Dodecahedranes and Allied Spherical Molecules

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Contents

Leo Paquette was born in Worcester, MA, on July 15, 1934, and received his B.S. degree magna cum laude from Holy Cross College. After graduate studies at M.I.T. (Ph.D. 1959), he joined the Upjohn Co. as a Research Associate for 4 years. He joined the faculty of The Ohio State University in 1963 and was appointed Professor in 1969, Kimberly Professor in 1981, and University Distinguished Professor in 1987. Professor Paquette's research interests reside in the synthesis and study of theoretically interesting molecules as well as natural products and the development of new synthetic methodology. His research group is also involved in studies of π-facial selectivity, molecular recognition, and reactivity within organometallic complexes. Professor Paquette's research has been recognized by awards from the Sloan, Guggenheim, and Humboldt Foundations, the Morley Medal (1971), the ACS Award for Creative Work in Synthetic Organic Chemistry (1984), the Arthur C. Cope Scholar Award (1987), and election to the National Academy of Sciences (1984). His nonscientific interests include philately, softball, and gardening.

I. Introduction

The aesthetic quality of the dodecahedron, the largest of the convex polyhedra once believed to constitute the building block of heavenly matter, was fully appreciated in ancient times. The particular fondness of this shape, aptly captured by Plato in his *Timaeus*[1] and considerably later by Kepler in his remarkable booklet *Sexangular Snow*,[2] set the stage for eventual passage more than three centuries later of similar intense interest into the realm of synthetic organic chemistry.[3] The impressively high I_h symmetry (120 identity operations) of its chemical equivalent, dodecahedrane (**1**, $C_{20}H_{20}$),[4]

1

achieved by proper juxtapositioning of 12 five-membered rings involving 20 identical methine units and 30 cis,syn ring junctions, is comparably exquisite in its consequences. For example, each sp^3-hybridized carbon atom attains ideal tetrahedral character, a phenomenon rarely encountered at this level of structural complexity.

The chemist's fascination with **1** is further fueled by the absence of structurally allied substances in nature,[5] the presence of a cavity incapable of solvation, its unusually high structural rigidity, and much more. The molecular transliteration of the dodecahedron into **1** has been touted as "a synthetic challenge of substantial and significant proportions".[6] Others have come to regard the feat as the "Mount Everest of Alicyclic Chemistry".[7]

The purpose of the present review is threefold: (a) to provide the reader with a broad overview of the various ways in which possible approaches to **1** were designed by the many research groups actively pursuing its acquisition (the chemical literature is covered to mid-1988 and consequently extends considerably beyond the time limitations extant in earlier reviews of this field[3b,6,8,9]); (b) to serve as a compilation of the physical, chemical, and pharmacological properties of those dodecahedranes known at present, thereby providing focus for the enormous underlying potential of these molecules in a host of synthetic and physical-organic studies, as well as for the design of possible new therapeutic agents of unusual structure; and (c) to make clear that our knowledge of dodecahedrane chemistry has only begun to evolve and that the odyssey of inquiry into the properties of spherical molecules as a separate structural class has merely been initiated in the 1980s.

II. Properties Predicted for Dodecahedrane

The heat of formation of dodecahedrane has been estimated by several computational methods and the values are seen to differ substantially. Whereas MNDO

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predicts the value to be strongly negative (−46.9 kcal/mol),[10] the data from molecular mechanics suggest the actual value to be much closer to zero (−0.22 kcal/mol).[11] In striking contrast, MINDO/3[12] and MM2 methods[13] skew the value strongly in the positive direction (62.3 and 22.5 kcal/mol, respectively). The most recently determined 6-31G* (SCF) energy places the homodesmic heat of formation of **1** at 4.6 kcal/mol.[14] On the basis of this last value and the ΔH_f(298 K) of unstrained $C_{20}H_{20}$ (−21.8 kcal/mol) as estimated by Franklin's group equivalents,[15] Disch, Schulman, and Sabio have concluded that the strain energy of dodecahedrane is only 26 kcal/mol. Given the wide divergence of results, however, it is imperative that the ΔH_f of **1** be determined experimentally, since in many cases the values represent a sizable extrapolation of the force field.[16]

With the recent advent of MM3, it has proven possible to approximate with high precision the structures of dodecahedrane and of substituted monoseco derivatives, as independently determined crystallographically at low temperatures.[17] In other work, the electronic structure of **1** has been ascertained by two groups, one of which applied the molecular orbital method PRDDO,[18] the other a uniform set of SCF molecular orbital wave functions.[19] The Pitzer study optimized CC and CH distances to 0.001 Å and provided ionization potentials for all valence shells.

Other molecular properties that have been subjected to theoretical scrutiny are its vibrational frequencies,[20] NMR spin–spin coupling constants,[12,21] and charge density.[22] Thus, Ermer predicted that **1** would have only three infrared-active bands at 2898, 1310, and 760 cm^{-1} and eight Raman signals (2899, 2895, 1300, 1166, 1101, 846, 732, and 395 cm^{-1}). From the estimated amount of s character in the dodecahedrane C–H bond, ^{13}C–H coupling constant values of 128.1 and 125.3 Hz were derived. Finally, the lack of any low multipole moments in **1** led Schulman to predict that "dodecahedrane in the vapor phase will resemble a large rare gas molecule in its physical properties". On this basis, it might be expected that **1** should sublime more readily than anticipated for a molecule of its molecular weight.

The possibility of capturing an atom or ion inside the dodecahedrane cage has also been investigated computationally.[12,18] The binding energies for these inclusion compounds, $C_{20}H_{20}X$, give little evidence for being energetically favorable, except perhaps for that involving Be^{2+}.[18] However, steric compression within this cavity is severe, and any stable inclusion compounds will need to be elaborated by proper insertion of the ion or atom at the molecular center prior to installation of the final two or three framework bonds, since penetration of the intact dodecahedrane sphere is energetically not realistic. There exists as yet no precedent for a synthetic maneuver of this type.

III. Retrosynthetic Analysis of Dodecahedrane Construction

Many ways exist in principle to dissect the dodecahedrane molecule for the ultimate purpose of planning its total synthesis. The number of potential routes is large because of the exceptional symmetry of the target; all of the methine units involved in its construction

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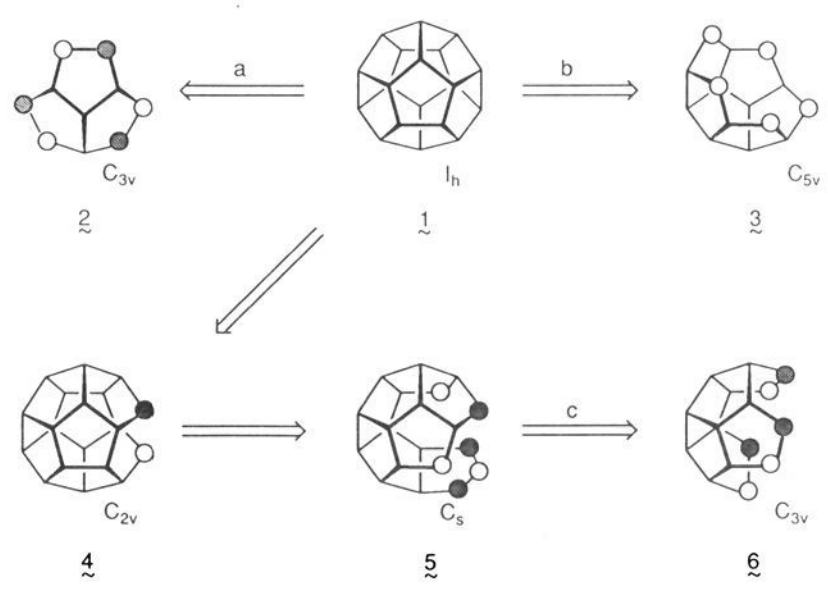

ultimately become identical when the last bond is finally installed! The spherical nature of **1** does demand, however, that every carbon be incorporated into the framework specifically in that stereochemical sense where the small hydrogen substituent finds itself on the molecular exterior, i.e., positioned on the less sterically congested convex surface. Clearly, attention to this stereochemical detail is paramount.

Beyond that, consideration needs to be accorded to the possible advantages or disadvantages associated with a convergent scheme[23] relative to a serial (stepwise) synthesis. As Bertz has noted,[24] topological complexity needs to be examined alongside possible synthetic efficiency when comparing alternate routes.

Scheme 1 illustrates three convergent approaches to **1**.[25] The open circles within the formulas represent the sites where functionality is essential, while the somewhat smaller solid circles serve to indicate the location of potentially useful supplementary functional groups. In each of these examples, one necessarily must deal with the proper conjoining of two segments precisely in that manner which will permit installation of the remaining interconnective bonds. For a triquinane such as **2**, the second structural component is an identical tricyclic C_{10} molecule and the requisite dimerization (path a) must be critically analyzed in the light of relevant steric and entropic factors that need to be overcome. In the case of [5]peristylane, the "capping" process is necessarily restricted to a functionalized cyclopentane ring (path b). Along similar lines, adherence to the C_{3v} nature of C_{16}-hexaquinacene (**6**) requires that its reaction partner be trimethylenemethane or a closely related molecule possessing incipient threefold axial symmetry (path c).

All three of these approaches share in common the need that the first interconnective bond be installed from the more congested surface of each structural segment (see **7** and **8**). Since this contrasteric course

will not normally be followed, ingenious tactics need to be applied to resolve the problem properly. Those developed so far will be discussed in section IV.

Complications of the type discussed above can, a priori, be considered more manageable when only a

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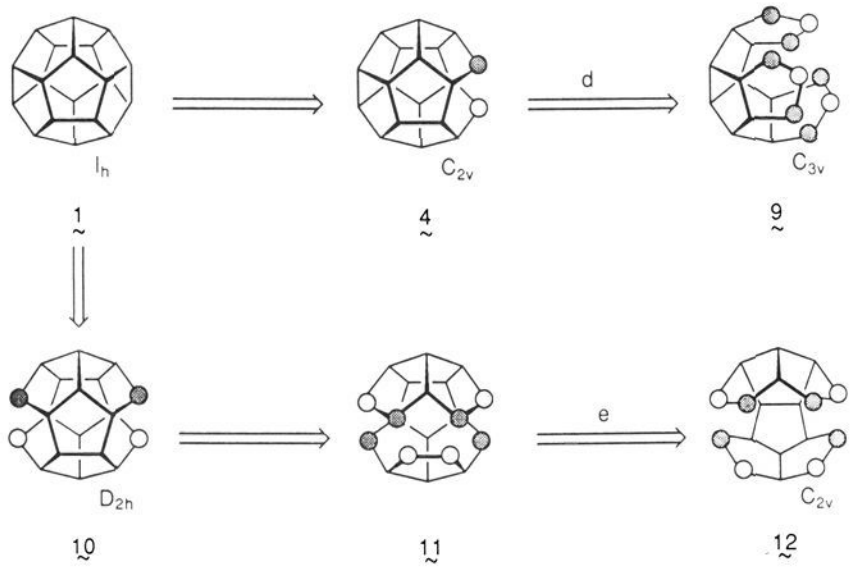

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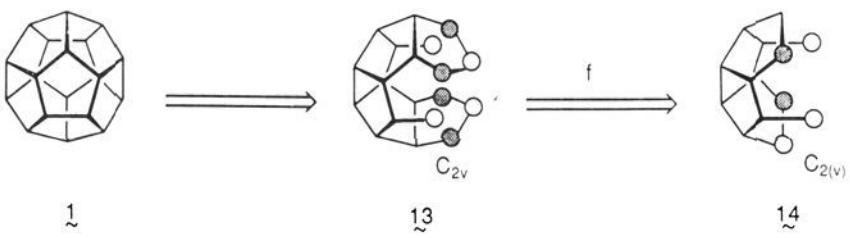


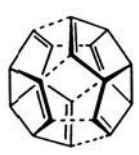
single discrete "CH" unit needs to be introduced as in the case of **9** (Scheme 2, path d). For example, the involvement of a highly oxidized carbon atom (aldehyde, ester) might permit exo protonation of the derived enolate anion under highly controlled conditions with proper resultant spatial orientation of the twentieth framework carbon. If, on the other hand, the molecular dissection proceeds along the course **10** → **11** → **12** (path e), one sees that proper stereochemical fusion of the upper and lower halves has already been achieved if **12** can be assembled. It remains to "stitch together" the four "open seams" in proper sequence to arrive at dodecahedrane.

The strategy just described has important advantages that can be profited from in alternative ways. Scheme 3 illustrates a relevant generic example (path f). The proper preorientation of all 20 carbon atoms in C_{2v}-hexaquinane **13** is clearly apparent. Furthermore, this structural element carries over to the somewhat less advanced intermediate **14**. By design, this access route is more serial than convergent. This distinction need not translate into lessened synthetic efficiency because the important stereochemical issues are capable of being addressed more readily.

IV. Synthetic Strategies Investigated

A. Dimerization Schemes

The concept of triquinacene dimerization (see **15**), developed independently by Woodward[26] and by Jacobson[27] more than 20 years ago, remains to be realized.



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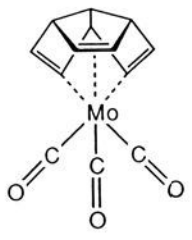

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The overall process, expected to be exothermic by approximately 97 kcal/mol as a result of the formation

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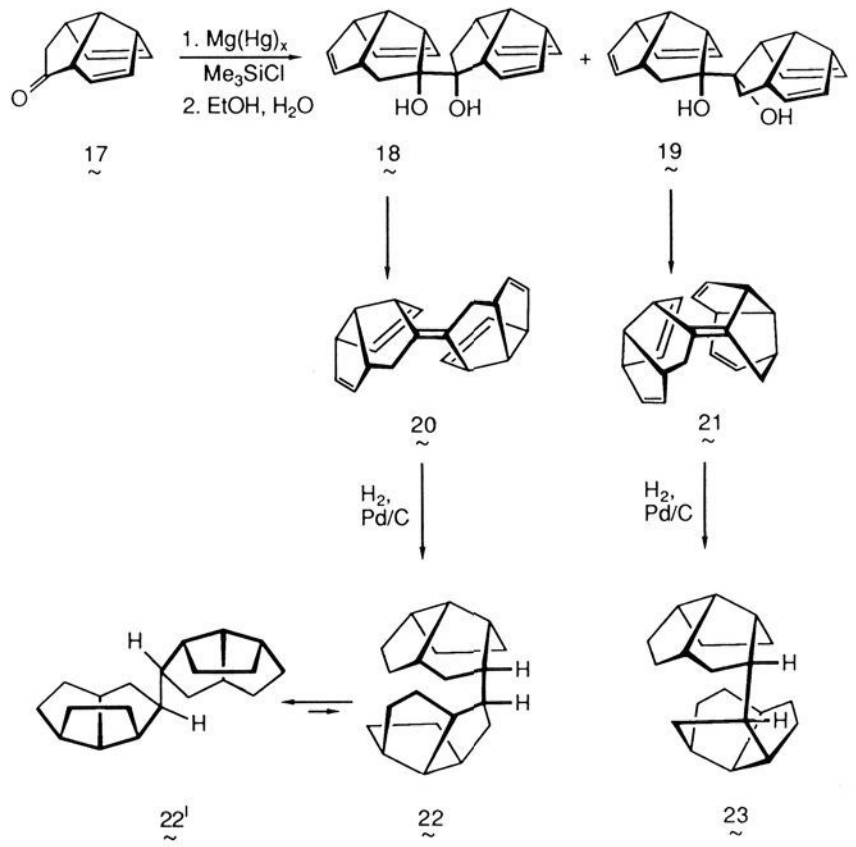
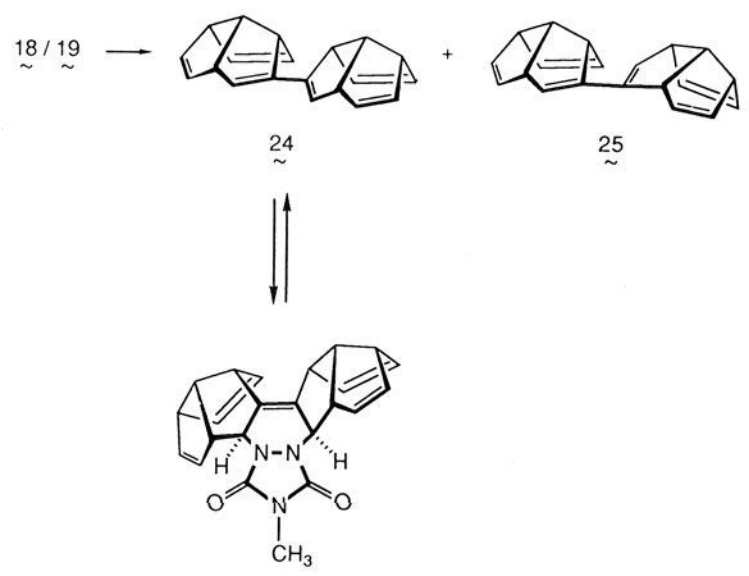


SCHEME 5



of six C–C σ bonds with concurrent loss of six C–C π bonds, has not been achieved thermally, photochemically, or by means of transition-metal catalysis. As alluded to earlier, statistical, entropic, and steric factors combine to disallow the simultaneous rehybridization of 12 trigonal carbons with interconnective bond formation required from the endo direction in the most congested mutual orientation possible. Although triquinacene has subsequently been shown to react with $Mo(CO)_6$ to give **16** and with $(CH_3CN)_3W(CO)_3$ to give the tricarbonyltungsten analogue,[28] the small size of the dodecahedrane cavity effectively precludes the "sandwiching" of such large metal ions within the molecular interior.

Due to the inherent dissymmetry of monosubstituted triquinacenes, dimerization of such derivatives will generate both meso and *dl* products if the monomer is racemic. Indeed, pinacolic reduction of **17** gives rise to approximately equal amounts of **18** and **19** (Scheme 4).[29] Only when bonding between optically pure triquinacenes of the same configuration results can it be guaranteed that formation of the meso dimer will be precluded. Indeed, submission of enantiomerically pure (+)-**17** to the same reductive coupling led exclusively

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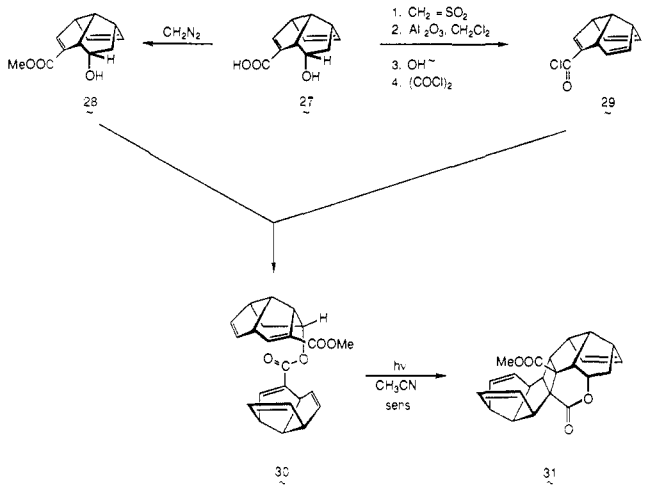

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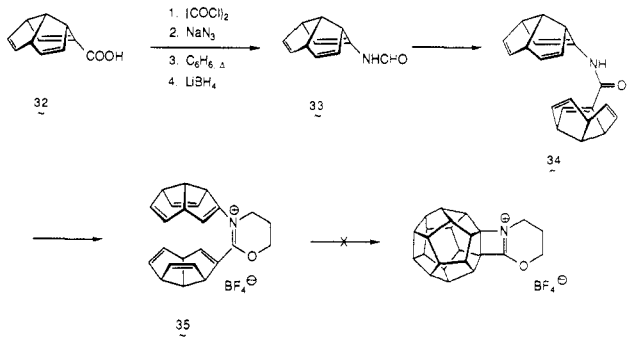

to 18 because of enforced enantiomer recognition. The strong preference for mutual exo bonding is to be noted. Conversion of these diols to their thiocarbonates and subsequent heating with triethyl phosphite provided **20** and **21** stereospecifically. Their individual catalytic hydrogenation delivered *dl*- and *meso*-bivalvane (**22** and **23**), respectively, X-ray crystallographic studies of which have been reported.[30]

Ion the preceding study, diols **18** and **19** were separated by preparative high-pressure chromatography. A nonchromatographic technique has also been devised (Scheme 5).[31] The procedure involves direct dehydration of the **18**/**19** mixture to give **24**/**25** and treatment of these unpurified hexaenes with 0.5 molar equiv of *N*-methyltriazolinedione. Under such conditions, only meso isomer **24** enters into Diels–Alder reaction since only its s-cis conjugated diene conformation allows for simultaneous exo bonding of the dienophile to both termini. Adduct **26**, which separates from solution, can be reconverted to **24** by standard hydrolysis–oxidation methods.

Attempts to effect proper dehydrogenative closure of **22** has not succeeded, perhaps because the conformation **22′** is strongly favored (X-ray analysis).

For purposes of stereochemical control, Woodward and Repic first resolved hydroxy acid **27** and subsequently converted it in part to **28** and in part to **29** (Scheme 6).[32] When these two components (necessarily of identical configuration) were combined in the presence of lithium 2,2,6,6-tetramethylpiperidide, diester **30** was obtained. Upon sensitized irradiation, **30** underwent intramolecular [$2\pi + 2\pi$] cyclization to furnish **31**. Unfortunately, the ester and lactone functionalities

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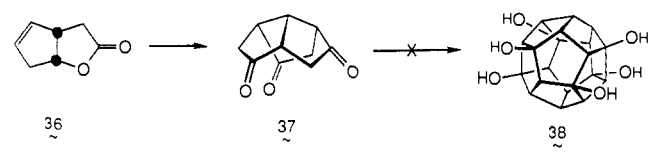
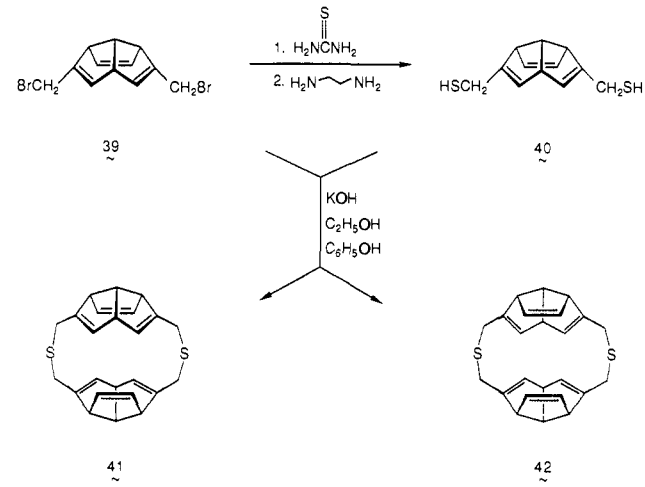


SCHEME 9



in **31** proved to be very resistant to hydroxide ion and to other reagents normally anticipated to cause ring opening.

Deslongchamps and Soucy succeeded in resolving triquinacene-2-carboxylic acid (**32**) and transforming this intermediate into the (+)-2-formamido derivative (**33**, Scheme 7).[33] Condensation of **33** with the acid chloride of (+)-**32** gave the secondary amide **34**. From this point, the cyclic imidate salt **35** was prepared, but cyclization to the dodecahedrane nucleus was not successfully implemented.

In yet a different assault on the problem, Serratosa has found it possible to prepare the known[34,35] C_3-triketone **37** in an enantioselective manner starting from optically pure lactone **36** (Scheme 8).[36] This recent achievement represents the first time that the absolute configuration of an optically active perhydrotriquinacene has been established by chemical intercorrelation. Despite access to **37**, however, its multiple aldol condensation under equilibrating conditions has not yet yielded the dodecahedrane stabilomer **38**.

Coupling of the dibromide **39** with dimercaptan **40** results in formation of a 3.5:1 mixture of the *anti*- and *syn*-triquinacenophanes **41** and **42** (Scheme 9).[37] These isomers have been separated chromatographically and their identities established by X-ray structure determination of **41**. Although cyclization of a phane such as **41** appears feasible on the basis of molecular model calculations, the overall process has not been observed.[38]

B. From Various Polyquinane Fragments

The foundation of the Eaton approach to dodecahedrane was the concept that a properly functionalized C_{15}-hexaquinane could be capped by a cyclopentane subunit.[39] As matters have turned out, it proved to be a relatively easy matter to craft from diketone **43** the tetracyclic intermediate **44** and subsequently the triply oxygenated [5]peristylane **45** (Scheme 10). Exposure of **45** to base under mild conditions induces the β-

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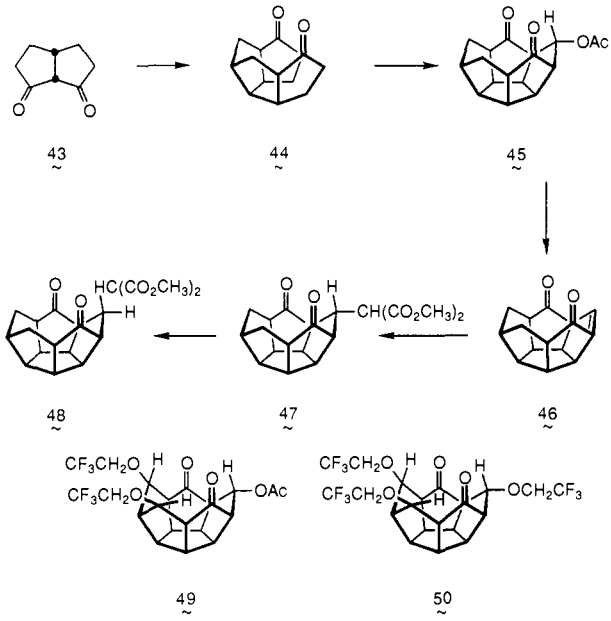
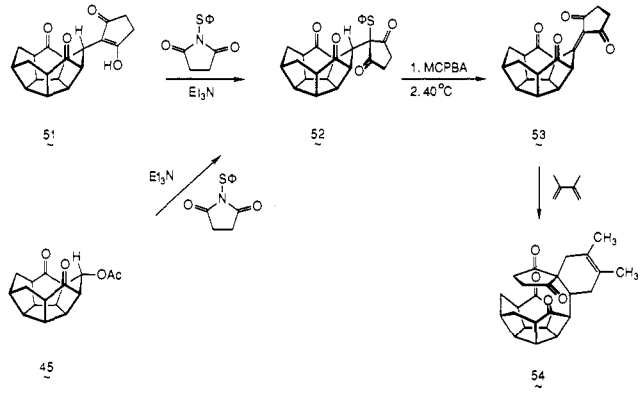


SCHEME 11



elimination of acetate ion and formation of the reactive peristylenone **46**.[40] In the presence of malonic ester, readdition materializes to give **47**. A series of three steps allows the desired endo stereoisomer to be obtained. Additionally, sequential addition–elimination reactions performed on **45** have been found to provide synthetic entry to **49** and **50**, compounds functionalized at all five methylene positions of the parent [5]peristylane hydrocarbon.

Following the development of a reliable method for the synthesis of 2-alkylidene-1,3-cyclopentanediones,[41] the protocol was applied to both **45** and **51** (Scheme 11). Once **53** was in hand, Diels–Alder addition of 2,3-dimethylbutadiene to its electron-deficient double bond was deployed to deliver **54**.[42] Although the spiro-linked five-membered ring now finds itself correctly oriented vis-ä-vis the [5]peristylane base, additional bond formation within **54** or more densely functionalized derivatives of this molecule have not been reported.

When unstable 9,10-dihydrofulvalene (**55**) is allowed to react with dimethyl acetylenedicarboxylate, domino Diels–Alder reaction occurs to give an easily separable mixture of diesters **56** and **57**.[43,44] The diacid derived from **56** has been transformed in several steps to C_{16}-hexaquinacene (**61**, Scheme 12).[45] The precursor enedione **60**, an X-ray crystal structure analysis of which is documented,[46] has been converted to a series of

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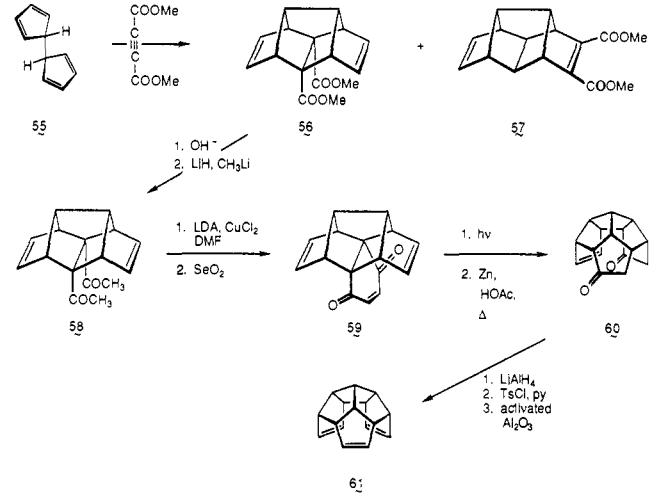

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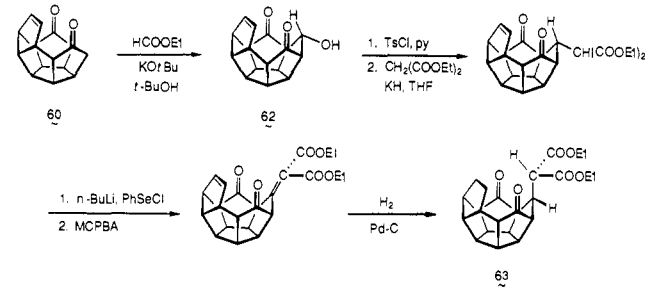
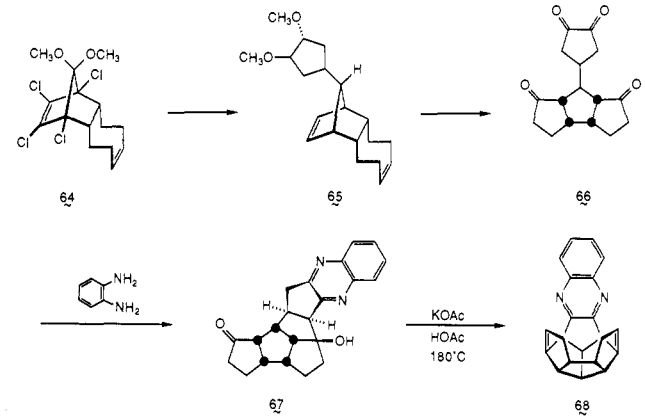


SCHEME 14



C_{17}-heptaquinane derivatives via the alcohol **62** (Scheme 13).[47] Like the Eaton study described above, complications arose during attempts to transform **63** into a dodecahedrane.

In a vastly different approach to C_{16}-hexaquinanes, Eaton prepared the Diels–Alder adduct **64** and transformed it via **65** to tetraketone **66** (Scheme 14).[48] Trapping of this intermediate with *o*-phenylenediamine resulted not only in quinoxaline formation but also in unexpected elaboration of an additional C–C bond as seen in **67**. However, when **67** was heated with potassium acetate in acetic acid at 180 °C, retrograde cleavage preceded twofold dehydration to deliver ultimately the heterocycle **68**. Although this end product is most structurally attractive, it did not prove serviceable as a dodecahedrane precursor.

While working in our group, Hales was able to demonstrate that sequential reduction and hydrolysis of **56** leads efficiently to *endo,endo*-diacid **69**.[49] Arndt–Eistert

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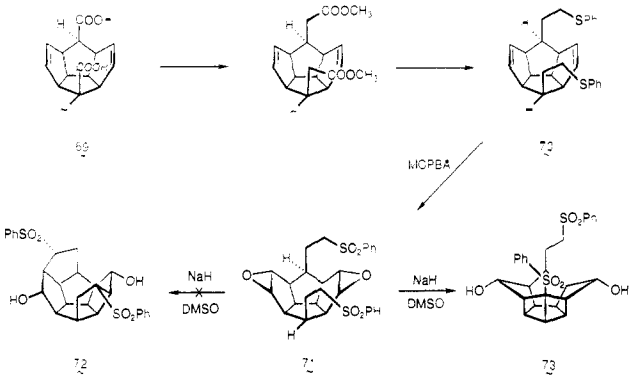

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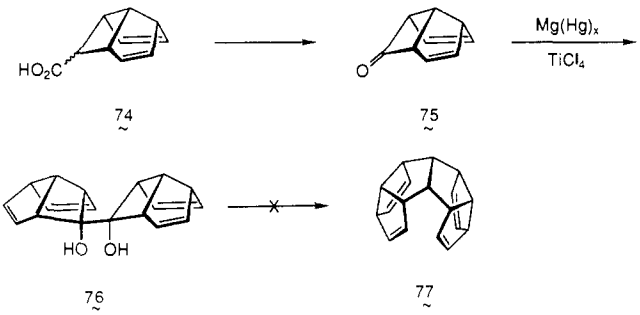


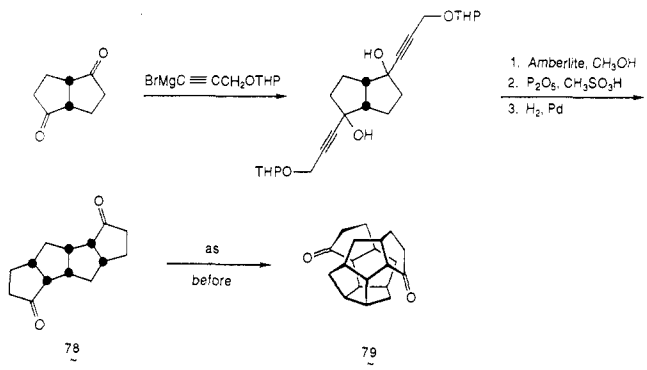
homologation, conventional elaboration of bis(thioether) **70**, and exhaustive oxidation were utilized to arrive at **71** (Scheme 15). The plan was to deploy the anion of **71** in a manner that would lead to **72**. However, the principal product proved to be the unwanted **73**. Other epoxides of related structural type have likewise resisted comparable intramolecular cyclization, presumably because of complications stemming from structurally enforced misalignment of the nucleophilic center relative to the proper oxirane C–O bond.[34]

In an attempted extrapolation of the synthesis of bicyclo[3.3.0]oct-1(5)-ene from cyclobutanone,[50] Ternansky oxidatively decarboxylated nortriquinacenecarboxylic acid **74**[51,52] and reductively coupled the resulting ketone (**75**) to diol **76** in low yield (Scheme 16).[53] Notwithstanding this success, his efforts to transform **76** into C_{18}-hexaquinacene (**77**) were to no avail.

On the other hand, McKervey and co-workers have succeeded admirably at preparing the C_{20}-hexaquinane **79** through deployment of an iterative approach and only four reagents (Scheme 17).[54] The all-cis stereochemistry that materializes in **78** and **79** derives from steric control of the approach of hydrogen to the double bonds in the immediate cyclopentenone precursors. Proof of the stereochemical features of **79** was gained via single-crystal X-ray diffraction analysis. By means of this technique, the diketone was shown to possess advantages and disadvantages for dodecahedrane synthesis. While the two carbonyl groups are sufficiently proximate to the relevant transannular methylene groups, severe intramolecular overcrowding forces the molecule to adopt an "opened out" conformation that is both distorted and twisted. Suffice it to say that **79** has to this point in time failed to provide any 1.

Baldwin's imaginative route to the C_{19}-hexaquinane **82** began with the known tetracyclic triketone **80** (Scheme 18).[55] Following selective protection of the less hindered carbonyl group and cyclopentenone annulation of the two remaining reactive centers, **81** was obtained.[56] For reasons of steric congestion, only one of the double bonds in **81** could be induced to undergo hydrogenation. The exceptional proclivity of **82** for intramolecular transannular Michael addition as in **83** precluded it from serving as a potential dodecahedrane precursor.

SCHEME 17



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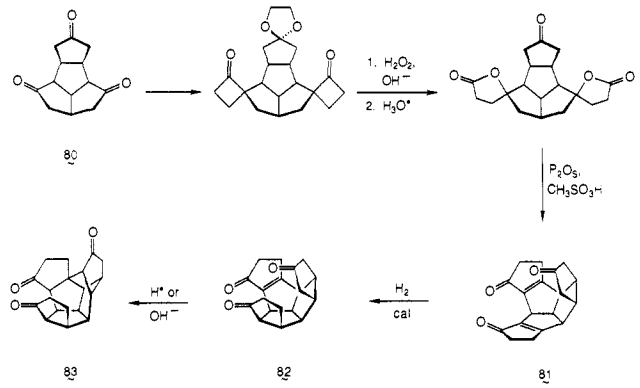

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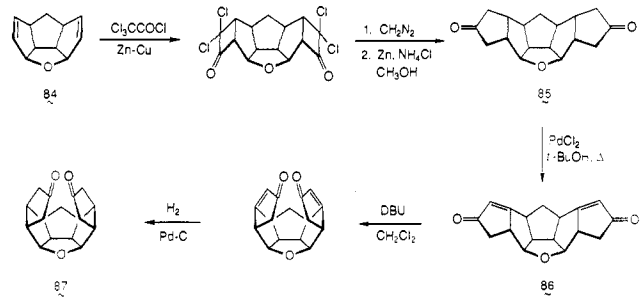

A somewhat more recent model study by Mehta has demonstrated that it is possible to elaborate the C_{12}-oxatetraquinane **84** into the spherical oxahexaquinanedione **87** (Scheme 19).[57] Some of the more notable transformations successfully implemented here include the smooth twofold oxidation of **85** upon exposure to palladium dichloride and air and the efficient epimerization in both sectors of the molecule when **86** is treated with DBU. The ensuing catalytic hydrogenation is limited to the convex surface and consequently conveys to **87** the proper topology for achieving close intramolecular contacts.

C. The Secododecahedrane Cyclization Route

By applying a cross-corner oxygenation scheme to **56**, Paquette was able to take subsequent advantage of the

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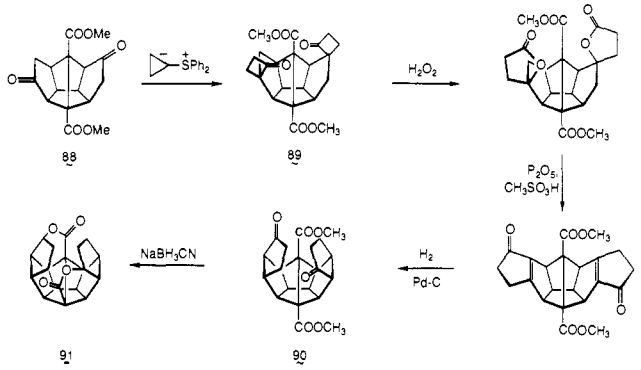
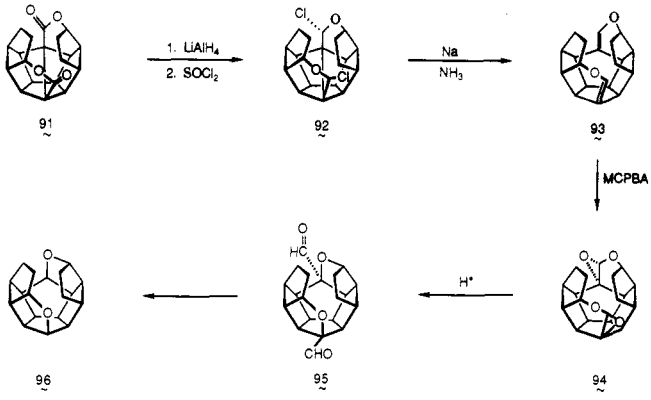


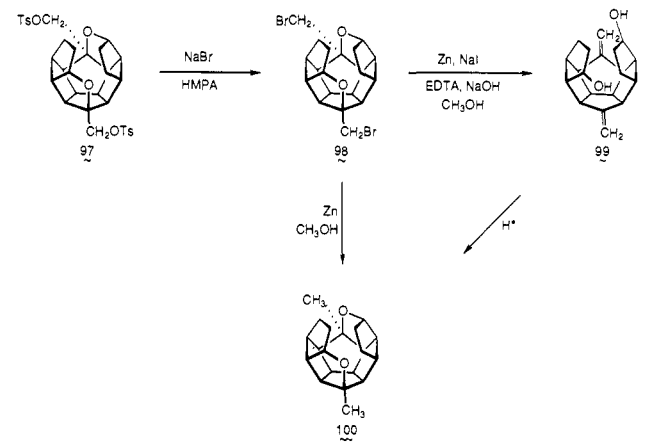
SCHEME 21



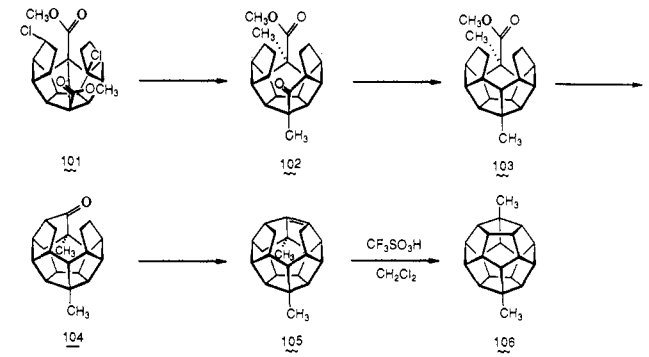
C_2 symmetry of diketo diester **88**.[58] In essence, the task of elaborating dodecahedrane was thereby reduced to one of selectively manipulating only two different symmetry-related functional groups, ketone and ester. In the next step, six more carbon atoms were added to the preexisting C_{14} frame (**89**, Scheme 20), thereby necessitating that no future reagent adventitiously exceed the targeted C_{20} level, at least formally.[59] As usual, catalytic hydrogenation proceeded stereospecifically to project the cyclopentanone rings in the inner regions of the developing sphere. The highly folded topography of **90** was confirmed by sodium cyanoborohydride reduction to furnish dilactone **91**. The five synthetic steps in Scheme 20 not only preserve the C_2 character of the starting material but deliver as well a C_{20} product that can be viewed as possessing a single functional group.

It should be recognized that dilactone **91** already possesses 12 syn-cis-fused methine hydrogens, more than half the total required by 1. In order to establish that molecules having spherical contours such as are present in **91** are amenable to conventional synthetic transformations, its conversion to the C_2-dioxa-C_{20}-octaquinanes **96** and **100** was next successfully undertaken (Schemes 21 and 22).[60,61] Although the dilactol resulting from kinetically controlled hydride reduction of **91** was the endo,endo isomer, its dissolution in thionyl chloride resulted in quantitative conversion to the highly relative chloro ether **92**. Reductive cleavage of the central bond in this intermediate was effected with sodium in liquid ammonia. The eventual formation of dialdehyde **95** is regarded to be the likely result of oxirane ring opening in **94** toward the tertiary cationic center with concurrent or subsequent 1,2-oxygen migration. Although decarbonylation of **95** proved troublesome, success was achieved upon irradiation of an intimate mixture of the dialdehyde, acetophenone,

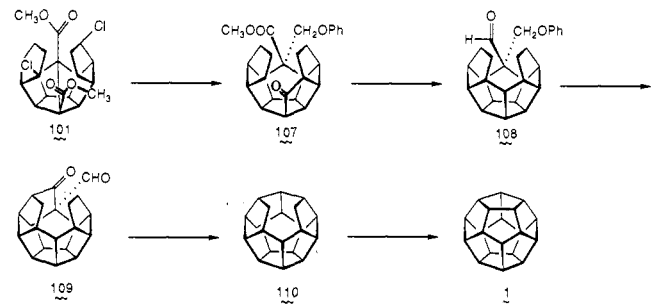
SCHEME 22



SCHEME 23



SCHEME 24

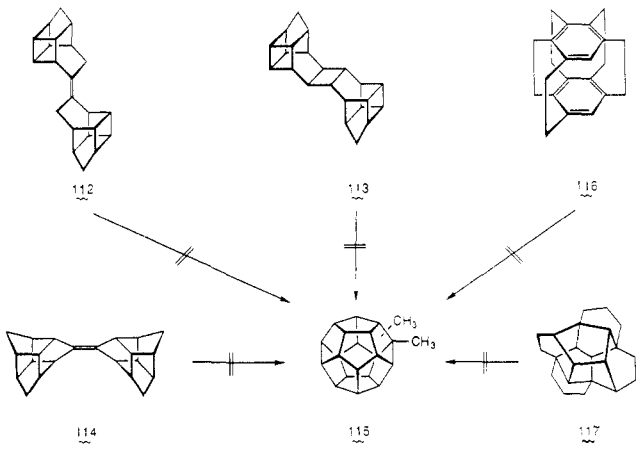


benzyl mercaptan, and ethyl benzoate at 140 °C under argon for several hours.

Replacement of the CHO groups in **95** by methyl substituents also had to be accomplished indirectly. Although dibromide **98** could be reduced to give **100**, it proved twice as efficient to proceed via diene diol **99** and to take advantage of the extreme sensitivity of its proximate functional groups to electrophilic reagents.

Although the chemical reactivity of **91** proved to be highly intricate,[58,62] the pivotal conversion to dichloro diester **101** was ultimately accomplished efficiently. Under the influence of lithium in liquid ammonia, **101** can be made to undergo either dimethylation to give **102** (Scheme 23)[63] or controlled monoalkylation to give **107** (Scheme 24).[64] With arrival at **102**, photochemical activation was found to be appropriate for inducing further ring closure regiospecifically in the front sector of the molecule since the ester group was unresponsive to the light. The further knitting of **103** made mandatory its reduction to the aldehyde. Two photochemical steps followed, though not sequentially, to deliver the secododecahedrene **105**.[65] Under strongly acidic

SCHEME 25



conditions, **105** underwent isomerization to **106** with installation of the final framework bond. The unexpected occurrence of a 1,2-methyl migration was substantiated by ^1H NMR, ^{13}C NMR, mass spectroscopy, and X-ray crystallography.[65a,66]

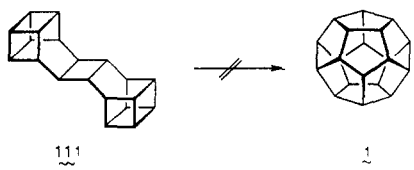
As matters worked out, **107** could be similarly crafted into **108**. This intermediate was transformed into **109** by sequential photocyclization, Birch reduction, acid hydrolysis, and pyridinium chlorochromate oxidation. Although **109** could be decarbonylated prior to subsequent light-induced ring closure,[67] it has proven substantially more expedient to irradiate **109** directly.[68] The necessary dehydrogenation of **110** to give **1** was initially accomplished with H_2-presaturated 10% palladium on carbon at 250 °C.[67] More recently, better catalyst systems have been developed for this purpose.[68,69]

It is important to recognize that the successful preparations of **1** and **106** just described were intimately linked to the utilization of three photochemical steps at key points late in the syntheses. This is a direct consequence of the heightened level of nonbonded steric interaction present in these molecules, which increases steadily in the progression from triseco to diseco to monoseco status.[70] The sizable levels of energy available in light-induced reactions enable these otherwise formidable barriers to be crossed.

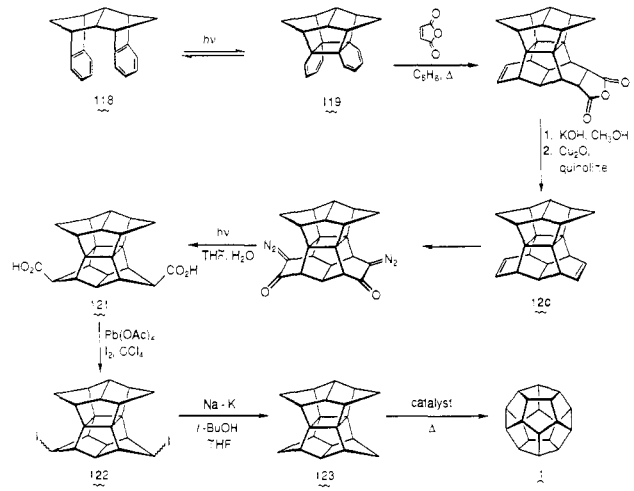
D. Isomerization Pathways

Several attempts have been made to adapt the earlier work of Schleyer in the adamantane field[71] to the possible elaboration of dodecahedranes by Lewis acid promoted isomerization. This thrust was supported additionally by extensive graph theoretical and molecular mechanics calculations showing dodecahedrane to be the $C_{20}H_{20}$ stabilomer and by a wide margin.[72] However, no transposition of this type (other than the **105** → **106** process) was documented prior to 1987.

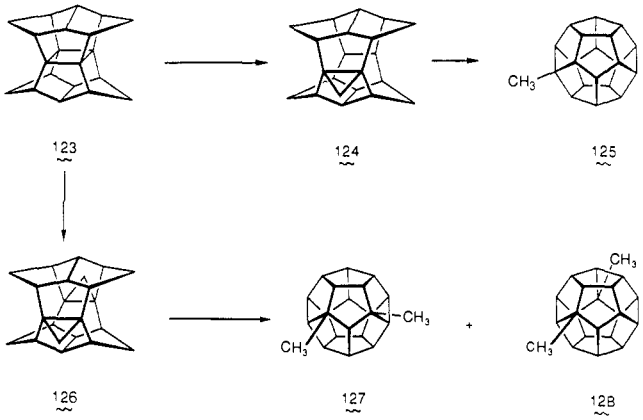
Perhaps the earliest disappointment is that reported by LeGoff.[73] Despite the potential release of 178 kcal/mol of strain energy, the basketene dimer **111** has



SCHEME 26



SCHEME 27

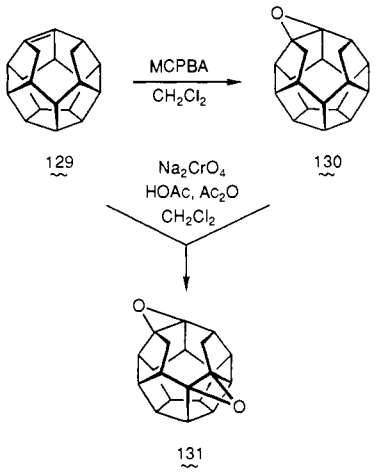


not yielded to conversion to **1**. More recent efforts by Grubmüller[7] have similarly come to naught (Scheme 25). In the belief that latent methyl groups might provide greater useful driving force to the desired isomerizations, $C_{22}H_{24}$ hydrocarbons **112**–**114** were examined in the presence of different catalysts. No evidence could be garnered for the conversion to **115**. Schleyer's efforts to engage **116** and **117** have similarly not generated the desired result.[74]

The most notable success in this area has come from Prinzbach's laboratory, where advantage was taken of the availability of pagodane (**123**, Scheme 26).[75] Synthetic entry to this undecacyclic $C_{20}H_{20}$ hydrocarbon was gained imaginatively from **118**, an intermediate readily available from isodrin.[76] [6 + 6] photocycloaddition within **118** delivers **119**, which adds 1 equiv of maleic anhydride stereospecifically. Once diene **120** becomes available, ring contraction of the two olefinic bridges is accomplished via **121** and **122**. In gas-phase isomerization experiments conducted in a flow apparatus over various catalysts at 250–450 °C, pagodane was converted to complex, multicomponent mixtures. Dodecahedrane was one of these and its relative abundance ran the gamut from 0.1% to an optimized 8%.[77]

In a further development, pagodane (**123**) has been transformed into the cyclopropane derivatives **124** and **126** (Scheme 27).[77] Heating of these intermediates with 10% palladium on charcoal under an atmosphere of hydrogen has provided product mixtures in which the previously known methyl- (**125**)[64a] and dimethyldodecahedranes **127** and **128**[69] were identified.

SCHEME 28



V. Actual Properties of Dodecahedrane

As demanded by the very high symmetry of 1, its ^1H and ^{13}C NMR spectra (in $CDCl_3$) are characterized by singlets, the former at δ 3.38 and the latter at δ 66.93.[67] The relatively low-field chemical shift of the dodecahedryl protons is thought to arise as the direct result of strong deshielding by the three adjoining, fully eclipsed C–H bonds. The impact of neighboring C–C bonds is less dramatic, as reflected in the chemical shift of those protons flanking the methyl group in **125** (δ 2.92)[64a] and more extensively methylated dodecahedranes. In 1, the experimental ^{13}C–H coupling constant is 134.9 Hz, somewhat larger than the predicted values.

The vibrational frequencies of 1 agree fully with the existence of a highly rigid network of interlinked methine units. Only three infrared-active bands (2945, 1298, 728 cm^{-1}) and eight Raman frequencies (2954, 2938, 1324, 1164, 1092, 840, 676, 480 cm^{-1}) are observed.

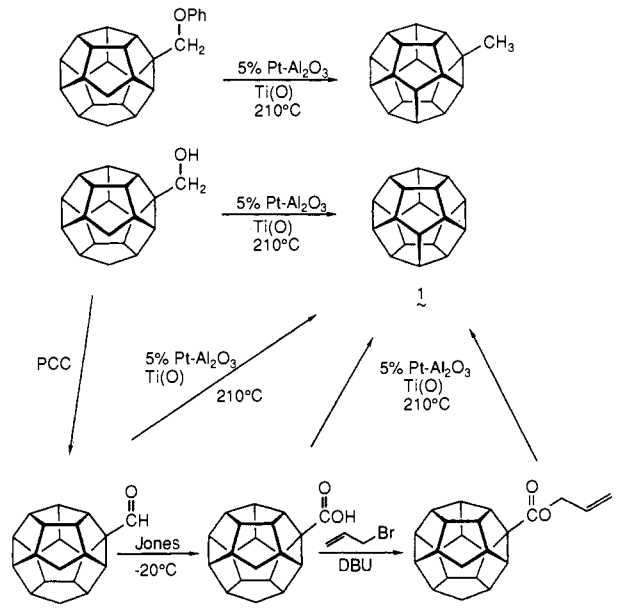
The melting point of dodecahedrane is unusually high (430 ± 10 °C) for its molecular weight. The relatively low precision is the result of the quite rapid rate of heating needed to circumvent the marked propensity for sublimation in this temperature range. The density of 1 (1.448 g/cm^3) is higher than that of **106** (1.412 g/cm^3), the good lattice packing likely contributing in part to the melting behavior.

Dodecahedrane is optically isotropic and crystallizes from benzene as face-centered cubic crystals. Although it had been widely anticipated that 1 would not crystallize in any preferred orientation,[78] this is not the case. Rather, dodecahedrane takes advantage of the highest crystallographic symmetry available to it, thereby allowing successful X-ray crystallographic analysis.[79] The intracavity distance is 4.310–4.317 Å.[80]

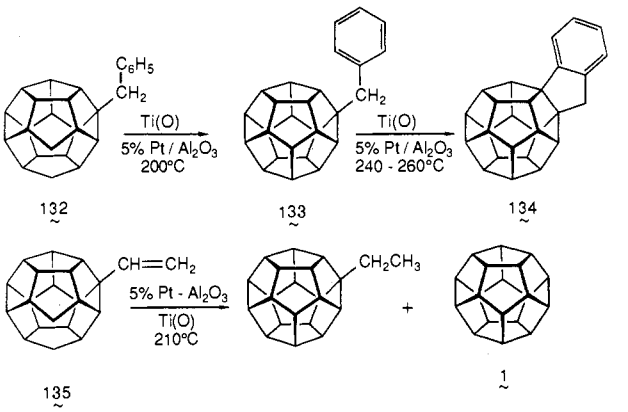
The mass spectrum for dodecahedrane is also characterized by a single line due to the molecular ion. This absence of measurable fragmentation peaks is characteristic of dodecahedranes in general and signals a kinetic impedance to ejecting methine units in stepwise fashion from the structurally stable spherical shape. Monosecododecahedranes, on the other hand, exhibit fragmentation patterns characteristic of other hydrocarbons.

The pronounced internal stress present in monosecododecahedranes has been quantified by X-ray crystallographic analysis.[17,66] A chemical ramification of this high-level nonbonded steric interaction is the remarkable ease with which **129** and **130** experience chromate oxidation at fully saturated carbon to generate the C_2-symmetric diepoxide **131** (Scheme 28).[81]

SCHEME 29



SCHEME 30

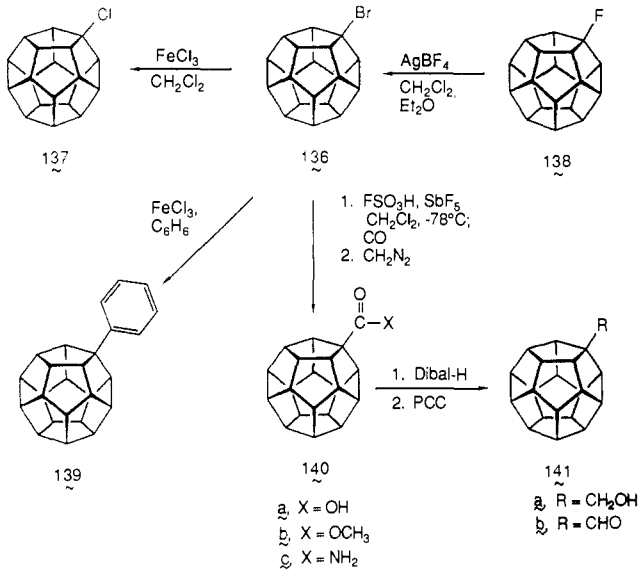


VI. Monofunctionalization of the Dodecahedrane Framework

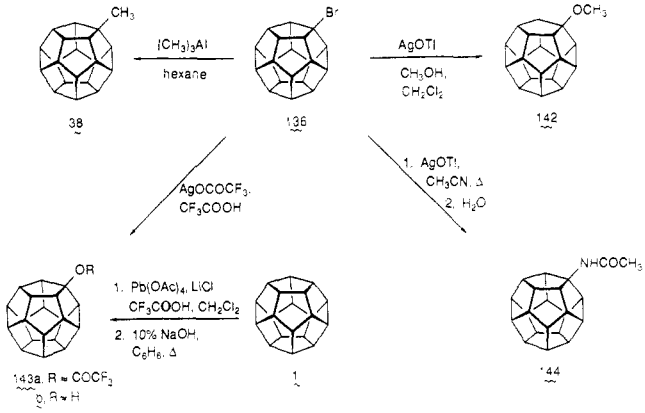
Recent improvements in Paquette's synthesis of dodecahedrane[68] now make possible its acquisition in lots of 25 mg or so. These developments have made possible a systematic investigation of its chemical reactivity. Since the dehydrogenative process that is deployed to install the final carbon–carbon bond is, in general, rather intolerant of heteroatomic pendant groups (Scheme 29), the ability to gain access to substituted dodecahedranes by chemical functionalization of 1 holds considerable importance. Alkyl and aralkyl groups are not capable of undergoing comparable hydrogenolytic cleavage and can be utilized in synthetically useful ways as shown in Scheme 30. In this context, the stepwise conversion of benzylsecododecahedrane **132** to benzyldodecahedrane (**133**) and ultimately to the fused indano derivative **134** is particularly notable.[69]

When 1 is stirred in liquid bromine at room temperature, monobromide **136** is produced quantitatively.[68,82] With **136** in hand, conversion to the chloride and fluoride could be effected readily (Scheme 31). Its exposure to ferric chloride in benzene solution leads

SCHEME 31



SCHEME 32



conveniently to the phenyl derivative (**139**). Dissolution of the bromide in magic acid and subsequent exposure to carbon monoxide at −78 °C gave the carboxylic acid (**140a**) and subsequently the other important substrates **140b**–**141b**.

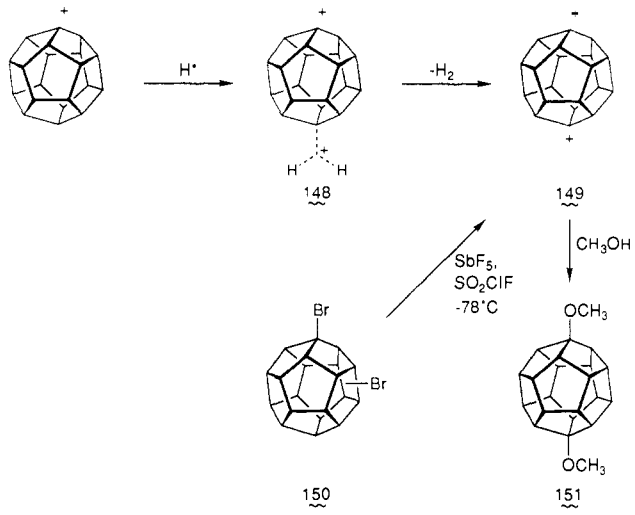
Still more varied functionalization has been realized by other avenues. Particular note should be taken of the ease with which the formation of oxygenated (**142**, **143**) and aminated derivatives (**144**) can be achieved (Scheme 32).

The availability of these functionalized dodecahedranes has made possible a comprehensive analysis of general trends in their ^1H and ^{13}C NMR spectra.[68] These data have significance since no closely comparable prototypes exist. Furthermore, since the pendant groups do little to alter the 0° dihedral angle between vicinal protons, the interrelationship between the several types of all-eclipsed protons and their chemical shifts is of fundamental significance.

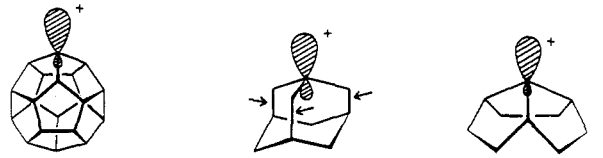
VII. The Dodecahedryl Cation and 1,16-Dodecahedryl Dication

Many of the reaction conditions described in the preceding section suggest that transient generation and trapping of the dodecahedryl cation has been efficiently exploited. When careful consideration is given to the unique geometry and rigid conformational features of 1, it is apparent that ideal sp^3 hybridization is virtually

SCHEME 33



required at every carbon atom. Consequently, any framework position cannot be expected to accommodate planarity readily as positive charge begins to develop there. Moreover, as seen in **145**, the dodecahedryl



145 146 147

cation is clearly devoid of the normal stabilizing effect of alkyl substitution, since no C–C or C–H bond can be oriented trans to the vacant, strongly directed orbital. These geometric constraints are not present in the 1-adamantyl cation (**146**), but surface again in the 10-perhydrotriquinacenyl cation (**147**). Unlike the high solvolytic reactivity of *tert*-adamantyl derivatives,[83] the tosylate precursor of **147** experiences a 10^{19}-fold solvolytic rate retardation.[84]

The hypothetical involvement of **145** has been confirmed by its generation and spectroscopic characterization under long-lived stable-ion conditions.[85] Careful dissolution of **137** in cold (−78 °C) SO_2ClF containing SbF_5 gave rise to a species characterized by three proton absorptions [δ 4.64 (br, 3 H), 3.05 (br, 7 H), 2.59 (br, 9 H)] and six carbon signals [δ 363.9 (s), 81.1 (d), 64.4 (d), 64.1 (d), 63.0 (d), 60.9 (d)]. Although **145** is responsible for these observations, the cation was found to be static and incapable of 1,2-hydride shifts that would achieve full equivalency and 20-fold degeneracy to its carbon and hydrogen atoms. The barrier for operation of this degenerate rearrangement, despite excellent alignment of the C–H bonds, has been estimated to be 15 kcal/mol. This value is substantially in excess of that for related processes in cyclopentyl[86] and bicyclo[3.3.0]octyl cations.[87]

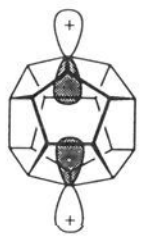
On standing or warming, solutions of **145** are slowly and irreversibly transformed into the unique, highly electron-deficient 1,16-dication **149**, the formation of which has been rationalized in terms of protolytic ionization of the transannular C–H bond as shown in hypercarbon intermediate **148** (Scheme 33).[85] For **149**, only two ^1H [δ 4.74 (br, 6 H), 3.23 (br, 12 H)] and three ^{13}C absorptions [δ 379.2 (s), 78.8 (d), 59.8 (d)] are seen,

in agreement with its D_{3d} symmetry.

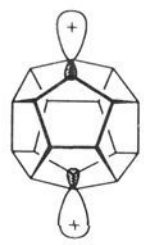
Dication **149** is stable at 0 °C for several days. Its structure was proven by independent generation via ionization of the dibromide mixture **150** and by quenching in methanol to give the dimethoxy derivative **151**. The transformation of **150** into **149** allows for ionization to occur at the other available sites. However, only **149** is seen and it is also a static species. Consequently, 1,2-hydride shifts must occur readily within the dication, but these migrations remain slow on the NMR time scale. For electrostatic reasons, the positive charges want to be as mutually distal as possible.

The ready preparation of **149** paves the way for effective regioselective functionalization of the dodecahedrane framework (Scheme 34). The problem of enumerating the many possible isomeric polysubstituted dodecahedranes has been addressed by three research groups,[22,64a,88] all of which have made recourse directly or indirectly to Polya's theorem.[89]

According to semiempirical SCF–MO calculations, the dodecahedrane skeleton is incapable of accommodating a planar cation geometry (see **154**). The situation is still more acute in the 1,16-dication (see **155**),[85b] which is considered to be the first true sp^3-hybridized carbocation. The static nature of both species has been computationally shown to be due to unfavorable bending in the bridged transition state for intramolecular 1,2-hydride shifting on the convex surface of the sphere as in **156**.



154



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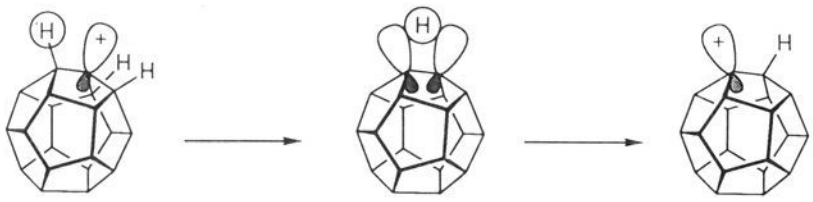
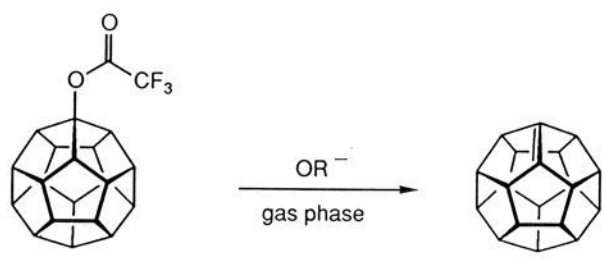


156

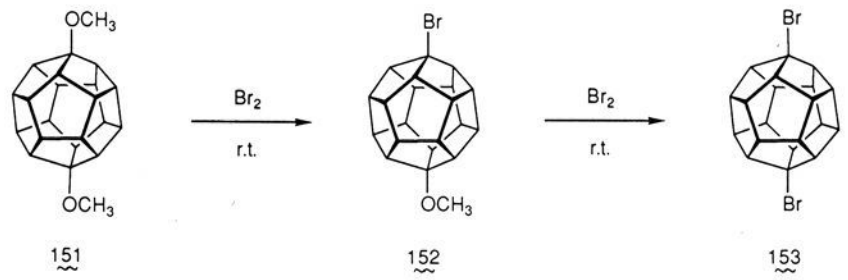
VIII. Dodecahedrene

Dodecahedrene (**157**) holds interest as a highly strained olefin since its olefinic carbons should exhibit a high degree of pyramidalization and probably near-tetrahedral geometry. Although **157** has not yet yielded to preparative-scale synthesis, its generation has been inferred from gas-phase ion–molecule reactions performed on **143a** in a trapped ion cell of a mass spectrometer.[90] The requisite β-elimination was achieved under ion cyclotron resonance conditions in the presence of bases such as hydroxide and methoxide ions. The latter reaction is calculated to be exothermic by 41.5 kcal/mol. Since comparable elimination does not occur with ethoxide ion (exothermicity of 38.5 kcal/mol), the amount of extra energy necessary to produce **157** appears to have boundary limits of 40 ± 3 kcal/mol. Comparison of this heat of hydrogenation value with those of other distorted olefins indicates that the olefinic carbon atoms of **157** have nearly tetrahedral character.



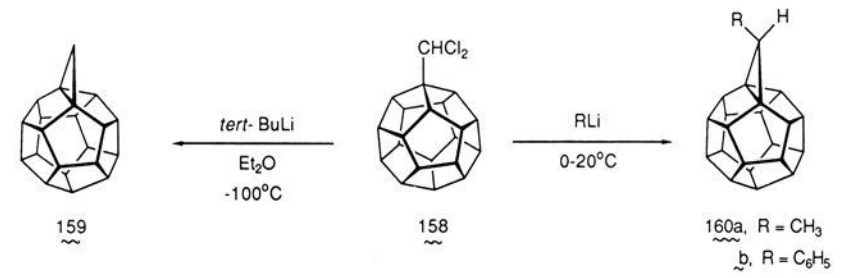
143a 157

SCHEME 34



151 152 153

SCHEME 35



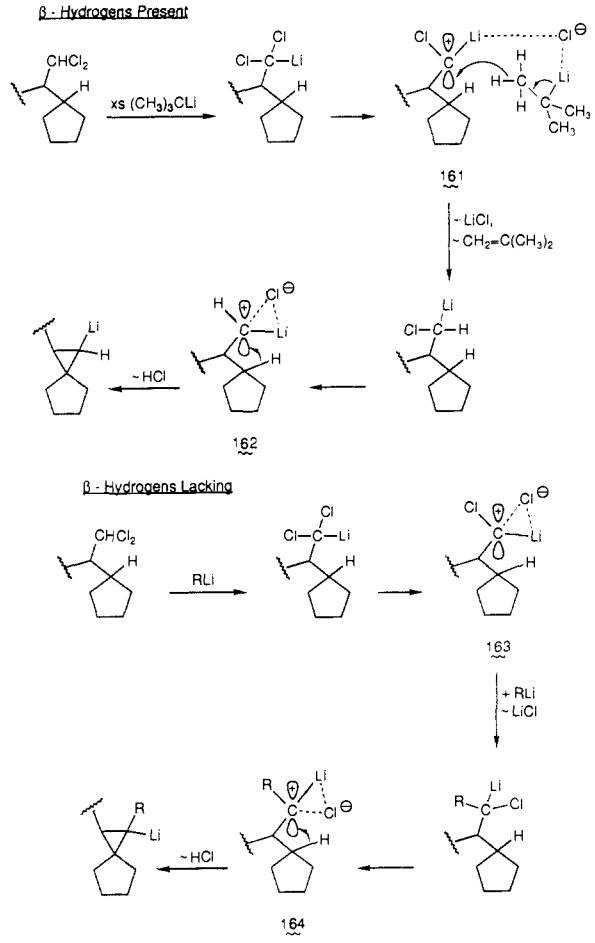
159 158 160a, R = CH_3 b, R = C_6H_5

IX. Cyclopropadodecahedranes

Fusion of a cyclopropane ring to the dodecahedrane framework has been achieved in two steps from the parent hydrocarbon.[91] Reaction with dichlorocarbene under phase-transfer conditions delivers the (dichloromethyl) derivative **158**, which is capable of rapid intramolecular C–H insertion when treated with *tert*-butyllithium in ether at −100 °C (Scheme 35). Additionally, excess methyl- or phenyllithium acts on **158** in ether solution at 0 °C to give **160a** and **160b**. When examined by X-ray crystallography, **160b** was found to possess a three-membered ring free of distortion. On the other hand, those pentagonal rings of the dodecahedryl subunit in the immediate vicinity of the cyclopropane are nonplanar and clearly take up essentially all of the strain.

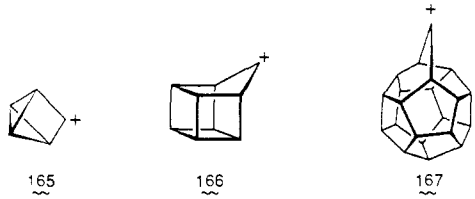
The distinctly different pathways followed by **158** while progressing to either **159** or **160** appear to be linked to involvement of cationic chloro carbenoids[92] and to the presence or absence of β-hydrogens in the organolithium reagent (Scheme 36).[93] When *tert*-butyllithium is involved, arrival at **161** sets the stage for intermolecular delivery of a hydride ion as shown. When the chloro carbenoid product experiences ionization of its second chlorine atom as in **162**, the system responds by losing a proton, providing the latter is aligned properly to permit installation of the cyclopropane bond without incurring high levels of strain. When the lithium reagent is devoid of β-hydrogens, the lithium reagent behaves instead as a nucleophile since arrival at **163** cannot be accompanied by intermolecular hydride abstraction. Following the production of **164**, intramolecular collapse with the loss of HCl affords the substituted cyclopropane.

SCHEME 36



X. Homododecahedranone and the Degenerate 21-Homododecahedryl Cation

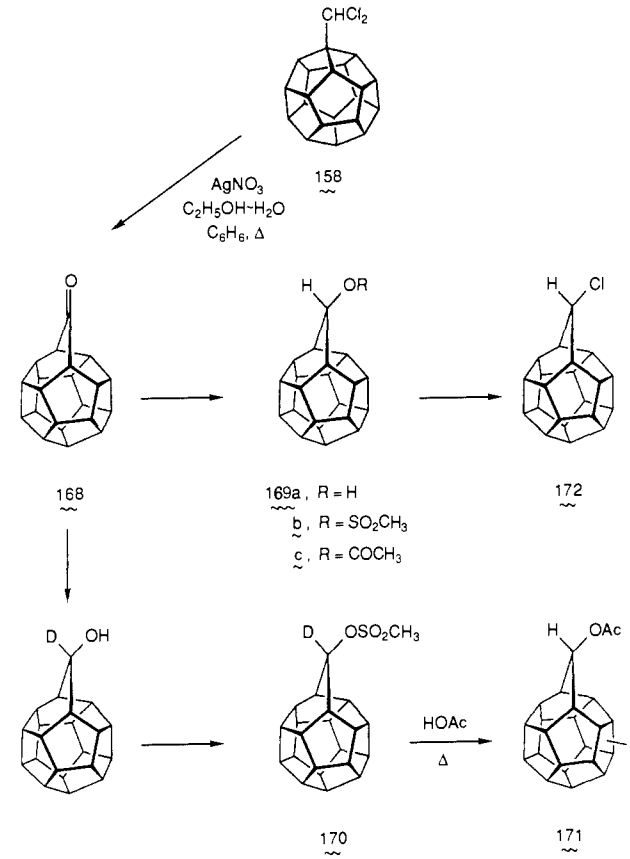
In principle, the $(CH)_n^+$ ions derived from monohomologated polyhedra have the latent capability for achieving spectacular levels of degenerate isomerization. For the homotetrahedryl species **165**,[94] 5!/2 or 60 possible unique structural arrangements are possible if each C–H could be somehow tagged. The multiplicity of realizable structures increases with molecular size. Thus, the homocubyl cation has the potential of making 9!/2 or 181 440 degenerate isomers available.[95] Still more remarkable is the 21-homododecahedryl cation (**167**). Should full equivalency materialize by way of simple Wagner–Meerwein 1,2-carbon shifts, the number of possible different arrangements is staggering: 21!/2 or 2.56×10^{19}. The different connectivities would, as usual, be recognizable only in the presence of suitable isotopic labeling.



165 166 167

Necessary expansion of the dodecahedrane framework with incorporation of a ketonic carbon has been realized from **158** by silver ion promoted rearrangement–hydrolysis (Scheme 37).[91,93,96] The structural features of the resulting homododecahedranone (**168**), elucidated by X-ray crystallographic analysis, suggested that S_N1 solvolysis of methanesulfonate ester **169b** should proceed at a rate comparable to that of the corresponding 2-adamantyl derivative, and this was found to be the case.

SCHEME 37



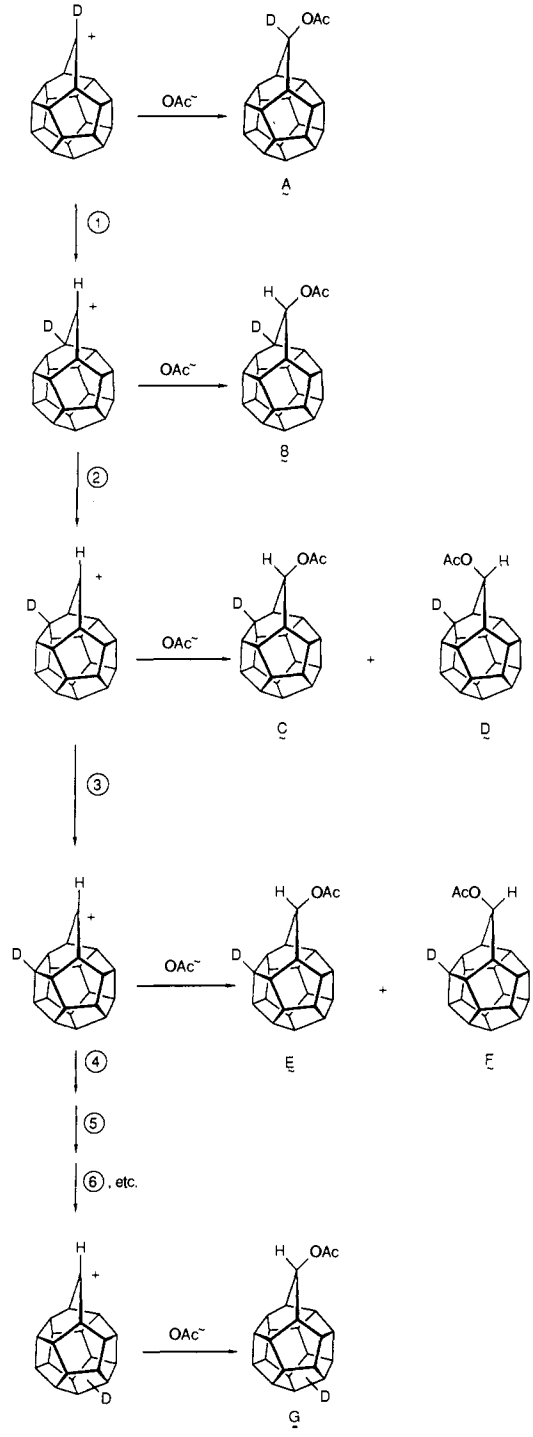
Of greater consequence, ionization of **169b** to the homododecahedryl cation proceeds with retention of the intact polycyclic framework. For the purpose of assessing the level of C–H scrambling in **167**, the monodeuterated mesylate **170** was prepared and the derived d_1 acetate product mixture analyzed by ^2H NMR spectroscopy. Deuterium migration around the sphere does indeed occur under these short-lived conditions. Although complete degeneracy is not realized, the results point to predominant adoption of a nonstereospecific process involving a fully solvated cation. In Scheme 38, it can be seen that more than three Wagner–Meerwein shifts are necessary before the isotopic label can exit the six-membered ring. The observed conversion to stereoisomeric pairs of acetates (i.e., C/D and E/F) and the ultimate production of **171** (or G) cannot be interpreted in terms of tight ion pairs exhibiting high stereospecificity.

Unfortunately, an attempt to transform chloride **172** into **167** in magic acid solution at low temperature did not prove successful. Instead, two different cationic species are formed, thereby signaling that the structural strain present in the 21-homododecahedryl cation can be alleviated under long-life conditions through irreversible conversion to more stable entities.

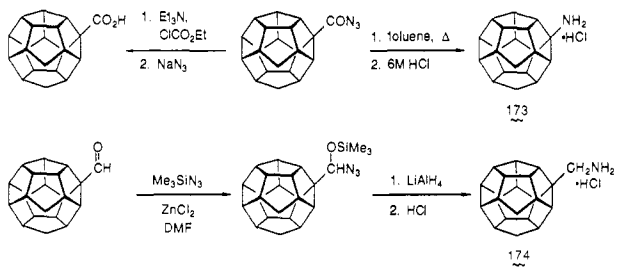
XI. Amino-Functionalized Dodecahedranes

Interest in the acquisition of amino derivatives of 1 stems from possible enhancement of the efficacious

SCHEME 38

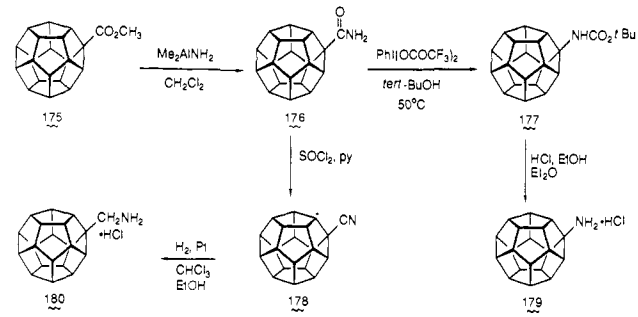


SCHEME 39

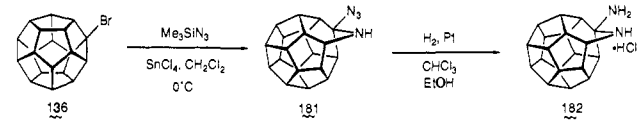


antiviral and anti-Parkinsonian properties of 1-aminoadamantane. Recently, several spherical molecules in this general category have become available.[97] The pair of monoseco amines **173** and **174** (Scheme 39) were

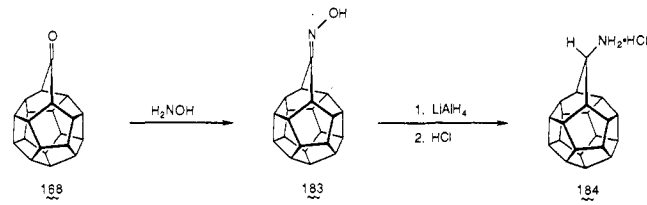
SCHEME 40



SCHEME 41



SCHEME 42



readily prepared from intermediates currently being utilized by the Paquette group in their improved dodecahedrane synthesis.

Although many routes to the dodecahedryl amines **179** and **180** exist a priori, several proved nonworkable because dodecahedrane does not exhibit reactivity directly comparable to that of adamantane. The protocol that ultimately proved successful began with ester **175** (Scheme 40).[97] Following near-quantitative conversion to amide **176**, Hoffmann rearrangement and dehydration led to **177** and **178**, respectively. While acid hydrolysis of **177** eventuated in smooth hydrolysis to **179**, hydrogenation of **178** over platinum in ethanol containing a small amount of chloroform provided for direct in situ formation of the hydrochloride salt **180**.

The ring-expanded azahomododecahedryl azide **181** was produced when bromododecahedrane was treated with aziodotrimethylsilane in the presence of stannic chloride (Scheme 41).[97] Migration of a framework carbon–carbon bond to nitrogen is believed to materialize within the intermediate azide with accompanying loss of nitrogen to deliver an imine. The latter compound is assumed to be adequately strained to allow rapid 1,2-addition of Me_3SiN_3. The transformation of **181** to **182** was achieved as before by hydrogenation over Adams catalyst in the presence of chloroform.

Along other lines, homododecahedranone (**168**) was converted via its oxime (**183**) into the homododecahedrylamine hydrochloride **184** (Scheme 42).[98]

The single most striking property of **173**, **174**, **179**, **180**, **182**, and **184** in the standard influenza A virus assay is their toxicity, with a maximum appearing in **179**.[97] The data indicate **173** and **174** to be the most active antiviral agents of the set, their capacity for inhibition being 5- to 10-fold less than that of aminoadamantane hydrochloride. Homoaza derivative **182** also exhibits quite good activity at high doses, although some toxicity is seen concurrently and its efficacy drops

off precipitously. Thus, high symmetry alone need not promote antiviral effects.

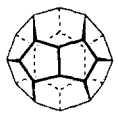
Since toxicity reaches a maximum with **179** and **180**, these compounds have also been evaluated for activity against leukemia cells in vitro. The preliminary data for **179** show it to be effective at doses below 5 μg/mL. Subjects of current interest include the mechanism of action of these amines and the possible clean separation of antiviral and antileukemic activities by simple structural modification.

XII. Future Outlook

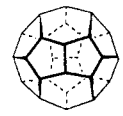
The problem of gaining access to dodecahedrane in amounts useful for extended stufy of its chemical reactivity has been resolved in large part. Nonetheless, alternative new routes that would provide still greater accessibility to this structurally interesting hydrocarbon would certainly be welcome.

Although 1,16-disubstituted dodecahedranes are presently available via dication **149**, there exists a need to deal with protocols for alternative difunctionalization of the spherical framework in other completely regiocontrolled ways. Progress in this area is apt to be quite dependent on our knowledge of the behavior of reactive intermediates that possess the dodecahedryl framework, and interest in such systems will develop with certainty in the near future.

New molecules bearing a close relationship to dodecahedrane are likely to appear on the horizon eventually. These include azadodecahedrane, azahomododecahedrane, homododecahedrenes, tethered dodecahedranes, and optically active homododecahedryl systems. In addition, the quest for second-generation molecules such as the pentakai- (**185**) and hexakaidecahedranes (**186**) can be expected to be undertaken by those who welcome synthetic challenges of such enormous proportion.



185



186

In short, the excitement evoked by an unusual molecule such as dodecahedrane will hardly end with its successful synthesis. A few substituted dodecahedranes are already known that have impressive biological activity. These may foreshadow the existence of possible therapeutic potential in a broad spectrum of derivatives yet to be synthesized, and some commitment of time is certain to be made in this direction as well as toward goals not specifically mentioned above. The backdrop of information in the dodecahedrane field is now adequately large to promote additional multipronged scientific adventure which should attract synthetic and mechanistic chemists for many years to come.

Registry No. Dodecahedrane, 4493-23-6.

XIII. References and Notes

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