TETRAHEDRON REPORT NUMBER 66

TOWARDS DODECAHEDRANE

PHILIP E. EATON

Searle Chemistry Laboratory, Department of Chemistry, The University of Chicago, Chicago, IL 60637, U.S.A.

INTRODUCTION

The five convex, uniform polyhedra—the Platonic solids—are the tetrahedron, the cube, the octahedron, the icosahedron and the dodecahedron (Fig. 1). Their constructions were defined mathematically by the Pythagorians and by Theaetetus in the 5th to 4th centuries B.C. and are described correctly in the 13th and last book of Euclid's *Elements of Geometry*.

These exquisitely simple, symmetric shapes have delighted and enlightened the thoughtful for generations. Plato wrote in *Timaeus* "... of the earth arising from the cube, fire from the pyramid, air from the octahedron, water from the icosahedron, and the sphere of the universe from the dodecahedron". Two thousand years later, Johannes Kepler saw with his mind's eye our solar system constructed of planetary spheres inscribed and circumscribed within a set of these symmetric solids. Indeed, as Herman Weyl said, "Symmetry ... is one idea by which man through the ages has tried to comprehend and create order, beauty and perfection".

For the chemist, the aesthetic appeal of the Platonic solids leads to the challenge of realizing their molecular equivalents—transforming vertices into atoms. Inorganic chemistry is rich with examples. There are tetrahedral clusters (As_4, P_4, S_4) and octahedral complexes ($IrCl_6)^{3-}$ and molecules (SF_6). $Cu_6[S_2CC(CN)_2^{2-}]_6^{4-}$ has the full O_h symmetry of the cube. Icosahedral cages are common in boron chemistry, e.g. $(B_{12}H_{12})^{2-}$. There is, however, no known example of an inorganic molecule or ion shaped like a regular dodecahedron.[1]

For the organic chemist, hearing the beat of a different drummer, translation of the Platonic solids into real molecules has always meant synthesis of tetrahedrane, cubane and dodecahedrane (Fig. 2). These are compounds of tetravalent carbon, made up as appropriate of four, eight or twenty methine units (CH). Octahedrane and icosahedrane are purposely left out. The first is formally an allotropic form of elemental carbon; the other requires pentavalent carbon. These are goals for others more comfortable with such things.
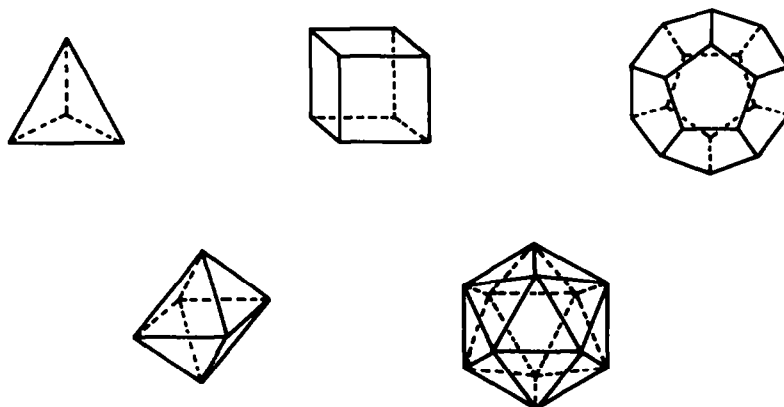

Fig. 1. The Platonic solids: (top) tetrahedron, cube, dodecahedron, (bottom) octahedron, icosahedron.
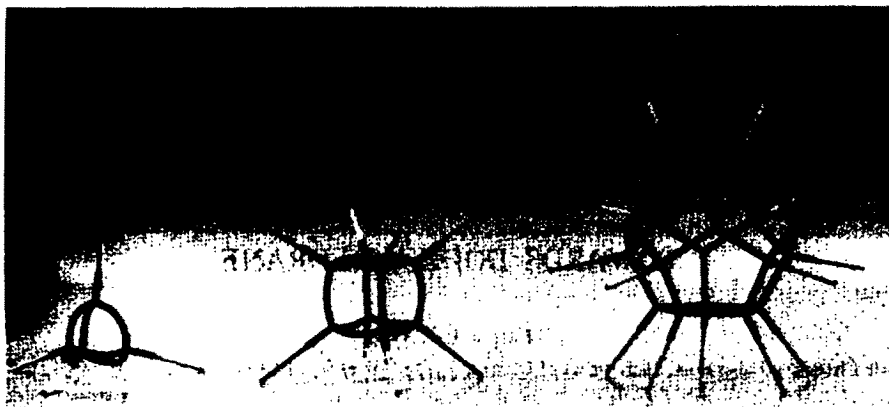
Fig. 2. Tetrahedrane, cubane, dodecahedrane.

Cubane

Cubane is the only unsubstituted organic polyhedrane known at this time. Its first synthesis was achieved in my laboratory in 1964 by the route outlined in Chart 1.[2] A few more or less interesting variants on the original synthetic scheme have been introduced,[3] but the Favorskii-like contraction of an intermediate bromoketone (like 4→5) remains the singularly successful, tactical entry into the system. At least several pounds of p-cubanedicarboxylic acid and 15–20 g of the hydrocarbon have been prepared.
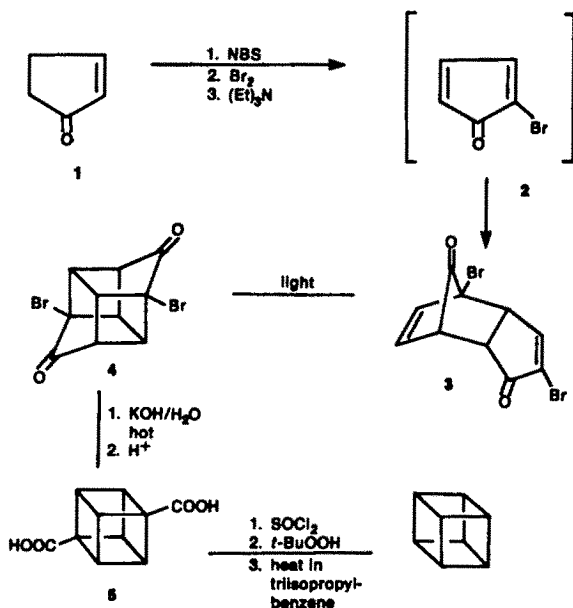

Perfluoroöctamethylcubane (6) has been obtained by photocyclization of the tricyclooctadiene derived from perfluoro-2-butyne (eqn 1).[4]
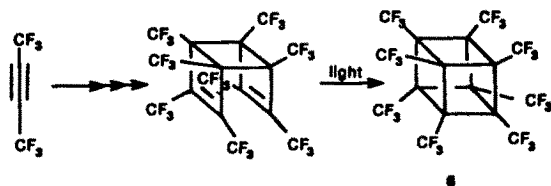
$$(1)$$

When the synthesis of cubane was undertaken, we were most worried about the potential instability of the system. Cubane is obviously a highly strained molecule; substantial distortions from the usual bonding parameters of tetrahedral carbon are required to accommodate the rigid geometric demands of the skeleton. It was not at all clear whether or not cubane would be isolable under ordinary conditions. However, as we were to find, although the strain energy is indeed large (*ca.* 14 kcal/mole/C–C-bond),[5] the kinetic stability of cubane is extraordinary. In solution at 200°, cubane is converted only slowly by way of cuneane (7) and semibullvalene (8) to cyclooctatetraene (eqn 2).[6] It is not known whether this slow thermolysis (2 weeks) proceeds uncatalyzed or if it requires traces of transition metal ions. Certainly, it is clear that transition metal ions (e.g. Ag^{1+}, Pd^{2+}, Rh^{1+}) at higher concentrations induce exceedingly rapid ring opening and/or rearrangement reactions.[7]

$$(2)$$
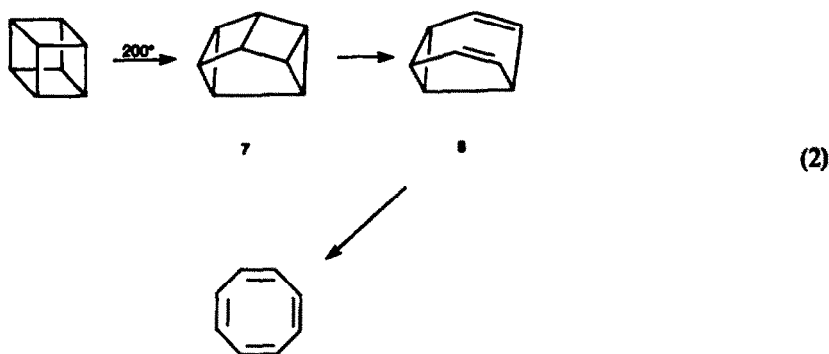
Cubane and its derivatives have been much examined. The crystal structure,[8] thermochemistry,[9] carbon hybridization,[2,10] kinetic acidity,[11] hydrogenation,[12] NMR spectra,[13] photoelectron spectrum,[14] far UV, IR and Raman spectra,[15] appearance potentials,[9,16] valence isomerizations,[7] electrochemical oxidation,[17] transmission of substituent effects,[18] radical formation,[19] and pharmacology[20] have all been studied. If one needed justification for the synthesis of such molecules, surely it can be found in the results (and surprises) of these studies. Some of the properties of the cubane system are listed in Table 1.

Table 1. Selected properties of cubane*

|	
m.p.	130–131°C
b.p.	~ 130°C
IR	2992, 1235, 852 cm^{-1}
UV	clear
δ ^1H	4.04 ppm
δ ^{13}C	47.3 ppm
J $^{13}C–H$	155 Hz
% s C–H	31%
C–C length	1.550 ± 0.003 Å
C–H length	1.06 ± 0.05 Å
C–C–C Angle	90.0 ± 0.5°
ΔH_f^o 298°	144.5 ± 1.3 kcal/mole
strain	166 kcal/mole

*For references see text.

Tetrahedrane

Tetrahedrane, $(CH)_4$, the "simplest" of the Platonic hydrocarbons is still unknown. The system must be very strained, probably about 20–22 kcal/mole/C–C bond. Although concerted cleavage to two acetylenes or reorganization to cyclobutadiene is orbital symmetry forbidden, bond opening to a diradical provides a ready path for decomposition, as does protonation of this extreme example of a bicyclobutane. These problems with strain and stability make plausible the speculation that some of the many approaches to tetrahedrane that have been tried may have worked, but that the molecule failed to survive its creation, e.g. eqn (3).[21]

(3)
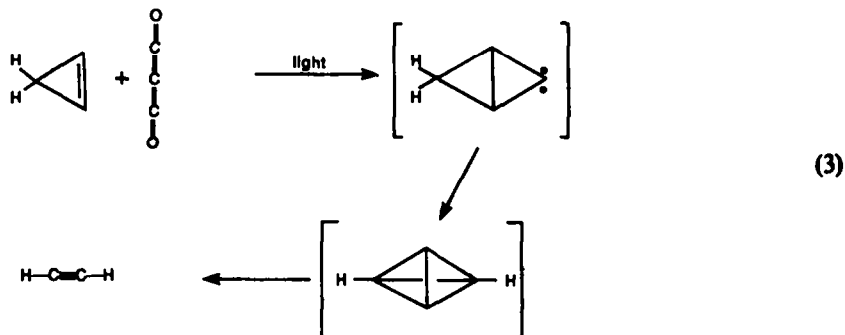
Recently, two reports from Germany of fruitful entry into the tetrahedrane system have appeared. In both cases, tetralithiotetrahedrane (9) and tetra-t-butyltetrahedrane (10), the tetrahedrane frame is fully substituted, and this may well have much to do with the stability of these compounds.

9   10
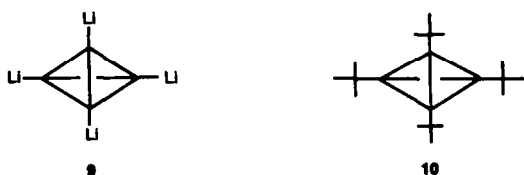
The first of these tetrasubstituted tetrahedranes was prepared by the Schleyer group at Erlangen.[22] The approach followed from a suggestion of Dill that σ-donating, π-accepting substituents like lithium could work to relieve strain and stabilize the tetrahedrane skeleton.[23] UV irradiation of a dilute solution of dilithioacetylene in liquid ammonia at $-45°$ is reported by the Erlangen group to give a microcrystalline powder stable under argon at $-20°$ (eqn 4). The spectroscopic properties of this material are quite different from those of the starting material. Field desorption mass spectroscopy indicates the formula C_4Li_4. Chemically, nothing has yet been reported beyond hydrolysis to acetylene. These results "... although not definitive, are encouraging".[22] It is interesting to note as pointed out in the report that *ab initio* molecular orbital calculations for tetralithiotetrahedrane indicate that the preferred structure may well be the face-centred arrangement 11.

$LiC \equiv CLi$ $\xrightarrow[\substack{NH_3 \\ -45°}]{\text{light}}$

9   11

(4)
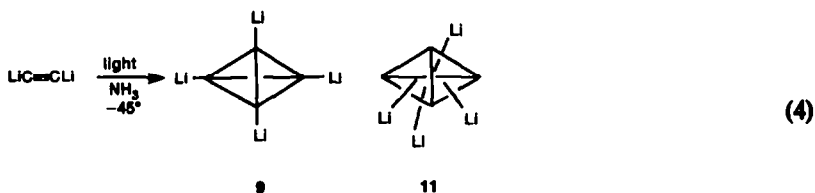
Tetra-t-butyltetrahedrane (10), a tetrahedrane in the more classic traditions of organic chemistry, is the achievement of the Maier group at Marburg in 1978.[24] The synthesis is outlined in Chart 2. The critical steps are the 254 nm light-induced isomerization and decarbonylation of tetra-t-butylcyclopentadienone (12) at low temperature. The sequence probably represents the most sophisticated use of light as a "reagent" in synthesis. Each irradiation requires exacting control.

Tetra-t-butyltetrahedrane has been characterized acceptably by optical, NMR, and mass spectroscopy. Most remarkably, it is an air stable, crystalline substance, m.p. 135° (dec.). Final confirmation of structure is expected soon from an X-ray analysis in progress. Isomerization of tetra-t-butyltetrahedrane to tetra-t-butylcyclobutadiene (13) occurs (eqn 5), but only at elevated temperature. Maier rationalizes intelligently the extraordinary stability of this tetrahedrane by noting that the lengthening (breaking) of any one of the tetrahedrane frame bonds is opposed by the bulk steric interactions of the separating t-Bu groups with the others on the skeleton. This leads to his formulation of the intriguing "all-or-nothing" principle, according to which only unsubstituted tetrahedrane (no substituents to stabilize radical intermediates) or tetrahedranes with bulky substituents at each vertex have a chance of
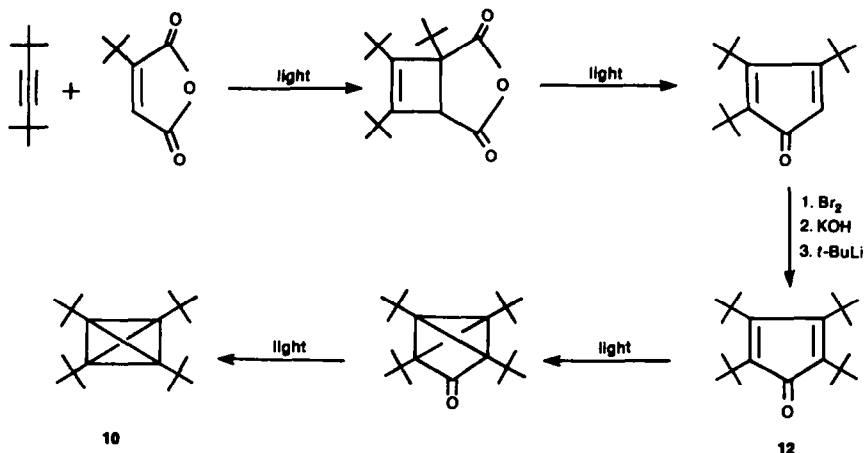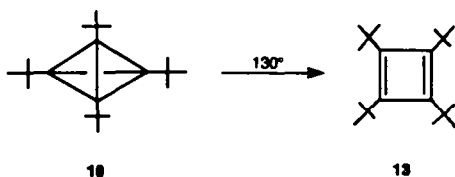
Chart 2.

being isolated.[24]

$$(5)$$

Dodecahedrane

Neither dodecahedrane nor any derivative has been isolated or prepared to date (November, 1978). The reason is not to be found in any instability of this polyhedrane, for quite unlike cubane and tetrahedrane, the strain in dodecahedrane is small. As will be considered later in this Report, most calculations put the strain energy at well less than 100 kcal/mole; this is trivial once divvied up amongst the many C–C bonds of the skeleton. Only very slight distortions from idealized tetrahedral carbon are needed to construct dodecahedrane. The problem, of course, is the real world route to this construction.

Dodecahedrane presents a synthetic challenge of substantial and significant proportions. Success requires the bonding together properly of twenty methine units, forming altogether thirty C–C bonds and twelve 5-membered rings.[25] For some perspective on the magnitude of this problem, recognize that the perhydro-1,2-cyclopentenophenanthrene ring system of the familiar steroids requires only seventeen carbons, twenty C–C bonds and four rings. There are, however, more subtle hurdles than numbers of rings and bonds.

At first thought it might appear that the high symmetry of dodecahedrane leaves the challenge of its synthesis without the problems of stereochemical control that so complicate (and enrich) the synthesis of natural products. Of course this is not so. Careful stereochemical control is required. The proton on each of the twenty carbons of dodecahedrane must be cis to the other nineteen protons. All twenty protons of dodecahedrane must be on "one side" of the molecule—the outside. Although epi-dodecahedrane is a fascinating compound, it is not the immediate objective of this particular synthetic adventure.

Said in another way, each of the thirty ring fusions in dodecahedrane must be cis and syn to one another. The cis fusion of cyclopentane rings is a simple matter when only two rings are involved. cis-Bicyclo[3.3.0]octane (14) is well-known and about 6 kcal/mole more stable than its trans isomer 15.[26]

The troubles begin when more rings are involved. Obviously, for example, transannular effects will destabilize the all *cis,syn*(acs)tetracyclic compound **16** relative to its *cis,syn,cis,anti,cis* isomer **17**.

16   **17**

The problem escalates quickly as continued *cis* and *syn* ring building turns the molecule more and more in upon itself. Non-bonded interactions become dominant features and matters of major concern. Consider, for example, the secododecahedrane **18**. It is extremely congested about the "unmade" bond. The endo H-atoms are close upon one another, and the rigidity of the system prevents them from moving apart.

18
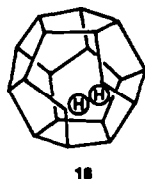
Although dodecahedrane itself is nearly strain free, its progenitors are not so blessed. We must expect that unavoidable transannular strains and unwanted transannular reactions in these systems will interfere with and perhaps interrupt seemingly well-laid plans to reach dodecahedrane.

The main purpose of this Report is to examine approaches to the synthesis of dodecahedrane under active investigation. To my knowledge, the principal work in the area is being done by my group at the University of Chicago and the groups of Woodward at Harvard, Paquette at Ohio State, and Schleyer at Erlangen with Grubmüller and McKervey at Cork. I will concentrate my discussion on these efforts. If I fail to give proper mention, I can only apologize sincerely to those others in the area of whose work I am unaware.[27] I am grateful to Professors Woodward, Paquette and Schleyer for providing me access to some of their unpublished work.

Dodecahedrane by isomerization

It is altogether likely that dodecahedrane is the most stable $C_{20}H_{20}$ polycycloalkane. This raises the possibility that if a proper, kinetically feasible path can be opened, non-dodecahedrane, $C_{20}H_{20}$ polycycloalkanes can be induced to isomerize to dodecahedrane. This idea is an extension of the very important discovery by Schleyer in 1957 that adamantane, the most stable $C_{10}H_{16}$ polycycloalkane, can be prepared effectively by Lewis acid induced reorganization of less stable $C_{10}H_{16}$ compounds (e.g. eqn 6).[28,29]

(6)

Such transformations are carbonium ion rearrangements of enormous complexity. The 1977 paper of Ōsawa *et al.* gives a marvelous analysis of this process, mating instinct, graph theory and computer calculation.[30]

LeGoff at Michigan State[31] and, independently, Schleyer at Princeton[32] tried in the early 1970s to bring about the isomerization of the basketene photodimer **19** ($C_{20}H_{24}$) to dodecahedrane using a variety of Lewis acid catalysts (eqn 7). These attempts were completely without success. Apparently the great strain in the starting material, which contains many cyclobutane rings, results instead in destructive

disproportionation of the molecule.

$$\text{(7)}$$
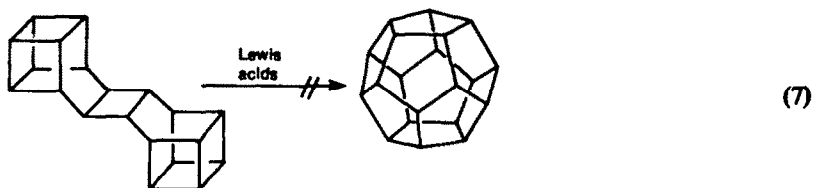
19

It is known that rearrangement of some $C_{11}H_{18}$ systems to methyladamantane **20** (e.g. eqn 8) proceeds more easily than that of $C_{10}H_{16}$ systems to adamantane itself (eqn 6). Presumably, the "extra" carbon in the C_{11} relieves some of the strain in the starting material and perhaps in the intermediates along the reaction path, reducing destructive side reactions, and thus helps to overcome mechanistic bottlenecks.[33]

$$\text{(8)}$$
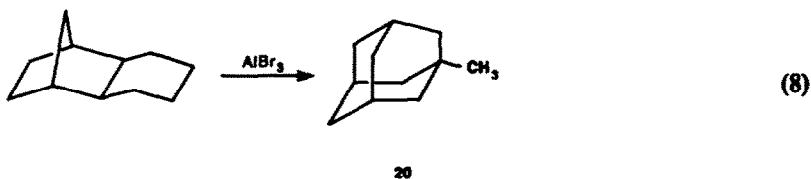
20

Accordingly, Schleyer and Grubmüller have attempted to isomerize various $C_{22}H_{24}$ compounds (two extra carbons) to the dimethyldodecahedranes (eqn 9).

$$\text{(9)}$$
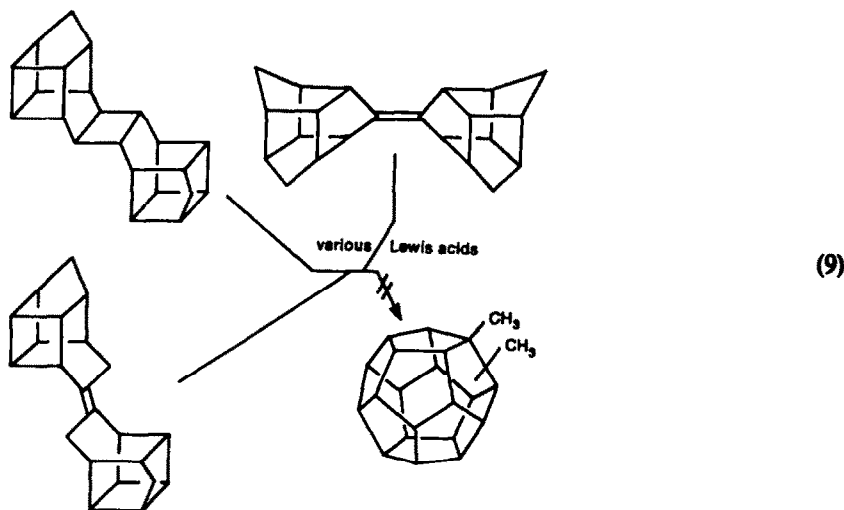
Probing the product mixture for success is a non-trivial problem. In the original experiments, dodecahedrane itself could have been recognized easily by its single, sharp proton magnetic resonance signal (twenty protons are equivalent), but there are five, non-enantiomeric dimethyldodecahedranes, a mixture of which would give a hopelessly complex PMR spectrum. The present analytic technique uses mass spectroscopy and looks for signals at m/e 15 mass units below the parent, corresponding to loss of a methyl group. To date, no such signal has been observed at a significant level.[34] The work continues.

Such approaches to dodecahedrane have to them some of the quality of eqn (10).

$$\text{Billy Batson} \xrightarrow{\text{SHAZAM!}} \text{CAPTAIN MARVEL} \qquad \text{(10)}$$

As such, they deserve both praise and criticism. The potential for good is great, but reliance on magical forces may prove debilitating.

Dodecahedrane by dimerization

As we shall see, antithetic dissections of dodecahedrane to find possible progenitors can be carried out in a variety of ways. The most obvious, at least in hindsight, cuts dodecahedrane in half into two $C_{10}H_{10}$ fragments (eqn 11).

$$(11)$$
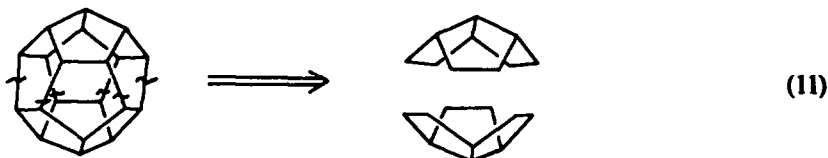
The forward reaction in the real world of synthesis is then production of dodecahedrane by dimerization of triquinacene (21, eqn 12).

$$(12)$$

21
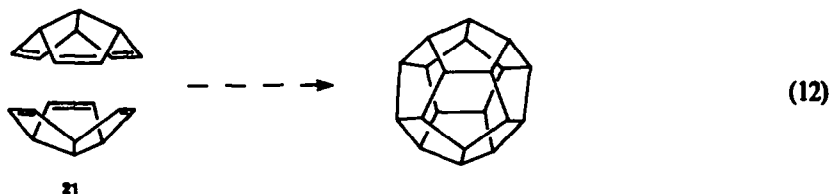
This idea became popular in the early 1960's and was speculated upon independently by Muller in Holland,[35] Jacobson in Sweden,[36] and Woodward et al. at Harvard,[37] the last as part of their 1964 report of the first synthesis of the hitherto unknown "monomer", triquinacene.

This first synthesis of triquinacene is outlined in Chart 3.[37] It begins with the now troublesome insecticide Isodrin (22), which contains two of the three 5-membered rings to be included in the final product. Reduction via the Winstein procedure gives the dechlorinated ene-ol 23.[38] Oxidation of the alcohol with chromic trioxide in pyridine and epoxidation of the olefin from its less hindered side gives the corresponding epoxy-ketone 24. Trans-skeletal ring closure via attack of the α-carbonyl anion from 24
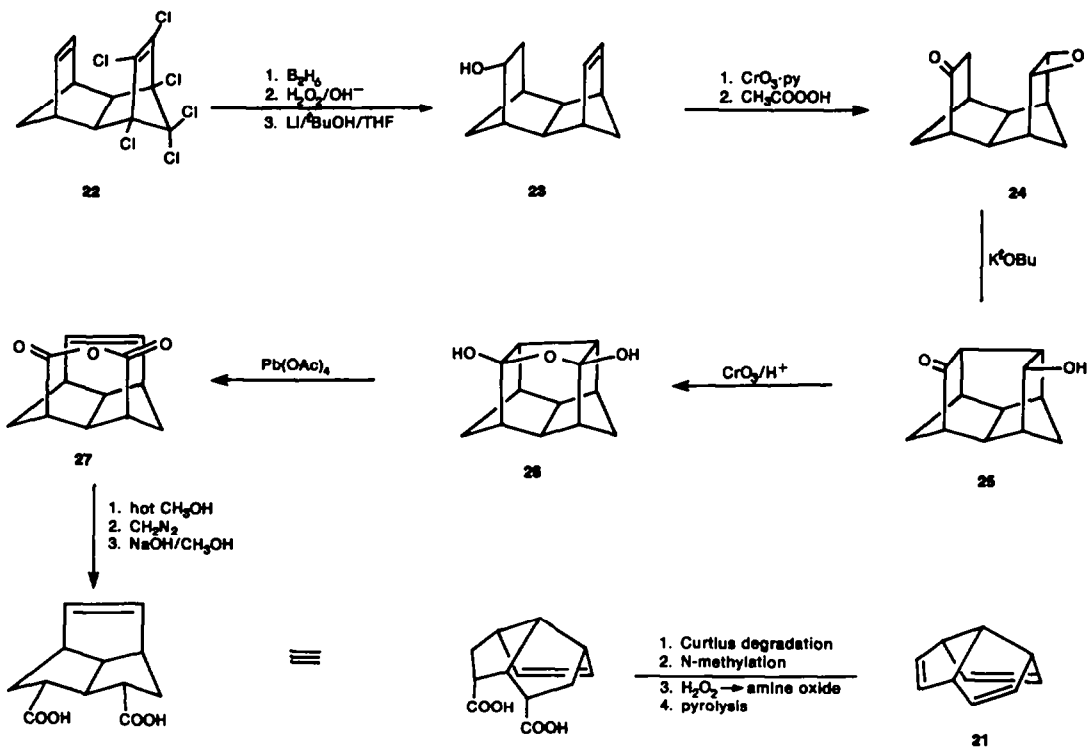

Chart 3.

on the rear of the nearby epoxide forms the hydroxyketone 25 and the third 5-membered ring needed for triquinacene. Oxidation to the corresponding diketone gives its stable, bridged hydrate 26. The "extra" rings, whose restraining forces and geometric requirements have been used so powerfully to this point, are now removed by a remarkable oxidative cleavage of 26 with lead tetracetate. The product, the anhydride 27, requires only the conceptually minor, although many, functional group manipulations illustrated to complete the synthesis.

A very different synthesis of triquinacene was reported by Jacobson in 1967.[36b,39] As shown in Chart 4, base-induced decomposition of the bis-N-nitroso compound 28 generates 1,4-bis(diazo)butane (29) which reacts in remarkably good yield with cyclohexanone to give the bicyclic ketone 30 (recall the ring enlargement of cyclohexanone to cycloheptanone on reaction with diazomethane). Thermal decomposition of the sodium salt of the tosylhydrazone of 30 at 135–175° apparently proceeds through a carbene and its insertion into the C–H bond four carbons away. The saturated hydrocarbon product, the triquinane 31, is reported to form in very high yield. Chlorination/dechlorination under rather forcing conditions gives perchlorotriquinacene 32, which on more standard reductive dechlorination is converted to triquinacene itself.
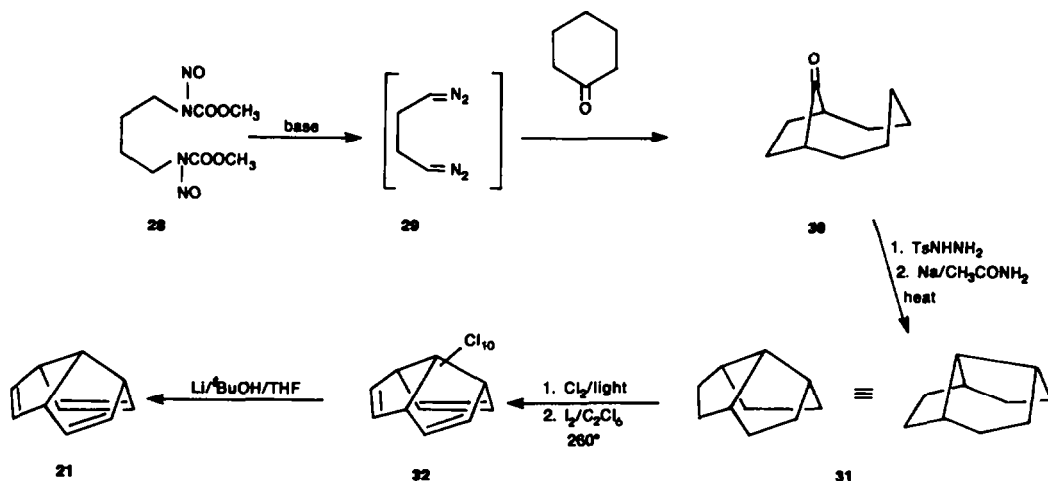

Chart 4.

There are yet other syntheses of triquinacene. One more, of more recent vintage, is included here for it provides probably the most expeditious route to substantial quantities of the compound. The approach (Chart 5), developed by Deslongchamps et al. at Sherbrooke,[40] realizes the triquinacene nucleus in just a few steps from Thiele's acid (33), available commercially, or more economically from carboxylation of cyclopentadiene anion. Degradation via its bis-azide gives the diketone 34, in which two of the three 5-membered rings needed in triquinacene are connected correctly; the elements of the third are there, but one position of attachment is wrong. Selective cleavage at this point can be effected photochemically to give the ene-aldehyde 35, which can then be cyclized correctly to 36. Reduction, mesylation, and elimination over basic alumina completes this preparation of triquinacene. Full experimental details for this procedure have been published recently, along with an instructive commentary on the evolution of the approach.[41] This route allows also the ready preparation of substituted triquinacenes. For example, as shown in the branch in Chart 5, reaction of 37 with methyl Grignard, followed by eliminations and oxidations gives 2-carboxytriquinacene (38) in a very practical way.[42]

The chemistry of triquinacene and its derivatives has received a great deal of attention, and profitably so. The results and insights so obtained have more than justified the effort put forth to achieve its synthesis. Paquette provides a thorough survey in his highly recommended review of polyquinanes.[43] For our purpose here, it is sufficient to note that triquinacene has resisted all attempts to cause its dimerization to dodecahedrane. The usual photochemical dimerization procedures lead only to polymerization.[44] Triquinacene is extraordinarily stable thermally. It is recovered unbothered after two hours in concentrated solution in heptane at 400° under 40,000 atmospheres pressure![45] For the most part, the depressing drumroll of dimerization attempts that failed is not in the literature. I am assured by word-of-mouth that most everything has been tried, including such clever ideas as using metal

Chart 5.
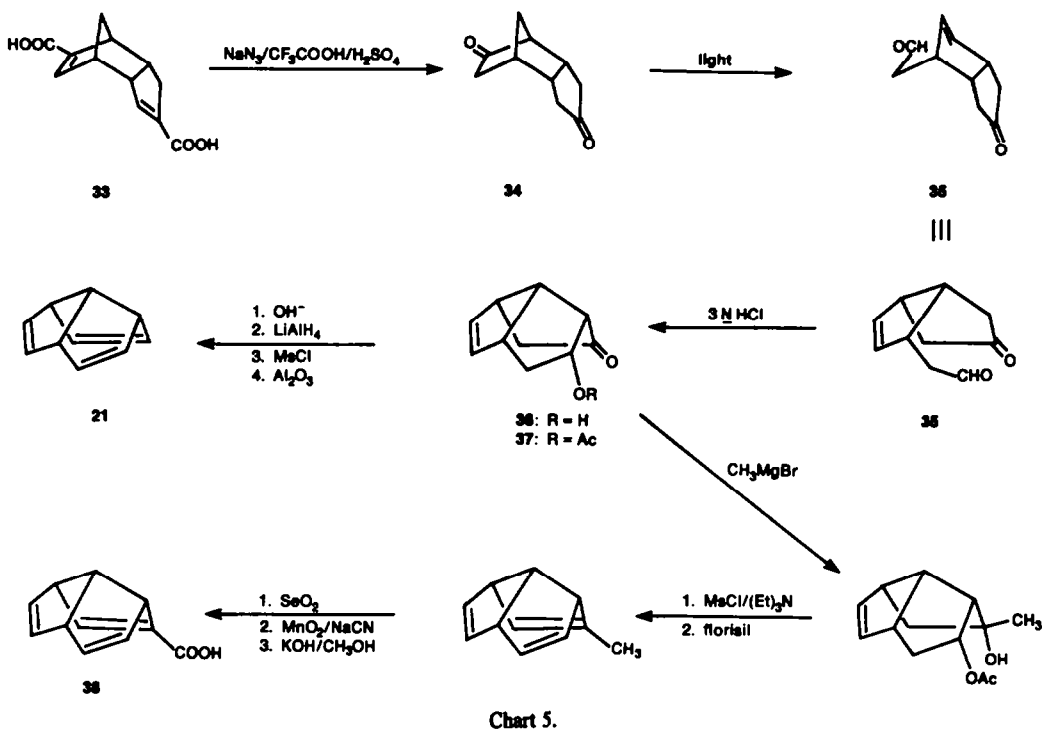
complexes to hold two triquinacenes together in the correct orientation. The search, no doubt, continues. Perhaps, there is more to be said for eqn (10).

Dodecahedrane from bivalvanes

It was, I think, clear from the beginning that there was really little chance that two independent triquinacene molecules could be induced to come together correctly and form the six (!) bonds needed to make dodecahedrane. Statistical and steric considerations alone make the process unlikely. Certainly, however, the linking together of two triquinacenes can be approached a good deal more patiently. Controlled introduction of one or two covalent bonds between two triquinacene units might be used to make later, perhaps less controlled closure steps more probable, at least geometrically. Thus, for example, it would clearly be of help if some early, initial union were made so that the two "halves" would be *endo* to one another rather than *exo*, **39** rather than **40**.
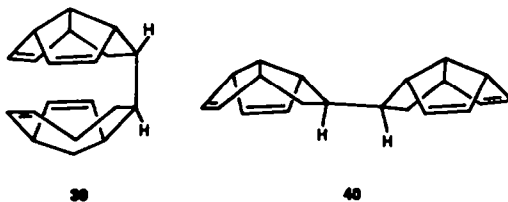
This is no simple matter, for **39** is sterically less favorable than **40**. Paquette and Woodward *et al.* have addressed this problem. Paquette's approach is considered here;[45] Woodward's, in the next section.

Pinacol dimerization (Chart 6) of the triquinacene ketone **41** gives only the products, **42** and **43**, of *exo,exo* joining, a point demonstrated by PMR coupling constant analysis.[46b] Note that this dimerization produces two new asymmetric centers; **42** is a *dl* mixture; **43** is a *meso* compound. Decomposition of the corresponding cyclic thionocarbonates in hot triethyl phosphite gives stereospecifically the alkenes **44** and **45**. Catalytic reduction with hydrogen over rhodium-on-carbon, although slow, proceeds in high yield to *dl*- and *meso*-bivalvane, **46** and **47**, respectively. (The nomenclature derives from that of the two-shelled mollusks.) The assignments of *endo,endo* stereochemistry to bivalvanes **46** and **47** follows from the logical expectation that hydrogenation will occur *cis* and from the (much) less hindered *exo* face of the precursor olefins.

A close look at the relation of the two rings within *dl*- and *meso*-bivalvane reveals a marvelous

1. Mg(Hg)/(CH₃)₃SiCl
2. EtOH/H₂O

1. KH
2. CS₂
3. CH₃I
4. hot (EtO)₃P
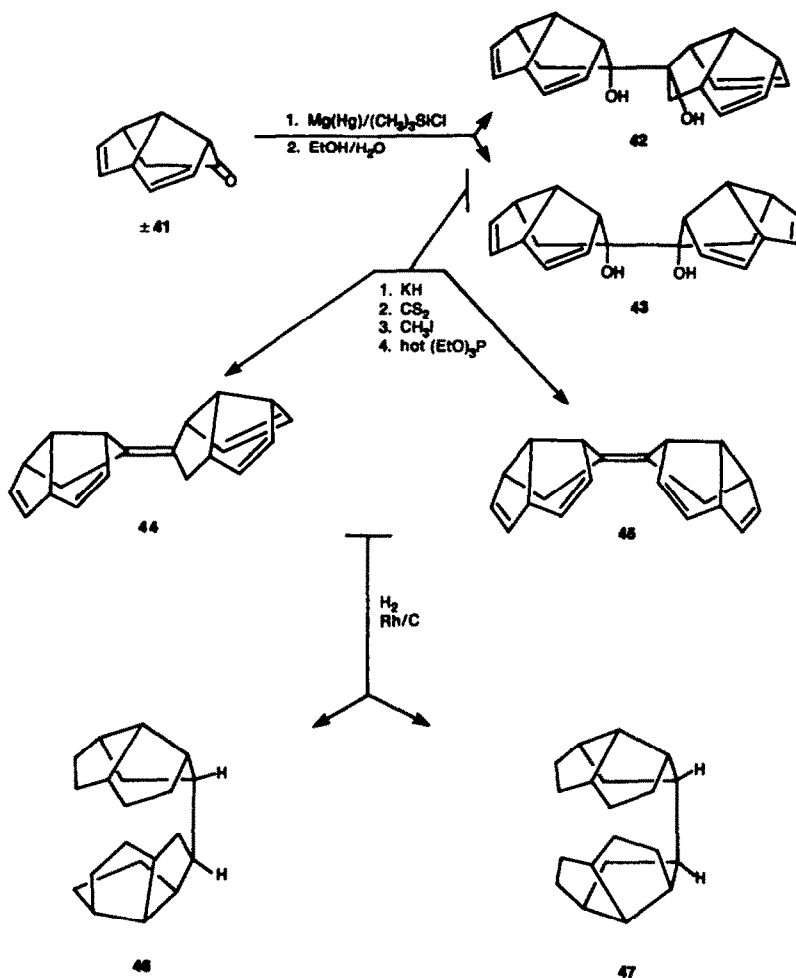
H₂
Rh/C

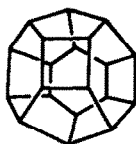± 41

42

43

44

45

46

47

Chart 6.

subtlety—only the *dl* bivalvane is akin to the Platonic, pentagonal dodecahedrane. *Meso* bivalvane is cousin instead to the non-uniform, irregular dodecahedrane **48**, an interesting compound to be sure, but not the present goal.

48

If one traces back through Chart 6 and examines carefully the initial pinacol coupling, it can be seen that production of *meso*-bivalvane arises in the coupling of the enantiotopes of the starting material ($R + S$ or $S + R$). The *dl*-bivalence comes on coupling like isomers ($R + R$ or $S + S$). Accordingly, Paquette has found that only the *dl*-bivalvane series is produced starting from enantiotopically pure (+)-(S)-**41**. Efficient production of *dl*-bivalvanes, as required if they are to be precursors of dodeca-hedrane, requires either an easy, large-scale method for the resolution of **41**, which has not yet been achieved, or a ready, high recovery separation of a *dl*-bivalvane from its *meso* diastereomer somewhere along the line. Paquette and coworkers have done the latter very neatly indeed, as outlined in Chart 7.[46c] The hexaenes **49** and **50** are formed by phosphorus oxychloride in pyridine dehydration of the diols **42** (*dl*) and **43** (*meso*) obtained from pinacol coupling of racemic **41**. The 1,3-conjugated diene sub-unit

within **50** turns out to be more reactive than that in **49** in Diels–Alder addition to N-methyl-triazolinedione. Presumably, different steric effects make it more difficult for the latter to take on the s-*cis* conformation required for Diels–Alder addition. Treatment of the mixture of **49** and **50** with just enough N-methyltriazolinedione for reaction with the contained **50**, removes **50** and leaves the hydrocarbon fraction 96% enriched in the desired isomer. Not to be wasteful, **50** can be regenerated from its Diels–Alder adduct by hydrolysis and oxidation.
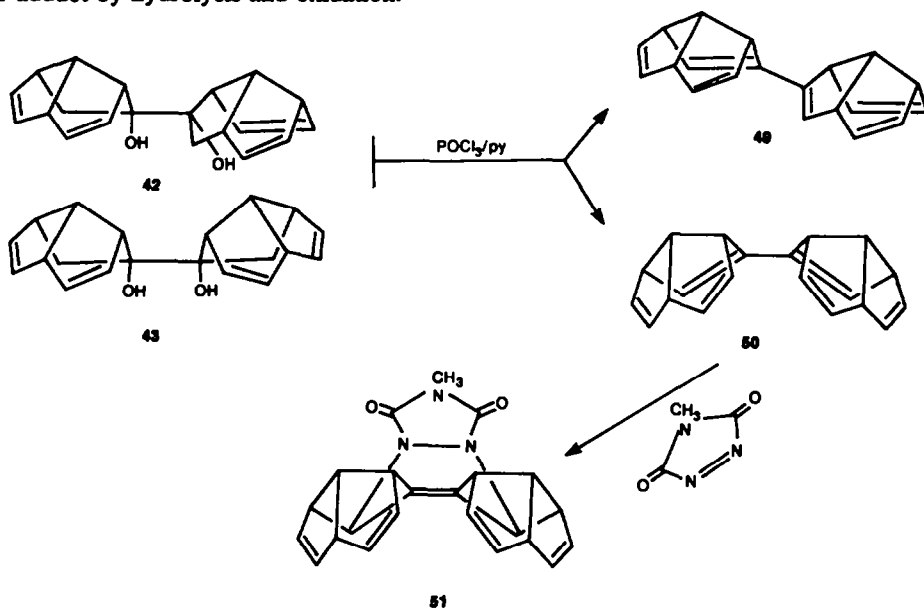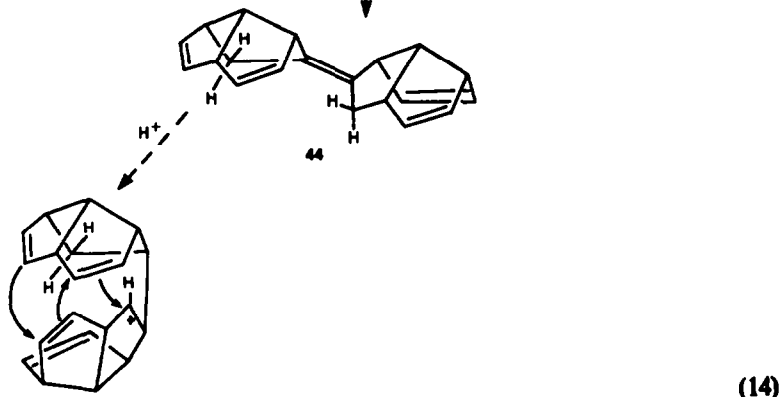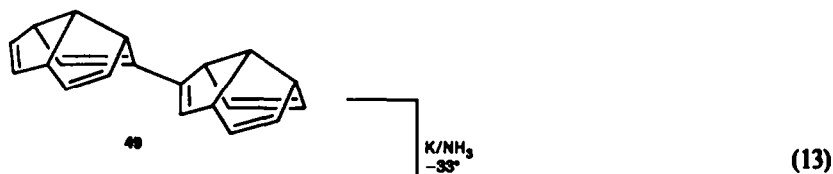

Chart 7.

1,4-Reduction (eqn 13) of the conjugated 1,3-diene within the *dl*-bivalvane **49** with alkali metal in ammonia occurs primarily *trans* and gives the pentaene **44**, $C_{20}H_{20}$.[46c] One can imagine an acid-induced cyclization of **44** or a simple relative to dodecahedrane (eqn 14), but this has yet to be accomplished.


$$(13)$$

$$(14)$$

Dodecahedrane from other triquinacene dimers

Repič, in his 1976 doctoral dissertation at Harvard, proposes that dodecahedrane might be achieved from the zippering together of two triquinacene-derived radicals held (generated) in such a way that the necessary orientation can be obtained easily.[47] Thus, as shown in eqn (15), cleavage of one of the strained cyclobutane bonds in the *endo,trans,endo* triquinacene dimer **52** would initiate the reaction (→ **53**), whilst the remaining bond enforces the essential *endo,endo* configuration necessary (but perhaps not sufficient) for complete closure.

$$(15)$$
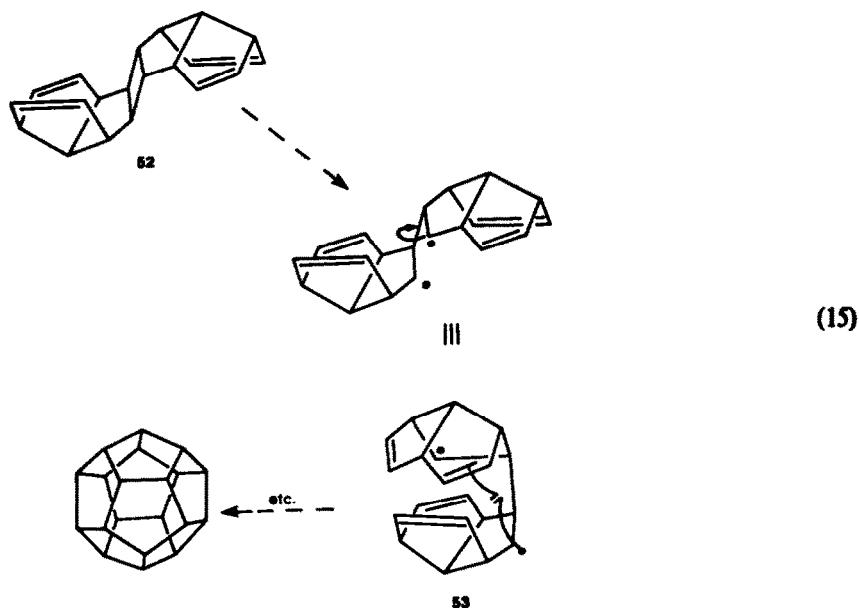
As before with the bivalvanes, the uniform, pentagonal dodecahedrane can only be obtained if the triquinacene derived parts are of the same chirality, as they are in **52**. If, on the other hand, as in the *endo,cis,endo* dimer **54**, the triquinacene sub-units are reflections of one another, closure would lead not to the Platonic dodecahedrane, but to its non-uniform isomer **48** (eqn 16).


$$(16)$$
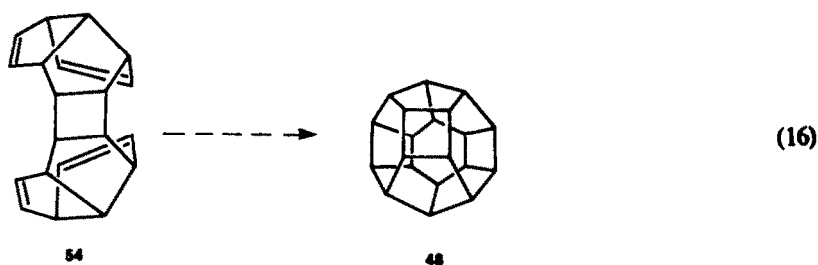
To make a diradical like **53** fairly accessible energetically some substituents on **52** facilitating the initiating homolytic bond cleavage of eqn (15) are needed. The carbomethoxy group is a reasonable choice; the problem then becomes the regio- and stereospecific synthesis of **56**, the 2 + 2, head-to-head, *endo,endo* photodimer of an enantiomerically pure 2-carbomethoxytriquinacene (**55**, eqn 17).

$$(17)$$
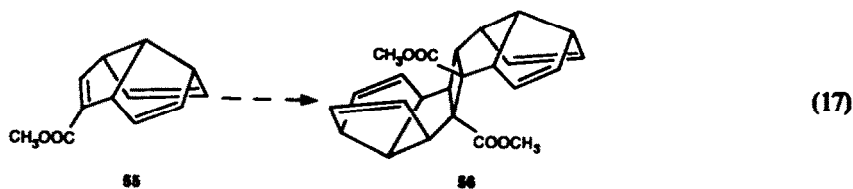
Given the earlier experiences with triquinacene dimerization, it is unreasonable to expect the dimerization of eqn (17) to occur in anything but miniscule yield. Some temporary bonding, introduced in

controlled fashion, is needed to hold the sub-units in such a way that only the desired dimer is geometrically possible. To this end, Repič working with Woodward connected two triquinacenes of the same handedness by an ester linkage making 57 in which the geometric restrictions are such that only the *endo,trans,endo* compound 58 can result from internal 2 + 2 photocycloaddition (eqn 18).

$$\tag{18}$$
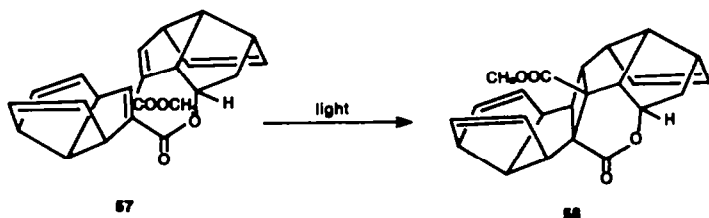
57   58

The synthesis of the necessary parts of 57 is given in Chart 8. The particular approach illustrated to 2-carbomethoxytriquinacene and its precursor hydroxy ester 64 was worked out at Harvard[47] and, in similar fashion, independently at Ohio State at about the same time.[46a,48] The method is derived from the finding that cyclooctatetraene iron tricarbonyl (59) undergoes 1,3-addition to tetracyanoethylene to give complex 60, from which the tetracyanodihydrotriquinacene 61 can be freed by oxidation with ceric ion.[49] Acid hydrolysis of 61 at elevated temperature is accompanied by decarboxylation and internal lactonization (→ 62). Barton iodination (→ 63) and subsequent hydrolysis and dehydroiodination gives, after
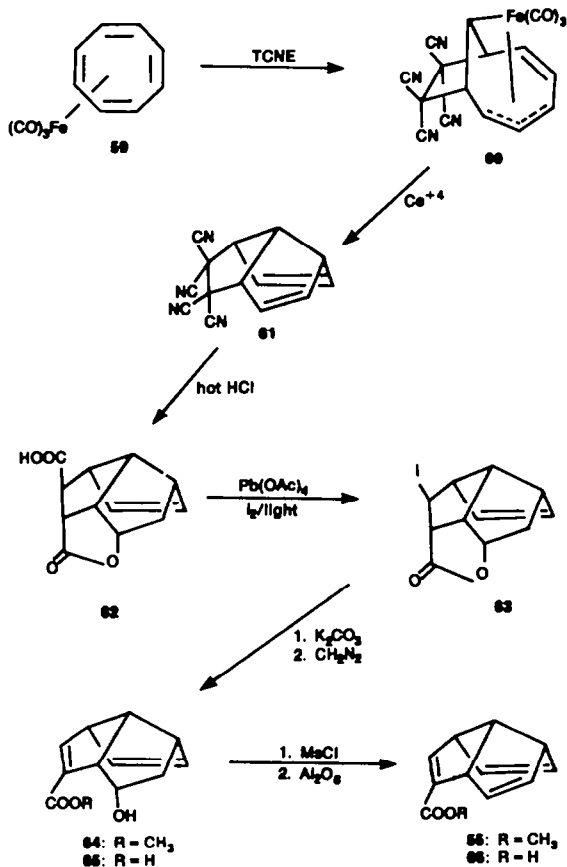

Chart 8.

esterification, hydroxy ester 64. Dehydration either directly by the Burgess procedure or *via* the mesylate and elimination over neutral alumina introduces the third double bond and forms racemic 55.

Resolution of the hydroxy acid 65 can be accomplished by crystallizing its (−)-quinine salt from benzene–ether. The dextrotary isomer gives, after elimination, dextrorotary 2-carboxytriquinacene (66), enantiomerically identical (conveniently) to that prepared and resolved earlier by Fukanaga directly from triquinacene via carboxylation of its Grignard.[30] Combination of the acid chloride from this (+)-acid and

the lithium salt of the (+)-hydroxy ester of **64**, known by the scheme just given to be of the same handedness, gives the desired ester **57** containing two like-handed triquinacene units. This combination was, in fact, achieved only after major effort. The *endo* OH group in **64** is extremely hindered sterically, as might be expected, but in addition even the acid chloride from **66** is very unreactive. In any case, exactly as planned, **57** once made undergoes sensitized photocyclization to **58** in good yield (eqn 18). Unfortunately, the plan then broke down, Repič could not find a method to convert **58** to the desired diester **56** of eqn (17). A vast army of reagents and techniques was deployed without success. The lactone ring is very stable. For example, most of **58** could be recovered unchanged after 1 hr at 100° in dimethyl sulfoxide saturated with potassium hydroxide in the presence of Kryptofix. Such frustrations are particularly common in compact polycycle chemistry where geometric constrains can enforce sometimes unwanted interactions between groups. There is little solace in this however. The work continues; one idea, mentioned at the end of Repič's thesis, is sketched out in Chart 9. Hopefully, the bond breaking **58→67** will leave the lactone more amenable to hydrolysis, it then being possible for its components to get out of one another's way.
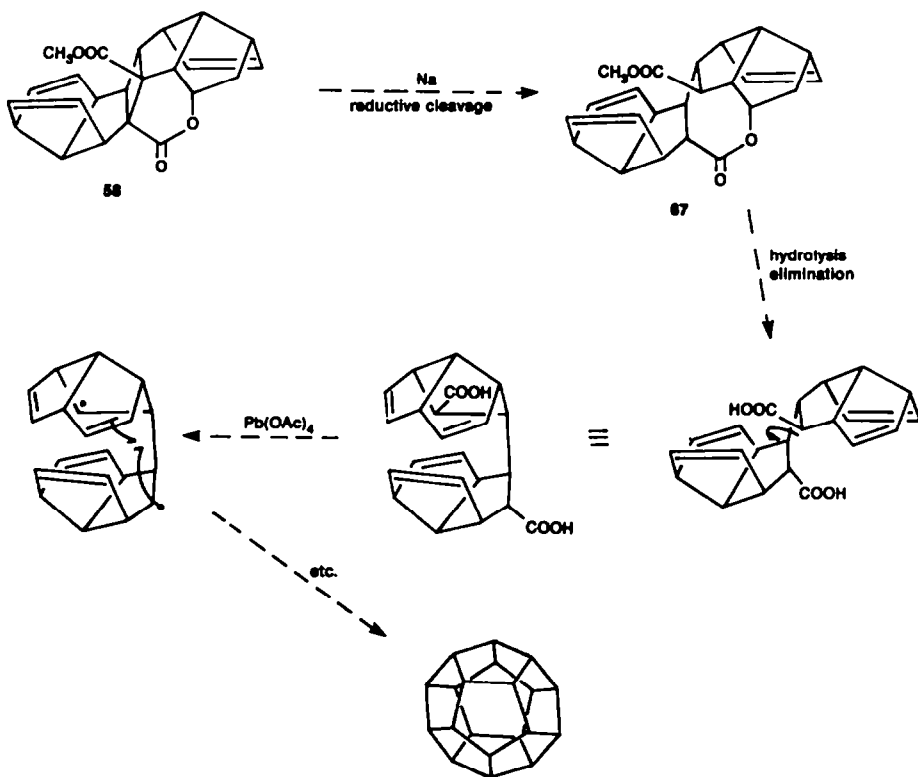

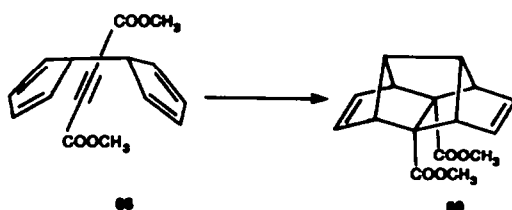Chart 9.

Dodecahedrane from the "domino Diels–Alder reaction"

In the late 1960s Hedaya with his group at Union Carbide, Tarrytown, discovered the twice-over Diels–Alder addition of 9,10-dihydrofulvalene (**68**) to dimethyl acetylene dicarboxylate (eqn 19).[51,52]

(19)

Adduct 69 can be obtained in good amounts, about 25 g (12%) starting from 100 g of cyclopentadiene. A detailed experimental procedure has been published by Paquette, who coined the term "domino Diels–Alder reaction" for the inter/intra molecular addition which forms 69.[52] The compound contains numerous *cis,syn* fused 5-membered rings, a point made more obvious by cleavage of the strained central bond and redrawing the product as in eqn (20). As such it is certainly a candidate for elaboration into dodecahedrane.

$$(20)$$
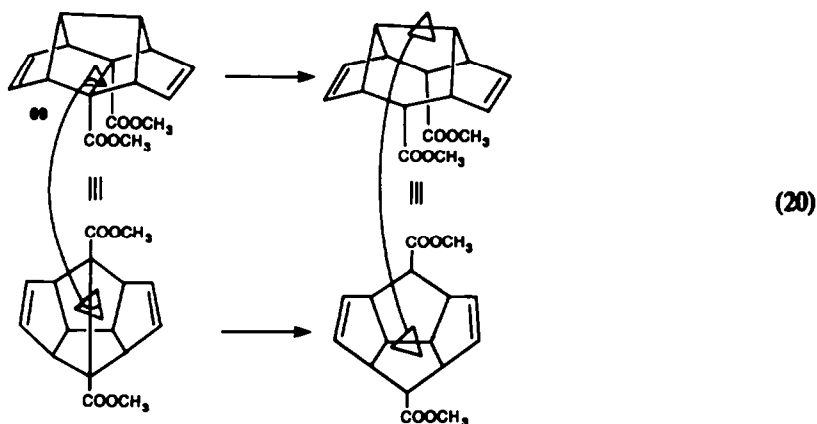
Hedaya recognized this point, but it was not pursued substantially until the Paquette group at Ohio State, also active in the area, took it on. Only a small fraction of the very pretty work of that group can be fit in here; I will focus on that giving a "feel" for the concepts and the associated frustrations.[53]

Adduct 69, is fairly well functionalized and has four of the twelve 5-membered rings and twelve (fourteen with the carboxyl carbons) of the twenty carbons of dodecahedrane. A variety of methods to add carbons and rings are available to build upon this foundation. Chart 10 starts with "cross-corner" oxygenation of 69; iodolactonization is used to control the positioning of the two ketone groups introduced in formation of 70. The additional carbons needed to reach the C_{20} count are added either (70→71) with Trost's diphenylsulfonium cyclopropylide (which requires an equivalent of silver salt for its preparation)[53a] or less expensively with Magnus' trimethylsilylallyl anion (70→72).[53b] Oxidation of either 71 or 72 gives dilactone 73. Intramolecular Friedel–Crafts acylation of the Dev type using our reagent of phosphorus pentoxide in methanesulfonic acid gives the bis-cyclopentenone 74 in very good yield. Catalytic reduction of the double bonds in 74 over palladium-on-carbon occurs on the less-hindered outer surface giving 75. Borohydride reduction of the ketone groups, again from the outer side, and ready internal transesterification produces the dilactone 76. This has the full complement, counting the carbonyl groups, of twenty carbons needed for dodecahedrane. Except for one unnecessary bond, which traces back to the acetylene in eqn (19), these are bound together correctly, if still insufficiently. Reductive cleavage of the "extra" C–C bond, made possible by its carbonyl substituents, can be effected readily. The bis-trimethylsilyl enol ether is formed on reduction of 76 with sodium in refluxing toluene in the presence of trimethylsilyl chloride. Hydrolysis of the enol ether gives the dilactone 77; protonation at the vinyl carbons coming, of course, to the more-open "out" side of the rather spherically-shaped intermediates.
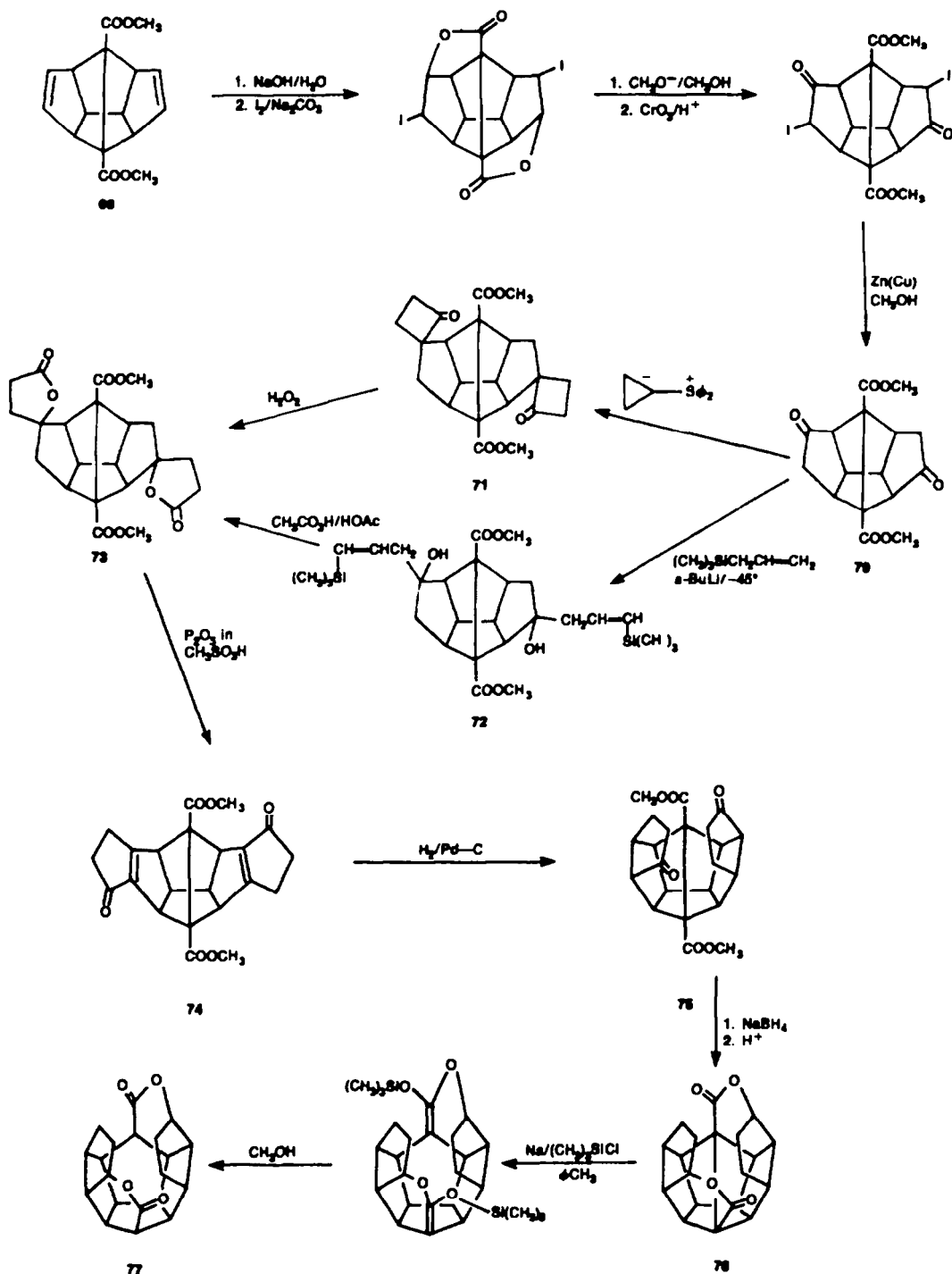
Chart 10.

The two lactone rings of 77 are 6-membered; removal of the ethereal oxygen from each by some sort of reverse Baeyer–Villiger reaction would leave two 5-membered carbocyclics, appropriate to the target molecule. Unfortunately, no general "reverse Baeyer–Villiger reagent" has yet been developed—a sore lack. In the case at hand, the very clever idea to use an acid-induced elimination and intramolecular acylation to accomplish contraction of dilactone 77 to bis-enone 78 goes astray and results instead in isomerization to the less-compact polycycle 79 (eqn 21).

(21)
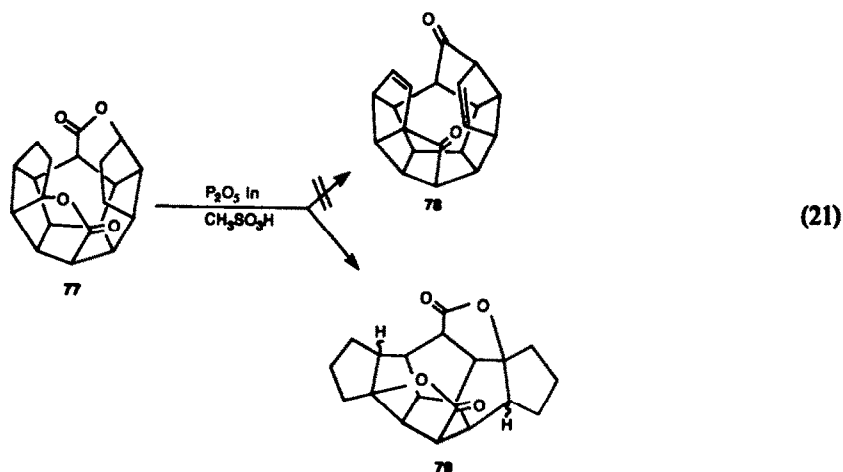
Compound **78** is an exceedingly attractive intermediate: the sp^2 character of the abutting carbons minimizes steric crowding; the inside lobes of the p orbitals are well positioned for transannular bonding. It is not hard to imagine that the dodecahedrane frame could be "knitted" together in one fell swoop by reduction of **78**.[53b] Intramolecular Prins reaction of the bis-enal **80** might produce **78** (Chart 11), but so far all attempts to make it have failed. The problems arise in the sensitivity of dilactone **77** to unwanted transannular cyclizations under either alkaline or acidic conditions. The Dieckman closure **77**→**81** and the related acid-induced conversion **77**→**82** are illustrative.
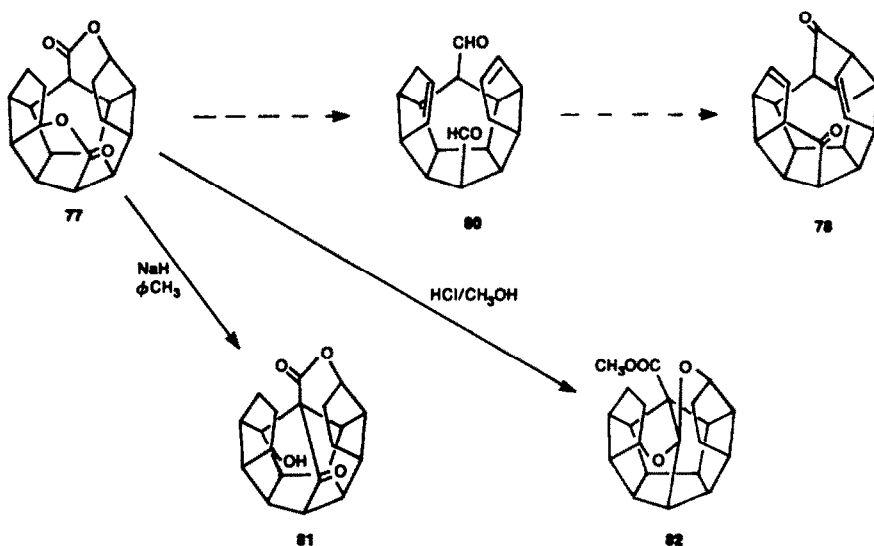

Chart 11.

In attempts to obviate these difficulties with transannular closures, various conversions with **76**, in which the extra bond is still in place, were examined (Chart 12). Although it is possible to take **76** to the mono-ene **83**, this cannot be driven on to the needed diene **84**. Cleavage of both lactone rings in **76** can be accomplished with methanolic HCl giving **85**, but all attempts to form **84** by eliminations from **85** have failed. When the conditions are escalated, lactone **76** reforms.
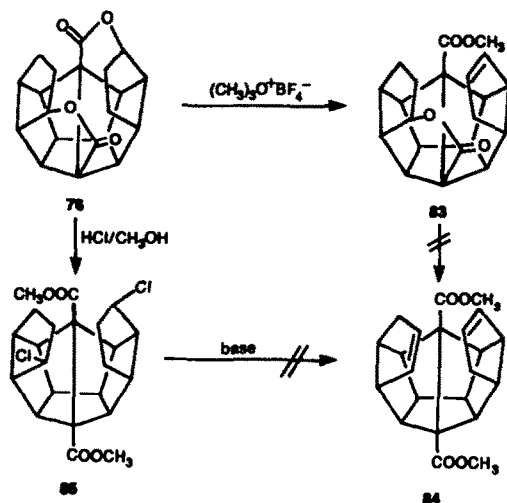
Chart 12.

Controlled lithium aluminum hydride reduction of **76** gives the dilactol **86**, which with thionyl chloride forms the corresponding chloro ether **87** (Chart 13). Treatment of **87** with silver perchlorate in attempts to induce ring opening with elimination via oxonium ions gives instead rearrangement with cleavage of the strained central bond. The extraordinary, stable, tertiary perchlorate **88** is produced. Sodium in liquid ammonia reduction of **87** occurs with cleavage of the central bond, giving **89** in high yield. Transannular cyclizations again become important, e.g. **89**→**90**. In a side scheme, epoxidation of **89**, acid-induced ring cleavages and decarbonylation produce, as illustrated, the dioxa-C_{20}-octaquinane **91**, the first example, albeit a heterocyclic one, of an *acs* quinane of this degree of cyclicity.[54]

Chart 13.
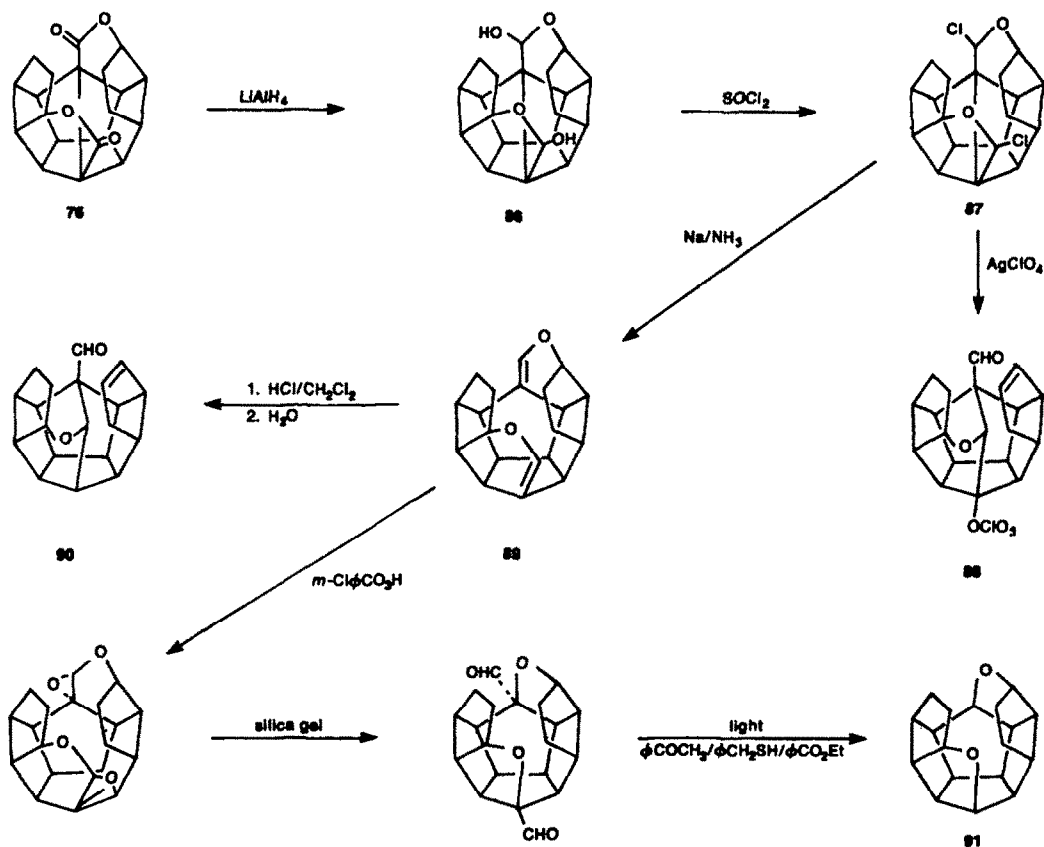
Dodecahedrane via C_{16}-hexaquinacene

Other approaches to dodecahedrane arise on thinking about other ways in which 5-membered rings can be grouped together interestingly. A few minutes consideration of a model of triquinacene (21) and its splendid symmetry leads irresistibly to thoughts of its relative 92, C_{16}-hexaquinacene, and questions just like those asked about triquinacene: Does the 6π system of 92 have homoaromatic character? Will this arrangement of double bonds complex metal ions in a special way? Can 92 be used to make dodecahedrane?

21   92

Paquette *et al.* reported in late 1977 the first, and very fine indeed, synthesis of C_{16}-hexaquinacene.[55] As outlined in Chart 14 the route starts with the diacid 93, derived from the domino Diels–Alder reaction described earlier (see eqn 19). This compound contains fourteen of the requisite sixteen C atoms. The two others needed are added by forming the bis-methylketone 94. Oxidative coupling of the bis-enolate of 94 with cupric chloride using Saegusa's method gives 95; note that the new bond made is needed only during the intermediate steps of the synthesis. Selenium dioxide oxidation takes 95 to the ene-dione 96. As in simpler examples, like the Diels–Alder cyclopentadiene-quinone adduct, this undergoes internal photocyclization to 97 efficiently. Zinc and acetic acid causes reductive cleavage of 97, first at the central bond (→ 98)—in this special case more strained than the cyclobutane bond on the other side of the activating carbonyl groups—and then of the cyclobutane (→ 99). Redrawing, always an important operation in polycyclic chemistry, shows that the product (100) of this double cleavage has the desired carbon framework. Reduction and elimination gives the triene target, C_{16}-hexaquinacene.
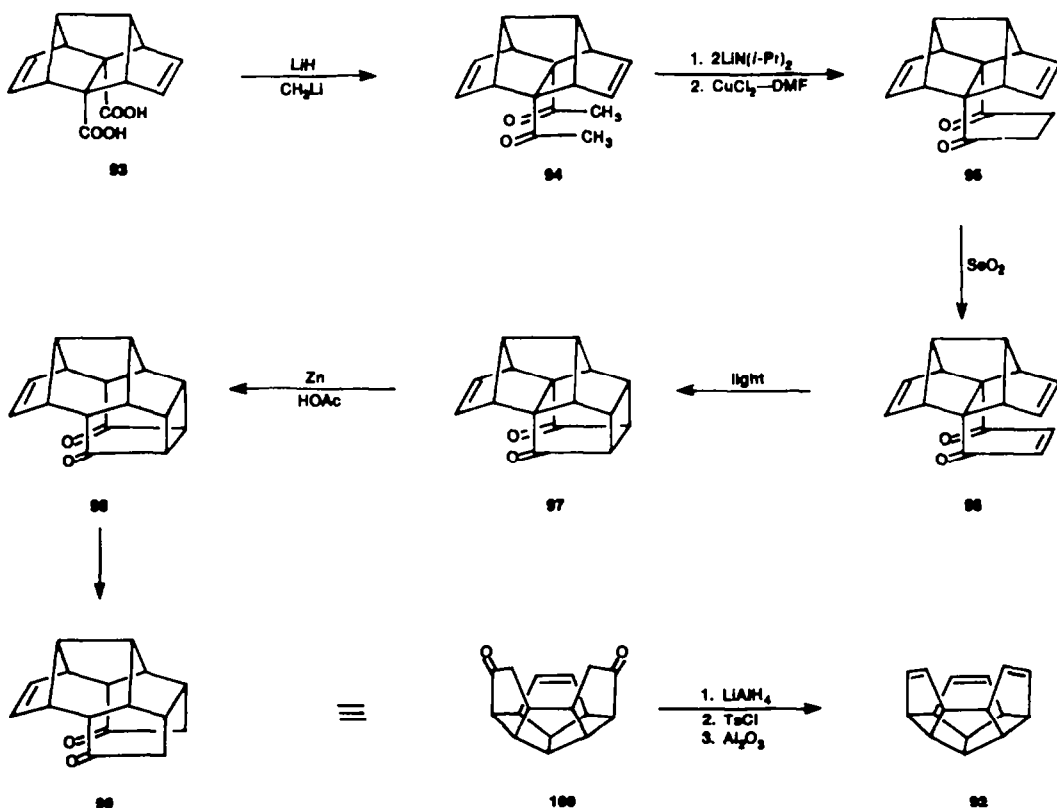
Chart 14.

X-ray and photoelectron studies of C_{16}-hexaquinacene done by Christoph and Gleiter in conjunction with Paquette lead, disappointingly, to the conclusion that there is no special homoaromatic character in this fascinating molecule.[56] No doubt, there is still much of great interest to be found otherwise in its chemistry.

The ene-dione 100 is an excellent candidate for elaboration to dodecahedrane. Four carbons must be added, and six rings built. An idea of the approaches underway at Ohio State can be gotten from consideration of the conversions shown in Chart 15.[57]

Chart 15.
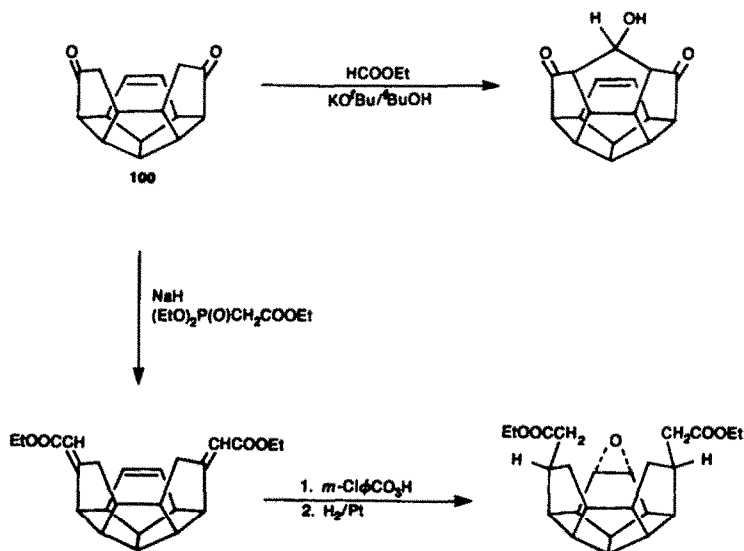
My own group at Chicago has also been working on the C_{16}-hexaquinacene system and its possibilities as a dodecahedrane precursor. Our work is quite different from that of the Ohio State group and presents another view of how to build up multi-5-membered ring systems with control of stereochemistry.[58] As shown in Chart 16, we start with the Diels–Alder adduct 101 of 1,1-dimethoxy-tetrachlorocyclopentadiene to 1,5-cyclooctadiene. The *endo* stereochemistry of this compound follows from its ready photocyclization to the corresponding cage system, as described elsewhere for our synthesis of reduced [0.0]paracyclophanes.[59] Dechlorination of 101 using sodium dispersion in a modification of the classic Winstein procedure and subsequent acid hydrolysis of the ketal gives the norbornenone 102. The overall yield of these reactions is very good, and they can all be run easily on mole scale. The use of sodium dispersion in the Winstein procedure avoids over-reduction and removes the need to use large excesses of the metal.

As hoped for, addition of the organolithium from *trans*-3,4-dimethoxycyclopentyl chloride to 102 is stereoselective, favoring by 93 to 7 approach to the carbonyl on a path above the norbornene double bond. Conversion of the anti alcohol 103 so formed to the *anti* chloride and subsequent reduction of the chloride with sodium cyanoborohydride in nitromethane at 0° gives 104 with complete retention of stereochemistry at the bridge. These reactions, as expected, occur via anchimerically stabilized cations; the interaction preserving the desired configuration. A by-product (15%) of the reduction step is the cyclopropane 105 formed by delivery of hydride to the "wrong" corner of the intermediate ion. Interestingly, this cyclopropane is the main product of reduction with lithium aluminum hydride.

Oxidative cleavage of both double bonds of **104** with ruthenium tetroxide/potassium metaperiodate gives a mixture of products, including the tetraacid **106** and its various anhydrides. Treatment of the entire crude under Perkin-like conditions—potassium acetate in acetic anhydride at 180°—followed by hydrolysis and decarboxylation of the product mixture in aqueous acid gives the desired cyclopentyl triquinane **107** in 65% yield overall from **104**. An exceedingly pleasing result!
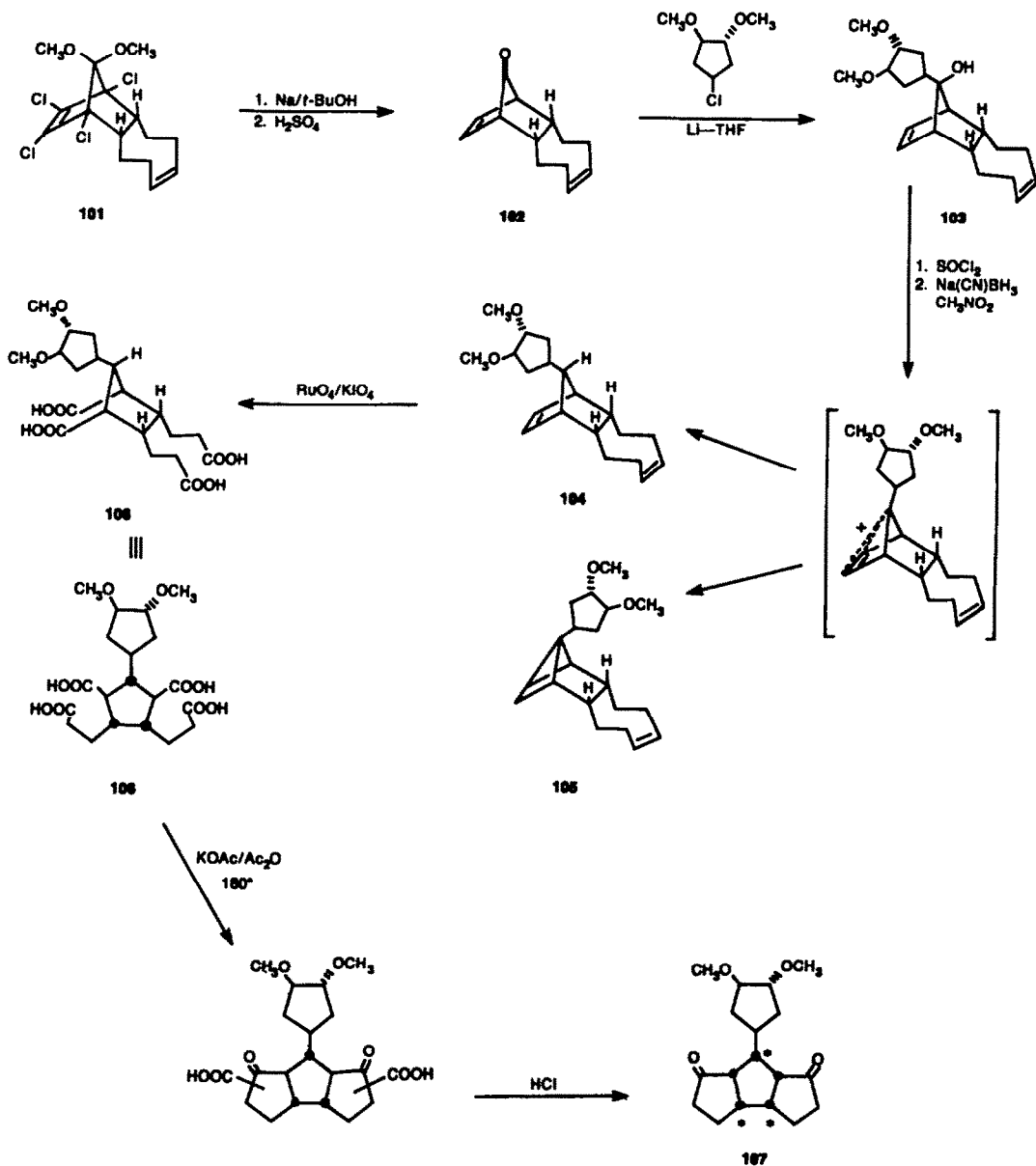

Chart 16.

The *syn* relation of the hydrogens at the three critical positions (*) of **107** follows from their relation in **104**. The remaining centers on the central, fully substituted cyclopentane ring of **107** are made epimerizable by the adjacent carbonyls. The all-*cis,syn* stereochemistry drawn reflects the penchant of the bicyclo[3.3.0]octane system for *cis* fusion[60] and is in agreement with an analysis of the degeneracies in the ^{13}CMR spectrum of **107**.

Hydrolysis of the methyl ethers, stepwise oxidation to the α-diketone and reaction with o-phenylenediamine takes **107** to the quinoxaline **108**, a pentaquinane (Chart 17). Somewhere along the way a new carbocyclic ring forms. It is not clear at what point this aldol closure occurs. In any case, it is the "wrong way 'round". Compound **108** does not have all-*cis,syn* stereochemistry; closure of the sixth ring is therefore not feasible sterically. Fortunately, the quinoxaline part is more useful than just as a mask for the α-diketone. The quinoxaline C=N is capable of stabilizing α-anions. Thus, **108** can be put into equilibrium with the open compound **109** and it, in turn, can be driven to close in the desired direction. Heating **108** at 180° with potassium acetate in acetic acid gives the C_{16}-hexaquinacene derivative **110**; the structure of which follows unambiguously from consideration of its ^1H and ^{13}C NMR spectra.[52a]
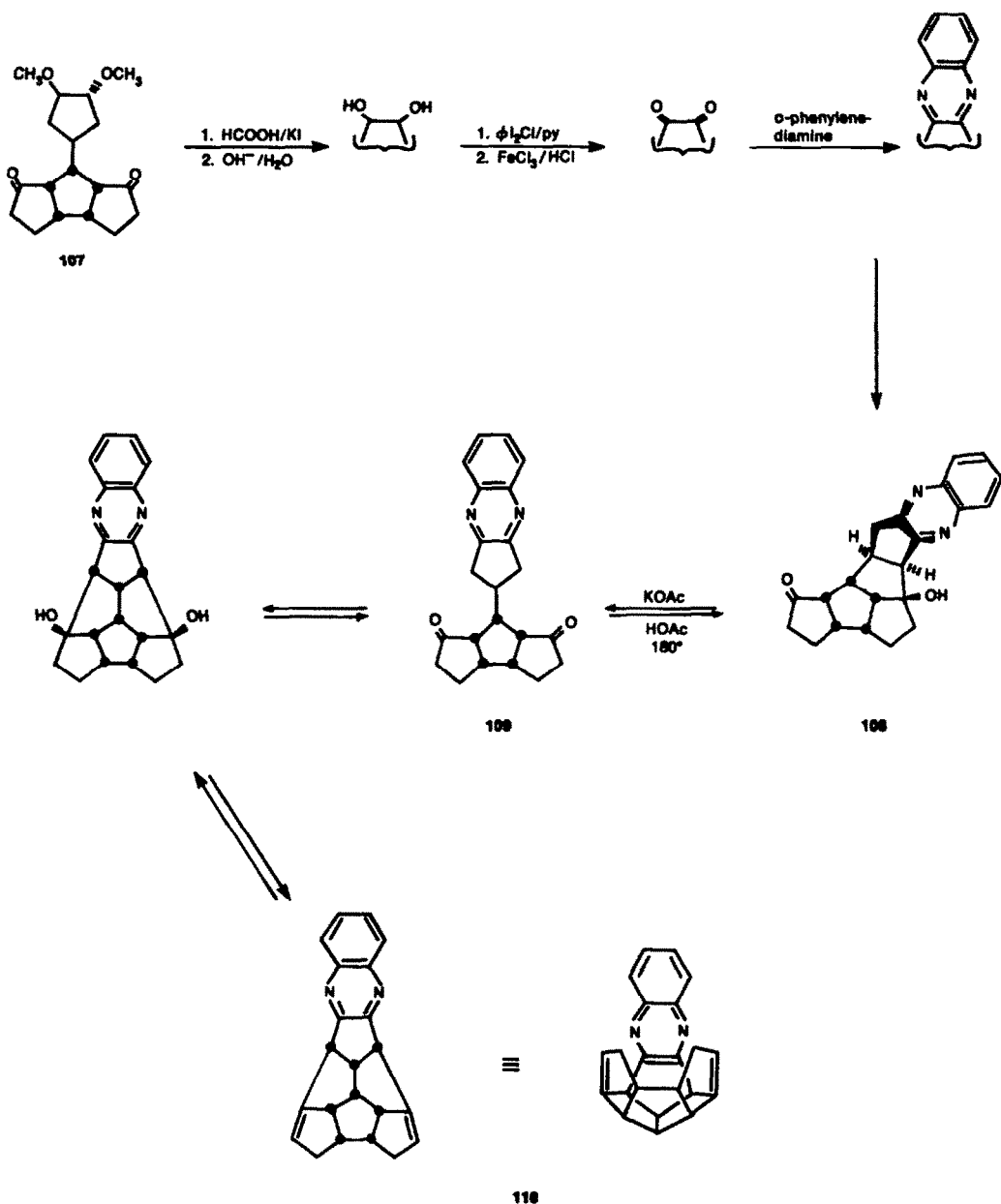

Chart 17.

Although it should be simple to effect isomerization of the very strained double bonds in 110 into the essentially strainfree positions of 111, we have yet to be able to accomplish this smoothly. Once this annoying hurdle is cleared, we can embark on the elaboration of this C₁₆-hexaquinacene to dodecahedrane. The outline offered in Chart 18 is meant to serve only as an illustration of what might be possible. Control of stereochemistry depends on reagents approaching preferentially from the outer side of the developing dodecahedrane sphere, a most likely and familiar expectation.[61]
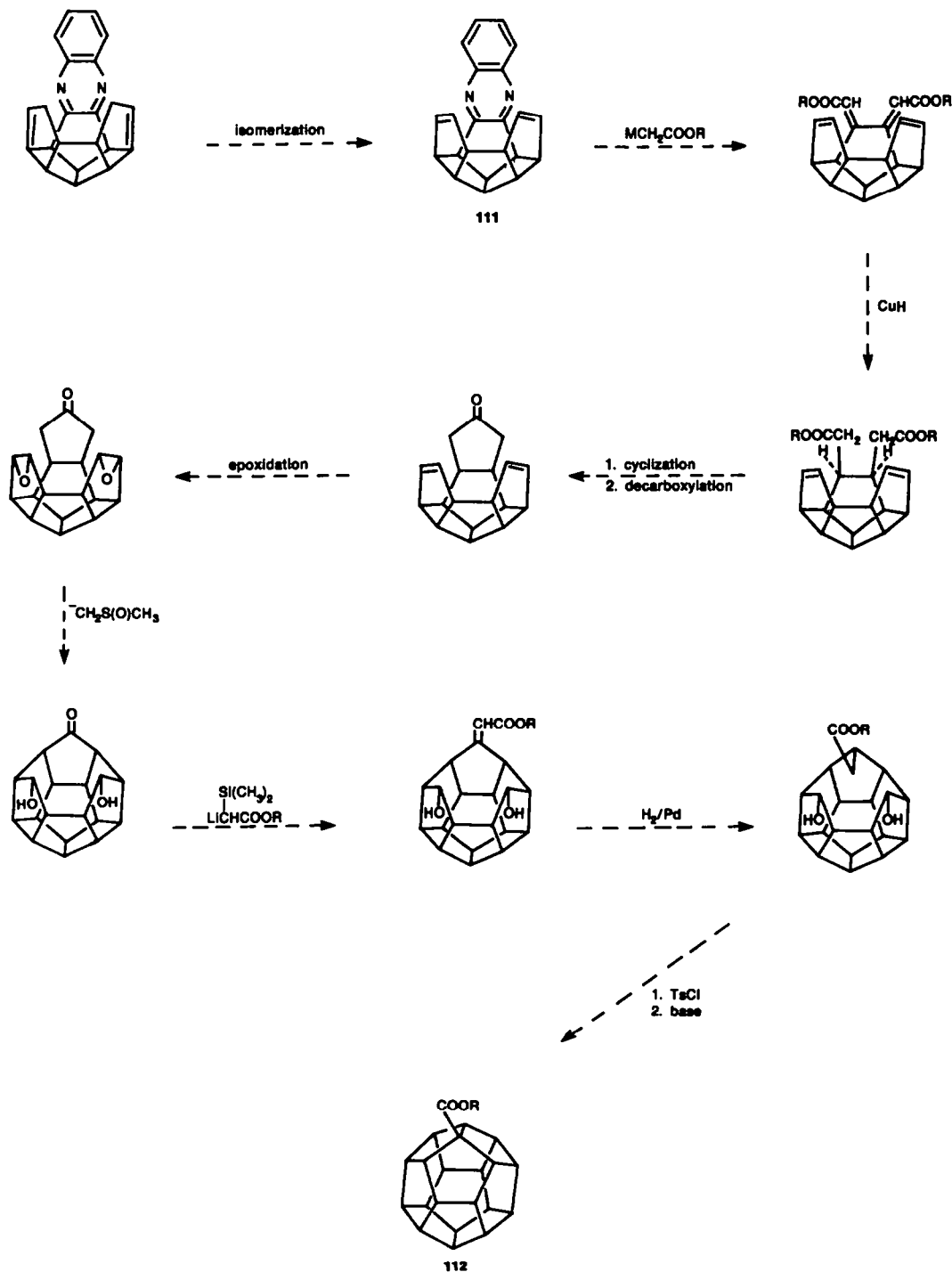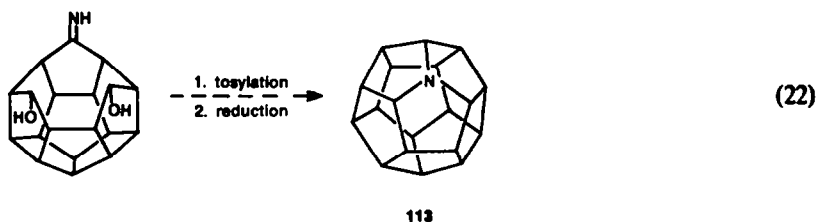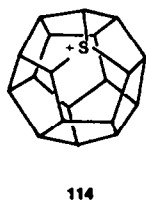

Chart 18.

Modifications of the scheme in Chart 18 in its last steps should permit access to the important heterododecahedranes; for example, as in eqn (22), azadodecahedrane 113.


$$(22)$$

113

Similarily, via the thioketone, thiadodecahedrane salts (114) should become available.

114

Dodecahedrane via peristylane

The main work in my group directed toward dodecahedrane is based on the idea that the molecule can be considered for purposes of synthetic design as made up from two sub-units, cyclopentane and the C_{15}-hexaquinane 115 (eqn 23). We have named this hexaquinane "peristylane" from the Greek περιστῦλον, a group of columns arranged about an open space and designed to support a roof.[62]

$$(23)$$

115
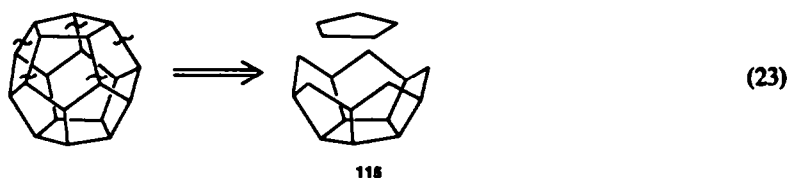
The frame of peristylane ($C_{15}H_{20}$) is made up of fifteen C atoms joined together by twenty C–C bonds into six fused 5-membered rings. The unsubstituted system has five mirror symmetry planes intersecting along a 5-fold rotation axis. Peristylane is shaped rather like a bowl with a fluted rim. Although unquestionably less complex than dodecahedrane, peristylane presents a synthetic problem of substantial dimensions. Our design of the synthesis has already been published in detail.[63] It depends conceptually on an antithetic dissection to lesser systems. This sort of approach to tactical synthesis design starts with the target molecule itself and moves backwards in stepwise fashion, breaking bonds along the way, in search of a reasonable starting material. Corey has put into words the "rules of the game" of this classic mental exercise of the synthetic organic chemist.[64]

As can be seen, the intermediates 116 → 122 in our synthesis have a mirror plane of symmetry in common with one another and the peristylane product. This feature was sought purposefully in the design of the synthesis. 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 under-appreciated, is that it is much easier to interpret, understand, and be guided by the nuclear magnetic resonance spectra of intermediate reaction products if the starting material is symmetric and the desired product is supposed to be.

As it was to turn out (Chart 19), this sort of synthesis planning paid off well.[63] Two stage hydroxypropylation of cis-bicyclo[3.3.0]octane-2,8-dione (116) followed by oxidation with chromic acid gives the bis-lactone 117. Acid-induced elimination and then internal acylation to bis-enone 118 occurs in high yield on treatment with phosphorus pentoxide in methanesulfonic acid. Catalytic hydrogenation of
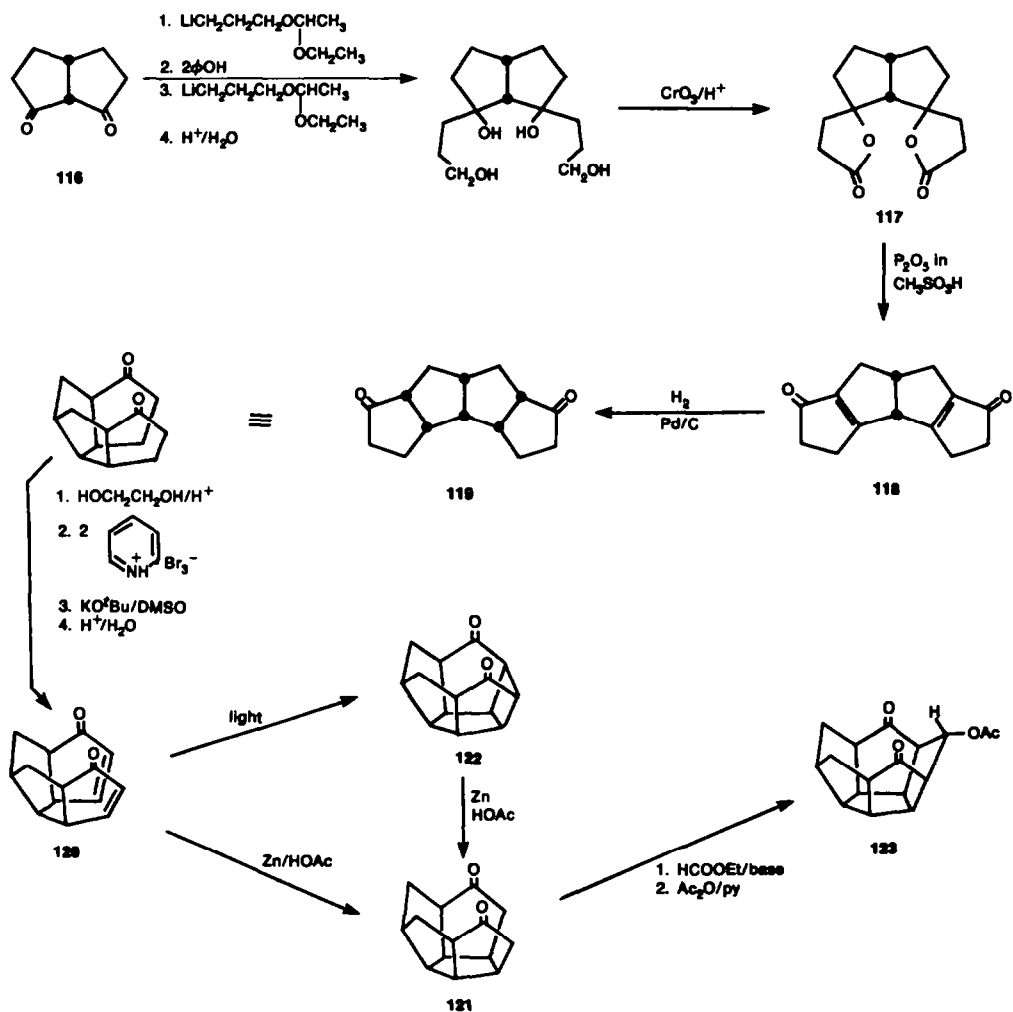

Chart 19.

118 over specially treated palladium-on-carbon goes on the more open face and establishes the all-important *cis,syn* stereochemistry in 119, an *acs*-C$_{14}$-tetraquinane.[65] Conversion of 119 to 120 uses what has become a fairly standard technique for the introduction of unsaturation α,β to ketones— bromination/dehydrobromination of intermediate ketals. Closure of 120 to the *acs*-C$_{14}$-pentaquinane 121 is then done either by direct reductive coupling or by way of the photo-closed norperistylane 122 and reductive cleavage, as illustrated. The introduction of the fifteenth C atom and closure of the sixth ring is accomplished by reacting 121 with ethyl formate and proceeds readily if the pH is controlled carefully during the course of the reaction. The structure of peristylane 123 has been confirmed fully by single crystal X-ray analysis by Nowacki and Scarbrough at Bern.[66]

This synthesis required amongst other things finding a good, general reagent for hydroxypropylation[67] and developing a new reagent, phosphorus pentoxide in methanesulfonic acid, for acid-induced cyclizations.[68] These reagents are now finding wide use in synthesis. A similar note could be appended to each of the efforts directed towards dodecahedrane, for the "spin-offs" from each group's work have been quite considerable.

Elaboration of the peristylane system to dodecahedrane requires a good deal of bond making and the addition of five more C atoms. Condensation of 121 with aldehydes works very well (eqn 24) and offers a route to peristylanes carrying more carbons. Unfortunately, the products of these condensations always have the substituent *exo* to the cavity of the peristylane, in the less-hindered environment, the wrong stereochemistry for the rest of the synthesis.


$$(24)$$
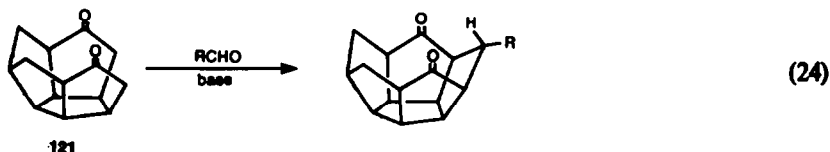
To circumvent this, condensation of 121 with esters was tried in the expectation of obtaining alkyl substituted hydroxyperistylane diones, e.g. 125 in Chart 20. Dehydration of 125 and conjugate reduction


Chart 20.
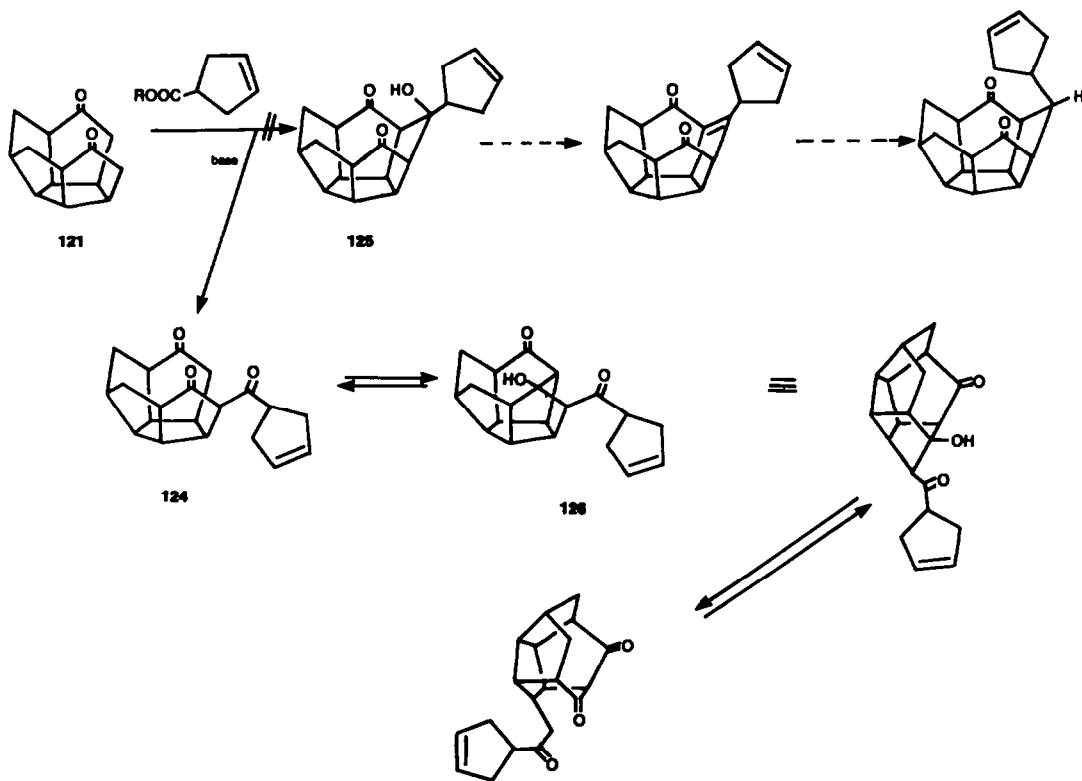
of the product olefin from its more open face would configure the substituent properly (*endo*) for the final closure reactions. This original plan was never achieved. Condensation of 121 with esters more complex than ethyl formate stops at the β-diketone stage (e.g. 124) without closure to the substituted peristylane. This is true even if enolization of the β-diketone system is blocked by subsequent alkylation. Attempts to drive the reaction forward lead down an unexpectedly open path to the new ring systems 126 and 127. Even though it can be shown that 124, 126 and 127 are in mobile equilibrium, we have not yet been able to pull the mixture towards 125 or its dehydration product.[69]

An alternate approach to a peristylane like 125 is shown in Chart 21. The symmetrical keto bis-ketal 128 can be made selectively from peristylane 2,4,6-trione in good yield. Unfortunately, the adducts of various Grignard or organolithium reagents to the carbonyl group of 128 are exceedingly fragile, collapsing in a multitude of unlikely ways even during the most gentle of work-ups.[70]

HOCH₂CH₂OH/H⁺ → 128

1. RLi
2. buffer

Chart 21.
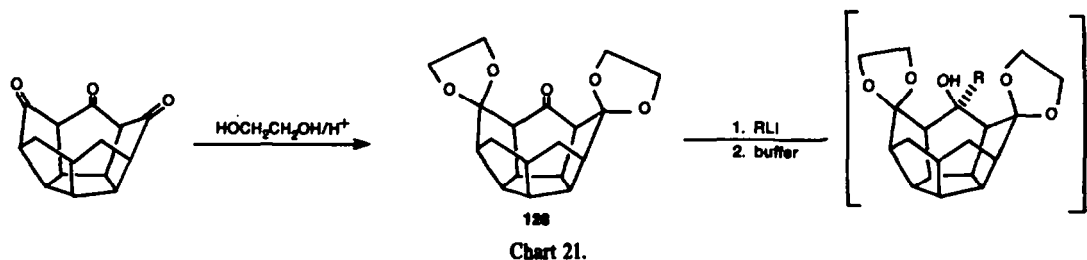
Failures and frustrations of this sort now seem a little less grevious. We have finally a good procedure for the preparation of peristylanes carrying synthetically useful substituents, properly configured. The method depends on the intermediacy of peristylenones, α,β-unsaturated ketones of high reactivity.[71] Such enones, like 129, are very strained, reacting rapidly even with furan at room temperature (eqn 25).

$$(25)$$
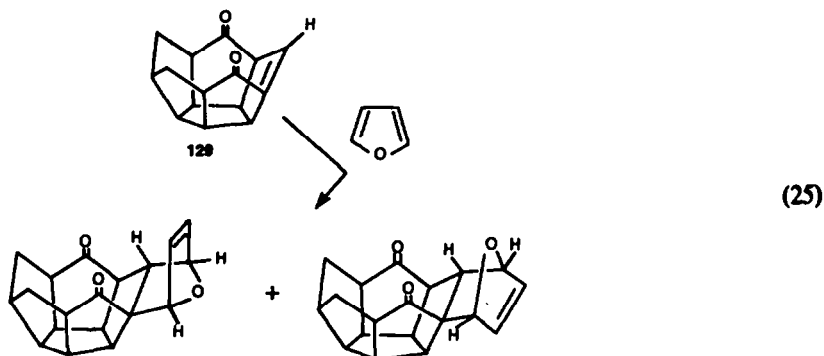
Spectroscopic studies reveal that the double bond in 129 is twisted, and that conjugation with the adjacent carbonyl group is incomplete. Still, the compound can be generated under very mild conditions (eqn 26) and, in special cases (eqn 27), can even be isolated.

$$(26)$$

$$(27)$$
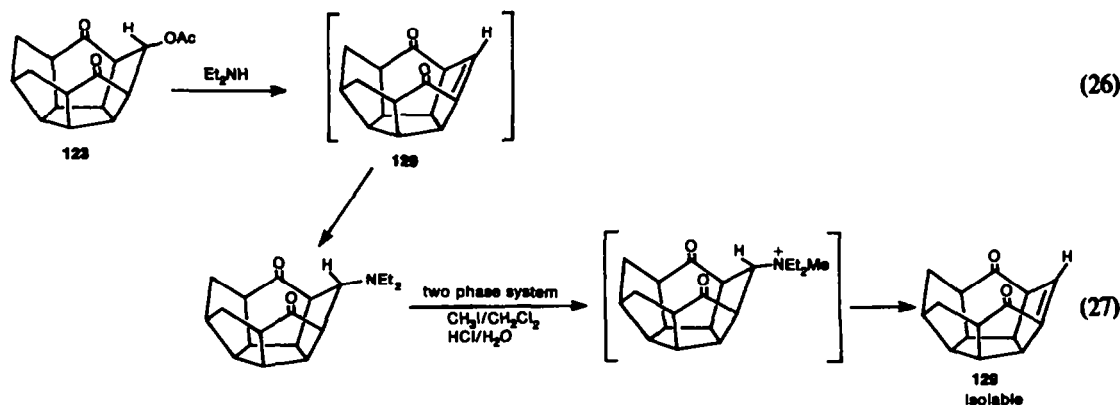
Peristylenone 129 is very sensitive to nucleophilic attack. (Equation (27) is successful only because the two phase system contains a haven for 129 in which the nucleophile concentration is low.) Carbon anions, particularly those stabilized by alpha carbonyl groups, add readily in Michael fashion to 129. Thus, we can make substituted peristylanes like 130–132 in high yield. This is done most conveniently directly from 123, forming 129 *in situ* (eqn 28). Note that compound 132, produced by addition of cyclopentane-1,3-dione, contains all twenty C atoms needed for dodecahedrane.

$$ \tag{28} $$

130: R = —CH(CO$_2$CH$_3$)$_2$
131: R = —CH(NO$_2$)COOCH$_3$

132: R =
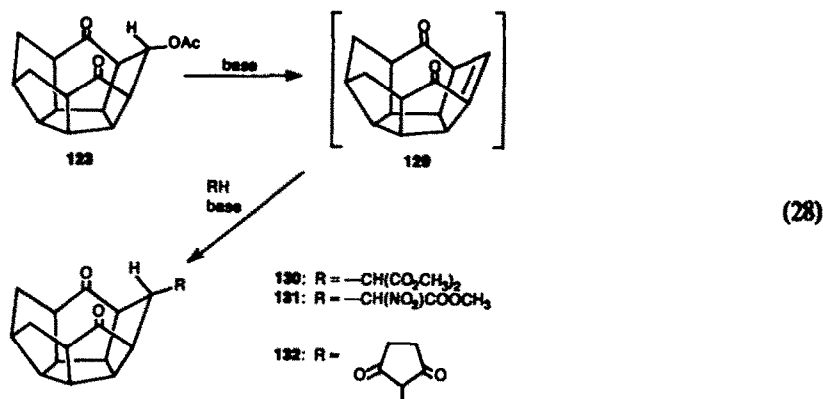
Nucleophilic additions to 129 all occur from the less-hindered, outer side of the peristylane bowl. The configuration at the point of attachment must be inverted, *exo → endo*, to obtain proper dodecahedrane precursors. Our method is based quite simply, as in earlier schemes, on introduction of a double bond and its subsequent hydrogenation under kinetic control, i.e. delivery of hydrogen to the less-hindered face. The method is illustrated in Chart 22 for the inversion of the malonate group of 130. It proceeds by phenylselenenylation of the malonate enolate (→ 133), oxidation to the selenoxide (134), and the spontaneous elimination of phenylseleninic acid (→ 135). This sequence of reactions for the introduction of a double bond via selenium containing intermediates is derived, of course, from the exceedingly nice studies of Sharpless, and of Reich *et al.*[72] of which we have made much use. In the case illustrated, the overall yield, 130 → 135, is a satisfying 70%. Reduction of 135 to 136 with hydrogen over palladium-on-carbon is slow, probably reflecting the difficulty of pushing the malonyl group in toward the middle of the

Chart 22.
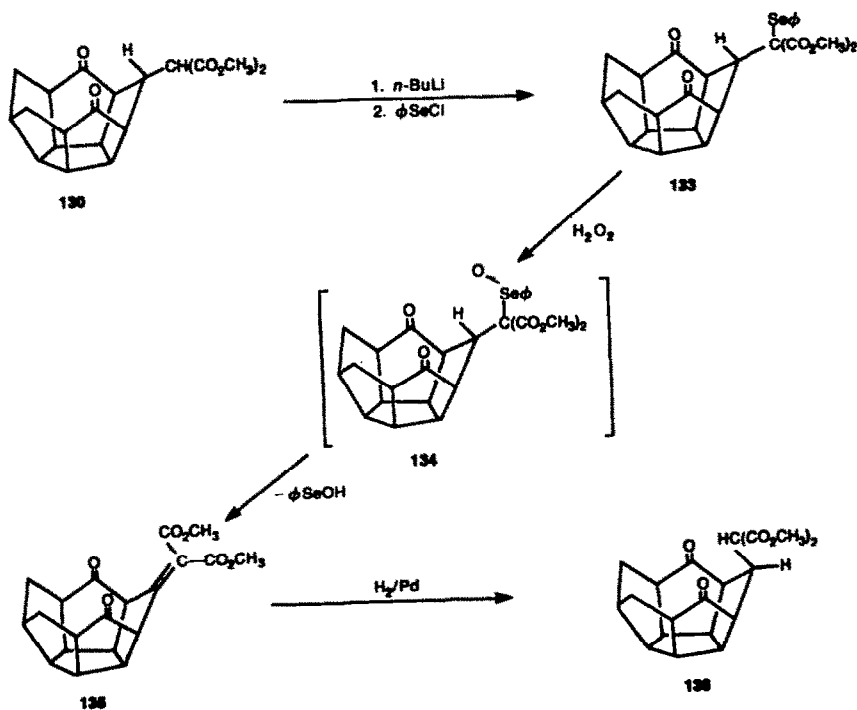
peristylane. The yield, however, is very good. The sterically encumbered *endo* malonate group in 136 behaves quite differently from the more normal *exo* malonate in 135, e.g. in the PMR spectrum the central malonyl proton resonance is shifted 1.1 ppm downfield and appears below even the resonance of the methyl ester.[71]

The "roofing" of peristylane to make dodecahedrane requires that the five points of attachment (i.e. the five methylene carbons) be functional in some useful way. Our original entry into the system, compound 123, Chart 19, has only three of these in this state. We have recently combined our work on peristylenones with our experiences in the introduction of double bonds via selenenylation to deal with the functionalization of the remaining methylene groups. The procedure is shown in Chart 23. Bis-selenenylation of 123 via the preferred enols gives the symmetrical bis-selenide 137, which is oxidized by low temperature ozonization to the corresponding bis-selenoxide 138. This is not isolated, but is left to decompose in the presence of a suitable nucleophile. Presumably, sequential elimination-addition reactions occur involving reactive intermediate peristylenones. If, as illustrated, the decomposition of 138 is run in trifluoroethanol containing potassium carbonate, the ultimate product is the tris(trifluoroethoxy)peristylane dione 139—functional at all five methylenes of the parent hydrocarbon.[71]
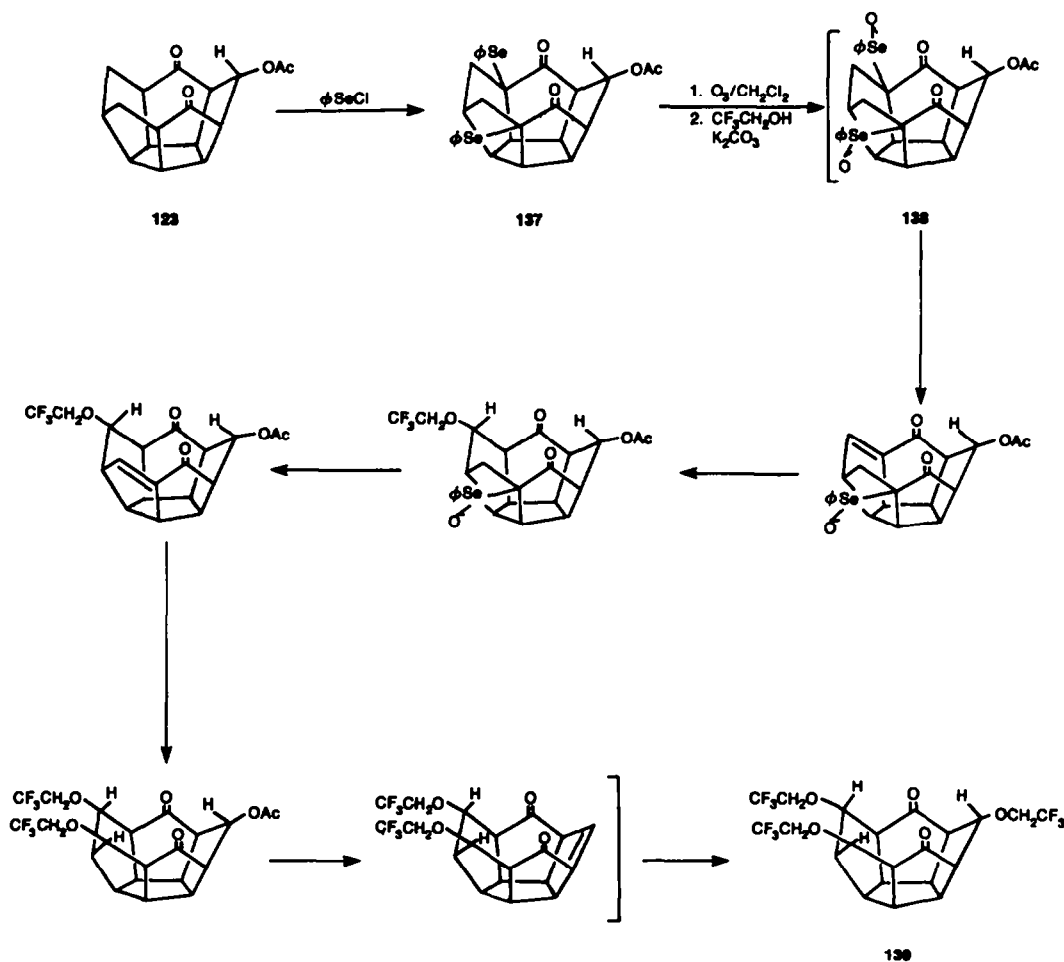
Chart 23.

It remains now to combine the ideas and elements in eqn (28) and Charts 22 and 23 to complete the synthesis of dodecahedrane by way of peristylane. A "paper" route is outlined in Chart 24; no doubt further work at the bench will cause us to modify it.[73]
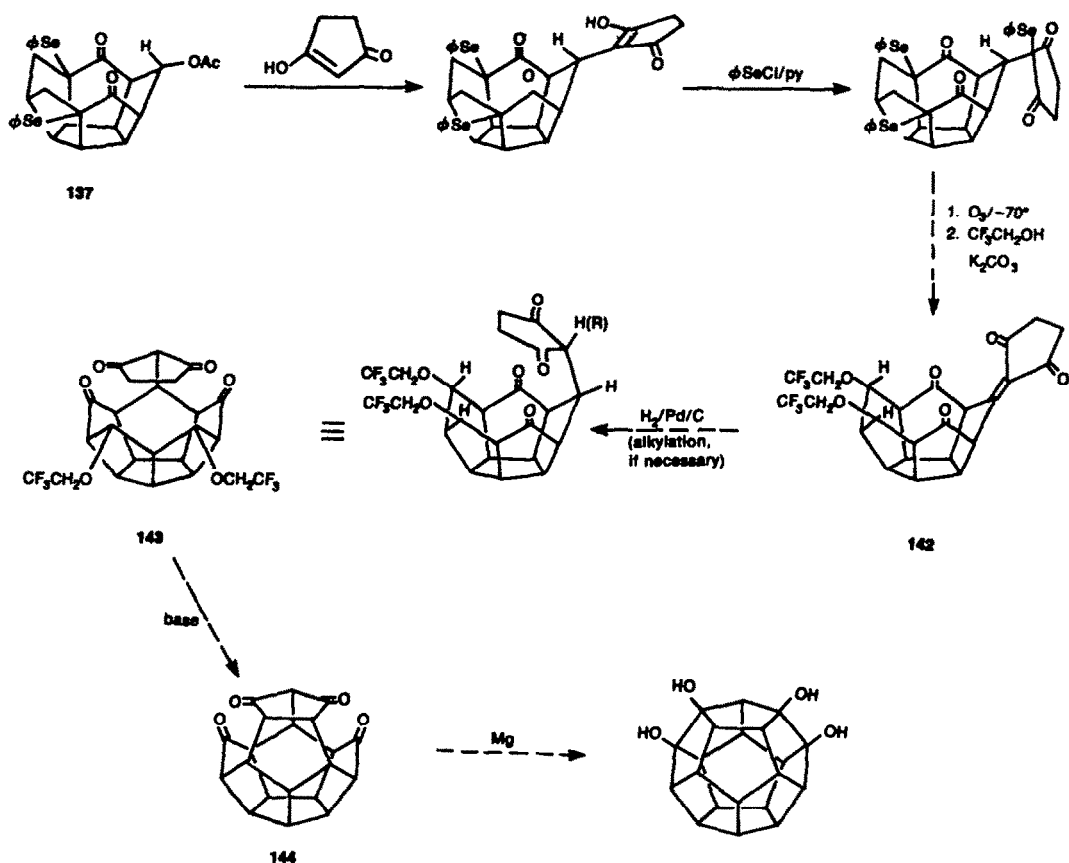
Chart 24.

The critical step in this scheme is the closure of **143** to **144**, expected to occur by way of intermediate persitylenones. Direct displacement reactions (internal alkylations) may prove a useful alternate. As the cyclopentane-dione ring is free to rotate, other closures may occur from other conformers. It may be necessary therefore to fix this ring in position. We can perhaps take advantage of the reactivity of the double bond in **142** and set the ring, as for example in **145** (eqn 29), in such a way that only closure in the desired fashion is stereochemically possible.

(29)
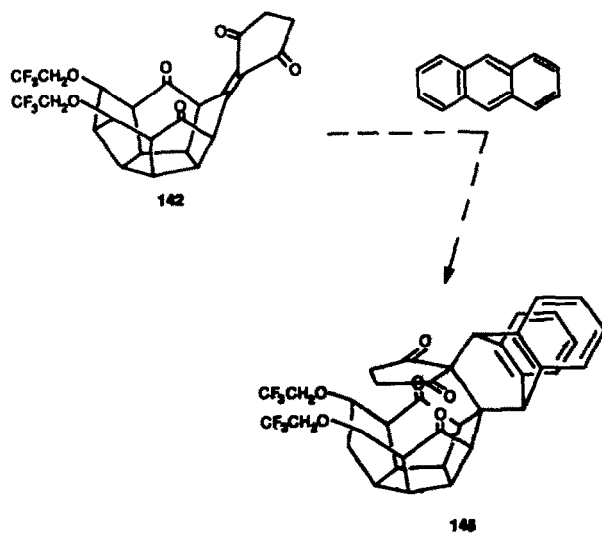
Dodecahedrane—Future prospects

Much yet remains to be done to achieve dodecahedrane. With perhaps 50 man-years altogether invested already in attempts at its synthesis, it is reasonable to ask if there is something more about the compound than just its aesthetic appeal to justify the effort. Indeed there is!

Dodecahedrane and its close precursors and relatives are examples of polycyclic systems quite different in construction, size, rigidity and strain from ring systems now known. To synthesize such compounds, new ways of building and manipulating the skeletons of complex systems need to be developed. Accordingly, the work contributes to the growth of tactical synthesis, a discipline of established utility. Beyond the general appeal of developing new systems, syntheses and methods, the search for routes to dodecahedrane continues for there is much to be done with the molecule once it is in hand. The synthesis of dodecahedrane will make possible further fundamental investigations and open doors to new chemistry. A small part of this can be speculated on here.

Dodecahedrane has been considered in a number of theoretical studies. Several calculations of its heat of formation have been made. Different methods give different values; these are listed in Table 2. The MINDO/3 estimate by Schulman and Disch is much higher than those from other methods. As pointed out by these authors, MINDO/3 often overestimates considerably the heat of formation of "globular" molecules.[74b] The differences in the Engler, Andros and Schleyer (EAS)[5] and the two Allinger force field calculations (MM1,[5,75] MM2[76]) arise primarily in the different weights given to non-bonded C···H and H···H interactions, of which there are many in dodecahedrane. In the second and better Allinger calculation the hydrogens are treated as "smaller and softer".[76] Still, the difference between EAS and MM2 is over 20 kcal/mole, very large by comparison to the usual close agreement between the methods. Clearly, an experimental determination of the heat of formation of dodecahedrane will be revealing.

The strain energy in dodecahedrane can be estimated (Table 2) from the variously calculated heats of formation,[77] or by the sum of strains (SSSR).[78] The values range from about 40 to about 100 kcal/mole. Most of this comes from torsional strain, for in the undistorted dodecahedrane (I_h symmetry) the conformations about each of the C–C bonds are exactly eclipsed. Angle strain is extremely small, 108° vs 109° 28'. Ermer has found by molecular mechanics calculations that it would be energetically unprofitable for dodecahedrane to distort from I_h symmetry, paying for the reduction in torsional strain with an increase in angle strain.[79] In any case, the total strain energy in dodecahedrane is not significant when considered on a per bond basis.

Table 2. Calculated thermodynamic properties of dodecahedrane at 298°[a]

	ΔH_f° (kcal/mole)	Strain (kcal/mole)
MINDO/3	+62.3	105.4
EAS	−0.22	42.98
MM1	+45.28	88.38
MM2	+22.5	65.60
SSSR (corr.)	—	42.58

[a]For references see text.

Many other things have been predicted for dodecahedrane. Schulman *et al.* have published two fascinating theoretical studies of dodecahedrane.[74a,80] The symmetry of the molecule reduces the work of some of the calculations involved to practical dimensions. As a case in point, rather than the 6555 independent harmonic force constants that would be needed to describe a completely asymmetric 40-atom molecule, 74 suffice for I_h dodecahedrane.[74a] There are only three IR active modes and eight Raman active modes. Ermer has calculated all the vibrational frequencies; e.g. IR active, 2898, 1310 and 760 cm^{-1}.[79]

The orbital energies of dodecahedrane have been calculated by both MINDO/3 and the less satisfactory INDO method.[74] Photoelectron spectroscopy, when the molecule is in hand, will assist in refinement of these and other such theoretical exercises.

The NMR spectra of dodecahedrane will of course be delightfully simple. There will, however, be much information in the nuclear spin–spin coupling constants. Schulman has calculated these.[74b] Of particular note for future experimental evaluation is the large difference in the size of $J_1(^{13}C-H)$ predicted by perturbation techniques (102.7 Hz) and that calculated by semi-empirical methods (125.3 Hz) derived from values in already known systems.[81]

The "free-space" within dodecahedrane is quite small. Taking the C–C bond length as 1.54 Å and the carbons as sizeless points, the distance between opposite vertices along one of the 3-fold axes is about 4.32 Å. But C atoms are not sizeless; taking a van der Waal's radius of 1.60 Å reduces the cavity to about 1.1 Å in diameter. Various estimates have been made, again in various ways, of the energetics of dodecahedrane inclusion compounds. The calculated destabilizations for a helium atom within dodecahedrane range from about 7 to about 46 kcal/mole.[36a,74b,82] Schulman has considered theoretically a number of other inclusion compounds in great detail.[74b] His results are intriguing. Inclusion of a hydrogen molecule ($\Delta E = +48$ kcal/mole), a neutral lithium atom (+ 25 kcal/mole) or an electron (+ 149 kcal/mole) leads to substantial destabilization. On the other hand, significant stabilization is predicted for inclusion of H^+ ($\Delta E = -130$ kcal/mole), Li^+ (−162 kcal/mole) or, most remarkably, a neutral beryllium atom (−519 kcal/mole). The extraordinary stabilization for $C_{20}H_{20}Be$ results from considerable charge transfer. As Schulman points out quite fairly "clearly this case deserves more extensive study even if the predicted stability seems much too large".

Ionization of appropriate dodecahedrane derivatives in very strong, non-nucleophilic acids should produce the dodecahedryl carbonium ion (146).[83] At low temperature, this should be a stable entity of non-fluctuating structure.

146
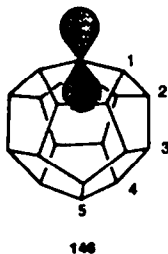
The interactions of the five successive sets of hydrogen and carbon nuclei with the empty p orbital of this ion, as determined by PMR and ^{13}CMR spectroscopy, should provide a delicate probe of the shape, size, and extent of the orbital (cf. the work of Olah on the adamantyl cation[84]). Complementary information might come from evaluating the corresponding dodecahedryl radical and anion. Taken together, these data should give a good picture of the nature of the cavity in dodecahedrane.

1,2-Hydride shifts on the surface of the dodecahedryl carbonium ion should occur at nominal temperature. The shift converts one dodecahedryl carbonium ion into another. In the simplest case, that of the unsubstituted ion, the process in degenerate. As the rate of hydride shift becomes large (increasing temperature), hydride circumambulation produces an ion probably best described as a spherical shell of 20 "identical" C atoms, each + 1/20 charged, surrounded by a concentric shell of 19 "identical" H atoms.[85] (These "identities" are a product of time averaging, not symmetry; there is no regular polyhedron with 19 vertices.)

In the presence of a suitable proton acceptor, the dodecahedryl carbonium ion should form the olefin dodecahedrene (147). Other synthetic approaches are of course available. Although quite strained, there can be little doubt that dodecahedrene will be long-enough-lived for characterization; its 20 carbon frame can accommodate the strain without undue disruption. The double bond will be distorted in an interesting way; it will not be twisted, as common in many strained polycycles, but rather bent in the sense shown in drawing 148.
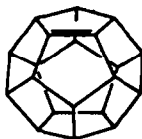
147   148

Dodecahedrene offers useful synthetic possibilities. It will probably dimerize fairly readily, providing entry into C_{40} cage systems, etc. Addition of bromine to dodecahedrene under ionizing conditions can lead, via hydride shifts, to the five possible disubstituted dodecahedrane isomers.[86] From these, the five mono-substituted dodecahedrane carboxylic acids could be obtained. Possession of this set of geometrically defined compounds would permit the most detailed evaluation yet of the through-space vs the through-bond mechanism for the transmission of inductive effects (see the work of Stock[18a] and of Farrell[18b] on the cubane acids).

Dodecahedrane and its precursors, etc. offer interesting possibilities biologically. Polycyclic hydrocarbons of cage-like structure appear to be excellent carriers for functional groups of pharmacological significance.[87] A prevalent idea is that the hydrocarbon portion promotes lipid solubility and aids adsorption on or passage through biological membranes.[88] Long chain hydrocarbons, condensed aromatics and substituted (branched) cage systems of less globular shape are usually less effective. It is encouraging to note in speculating about the future of dodecahedrane that 1-adamantyl amine hydrochloride (marketed as "Symmetrel") is used successfully for the treatment of Asian Flu and, separately, for the alleviation of Parkinson's disease.

REFERENCES

[1] F. A. Cotton and G. Wilkinson, *Advanced Inorganic Chemistry*, pp. 21, 30–36. Interscience, New York (1972).

[2] P. E. Eaton and T. W. Cole, Jr., *J. Am. Chem. Soc.* **86**, 962, 3157 (1964); T. W. Cole, Jr., Ph.D. Dissertation, The University of Chicago (1966).

[3a] J. C. Barborak, L. Watts and R. Petit, *J. Am. Chem. Soc.* **88**, 1328 (1966); [b] P. E. Eaton and T. W. Cole, Jr., *Chem. Comm.* 1493 (1970); [c] N. B. Chapman, J. M. Key and K. J. Toyne, *J. Org. Chem.* **35**, 3860 (1970); [d] T.-Y. Luh and L. M. Stock, *Ibid.* **37**, 338 (1972); [e] A. J. H. Klunder and B. Zwanenburg, *Tetrahedron* 4131 (1972); [f] E. W. Della and H. K. Patney, *Aust. J. Chem.* **29**, 2469 (1976).

[4] L. F. Pelosi and W. T. Miller, *J. Am. Chem. Soc.* **98**, 4311 (1976).

[5] E. M. Engler, J. D. Andose and P. v. R. Schleyer, *Ibid.* **95**, 8005 (1973).

[6] P. E. Eaton and E.-P. Krebs, unpublished determination.

[7] L. Cassar, P. E. Eaton and J. Halpern, *J. Am. Chem. Soc.* **92**, 3515, 6366 (1970).

[8] E. B. Fleischer, *Ibid.* **86**, 3889 (1964).

[9] B. D. Kybett, S. Carroll, P. Natalis, D. W. Bonnell, J. L. Margrave and J. L. Franklin, *Ibid.* **88**, 626 (1966).

[10] E. W. Della, P. T. Hine and H. K. Patney, *J. Org. Chem.* **42**, 2940 (1977).

[11] T.-Y. Luh and L. M. Stock, *J. Am. Chem. Soc.* **96**, 3712 (1974).

[12] R. Stober and H. Musso, *Angew. Chem.* **89**, 430 (1977).

[13] J. T. Edward, P. G. Farrell and G. Langford, *J. Am. Chem. Soc.* **98**, 3075, 3085 (1976).

[14a] N. Bodor, M. J. S. Dewar and S. L. Worley, *Ibid.* **92**, 19 (1970); [b] P. Bischof, P. E. Eaton, R. Gleiter, E. Heilbronner, T. B. Jones, J. Musso, A. Schmelzer and R. Stober, *Helv. Chim. Acta* **61**, 547 (1978); [c] See also, J. M. Schulman, C. R. Fischer, P. Solomon and T. J. Venanzi, *J. Am. Chem. Soc.* **100**, 2949 (1978).

[15a] S. A. Rice and J. Jortner, unpublished; [b] J. M. King, M.S. Thesis, Atlanta University (1975).

[16] M. L. Gross, *Org. Mass Spectrom.* **6**, 827 (1972).

[17] P. G. Gassman and R. Yamaguchi, *J. Org. Chem.* **43**, 4392 (1978).

[18a] T. W. Cole, Jr., C. J. Mayers and L. M. Stock, *J. Am. Chem. Soc.* **96**, 4555 (1974); [b] J. T. Edward, P. G. Farrell and G. E. Langford, *J. Org. Chem.* **42**, 1957 (1977).

[19] T.-Y. Luh and L. M. Stock, *J. Org. Chem.* **43**, 3271 (1978).

[20] For example, [a] L. L. Loeffler, *U.S. Pat.* 1203538 and 1909666, Merck and Co., Inc.; [b] W. A. Gregory, *U.S. Pat.* 710126, E. I. duPont deNemours and Co.

[21a] P. B. Sheulin and A. P. Wolff, *J. Am. Chem. Soc.* **92**, 5291 (1971); [b] H. A. Staab, E. Wehninger and W. Thorwart, *Chem. Ber.* **105**, 2590 (1972); and Refs. therein.

[22] G. Rauscher, T. Clark, D. Poppinger and P. v. R. Schleyer, *Angew. Chem. Int. Ed. Engl.* **17**, 276 (1978).

[23] J. D. Dill, Ph.D. Proposition, Princeton University (1975).

[24] G. Maier, S. Pfriem, U. Schäffer and R. Matusch, *Angew. Chem. Int. Ed. Engl.* **17**, 520 (1978); G. Maier and S. Pfriem, *Ibid.* **17**, 519 (1978).

[25] This, of course, is a preceptually biased number. By another way of counting there are 1168 rings in dodecahedrane; see E. J. Corey and G. A. Peterson, *J. Am. Chem. Soc.* **94**, 460 (1972).

[26] J. W. Barrett and R. P. Linstead, *J. Chem. Soc.* 611 (1936).

[27a] Dr. I. T. Jacobson, University of Lund, was asked to provide me with an update of his work in the area, but did not. [b] Note added in proof:

Professor D. G. Farnum of Michigan State University has informed me that his group is now working towards dodecahedrane via the elaboration and dimerization of well-functionalized bicyclo[3.3.0]octadienes.

[28]P. v. R. Schleyer, *J. Am. Chem. Soc.* **79**, 3292 (1957).

[29]For a review of such isomerization methods see M. A. McKervey, *Chem. Soc. Rev.* **3**, 479 (1974).

[30]E. Ōsawa, K. Aigauri, N. Takaishi, Y. Inamoto, Y. Fujikura, Z. Majerski, P. v. R. Schleyer, E. M. Engler and M. Farcasiu, *J. Am. Chem. Soc.* **99**, 5361 (1977).

[31]N. J. Jones, W. D. Deadman and E. LeGoff, *Tetrahedron Letters* 2087 (1973).

[32]J. L. Fry and P. v. R. Schleyer, unpublished observation.

[33]P. v. R. Schleyer and R. D. Nicholas, *Tetrahedron Letters* 305 (1961).

[34]P. v. R. Schleyer, private communication.

[35]D. M. Muller, *Chem. Weekblad* **59**, 334 (1963).

[36a]I. T. Jacobson, Ph.D. Thesis, University of Lund (1973); [b]I. T. Jacobson, *Acta Chem. Scand.* **21**, 2235 (1967).

[37]R. B. Woodward, T. Fukunaga and R. C. Kelly, *J. Am. Chem. Soc.* **86**, 3162 (1964).

[38]For this and the other synthetic procedures mentioned, details and references for the individual steps should be sought in the parent papers.

[39]For additional discussion and experimental detail see I. T. Jacobson, *Chemica Scripta* **5**, 174 (1974); and Refs. therein.

[40]C. Mercier, P. Soucy, W. Rosen and P. Deslongchamps, *Synth. Comm.* **3**, 161 (1973).

[41]P. Deslongchamps, U. O. Cheriyan, Y. Lambert, J.-C. Mercier, L. Ruest, R. Russo and P. Soucy, *Can. J. Chem.* **56**, 1687 (1978).

[42]P. Deslongchamps, private communication.

[43]L. A. Paquette, *Fortschr. Chem. Forschung* in press.

[44]L. A. Paquette, J. D. Kramer, P. B. Lavrik and M. J. Wyvratt, *J. Org. Chem.* **42**, 503 (1977). See also D. Bosse and A. deMeijere, *Angew Chem.* **86**, 706 (1974).

[45]J. A. Gladysz, *Chem. Tech.* in press.

[46a]L. A. Paquette, W. B. Farnham and S. V. Ley, *J. Am. Chem. Soc.* **97**, 7273 (1975); [b]L. A. Paquette, I. Itoh and W. B. Farnham, *Ibid.* **97**, 7280 (1975); [c]L. A. Paquette, I. Itoh and K. B. Lipkowitz, *J. Org. Chem.* **41**, 3524 (1976).

[47]O. Repič, Ph.D. Dissertation, Harvard University (1976).

[48]L. A. Paquette, S. V. Ley and W. B. Farnham, *J. Am. Chem. Soc.* **96**, 312 (1974).

[49a]D. J. Ehntholt and R. C. Kerber, *J. Orgmet. Chem.* **38**, 139 (1972); [b]L. A. Paquette, S. V. Ley, M. J. Broadhurst, D. Truesdell, J. Fayos and J. Clardy, *Tetrahedron Letters* 2943 (1973).

[50]T. Fukunaga, unpublished work.

[51a]D. McNeil, B. R. Vogt, J. J. Sudol, S. Theodoropulos and E. Hedaya, *J. Am. Chem. Soc.* **96**, 4673 (1974); [b]L. A. Paquette and M. J. Wyvratt, *Ibid.* **96**, 4671 (1974).

[52]L. A. Paquette, M. J. Wyvratt, H. C. Berk and R. E. Moerch, *Ibid.* **100**, 5845 (1978).

[53a]L. A. Paquette, M. J. Wyvratt, O. Schallner, D. F. Schneider, W. J. Begley and R. M. Blankenship, *Ibid.* **98**, 6744 (1976); [b]L. A. Paquette, M. J. Wyvratt, O. Schallner, J. L. Muthard, W. J. Begley, R. M. Blankenship and D. Balogh, submitted for publication; [c]L. A. Paquette, *Chimia* **32**, 295 (1978).

[54]D. Balogh, W. J. Begley, D. Bremner, M. J. Wyvratt and L. A. Paquette, *J. Am. Chem. Soc.* **101**, 749 (1979).

[55]L. A. Paquette, R. A. Snow, J. L. Muthard and T. Cynkowski, *J. Am. Chem. Soc.* **100**, 1601 (1978).

[56]G. A. Christoph, J. L. Muthard, L. A. Paquette, M. C. Böhm and R. Gleiter, *Ibid.* **100**, 7782 (1978).

[57]L. A. Paquette, R. Sobczak and M. Osborn, private communications.

[58a]R. Sidhu, Ph.D. Dissertation, The University of Chicago (1977); [b]P. E. Eaton, R. Sidhu and G. Langford, unpublished work.

[59]P. E. Eaton and U. Chakraborty, *J. Am. Chem. Soc.* **100**, 3634 (1978).

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

[61]P. E. Eaton and T.-C. Chou, unpublished.

[62]P. E. Eaton and R. H. Mueller, *J. Am. Chem. Soc.* **94**, 1014 (1972).

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

[64]For a discussion, see E. J. Corey, *Q. Rev. Chem. Soc.* **25**, 455 (1971).

[65]For a discussion of quinane nomenclature, see footnote 2, Ref. 63.

[66]F. E. Scarbrough and W. Nowacki, *Z. Kristallogr.* **130**, 395 (1974).

[67]P. E. Eaton, G. F. Cooper, R. C. Johnson and R. H. Mueller, *J. Org. Chem.* **37**, 1947 (1972).

[68]P. E. Eaton, G. R. Carlson and J. T. Lee, *Ibid.* **38**, 4071 (1973).

[69]P. E. Eaton, G. R. Carlson and D. A. Cullison, unpublished observations.

[70]P. E. Eaton and D. A. Cullison, unpublished observations.

[71]P. E. Eaton, G. D. Andrews, E.-P. Krebs and A. Kunai, *J. Org. Chem.* **44**, 0000 (1979).

[72a]K. B. Sharpless, R. F. Laver and A. Y. Teranishi, *J. Am. Chem. Soc.* **95**, 6137 (1973); [b]H. J. Reich, J. M. Renga and I. L. Reich, *Ibid.* **97**, 5434 (1975); [c]For additional Refs. and contributions see D. L. J. Clive, *Tetrahedron* **34**, 1049 (1978).

[73]P. E. Eaton W. Bunnelle, in progress.

[74a]J. M. Schulman, T. Venanzi and R. L. Disch, *J. Am. Chem. Soc.* **97**, 5335 (1975). [b]J. M. Schulman and R. L. Disch, *Ibid.* **100**, 5677 (1978).

[75]N. L. Allinger, M. T. Tribble, M. A. Miller and D. W. Wertz, *Ibid.* **93**, 1637 (1971).

[76]N. L. Allinger, *Ibid.* **99**, 8127 (1977).

[77]By subtraction of ΔH_f from the strain-free enthalpy of formation estimated from group equivalents, see Ref. 5.

[78]J. Gasteiger and O. Dammer, *Tetrahedron* **34**, 2939 (1978).

[79]O. Ermer, *Angew. Chem. Int. Ed. Engl.* **16**, 411 (1977).

[80]See also, H. P. Schultz, *J. Org. Chem.* **30**, 1361 (1965).

[81]M. D. Newton and J. M. Schulman, *J. Am. Chem. Soc.* **96**, 17 (1974).

[82]N. L. Allinger, private communication.

[83]But in this regard it is well to remember the difficulties encountered in solvolysis of 10-substituted perhydrotriquinacenes; see, R. C. Bingham and P. v. R. Schleyer, *J. Am. Chem. Soc.* **93**, 3189 (1971).

[84a]P. v. R. Schleyer, R. C. Fort, W. E. Watts, M. B. Comisarow and G. A. Olah, *Ibid.* **86**, 4195 (1964); [b]G. A. Olah and G. Liang, *Ibid.* **95**, 194 (1973).

[85]This is not meant to be the counterpart of the carbanion *stabilized by a 'rolling charge'* of Schultz, see Ref. 80.

[86]For a calculation of number of isomers for various polysubstituted dodecahedranes, see Ref. 74a.

[87]For a review, see J. S. Wishnok, *J. Chem. Educ.* **50**, 780 (1973).

[88]K. Gerzon and D. Kau, *J. Med. Chem.* **10**, 189 (1967).