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 requisite synthetic manipulations and permitting maximum utilization of 13C 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 wonder (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 construction 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 (2), has developed rapidly. This \((\text{CH})_{20}\) hydrocarbon holds particular fascination because it possesses the highest known point group symmetry \((\text{I}_h, \text{icosahedral})\), its relatively strain-free carbon network uniquely encloses a cavity incapable of solvation, and its topology is most aesthetically 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 antiviral characteristics of its amino derivative is also awaited (15).

The tactical elaboration of \(3\) constitutes a major synthetic challenge. Most of the imaginative schemes examined to this time have involved the construction of polyfused cyclopentanoïd networks less intricate than \(3\) and have necessarily depended upon the proper juxtapositioning of two structural units to achieve the target objective. The concept of triquinacene dimerization (see \(4\)) as developed independently by Woodward (5) and Jacobson (10), Eaton's capping of peristylane as in \(\zeta\) (11), and Paquette's stitching of \(\delta\)-bivalvane (see \(6\) (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 dissection was expected to significantly abbreviate the number of steps required and also permit 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 reporting 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 acetylenedicarboxylate (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 behavior exhibited by certain paracyclophanes (17), although 7 does not share with such molecules a tightly compressed pair of near parallel \( \pi \) networks. In fact, because 7 is a molecule 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.

\[
\begin{align*}
\text{H} + \text{COOCH}_3 & \rightarrow \\
\text{H} & + \text{COOCH}_3 \\
\text{II} & \rightarrow \\
\text{II} & + \text{COOCH}_3
\end{align*}
\]

In the first instance, the ensuing cycloaddition serves to compress the dienophile between the two diene components (see 5) and is therefore referred to as a pincer Diels-Alder process. On the other hand, tetracyclic diester 9 is formed from a domino Diels-Alder sequence (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 permits their efficient separation through selective saponification of the latter.

The next stage required the preparation of diketo diester 14 in quantity. Since hydroboration-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 iodolactonization 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

\[
\begin{align*}
\text{COOH} & \rightarrow \\
\text{COOH} & \rightarrow \\
\text{I} & \rightarrow \\
\text{OH} & \rightarrow \\
\text{OH} & \rightarrow \\
\text{COOCH}_3 & \rightarrow \\
\text{COOCH}_3 & \rightarrow \\
\end{align*}
\]
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 $1^6$ 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 stereochemical control in the immediately ensuing transformations.

In this context, bis-spiroannulation of 14 with cyclopropylidichloridiphenylsulfonium 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 reaction achieves twofold addition of three carbon atoms to a preexisting C14 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 additional 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 transformed into bicyclopentenone 17 through treatment with phosphorus pentoxide in methanesulfonic 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 exclusively 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 continuously maintained, this dilactone can be viewed as an intermediate possessing but one functional group. Its sphericity 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 \( \text{19} \). In the presence of sodium and trimethylsilyl chloride in refluxing toluene, there is produced bistrimethylsilyl enol ester \( \text{20} \), hydrolysis of which in methanol delivers dilactone \( \text{21} \). The exact structure of \( \text{21} \) 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, \( \text{21} \) is a triseco precursor to \( \text{3} \) 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 purposes. This is because both \( \text{19} \) and \( \text{21} \) respond by simple Wagner-Meerwein rearrangement to the thermodynamically more stable isomeric lactones \( \text{22} \) and \( \text{23} \) rather than by more customary dehydrative ring contraction.

As an alternative to the above, our attention became focused on \( \text{24} \) (R = H, blocking group, or transannular bond). At this stage, such a dialdehyde might be induced to undergo intramolecular Prins reaction to give \( \text{25} \). At this point, the internal bond, if present, should
be capable of suitable cleavage as before. Any blocking groups could similarly be reductively 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 functionalized 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 unwanted transannular cyclization under both alkaline and acidic conditions. Several informative examples are illustrated below. The apparent sensitivity of 20 also appears to exclude 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 intramolecular tendencies under such circumstances.

Subsequent recourse to closed dilactone 19 also proved unrewarding at first, but for another reason. When treated with trimethylsilylfluoroborate in dichloromethane or hydrogen 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 accompanies conversion to 29 and 31 leads to improper stereoaignment 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 \( \text{19} \) can be achieved by its hydride reduction to lactol \( \text{34} \) which can also be prepared directly from \( \text{18} \) under comparable conditions. The indicated 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, \( \text{34} \) experiences quantitative conversion to chloro ether \( \text{35} \) with preservation of the aldehyde oxidation level. Our original intention was to capitalize on the inherent stability of oxonium ions and cause ring opening of \( \text{36} \) to \( \text{24} \) with the aid of silver salts. At this point, our naiveté about the proclivity of such molecules for rearrangement became apparent again. When \( \text{36} \) was treated with anhydrous silver fluoroborate or perchlorate in dry benzene, the products isolated in good yield proved to be \( \text{36} \) and \( \text{37} \). The identical reaction course is followed upon exposure of \( \text{36} \) to Meerwein's reagent. The remarkable structural features of \( \text{37} \) 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 covalent 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 depa-

ture 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 37. The

availability of 37 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, 37 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
The initial experiments with $40$ were carried out almost simultaneously with those of its di-
epoxide congener $46$. Like $46$, this $\alpha,\beta$-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 silici-
a gel, for example, $46$ experiences isomerization to a dialdehyde which has been tentative-
ly assigned structure $49$ 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 $49$ 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 $46$ the parent dioxa tri-
seco dodecahedrane $51$ 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.

\[
\begin{align*}
46 & \xrightarrow{\text{silica gel}} \text{CH}_2\text{C}_2 \quad 47 \quad \text{NaBH}_4 \\
\text{HOCH}_2\text{CH}_2\text{OH} & \quad \text{CH}_3\text{OH} \quad (\text{H}_2\text{SO}_4) \\
49 & \quad \text{CH(OCH}_3\text{)}\_2 \quad 50 \\
46 & \quad \text{HO} \\
51 & \quad \text{HO} \\
\end{align*}
\]

Should the ring opening of $46$ in the opposite direction prove experimentally feasible, then
a route to $52$ ($R = \text{OR}^\prime$) 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 $52$ to $53$ under
identical conditions. Evidently, the first formed carbanion finds transannular ring opening
of the second epoxide ring as in $52$ kinetically feasible.

\[
\begin{align*}
46 & \xrightarrow{\text{Na}_2\text{NH}_3, \text{C}_2\text{H}_5\text{OH}} \text{CH}_2\text{C}_2 \quad 52 \\
\text{HO} \quad \text{OH} & \quad \text{OH} \\
52 & \quad \text{HO} \quad \text{OH} \\
\end{align*}
\]
Although the latent reactivities of such molecules as 19, 21, 31, 33, 35, 39, and 46 hold considerable promise for continued progress toward 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 methyl lithium is converted to diketone 55. To construct the cyclohexanediol 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 disopropylamide at -8°. 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 (1,2) cycloadditions and polymerization under these conditions.

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

It now becomes appropriate to consider a stereochemical question central to our synthetic plan. Thus, we see that the structural factors prevailing in 56 enforce an essentially orthogonal relationship between the carbonyl π 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 overlap between the carbonyl groups and the internal cyclobutane bond, this second-stage reduction can be accomplished without difficulty by merely raising the reaction temperature to 1000°. 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 fascinating hexaquinacene molecule (63). Our interest in triene 63 is in some respects tangential 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.

William Begley  Otto Schallner
Robert Blankenship  David Schneider
David Bremner  Robert Snow
Tadeusz Cynkowski  Matthew Wyvratt

We gratefully acknowledge as well the National Institutes of Health for their financial support which permitted the reduction of our ideas to practice.

REFERENCES


2. For early fallacious claims of tetrahedrane syntheses and their discreditation, see:
   (a) R. M. Beesley and J. F. Thorpe, Proc. Chem. Soc. 25, 346 (1913); J. Chem. Soc., 591 (1920);

3. For new data on the possible transitory existence of tetrahedranes, consult:


