QUEST FOR THE PENTAGONAL DODECAHEDRANE

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Abstract - An account of two synthetic approaches to the pentagonal
dodecahedrane based upon the "pincer" Diels-Alder reaction of 9,10-
dihydrofulvalene and dimethyl acetylenedicarboxylate is given. In
both schemes, the strategem calls for the maintenance of symmetry
in all intermediates as a means of minimizing the total number of re-
quisite synthetic manipulations and permitting maximum utilization of
^{13}C NMR spectroscopy.

Men of learning in ancient Greece took especial concern for "the putting together of cosmic
figures," their regular polyhedra whose mathematical elegance inspired considerable won-
der (1). The heritage of that wonder inevitably passed into the realm of synthetic organic
chemistry and attracted the practitioners of this science to apply their skills to the con-
struction from carbon and hydrogen of such strained molecules as tetrahedrane (1) (2,3) and
cubane (2) (4). In more recent years, both theoretical (5-8) and experimental interest (9-14)
in the most complex of the Platonic solids, the pentagonal dodecahedrane (3), has developed
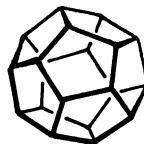

1   2   3

rapidly. This (CH)$_{20}$ hydrocarbon holds particular fascination because it possesses the
highest known point group symmetry (I_h, icosahedral), its relatively strain-free carbon net-
work uniquely encloses a cavity incapable of solvation, and its topology is most aestheti-
cally appealing. Furthermore, 3 can be expected to display novel physical properties and
to serve as a template for a host of physical-organic studies. An assessment of the anti-
viral characteristics of its amino derivative is also awaited (15).

The tactical elaboration of 3 constitutes a major synthetic challenge. Most of the imagi-
native schemes examined to this time have involved the construction of polyfused cyclopenta-
noid networks less intricate than 3 and have necessarily depended upon the proper juxta-
positioning of two structural units to achieve the target objective. The concept of tri-
quinacene dimerization (see 4) as developed independently by Woodward (9) and Jacobson (10),
Eaton's capping of peristylane as in 5 (11), and Paquette's stitching of dl-bivalvane (see
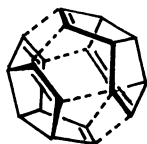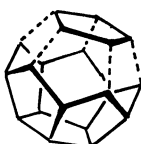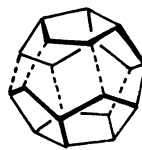
4   5   6

6) (12) fall into this category. Methods for surmounting the obviously adverse entropic and
steric demands of these reactions remain to be developed.

To bypass such complications, we have sought synthetic approaches which deploy most, if not
all of the constituent 20 carbon atoms in proper relative spatial relationship. An addi-

tional self-imposed restriction was maintenance of C_2 symmetry in all intermediates, if at
all possible, in order to capitalize on the inherent symmetry of 3. This antithetic dis-
section was expected to significantly abbreviate the number of steps required and also per-
mit maximum utilization of ^{13}C NMR spectroscopy. This conceptual approach has cleared the
way for the preparation of a number of highly condensed analogs of 3 as will be discussed
in this lecture. Unfortunately, a number of stumbling blocks have deterred us from repor-
ting the completed total synthesis of 3 at the time of this International Congress.

The pivotal molecular cornerstone, diester 8, can be prepared in one laboratory operation
through oxidative coupling of sodium cyclopentadienide with iodine at low temperature (16)
and direct treatment of the resulting 9,10-dihydrofulvalene (7) with dimethyl acetylenedi-
carboxylate (13, 14). We see therefore that the 12 cyclopentane rings and 30 carbon-carbon
bonds in 3 are projected to derive their ancestry from the simple, inexpensive commodity,
cyclopentadiene. This multiple cycloaddition scheme was patterned upon the chemical be-
havior exhibited by certain paracyclophanes (17), although 7 does not share with such mole-
cules a tightly compressed pair of near parallel π networks. In fact, because 7 is a mole-
cule of C_{2v} symmetry which likely prefers to adopt the conformation illustrated, initial
capture of the acetylenic diester takes place from both the "endo" and "exo" directions.
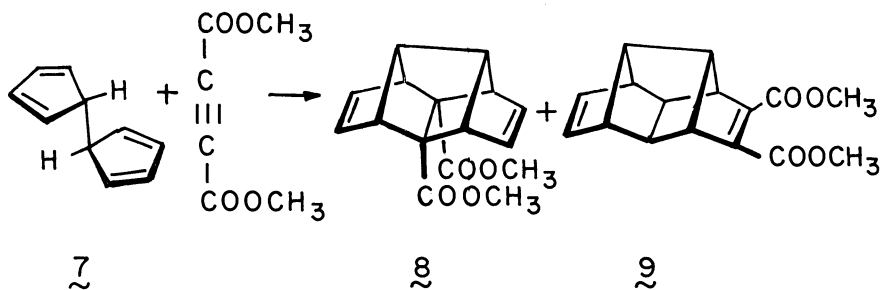
In the first instance, the ensuing cycloaddition serves to compress the dienophile between
the two diene components (see 8) and is therefore referred to as a pincer Diels-Alder pro-
cess. On the other hand, tetracyclic diester 9 is formed from a domino Diels-Alder se-
quence (13, 18). Either process is seen to lend itself readily to the formation of four
new C-C bonds and to the facile construction of a rather elaborate polycyclic structure.
Conveniently, the differently hindered nature of the carbomethoxyl groups in 8 and 9 per-
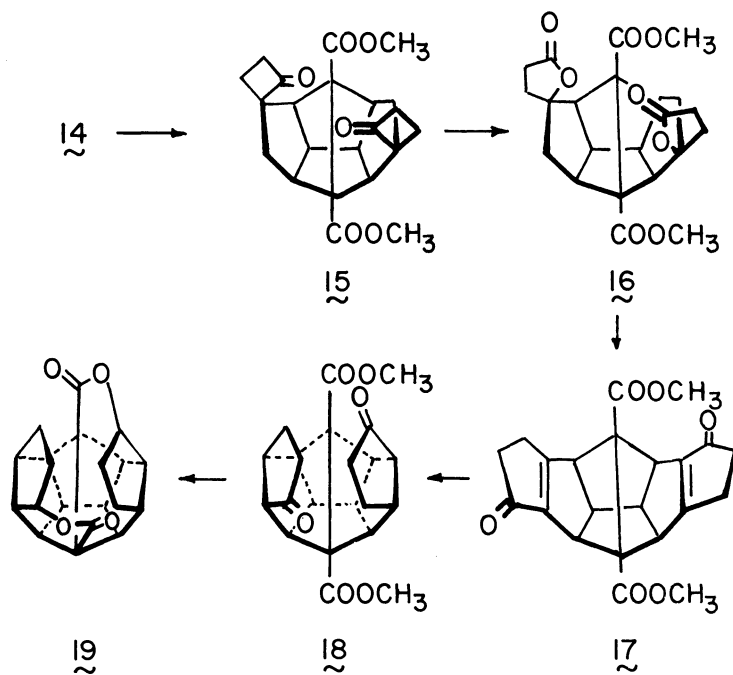mits their efficient separation through selective saponification of the latter.

The next stage required the preparation of diketo diester 14 in quantity. Since hydrobora-
tion-oxidation or oxymercuration of 8 does not lead predominantly to 14 (13), an entirely
regiospecific "cross-corner" oxygenation scheme had to be developed. This was successfully
accomplished from the derived diacid 10 as indicated in the ensuing chart. Through iodo-
lactonization of 10, the carboxyl groups were engaged in neighboring group participation
in a manner which properly positions the key oxygen atoms. Alkaline hydrolysis of 11 with
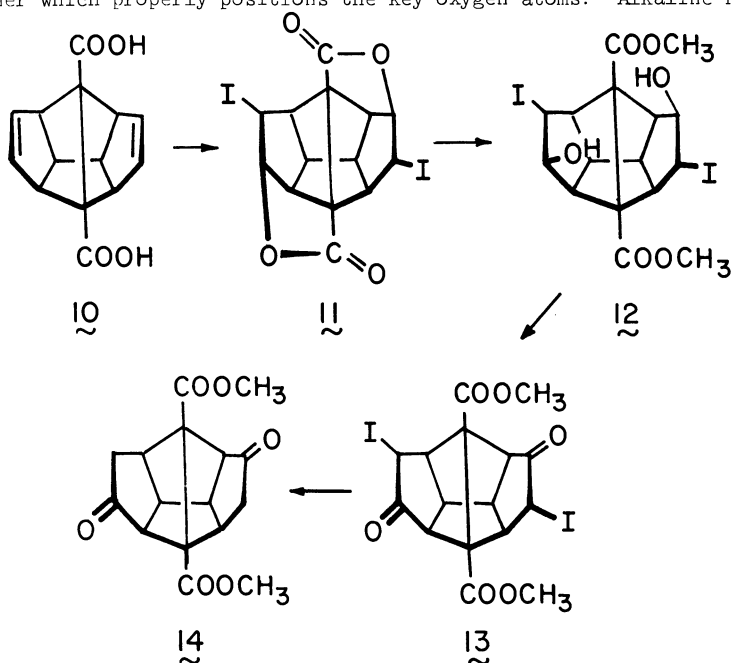
catalytic quantities of sodium methoxide in methanol at room temperature resulted in lactone
cleavage with retention of the iodohydrin part structures. Subsequent Jones' oxidation and
reductive removal of the iodine atoms furnished 14 exclusively. This sequence of steps,
which can conveniently be carried out on a 100 gram scale, is as clean and delightful as one
would hope to encounter. All of the intermediates are highly crystalline and the overall
conversion to 14 from 8 proceeds in 80% yield (13).

At this point, let us recognize explicitly the C_2 symmetry of 14 which reduces our analysis
of its subsequent chemistry to a problem of manipulating only two different carbonyl groups.
Further, 14 and its precursors are seen to contain an unnecessary central bond. While its
cleavage can be easily achieved at several points, this bond has been retained to maintain
norbornene character in the structural halves and thereby guarantee excellent stereochemi-
cal control in the immediately ensuing transformations.

In this context, bisspiroannulation of 14 with cyclopropyldiphenylsulfonium ylide proceeded
to generate a mixture of isomeric cyclobutanones highly enriched in the indicated endo,endo-
stereoisomer 15. This step gains particular significance when it is recognized that the re-
action achieves twofold addition of three carbon atoms to a preexisting C_{14} framework (the
ester methyl groups are excluded) and consequently delivers an axially symmetric product
possessing the same carbon content as the pentagonal dodecahedrane. In principle, no addi-


tional carbon atoms need be introduced and further chemical modification of 15 is limited
to the construction of new five-membered rings through suitable deployment of the existing
framework.

By exposing 15 to 30% hydrogen peroxide, access was gained to 16 which was readily trans-
formed into biscyclopentenone 17 through treatment with phosphorus pentoxide in methane-
sulfonic acid. The stereochemistry of four additional carbons was now fixed merely by
catalytic hydrogenation. Because the unsaturated linkages in 17 partake of norbornene
character, delivery of hydrogen from the sterically less encumbered exo (or, in this case,
convex) surface should be greatly preferred. In fact, this reaction pathway operates ex-
clusively with resultant projection of the cyclopentanone units into the inner regions of
the developing sphere (cf 18). Transformation of the spiro functionality in 15 to lateral
ring fusion as in 18 can therefore also be achieved with high efficiency.

That 18 is a highly folded molecule can be shown by its sodium borohydride reduction which
leads to further cyclization and formation of 19. Since a molecular C_2 axis has been con-
tinuously maintained, this dilactone can be viewed as an intermediate possessing but one
functional group. Its sphericality appears from various molecular models to be adequate
to seriously impede the entry of solvent into its cavity. This phenomenon has an important
impact on the subsequent synthetic plan, since further molecular manipulation of the system
should now require little additional attention to stereochemical detail. In other words,
all reagents were presumed to be relegated hereafter to convex approach.

This feature was used to advantage in the reductive cleavage of the internal bond in 19.
In the presence of sodium and trimethylsilyl chloride in refluxing toluene, there is pro-
duced bistrimethylsilyl enol ester 20, hydrolysis of which in methanol delivers dilactone
21. The exact structure of 21 has subsequently been confirmed through an X-ray crystal
structure analysis by Prof. W. Nowacki and Dr. P. Engel (19). As a result of their efforts,
the molecular dimensions of this compound in the solid state have become known.
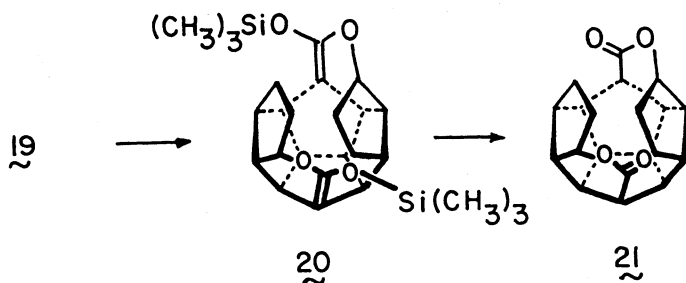

As constituted, 21 is a triseco precursor to 3 having all 20 carbon atoms predisposed in the
proper fashion. To arrive at the target molecule, there must be developed a dehydrative retro
Baeyer-Villiger sequence which will not trigger transannular reaction, and ultimate three-
fold C-C bond formation. We do not have time to discuss here all of the facets to this
problem which have been studied. Those that deserve special mention follow.

Firstly, strongly acidic conditions have proven entirely inadequate for our initial pur-
poses. This is because both 19 and 21 respond by simple Wagner-Meerwein rearrangement to
the thermodynamically more stable isomeric lactones 22 and 23 rather than by more custo-
mary dehydrative ring contraction.
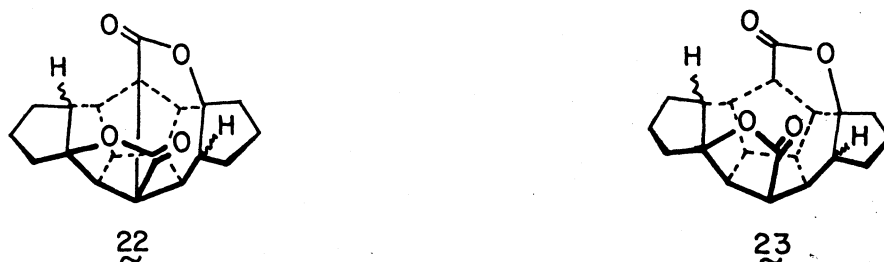
As an alternative to the above, our attention became focused on 24 (R = H, blocking group,
or transannular bond). At this stage, such a dialdehyde might be induced to undergo intra-
molecular Prins reaction to give 25. At this point, the internal bond, if present, should
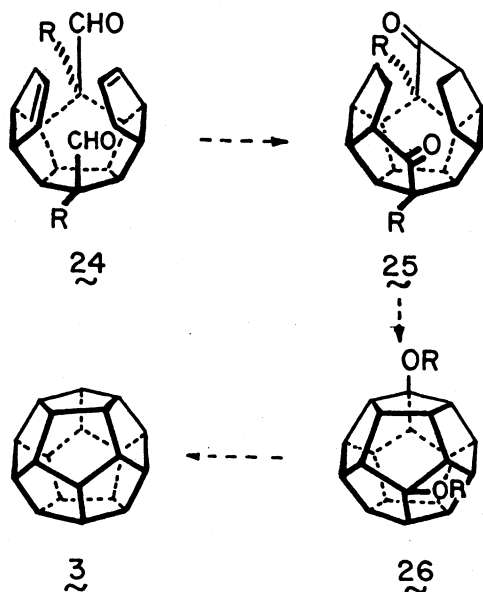
be capable of suitable cleavage as before. Any blocking groups could similarly be reductive-
ly removed as a consequence of their location alpha to the carbonyl groups. In 25 (R = H),
severe steric crowding has been minimized as a result of the sp²-character of the six func-
tionalized carbon atoms. Also, it is clear from molecular models that the internal lobes of
the p orbitals are exceedingly well disposed for transannular bonding, such that reduction
of 25 under pinacolic conditions might result in "stitching" of the molecular framework to
give diol 26. Subsequent removal of the hydroxyl groups should prove uneventful.

It was, of course, disappointing to learn that dilactone 21 is extremely susceptible to un-
wanted transannular cyclization under both alkaline and acidic conditions. Several informa-
tive examples are illustrated below. The apparent sensitivity of 20 also appears to ex-
clude its application to such chemistry. Given the low degree of solvation, if any, in the
interior of these molecules and the reasonable proximity of transannular centers, it is not
surprising that a reactive functional group, once generated, acquired hyperreactive intra-
molecular tendencies under such circumstances.
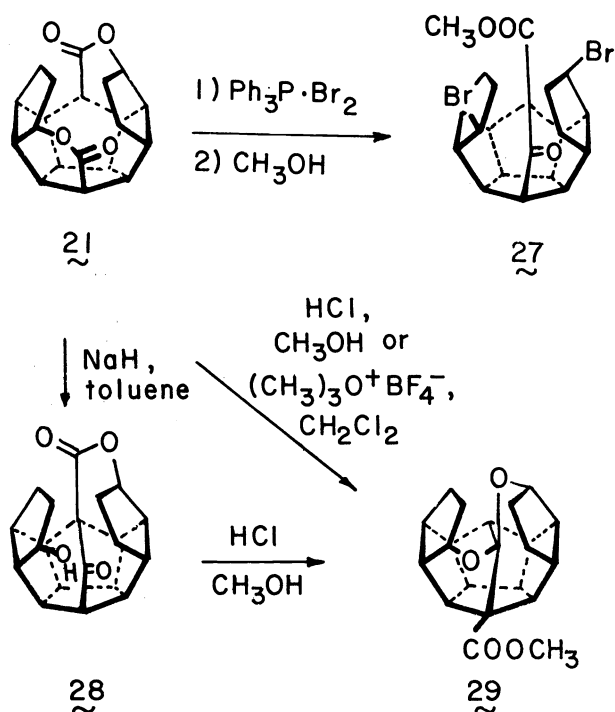
Subsequent recourse to closed dilactone 19 also proved unrewarding at first, but for ano-
ther reason. When treated with tr...ethyloxonium fluoroborate in dichloromethane or hydro-
gen bromide in methanol, cleavage of one lactone ring could be achieved, but not the other
even under forcing conditions. Evidently, the substantial conformational change which ac-
companies conversion to 30 and 31 leads to improper stereoalignment for facile repetition
of the first reaction. This drawback can be overcome with other more powerful reagents such
as triphenylphosphine dibromide in acetonitrile and hydrogen chloride in methanol, but 32
and 33 have not yet proven to be serviceable precursors to 24.
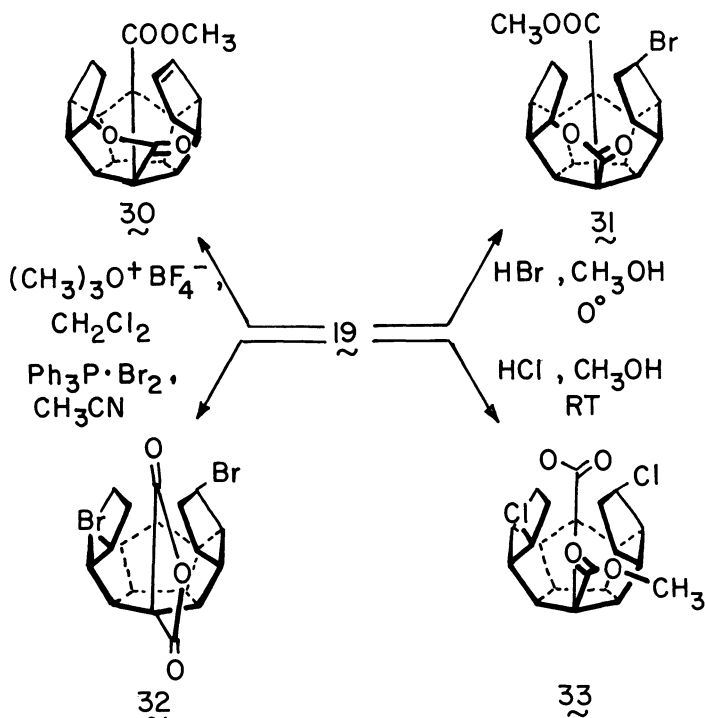
Far greater control of the reactivity of 19 can be achieved by its hydride reduction to lac-
tol 34 which can also be prepared directly from 18 under comparable conditions. The indi-
cated structure is not the result of kinetic control; rather, equilibration of the hydroxyl
groups to the more stable exo environment occurs during workup. Upon dissolution in thionyl
chloride, 34 experiences quantitative conversion to chloro ether 35 with preservation of the
aldehyde oxidation level. Our original intention was to capitalize on the inherent sta-
bility of oxonium ions and cause ring opening of 35 to 24 with the aid of silver salts.
At this point, our naïveté about the proclivity of such molecules for rearrangement became
apparent again. When 35 was treated with anhydrous silver fluoroborate or perchlorate in dry
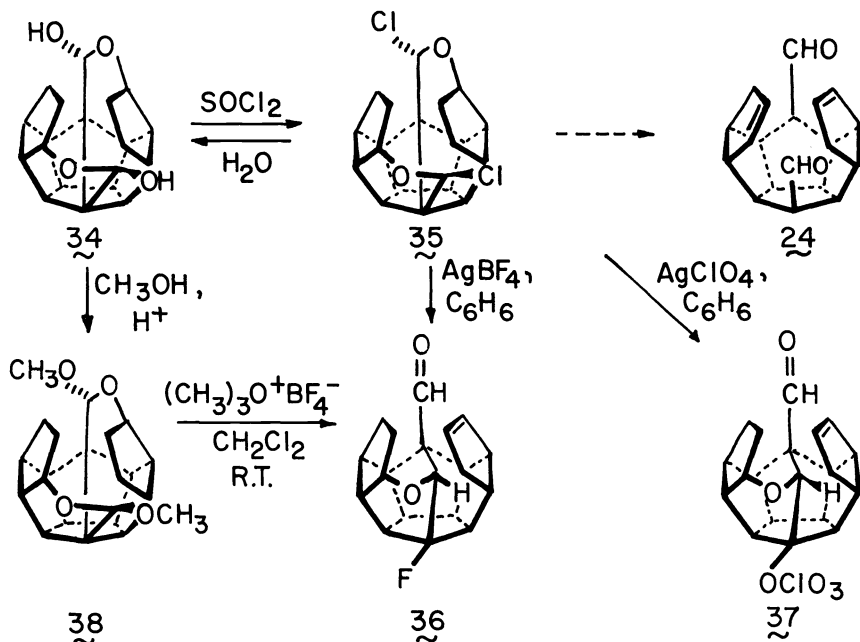
benzene, the products isolated in good yield proved to be 36 and 37. The identical reaction
course is followed upon exposure of 38 to Meerwein's reagent. The remarkable structural
features of 37 prompted us to seek out Professor Nowacki's assistance once again (19). The
X-ray results not only confirmed the structural assignment, but demonstrated the fully co-
valent character of the C-O bond to perchlorate as well. Although the precise timing of

this rearrangement has not been unequivocally established, we are of the opinion that de-
parture of the first chloride ion is accompanied by a 1,2-shift of the central bond (with
relief of steric strain) to generate a tertiary cationic center which captures the only
anion available (generally very nonnucleophilic). Only subsequently is the desired frag-
mentation believed to occur in the other half of the molecule.

Although the above excursion had to be made, it quite clearly did not conform to our single-
minded goal of maintaining axial symmetry. Fortunately, bischloro ether 35 is capable of
efficient sodium/liquid ammonia reduction with conversion to the bisdihydropyran 39. The
availability of 39 immediately led us to consider the preparation of 24 (R = CH₃). Although
this dialdehyde would give rise ultimately to a symmetrically substituted dimethyl dodeca-
hedrane if subsequent experimentation proceeded satisfactorily, we saw several advantages
to its exploitation. Perhaps the most obvious feature was the likely reduction in trans-
annular side reactions. Therefore, 39 was converted by means of the Simmons-Smith reagent
to 40 as a prelude to its ring opening with acid. Wenkert and coworkers (20) had previously
established that cyclopropanated vinyl ethers are particularly sensitive to acid and re-
arrange under such conditions to α-methylated carbonyl compounds, precisely as desired.
But our a priori considerations had not accounted for the possibility of cyclopropyl par-
ticipation as in 41 which, of course, was later shown to be the preferred reaction course.
In acidic methanol, 40 was transformed exclusively to unwanted 42!

Accordingly, we were forced to develop an alternative synthesis of the dialdehyde or its
equivalent. To this end, 40 was heated with N-bromosuccinimide. Smooth ring cleavage oc-

curred to give 43, treatment of which with tri-n-butyltin hydride removed the bromine atoms
in conventional fashion. At this stage, the methyl groups are properly positioned and the
aldehyde oxidation level has been retained. Currently, effort is being launched to pursue
further development of the chemistry of this intermediate.
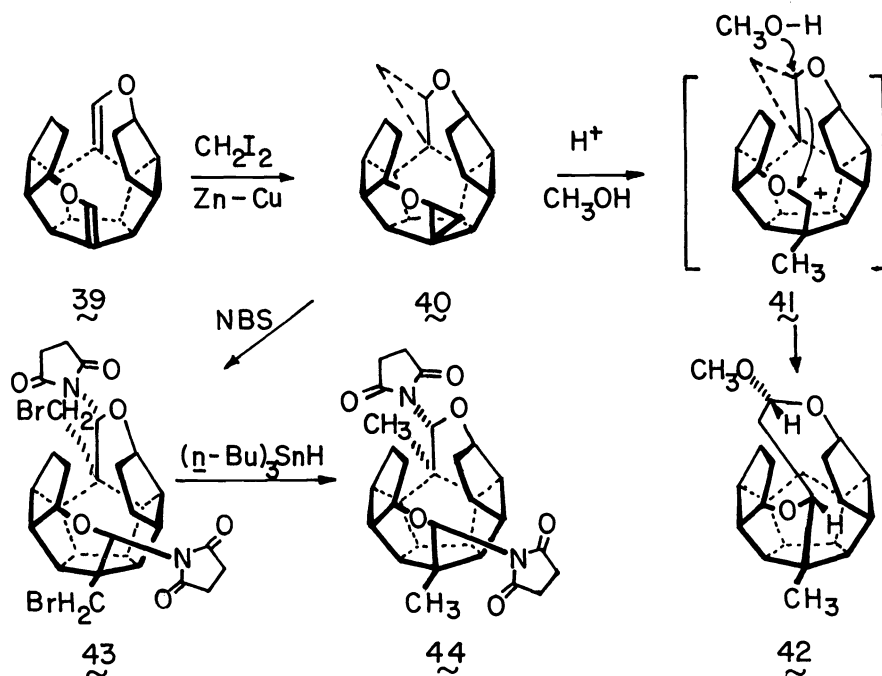
Mention should be made at this point that a pair of methyl (or other) groups can otherwise
be introduced considerably earlier in the scheme. The transformation of lactone 19 to 45
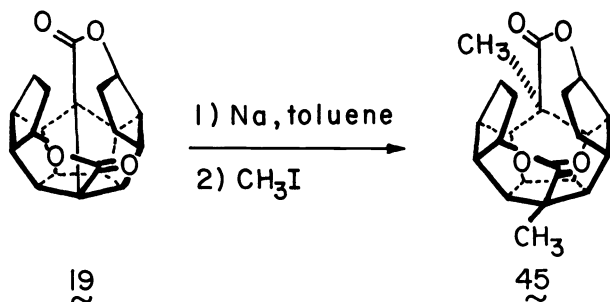
is representative.

The initial experiments with 40 were carried out almost simultaneously with those of its di-
epoxide congener 46. Like 40, this α,β-epoxy ether possesses two strained three-membered
rings rigidly held in rather close transannular proximity. But contrary to 40, the response
of 46 to electrophilic reagents does not lead to transannular bonding. When placed on sili-
ca gel, for example, 40 experiences isomerization to a dialdehyde which has been tentative-
ly assigned structure 48 chiefly on the basis of ^{1}H and ^{13}C NMR data and a limited number of
chemical transformations (→ 49 and 50). We regard the formation of 48 to be the likely re-
sult of epoxide opening toward the tertiary cation center with concurrent or subsequent 1,2-
oxygen shift as shown in 47. The possibility of elaborating from 48 the parent dioxatri-
secododecahedrane 51 is presently under investigation. A direct comparison of the intimate
structural features of 51 with those of the related hydrocarbon (not yet available) should
be interesting because of the anticipated diminished strain energy in the former.
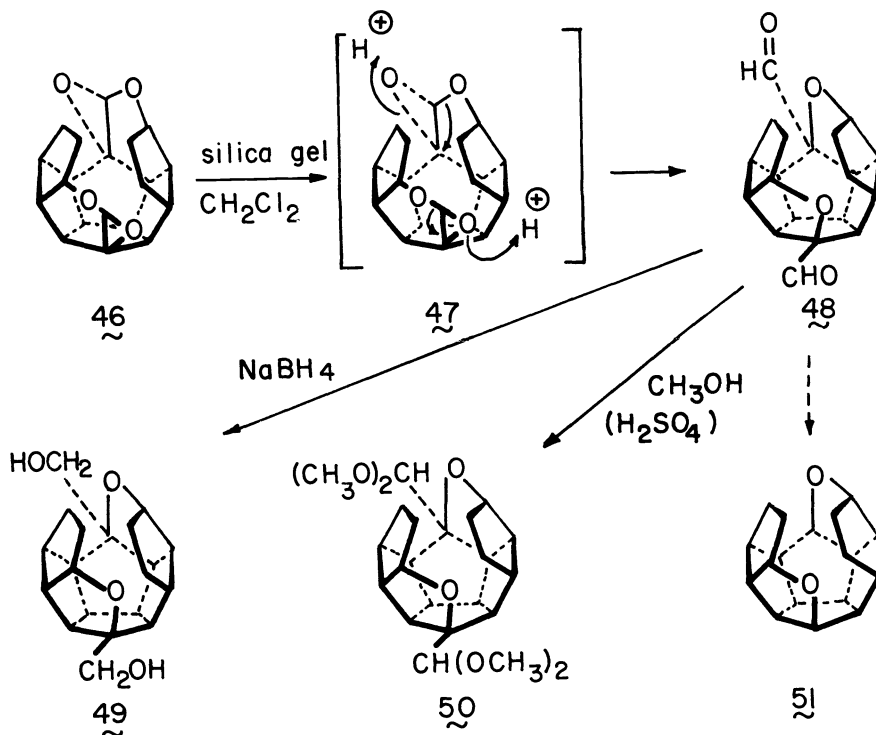
Should the ring opening of 46 in the opposite direction prove experimentally feasible, then
a route to 24 (R = OR') might become available. Although this question has hardly been ex-
plored, some promising preliminary observations are already in hand.

The above discussion should not leave the reader with the impression that 46 is not guilty
of transannular infractions. Perhaps the most blatant example can be found in its conver-
sion to the closed tetraol 53 when reduced with sodium in liquid ammonia containing a pro-
ton source such as ethanol. That the strained internal sigma bond had been reintroduced was
established spectroscopically and by independent conversion of closed lactol 34 to 53 under
identical conditions. Evidently, the first formed carbanion finds transannular ring opening
of the second epoxide ring as in 52 kinetically feasible.
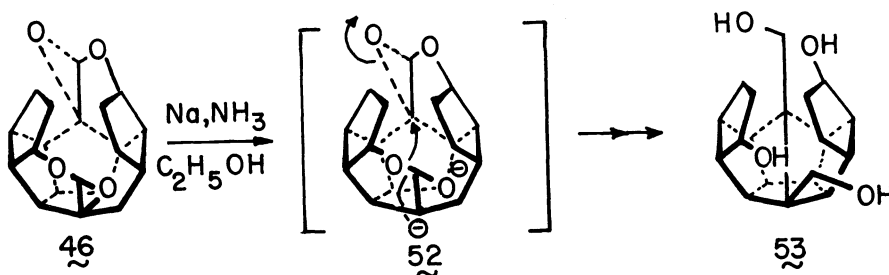
Although the latent reactivities of such molecules as 19, 21, 34, 35, 39, 40, 43, and 46 hold considerable promise for continued progress towards a synthesis of the pentagonal dodecahedrane, other studies with structurally related molecules have been advancing in an encouraging manner as well. The second chapter of this story, like the above, relies partly for aesthetics and partly for brevity in synthetic manipulation upon symmetry. The starting point is the readily available diacid 54 which through reaction with two equivalents of lithium hydride and excess methyllithium is converted to diketone 55. To construct the cyclohexanedione part structure of 56, use was made of the cupric ion-promoted coupling reaction of enolate anions developed by Saegusa and coworkers (21). To preclude aldolization, 55 had to be treated with two equivalents of lithium diisopropylamide at -78°. Further, maximum yields of 56 could only be realized by inverse addition of the resulting dienolate solution to cupric chloride in dimethylformamide-tetrahydrofuran in the cold. Subsequently, 56 was heated with selenium dioxide in dioxane solution to introduce a third double bond as in 57. This procedure is seen to elaborate a molecule which can be considered to be the formal pincer Diels-Alder adduct of the unknown benzoquinonyne and 9,10-dihydrofulvalene. Diketone 57 is expectedly labile at more elevated temperatures, experiencing retrograde (4+2)π cycloadditions and polymerization under these conditions.
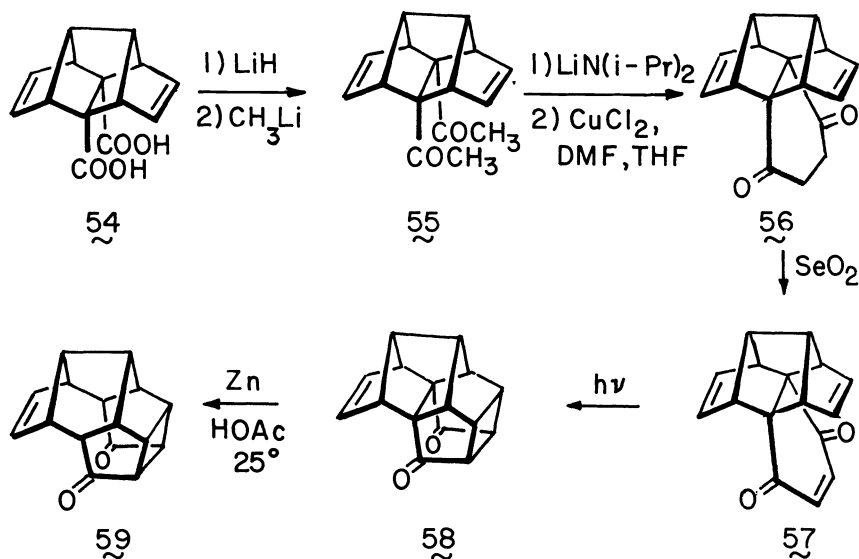

Fortunately, this has not proven to be a serious problem and 57 can be efficiently photocyclized to its highly strained cage isomer 58.

It now becomes appropriate to consider a stereoelectronic question central to our synthetic plan. Thus, we see that the structural factors prevailing in 56 enforce an essentially orthogonal relationship between the carbonyl pπ orbitals and the central sigma bond (see 60). This specifically means that reductive cleavage of this 1,4-dicarbonyl system should not be possible, and in accord with theory (22) we have found 26 to be stable to the most forcing reducing agents. The entire situation changes when we progress to 58 for in this diketone both 1,4-dicarbonyl subunits are now ideally aligned for maximum through-bond interaction (see 61). In model systems closely related to the caged part structure in 58 (23),

simple treatment with zinc and acetic acid at room temperature proves adequate for cleavage of the internal cyclobutane bond. In contrast, comparable reduction of 58 leads exclusively to fission of the central norbornyl bond to deliver 59. This result provides mute but convincing testimony of the strain present at this site in the molecule. Once this bond is ruptured, the structure adopts a more spherical contour and begins its more advanced stage of evolution toward dodecahedrane.

Although this conformational realignment does detract from the original ideality of the over-
lap between the carbonyl groups and the internal cyclobutane bond, this second-stage reduc-
tion can be accomplished without difficulty by merely raising the reaction temperature to
100°. Under these conditions, both 58 and 59 are converted to the beautifully crystalline
diketone 62. With the aid of a small amount of mental gymnastics (and suitable redrawing),
it is seen that 62 is in reality a symmetrical tetrahydro hexaquinacenedione endowed with
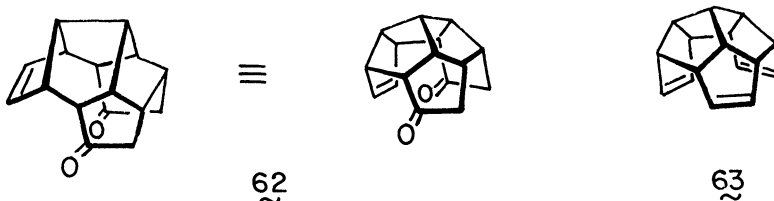
functionality anticipated to be adequate for proper introduction of four additional carbon
atoms in a manner suitable for closing of the sphere. Again, such studies are progressing
at this very moment, as are efforts to transform 62 into the heretofore elusive and fas-
cinating hexaquinacene molecule (63). Our interest in triene 63 is in some respects tan-
gential to the dodecahedrane effort but in direct line with our attempted quantification
of homoaromaticity (24).

In the listing below are cited the names of those chemists who have been
associated with me in this endeavor. Their initiative, skill, enthusiasm,
and devotion have proven to be the prime factors underlying the progress
which has been made in such a relatively short time. William Begley, Otto
Schallner, Robert Snow, and Matthew Wyvratt deserve special mention for
their major contributions. I hereby express a deep sense of indebtedness
to them all.

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