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A NEW APPROACH TO ALL—*CIS* TRIQUINANE SYNTHESIS AND A NEW ROUTE TO THE C_{16}—HEXAQUINANE SYSTEM

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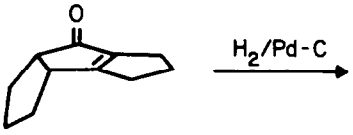
Abstract—A new synthesis of all-*cis* triquinanes is presented. The examples bear a *cis* substituent on the fifth position of the central ring, and are thus all-*cis* pentasubstituted cyclopentanes. The stereo-controlled addition of organometallics of 7-ketonorbornenes is considered, as is "reductive solvolysis" of such adducts to the corresponding hydrocarbons. The preparation of *trans*-3,4-dimethoxycyclopentyl chloride is given, as is that of the corresponding organolithium. The use of quinoxaline derivatives in aldol-type reactions is considered, with examples. A new approach to the C_{16}-hexaquinane system is developed. The ring systems reported include: tricyclo-[8.2.1.$0^{2,9}$]tridecane, tricyclo[6.3.0.$0^{3,7}$]undecane, tetracyclo-[10.1.0.$0^{2,9}$.$0^{10,13}$]tridecane, pentacyclo[8.5.1.$0^{2,6}$.$0^{7,16}$.$0^{11,15}$]hexadene and hexacyclo[8.5.1.$0^{2,6}$.$0^{3,14}$.$0^{7,16}$.$0^{11,15}$]hexadecane.

Stereochemical control in the preparation of simple all-*cis* quinanes[1] can be achieved by catalytic *cis*-addition of hydrogen to the less hindered face of the appropriate olefin. Thus, reduction of **1** gives the all-*cis* triquinane **2** (a matter of no surprise).[2] Pleasingly, the same sort of classical approach works well for the production of very



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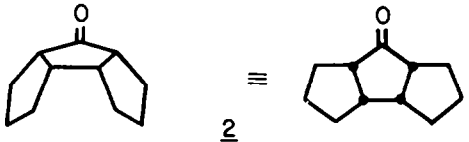

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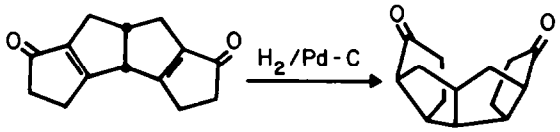
much more involuted polyquinanes, for example, the tetraquinane **3**,[3] the bridged C_{18}-hexaquinane **4**,[4] and the *endo*-substituted peristylane **5**.[5]



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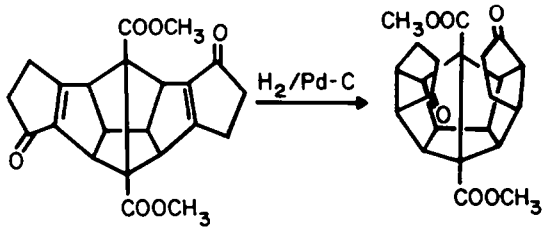

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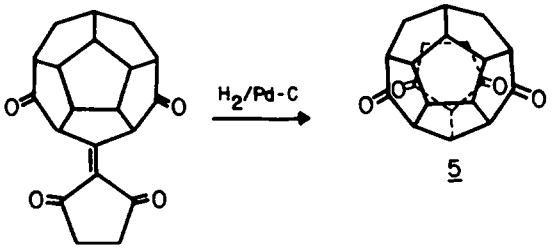

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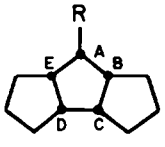
This approach is necessarily limited to situations in which the appropriate precursor can be made cleanly and in respectable amount, a stipulation which limits the applicability of the method. In this paper we present a new scheme to achieve stereochemically controlled synthesis of all-*cis* triquinanes, even those carrying a fifth *cis* substituent (R) on the central 5-membered ring, i.e. compounds like **6**, and, looking ahead, compounds like **7** which lack only two bonds of the C_{16}-hexaquinane system.



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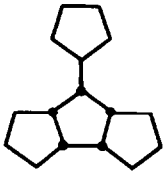

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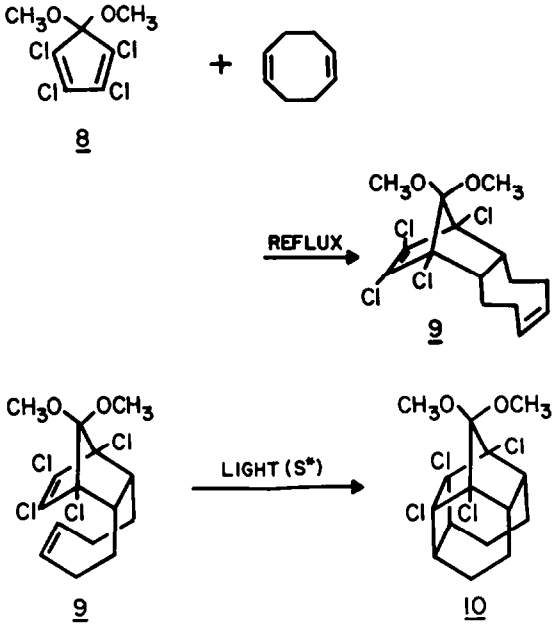
In this new scheme, the carbon framework of the triquinane is built by a Diels–Alder addition, followed by an oxidative cleavage, and then a Dieckmann recyclization. The R substituent is put in early using an organometallic addition to the non-enolizable norbornenone derived from the Diels–Alder product. As will be appreciated as we work through the details of a particular synthesis, relative stereochemistry is set at the lettered positions in **6** (see drawing): (a) *cis* at C,D as a result of a *cis-endo* Diels–Alder addition; (b) *cis* at position A by way of the special properties of the 7 position of the norbornene sub-unit within the Diels–

Alder adduct; and (c) *cis* at B,C and *cis* at D,E by equilibration to the more stable epimer at sites B and E labilized by adjacent carbonyl groups.

The Diels–Alder addition

The reaction of 1,2,3,4 - tetrachloro - 5,5 - dimethoxycyclopentadiene (**8**) with 1,5-cyclooctadiene was first reported by Fray *et al.* in 1968.[6] The addition goes easily in good yield in refluxing (150°) cyclooctadiene: as initially reported, 55% using a four-fold excess; in our procedure, 80% using a nine-fold excess. Isolation of the major (and perhaps only) 1:1 adduct (**9**) is straightforward. As the starting materials are very readily available,

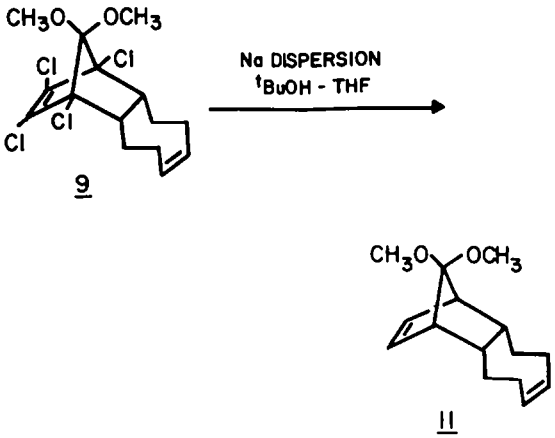


it is a simple matter to obtain a pound of compound **9** in one run.

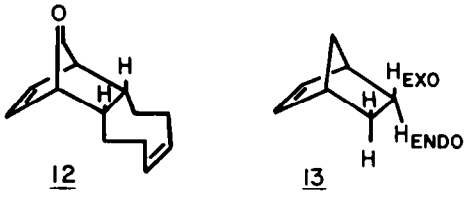
The spectroscopic properties of **9** given in the Experimental Section are completely consistent with the gross structure, but say nothing about the all-important stereochemistry at the fusion of the norbornene and the cyclooctene rings. As we have reported elsewhere,[7] sensitized ultraviolet irradiation of **9** results in its photoclosure to cage compound **10**. This is good evidence that **9** has the *cis-endo* configuration at the junction of the rings, as only this geometry permits intramolecular photoclosure.

It is not quite clear why the Diels–Alder reaction of **8** and 1,5-cyclooctadiene should give only the *endo* adduct. Predilection for the formation of *endo* adducts in Diels–Alder reactions is usually ascribed to Alder's rule of "maximum π-overlap".[8] The rule is not applicable in the present case for it is unlikely that the other double bond in 1,5-cyclooctadiene, the one remote from the reaction centers, would play any significant role in the transition state of the reaction. Instead, preferred formation of the *endo* adduct might come quite simply as a result of steric factors. Inspection of models shows that in the diene–dienophile biplanar transition state for *exo* adduct formation there is substantial steric interaction between a methoxy group of diene **8** and the methylene groups adjacent to the reacting double bond of 1,5-cyclooctadiene. This steric interaction is considerably less in the transition state for *endo* addition. If this simple steric argument holds, there should be no difference in the stereochemistry of adduct formation if the mono-olefin cyclooctene were used in place of 1,5-cyclooctadiene in reaction with **9**. Indeed, Diels–Alder reaction between diene **8** and excess cyclooctene gives in quantitative yield the *endo* adduct as the single product (at least 98% pure by glc).[9]

The four chlorines on the diene ketal **8** are there as a matter of necessity, there being no possibility of using the unstable "parent", cyclopentadienone ketal, in an addition reaction with a dienophile as unreactive as cyclooctadiene.[10] Reductive dechlorination of the Diels–Alder adducts of **8** and its relatives is a familiar process using one or another version of the original Winstein procedure (lithium and t-butyl alcohol, THF).[11] Over-reduction, namely saturation of the norbornene double bond within such adducts, is a particularly troublesome side reaction of the original method. In the Gassman modification, in which sodium is substituted for lithium, the problem is somewhat less, but the yields are still only moderate, and the work-up can be tedious.[12] In reductive dechlorination of **9** to **11**, the standard Gassman procedure using a 100% excess of lump sodium gives a slow reaction, a great deal of over-reduction, and a poor yield. The problems are resolved by switching to sodium dispersion. This quarters the time for complete disappearance of starting material and reduces the need for excess sodium. With these changes, over-reduction of **11** is not a significant problem, the work-up is less hazardous than usual, and the yield is uniformly good (66% of **11** greater than 95% pure).



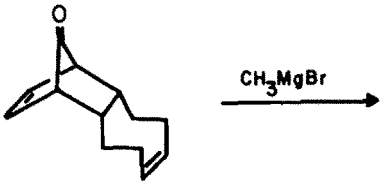
Hydrolysis of the ketal grup of **11** with aqueous sulfuric acid gives the corresponding ketone **12** in excellent yield as large white needles. As with **9**, the spectroscopic information is appropriate to the gross structure, but does not directly establish the key point, the stereochemistry at the norbornene–cyclooctene junction. Are the hydrogens H_2H_9 *exo* (as drawn) or *endo*?



In simple norbornenes (see **13**) the values of the vicinal coupling constants $J_{H(bridgehead)H(exo)}$ and $J_{H(bridgehead)H(endo)}$ are quite different, averaging 3-4 Hz and 0-2 Hz, respectively.[13] Application of this criterion should allow one to establish the stereochemistry at C-2 and C-9. It is, however, not possible to do this by simple first-order coupling analysis of the NMR spectrum of **12**. The matter is much complicated by virtual coupling and can only be understood by a detailed analysis.[14] Fortunately, re-iterative computer simulation of the H_1H_{10} resonance in the observed 270 MHz spectrum of **12** permits extraction of the key coupling constant: $J_{H_1H_2} = J_{H_9H_{10}} = 3.6$ Hz. This is appropriate for the configuration (exo hydrogen) given **13**. It is not possible to simulate the H_1H_{10} resonance reasonably using the smaller coupling constant expected for the other configuration.

Addition of the R group

Methyl Grignard is known to add easily to the carbonyl group of 7-norbornenone. *Syn* attack relative to the double bond is favored:[15] thus (correcting for the confusions of nomenclature), the preferred product is the *anti* alcohol. Although there has been considerable speculation to the point, it is still not clear whether this stereochemical preference is a result of steric or electronic effects.[15,16] In either case, a similar preference for *syn* addition would be expected for the reaction of methyl Grignard with ketone **12**. It is indeed observed; the reaction gives almost exclusively the *anti* alcohol **14** rather than the *syn* isomer **15** (*ca.* 40:1).



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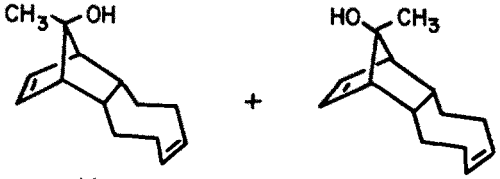
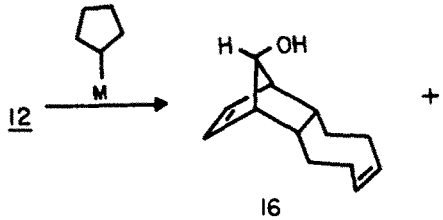


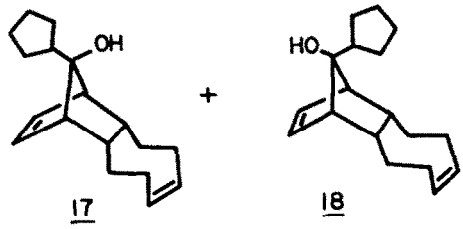
14 **15**

In line with previous observations, the reaction of **12** with methyl lithium is less stereoselective.[17,18] The *anti*:*syn* ratio of products is about 9:1. With both isomers so in hand, the configuration at the new center can be established following well-tried rules.[17] In the *syn* alcohol intramolecular hydrogen bonding to the proximate norbornene double bond leads to a characteristic infrared absorption near 3580 cm^{-1} absent in *anti* isomer. In the PMR spectra, the norbornene vinyl proton signal is characteristically at lower field for the *syn* alcohol ($\delta = 6.17$ for **15**) than for the *anti* alcohol ($\delta = 6.01$ for **14**).

Compound **14** is a useful model system. We are really interested, however, in examples carrying more elaborate substituents, in particular functionalized cyclopentanes as polyquinane precursors. Addition of secondary Grignards to norbornenones, however, is not usually successful.[15] For example, reaction of cyclopentyl magnesium chloride with ketone **12** gives only reduction to



12 **16**

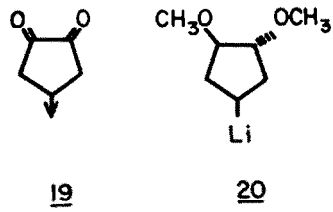


17 **18**

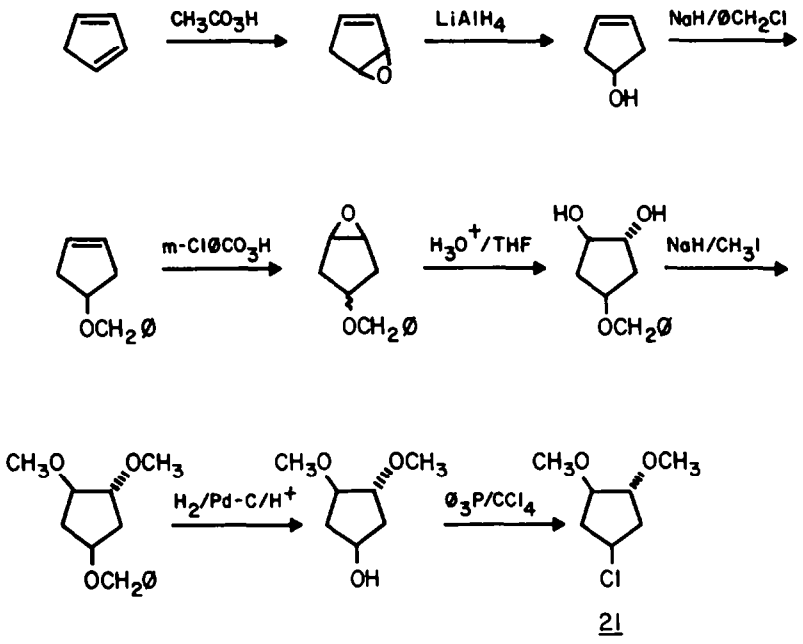
the secondary alcohol **16** rather than either of the possible addition compounds **17** or **18**.

We were aware, fortunately, of the report by Warkentin and Clark that secondary and tertiary organolithium reagents add to norbornenone without significant competition from the reduction side path.[17] We were very pleased to find that reaction of **12** in diethyl ether with cyclopentyl lithium in cyclohexane gives only about 5% reduction, about 10% *anti* addition (**18**), and about 85% of the desired *syn* addition (**17**) (relative amounts, various conditions). These figures are not significantly tied to reaction temperature over the range −45° to +25°. Benzene in place of diethyl ether leads to much less reduction, but no important change in the *syn*:*anti* ratio of addition. Use of tetrahydrofuran, a more basic and better co-ordinating solvent, eliminates the reduction bypath altogether and, more importantly, *gives a syn*:*anti ratio better than* 13:1. Again, reaction temperature seems relatively unimportant; the ratio is nearly invariant for runs at −50° or at 0°.

More complex substituents can be put on the frame of **12** by similar addition reactions at its carbonyl group. As will become apparent, addition of the 3,4-cyclopentanedione unit **19** provides a useful C_{16}-hexaquinane precursor. To do this, however, it is necessary to construct its synthon equivalent, for clearly the organolithium reagent corresponding to **19** would self-destruct. We chose to use the organolithium **20**. To this end, *trans* - 3,4 - dimethoxycyclopentyl chloride (**21**) was prepared as shown in Sequence I and described in the Experimental Section. Each step goes in good yield (about 90%), and



19 **20**

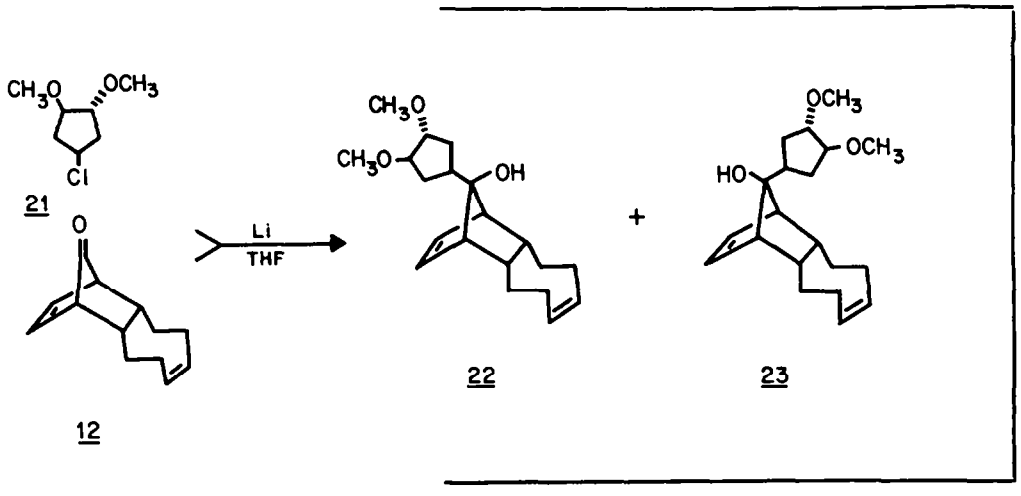


Sequence 1.

it is easy to accumulate a large amount of the chloride in a relatively short time. Note that the *trans* relation of the methoxyl groups allows us to ignore the question of configuration at the halide-carrying carbon and its metal derivative (see Sequence 1).

Reaction of the substituted cyclopentyl chloride **21** with lithium dispersion in THF-heptane followed by reaction with norbornenone **12** fails to give any of the desired addition product. Close examination shows that **20** is converted (by THF?) in the process to *trans* - 1,2 - dimethoxycyclopentane before addition to **12** occurs. To circumvent this, the addition is performed in Barbier fashion; the chloride **21**, lithium dispersion in heptane, and ketone **12** in THF all together at 0–20°. This works well; an 80% yield of the epimeric alcohols **22** and **23** is obtained, favoring the desired isomer **22** by about 13:1.

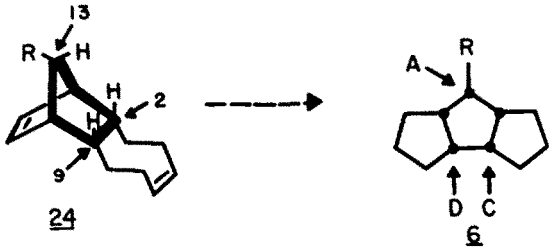
As for the earlier cases, the configuration at carbon number 13 of adducts **22** and **23** can be determined spectroscopically. The *anti* addition/*syn*-ol **23** shows the expected intramolecular hydrogen bonded hydroxyl absorption at 3580 cm^{-1} and the norbornene vinyl proton resonance at lower field (6.19 ppm) than that of the *anti*-ol **22** (5.99 ppm). In configuration **22** the non-symmetric *trans*-dimethoxy-cyclopentane unit is much nearer the norbornene vinyl carbons than it is in **23**. In accord with this, the norbornene vinyl carbon chemical shift difference is greater (0.5 ppm) in **22** than in **23** (0.2 ppm).



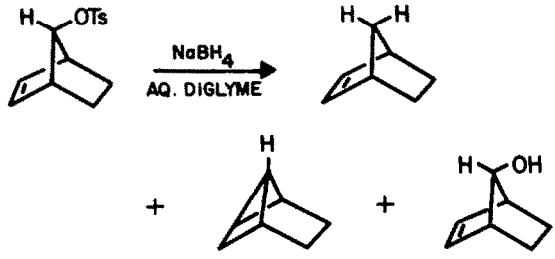
Control of stereochemistry at position A

What is now carbon number 13 in adducts **14**, **17** and **22** is to become position A in the all-*cis* triquinanes **6** as the synthesis develops. For this to occur with position A

correctly configured, the *anti* hydroxyl group at C-13 must be replaced by hydrogen with retention of stereochemistry. (This is easy to see if one recognizes now that the 5-membered ring outlined in bold in drawing 24 is to become the central ring in **6**; positions 2, 9 and 13 of **24** correspond, respectively, to the positions C, D, and A of **6**.)



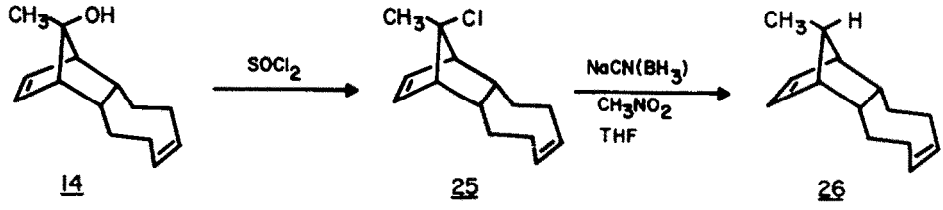
reaction becomes a reduction. Brown[19] and Winstein,[20] independently showed that "solvolysis" of *anti*-7-norbornenyl tosylate or chloride in aqueous diglyme in the presence of sodium borohydride gives norbornene, tricyclo[4.1.0.0]-heptane, and some of the *anti* alcohol (eqn 1).

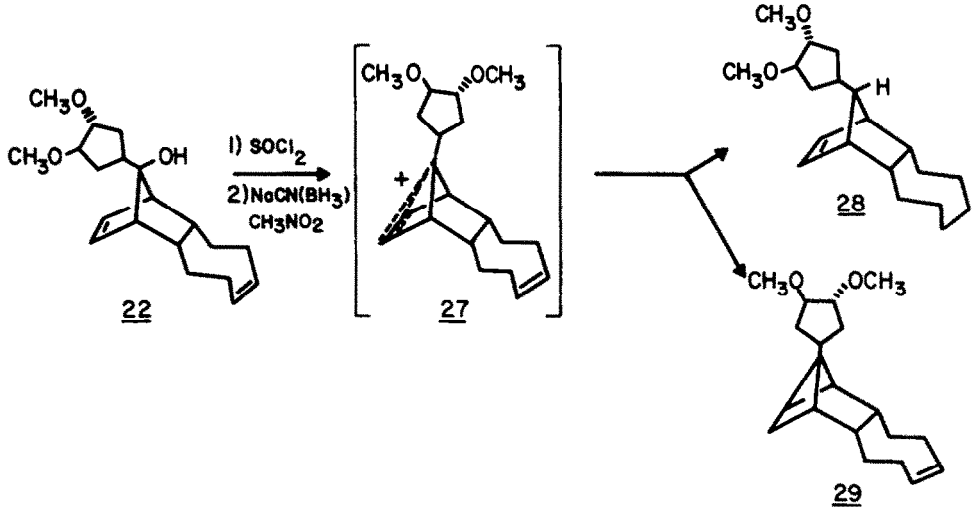


(eqn 1)

The need to substitute hydrogen for an *anti* substituent on the methano bridge of a norbornene with retention of configuration is easily met. The approach has as its root one of the best known results in physical organic chemistry: ionization of *anti*-7-norbornenyl derivatives is assisted anchimerically by the double bond and, as a result, substitution occurs with retention of configuration. In the familiar cases, the intermediate carbonium ion is captured by the solvent acting as nucleophile. Examples more relevant to the need here are those in which hydride ion is the nucleophile, and the

Conversion of the *syn*-methyl/*anti*-ol **14** with thionyl chloride to the corresponding chloride **25** and then reduction with sodium cyanoborohydride in nitromethane at 0–10° gives the *syn*-methyl hydrocarbon **26** in good yield. There is no evidence for production of the *anti* isomer. Similar treatment of **22** gives, by way of some ion like **27**, only the *syn* compound **28** and the cyclopropane **29** in a ratio of 85:15. These can be separated fairly readily by chromatography on silver nitrate impregnated silica gel, and the desired one obtained pure in 70% yield overall from the parent alcohol **22**.



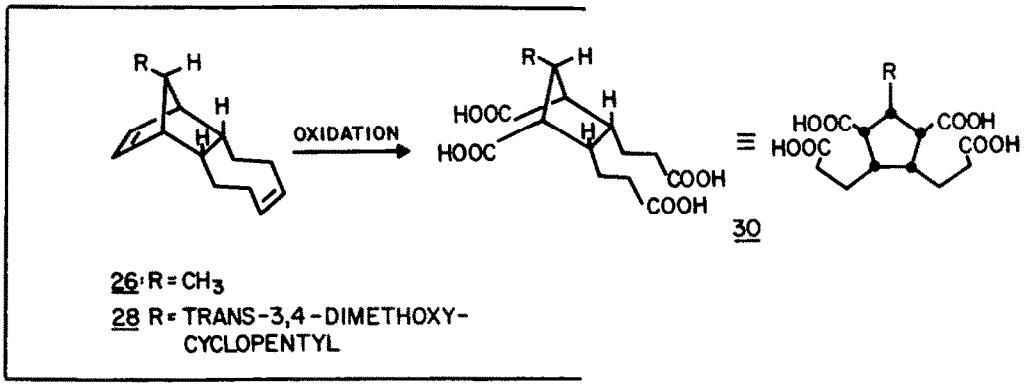


Rather a lot of searching was done before these "best" conditions were found. A few brief comments on other reagents and conditions tried may prove useful in the future. Although zinc bromide-sodium cyanoborohydride has been used successfully in the hydridolysis of a somewhat similar system,[21] this combination does not react usefully with the *anti* alcohol **17**. Treatment of **17** with an equimolar mixture of lithium aluminum hydride and tin tetrachloride (→aluminum chloride and stannane) produces a mixture of the *syn* and *anti* 13-(1-cyclopentenyl) derivatives, presumably by way of elimination and isomerization. Apparently, stannane is not effective in trapping the putative intermediate carbonium ion. On the other hand, a 1:1 molar combination of aluminum chloride with lithium aluminum hydride in ether (→ AlH_2Cl) reacts with *anti* alcohol **22** to give a 1:1 mixture of the desired compound **28** and its cyclopropyl isomer **29**. Alcohol **17** gives comparable results. Reduction of chloride **25** with sodium borohydride in 35:65 aqueous diglyme (the original Brown–Winstein conditions) gives a 60:40 ratio of **28** to **29**. The ratio is somewhat worse (55:45) in 1:1 aqueous ethanol. Sodium cyanoborohydride in THF at 50° gives 72:28 **28** to **29** and about the same in acetonitrile at room temperature. In nitromethane, the preferred solvent, the ratio (rough numbers) improves slowly as the temperature is lowered: 100°, 2:1; 50°, 3:1; 20°, 4:1; 0°, 5.5:1. Below 0°, the reaction is too slow to be useful.

The structures of these reduction products follow by analogy to the original examples.[19,20] The fact that only one of the two possible stereoisomers at position 13 is produced is strong evidence that anchimeric involvement of the double bond is indeed controlling the stereochemistry of these reactions, just as expected. It should be noted in passing that the cyclopropyl-containing material formed as a by-product in the reduction of **25** is actually a mixture of two diastereomers. The proton-decoupled CMR spectrum at 22.63 MHz of the material shows 23 resonance lines; 20 would be expected for a single isomer, 40 for a pair. Coincidental overlap of most lines is certainly probable for such closely related isomers.

Cleavage and re-cyclization

Appropriate precursors for **6**, the substituted triquinanes sought after, can be obtained by oxidative cleavage at the two double bonds of the position 13 substituted Diels–Alder adducts **26** and **28**. Thus, it can be seen in drawing **30** that the tetra-acid resulting from such cleavage is set-up for closure into the triquinane system, e.g. by Dieckmann cyclization of the corresponding tetraester or some variant thereof. (Note: in **30** the configuration at the centers α to the carboxyl groups is uncertain; these centers *may* invert during the oxidation. As will be seen, this is not a matter of concern.)



30

26 R = CH_3

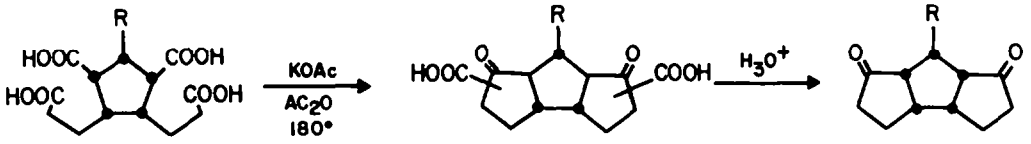
28 R = TRANS-3,4-DIMETHOXY-CYCLOPENTYL

We were to find, after many failures and frustrations, that oxidative cleavage with ruthenium tetroxide works best for the systems at hand. Even so, the oxidation gives a complex mixture of products, containing both free carboxylic acid groups and anhydrides. Attempts to separate and characterize the individual products or to convert them all to the "tetra-ester" were not profitable. It proved better to proceed blindly directly to the re-cyclization step.

There are, of course, a variety of procedures available for the cyclization of adipic acids to 5-membered rings. With the clue at hand that the oxidation mixture contains products with anhydride groups, Perkin-type conditions were chosen. This works well. Thus, the unrefined oxidation mixture is heated with acetic anhydride and potassium acetate, first at reflux and then at 180°. The crude, after excess acetic acid anhydride is removed, is refluxed over-night in methanol with 20% aqueous sulfuric acid to ensure hydrolysis of intermediate anhydrides and decarboxylation of the various α-keto-acids (**31**) that result from the cyclization. Overall, this procedure gives 15% (not-optimized) of **32** from **26** and 65% overall of **33** from **28** (see top p. 4485).

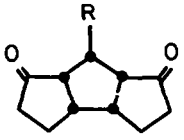
Stereochemistry at B,E

As nowhere in the conversions of **26**→**32** and **28**→**33** are the centers at C_{13}, C_2 or C_9 in the starting compounds made labile to epimerization, it can be assumed reasonably that the *syn* relationship of the hydrogens at these positions is maintained in the product triquinanes at the corresponding centers A, C and D. The remaining triquinane centers B and E are α to ketones and are epimerizable. Configurations are set here, considering the natal reaction, under equilibrating conditions. There are, therefore, three possible outcomes for the stereochemical arrangement of the five substituents about the central 5-membered ring: all-*cis* (**34a**); *cis, cis, cis, trans* (**34b**); *trans, trans, cis, trans* (**34c**). Only the first of these has all *cis*-fused 5-membered rings. The *cis* fusion is 6 kcal mole^{-1} more stable than the *trans* in the parent system.[22] Much of this difference can still be expected here; it is known, for example, that the triquinane ketone **2** is most stable in the all *cis* configuration.[2] Thus,

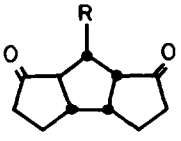


30 31

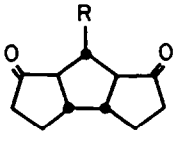
32: R = CH_3
33: R = TRANS-3,4-DIMETHOXY-CYCLOPENTYL



34A



34B



34C

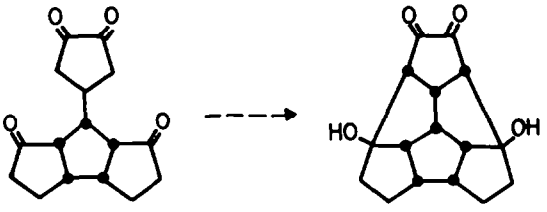
stereochemistry **34a** is assigned to the compounds actually isolated.

Some confirmation for this assignment is available from the proton-decoupled CMR spectra of **32** and **33**. There are only seven lines in the former; this is too few for the non-symmetric arrangement in configuration **34b**, which should give rise to twelve absorptions. The spectrum of **33** (C_1 symmetry in all arrangements) has sixteen lines, two less than expected (coincidental overlap), but six of these occur as close pairs, presumably reflecting the inherent C_s symmetry of the frame atoms in arrangement **34a**. The CMR results are of course equally in accord with the doubly trans-fused isomer **34c**, but this configuration is ruled out on thermodynamic grounds.

The C_{16}-hexaquinane System

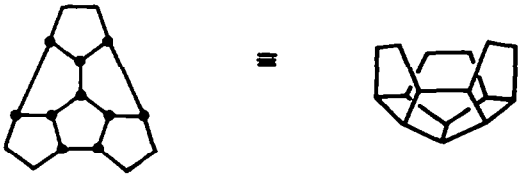
Our real impetus for the development of this methodology was to obtain entry into the C_{16}-hexaquinane system **35**. Very few compounds with this carbon skeleton are known; besides what is given here, only the synthetic approach worked out by Paquette *et al.* is available.[23] That very fine synthesis is based on the domino Diels–Alder addition of dihydrofulvene to dimethyl acetylene dicarboxylate; enviably, the essential stereochemical features are locked-in at the outset. The approach presented here is conceptually very different and provides an alternative for the tactical synthesis of such polyquinanes.

The all-*cis* tetraketone **36** seems an ideal precursor, both functionally and geometrically, for the C_{16}-hexaquinane **37**. Only aldol closures of easily formed enolates into well-placed carbonyl groups are required.



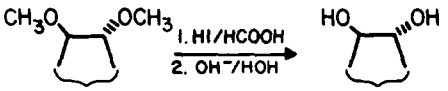
36 37

The triquinane **33**, prepared in the sequence just described, is the tetraketone **36** masked as necessary to survive the synthesis. Deprotection requires hydrolysis of the ether groups to the corresponding diol and then oxidation. After numerous less-than-completely satisfactory attempts, we settled on cleavage of the ether groups with potassium iodide in formic acid. After base hydrolysis of the formate esters that form incidental to the cleavage, this gives the *vic*-cyclopentane diol **38** in 63% yield as a well-defined crystalline solid. Although oxidation of model 1,2-cyclopentanediols to the corresponding 1,2-diones works moderately well using Whitesides' method of transition metal catalyzed hydrogen transfer to an appropriate acceptor,[24] treatment of **38** with (for example) tris(triphenylphosphine)ruthenium dichloride and benzalacetone is not useful. Other reagents tried, with an equal lack of success, included silver carbonate on celite (not reproducible) and DMSO sulfur trioxide (C–C bond cleavage). After much searching, we found it best to oxidize **38** stepwise, first with

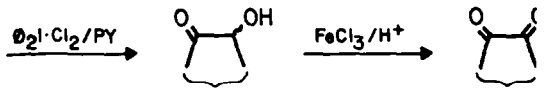


35

iodobenzene dichloride[25] in pyridine to the acyloin(s) **39**, and then, in traditional fashion, with ferric chloride in hydrochloric acid.

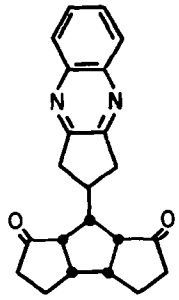


33 **38**

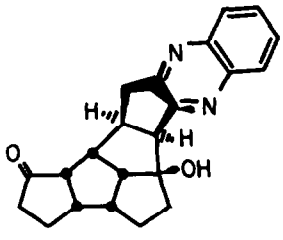


39 **36**

Enolizable α-diketones are notoriously difficult compounds to handle and characterize. To avoid this, the crude product from oxidation of **39** was treated with *o*-phenylenediamine to trap the dione as its quinoxaline derivative **40**. It was soon clear, however, that the material so obtained is not **40**, but an isomer lacking the plane of symmetry. Twenty-two different signals are resolved in the proton-decoupled CMR spectrum of the product; one for each of the carbons in $C_{22}H_{22}O_2N_2$. Of the seven signals at chemical shifts appropriate to sp^2 hybridized carbon, only one is at low enough field to belong to a ketone group. Pentaquinane structure **41** is assigned to the compound actually isolated. The infrared and PMR spectra confirm the presence of the hydroxyl group on a quaternary carbon atom. It is not clear whether the aldol closure which relates the skeletons of **40** and **41** occurs before or after the conversion of the α-diketone unit to the quinoxaline.

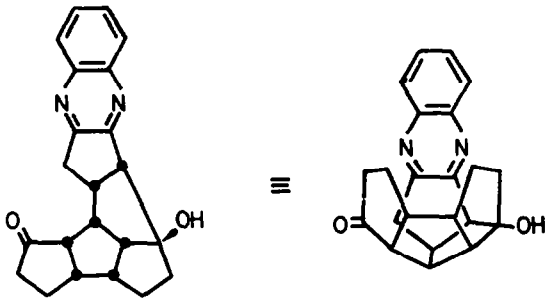


40

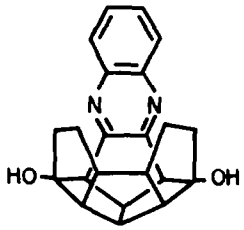


41

Although the PMR data is consistent with structure **41** as drawn, some other configurational arrangements can only be eliminated by reference to the high strain expected for 5-membered rings fused *trans*.[22] As has been noted already, there is good precedent for decision making in this way, provided the compound is formed under equilibrating conditions, as it is here. Such thinking leaves only **41** and its isomer **42** as reasonable alternatives. The latter can be eliminated as it would be expected to undergo closure to **43** under the conditions of its formation to remove the fairly awkward crowding of atoms within its bowl-like interior. Such closure would in fact produce a C_{16}-hexaquinane, our exact goal. We must therefore purposefully effect isomerization of **41** to **42**.

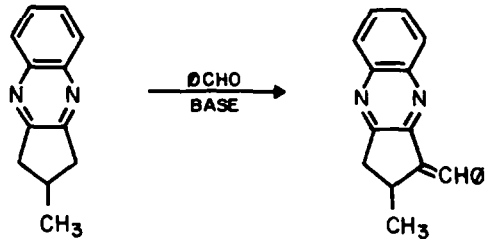


42



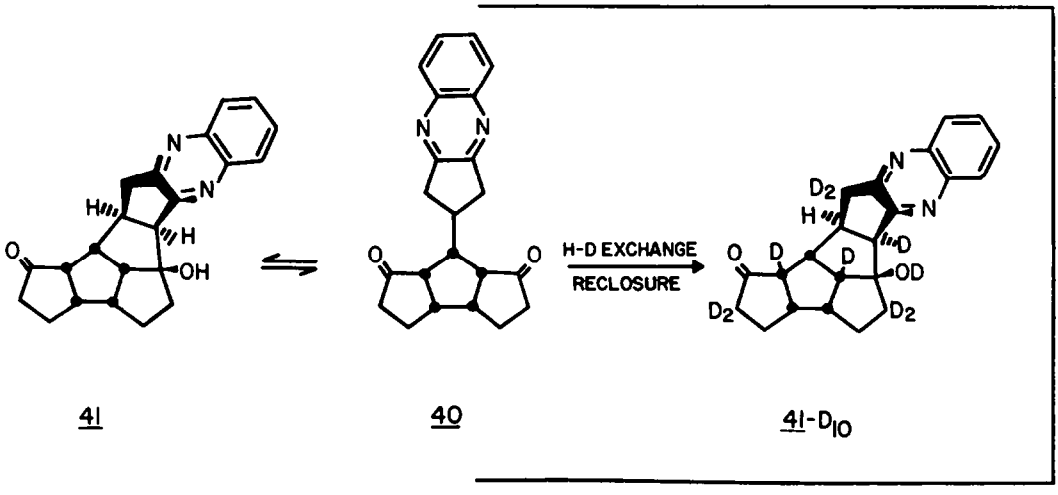
43

Quinoxalines are more than just protecting derivatives of α-diketones. The imine sub-unit can mimic the properties of a carbonyl group, at least to some degree. We find, for example, that the model quinoxaline **44**, just like a simple α-methylene ketone, reacts with base and benzaldehyde to give a benzylidene derivative (**45**). Clearly, the quinoxaline stabilizes the enol or enolate ion



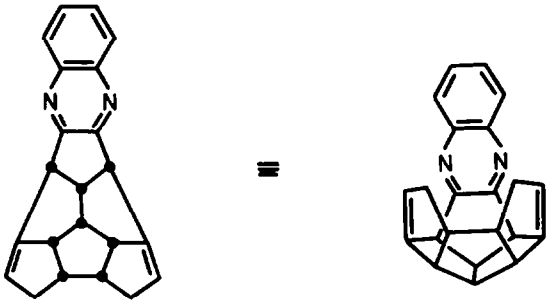
44 **45**

equivalent that must be an intermediate in this condensation reaction. With this in mind, it is reasonable to propose that **41** can be put into equilibrium with the uncyclized precursor **40**. Although **41** seems unchanged on being refluxed several hours with sodium acetate in ordinary protio-acetic acid, if acetic acid-OD is used instead, re-isolation of **41** gives material containing up to ten deuterium atoms as determined by high resolution mass spectroscopy. To account for this, we propose that **41** opens (reverse aldol) to **40** in which there are ten exchangeable sites (ignoring the aromatic protons which are unaffected under these conditions). Closure of **40**-d_{10} gives **41**-d_{10} as illustrated.



41 40 41-D_{10}

The important point here is that the quinoxaline, acting as a ketone equivalent, permits repeated access to **40**. Closure of **40** to **42**, the less stable isomer of **41**, might occur from time-to-time. In this event, further closure to hexaquinane **43** is a likely expectation, as mentioned before. Indeed, when **41** is heated with potassium acetate in acetic acid in a sealed tube at 180°C this sort of process must occur for the diene **46**, **43** minus $2H_2O$, is formed. A most pleasing result!



46

The structure of the hexaquinane **46** follows from spectroscopic considerations. Each different proton resonance (see Experimental) is resolved at 270 MHz. Mirror-plane symmetry is apparent in the PMR signals of the aromatic sub-grouping. This is confirmed for the molecule as a whole in the proton-decoupled CMR spectrum which contains only twelve signals for this 22 carbon system. Appropriately, the coupled CMR spectrum shows that there are three different kinds of quaternary carbons, eight kinds of tertiary carbons and one kind of secondary carbon. We will consider the chemistry of this C_{16}-hexaquinane derivative in future papers.

EXPERIMENTAL

Proton nuclear magnetic resonance (PMR) spectra were recorded on a Bruker HS-270 spectrometer; for samples of less than 5 mg, the machine was operated in Fourier mode using the Nicolet Instrument Corporation 1080 computer system for data acquisition and manipulation. Spectra were recorded for convenience on a compressed scale (3 Hz/mm); therefore, the shifts and coupling constants quoted are no better than ±0.02 ppm and ±1 Hz, respectively, sufficient accuracy for the purpose. Carbon-13 nuclear magnetic resonance (CMR) spectra were recorded on a Bruker HX-90E spectrometer operating at a frequency of 22.63 MHz. The spectrometer was interfaced with a Nicolet Instrument Corporation 1080 Data System, and the combined system was operated in the pulse-Fourier transform mode. Unless otherwise specified, all NMR spectra are for solutions in deuterio-chloroform containing tetramethylsilane as an internal standard. Chemical shifts (δ) are in parts per million downfield therefrom.

Mass spectra were run at 50 eV and resolution 10,000 on an Associated Electrical Industries MS-902 spectrometer computerized for on-line data collection and manipulation. Perfluorokerosene was used as internal reference. Melting points were taken on a Hoover Unimelt apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories Inc, of Skokie, Illinois.

Analytical vapor phase chromatography was performed on 5′ × 1/8″ stainless steel columns in a Varian Aerograph 1700 dual column gas chromatograph equipped with temperature programmer. The analytical column used was packed with 3% OV-17 on 60/100 mesh gas chrom Q. Analytical thin layer chromatography was done on 0.25 mm thick precoated silica gel (SIL G-25 UV_{254}) or alumina (ALOX-25 UV_{254}) layers on glass plates prepared by Macherey-Nagel & Co. High pressure column chromatography was done on a system home-built with columns, plumbing and valves supplied by Chromatronix, Inc. and a dual piston mini-pump built by Milton Roy Co. The column was a

1.3 × 55 cm glass tube packed with 10–40 μ silica gel H supplied by EM Reagents.

Solvents were purified and dried as appropriate. Tetrahydrofuran, benzene, and ether were distilled from lithium aluminum hydride and stored under nitrogen. Methylene chloride was distilled under nitrogen from sulfuric acid. Carbon tetrachloride was distilled from phosphorus pentoxide. Ethanol was removed from chloroform by adsorption on alumina. Removal of solvent *in vacuo* refers to evaporation of solvent at aspirator pressure on a Büchi rotary evaporator.

1,10,11,12 - *Tetrachloro* - 13,13 - *dimethoxytricyclo*[8.2.1.$0^{2,9}$]-*trideca* - 5,11 - *diene* (**9**)

A solution of 1,2,3,4 - tetrachlorodimethoxycyclopentadiene **8** (400 g, 1.515 mol) in 1,5 - cyclooctadiene (1600 ml, 13 mol) in a 3-L, round-bottomed flask, equipped with reflux condenser and nitrogen inlet, was refluxed for 6 hr. The excess cyclooctadiene was removed on the rotary evaporator at aspirator pressure and then by distillation at 75°/60 torr. The residue was treated with ether (500 ml). The 2:1 adduct precipitated as a white solid (approx. 60 g) and was removed by filtration.[26] The filtrate was concentrated *in vacuo* to a dark brown, viscous liquid. This was distilled at 165–168°/20 millitorr to give pure 1:1 adduct **9**, which crystallized on standing (451 g, 80%). A small sample was recrystallized from methanol: m.p. 71–72° (lit[6] m.p. 71–72°); PMR 5.83–5.70 (2H, m), 3.60 (3H, s), 3.57 (3H, s), 2.73 (2H, d with additional fine structure, J = 12 Hz), 2.46–2.27 (2H, m), 2.15–1.94 (4H, m), 1.56–1.36 ppm (2H, m); CMR 131.6, 129.0, 111.8, 79.5, 52.6, 51.5, 50.9, 24.9 ppm.

13,13 - *Dimethoxytricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *diene* (**11**)

Clean sodium sand (105.0 g, 4.57 g-atoms) was obtained from approximately 400 ml of a 40% dispersion of sodium in mineral oil (Alfa) by washing well with dry pentane under nitrogen. It was slurried with dry tetrahydrofuran (1800 ml), and the slurry transferred to a 5 L, 3-necked flask equipped with mechanical stirrer, reflux condenser, nitrogen inlet and addition funnel. The mixture was brought to reflux using a heating mantle, and t.-butanol (200 ml) was added over a period of 5-10 min. (Care! Hydrogen evolution.) The mantle was then turned off, and the dropwise addition of a solution of the Diels–Alder adduct **9** (152.2 g, 0.408 mol) and t-butanol (125 ml) in dry tetrahydrofuran (300 ml) was started immediately. Addition was continued at the rate necessary to maintain steady reflux. After the addition was complete (approx. 1 hr), the reaction mixture was refluxed for an hour, then excess sodium was destroyed by the cautious, dropwise addition of methanol (400 ml). Reflux was maintained for a further 2 hr, after which excess solvent (approx. 1500 ml) was distilled from the reaction flask. The purple residue was poured into ice water (2 L). The aqueous phase was extracted with ether (4 × 250 ml). The combined extract was washed with brine (2 × 150 ml), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to leave a brown oil. Rapid distillation at 2 torr at 115–135° gave a bright yellow oil (89.1 g, 88%). Further purification was achieved by careful distillation through a 55-cm platinum spinning band column (Nester-Faust). The product distilled at 75–78° near 1 torr and was obtained as a colorless liquid (60.3 g, 66%). Glc analysis (175°) indicated that it was greater than 95% pure. An analytical sample was obtained by high pressure liquid chromatography (chloroform as eluant) followed by molecular distillation: PMR 6.12 (2H, unsymmetrical t), 5.81–5.68 (2H, m), 3.25 (3H, s), 3.14 (3H, s), 2.77–2.69 (2H, m), 2.58–2.42 (2H, m), 2.34–2.18 (2H, m), 2.08–1.91 (2H, m), 1.81–1.66 (2H, m), 1.53–1.33 ppm (2H, m). Calc. for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40; found: C, 76.77; H, 9.63%.

Tricyclo[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *dien* - 13 - *one* (**12**)

A solution of **11** (98.0 g) in ether (250 ml) was placed in a 2-L kettle equipped with a vibromixer. Aqueous sulfuric acid (10 mol.%, 1 L) was added, and the mixture was stirred for 22 hr. Glc analysis (170°) after this time showed no remaining starting material. The organic layer was separated, and the aqueous phase extracted with ether (2 × 100 ml) The combined extract was washed with 10% aqueous sodium carbonate solution (100 ml) and then brine (100 ml). The pale yellow solution was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a white solid (79 g). This was crystallized from petroleum ether (30–60°) to give pure ketone **12** (67.3 g, 85%) as large needles. An analytical sample was prepared by two recrystallizations from petroleum ether followed by sublimation at 20 torr at 60°: m.p. 65.6–67°; IR (CCl_4) 3020 (w), 2935 (m), 1790 (s), 1775 (s), 1120 cm^{-1} (m); PMR 6.46 (2H, unsymmetrical t), 5.83–5.67 (2H, m), 2.91–2.79 (2H, m), 2.59–2.40 (2H, m), 2.38–2.21 (2H, m), 2.12–1.96 (2H, m), 1.94–1.78 (2H, m), 1.71–1.49 ppm (2H, m); CMR 205.2, 131.9 (2), 54.9, 40.7, 30.1, 25.4 ppm; *m/e* calc. for P^+–C_3H_4O, 132.0939; found: 132.0927. Calc. for $C_{13}H_{16}O$: C 82.98; H, 8.51; found, C, 82.97; H, 8.52%.

13 - *syn* - *Methyltricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *dien* - 13 - *anti* - *ol* (**14**) *and* 13 - *anti* - *methyltricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *dien* - 13 - *syn* - *ol* (**15**)

(*a*) A 100-ml, 3-necked flask equipped with nitrogen inlet, low-temperature thermometer, and magnetic stirrer was charged with 1.00 g (5.34 mmol) of ketone **12** and tetrahydrofuran (25 ml). The solution was cooled to 4° and then 2.2 ml methyl magnesium bromide in diethyl ether (5.9 mmol, 10% excess; Aldrich, 2.7M) was added dropwise by syringe over 5 to 10 min, slowly enough that the temperature of the reaction mixture remained below 9°. The resulting clear solution was stirred for 2.5 hr at ice temperature, and then another 0.5 ml of the Grignard solution was added rapidly; the temperature rose several degrees and then dropped back. The now cloudy white ice-cold solution was stirred a further 1.5 h, after which aqueous saturated ammonium chloride solution (25 ml) was added cautiously. After the weekend, the layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined organic portion was brine-washed, dried over magnesium sulfate, and concentrated at reduced pressure to give 1.06 g of white solid. Examination by tlc (methylene chloride, iodine visualization) showed one spot, R_f 0.21 (**14**). Examination by 270 MHz PMR spectroscopy showed high-field methyl signals at 1.26 (**14**) and 1.31 ppm (**15**) in a ratio of about 40:1. The solid was chromatographed on 50 g of silica gel (Baker, 60-200 mesh) with methylene chloride) to give 0.940 g (80% yield) of **14** as a white solid.

(b) A 1-L, 3-necked flask equipped with dropping funnel, nitrogen inlet, low-temperature thermometer, and magnetic stirrer was charged with 12.0 g (0.064 mole) of ketone **12** and tetrahydrofuran (400 ml). The clear solution was cooled to 3° and then 44 ml of methyl lithium in diethyl ether (0.070 mole, 9.5% excess; Alfa, low halide, 1.6M) was added dropwise, slowly enough that the temperature of the reaction mixture remained below 8°. The resulting clear orange solution was stirred a further 1.25 hr at ice temperature. Water (460 ml) was then added cautiously, followed by methylene chloride (400 ml). The aqueous layer was extracted twice with methylene chloride. The combined organic extract was brine-washed, dried over sodium sulfate, and concentrated at reduced pressure to afford 13.1 g of clear yellow oil. Examination *via* TLC as above showed two spots, R_f 0.21 (major, **14**) and R_f 0.13 (minor, **15**). The PMR spectrum showed a product ratio of about 9.7:1, **14** to **15**. The mixture was chromatographed on 500 g silica gel to give 9.06 g of **14** as a white solid: m.p. 55–58°; IR (CCl_4) 3640 (sharp) and 3510 cm^{-1} (broad); PMR 6.06–6.00 (2H, unsymmetrical t), 5.80–5.67 (2H, m), 2.66–2.58 (2H, br d), 2.25–2.16 (4H, m), 2.10–1.91 (2H, m), 1.82–1.65 (2H, m), 1.63 (1H, br s), 1.51–1.30 (2H, m), 1.27 ppm (3H, unsymmetrical t); CMR 135.3, 132.1, 91.0, 58.3, 42.9, 30.4, 26.2, 20.8 ppm.

Further elution with methylene chloride gave 1.25 g of a mixture of **14** and **15** and then 0.5 g of pure **15** as a pale yellow solid: m.p. *ca.* 40°; IR (CCl_4) 3590 cm^{-1} (sharp); PMR 6.17 (2H, unsymmetrical t), 5.78–5.64 (2H, m), 2.78 (1H, br s), 2.49–2.32 (4H, m), 2.31–2.14 (2H, m), 2.05–1.85 (2H, m), 1.81–1.63 (2H, m), 1.60 (1H, s), 1.45–1.19 (2H, m), 1.32 ppm (3H, br s); CMR 134.8, 131.7, 90.3, 59.2, 42.2, 30.4, 25.7, 18.5 ppm.

Silica gel chromatography of the product mixture from a

smaller scale reaction (1.0 g of **12**) afforded a cleaner separation of **14** (0.81 g, 69%) from **15** (0.090 g, 7.7%).

anti - *Tricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *dien* - 13 - *ol* (**16**)

Magnesium turnings (0.24 g, 10 mg-atom) were stirred in dry tetrahydrofuran (8 ml) in a 50-ml, 3-necked, round-bottomed flask equipped with nitrogen inlet, addition funnel, and reflux condenser. Cyclopentyl chloride (0.21 g, 2.0 mmol) was introduced, and the mixture stirred at room temperature for 15–20 min. As there was no evidence of Grignard formation, 1,2-dibromoethane (10–15 μL) was syringed in; the reaction started almost immediately, and the flask became warm. External heating was started, and the mixture was maintained at 50° for 1 hr. The greenish-gray solution was then cooled to 35°, and ketone **12** (0.19 g, 1.0 mmol) in dry tetrahydrofuran (2 ml) was added rather rapidly. The temperature was maintained at 40° for 10 min, then the reaction was quenched by adding to it a stirred solution of saturated aqueous ammonium chloride (20 ml). The aqueous phase was extracted with ether (2 × 10 ml). The combined organic extract was washed with brine (10 ml), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give **16** (0.19 g, 100%) as a colorless, crystalline compound. An analytical sample was obtained by sublimation at 80° at 0.5 torr: m.p. 85.5–86.5°; PMR (C_5D_5N) 6.08 (2H, unsymmetrical t), 5.88–5.71 (2H, m), 5.07 (1H, br s), 3.91 (1H, s), 3.04–2.88 (2H, m), 2.70–2.58 (2H, m), 2.38–2.20 (2H, m), 2.12–1.97 (2H, m), 1.87–1.70 (2H, m), 1.65–1.44 ppm (2H, m); *m/e* P^+ calc. for $C_{13}H_{18}O$, 190.1357; found, 190.1323.

13 - *syn* - *Cyclopentyltricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *dien* - 13 - *anti* - *ol* (**17**) *and* 13 - *anti* - *cyclopentyltricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *dien* - 13 - *syn* - *ol* (**18**).

A solution of the ketone **12** (4.50 g, 24 mmol) in dry tetrahydro - furan (100 ml) was placed in a 3-necked, 250-ml, round-bottomed flask equipped with nitrogen inlet, addition funnel, and thermometer. The solution was cooled to −45° with a Dry Ice-acetone bath, and a solution of cyclopentyl lithium in cyclohexane (2.25 M, 12.0 ml, 27 mmol, Foote Mineral) was added slowly over approximately 15–20 min with good stirring. The reaction mixture was stirred for 15 min more and then warmed to −30° at which point it was quenched by addition of saturated aqueous ammonium chloride solution (25 ml). The whole was warmed to room temperature. Most of the tetrahydrofuran was removed *in vacuo*. The aqueous residue was extracted with ether (3 × 10 ml). The extract was washed with brine (1 × 10 ml), dried over magnesium sulfate and filtered. The filtrate was concentrated *in vacuo* to yield a crude crystalline product mixture (6.3 g). Crystallization from petroleum ether (30–60°) gave the *anti* alcohol **17** as large plates (5.16 g, 84%): m.p. 61–62°; IR (CCl_4) 3615 cm^{-1} (w); PMR 6.00 (2H, unsymmetrical t), 5.83–5.67 (2H, m), 2.78–2.47 (3H, m), 2.44–2.19 (4H, m with d at 2.36, J = 2 Hz); 2.14–1.94 (2H, m), 1.94–1.69 (3H, m), 1.67–1.22 ppm (10H, m); CMR 134.6, 132.1, 94.2, 56.8, 43.2, 42.9, 39.3, 30.6, 27.4, 26.4, 26.3 ppm; *m/e* P^+ calc. for $C_{18}H_{26}O$, 258.1983; found, 258.2000.

A small amount of the pure *syn*-alcohol **18** was isolated from a mixture of the *syn* (R_f 0.18) and *anti* (R_f 0.23) alcohols by high pressure liquid chromatography using a 1:1 v/v mixture of chloroform-hexane as eluant. The crude crystalline compound was recrystallized from acetonitrile to give **18** as colorless needles: m.p. 78–80°; IR (CCl_4) 3575 cm^{-1} (w); PMR 6.16 (2H, unsymmetrical t), 5.79–5.64 (2H, m), 2.53 (2H, br s, J = 2 Hz), 2.51–2.16 (6H, m), 2.04–1.87 (2H, m), 1.81–1.22 ppm (12H, m); *m/e* P^+ calc. for $C_{18}H_{20}O$, 258.1983; found, 258.1993.

Trans - 3,4 - *Dimethoxycyclopentyl chloride* (**21**)

(*a*) 4 - *Benzyloxycyclopentane*. Sodium hydride (Alpha, 50% dispersion, 30.0 g, 0.625 mol) was stirred in dry benzene (100 ml) in a 3-necked, 1 L flask equipped with nitrogen inlet, addition funnel, condenser, and mechanical stirrer. The flask was cooled in an ice-bath. A solution of 4-cyclopentenol (40.0 g, 0.48 mol) prepared according to Crandall[27] in dry benzene (100 ml) was added dropwise over a period of 0.5 hr. After the addition was completed, the mixture was stirred at room temperature until the evolution of hydrogen ceased (approx. 1 hr). A solution of benzyl chloride (70.0 g, 0.55 mol) in dry benzene (150 ml) was then added dropwise, and the mixture was brought slowly to reflux. (Upon the initial heating there was an exothermic reaction with some foaming, but this soon subsided.) The reaction mixture was refluxed gently overnight, and then cooled. The excess sodium hydride was destroyed by cautious addition of methanol in benzene. The mixture was filtered and washed with water (2 × 50 ml). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to leave a light-red liquid. This product was fractionated. The desired benzyl ether was obtained boiling at 90° at 1 torr as a colorless, mobile liquid (76.0 g, 91%): PMR 7.38–7.20 (5H), 5.67 (2H, br s), 4.48 (2H, s), 4.28 (1H, septet, J = 3 Hz), 2.58 (2H, d of d, J = 16.5 Hz and 6 Hz), 2.46 ppm (2H, d of d, J = 17 Hz and 3 Hz); *m/e* P^+ calc. for $C_{12}H_{14}O$, 174.1044; found, 174.1034.

(*b*) 4 - *Benzyloxycyclopentane* - 1,2 - *oxides*. A solution of 4-benzyloxycyclopentene (59.8 g, 0.344 mol) in methylene chloride (170 ml) was placed in a 3-necked, 2 L flask equipped with mechanical stirrer, nitrogen inlet, addition funnel, and reflux condenser. The reaction vessel was cooled in an icebath. A solution of m-chloroperbenzoic acid (Aldrich, 69.8 g, 0.404 mol, 85% titer) in methylene chloride (630 ml) was added dropwise over a period of 1.5 hr. The mixture was allowed to warm slowly to room temperature, stirred for 4 hr, and then brought to reflux for 1.5 hr. After cooling, the solution was filtered, washed with 10% aqueous sodium sulfite solution (300 ml) followed by 10% aqueous sodium carbonate solution (2 × 300 ml), then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. This left the crude epoxide mixture as a light-yellow oil (65.3 g, quantitative). Glc analysis (200°) indicated approximately equal amounts of the two isomeric epoxides. A small amount of each was obtained by preparative glc (analytical OV-17, 60 ml/minute, 210°: isomer A, retention time 4.1 min; isomer B, retention time 5.8 min): PMR isomer A 7.39–7.17 (5H, m), 4.37 (2H, s), 3.81 (1H, pentet, J = 7 Hz), 3.42 (2H, s), 2.42 (2H, d of d, J = 15 Hz and 7 Hz); PMR isomer B 7.37–7.19 (5H, m), 4.42 (2H, s), 4.00 (1H, J = 7.5 Hz), 3.47 (2H, s), 2.14 (2H, d, J = 15 Hz), 1.89 ppm (2H, d of d, J = 15 Hz and 7.5 Hz); *m/e*, no parent ion found, calc. for $P^+ - O$, 174.1044; found, 174.1046; calcd for $P^+ - C_3H_8O$, 106.0424; found, 106.0418.

(*c*) 4 - *Benzyloxycyclopentane* - *trans* - 1,2 - *diol*. A solution of crude 4 - Benzyloxycyclopentane - 1,2 - oxides (81.7 g, 0.43 mol, prepared as just described) in a mixture of 0.5 N sulfuric acid (500 ml) and tetrahydrofuran (900 ml) was kept at room temperature for 16 hr. The solution was then neutralized with dilute aqueous sodium carbonate solution. The bulk of the tetrahydrofuran was removed *in vacuo*. The residue was extracted with chloroform (4 × 250 ml). The extract was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 4 - benzyloxycyclopentane - *trans* - 1,2 - diol as a viscous, light yellow oil (83.2 g, 93%), used in the next step without further purification: PMR 7.39–7.20 (5H, m), 4.39 (2H, s), 4.20–3.93 (4H, m), 3.88–3.77 (1H, m), 2.30–2.07 (2H, m), 1.83–1.52 ppm (2H, m).

(*d*) 4 - *Benzyloxycyclopentane* - *trans* - 1,2 - *diol dimethyl ether*. Sodium hydride (50% dispersion, 32.0 g, 0.67 mol) was stirred in dry tetrahydrofuran (400 ml) in a 2 L, 3-necked flask equipped with nitrogen inlet, efficient condenser, mechanical stirrer, and addition funnel. The flask was cooled in an ice bath. A solution of 4 - benzyloxycyclopentane - *trans* - 1,2 - diol (55.5 g, 0.267 mol) and methyl iodide (80 ml) in dry tetrahydrofuran (400 ml) was added dropwise over a period of 3 hr. (Caution! Considerable hydrogen evolution.) The reaction mixture was then allowed to warm to room temperature. It was stirred overnight; the reaction was completed by finally refluxing the mixture for 1 hr. Excess sodium hydride was destroyed by cautious addition of methanol (20–30 ml). The reaction mixture was filtered through a cake of Celite to avoid subsequent emulsion problems. Most of the tetrahydrofuran was removed *in vacuo*. Water (150–200 ml) was added to the residue, and the aqueous

phase was extracted with ether (4 × 175 ml). The extract was washed with brine (100 ml), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a brown oil. This was distilled under vacuum. The title compound was obtained as a colorless liquid boiling at 120°/0.8 torr, pure by glc (57.4 g, 91%): PMR 7.32–7.17 (5H, m), 4.41 (2H, s), 3.97 (1H, pentet, J = 6 Hz), 3.81–3.73 (1H, m), 3.62–3.54 (1H, m), 3.29 (3H, s), 3.26 (3H, s), 2.33–2.22 (1H, m), 2.06–1.94 (1H, m), 1.89–1.78 (1H, m), 1.72–1.58 ppm (1H, m); *m/e*, parent ion not found; P^+ calc. for $C_{14}H_{20}O_3$, 236.1412; calc. for $P^+ - C_7H_8$, 144.0786; found, 144.0793; calc. for $P^+ - C_8H_{10}$, 114.0681; found, 114.0683.

(*e*) *trans* - 3,4 - *Dimethoxycyclopentanol.* 4 - Benzyloxycyclopentane - *trans* - 1,2 - diol dimethyl ether (107.6 g, 0.456 mol) was dissolved in glacial acetic acid (250 ml) in a 500 ml Parr pressure bottle. Commercial 10% palladium-on-charcoal catalyst and 70% perchloric acid (1 ml) were added. The hydrogenolysis was carried out in a Parr Shaker at 50 psi. Take-up of hydrogen proceeded at a steady rate; the reaction was judged to be complete when rapid uptake of hydrogen ceased (approx 30–45 min). The mixture was filtered through a cake of Celite and then concentrated *in vacuo* to give a clear liquid. This was dissolved in methylene chloride (300 ml). The solution was washed with 10% aqueous sodium carbonate solution (2 × 75 ml) followed by brine (50 ml), dried with magnesium sulfate and concentrated *in vacuo.* The residue was distilled to give pure alcohol (53.1 g, 80%) as a colorless, mobile liquid: b.p. 60°/0.7 torr; PMR 4.37–4.26 (1H, m), 3.92–3.82 (1H, m), 3.76–3.68 (1H, m), 3.38 (3H, s), 3.34 (3H, s), 3.10 (1H, br s), 2.24–2.00 (2H, m), 1.91 (1H, d of t, J = 15 Hz and 6 Hz), 1.74 ppm (1H, br d, J = 15 Hz); *m/e* P^+ calc. for $C_7H_{14}O_3$, 146.0942; found, 146.0949.

(*f*) *trans* - 3,4 - *Dimethoxycyclopentyl chloride* (**21**). A solution of *trans* - 3,4 - dimethoxycyclopentanol (52.4 g, 0.36 mol) in a mixture of carbon tetrachloride (50 ml) and methylene chloride (350 ml) was put into a 1-L, three-necked flask equipped with nitrogen inlet, reflux condenser and addition funnel. A solution of triphenylphosphine (108 g, 0.40 mol, 15% excess) in methylene chloride (215 ml) was added. The reaction mixture was refluxed for 2 days. Glc analysis at this point (analytical OV-17, 150°) indicated that the reaction was 85% complete. Further refluxing did no good. The mixture was concentrated *in vacuo* to leave an oily white solid. Pentane (1 L) was added to precipitate triphenylphosphine oxide, which was removed by filtration. The filtrate was concentrated *in vacuo* to leave a light green oil (55 g). This was dissolved in a mixture of carbon tetrachloride (8 ml) and methylene chloride (250 ml). Triphenylphosphine (20 g) was added, and the mixture was refluxed for 16 hr, at which point glc analysis indicated that the starting material was gone. Work-up was effected as before. Distillation gave the product as a colorless, highly mobile liquid (52.3 g, 88%): b.p. 60°/4 torr; IR (film) 2985 (m), 2940 (s), 2825 (m), 1455 (m), 1200 (w), 1110 (s), 700 cm^{-1} (s); PMR 4.26 (1H, pentet, J = 6 Hz), 3.88–3.79 (1H, m), 3.70–362 (1H, m), 3.32 (3H, s), 3.29 (3H, s), 2.63–2.51 (1H, m), 2.22–2.10 (2H, m), 1.88 ppm (1H, d of t, J = 15 Hz and 6 Hz); *m/e* P^+ calc. for $C_7H_{13}O_2Cl$: 166.0574, 164.0604; found: 166.0588, 164.0617.

13 - *syn* - (*trans* - 3,4 - *dimethoxycyclopentyl*) - *Tricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *dien* - 13 - *anti* - *ol* (**21**) *and* 13 - *anti* - (*trans* - 3,4 - *dimethoxycyclopentyl*) - *tricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *dien* - 13 - *syn* - *ol* (**23**)

A solution of **12** (38.5 g, 0.205 mol) in dry tetrahydrofuran (600 ml) and lithium dispersion in heptane (55% metal, 7.30 g, 0.57 g-atom, Foote Mineral) was placed in a 2 L kettle equipped with vibromixer, addition funnel, and argon inlet. The kettle was cooled in an icebath; a solution of 3,4 - *trans* - dimethoxycyclopentyl chloride **21** (34.4 g, 0.21 mol) in dry tetrahydrofuran (100 ml) was added fairly quickly (approx 2 min) with vigorous stirring. The colorless reaction mixture soon turned a deep yellow-brown, and the lithium metal surface became shiny. The reaction mixture was maintained at ice-bath temperature for 1 hr and then warmed to room temperature. After 16 hr, the mixture was filtered to remove excess lithium, and the filtrate was concentrated *in vacuo.* Water (500 ml) was added to the residue, and the aqueous phase was extracted with ether (4 × 300 ml). The combined extract was washed with brine and dried over magnesium sulfate. The yellow solution was filtered, and the filtrate concentrated *in vacuo* to a light brown oil. Addition of pentane (1 L) caused precipitation of a white flocculent polymeric substance that was removed by filtration and discarded. The filtrate was concentrated *in vacuo* to give a yellow viscous oil that crystallized on standing (57 g, 88%). Glc analysis (235°) indicated a 93:7 *anti*/*syn* ratio of isomeric alcohols. Pure *anti* alcohol **22** was obtained by two crystallizations from ether at 0°: m.p. 65–65.8°; IR (CCl_4) 3455 cm^{-1} (m); PMR 5.99 (2H, unsymmetrical t), 5.81–5.67 (2H, m), 3.78–3.71 (1H, m), 3.66 (1H, broad d, J = 5 Hz), 3.47 (1H, s), 3.36 (3H, s), 3.29 (3H, s), 3.06–2.91 (1H, m), 2.78–2.61 (2H, m), 2.38–2.17 (4H, m), 2.12–1.33 ppm (10H, m); CMR 134.8, 134.3, 132.2, 94.2, 84.9, 84.7, 56.9, 56.5, 56.0, 43.3, 43.1, 35.2, 31.8, 30.8, 30.6, 26.2 ppm; *m/e* P^+ calc. for $C_{20}H_{30}O_3$, 318.2193; found, 318.2222. Calc. for $C_{20}H_{30}O_3$: C, 75.47; H, 9.42; found: C, 75.73; H, 9.62%.

A small amount of pure *syn* alcohol **23** was isolated from the *syn* (R_f 0.24) and *anti* (R_f 0.37) mixture by high pressure liquid chromatography on silica gel using ethyl acetate-chloroform (1:9, v/v) as eluant: IR (CCl_4) 3580 cm^{-1} (w); PMR 6.17 (2H, br), 5.78–5.64 (2H, m), 3.79–3.63 (2H, m), 3.38 (3H, s), 3.37 (3H, s), 2.72–2.58 (2H, m), 2.56–2.49 (2H, m), 2.47–2.34 (2H, m), 2.33–2.18 (2H, m), 2.14–1.88 (4H, m), 1.83–1.58 (4H, m), 1.49–1.30 ppm (2H, m) ; CMR 134.8, 134.6, 132.0, 92.9, 86.2, 85.6, 57.5, 57.3, 56.9, 56.8, 42.2, 35.1, 30.7, 30.2, 29.6, 25.9 ppm; *m/e* P^+ calc. for $C_{20}H_{30}O_3$, 318.2193; found, 318.2180.

13 - *syn* - *Methyltricyclo*[8.2.1.$0^{2,9}$]*trideca* - 5,11 - *diene* (**26**)

A 250-ml, round-bottomed flask equipped with a magnetic stirrer and a Claisen adapter fitted with an addition funnel, a nitrogen inlet, low-temperature thermometer, and magnetic stirrer was cooled in an ice-bath and charged with 7.51 g (34.1 mmol) of **14** and anhydrous diethyl ether (75 ml). The clear solution was cooled to 3°, and then reagent grade thionyl chloride (15 ml) was added dropwise over a 0.5 hr period, keeping the temperature of the reaction mixture below 5°. The ice-cooled, clear, pale yellow solution was stirred for 1.75 hr, then the solvent and most of the excess thionyl chloride were removed at reduced pressure. The crude chloride (**25**) was stored overnight at − 10° under nitrogen and then used without purification.

A 500-ml, 3-necked flask equipped with a dropping funnel, nitrogen inlet, low-temperature thermometer, and magnetic stirrer was charged with sodium cyanoborohydride powder (15.1 g, 0.252 mole, Alfa-Ventron) and 75 ml nitromethane (Aldrich, 96%). The flask was placed in an ice bath and the solution cooled. A solution of the crude chloride **25** in nitromethane (40 ml) and dry tetrahydrofuran (4 ml) was added slowly to the cold hydride suspension over 0.5 hr, keeping the temperature below 4°. The resulting ice-cold, milky white suspension was stirred for 4 hr, and then 10% hydrochloric acid (125 ml) was added dropwise, slowly enough to maintain the temperature below 9°. Vigorous gas evolution was noted. The ice-bath was removed, and the reaction mixture was stirred overnight under nitrogen. The mixture was then salted, and diluted with methylene chloride (200 ml). The suspension was filtered, and both the white filter cake and the aqueous layer were washed twice with methylene chloride. The combined organic portion was washed with aqueous saturated sodium bicarbonate, brine, and then concentrated at reduced pressure. The residue was taken up in pentane (300 ml), and the solution dried over magnesium sulfate, and then concentrated at reduced pressure to afford 6.2 g of clear oil. Examination by glc (150°C) showed one major peak (98% of total area) with a retention time of 3.9 min. Examination by tlc (elution was methylene chloride, visualization with iodine) showed one spot, R_f 0.35. This crude material was distilled evaporatively at 100–200°/6 mm in a kugelrohr oven (most of the material came over at ~ 110°) to afford 4.80 g (69%) of a clear mobile oil: PMR 5.91 (2H, br s), 5.78–5.64 (2H, m), 2.39 (2H, br s), 2.34–2.11 (4H, m), 2.02–1.84 (3H, m), 1.78–1.62 (2H, m), 1.43–1.22 (2H, m), 0.76 ppm (3H, d, J = 6.4 Hz); CMR 132.9, 132.1, 56.1, 55.8, 46.2, 31.2, 26.2, 12.2 ppm.

13 - *syn* - (*trans* - 3,4 - *dimethoxycyclopentyl*) - *Tricyclo*[8.2.1.$0^{2,9}$] - 5,11 - *diene* (**28**) *and* 13 - (*trans* - 3,4 - *dimethoxycyclopentyl*)*tetracyclo* - [10.1.0.$0^{2,9}$.$0^{10,13}$]*trideca* - 5 - *ene* (**29**)

The *anti* alcohol **22** (9.14 g, 28.7 mmol) was dissolved in a mixture of dry diethyl ether (15 ml) and thionyl chloride (15 ml) in a 100-ml, round-bottomed flask equipped with nitrogen inlet. The mixture was stirred for 3 hr at room temperature, then the volatiles were removed *in vacuo*. The oily residue was dissolved in nitromethane (90 ml), and the flask was placed in a large Dewar containing much ice, and the solution cooled to 0°. Sodium cyanoborohydride (7.5 g, 0.119 mole) was *then* added, and the mixture was stirred mechanically at 0° for 19.5 hr. After it was stirred for an additional 7.5 hr at room temperature, the reaction mixture was concentrated *in vacuo*, leaving a brown paste. A mixture of water and methylene chloride was added to the residue, and the aqueous phase was acidified to pH 1 with dilute hydrochloric acid. The organic layer was separated and washed with dilute brine, then again with dilute hydrochloric acid and brine, and finally concentrated *in vacuo*. The yellow oily residue was taken up in pentane. The pentane solution was dried over magnesium sulfate, filtered and concentrated *in vacuo*, leaving the crude product as a pale yellow oil (7.2 g, 83%). Glc analysis (225°) indicated a 85:15 mixture of diene **28** and the cyclopropyl compound **29**. Chromatography on 20% silver nitrate impregnated silica gel (200 g, Hi-Flosil AG, Applied Science) using as eluant a mixture of ethyl acetate-hexane (8:92, v/v) gave pure **28** as a clear, colorless oil (6.12 g, 70% yield): PMR 5.91 (2H, unsymmetrical t), 5.76–5.61 (2H, m), 3.66–3.52 (2H, m), 3.32 (3H, s), 3.28 (3H, s), 2.57–2.48 (2H, m), 2.34–2.16 (4H, m), 2.10–1.87 (4H, m), 1.81–1.51 (4H, m), 1.47–1.28 (3H, m), 1.10–0.94 ppm (1H, m); CMR 133.1, 133.0, 132.1, 86.9, 86.0, 69.1, 57.0, 56.5, 53.2, 45.7, 36.6, 35.6, 31.8, 31.1, 26.1 ppm; *m/e* P^+ calc. for $C_{20}H_{30}O_2$, 302.2245; found, 302.2243.

The cyclopropane **29** was isolated as a mixture of diastereoisomers from the early fractions of the chromatography. A sample was purified further by distillation at 155° at 10 millitorr: IR (CCl_4) 3015 cm^{-1} (w); PMR 5.76–5.54 (2H, m), 3.72–3.62 (2H, m), 3.37 (3H, s), 3.34 (3H, s), 2.74–2.54 (2H, m), 2.44–1.68 (12H, m), 1.61–1.42 (1H, m), 1.42–1.26 (3H, m), 1.23–1.05 ppm (2H, m); CMR 130.9, 129.8, 86.9, 86.0, 57.0, 56.5, 50.5, 46.8, 43.0, 42.9, 39.2, 35.3, 35.2, 34.6, 34.3, 34.3, 32.6, 32.4, 28.6, 28.3, 25.4, 22.1, 17.7 ppm; *m/e* P^+ calc. for $C_{20}H_{30}O_2$: 302.2245; found: 302.2227.

all - *cis* - 2 - *Methyl* - *tricyclo*[6.3.0.$0^{3,7}$]*undeca* - 4,11 - *dione* (**32**)

A solution of **26** (4.63 g, 0.0227 mole) in carbon tetrachloride (250 ml) was put in a 3 L kettle equipped with a Vibromixer and overlaid with a suspension of sodium meta-periodate (45.3 g, 0.212 mole) in water (450 ml). Hydrated ruthenium dioxide (0.916 g) was added, and the mixture was stirred thoroughly for 70 hr. It was then diluted with 95% ethanol (450 ml) over a 0.5 hr period, slowly enough that the temperature of the dark green mixture remained below 35°. The resulting white suspension was mixed a further 0.5 hr and then filtered. The filter-cake was washed with carbon tetrachloride and water. The combined filtrate (*ca.* 1500 ml) was concentrated at reduced pressure. The residue was taken-up in absolute ethanol, filtered, dried over sodium sulfate, and the solution concentrated at reduced pressure to give 7.6 g (101% material recovery) of brown foam, presumably containing the tetra-acid **30** ($R=CH_3$) etc.

A 100-ml, long-neck flask equipped with a nitrogen inlet, condenser, and magnetic stirrer was charged with 1.019 g of the above, acetic anhydride (50 ml) and potassium acetate (0.46 g). The suspension was heated with stirring at 135° for 17.5 hr. The solution was then cooled to room temperature and divided into eight portions (a matter of experimental convenience). Each was sealed in a glass pressure tube and heated to approx. 190° for 24 hr. The tubes were then cooled, opened, and the contents combined and concentrated at reduced pressure. Water (48 ml), concentrated sulfuric acid (12 ml), and methanol (40 ml) were added to the black tarry residue. This mixture, in a condenser-equipped 250-ml flask, was heated with stirring at 95° for 24 hr and then stirred at room temperature over the week-end. Water (250 ml) was added, and the pH of the solution adjusted to 12 by addition of potassium hydroxide (22.6 g), keeping the temperature below 25°. More potassium hydroxide (300 ml, 1M solution) was added along with diethyl ether (200 ml), and sodium chloride (10 g). The resulting emulsion was stirred magnetically for 0.5 hr. The aqueous layer was extracted twice with a total of 500 ml diethyl ether. The combined extract was concentrated at reduced pressure. The residue was taken-up in ether, dried over magnesium sulfate, and concentrated at reduced pressure. This was repeated to afford 0.58 g of a mixture of immiscible clear and brown oils. The mixture was chromatographed on silica gel (35 g) with 5% ethyl acetate in methylene chloride to give 0.09 g (15% yield) of **32** as a yellow gum. Examination by tlc (eluting with 10% ethyl acetate in methylene chloride; visualizing by charring with 12-molybdophosphoric acid) showed one spot, R_f 0.28. Examination by glc (6', 3% OV-17, programmed 10 min at 150°, then 10°/min to 225°, 10 min at 225°) showed one major peak: PMR 3.09–2.95 (2H, m), 2.88–2.71 (3H, m), 2.39–2.24 (4H, m), 2.16–2.00 (2H, m), 1.87–1.72 (2H, m), 1.04 ppm (3H, d, J = 7 Hz); CMR 220.0 (s), 57.1 (d), 45.2 (d), 40.3 (t), 37.1 (d), 22.3 (t), 14.0 ppm (q).

all - *cis* - 2 - (*trans* - 3,4 - *dimethoxycyclopentyl*)*Tricyclo*-[6.3.0.$0^{3,7}$] - *undeca* - 4,11 - *dione* (**33**)

A solution of **28** (9.0 g, 30 mmol) in carbon tetrachloride (230 ml) and a solution of sodium metaperiodate (56 g, 262 mmol) in water (400 ml) was placed in a 2 L kettle equipped with a vibromixer. The vibromixer was turned on and adjusted carefully so that vigorous mixing of the two phases occurred. On addition of ruthenium dioxide hydrate (0.2 g, Englehard), the reaction mixture turned bright yellow; it then darkened progressively to a dirty greenish-red. Ethanol (400–500 ml) was added after 40 hr; the mixture was vibromixed for a few minutes more, and then filtered. The filtrate was concentrated *in vacuo*, and the residue was taken up in ethanol (250 ml). The dark green solution was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a viscous residue. Removal of the remaining volatiles under high vacuum (2 millitorr, 16 hr) left a dark green flaky solid (14 g): IR ($CHCl_3$) 2950, 1810, 1763, 1740, 1440 cm^{-1}. This was dissolved in acetic anhydride (40 ml), and the solution transferred to a 250-ml, round-bottomed flask equipped with a nitrogen inlet. Potassium acetate (4.5 g) was added, and the mixture was refluxed for 22 hr under nitrogen. The dark red mixture was then divided into five equal fractions and each was heated in a 40 ml, heavy wall, glass pressure tube (Fischer and Porter) for 16 hr at 180°. The solutions were then recombined, and the acetic anhydride removed *in vacuo*. The residue was dissolved in a mixture of 20% aqueous sulfuric acid (60 ml) and methanol (40 ml), and this was refluxed for 24 hr. The mixture was then extracted with chloroform (3 × 40 ml). The extract was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a black viscous tar (14 g). This was chromatographed on silica gel (250 g) eluting with methylene chloride-ethyl acetate (1:1, v/v) to give **33** as a dark red oil (5.8 g, 64%). Glc analysis (265°, 27 ml/minute) indicated that this material was of good purity. Crystallization from ether gave beautiful prisms: m.p. 95–96°; PMR 3.78–3.67 (2H, m), 3.37 (3H, s), 3.35 (3H, s), 3.13–3.00 (2H, m), 2.89–2.56 (4H, m), 2.39–1.89 (10H, m), 1.56–1.41 (1H, m), 1.26–1.09 (1H, m); CMR 219.6, 219.4, 86.7, 85.5, 57.1, 56.4, 55.1, 54.8, 51.1, 43.1, 43.0, 38.8, 37.2, 35.6, 31.5, 21.0 ppm; *m/e* P^+ calc. for $C_{18}H_{26}O_4$: 306.1830; found: 306.1860.

all- *cis* - 2 - (*trans* - *cyclopentane* - 3,4 - *diol*)*Tricyclo*-[6.3.0.$0^{3,7}$]*undecea* - 4,11 - *dione* (**38**)

A solution of **33** (5.6 g) in 97% formic acid (55 ml) was made in a 250-ml, round-bottomed flask equipped with condenser and nitrogen inlet. Potassium iodide (35 g) was added, and the mixture was refluxed for two days. The reaction was followed by monitoring the disappearance of the methoxy peaks in the PMR spectrum. The mixture was cooled and concentrated *in vacuo* to a nearly black, viscous oil. Water (50 ml) was added, and the aqueous phase extracted with a mixture of ether and methylene

chloride (2:1, v/v, 4 × 25 ml). The extract was concentrated *in vacuo*, and the residue was taken up in chloroform (50 ml). This solution was washed with dilute aqueous sodium thiosulfate solution (2 × 20 ml) to remove iodine and then dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a dark red oil (5.8 g), thought to be a bis-formate: IR ($CHCl_3$) 2970 (w), 1732 (s), 990 cm^{-1} (s); PMR 8.06 and 8.04 (2H, singlets), 5.36–5.20 (2H, m), 3.17–2.94 (3H, m), 2.93–2.80 (1H, m), 2.76–2.61 (2H, m), 2.44–1.90 (10H, m), 1.87–1.72 (1H, m), 1.42–1.27 ppm (1H, m). This was taken up in ethanol (30 ml), and the solution was stirred with saturated aqueous sodium bicarbonate solution (15 ml) at room temperature for 12 hr. The mixture was then diluted with methylene chloride (50 ml). The organic phase was separated, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a brown-red viscous oil (3.9 g). The crude product was purified by chromatography on silica gel eluting with methylene chloride followed by ethyl acetate. The diol **38** was obtained as a fluffy brown solid (3.0 g, 63% yield). Crystallization from chloroform gave material of m.p. 160.5–162.5°; PMR 4.12 (1H, br q), 4.08–3.98 (1H, br m), 3.14–3.00 (2H, m), 3.00–2.83 (1H, m), 2.76–2.55 (3H, m), 2.41–1.86 (10H, m), 1.83–1.69 (1H, m), 1.64 (2H, s), 1.31–1.27 ppm (1H, m); *m/e* P^+ calc. for $C_{16}H_{22}O_4$: 278.1517; found: 278.1516.

4,5 - *Quinoxalino*[2,3]*pentacyclo*[8.5.1.$0^{2,6}$.$0^{7,16}$.$0^{11,15}$]*hexadeca* - 7 - *ol* - 14 - *one* (41).

(*a*) *Oxidation of* **38** *to the acyloins* **39**. A solution of diol **38** (2.90 g, 10.4 mmol) in a mixture of chloroform (50 ml) and dry pyridine (5 ml) was placed in a 100-ml, round-bottomed flask equipped with a nitrogen inlet and well-protected from light with aluminum foil wrappings. The flask was cooled in an ice-bath, and iodobenzene dichloride (3.0 g, 10.9 mmol, freshly prepared) was added under a stream of nitrogen. The ice-bath was removed. The reaction mixture was stirred at room temp for 16 hr, then quenched by pouring it into 10% hydrochloric acid (30 ml). The mixture was extracted with chloroform. The yellow extract was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give a dark red oil. Iodobenzene was removed by chromatography on silica gel, eluting with chloroform followed by ethyl acetate. The acyloins **39** were obtained from the latter fractions as a fluffy, dirty brown solid (2.5 g, 87%), used without further purification: IR ($CHCl_3$) 2965 (m), 1732 (s), 1245 cm^{-1} (m), 910 (m); PMR 4.31–4.06, 3.20–1.12 ppm.

(*b*) *Oxidation of* **39** *to the diketone* **36**. A solution of ketols **39** (2.4 g, 8.7 mmol) in a mixture of tetrahydrofuran (2 ml) and 2N HCl (50 ml) was made in 100 ml round-bottomed flask equipped with a condenser. Ferric chloride hexahydrate (2.90 g, 10.7 mmol) was added; the mixture was stirred vigorously and brought to reflux for 10 min. It was then cooled, and extracted with chloroform (3 × 15 ml). The extract was dried over magnesium sulfate, filtered and concentrated *in vacuo* to give **36** as a brown solid (1.8 g, 76% yield), used in the next step without further purification: IR ($CHCl_3$) 2975 (m), 1727 (s), 1683 (m), 1390 (m), 1125 cm^{-1} (m); PMR 7.14 (br s), 6.74, 6.59, 6.57 (doublets, J = 3 Hz), 4.20–1.17 ppm (m).

(*c*) *Conversion of* **36** *to the quinoxaline* **41**. A solution of crude **36** (1.7 g) in ethanol (40 ml) was refluxed with purified o-phenylenediamine (0.7 g) and sodium acetate (50 mg) for 4 hr, then cooled and concentrated *in vacuo*. Methylene chloride (50 ml) was added to the residue, and the mixture was filtered to remove sodium acetate. The dark red solution was concentrated *in vacuo*, and the residue was flushed through a short column of alumina with chloroform–ethyl acetate (1:1, v/v) to give **41** as a tan flaky solid (0.8 g, 37%). A small sample was sublimed at 10 millitorr at 70°: m.p. 72–76°; IR (KBr) 3440 (s), 2960 (s), 1731 (s), 1410 (m), 1325 (m), 1128 (m), 1054 (m), 770 cm^{-1} (s); PMR 8.10–7.90 (2H, m), 7.80–7.63 (2H, m), 5.85 (1H, br s), 3.64 (1H, d, J = 7 Hz), 3.35 (1H, d of d, J = 18 Hz and 6.5 Hz), 3.19 (1H, d, J = 18 Hz), 3.10–2.95 (2H, m), 2.94–2.73 (3H, m), 2.59–2.28 (3H, m), 2.27–1.82 (5H, m), 1.57–1.39 ppm (1H, m); CMR 221.3, 160.7, 160.5, 141.6, 140.0, 129.2, 129.0, 128.6, 128.4, 91.7, 66.2, 58.8, 55.9, 50.9, 48.1, 46.7, 44.5, 43.0, 40.8, 38.3, 27.4, 22.0 ppm; *m/e* P^+ calc. for $C_{22}H_{22}O_2N_2$: 346.1681; found: 346.1691.

4,5 - *Quinoxalino*[2,3]*hexacyclo*[8.5.1.$0^{2,6}$.$0^{3,14}$.$0^{7,16}0^{11,15}$]*hexadeca* - 7,13 - *diene* (**46**)

A mixture of **41** (50 mg), potassium acetate (0.48 g), and acetic acid (2 ml) was sealed in a small pressure tube with a magnetic stirring bar. The tube was heated with stirring for 6 hr in an oil bath maintained at 180°. After cooling, the contents of the tube were poured into water (30 ml), and the mixture was extracted with methylene chloride (3 × 10 ml). The extract was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to leave a dark brown oil. This was chromatographed on a small silica gel (10 g) column eluting with chloroform-ethyl acetate (9:1, v/v) to give the crude product as a yellow solid. The more polar components, eluted from the column with pure ethyl acetate, were reheated at 180° for 3 hr with potassium acetate and acetic acid as before. Similar work up followed by preparative thin layer chromatography on a 10 × 20 cm silica gel plate gave a small amount more of the desired product. The crude was rechromatographed on silica gel to give pure **46** as a pale yellow solid (13 mg, 29%). A sample was crystallized from benzene-ether: m.p. 186° (dec); IR (KBr) 3225 (w), 2930 (s), 2850 (m), 1655 (w), 1365 (m), 1320 (s), 1202 (m), 1130 (m), 803 (w), 775 cm^{-1} (s); PMR 8.15–8.03 (2H, m), 7.78–7.63 (2H, m), 4.82 (2H, br), 4.22–4.00 (3H, m), 3.98–3.83 (2H, m), 3.03–2.84 (3H, m), 2.63 (2H, br d, J = 17 Hz), 2.39 ppm (2H, br d with additional fine structure, J = 17 Hz); CMR 160.3, 154.4, 141.9, 128.9, 128.6, 125.1, 67.6, 59.9, 49.4, 49.2, 45.1, 38.6 ppm; UV (95% aqueous ethanol) λ_{max} 242 (ϵ 27,220), 320 nm (10,520); *m/e* P^+ calc. for $C_{22}H_{18}N_2$: 310.1469; found: 310.1481.

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