleyer,[3] one using his, the other based on Allinger's estimate of the force fields involved. The results differ by nearly a factor of 2 and lead to strain energy estimates differing similarly. The higher value (Allinger) arises mainly in a larger estimate for nonbonded H···H interactions. In either case, however, the calculated strain energy of peristylane (38 or 65 kcal/mol) is still small, amounting at most to about 3 kcal/mol/C–C bond (cf. cubane at 16–18 kcal/mol/C–C bond).

Synthetic Design. Although unquestionably less complex than dodecahedrane, peristylane presented a synthetic problem of substantial dimensions. Simply stated, the problem was to put 15 carbon atoms together into six fused five-membered rings, maintaining control of relative stereochemistry as each of the ten ring junctions was constructed.

At the time this work was begun, there were only a few carbon systems known with more than two five-membered rings fused together. To our knowledge, the triquinacenes[1a] and the hirsutic acids[4] were the only firm examples. These systems each contain three five-membered rings.[5] No higher examples were known. As peristylane is hexacyclic, much needed to be done. An antithetic dissection to lesser systems was clearly called for. This sort of conceptual approach to the design of a synthesis starts with the molecule itself and moves backwards in stepwise fashion, breaking bonds along the way, in search of a reasonable starting material.[6] Thus, a pentacyclic precursor of the hexacyclic peristylane was arrived at by simply imagining the removal of one methylene group and with it two carbon–carbon bonds and one ring from peristylane. This sort

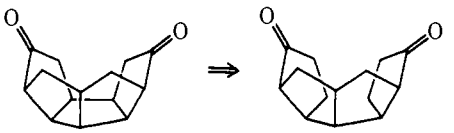


of mental dissection of a complex molecule down to simpler structures is not useful unless reasonable chemical processes from the real world can be found to repair the hypothetical undoings of the antithetic process. At the bench, conversion of the C_{14}-pentaquinane system above into a peristylane would require the introduction of a methylene bridge between two specific positions of special reactivity. Suitable activation would be provided in the diketone **1**; alkylation with a dihalomethane might actually give the peristylane **2.**



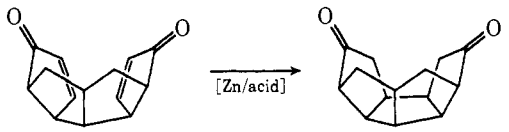
1 **2**

A source for the C_{14}-pentaquinane must next be found. It might be derived from the tetracyclic diketone **3** suggested by removal of one skeletal bond and one ring from **1**. The positions



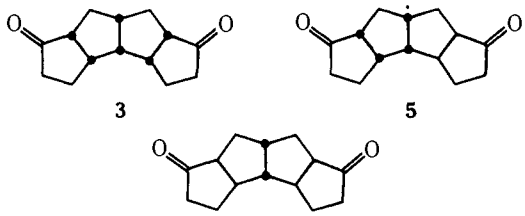
1 **3**

β to the carbonyl groups of diketone **3** would need to be activated for conversion to **1**. The bis-enone **4** has the necessary features; internal β-pinacol coupling would close it to **1**. Conveniently, the all-cis, all-syn stereochemistry of **4** holds the coupling β carbons in close proximity.



4 **1**

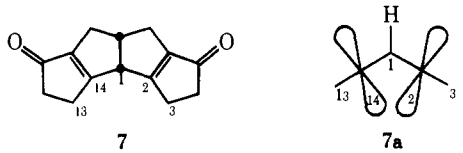
Little imagination was needed to see that a proper parent of bis-enone **4** was its precursor-in-thought, the saturated diketone **3**. The most critical aspect of this C_{14}-tetraquinane was its stereochemistry. The ring fusions must each be cis. This is the thermodynamically favored situation in simpler systems; the cis ring fusion of bicyclo[3.3.0]octane is known to be 6 kcal/mol more stable than the trans.[7] However, in **3** the rings must also be fused syn to one another. This all-syn arrangement is the most sterically crowded of the three possible cis-fused systems, **3**, **5**, and **6**. Since **3** is unfavored thermodynamically,



3 **5**

6

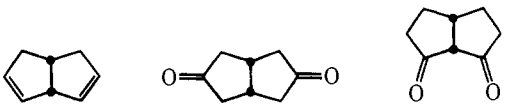
its synthesis had to be sought in a process controlled kinetically. Catalytic hydrogenation of the bis-enone **7** presented a reasonable opportunity for such control. The enone appears V-shaped when viewed head-on as in **7a**. Catalytic hydrogenation from the less hindered, outer side of the V would produce the diketone with the desired stereochemistry at the six junctions.



7 **7a**

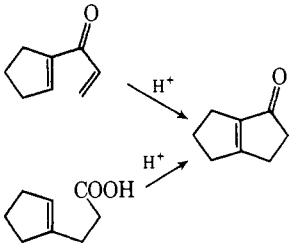
The projected intermediates **1**, **2**, **3**, **4**, and **7** have a mirror plane of symmetry in common with one another and with peristylane. This feature was sought purposefully in the execution of the antithetic dissection. It is a reasonable principle for pragmatists that the tactical synthesis of a symmetric molecule is often best accomplished from precursors having the same symmetry element(s) comparably located. This practice usually leads to a more direct and conceptually simpler synthesis than would otherwise be the case. Another benefit, sometimes underappreciated, is that it is much easier to interpret, understand, and be guided by nuclear magnetic resonance spectra of intermediate reaction products if the starting material is symmetric and the desired product is supposed to be.

Consideration must now be given to the synthesis of the tetracyclic bis-enone **7**. The choice of a precursor was not especially obvious, until one applied the notion of maintaining useful symmetry elements. *cis*-Bicyclo[3.3.0]octane has a mirror plane passing through a bound pair of carbon atoms exactly as in compounds **1**, **2**, **3**, **4**, and **7**. The ring system is fairly well-known.[8] Three carbon atoms have to be added to each ring to provide sufficient atoms to buildup the skeleton of **7**. Introduction of these atoms would require that the bicyclic compound carry proper handles. Carbonyl or olefin groups would be best as the majority of carbon–carbon bond forming reactions involves one or the other group. The symmetry principle indicated that these groups would be best placed in such a way as to retain the mirror plane of the parent. These considerations suggested diene **8** and the diketones **9** and **10**, all known compounds,[8] as potentially suitable substrates for symmetrical bis annulation to the tetraquinane **7**.



8 **9** **10**

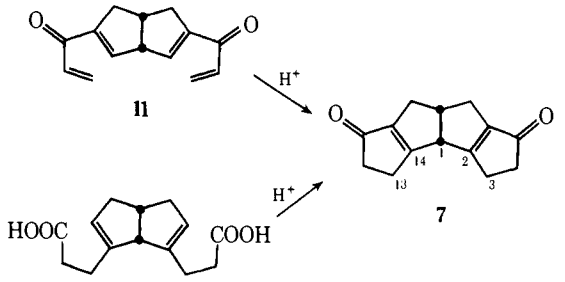
The desired quinane contains two α,β-unsaturated cyclopentenone subunits. Excellent methodology exists for the preparation of conjugated cyclopentenones. Variations on the Friedel–Crafts reaction are of particular utility; acid-catalyzed cyclizations of cross-conjugated ketones (eq 1)[9] or of γ,δ-unsaturated acids (eq 2)[10] are effective methods. If such re-



(1)

(2)

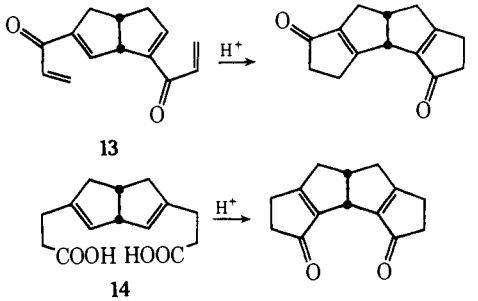
actions can be extended to polyfunctional cases, cyclization of **11** or **12** should give the required quinane bis-enone.



11 **7**

12

Synthesis of **11** or **12** from **8**, **9**, or **10** required attachment of suitably functionalized three-carbon chains, one on each ring. These additions must be controlled carefully. Improper introduction of the chains, as in **13** or **14**, would lead to one or another of the many unwanted isomers of **7** (e.g., eq 3). This

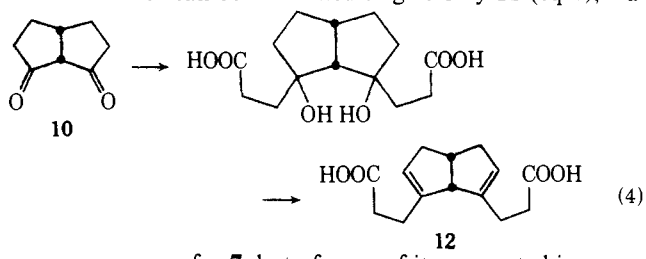


13 **14**

(3)

consideration effectively eliminated diene **8** and diketone **9** as acceptable precursors. Sufficient differentiation between the

reactive sites of the olefin bonds in **8** (e.g., in acylation reactions) or the positions α to the carbonyl groups in **9** (e.g., in addition/elimination reactions) cannot be accomplished without inordinate difficulty. Diketone **10,** fortunately, does not suffer from equivalent limitations. Addition of a propionic acid chain to each of its carbonyl carbons followed by elimination of water can be controlled to give only **12** (eq 4),[11] a

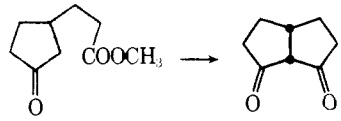


10 **12** (4)

proper precursor for **7,** but of none of its unwanted isomers. As we shall discuss later, a synthon equivalent to a $-CH_2CH_2COOH$ nucleophile was developed in the course of this work especially for this addition.

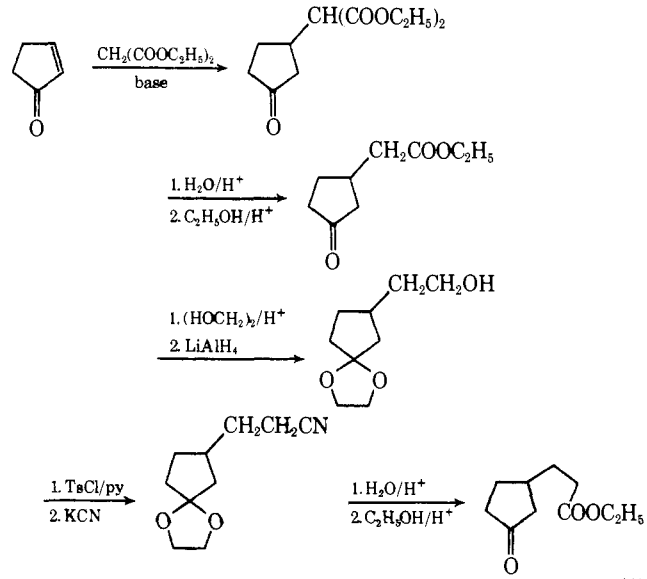
The general planning phase of the peristylane synthesis was now complete. The process of ring building can be divided conveniently into four stages: (a) construction of the bicyclic system; (b) symmetrical elaboration into the all-cis, all-syn (C_s)-C_{14}-tetraquinane system; (c) closure to a C_{14}-pentaquinane; and finally (d) addition of the 15th carbon atom and closure to the hexacyclic peristylane framework. The proof of any synthetic plan lies, of course, in its implementation.

***cis*-Bicyclo[3.3.0]octane-2,8-dione.** The first stage going forward in the peristylane synthesis was the preparation of diketone **10** in quantity. The single literature preparation available reported production of **10** in 30% yield by internal Claisen condensation of keto ester **15** induced by sodium hydride in benzene (eq 5, but **15** as the ethyl ester).[8c]



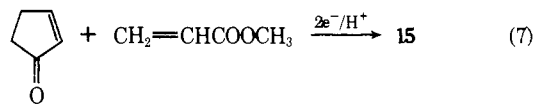
15 **10** (5)

The relatively simple appearance of keto ester **15** belied the effort necessary for its large scale synthesis. The reported preparation of Stetter et al.[8c] started from 2-cyclopentenone and proceeded via Michael addition of malonate, hydrolysis and decarboxylation, and classic chain lengthening (eq 6). Eight steps were required for an overall 17% yield (not optimized).



(6)

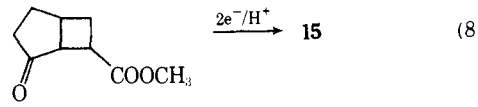
A synthesis more amenable to scale-up and requiring less effort was needed. Alternate approaches to **15** were sought with diligence, both on paper and in the laboratory. The simplest paper synthesis of keto ester **15** was reductive coupling of 2-cyclopentenone and methyl acrylate (eq 7). Indeed, treatment



(7)

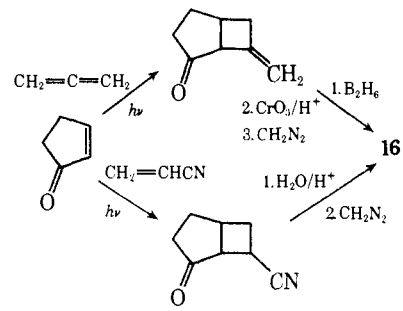
of these substances together in acetic acid with zinc or magnesium metal produced **15,** but only in trace amounts. Polymerization was, as expected, the predominant reaction. One hopes that in the future satisfactory methods will be found for controlling such mixed reductive couplings.

Alternatively, keto ester **15** could be approached (on paper) by reductive cleavage (decoupling) of the bicyclic keto ester **16** (eq 8). Compound **16** was prepared by two routes: (a) the



16 (8)

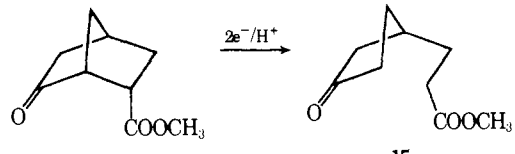
major photoadduct of allene to 2-cyclopentenone[12] was hydroborated, oxidized, and esterified (eq 9); and (b) the appropriate acrylonitrile photochemical adducts to 2-cyclopentenone were hydrolyzed and esterified (eq 10). Treatment of



(9) (10)

16 with zinc powder in refluxing propionic acid did give some cleavage to **15.** However, the approach was abandoned quickly as neither route to **16** was satisfactory for large-scale work.

Reductive cleavage of keto ester **17** (eq 11) was a more at-

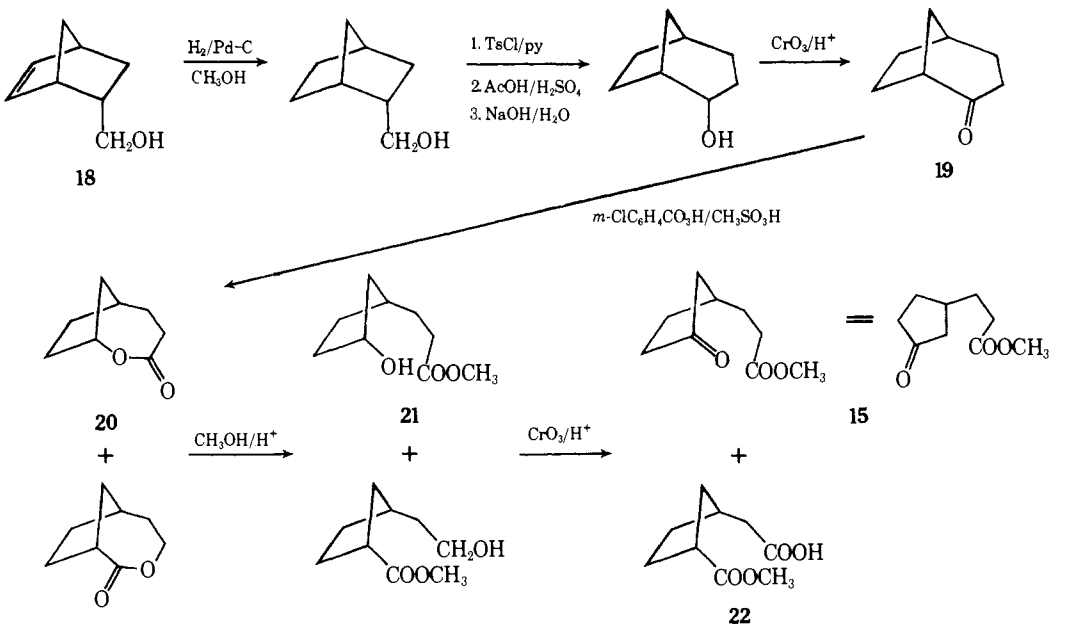


17 **15** (11)

tractive possibility as this material is very readily available.[13] However, quite disappointingly, this ester and its exo isomer were inert to zinc powder even in refluxing propionic acid.[14]

In due course, two new methods were developed for the preparation of keto ester **15** in synthetically useful amounts. The first of these, as outlined in Scheme I, started with 5-hydroxymethylbicyclo[2.2.1]hept-2-ene (**18**), prepared commercially and cheaply by Diels–Alder addition of cyclopentadiene to allyl alcohol. We converted **18** to bicyclo[3.2.1]-octan-2-one (**19**) following the fine scheme of Nedenskov et al.,[15] viz., catalytic olefin hydrogenation, preparation and solvolytic rearrangement of the tosylate, and subsequent hydrolysis and oxidation. We prepared 200–300-g quantities of **19** in single runs by this method in excellent yields. Baeyer–Villiger oxidation of **19** with *m*-chloroperbenzoic acid with methanesulfonic acid as catalyst produced a mixture of lactones; isomer **20** predominated, as was expected.[16] Opening and polymerization of the lactones under the reaction conditions produced polyesters, but these did not interfere with the

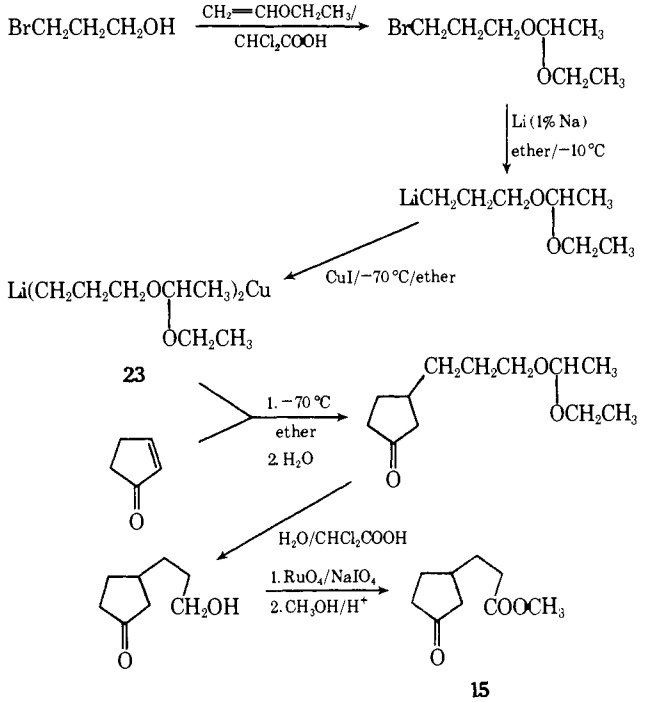
Scheme I



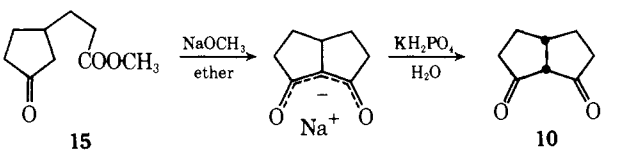
synthesis. Acid-catalyzed methanolysis of the mixture of polyesters and lactones gave a mixture of hydroxy esters, **21** predominating. Jones oxidation of the mixture gave the required keto ester **15** and the acid ester **22,** which was removed by extraction into aqueous base. By this route, keto ester **15** was obtained from bicyclo[3.2.1]octanol in an overall yield of 35–40%. Although the route was long, it did provide for the preparation of substantial quantities of **15** from relatively cheap starting materials.

A more graceful and shorter approach to the desired keto ester was also developed. It proceeded by conjugate addition of the lithium organocuprate **23** derived from 3-bromopropanol to 2-cyclopentenone (Scheme II). Acid hydrolysis of the adduct, oxidation of the product alcohol, and subsequent Fisher esterification gave the keto acid in 50% yield overall. We have already published the details of this method in full.[17] This scheme is the method of choice, for although cyclopentenone is costly, less labor and effort is involved in its conversion to **15** than in the transformations of Scheme I.

Scheme II



The final step in the first stage of the peristylane synthesis was closure of keto ester **15** to *cis*-bicyclo[3.3.0]octane-2,8-dione (**10**) by internal Claisen condensation (eq 5). This transformation was carried out in much higher yield than that reported by Stetter[8c] by treating **15** with a slight excess of sodium methoxide in dry ether. The reaction was driven to completion by precipitation of the sodium salt of the product β-diketone. For high yields, this reaction must be worked up with care. The β-diketone was fragile and was opened rapidly by acid or base in polar media. It was best to quench the reaction by addition of the mixture *to* a very well-stirred (Vibromixer) solution of potassium dihydrogen phosphate in water. In this way, the cyclization was carried out reproducibly with yields of dione of 85–95%.



(C_s)-C_{14}-Tetraquinanes. The preparation of diketone **10** marked the end of the first stage of the peristylane synthesis. According to plan, the second stage was elaboration of this eight-carbon bicyclic diketone to the 14-carbon olefin acid **12** and its cyclization into the (C_s)-C_{14}-tetraquinane system.

The conversion of **10** to **12** required the reaction of a three-carbon nucleophile terminating in a carboxyl group with each carbonyl group of diketone **10.** This was no small problem; carbon nucleophiles of sufficient reactivity (e.g., organometallics) are in general incompatible with carboxyl groups or simple derivatives thereof. For example, in an old literature method[18] this point was ignored altogether, and the problem was attacked head-on—methoxytetralone, ethyl 3-bromopropionate, and magnesium metal were refluxed together in toluene; less than 30% of product was derived from addition of the Grignard to the ketone. The ester moiety was not sufficiently unreactive. Clearly, a carboxyl group must be masked more securely.

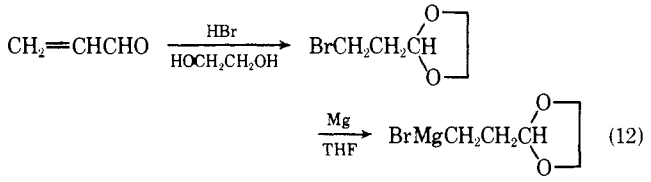
Orthoesters are masked carboxylic acids. Although Grignard reagents can be made to react with orthoesters, forcing conditions are generally required. Under milder conditions, therefore, a Grignard derived from an orthoester might be useful. A great deal of effort was put forth to prepare an orthoester of β-bromopropionic acid, a deceptively simple objective, but we were unable to make one. Other workers have

since encountered this difficulty and have offered reasonable explanations.[19]

A possible alternative to the orthoester mask, suggested by the work of Meyers,[20] was protection of the acid by incorporation into a dihydro-1,3-oxazine ring. Again, however, we could not prepare the necessary compound. The halide in such β-bromopropionic acid derivatives was too labile.

From the standpoint of minimal manipulation, the most desirable organometallic for the conversion of **10** to **12** would have had the terminal carbon in the carboxylic acid oxidation state. As we were unable to find such a reagent, we had to look instead for one in a lower oxidation state that we would correct later in the synthesis.

The Grignard **24** carries a carboxylic acid group in the reduced form of an aldehyde protected as its acetal. The reagent is known, having been generated from the parent bromide by reaction with magnesium in tetrahydrofuran (eq 12).[21] In our



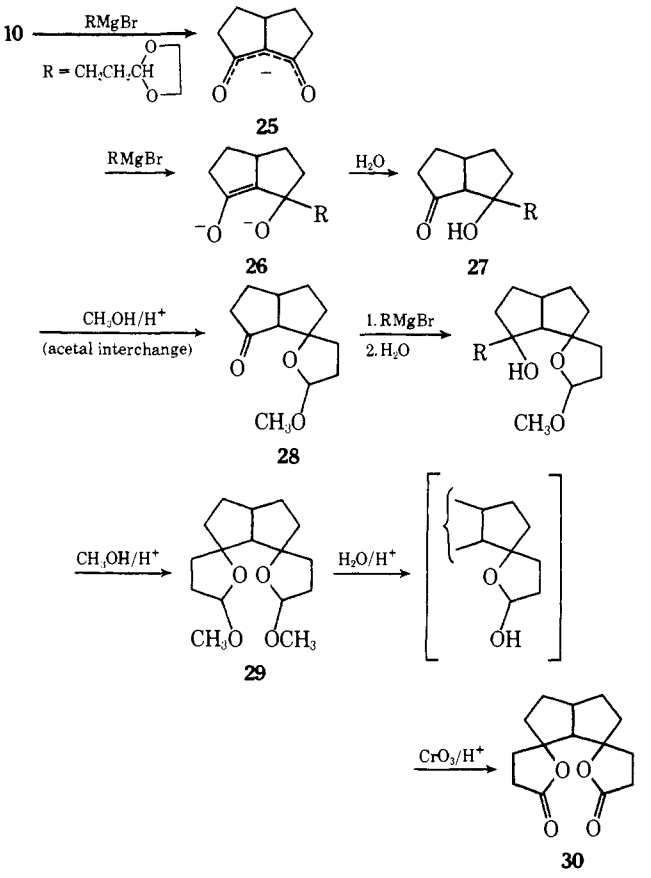
(12)

24

hands, this Grignard reagent was unstable; it polymerized readily above 35 °C. At room temperature, noticeable decomposition occurred within several hours. The corresponding lithium reagent could not be prepared usefully; it reacted further as it was formed.

The Grignard reagent **24**, although unstable, proved useful early in the development of the peristylane synthesis. Its use permitted the required addition of a three-carbon chain to each of the carbonyl groups of the β-diketone **10** (Scheme III). Experimentally, we found that each addition had to be performed as a separate step. In the first, 1 equiv of Grignard re-

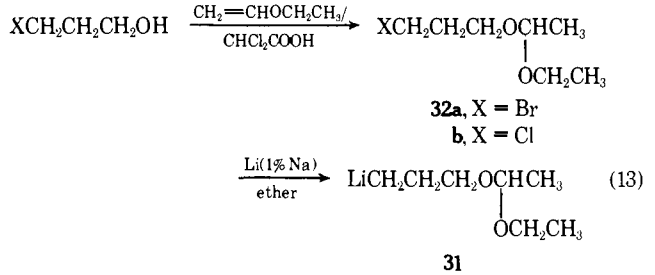
Scheme III



agent was consumed in the formation of the enolate anion **25**, which then reacted slowly over several hours with a second equivalent to afford the adduct **26**. No further reaction occurred even in the presence of a large excess of Grignard reagent. Aqueous workup gave the hydroxy ketone **27**. Treatment of **27** with excess Grignard did not result in addition to the carbonyl group. The first equivalent of Grignard reagent was consumed by reaction with the hydroxyl group. Apparently, the resulting oxygen anion effectively prevented further reaction. The problem was neatly circumvented by masking the irksome hydroxyl group in the internal acetal **28** formed by treatment of **27** with acidic methanol. The Grignard added easily to the ketone group of this compound. Treatment of the product with acidic methanol gave the diacetal **29**. The necessary adjustment of oxidation state (aldehyde → acid) was accomplished by the oxidation of **29** with aqueous chromic acid, probably via formation and oxidation of hemiacetal intermediates.[22] The final product was the dilactone **30**, which is, as we shall see, a useful relative of **12**.

This preparation, although successful, had several serious drawbacks. The instability of Grignard **24** limited the scale of reaction to about 0.1 mol, insufficient considering the long distance yet to be traveled to peristylane and dodecahedrane. Further, too often the reaction sequence failed completely without apparent cause. We were driven to look further afield for a more suitable three-carbon nucleophile carrying a potential carboxylic acid function.

In reward for a diligent search, we found finally that ethyl 3-lithiopropyl acetaldehyde acetal (**31**) was a good answer to our needs. We have already published a full paper on the preparation of this reagent and its uses for hydroxypropylation.[17] It will be useful, however, to recall a few salient points here. The organolithium **31** can be prepared in diethyl ether on a mole scale in excellent yield without difficulty from either the bromo or chloro acetals **32** (eq 13). These precursors can



(13)

31

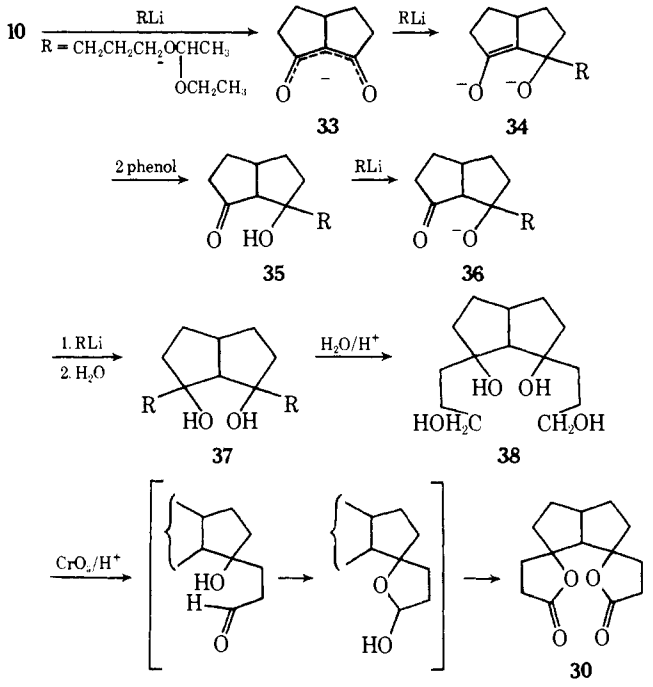
be made in large quantities easily by dichloroacetic acid catalyzed addition of the corresponding 3-halopropanol to ethyl vinyl ether. All of our initial work was done with the bromo compound. We found afterwards (with some surprise) that the lithium reagent could be formed as well from the chloro analogue and behaved similarly. As 3-chloropropanol is very much cheaper and much more readily available commercially than its heavier relative, its selection as the precursor of choice is clear.

At room temperature, 1 M solutions of lithium reagent **31** prepared in ether decomposed slowly, forming (in part) cyclopropane. The solutions were stable for months at −30 °C when protected appropriately. The reaction of **31** with ketone groups is typical of primary lithium reagents. Addition is rapid and proceeds in high yield. The acetal protecting group can be removed from the adducts by mild acid hydrolysis without disturbing the tertiary hydroxyl group generated in the addition reaction itself. Jones oxidation of the primary alcohol freed by removal of the protecting group can be used to raise the oxidation state of the terminal carbon atom to that of carboxylic acid.

Addition of the organolithium **31** to the carbonyl groups of β-diketone **10** had to be performed in two separate stages, each

of which required 2 equiv of the lithium reagent. In the first round (Scheme IV), the first equivalent of lithium reagent was

Scheme IV



consumed in generation of the enolate anion **33** from the starting β-diketone. Only one carbonyl group of this salt was reactive; the second equivalent of lithium reagent added to it, giving the dianion **34.** At this point, no further reaction occurred, even when much excess organolithium was present. Aqueous workup rapidly in carefully buffered medium gave crude hydroxy ketone **35.**

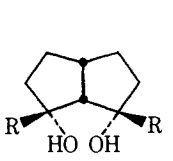
The infrared spectrum of **35** showed absorption bands at 3390 and 1740 cm^{-1}, assignable to hydroxyl and carbonyl groups, respectively. This hydroxy ketone was dried carefully and then taken into the second stage of the sequence without any further purification. It was added at low temperature to 2 equiv of the lithium reagent. The first of these reacted with the hydroxyl group (→ **36**); the second attacked the remaining ketone group. Aqueous workup gave crude dihydroxy diacetal **37.** The infrared spectrum of this crude showed hydroxyl absorption at 3440 cm^{-1} and only very weak carbonyl absorption.

The intermediate aqueous workup separating the two stages in the addition of the three-carbon chains to **10** was very inconvenient and time consuming. A more convenient way to carry out the essential protonation of the enolate anion **34** was sought. Addition of water or aliphatic alcohols in stoichiometric amounts (or more or less) to the reaction mixture at the end of stage one led only to much reduced yields at the end of the entire sequence. It became clear early that the β-hydroxy ketone **35** was quite unstable in base, presumably opening by reverse aldol cleavage of **36.** The problem was overcome successfully by quenching **34** with 2 equiv of phenol, the conjugate base of which was too weak to sustain a significant concentration of the alkoxide **36.** Even so, it was necessary that the quenching of **34** be done cold and very rapidly to avoid decomposition of **36,** which was necessarily generated in the course of this protonation. For the same reason, the second stage addition of the organolithium reagent had to be carried out quickly and at low temperature.

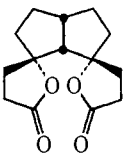
The final adduct **37** was hydrolyzed easily to the tetrol **38** by 0.03 M hydrochloric acid in aqueous ethanol. The volatile by-products, acetaldehyde and ethanol, were removed conveniently under vacuum along with the solvents. Neither **37** nor **38** was characterized; this would not have been useful. Crude tetrol **38** was oxidized with chromium trioxide in aqueous acid directly to dilactone **30,** identical with that obtained by the process outlined in Scheme III. Although this dilactone could have been formed by closure of the corresponding hydroxy acid under the acidic reaction conditions, it probably came about in more direct fashion. Aldehyde intermediates in the oxidation process would be expected to close rapidly to internal hemiacetals in the presence of acid. Such compounds would be oxidized quickly to lactones.[22]

Pure dilactone **30,** mp 154–155 °C, was obtained by this route in 45% yield overall from diketone **10.** The use of the lithium reagent **31** for its preparation is much preferred to the use of the Grignard reagent **24.** The organolithium is much more stable and can be employed on much larger scale than the Grignard. The route using **31** is shorter, both in time and operations. Thus, 15 g of pure dilactone **30** could be prepared in a few days from 20 g of diketone **10.** Considering the distance between **10** and **30** (starting material and product), we are content with this accomplishment.

The infrared spectrum of dilactone **30** showed a carbonyl absorption at 1773 cm^{-1}, consistent with the γ-lactone structure, and no hydroxyl or carboxylic acid absorptions. The ^1H NMR spectrum had no absorptions below δ 3. No determined effort was made to establish the stereochemistry of the compound. Only one isomer from a total of six possible was ever isolated from the synthetic sequence. A reasonable stereochemical scenario for the conversion of **10** to the diadduct **37** is easily arrived at. The initial addition of the organolithium is expected to occur from the less hindered side of the β-diketone enolate **33,** namely, from the same side as the hydrogen at the ring junction β to both carbonyl carbons. Protonation of the product (dianion **34**) should give the cis-fused isomer of **35,** which is certainly much more stable than the trans isomer. The addition of the second three-carbon chain is expected to occur from the less hindered, outer side of this V-shaped molecule. If these assumptions are true, then the stereochemical structure of diadduct **37** would be as drawn in **37a.** The corresponding dilactone is **30a.**



37a

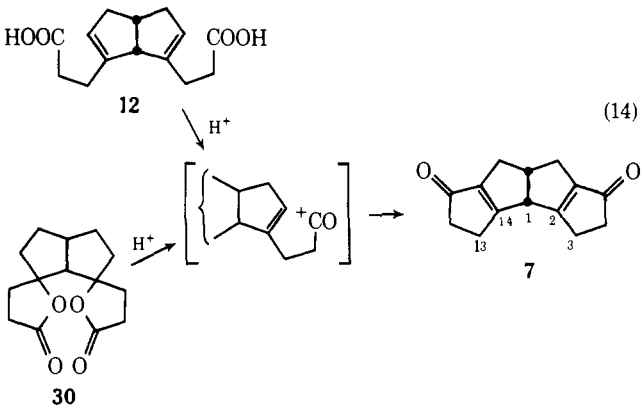


30a

Whether or not the stereochemistry of the dilactone actually produced can be arrived at by this connection is a moot point. The acidic conditions used in the hydrolysis and oxidation steps for conversion of **37** to **30** may well have been sufficient to isomerize whatever isomer was initially formed. The ^{13}C NMR spectrum of the isolated dilactone showed only eight resonances for the 14 carbon atoms. This is consistent with the stereochemical specifications of **30a,** but is not by any means proof for it. Whatever the stereochemistry of **30,** the spiro-fused centers would be destroyed in the very next step, and the ring fusion would be isomerized to the more stable cis arrangement, if that had not already occurred.

The second stage of the planned synthesis of peristylane depended critically upon successful conversion of the diene diacid **12** (or its equivalent) to the tetraquinane **7.** The dilactone **30** is the diene diacid **12** in a stable and convenient guise. We expected that **30** would react like **12** in the strong acid to be used to effect cyclization (eq 14).

Hot polyphosphoric acid was the first reagent tried. Although the reaction mixture turned completely black, and there was much unreacted lactone even after several hours of cooking, the presence of enone absorption in the infrared spectrum



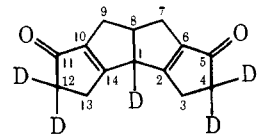
of the crude was unmistakeable and most encouraging. After a long and arduous search for optimum conditions, we found that the tetracyclic bis-enone **7** could be obtained in 65–70% yield by heating dilactone **30** at 75 °C for 5 days with a very large excess of polyphosphoric acid.

But polyphosphoric acid is a very exasperating reagent; it is a poor solvent, impossible to handle efficiently, or to stir effectively. The workup of the crude mixture from the conversion of **30** to **7** was a nightmare. A more convenient reagent was required. The usual proton acids (including methanesulfonic acid, sulfuric acid, fluorosulfonic acid, and hydrogen fluoride) and the Lewis acids (including boron trifluoride/acetic anhydride, aluminum chloride, and antimony pentafluoride), although useful in similar cyclizations, were not effective for the conversion of **30** to **7.** The dilactone was much more resistant to cyclization than model monolactones, probably because protonation of the intermediate ketone depressed the formation of essential carbonium ion intermediates. Treatment of **30** with trifluoromethanesulfonic acid, the strongest proton acid known, gave some enone, but the reaction stopped well short of completion. On the too simple idea that water generated in the reaction decreased the effectiveness of the acid, phosphorus pentoxide was added to remove it as it was formed. Indeed, after 2 days at room temperature with 5 wt % phosphorus pentoxide in trifluoromethanesulfonic acid, the dilactone was converted to bis-enone **7** in 65–73% yield.

In terms of speed, ease of handling, and ease of product purification, the trifluoromethanesulfonic acid/phosphorus pentoxide mixture is much preferred over polyphosphoric acid. Trifluoromethanesulfonic acid, however, is very expensive.[23] Happily, we found soon after these early results that solutions of 5–10 wt % of phosphorus pentoxide in ordinary methanesulfonic acid were very effective for the conversion of the dilactone to **7;** 80–90% yields were obtained routinely. The mixture of phosphorus pentoxide and methanesulfonic acid has proven to be a very useful and convenient substitute for polyphosphoric acid. We have discussed this in some detail in a full paper already published.[24]

Bis-enone **7,** mp 209–210 °C dec, formed long flat needles from 2-propanol. The infrared spectrum showed conjugated enone absorptions at 1690 and 1640 cm^{-1}. These values differ somewhat from those of 2-cyclopentenone itself (1710 and 1600 cm^{-1}), but are very like those of bicyclo[3.3.0]oct-1(5)-en-2-one (1690 and 1634 cm^{-1}), suggesting that they are characteristic of 2-cyclopentenones fully substituted on the double bond. The ultraviolet spectrum of **7** in 95% ethanol had maxima at 248 (ϵ 20 000) and 306 nm (ϵ 230) and a shoulder at 236 nm (ϵ 17 000). The expected π–π^* band of a conjugated cyclopentenone disubstituted on the double bond is at 236 ± 5 nm; bicyclo[3.3.0]oct-1(5)-en-2-one, for example, has maxima at 241 (ϵ 11 000) and 300 nm (ϵ 70). The difference is attributable to interactions between the proximate chromophores of bis-enone **7.**

The 270 MHz ^1H NMR spectrum of **7** showed a two-hydrogen multiplet at δ 4.02, due to the tertiary hydrogens at the central ring fusion, and a broadened doublet at 2.27 ppm arising from one stereochemical pair (endo or exo) of the protons on C-7,9 coupled (J = 18 Hz) to the other. Complex signals for ten additional protons appeared in the region of 2.5–3.0 ppm. Reaction of **7** with heavy water and sodium carbonate resulted in the rapid exchange of five protons for deuterons. The ^1H NMR spectrum of **7**-d_5 was sufficiently simple that the location of the deuterium atoms could be assigned with reasonable certainty as shown in **39.** The hydrogen at the central fusion C-8 appeared as a pentet ($J \sim 3$ Hz), being coupled to the hydrogen pairs on C-7 and C-9. The upfield doublet seen in the spectrum of **7** was not significantly changed; the partner to it became visible at approximately 2.8 ppm. A set of two hydrogen AB doublets corresponding to the exo–endo hydrogen pairs on C-3,13 was clearly resolved with centers at 2.56 and 2.68 ppm, J = 20 Hz. The ^{13}C NMR spectra of both **7** and **39** indicated that each compound had the desired mirror plane symmetry element.



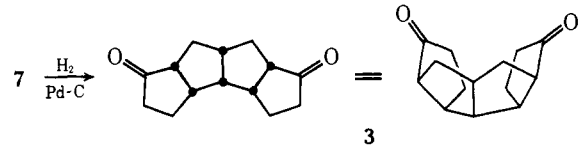
39

Two stereoisomers of bis-enone **7** are possible; the central ring fusion can be either cis or trans. The cis fusion of bicyclo[3.3.0]octane is more stable than the trans by 6 kcal/mol;[7] the trigonal carbons present in **7** would enhance this difference. In view of this, and considering the very strong epimerizing conditions used in the formation of **7,** the cis junction was guaranteed.

Completion of the planned second stage of the peristylane synthesis required stereochemically controlled reduction of the double bonds of **7.** Catalytic hydrogenation was picked as the method of choice, as this process generally delivers hydrogen cis to the less hindered side of an olefin. Thus, hydrogenation of **7** should give all-cis stereochemistry at each ring fusion and all-syn stereochemistry for the three ring fusions relative to one another, thereby fixing the essential geometric features of peristylane at this stage.

Hydrogenation at atmospheric pressure of bis-enone **7** in ethyl acetate at room temperature over commercial palladium-on-carbon catalyst produced two isomers, the desired material **3** and a minor compound, probably the syn,anti isomer. The ratio of isomers varied with the sample of the catalyst; the minor compound sometimes amounted to as much as 15% of the mixture and was quite difficult to separate on scale from **3.**

A search for optimum conditions was eventually well rewarded. The reduction was best done at about −20 °C in acetone over palladium-on-carbon that had been treated with acetic acid (to remove basic impurities) and then washed to neutrality with distilled water. Better overall stereoselectivity was obtained when the catalyst was conditioned overnight in the reaction solvent under hydrogen. With these procedures, it was possible to reduce **7** to **3** with as high as 99% stereoselectivity (eq 15).

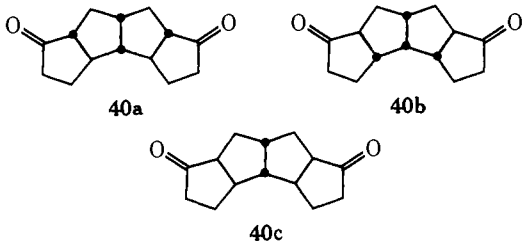


(15)

3

The product was purified by crystallization from cyclohexane as colorless, interleaved plates, mp 89–90 °C. The mass spectrum and the combustion analysis confirmed the tetra-

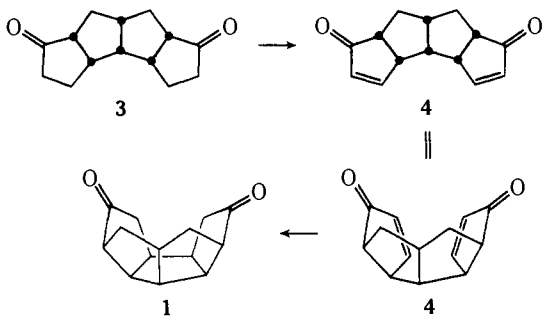
hydro relation of **3** to **7**. The infrared spectrum had carbonyl absorption at 1730 cm^{-1}, appropriate to a five-membered, saturated, cyclic ketone and consistent with the ultraviolet absorption maximum (ether solution) at 294 nm (ϵ 27). The proton-decoupled ^{13}C NMR spectrum showed only eight lines for the 14 carbons in the product in accord with the mirror plane symmetry element expected. These data are consistent with four stereoisomeric structures (**3** and **40a–c**) differing only in the geometry of the addition of hydrogen to **7**.



40a **40b** **40c**

Diketone **3** is a sterically crowded molecule. The opposing ethano hydrogens, particularly those β to the carbonyl groups, are in one another's way. This steric problem would be mitigated somewhat by epimerization at a methine carbon α to a carbonyl group or, more so, by epimerization at a β-methine position. Either process would lead to a trans-fused bicyclo[3.3.0]octane subunit in the tetraquinane. As we have no convenient way to equilibrate the arrangement at a β-methine position, it is not clear whether the crowding problem in **3** is severe enough to upset the normal preference of a bicyclo[3.3.0]octane for the cis ring fusion. We do know, however, that the α-methine positions in the major product from catalytic hydrogenation of **7** are configurationally stable to treatment with base strong enough to effect deuterium exchange. The original assignment of the specific structure **3** to the hydrogenation product rested on expectation and was vindicated, as shall be seen, by the ultimate success of the synthesis.

The C_{14}-Pentaquinane System. With the C_{14}-tetraquinane of (hopefully) correct geometry in hand, we were ready to take on the third stage of the peristylane synthesis—entry into the C_{14}-pentaquinane system. The rough plan was straightforward (eq 16): **3** → **4** by one sort of oxidation or another; and **4** → **1** by reductive coupling.

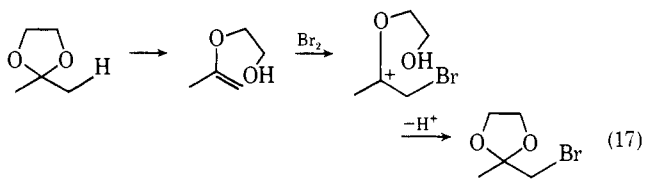


3 **4** **1** **4** (16)

One approach to the conversion of the saturated diketone **3** to the unsaturated derivative **4**, delightfully simple if it would have worked, was direct dehydrogenation by reaction with selenium dioxide, or with a high-potential quinone, or with palladium chloride.[25] Unfortunately, none of these reactions proved to be useful in the required sense.

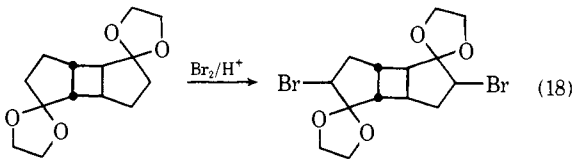
Conversion of diketone **3** into bis-enone **4** by a standard bromination/dehydrobromination sequence seemed possible. The first step would require monobromination of **3** at each and only the secondary sites α to its carbonyl groups. Model experiments with bicyclo[3.3.0]octan-2-one indicated that acid-catalyzed bromination at the α-methylene position would indeed be preferred. This was expected; enolization in the other direction would give a significantly strained system.[11] Although geminal dibromination is a troublesome side reaction in monobrominations of ketones, steric crowding would be expected to hinder this in **3**. Nonetheless, when bromination of **3** was attempted, difficulties were encountered immediately. The bromination products were unstable and unanticipated trans-skeletal reactions occurred as will be discussed in later papers.

Problems with bromination α to a carbonyl group and subsequent dehydrobromination to the corresponding conjugated enone are best handled via ketal intermediates.[26] The ketal of an enolizable ketone readily forms the related enol ether in the presence of a catalytic amount of acid. The enol ether is labile to electrophilic attack; bromine reacts with it instantly. This reaction leads ultimately to an α-bromo ketal (eq 17). It is



(17)

found experimentally that a second bromine cannot be introduced onto the same carbon as the first in these α-bromo ketals without drastically raising the reaction conditions.[26c] The required intermediate halo enol ether either forms much more slowly or is very much less reactive than the enol ether from the original ketal. This feature offers an important control mechanism in the bromination of polycarbonyl compounds. Thus, it is possible to dibrominate **41** once α to each carbonyl derived carbon atom without any significant contamination from geminally dibrominated material (eq 18). The same sort of control is not available in direct bromination of the diketone from which **41** is derived.[26b]



41 (18)

An additional benefit to bromination/dehydrobromination of ketones via their ketals is that the dehydrobromination can be effected smoothly on the bromo ketal with any of a number of strong bases. Dehydrobromination of an α-bromo ketone, on the other hand, is a very finicky conversion open to many damaging side reactions.

Conversion of diketone **3** to the corresponding ethylene ketal was straightforward (Scheme V). Reaction with ethylene glycol in the traditional manner produced **42** in essentially quantitative yield. Bromination of **42** was best done by treating it in tetrahydrofuran with 2 equiv of pyridinium hydrobromide perbromide. This easily weighed, crystalline solid is a convenient source of bromine.[27] In tetrahydrofuran it disproportionates with precipitation of pyridine hydrobromide and formation of the tetrahydrofuran–bromine complex. Sufficient pyridine hydrobromide remains in solution to catalyze the required conversion of ketal to enol ether. It is important that only high quality pyridinium hydrobromide perbromide be used in these reactions. Its titre, usually 90–95% of theory, should be established by titration against a standard olefin (e.g., cyclopentene) solution in an inert solvent. At the end point, the solution should be entirely colorless; a yellow or brown-yellow end point is a definite indication that the perbromide requires recrystallization.

The ^1H NMR spectrum of crude bisbromo ketal **43** showed a triplet (J = 6 Hz) at δ 4.46 assigned to the hydrogens on carbon bearing bromine. Based on **43**, the area of the triplet

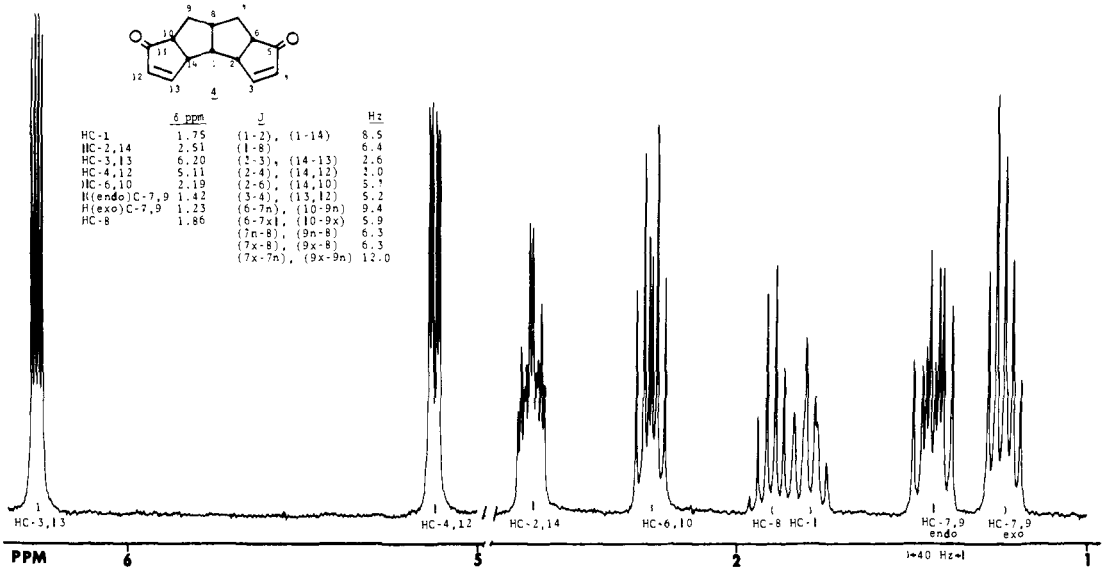
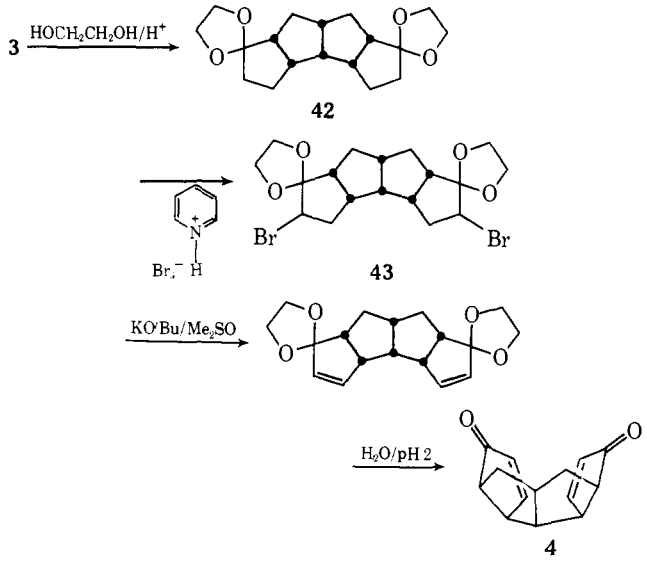


Figure 1. ^{1}H NMR spectrum at 270 MHz of *acs*-(C_s)-C_{14}-tetraquinane (**4**) in benzene-d_6. A completely satisfactory computer simulation was obtained using the shifts and couplings listed and a Lorentzian line width of 1 Hz; other possible couplings were taken to be zero.

Scheme V



signal was low relative to that of the higher field absorptions. The excess higher field signals probably belonged to protons of trans-skeletal reaction products. The crude material was not purified, but was used immediately in the next step.

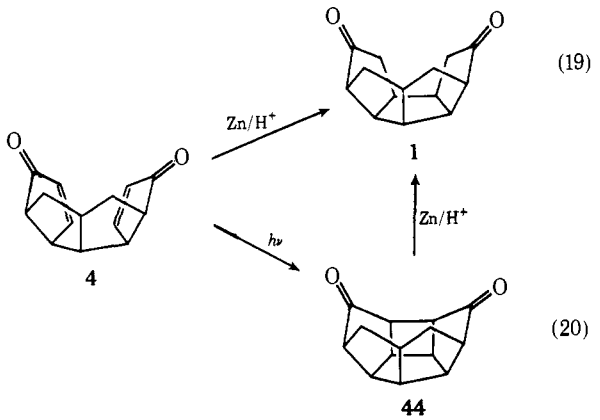
Elimination of hydrogen bromide from the bisbromo ketal was brought about with excess potassium *tert*-butoxide in dry dimethyl sulfoxide. The product was obtained pure easily by crystallization from cold, dry acetone. The vinyl hydrogen resonances in the 270-MHz ^{1}H NMR spectrum of purified bis-ene ketal appeared as one doublet of doublets at δ 6.30 (J = 5.5 and 2 Hz) and another at δ 5.58 (J = 5.5 and 3 Hz), each of which integrated for two hydrogens. The lower field absorption was probably due to the α-vinyl hydrogens. As expected, the bis-ene ketal was very sensitive to acid. Hydrolysis to bis-enone **4** occurred quickly in pH 2 (CH_3SO_3H) aqueous tetrahydrofuran. It was essential that the counterion of the acid hydrolysis catalyst not be very nucleophilic, and that the reaction be worked up promptly. Otherwise, the yield of the desired compound was lowered substantially by the formation of trans-skeletal products to be discussed in the future.

The pure bis-enone **4** melted at 84–85 °C. Catalytic hydrogenation regenerated its parent, the dione **3**, demonstrating that there was no change in the carbon framework during the bromination/dehydrobromination sequence. The infrared spectrum of **4** showed enone absorptions at 1698 and 1585 cm^{-1}, consistent with the conjugated cyclopentenone substructure. The ultraviolet n–π* absorption maximum in 95% ethanol was at 321 nm (ϵ 110). The π–π* maximum appeared at 228 nm (ϵ 13 000). The common position for simpler cyclopentenones unsubstituted on the double bond is 214 ± 5 nm, but the fusion to a five-membered ring apparently results in a bathochromic shift; e.g., the absorption maximum for bicyclo[3.3.0]oct-3-en-2-one is at 224 nm. The maximum for **4** was still higher, probably due to an interaction between the proximate enone chromophores. The proton-decoupled ^{13}C NMR spectrum of **4** showed only eight lines for the 14 carbon atoms, consistent with the expected mirror plane symmetry element. In the 270-MHz ^{1}H NMR spectrum of **4** in deuteriochloroform the olefinic hydrogens appeared as two well-defined doublets of doublets: the vinyl hydrogen β to the carbonyl at δ 7.75 (J = 5 and 2 Hz); the α-vinyl hydrogen at δ 6.03 (J = 5 and 2 Hz). These positions and the coupling pattern are characteristic of such α,β-unsaturated cyclopentenones. Each hydrogen resonance was almost completely resolved in the 270-MHz spectrum of **4** in benzene-d_6 solution. This spectrum is reproduced with an analysis in Figure 1.

The ordering of the C-7,9 exo–endo hydrogen resonances was based on the conclusion that the large 9.4 Hz coupling constant could best be matched via the Karplus relation to the dihedral angle between H(endo)C-7,9 and HC-6,10. By extensions of such correlations between coupling constant and dihedral angle, it appears that the average conformation of **4** has C-7,9 closer to the center of the molecule than C-5,11. As inspection of a molecular model will show, this corresponds to a distortion from the eclipsed conformation to one in which C-3,4,5,11,12,13 have moved somewhat toward coplanarity.

Five steps were required to take the bis-enone **7** to the isomeric bis-enone **4**, a lot of work to move double bonds from internal to external positions. Although the route was complicated by interfering trans-skeletal reactions, the desired compound was obtained in 40–55% overall yield. This phase of the peristylane synthesis was the most troublesome and the least satisfactory.

Closure of the C_{14}-tetraquinane bis-enone **4** to the C_{14}-pentaquinane dione **1** was accomplished in two ways: (a) direct reductive closure of **4** to **1** (eq 19); and (b) photochemical closure of **4** to the norperistylane **44** followed by reductive cleavage of **44** to **1** (eq 20). The first of these processes is an



(19)

(20)

intramolecular version of the known reductive coupling of 2-cyclopentenone.[28] The reaction can be viewed as a conjugate, or β-pinacol coupling. In the case at hand, the reacting centers are aligned correctly and held very near one another. Treatment of bis-enone **4** with zinc powder suspended in refluxing benzene with 15 vol % acetic acid resulted in the formation of two ketones in unequal amounts (~9:1). The major product proved to be diketone **1,** the product of the desired β-coupling. The minor product was diketone **3,** which must have arisen from independent, conjugate reduction of each enone system. The proportion of minor product was reduced when the reaction was run at lower acid concentration. Reduction of **4** in 10 vol % acetic acid in benzene gave only very little of **3.**

The alternative, two-step procedure for converting the C_{14}-tetraquinane **4** to the C_{14}-pentaquinane **1** started with photochemical closure to the cyclobutane **44.** Analogous photochemical dimerizations and cyclizations of unsaturated ketones are well-known.[29] The geometry of bis-enone is such that the double bonds are in close proximity, well-aligned for the desired reaction. The closure was carried out by irradiation of the bis-enone in benzene; the reaction was fast and went in high yield. As in all such reactions, over-irradiation must be avoided. Type I Norrish cleavage of saturated ketones is often a very facile process; thus, compound **44** was destroyed rapidly by the incident radiation if the irradiation were not stopped after most of the starting bis-enone (an internal filter) had reacted.

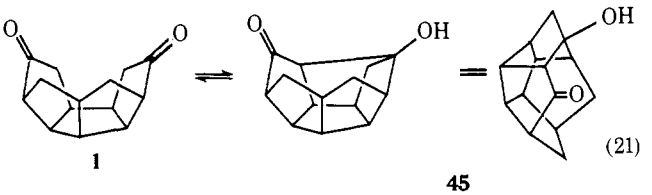
Sublimation of the crude photoclosed product and crystallization from ethyl acetate gave colorless flakes, mp >260 °C dec. The carbonyl band was observed at 1727 cm^{-1} in the infrared spectrum. The ^1H NMR spectrum showed no low field absorptions. The ^{13}C NMR spectrum confirmed the presence of a mirror plane symmetry element.

Cleavage of the hexacyclic norperistylane **44** to the pentaquinane **1** was accomplished by reduction with zinc powder in refluxing acetic acid. This reaction is an example of the reductive cleavage of γ-diketones met from time to time in the chemistry of strained systems.[30] The reaction in the case here was rapid and clean. The product, isolated in 85% yield, was identical with that obtained by way of the direct reductive coupling route. The two routes to **1** complemented one another usefully. The first, direct reduction of **4,** worked well if the bis-enone was quite pure; otherwise it was difficult to isolate the product. As purification of the enone was sometimes troublesome, less pure samples were best converted to the stable, high melting, easily purifiable photoclosed compound **44,** which was then taken on via the second path.

The three reactions used in the preparation of **1** from **4** provide good proof that the stereochemistry of **4** and its progenitor **3** is indeed all-cis and all-syn (acs), and that the carbonyl groups of these compounds are arranged as drawn. The photochemical closure of **4** could not have proceeded from a stereoisomeric compound. The reductive cleavage of **44** could only have occurred if the carbonyl groups were attached vicinally on the cyclobutane ring.

The ultraviolet absorption spectrum of diketone **1** in dioxane had a maximum at 311 nm (ϵ 20), reasonable for a saturated cyclopentanone. The infrared spectrum showed a carbonyl absorption at 1727 cm^{-1} and a weak, but real, hydroxyl band at 3355 cm^{-1}. The ^1H NMR spectrum confirmed the presence in all samples of an exchangeable hydroxyl proton, which must be that of tertiary alcohol as no signal for hydrogen on carbon bearing oxygen was evident. Numerous crystallizations of diketone **1** from cyclohexane or cold ether failed to improve its indistinct melting point, ca. 210–226 °C dec, or to change the spectral information.

The peak obtained on vapor-phase chromatographic analysis of **1** was badly deformed and much too broad for its retention time. Even the most highly purified samples of diketone **1** showed two spots on thin layer chromatographic analysis; on perpendicular development *each* of these in turn gave rise to two spots corresponding to the R_f values of the originals. These problems were shown to be caused by the ready equilibration of **1** with the isomeric hydroxy ketone **45,** formed by a trans-skeletal aldol cyclization (eq 21). Integration of the ^1H NMR spectrum indicated that the equilibrium mixture contained about equal parts of each component.



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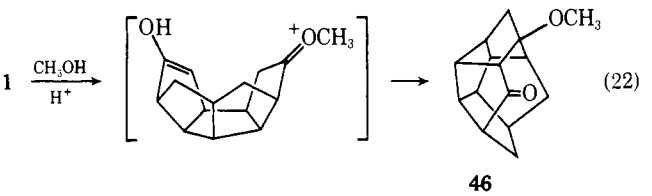
Good proof for the ease of the trans-skeletal bonding proposed in eq 21 was obtained by treating diketone **1** with acidic methanol (eq 22). A single compound, mp 68.5–69.5 °C, was



(22)

produced in high yield. The molecular formula of the material indicated the substitution of a methyl group for one hydrogen of compound **1.** The infrared spectrum showed a carbonyl absorption band at 1727 cm^{-1}, consistent with a cyclopentanone; there was no hydroxyl group absorption. The absorption maximum in the ultraviolet spectrum appeared appropriately at 310 nm (ϵ 19). The complex ^1H NMR spectrum exhibited a sharp, three-hydrogen singlet at δ 3.40 ascribed to a methyl ether. No other absorption attributable to hydrogen on carbon bearing oxygen was present; the 15 remaining hydrogens resonated at higher field. The ^{13}C NMR spectrum showed a separate signal for each of the 15 carbon atoms, only one of which was at low enough field to be a carbonyl carbon. These data led to the assignment of structure **46.** This product is thought to arise from attack of the enol of one carbonyl group upon the oxycarbonium ion derived from the hemiketal or ketal of the other carbonyl group.

Further support for the relation of **1** to **46** was obtained from the following. Diketone **1** has six exchangeable hydrogens α to carbonyl groups. Transformation of **1** to **46** replaces one of these hydrogens with a bond to carbon. Thus, if the scheme in eq 22 is correct, **1**-d_6 should give rise to a methoxy ketone **46** containing only five deuterium atoms. **1**-d_6 was prepared by exchange of **1** with methanol-*O*-*d* catalyzed by sodium methoxide. Mass spectral analysis of the methoxy ketone ob-

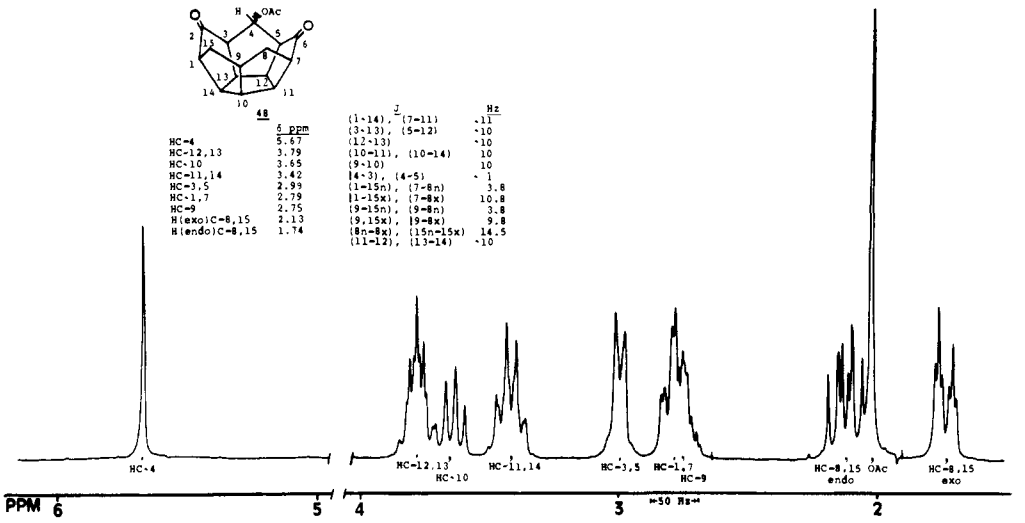
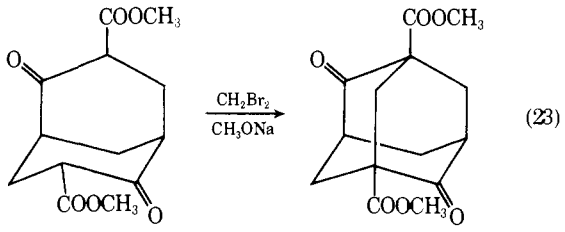


Figure 2. ^{1}H NMR spectrum at 270 MHz of peristylane **48** in deuteriochloroform solution. A satisfactory simulation of the spectrum was obtained with the shifts and couplings listed. Note that HC-5,11,12,13,14,3 must be treated as a complex system showing strong virtual coupling by way of $J(12\text{-}13)$.

tained by treatment of **1**-d_6 with methanol-*O*-*d*/dideuteriosulfuric acid showed, as predicted, a maximum of five deuterium atoms in the methoxy ketone.

The ease of formation of the hydroxy ketone **45** and the corresponding methoxy ketone **46** is surprising. These molecules are considerably strained as they contain a norbornane subsystem. The driving force for the closure of diketone **1** must certainly arise in the severe crowding of the proximate endo methylene hydrogens α to the carbonyl groups. Although twisting of the carbon framework would alleviate this hydrogen–hydrogen interaction somewhat, it would force one of hydrogens into the central cavity of the pentaquinane up against a carbonyl group. Apparently these interactions are of the same magnitude as the energy needed to shift the system toward the norbornane.

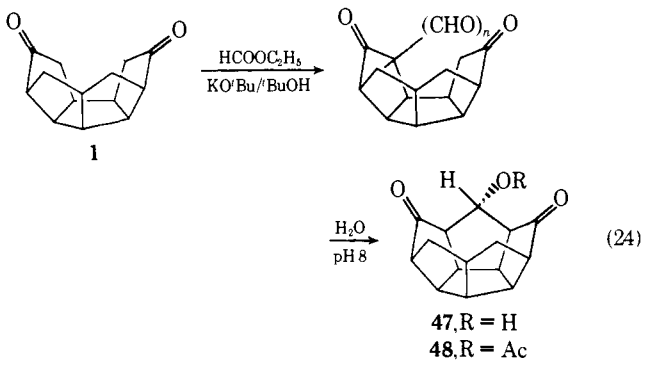
The Peristylane (C_{15}-Hexaquinane) System. The fourth and last stage of the peristylane synthesis required introduction of the 15th carbon atom and closure of the sixth ring. At least on paper, an obvious way to accomplish this was to react the diketone **1** with a dihalomethane and base in analogy to the method used by Prelog in 1941 for the construction of the adamantane system (eq 23).[31] In the case at hand, however, the



(23)

equilibrium of eq 22 complicated the matter. Attempted C-alkylation of **1** gave instead O-alkylation of **45**. For example, the major product of the reaction of **1** ⇌ **45** with methyl iodide and base was the methoxy ketone **46**. Attempts to close diketone **1** to a peristylane by reaction with diiodomethane failed completely.

Successful introduction of the 15th carbon atom onto **1** and subsequent closure to the first-made peristylane was accomplished by reaction of **1** with excess ethyl formate and potassium *tert*-butoxide in *tert*-butyl alcohol, followed by dilution and reaction of the mixture at pH 8 with water. This conversion (eq 24) probably went by way of the polyformylation of **1** in the strong base, closure, then or later, to the corresponding peristylane **47**, and hydrolytic loss of the excess formyl groups as formic acid brought about by aqueous base cleavage of the β-keto aldehyde systems. The very special conditions of reaction proved to be essential to high yield conversion of **1** to the peristylane **47**; yields as high as 95% were obtained frequently. Later we shall see that reactions of **1** with less special aldehydes than ethyl formate could be accomplished easily using much more routine methods.



(24)

47, R = H
48, R = Ac

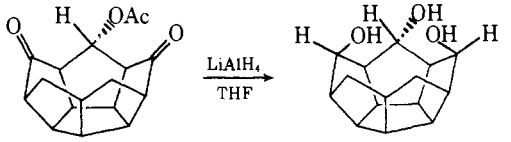
The hydroxydione **47** was the first compound to be made having the hexacyclic peristylane carbon framework. The ^{13}C NMR spectrum confirmed the presence of the expected mirror plane. The 270-MHz ^{1}H NMR spectrum of its acetate **48** is given and analyzed in Figure 2. The one-hydrogen singlet, 2.5-Hz wide at half height, at δ 5.67 for the hydrogen on the carbon bearing the acetate group was very informative. In the exo (outside) stereochemical arrangement indicated in **48**, the angle between the endo (inside) hydrogen on the carbon bearing acetate and the vicinal hydrogens on C-3 and C-5 is about 110°. From the Karplus relation,[32] this would lead to a small coupling constant. In the epimeric arrangement at C-4 the dihedral angle between the exo hydrogen and its two neighbors is near 0°; a significant coupling constant would be expected. As the ^{1}H NMR line at δ 5.67 for the hydrogen on C-4 was rather narrow, stereochemistry **48** was assigned. Although a rational kinetic argument can be constructed predicting the assigned stereochemistry, it is more likely that the exo orientation of the hydroxyl group was determined thermodynamically. The aldol **47** and its epimer at the hydroxyl carrying carbon atom would be interconvertible under the conditions of construction

The ^{1}H NMR signals in the spectrum of **48** due to the two types, endo and exo, of methylene hydrogens on C-8 and C-15 were particularly outstanding and interesting. One appeared as a doublet (J = 15 Hz) of triplets (J = 10 Hz) at δ 2.13; the

other, similarly structured (J = 15 and 4 Hz), appeared at δ 1.74. The large doublet splitting seen for both is certainly due to geminal (exo-endo) coupling. The triplet splitting arises in the coupling of each of these hydrogens to the two vicinal protons and the difference in coupling constant to the difference in dihedral angle between these hydrogens and their neighbors as just discussed for the hydrogen at C-4; namely, exo ~0°, endo ~110°. On this basis, the lower field resonance with the larger triplet coupling was assigned to the exo hydrogens on the methylene groups.

The structure of peristylane **48** was confirmed by single-crystal x-ray structure analysis by Nowacki and Scarbrough at Bern.[33] The crystals were monoclinic with four molecules per unit cell. The bond lengths and bond angles found did not differ remarkably from familiar values. The basal five-membered ring (C-10,11,12,13,14) showed only negligible deviation from planarity, as did one of the carbonyl containing rings (C-5,6,7,11,12) and its neighbor (C-7,8,9,10,11). On the other hand, none of the other three rings was planar. The carbonyl group at C-2 was displaced 0.2 Å from the best plane of C-1,2,3,13,14 toward the center of the system, whereas the similarly situated atoms C-4 and C-15 in the flanking rings were displaced oppositely. These distortions from mirror plane symmetry in the solid state are most probably the result of crystal packing forces. Clearly, they are averaged out in solution, at least on the NMR time scale.

Reduction of the acetoxyperistylane diketone **48** with lithium aluminum hydride in tetrahydrofuran gave the triol **49** (eq 25). The ^{1}H NMR spectrum of **49** in methanol-d_4 showed two

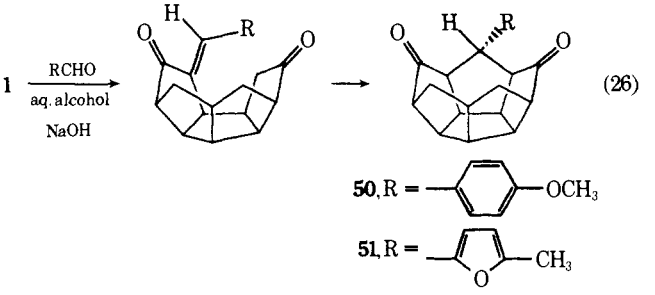


(25)

48 **49**

triplets due to protons on carbon bearing hydroxyl. The upper field triplet (δ 4.43, $J \sim 7.5$ Hz) was assigned according to its relative integral to the hydrogens introduced on carbons 2 and 6 during the reduction. The lower field triplet (δ 5.22, $J \sim 7$ Hz), which integrated for one hydrogen, was assigned to the single hydrogen on C-4, the carbon bearing acetate in precursor **48**. As there could have been no inversion of stereochemistry at this carbon during the reduction, it seemed odd at first that the coupling constant of the hydrogen at C-4 to the vicinal hydrogens changed from <2 Hz in **48** to 7 Hz in **49**. Inspection of space-filling models showed, however, that the equilibrium distance between C-2 and C-6 (the carbonyl carbons of **48**) must increase during the reduction to accommodate the steric requirements of the two endo hydroxyl groups, and that the dihedral angle between HC-4 and its neighbors must change as a result from about 110° in **48** to perhaps 140-150° in **49**. This was taken as a satisfactory explanation for the observed change in coupling constant between HC-4 and HC-3,5. It is not yet clear whether a similar explanation is sufficient to account for the dramatic difference in the spectra of **48** and **49** in the region due to the endo and exo methylene protons at C-8 and C-15. In the spectrum of **48** (vide supra) the lower field of these resonances (2.13 ppm) was split by couplings of 15 and 10 Hz, whereas the one at higher field (1.74 ppm) had J = 15 and 4 Hz. In the spectrum of **49**, the patterns were nearly reversed; the lower field resonance (2.24 ppm) had J = 15 and 5 Hz, and that at higher field (1.97 ppm), J = 15 and 11 Hz. Changes in dihedral angle could cause this change, but perhaps in **49** the exo hydrogens at C-8 and C-15 are at higher field than the endo, the reverse of the situation in **48**, as a result of substituent effects.

More elaborate peristylane derivatives were easy to prepare by expanding on the reaction of the pentaquinane dione **1** with aldehydes. Thus, condensation of **1** with *p*-anisaldehyde and with 2-methylfurfural gave the peristylanes **50** and **51**, respectively. Unlike the delicate procedure described earlier for the reaction of **1** with ethyl formate, these reactions were run with good yields simply by mixing the components together in aqueous alcoholic sodium hydroxide. Presumably the reactions occurred by way of an initial Claisen-Schmidt condensation followed by cyclization via an internal Michael addition (eq 26). If the Claisen-Schmidt condensation produced the in-



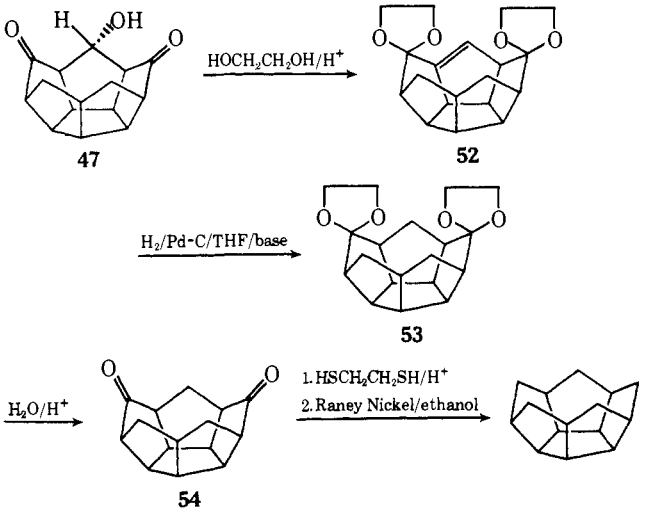
(26)

termediate α,β-unsaturated ketone with the R and carbonyl groups trans across the double bond,[34] the subsequent closure reaction would place the R group exo on C-4 in **50** and **51**, as illustrated. In any case, this is clearly the more favored arrangement; a large R substituent endo on C-4 would engender severe steric interactions. Only one of the two possible epimers at C-4 was produced in these condensation reactions. It was clear from the ^{1}H NMR spectra that the R group in each case occupied the exo position for, in accord with the discussion earlier of coupling vs. dihedral angle, the coupling of HC-4 to HC-3 and HC-5 was small (<2 Hz). Interestingly, changes in the ^{1}H NMR spectra much like those accompanying the reduction of **48** → **49** occurred on the reduction of **50** to the corresponding diol.

Peristylane. The synthesis of a new ring system can hardly be called complete until the parent hydrocarbon is prepared and characterized. We consider in this section the conversion of the hydroxyperistylane dione **47** to peristylane itself. There were many possible methods from which to select for the removal of the unwanted (for now) functional groups of **47**. We chose to take advantage of an unexpected observation.

As shown in Scheme VI, treatment of **47** with ethylene glycol and acid gave the unsaturated bisketal **52**, the structure

Scheme VI



of which followed from analytical and spectroscopic data and, most convincingly, from the ease with which **47** was regenerated on the reaction of **52** with aqueous acid. We did not expect that a peristylene, of which **52** is the first example, could be made so simply. The double bond is in an awkward position and quite strained. We shall show in future papers how much use

can be made of this. For now, it is sufficient to report that hydrogen over palladium-on-carbon reduced **52** to the saturated bisketal **53.** This reaction was completely clean if a small amount of aqueous base was purposefully added to the reaction solvent (THF); otherwise several hydrogenolysis by-products were also formed.

Hydrolysis of **53** with aqueous acid gave **54,** peristylane-2,6-dione, mp 314–315 °C. The proton-decoupled ^{13}C NMR spectrum of **54** was consistent with the expected C_s symmetry. As in the 270-MHz proton spectrum of **48** discussed earlier, the endo protons at C-8 and C-15 appeared as a doublet (J = 15 Hz) of triplets (J = 4 Hz) at δ 1.70, and the exo protons on these carbon atoms appeared similarly (J = 15 and 11 Hz) at somewhat lower field, δ 2.06. One other resonance appeared at relatively high field (δ 2.22). From the coupling constants, J = 14 (doublet) and 11 Hz (triplet), the absorption was assigned to the exo proton on the methylene group at C-4 between the two carbonyls. A signal for the corresponding endo proton did not appear separately. This proton is probably in the deshielding cone of the carbonyl groups, and its resonance is shifted downfield into those of the methine protons of the basal ring at ~2.7 ppm.

Thioketalization of **54** with ethanedithiol and acid gave the bisthioketal, which was reduced directly with Raney nickel in refluxing ethanol. The $C_{15}H_{20}$, hexacyclic hydrocarbon peristylane (C_{15}-hexaquinane) was obtained in 60% overall yield from **47.** Crystallization from methanol gave colorless plates of the pure material, mp 224 °C.

The 270-MHz ^1H NMR spectrum of peristylane showed only four groups of absorptions, each group of equal area: a broadened doublet at 3.14 ppm, $w_{1/2} \sim 12$ Hz, assigned to the five methine protons of the basal ring; a much broader envelope at 2.61 ppm, $w_{1/2} \sim 25$ Hz, due to the five methine protons along the rim of the peristylane bowl; a sharp doublet (J = 15 Hz) of triplets (J = 10 Hz) at 2.08 ppm due to the five exo protons of the methylene groups along the rim; and another sharp doublet (J = 15 Hz) of triplets (J = 4 Hz) at 1.78 ppm from the endo protons of those methylene groups. The proton-decoupled ^{13}C NMR spectrum at 22.63 MHz had absorption lines of approximately equal intensity at 63.1, 48.6, and 43.5 ppm; three signals only for the 15 carbons of the hydrocarbon, in accord with the fivefold symmetry of peristylane.

Experimental Section

Proton magnetic resonance spectra were taken at 270 MHz of solutions in deuteriochloroform unless otherwise noted and are referenced to internal Me_4Si. Spectra were recorded for convenience on a compressed scale (3 Hz/mm); for this reason, the shifts given are no better than ±0.02 ppm and the coupling constants are no better than ±1 Hz, sufficient accuracy for the purpose. Carbon magnetic resonance spectra were run at 22.63 or 15.09 MHz of solutions in deuteriochloroform using standard pulse techniques and white noise decoupling and are referenced to internal Me_4Si; chemical shifts are ±0.2 ppm. Approximate relative strengths are given parenthetically for methine and methylene carbon signals. Infrared spectra were taken of solutions in chloroform unless otherwise noted; positions of interesting absorptions are quoted ±5 cm^{-1}. High resolution mass spectra were recorded on a computer interfaced MS-902 spectrometer operating at 50 eV ionization voltage.

Vapor-phase chromatographic analysis was done on a Varian Aerograph 1700 dual column gas chromatograph equipped with temperature programmer on 5 ft × ⅛ in. stainless steel columns containing 5% OV-225 on 70/80 mesh Varaport 30, 5% SE-30 on 60/80 mesh Chromosorb W, or 5% Carbowax 20M on 60/80 mesh Chromosorb G. Analytical thin layer chromatography was performed on precoated silica gel or alumina plates with fluorescent indicator supplied by Quantum Industries or Macherey-Nagel Co. Visualization was accomplished under ultraviolet light or with iodine vapor. High pressure column chromatography was done with a system home built around columns, valves, and plumbing supplied by Chromatronix, and a dual-piston Milton Roy minipump. EM silica gel H(20–40 μm) was used as adsorbent.

The removal of solvent in vacuo refers to the evaporation of solvent at aspirator pressure on a Büchi rotary evaporator. The 0.75% ethanol in commercial chloroform was not removed prior to use, even for chromatographic operations. The portable cooling unit used was a KT-63 Haake/Brinkman Constant Temperature Circulator. Vibromixer stirrers were obtained from Chemapec, Inc.

Melting points were measured on a Hoover Unimelt apparatus and were not corrected. Elemental analyses were performed by Micro-Tech Laboratories, Inc., of Skokie, Ill.

β-(3-Oxocyclopentyl)propionic Acid, Methyl Ester (15). The goal of this reaction sequence was to prepare a large quantity of keto ester **15** efficiently; therefore, there was no need to purify or characterize intermediates thoroughly.

A. Preparation and Baeyer–Villiger Oxidation of Bicyclo[3.2.1]-octan-2-one (19). A solution of chromium trioxide (300 g, 3.0 mol), water (ca. 1 L), concentrated sulfuric acid (270 mL, 4.70 mol), and manganese sulfate (2 g) was added to a well-stirred mixture of bicyclo[3.2.1]octan-2-ol (286 g, 2.27 mol), chloroform (200 mL), and water (500 mL). The temperature of the reaction mixture was held between 5 and 25 °C with ice bath cooling. When the red color of the oxidant persisted in the reaction mixture, the addition was stopped. The product, bicyclo[3.2.1]octan-2-one (**19**), was extracted into chloroform (four 100-mL portions). The extract was washed with water, dilute ammonium hydroxide,[35] water again, and finally with saturated aqueous ammonium sulfate. The extract was dried over sodium sulfate and filtered directly into a 5-L, three-necked flask equipped with mechanical stirrer and efficient condenser. Methanesulfonic acid (10 drops) was added. Solid *m*-chloroperbenzoic acid (450 g, 85% titre, 2.21 mol) was added, first in small batches (10–20 g), and then in increasingly larger amounts, at a rate just sufficient to maintain gentle refluxing of the chloroform. More methanesulfonic acid (10 drops) was added carefully after each 100 g of the peracid was added. After the addition was completed, 1 L of chloroform was distilled off slowly over 90 min. VPC analysis on the SE-30 column, temperature programmed from 80 to 200 °C at 10°/min, indicated just a trace of unreacted ketone. The pot was cooled in ice water. Remaining peracid was destroyed by dropwise addition of aqueous sodium sulfite until a starch–iodide test proved negative. Aqueous sodium carbonate was added to dissolve the precipitated *m*-chlorobenzoic acid. The chloroform layer was drained, and the aqueous layer was extracted once with chloroform. The combined chloroform solution was washed with water and then with saturated aqueous ammonium sulfate and dried over sodium sulfate. Removal of the solvent in vacuo left an oil consisting mostly of polyesters derived from the opened lactones. The remaining volatiles (e.g., unreacted ketone) were removed at 0.5 Torr up to a pot temperature of 100 °C.

B. Methanolysis of the Baeyer–Villiger Product. The polyester residue was refluxed overnight with 500 mL of methanol and 10 drops of methanesulfonic acid. After 2 g of sodium carbonate was added, the methanol was removed in vacuo. The residue was taken up in 400 mL of dichloromethane. The solution was washed with water and then with saturated ammonium sulfate solution and dried over sodium sulfate. Removal of the solvent in vacuo gave a brown oil, which on distillation gave a mixture of hydroxy esters, bp 75–85 °C (0.05 Torr), containing the desired compound **21.** The pot residue from the distillation was refluxed overnight with 200 mL of methanol and 20 drops of methanesulfonic acid. Repeat workup and distillation as above gave an additional 34 g of hydroxy esters. VPC analysis (OV-225, 150 °C; SE-30, 110 °C) of the combined hydroxy esters (283 g) indicated that 80–90% of the mixture was compound **21.** The distillate was used without further purification in the next step.

C. Oxidation of Hydroxy Ester 21. A solution of chromium trioxide (300 g, 3.0 mol), water (700 mL), concentrated sulfuric acid (300 mL, 5.2 mol), and manganese sulfate (2 g) was added slowly to a stirred solution of the crude hydroxy esters (283 g) in acetone (500 mL) at 5 °C until oxidation was complete. The temperature was maintained at or below 5 °C during the entire oxidation. Additional water was added as necessary when precipitates interfered with effective stirring. The solid salts remaining at the end of the oxidation were dissolved in the minimum amount of water. The acetone layer was separated. The water layer was extracted twice with chloroform. The acetone layer and chloroform extract were combined and washed twice with 100-mL portions of dilute ammonium hydroxide and then dried over sodium sulfate. The solvent was removed on the steam bath, and the

residue was distilled to give keto ester **15**, bp 70–75 °C (0.03 Torr) (155 g, 40% yield overall from bicyclooctanol). VPC analysis on OV-225 at 150 °C indicated a purity of 85–95%. Redistillation gave material of sufficient purity (>95%) for cyclization to **10** (cf. ref 17).

***cis*-Bicyclo[3.3.0]octane-2,8-dione (10).** Solid sodium methoxide (40.0 g, 0.741 mol, from a freshly opened bottle of MCB material) was suspended in anhydrous ether (1.3 L) under argon in a carefully dried 3-L, three-necked, jacketed flask equipped with mechanical stirrer, condenser, addition funnel, thermometer, and gas inlet. Chilled water was passed through the flask jacket to hold the reaction mixture at 10–15 °C. A solution of keto ester **15** (103 g, 0.606 mol) in about 200 mL of ether was added over 1 h. The mixture turned yellow, and a yellow precipitate formed. After 4 h more at 10–15 °C, the mixture was quenched by suction transfer into a well-stirred solution of 550 g of KH_2PO_4 in 2 L of water. The ether layer was separated, and the aqueous layer was extracted twice with 150-mL portions of dichloromethane. The organic phases were combined and washed with 100 mL of saturated aqueous ammonium sulfate and dried over sodium sulfate. Distillation gave solid diketone **10**, bp 91–97 °C (0.03 Torr) (75.2 g, 90% yield). Crystallization from hexane/benzene gave large plates, mp 61–61.5 °C (lit.[8c] 63–64 °C): IR (CCl_4) 1776 (strong), 1730 cm^{-1} (weak); ^1H NMR δ 3.26 (1 H, hextet, $J \sim 6$ Hz, HC-5), 3.08 (1 H, d, $J = 8$ Hz, HC-1), 2.5–2.2 (6 H, m), 1.87 (2 H, m); ^{13}C NMR δ 209.0, 62.3 (1), 39.3 (1), 37.7 (2), 26.1 (2).

2,8-Dihydroxy-2,8-di(3-propionic acid)bicyclo[3.3.0]octane, Di-γ-lactone (30). Generation of the organolithium **31** and its additions to ketones **10** and **35** were best accomplished using two large flasks, arranged one atop the other. The upper flask was a 2-L, three-necked, jacketed reaction kettle having a drain tube with glass stopcock and a 24/40 male joint at the bottom. The flask was equipped with Vibromixer stirrer, low-temperature thermometer, and pressure-equalizing funnel topped with a gas inlet/bubbler. A loose plug of glass wool was placed in the drain tube above the stopcock. The drain tube was connected to the lower 5-L, four-necked flask, which was equipped otherwise just as the top flask. The entire apparatus was carefully dried. The upper flask was purged with argon, the lower with nitrogen. Provision was made for cooling: the upper flask by circulating chilled glycol/water through the jacket; the lower flask by raising up a dry ice/2-propanol bath sufficiently large to surround the flask completely.

A. Generation of Organolithium 31. Dry ether (250 mL) and 7 g (1 g-atom) of ½-in. lengths of lithium wire (1% sodium, Foote Mineral Co.) were put into the upper flask. A few milliliters of pure chloroacetal **32b**[36] was added, and the mixture agitated. Soon shiny spots appeared on the lithium wire, and the solution became cloudy. The flow of precooled coolant through the jacket was started. The temperature of the mixture was lowered quickly to −7 °C and then maintained between −15 and −7 °C as the remaining chloroacetal (75 g, 0.45 mol) was added over 60–90 min. The mixture was stirred after the addition was completed until the residual lithium metal tarnished (1–3 h). The solution was kept cold.

B. Addition of 31 to Diketone 10. A suspension of finely ground diketone **10** (23.0 g) in 500 mL of dry ether was cooled to −70 °C in the lower flask. The solution of lithium reagent **31** in the upper flask was added rapidly with good stirring. The upper flask was rinsed with 200 mL of ether which was also run into the lower flask. The contents of the lower flask (dianion **34**) were allowed to come up to room temperature over about 10 h (or overnight). Meanwhile, a second batch of organolithium was prepared in the upper flask using 84 g (0.5 mol) of chloroacetal **32b** and 8 g (1.15 g-atom) of lithium metal. The reagent, once made, was kept at −20 °C until used.

C. Protonation of Dianion 34. The mixture in the lower flask was cooled back to −70 °C. Dry, distilled phenol (37.7 g, 0.40 mol) in 100 mL of dry ether was added from the addition funnel as rapidly as consistent with maintaining the pot temperature below −60 °C. After the addition was completed, the mixture was allowed to warm to −30 °C (1 h) and then recooled to −70 °C. The product was hydroxy ketone **35:** ir (film) ν 3390, 1740 cm^{-1}.

D. Addition of 31 to Hydroxy Ketone 35. The second batch of organolithium reagent **31** was added to the very cold solution of **35** exactly as described in step **B**. The mixture was allowed to warm to room temperature slowly and then cooled to −20 °C and quenched with 1 L of saturated aqueous ammonium sulfate solution. The ether layer was separated; the aqueous layer was extracted with ether (two 500-mL portions). The combined extract was washed with 0.5 M aqueous sodium hydroxide (two 1-L portions) to remove phenol, followed by saturated brine and then dried over sodium sulfate and filtered. The ether was distilled on the steam bath; other light volatiles were removed on the rotary evaporator, first at aspirator pressure, and finally at 25 °C (0.5 Torr) to leave 68 g of oily dihydroxy diacetal **37.**

E. Tetrol 38. The crude dihydroxyl diacetal **37** was stirred with a mixture of 350 mL of 95% ethanol and 750 mL of 0.04 N hydrochloric acid until the whole was homogeneous (5–10 min). The solution was concentrated in vacuo to a volume of ca. 160 mL. A small aliquot was extracted with chloroform. The extract was dried over sodium sulfate, and the solvent was removed in vacuo to leave the very viscous tetrol **38:** ir (film) ν 3390 (strong), 1745 cm^{-1} (weak).

F. Dilactone 30. A 3-L, jacketed reaction kettle with a three-necked top and a bottom stopcock was equipped with thermometer, Vibromixer stirrer, and 500-ml addition funnel. Coolant from a portable refrigeration unit was circulated through the jacket. A solution of 86 g of chromium trioxide and 2 g of manganese sulfate in 1.5 L of water was prepared in the kettle; 680 mL of concentrated sulfuric acid was added with cooling and stirring. The aqueous tetrol solution from step D was added dropwise over 90 min during which the temperature was kept below 0 °C. An early problem with foaming was cured by the addition of 30 mL of dichloromethane. After the addition was completed, the mixture was stirred for 60 min at −5–0 °C and then allowed to warm to room temperature. The reaction mixture was extracted thoroughly with chloroform in the kettle with Vibromixer stirring. The extract was filtered through Celite and sodium sulfate and concentrated in vacuo to a brown oily solid. This was swirled with ether and filtered to give 20 g of light brown solid. Treatment of this crude dilactone with Norit A in 75 mL of 1-propanol followed by hot filtration and crystallization (three crops) gave 18.6 g (44% yield overall from **10**) of colorless flakes of dilactone **30:** mp 154–155 °C; IR ν 1773 cm^{-1}; ^1H NMR, multiplets with much fine structure centered at δ 2.6 (5 H), 2.2 (7 H), 1.9 (2 H), 1.6 (4 H); ^{13}C NMR δ 176.5, 93.3, 60.3 (1), 40.2 (1), 39.1 (2), 32.7 (2), 30.4 (2), 28.1 (2).

Anal. Calcd for $C_{14}H_{18}O_2$: P^+, 250.1205; C, 67.18; H, 7.25. Found: P^+, 250.1181; C, 67.16; H, 7.31.

Tetracyclo[6.6.0.0^{2,6}.0^{10,14}]tetradeca-2(6),10(14)-diene-5,11-dione (7). Phosphorus pentoxide (160 g) was suspended in 1440 g of methanesulfonic acid[24] (freshly distilled) in a 2-L, three-necked flask equipped with mechanical stirrer, thermometer, and nitrogen gas inlet/bubbler. The mixture was stirred at 50 °C under nitrogen until homogeneous (2–3 h). Dilactone **30** (20 g) was added; it dissolved in about 10 min. The reaction mixture gradually became red brown and finally a fluorescent purple. It was stirred at 50 °C for 24 h and then cooled below 5 °C and poured into 2.5 L of iced water. The aqueous mixture was stirred with 20 g of Norit A for about 1 h and then filtered through a layer of Celite. The brown filtrate was extracted thoroughly with chloroform (five 500-mL portions). The extract was washed once with saturated aqueous sodium bicarbonate solution and dried over sodium sulfate. Removal of solvent in vacuo left a light yellow to brown solid that was then dissolved in dichloromethane and passed through a short column of alumina. Elution with dichloromethane and evaporation of the solvent gave 16.8 g of light yellow solid. Crystallization from 2-propanol afforded 15.3 g (89%) of colorless, long flat needles of **7:** mp 209–210 °C dec; IR ν 1690, 1640 cm^{-1}; UV (95% ethanol) λ 236 (shoulder, ϵ 17 000), 248 (ϵ 20 000), 306 nm (ϵ 230); ^1H NMR δ 4.02 (2 H, m, HC-1 and HC-8), 2.80 (6 H, m, H(endo?)C-7,9 and H_2C-4,12), 2.62 (4 H, m, H_2C-3,13), 2.27 (2 H, d, $J \sim 18$ Hz, with additional smaller splittings, H(exo?)C-7,9); ^{13}C NMR δ 201.8, 180.5, 148.6, 55.2 (1), 51.2 (1), 40.4 (2), 32.4 (2), 24.6 (2).

Anal. Calcd for $C_{14}H_{14}O_2$: P^+, 214.0994; C, 78.48; H, 6.59. Found: P^+, 214.1021; C, 78.32; H, 6.61.

Exchange with D_2O catalyzed by sodium carbonate gave **7-d_5**: ^1H NMR δ 4.02 (1 H, pentuplet, $J \sim 3$ Hz, HC-8), 2.8 (2 H, d, $J \sim 18$ Hz, plus smaller splitting, H(endo?)C-7,9), 2.68 and 2.56 (2 H each, pair of doublets, $J \sim 20$ Hz, H_2C-3,13), 2.27 (2 H, as in **7**); ^{13}C NMR under conditions equivalent to that used for undeuterated **7** had clearly defined absorptions only at δ 181.3, 51.5, 32.9, and 25.0.

Tetracyclo[6.6.0.0^{2,6}.0^{10,14}]tetradecane-5,11-dione (3). Commercial 10% palladium-on-carbon hydrogenation catalyst was stirred with distilled water. Acetic acid was added dropwise until the pH of the suspension was steady between 5 and 6. The catalyst was filtered, washed very thoroughly with distilled water, and then dried in a vacuum desiccator for several days. As the stereoselectivity of catalyst from different bottles sometimes varied even after this treatment, a

very small scale hydrogenation was run to check each batch.

Proven catalyst (1.5 g) was suspended in 400 mL of acetone in a 1-L, jacketed kettle attached to a standard, atmospheric pressure hydrogenation apparatus. The kettle was equipped with a Vibromixer hydrogenation stirrer (H-1). This stirrer and its proper use were essential for rapid reduction. The air in the system was replaced by hydrogen in the standard way, and the catalyst suspension was stirred with hydrogen for 2 h at room temperature. After this, stirring was stopped, the suspension was cooled to −20 °C by passing coolant from a low-temperature bath through the jacket of the flask, and part (1 g) of the bis-enone **7** to be reduced was introduced. (Standard gas displacement techniques were used as needed to prevent admixture of hydrogen and oxygen.) Stirring was begun again; rapid hydrogen uptake occurred as the bis-enone dissolved. When gas uptake ceased, the stirring was stopped, and a small aliquot was taken from the solution. VPC analysis usually indicated that the reduction was proceeding with a stereospecificity greater than 97%. (The retention time of the unwanted isomer on 3% OV-225 at 230 °C was slightly less than that of the desired material.) If so, the remaining enone (5 g) was added to the main solution, and the reduction was continued at −20 °C. When hydrogen uptake was complete, the mixture was allowed to warm to room temperature; stirring was continued to ensure complete reduction. The hydrogen atmosphere was replaced with nitrogen, and the apparatus disassembled. The reaction mixture was filtered through a medium porosity fritted funnel to remove the catalyst, which was retained for future runs. The solvent was removed in vacuo; the residual oil solidified on standing. VPC analysis on OV-225 at 230 °C indicated an isomeric purity of 97–99%. Crystallization from cyclohexane gave colorless, interleaved plates of diketone **3**, mp 89–90 °C (5.6 g, 92% yield). In other runs, 15–25 g of bis-enone was converted to pure, crystalline **3** in yields of 92–97%: IR ν 1730 cm^{-1}; UV (ether) λ 294 nm (ϵ 27); ^1H NMR, multiplets centered at ~ 3.0 (6 H), 2.3 (8 H), 1.8 (2 H), 1.5 (2 H); ^{13}C NMR δ 220.1, 56.3 (2), 53.9 (1), 48.2 (1), 43.3 (2), 39.5 (2), 34.7 (2), 23.9 (2).

Anal. Calcd for $C_{14}H_{18}O_2$: P^+, 218.1307; C, 77.03; H, 8.31. Found: P^+, 218.1302; C, 77.08; H, 8.23.

Tetracyclo[6.6.0.0^{2,6}.0^{10,14}]tetradecane-5,11-dione, Bisethylene Ketal (42). Diketone **3** (7 g), benzene (200 mL), ethylene glycol (75 mL), and methanesulfonic acid (25 drops) were refluxed and stirred together overnight in a 500-mL flask beneath a Dean–Stark trap. The next day the mixture was cooled and then added slowly with good stirring *to* 500 mL of 5% aqueous sodium carbonate solution. The water layer was drained and extracted with benzene (two 200-mL portions). The combined benzene solution was washed with water (two 200-mL portions), then saturated brine, and dried over sodium sulfate. Removal of the solvent in vacuo gave a white solid that on crystallization from hexane afforded colorless plates of pure diketal **42** (8.8 g, 90% yield): mp 79.5–80.5 °C.

Anal. Calcd for $C_{18}H_{26}O_4$: P^+, 306.1831; C, 70.56; H, 8.55. Found: P^+, 306.1846; C, 70.34; H, 8.54.

Tetracyclo[6.6.0.0^{2,6}.0^{10,14}]tetradeca-3,12-diene-5,11-dione (4). A. Bromination. Diketal **42** (6.9 g, 22.5 mmol) was dissolved in tetrahydrofuran (140 mL, freshly distilled from lithium aluminum hydride) in a 250-mL, round-bottomed flask equipped for magnetic stirring and protected against moisture by positive nitrogen pressure. The flask was cooled in a dry ice–acetone bath for 15 min; the diketal partially crystallized. Solid pyridinium hydrobromide perbromide (16 g, 48.8 mmol) of known quality (see text) was added in one batch. The cold bath was removed, and the mixture allowed to warm. The reaction found its own temperature between −10 and 0 °C. The original orange color of the bromine–tetrahydrofuran complex discharged to yellow. At this point (starch–iodide test negative), pyridine (3.9 mL, 49 mmol) was added with vigorous stirring. The reaction mixture was then poured slowly into 130 mL of rapidly stirred, 10% aqueous sodium carbonate solution. This mixture was extracted with benzene (three 125-mL portions). The extract was washed twice with water and saturated brine and then dried over sodium sulfate. Removal of solvent in vacuo at 25 °C gave ca. 10 g of dibromo ketal **43** as a brown, soft solid; ^1H NMR δ 4.46 (t, J = 6 Hz). This crude product (which contained some 4-bromobutanol from HBr cleavage of THF) was not purified further, but was used directly in the next step.

B. Elimination. The crude dibromo ketal was stirred into 140 mL of dimethyl sulfoxide (dried over 4X molecular sieves and freshly distilled) under nitrogen containing alcohol-free potassium *tert*-butoxide (10.4 g, 91 mmol). The initial reaction was exothermic. After 20 h, the mixture was diluted with 350 mL of ice water and extracted with ether (four 200-mL portions). The extract was washed with water followed by saturated brine. Removal of solvent in vacuo left 6.9 g of light brown solid. This was taken up in dichloromethane, and the solution dried over sodium sulfate and passed through a column of Clearsorb (35 g). Removal of solvent in vacuo gave 6.0 g of slightly yellow solid that on crystallization from cold acetone (ca. 25 mL) afforded 5.2 g (76% yield from **42**) of bis-ene ketal as long, colorless needles: mp 126–127 °C; IR ν 3068, 1602, 1622 cm^{-1}; ^1H NMR δ 6.30 (2 H, d of d, J = 2 and 5.5 Hz, HC-4,12), 5.58 (2H, d of d, J = 3 and 5.5 Hz, HC-3,13), 3.94 (8 H, symmetrical multiplet), 3.36 (2 H, envelope, probably HC-1,8), 2.78 (2 H, q, J = 9 Hz, HC-6,10), 2.60 (2 H, m, HC-2,14?), 1.74 and 1.62 (2 H each, m, HC-7,9).

C. Hydrolysis. The pure ketal (4.3 g, 14.2 mmol) was dissolved in tetrahydrofuran (30 mL), and water (about 25 mL) was added until the solution just became cloudy. The cloudiness was dispelled with additional tetrahydrofuran, and then methanesulfonic acid was added drop by drop until pH test paper indicated a pH of 2. The solution was stirred for 5 min, then extracted with benzene (four 60-mL portions). The extract was washed with brine and dried over sodium sulfate. Removal of the solvent in vacuo left a crude solid that on crystallization from carbon tetrachloride gave 2.75 g (91% yield) of colorless, crystalline bis-enone **4**: mp 84–85 °C; IR ν 1698, 1585 cm^{-1}; UV (95% ethanol) λ 228 (ϵ 13 000), 321 nm (ϵ 110); ^1H NMR, see Figure 1; ^{13}C NMR δ 211.3, 165.5 (2), 134.0 (2), 53.4 (1), 52.7 (2), 50.2 (2), 47.8 (1), 30.5 (2).

Anal. Calcd for $C_{14}H_{14}O_2$: P^+, 214.0994; C, 78.48; H, 6.59. Found: P^+, 214.1015; C, 78.24; H, 6.70.

Hexacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,12}.0^{10,14}]tetradecane-5,11-dione. Norperistylane 44. A solution of 5 g of bis-enone **4** in 70 mL of dry benzene was put in a Pyrex photochemical cell concentric about a 450-W, Hanovia, mercury arc lamp. The cell was cooled by a rapid flow of water through an inner jacket separating the solution compartment from the lamp. The lamp was ignited. The progress of the photoclosure was monitored carefully by noting the disappearance of vinyl hydrogen absorption in the ^1H NMR spectrum of small aliquots taken directly from the reaction solution. As the reaction was quite rapid, it was wise to shut off the lamp during the analysis so as not to overshoot the end point. The irradiation was stopped finally when the vinyl hydrogen ^1H NMR signal was about 3–5% of its initial value. (Overirradiation must be avoided. In the particular apparatus used, the reaction took less than 30 min.) The solvent was removed in vacuo. If low quality bis-enone were used as starting material, product purification was best accomplished by HPLC on 20–40-μm silica gel eluted with 20 vol % ethyl acetate in benzene. If the starting material were of good quality, direct crystallization of the product from ethyl acetate gave pure norperistylane **44** (4.5 g, 90% yield): mp 260–310 °C dec; IR ν 1727 cm^{-1}, UV (dioxane) λ 317 nm (ϵ 27); ^1H NMR δ 3.76 (1 H, q, J ~ 10 Hz, HC-1), 3.4 (4 H, m) 3.29 (2 H, narrow m), 2.8 (1 H, q of t, J ~ 10 and 2 Hz, HC-8), 2.72 (2 H, br t, J = 10 Hz, HC-6,10(?)), 2.36 (2 H, d of t, J = 15 and 11 Hz, H(exo)C-7,9), 2.09 (2 H, br d, J = 15 Hz, H(endo)C-7,9); ^{13}C NMR δ 222.7, 64.9 (1), 57.3 (2), 54.8 (2), 47.0 (1), 45.9 (2), 45.2 (2), 42.2 (2).

Anal. Calcd for $C_{14}H_{14}O_2$: P^+, 214.0994; C, 78.48; H, 6.59. Found: P^+, 214.0991; C, 78.69; H, 6.62.

Pentacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{10,14}]tetradecane-5,11-dione (1). Method A. From Norperistylane 44. Diketone **44** (3.60 g) was dissolved in 30 mL of acetic acid in a 250-mL, round-bottomed flask equipped with mechanical stirrer and condenser. Zinc powder (12.5 g, Baker "Purified") was added with stirring. The mixture was refluxed for 7 h with vigorous stirring and then cooled. VPC analysis (SE-30, 240°) indicated that the reaction was complete. Benzene (80 mL) was added; the solids were filtered off and washed exhaustively with additional benzene. The solvents were removed in vacuo. The residue was taken up in chloroform. The solution was washed with 10% aqueous sodium carbonate solution and then dried over sodium sulfate. The solvent was removed in vacuo to leave a slightly yellow oil. Crystallization from cyclohexane gave diketone **1** (3.2 g, 89% yield).

Method B. From Bis-enone 4. Pure bis-enone **4** (2.4 g) was dissolved in 40 mL of 10 vol % acetic acid in benzene in a 100-mL, round-bottomed flask equipped with mechanical stirrer. Zinc powder (10 g, Baker "Purified") was added with stirring. The mixture was heated at 80 °C for 80 min. The contents of the flask were washed into a separatory funnel with benzene. The benzene layer was washed with water and saturated sodium bicarbonate solution and then dried over sodium sulfate. Removal of the solvent in vacuo left a colorless residue

(2.4 g). VPC analysis on OV-225 at 230 °C showed only diketone **1** and none of **3** or **4**.

Diketone **1** prepared by either method A or B was purified further by recrystallization from cyclohexane and from cold ether. The melting point remained indistinct, 210–226 °C, even after numerous recrystallizations. Even the best material gave two spots, R_f 0.5 and 0.7, on TLC analysis on silica gel plates eluted with 10 vol % tetrahydrofuran in chloroform. The material was an equilibrating mixture of **1** and **45** and was used as such in all subsequent experiments: IR ν 3355, 1727 cm^{-1}; UV (ether) λ 311 nm (ϵ 20); ^1H NMR 10 multiplet groups between δ 3.5 and 1.3.

Anal. Calcd for $C_{14}H_{16}O_2$: P^+, 216.1150; C, 77.75; H, 7.46. Found: P^+, 216.1141; C, 77.81; H, 7.41.

1-Methoxyhexacyclo[6.6.0.0^{2,12}.0^{4,11}.0^{6,10}.0^{9,13}]tetradecan-3-one (46). Diketone **1** (150 mg) was dissolved in 1 g of methanol in a 10-mL, round-bottomed flask, and 20 mg of methanesulfonic acid was added. The flask was stoppered, shaken once, and allowed to stand overnight. Powdered sodium carbonate (50 mg) was added the next day; the solvent was removed in vacuo. The slightly yellow residue was taken up in 5 mL of dichloromethane, and the mixture was filtered. The solution was passed through a 1 × 3 cm column of alumina with 70 mL of dichloromethane. The eluate was concentrated in vacuo. Crystallization of the residue from pentane gave the methoxy ketone **46** (116 mg in the first and only crop taken, 72% yield): mp 68.5–69.5 °C; IR (CCl_4) ν 1727 cm^{-1}; UV (ether) λ 310 nm (ϵ 19); ^1H NMR δ 3.40 (3 H, s, $-OCH_3$), 3.13 (2 H, m), 3.12–2.5 (7 H, m), 2.37 (1 H, d, J = 12 Hz), 2.2–1.8 (4 H, m), 1.40 (1 H, d, J = 15 Hz, of m); ^{13}C NMR δ 215.9, 92.6, 58.3, 56.9, 54.1, 53.9, 53.1, 52.6, 51.1, 48.7, 48.4, 48.1, 47.0, 45.2, 33.2.

Anal. Calcd for $C_{15}H_{18}O_2$: P^+, 230.1306; C, 78.23; H, 7.88. Found: P^+, 230.1315; C, 78.27; H, 7.88.

***exo*-4-Hydroxyhexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadecane-2,6-dione (47).** The diketone **1** (3.0 g) was added to a magnetically stirred solution of potassium *tert*-butoxide (10 g) in dry *tert*-butyl alcohol (75 mL) under nitrogen. The yellow-orange mixture was stirred for 1 h. Ethyl formate (150 mL, distilled from P_2O_5) was added in 10-mL portions. Vigorous gas evolution and rapid autocooling of the reaction mixture accompanied each addition. The mixture was kept at room temperature for 8 h after all the ethyl formate had been added. Some orange precipitate formed. The whole was poured with stirring into distilled water (500 mL), and the mixture was stirred at room temperature for 10 h. From time to time, particularly during the first few hours, 1 N aqueous sodium hydroxide solution was added to adjust the pH to 8 (some precipitates formed below pH 8). Finally, the mixture was acidified to pH 5 with dilute hydrochloric acid and extracted with methylene chloride (four 200-mL portions). The extract was dried and concentrated on the rotary evaporator to a viscous, yellow oil. Pumping on this oil at high vacuum led to its solidification to a foamy material that after trituration with ether left a tan microcrystalline powder (2.9 g, 86% yield). The ^1H NMR spectrum of this material indicated that it was **47** of good purity. Crystallization from acetone/hexane gave light yellow material of mp 256–257 °C with decomposition. Additional purification was not attempted: ^1H NMR δ 4.83 (1 H, s, HC-4), 3.83 (2 H, m, probably HC-12,13), 3.59 (1 H, q, J = 9 Hz, HC-10), 3.38 (2 H, q, $J \sim 9$ Hz, and smaller couplings, HC-11,14), 2.96 (2 H, d, J = 9 Hz, HC-3,5), 2.8 (3 H, m, HC-1,7,9), 2.09 (2 H, d of t, J = 14 and 10 Hz, H(exo)C-8,15), 1.67 (2 H, d of t, J = 14 and 4 Hz, H(endo)C-8,15); ^{13}C NMR δ 222.0, 83.7 (1), 65.9 (2), 63.7 (1), 55.9 (2), 54.0 (2), 52.1 (2), 47.1 (1), 37.8 (2).

***exo*-4-Acetoxyhexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadecane-2,6-dione (48).** The alcohol **47** (2.0 g) from the last procedure was dissolved in acetic anhydride (20 mL) and pyridine (5 mL). The solution was kept overnight at room temperature, and then most of the excess reagents were removed at room temperature in vacuo, first at aspirator pressure and then at 1 Torr. The residue was taken up in ether, and the solution washed with water followed by 2 N hydrochloric acid, saturated aqueous sodium bicarbonate solution, and then brine. Concentration in vacuo gave 1.8 g of yellow, highly crystalline material. Decoloration by elution through silica with 30% ethyl acetate/methylene chloride and crystallization from 1,2-dimethoxyethane gave colorless flakes of **48** (1.7 g, 73% yield): mp 169–173 °C with decomposition; IR ν 1742, 1227 cm^{-1}; UV (dioxane) λ 298 mμ (ϵ 75); ^1H NMR, see Figure 2.

Anal. Calcd for $C_{17}H_{18}O_4$: P^+, 286.1204; C, 71.31; H, 6.34. Found: P^+, 286.1210; C, 71.20; H, 6.48.

***endo,exo,endo*-2,4,6-Trihydroxyhexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadecane (49).** The acetate **48** (40 mg) was dissolved in 5 mL of tetrahydrofuran. Lithium aluminum hydride (300 mg) was added, and the mixture was stirred and refluxed for 30 min. The reaction mixture was cooled, and ethyl acetate (1 mL) was added drop by drop. Water (1 mL) was added slowly; the colorless solid that formed was removed by filtration and washed thoroughly with chloroform. The organic phases were combined, washed once with saturated brine, and dried over sodium sulfate. The solvent was removed in vacuo to afford a colorless solid, sparingly soluble in either chloroform or dichloromethane. The solid was swirled with a small quantity of chloroform; the undissolved portion was removed by filtration and air dried. The residue was the triol **49** (28 mg, 81% yield): mp 236–241 °C; ^1H NMR (CD_3OD) δ 5.22 (1 H, t, J = 7 Hz, H(endo)C-4), 4.9 (3 H, s, OH), 4.43 (2 H, t, $J \sim 8$ Hz, H(exo)C-2,6), 3.30 (1 H, m), 3.06 (2 H, m), 2.9–2.6 (3 H, overlapping m), 2.50 (2 H, m), 2.24 (2 H, d of t, J = 15 and 5 Hz), and 1.97 (2 H, d of t, J = 15 and 11 Hz).

***exo*-4-(*p*-Methoxyphenyl)hexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadecane-2,6-dione (50).** The pentaquinane dione **1** (200 mg) was mixed with *p*-anisaldehyde (150 μL) in 95% ethanol (4 mL) containing sodium hydroxide (0.5 mL of 15% aqueous solution). The orange mixture was stirred at room temperature over the weekend. The precipitate that formed was collected by filtration. The filtrate was diluted with water and extracted with chloroform. The extract and the precipitate were combined, and the mixture taken to dryness. The tan, solid residue was purified by HPLC on silica gel (20–40 μm). Elution with ethyl acetate followed by crystallization from ethyl acetate gave beautiful needles of adduct **50** (184 mg, 59%), mp 204–205 °C; ^1H NMR δ 7.12 (2 H, d, J = 9 Hz), 6.81 (2 H, d, J = 9 Hz), 4.16 (1 H, s, HC-4), 3.78 (2 H, m), 3.73 (3 H, s, OCH_3), 3.62 (1 H, q, J = 9 Hz), 3.36 (2 H, q, J = 10 Hz, and additional smaller couplings), 2.7 (5 H, m), 2.10 (2 H, d of t, J = 15 and 10 Hz, H(exo)C-8,15), 1.80 (2 H, d of t, J = 15 and ~3 Hz, H(endo)C-8,15).

Anal. Calcd for $C_{22}H_{22}O_3$: P^+, 334.1568. Found: P^+, 334.1629.

***exo*-4-[2-(5-Methyl)furyl]hexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadecane-2,6-dione (51).** Adduct **51** was prepared in 82% yield from **1** and 2-methylfurfural following the procedure described for **50**. The reaction, monitored by TLC, was complete in 14 h. The product was obtained pure directly on crystallization from ethyl acetate as colorless needles: mp 132–133 °C; ^1H NMR δ 5.87, 5.82 (1 H each), 4.23 (1 H, s, H(endo)C-4), 3.76 (2 H, symmetrical m), 3.63 (1 H, t, $J \sim 10$ Hz), 3.38 (2 H, q, $J \sim 10$ Hz, plus smaller couplings), 2.98 (2 H, doublet, $J \sim 9$ Hz, plus smaller couplings), 2.8 (3 H, overlapping m), 2.21 (3 H, s, $-CH_3$), 2.16 (2 H, d of t, J = 15 and 10 Hz, H(exo)C-8,15), 1.88 (2 H, d of t, J = 15 and 4 Hz, H(endo)C-8,15).

Anal. Calcd for $C_{20}H_{20}O_3$: P^+, 308.1411. Found: P^+, 308.1444.

Hexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadec-3(4)-en-2,6-dione, Bisethylene Ketal (52). Solid hydroxy diketone **47** (500 mg) was dissolved in a mixture of benzene (30 mL), ethylene glycol (5 mL), and *p*-toluenesulfonic acid (200 mg). The whole was refluxed with stirring overnight beneath a Dean–Stark trap. In the morning, the mixture was cooled and then poured slowly *into* stirred 10% aqueous sodium carbonate solution. This was extracted with benzene. The extract was dried and concentrated. The residue was purified by HPLC on 20–40 μm silica gel. Elution with ethyl acetate gave pure, crystalline ene bisketal **52** (550 mg, 78% yield): mp 99–100.5 °C; ^1H NMR δ 5.58 (1 H, br s, HC-4), 4.1–3.9 (8 H), 3.43 (1 H, m), 3.4–3.3 (5 H, m), 2.67 (1 H, t, $J \sim 12$ Hz), 2.54 (1 H, pentet (?), J = 9 Hz), 2.36 (1 H, m), and 2.1–1.6 (4 H, m).

Anal. Calcd for $C_{19}H_{22}O_4$: P^+, 314.1517. Found: P^+, 314.1477.

Hexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadeca-2,6-dione (54). A solution of the unsaturated ketal **52** (545 mg) in 25 mL of tetrahydrofuran containing 2 drops of 10% aqueous sodium carbonate solution and 200 mg of 10% palladium-on-carbon was exposed to hydrogen at atmospheric pressure in the standard way. Gas uptake was quick. Filtration through Celite and concentration in vacuo left colorless needles of **53** (512 mg, 93% yield), pure by TLC on silica gel. This material was dissolved in tetrahydrofuran. Hydrochloric acid (1 N, 10 mL) was added, and the mixture was stirred for 3 h at room temperature. Dilution with water, extraction with methylene chloride, and concentration in vacuo gave good quality, crystalline diketone **54** (342 mg, 86% yield): mp 314–315 °C; IR (film) ν 1732 cm^{-1}; ^1H NMR δ 3.6 (3 H, overlapping m), 3.34 (2 H, m), 2.9–2.6 (6 H), 2.22 (1 H, d of t, J = 14 and 11 Hz, H(exo)C-4), 2.06 (2 H, d of t, J = 15 and 11 Hz, H(exo)C-8,15), 1.70 (2 H, of t, J = 15 and 4 Hz, H(endo)C-8,15); ^{13}C NMR δ 225.5, 63.9 (1), 55.8 (4), 55.1 (2), 51.9

(2), 47.2 (1), 38.2 (2), 37.2 (1).

Anal. Calcd for $C_{15}H_{16}O_2$: P^+, 228.1150. Found: P^+, 228.1147.

Hexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadecane. Peristylane. A solution of diketone **54** (60 mg), ethanedithiol (500 mg), and *p*-toluenesulfonic acid (10 mg) in dry benzene (10 mL) was refluxed for 14 h. It was cooled and poured into 10% aqueous sodium carbonate (50 mL). The mixture was extracted thoroughly with benzene. The extract was washed three times with 15% aqueous sodium hydroxide, dried, and then concentrated in vacuo. Trituration of the residue with ether left the bisthioketal as a white powder (85 mg, 86%).

Anal. Calcd for $C_{19}H_{24}S_4$: P^+, 380.0760. Found: P^+, 380.0787.

Part of this material (50 mg) was dissolved in absolute ethanol (10 mL) and Raney nickel[37] (1 mL of settled material = 600 mg) was added. The mixture was refluxed for 3 h; the catalyst was removed, and the majority of the ethanol distilled at the steam bath. Crystalline product precipitated. Recrystallization from methanol gave the pure hydrocarbon as colorless plates (23 mg, 90% yield): mp 224 °C; ^{1}H NMR δ 3.14 (5 H, br d, $w_{1/2} \sim 12$ Hz, HC-10,11,12,13,14), 2.61 (5 H, symmetrical m, $w_{1/2} \sim 25$ Hz, HC-1,3,5,7,9), 2.08 (5 H, d of t, J = 15 and 10 Hz, H(exo)C-2,4,6,8,15), 1.78 (5 H, d of t, J = 15 and 4 Hz, H(endo)C-2,4,6,8,15); ^{13}C NMR δ 63.1 (5), 48.6 (5), 43.5 (5).

Anal. Calcd for $C_{15}H_{20}$: P^+, 200.1564. Found: P^+, 200.1594.

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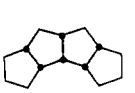
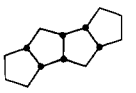
(2) The problems of nomenclature are as exasperating as ever. A referee from the American Chemical Society Nomenclature Committee has informed us that the "correct" systematic name for peristylane is tetradecahydro-3,4-methanocyclopenta[*cd*]pentaleno[6.1.2-*fgh*]pentalene. To us, this is useless obfuscation. In the von Baeyer system, "IUPAC 1957 Rules", *J. Am. Chem. Soc.*, **82**, 5545 (1960), peristylane is hexacyclo[7.5.1.0^{3,13}.0^{5,12}.0^{7,11}.0^{10,14}]pentadecane. This is a great deal more reasonable; a quick scan of the name actually gives some useful information—number of rings, number of ring atoms. We endorse heartily use of the von Baeyer system for formal nomenclature and encourage all to read the excellent presentation by D. R. Eckroth, *J. Org. Chem.*, **32**, 3362 (1967).

Nonetheless, conversational chemistry requires something simpler. We propose a colloquial nomenclature useful for referring to polycyclic systems made up only of highly condensed, fused, equal-size rings (no spiro fusions). Our proposal (for which we take responsibility) is an elaboration of the ideas of T. Jacobson Ph.D. Thesis, University of Lund, Sweden, 1973. The system states clearly the total number of carbon atoms, the number of basic rings, and the size of the basic ring. Thus, peristylane is C_{15}-hexaquinane. The system, like all others, requires some expression of the relative stereochemistry at the ring junctions. For the cases at hand, it suffices to use "*acs*", a shortening of all-cis, all-syn. Jacobson has shown that, starting with cyclopentane, there are 38 possible *acs*-quinanes on paths to dodecahedrane. The naming system, of course, has its limitations, as do all "convenient" systems. It does not specify some *acs*-quinanes sufficiently. There are, for example, two C_{14}-tetraquinanes, i and ii. If we



i



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add symmetry designations, we can distinguish these easily as (C_s)-C_{14}-tetraquinane and (C_2)-C_{14}-tetraquinane. The first isomer has a mirror plane of symmetry; the second has a twofold axis of rotation. Such additions suffice to separate all but four of the *acs*-quinane precursors to dodecahedrane. An additional tick will be sufficient to resolve this deficiency if the need ever arises.

Finally, we apologize, if only half-heartedly, for the continued use of the trivial name "peristylane"[1b] and for the introduction of its relative "norperistylane." We find it impossible to put the need for consistency above the joy of christening.

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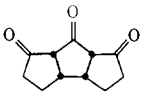

iii

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