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Synthetic studies in quest of Platonic hydrocarbon dodecahedrane

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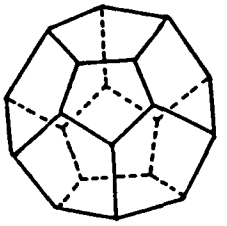
Abstract. In pursuit of Platonic hydrocarbon dodecahedrane 1, a retrosynthetic theme indicated in scheme 1, was formulated. The precursor tetraquinanedione synthon 5 was first designed through a photo-thermal olefin metathesis approach. The tetraquinanedione 5 was further elaborated to *exo*, *exo*-tetraquinane diester 15 through carbonyl homologation, oxidation, esterification sequence, scheme 5. Bis-cyclopentannulation of *exo*, *exo*-diester 15 by Greene methodology delivered a functionalised C_{20}-hexaquinane 44, having *exo*-annulated cyclopentane rings. Cyclopentane inversion was achieved by a set of reactions involving enone generation, double bond isomerisation and hydrogenation to give spheroidal (C_{2v})–C_{20}-hexaquinanedione-diester 47, the penultimate precursor of dodecahedrane 1. Several interesting transformations and rearrangements of polyquinanes are also described.

Keywords. Dodecahedrane; C_{2v}-tetraquinane dione; *cis*-Hexaquinane; bis-cyclopentannulation; cyclopentanone inversion.

Dodecahedrane (1)[+], a $C_{20}H_{20}$ hydrocarbon of I_h symmetry is one of the most structurally complex and aesthetically appealing polyquinanes known. The challenge of synthesising this platonic hydrocarbon of spheroidal shape, that arises through its twelve constituent *cis*, *syn* fused five-membered rings, has elicited a lot of interest from synthetic chemists around the world (Mehta 1978; Eaton 1979; Paquette 1979, 1984). Two outstanding efforts from the research groups led by Paquette and Prinzbach have resulted in the synthesis of dodecahedrane in 1982 and 1987, respectively (Ternansky *et al* 1982; Paquette *et al* 1983, 1987; Fessner *et al* 1987). Apart from these, it is known that synthetic efforts towards dodecahedrane were pursued or are currently being pursued in various other laboratories (Schleyer 1957; Woodward *et al* 1964; Jacobson 1967; Repic 1976; Eaton *et al* 1977, 1984; Deslongchamps and Soucy 1981; Roberts and Shoham 1981; McKervey *et al* 1981; Monego 1982; Baldwin and Beckwith 1983; Mehta and Nair 1983, 1985; Baldwin *et al* 1984; Carcellar *et al* 1986; D G Farnum and T A Monego – unpublished results; G Mehta and K R Reddy–unpublished results). Concurrently, the fascinating structural features of 1 have also been investigated by several theoretical chemists (Schulman *et al* 1975; Schulman and Disch 1978; Ermer 1977; Dixon *et al* 1981; Baum *et al* 1982). Synthetic efforts towards 1 were initiated in our laboratory in early 1981, when no successful approach to this challenging hydrocarbon was known. A perusal of the synthetic approaches that were in practice convinced us

[+] IUPAC nomenclature: Undecacyclo[9·9·0·0^{2,9}·0^{3,7}·0^{4,20}·0^{5,18}·0^{6,16}·0^{8,15}·0^{10,14}·0^{12,19}·0^{13,17}]eicosane.

* For correspondence



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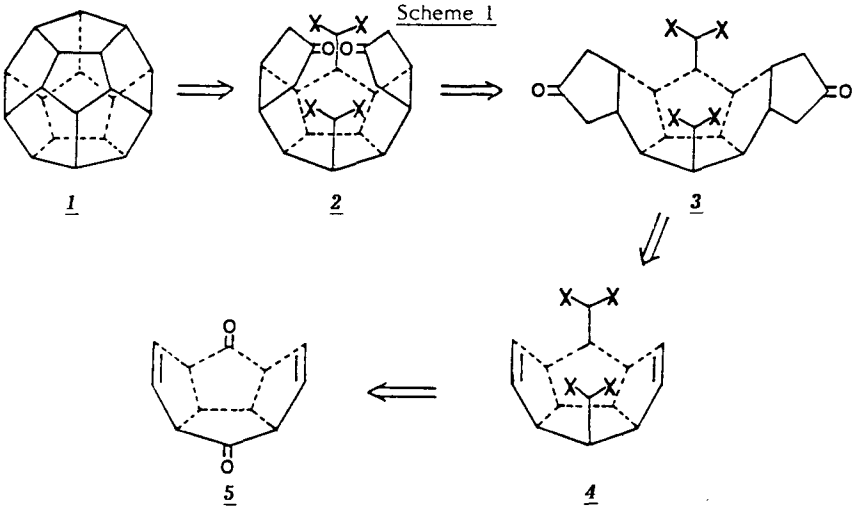
that a good chance of success lay in a strategy leaning heavily on symmetrization that could inherently overcome some of the problems caused by steric strain and non-bonded interactions. With this in view, a retrosynthetic analysis of 1 was carried out as depicted in scheme 1, which identified the symmetrical, highly functionalized C_{20}-hexaquinane 2 as the pivotal pretarget and the C_{12}-tetraquinane dione 5 as the key starting synthon. Hexaquinane 2, which retains a spheroidal contour has all the 20 carbon atoms as well as two strategically placed $-CX_2$ type functionalities for molecular stitching through a four-fold intramolecular displacement reaction on 2 (scheme 2) to furnish a secododecahedranedione 6. This

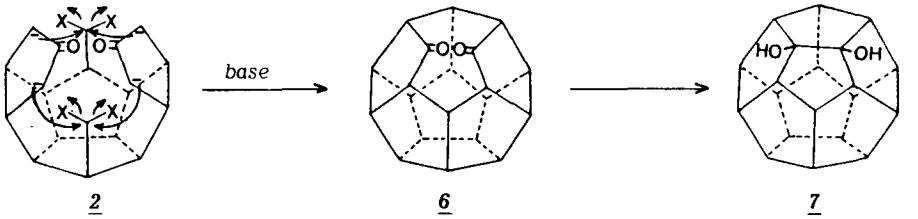
Scheme 1



1 2 3 4 5

ultimate precursor could then be enticed into a pinacolic coupling to deliver the dodecahedrane framework 7 as shown in scheme 2.

Scheme 2



2 6 7

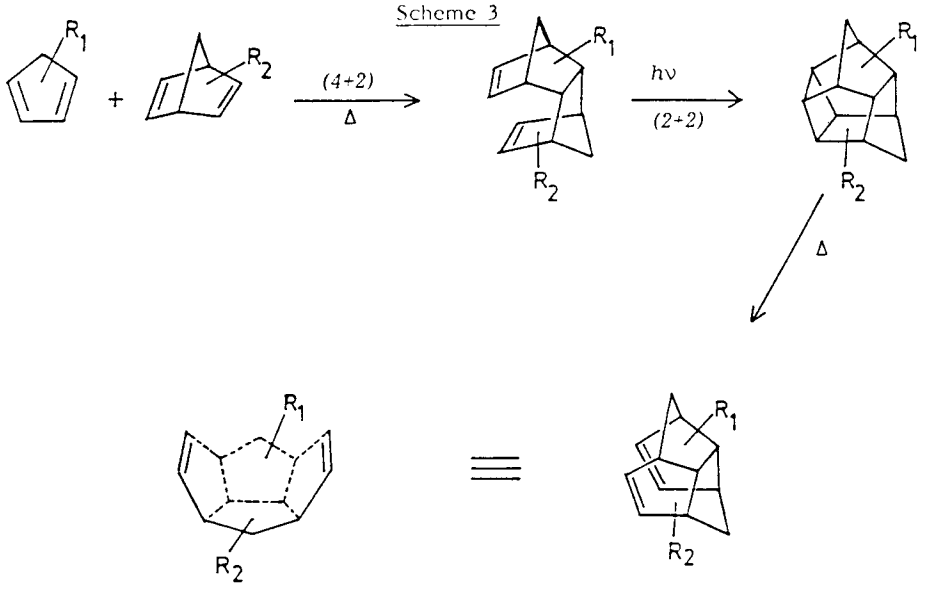
Emanating from this retrosynthetic analysis, our synthetic approach to 1 was divided into three stages of increasing complexity viz., (i) development of a new methodology towards the synthesis of the starting tetraquinane synthon, e.g., 5; (ii) adoption of a suitable cyclopentanone annulation and inversion strategy (viz., conversion of 4 → 2) and (iii) deployment of the molecular stitching plan using the two $-CX_2$ functionalities in 2 to close-in the sphere (scheme 2). Progress towards the implementation of this theme is described in this account.

Stage 1

Synthesis of the tetraquinanedione 5 and its further elaboration

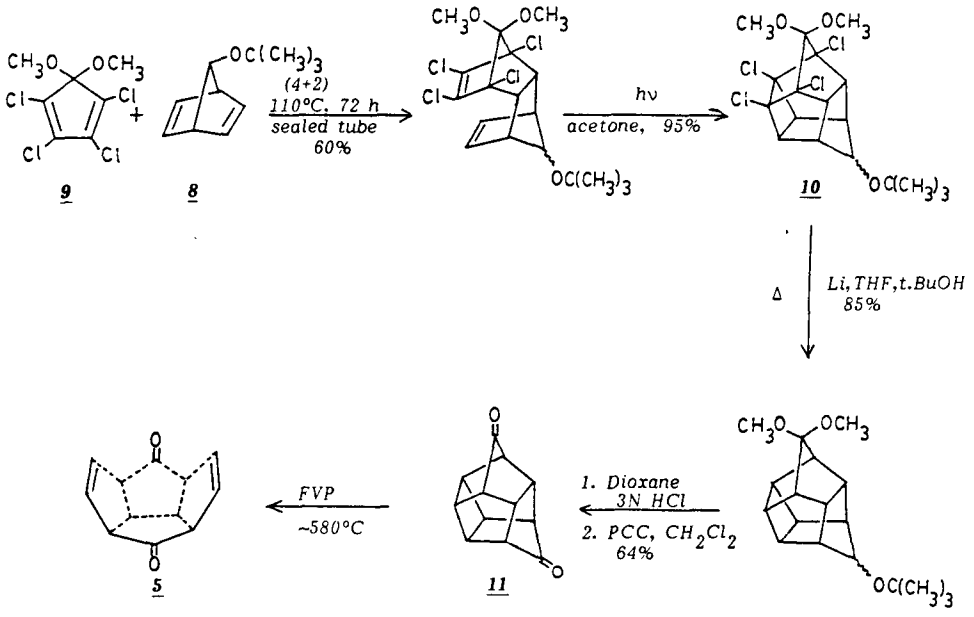
At the time of inception of this effort towards dodecahedrane, there were only two reported syntheses of functionalized tetraquinanes available in literature (Fukunaga and Clement 1977; Paquette *et al* 1978), both of which suffered from severe limitations during scale-up processes and one of them (Fukunaga and Clement 1977) did not deliver the requisite functionality. Therefore, we first turned our attention to a generalised approach to functionalized tetraquinanes. Borrowing pointers from our successful approach to triquinane synthesis (Mehta *et al* 1979, 1981), we devised a photo-thermal olefin metathetic approach as shown in scheme 3.

Scheme 3



For the synthesis of tetraquinanedione 5 as shown in scheme 4, the starting materials were identified as 7-*t*-butoxynorbornadiene 8 and tetrachlorodimethoxycyclopentadiene 9. Diels-Alder reaction between 8 and 9 followed by acetone sensitized $\pi^2s + \pi^2s$ closure of the *endo*-adducts resulted in the hexacyclic product 10 in 57% yield (see also Astin and MacKenzi 1975, Byrne *et al* 1974). A three-step sequence consisting of (i) dechlorination using Li-*t*-BuOH-THF, (ii) hydrolysis

Scheme 4

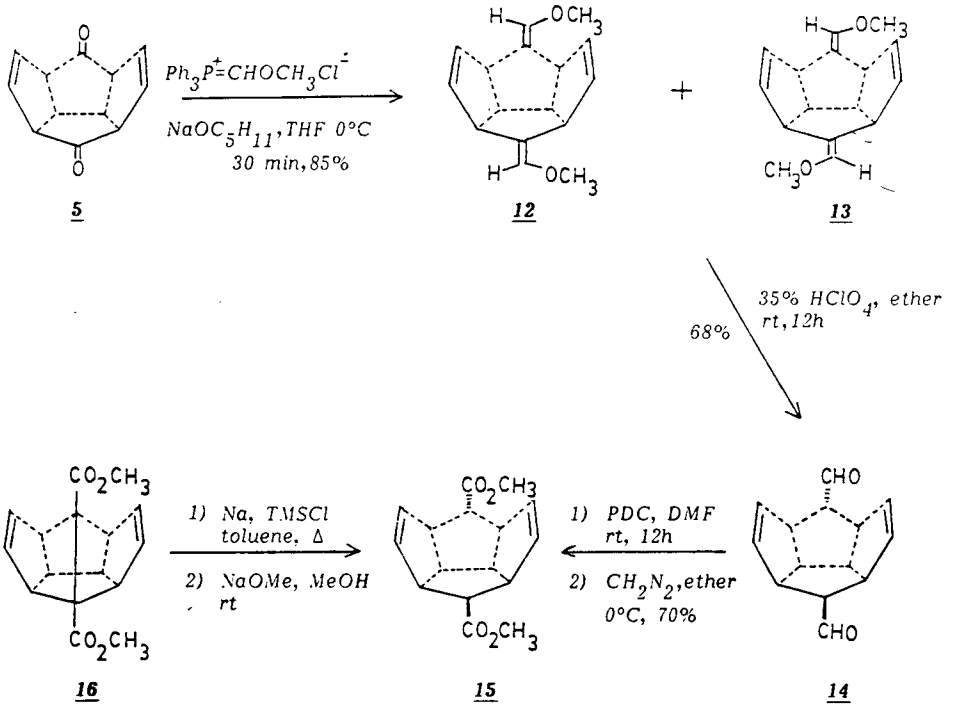


using 3N HCl in dioxane and (iii) PCC oxidation produced the symmetrical (^{13}C NMR: δ210·0, 48·8, 42·4, 41·8) caged, *bis*-homopentaprismane dione 11 in an overall yield of 55% (Mehta and Nair 1983, 1985b). Flash vacuum pyrolysis (Mehta *et al* 1979, 1981) of this diketone through a quartz tube preheated to 580°C provided the tetraquinanedione 5 in 70% yield (Mehta *et al* 1983; Paquette *et al* 1986; Sedelmeier *et al* 1986). The structure and C_{2v} symmetry of this dione could be readily deduced from its ^{1}H NMR spectrum and ^{13}C NMR signals at δ214·2, 133·5, 62·7, 43·2. Following this procedure, the dione 5 could be prepared in multi-gram quantities quite uneventfully.

In order to introduce an equivalent of $-CX_2$ group as per the theme of scheme 1, the tetraquinanedione 5 was further elaborated to the diester 15 (ester group as an equivalent of $-CX_2$ functionality) (G Mehta and K R Reddy, unpublished results). This was achieved through a two-fold carbonyl homologation followed by oxidation as shown in scheme 5. Wittig olefination on 5 with methoxymethylphosphorane gave a 1 : 2 mixture of 12 and 13. Acid hydrolysis of these enolethers to the thermodynamically more stable dialdehyde 14 and oxidation of the dialdehyde with PDC in DMF followed by esterification of the resulting diacid using diazomethane gave the *exo*, *exo*-diester 15. This diester was identical to that obtained by reductive cleavage and isomerization of the Hedaya-Paquette diester 16, scheme 5 (Paquette *et al* 1978). The diester 15 was considered eminently suitable for further evolution towards the target 1.

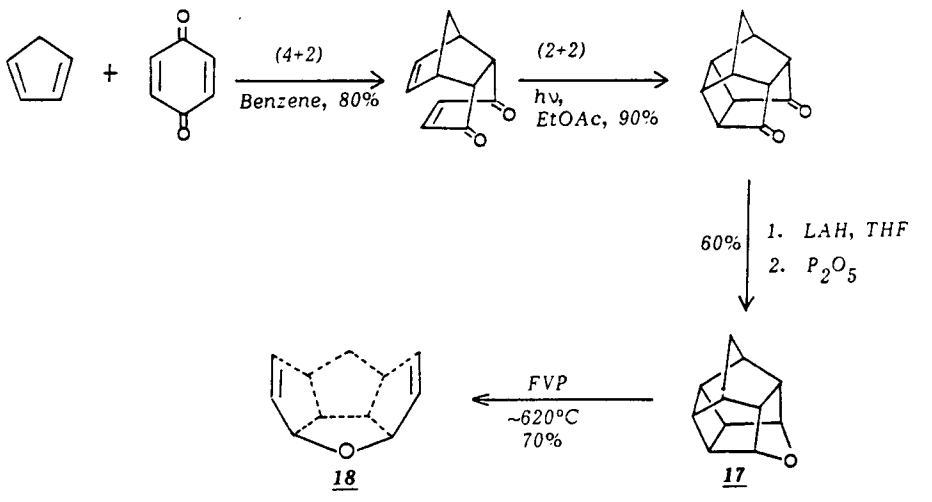
The photo-thermal olefin metathetic approach to the tetraquinanes described above was also adopted for the synthesis of oxa-tetraquinane 18, as this was more readily accessible through C_5 and C_6 building blocks as compared to the tetraquinanedione 5. Model studies for *bis*-cyclopentannulation and ring inversion strategy were, therefore, initially conducted using 18 (Mehta and Nair 1985). As

Scheme 5



shown in scheme 6, tetraquinane 18 was synthesized from benzoquinone and cyclopentadiene via the oxa-bird cage compound 17 in relatively few, high yielding steps.

Scheme 6

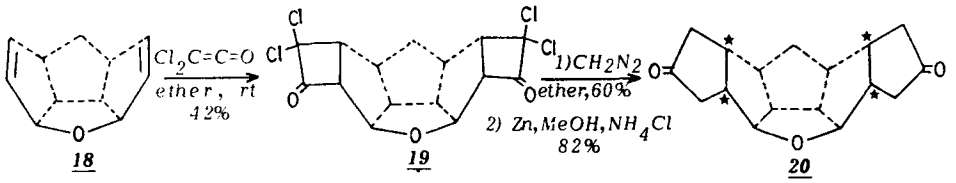


Stage 2

Bis-cyclopentannulation of tetraquinanes. Synthesis of spheroidal hexaquinanes

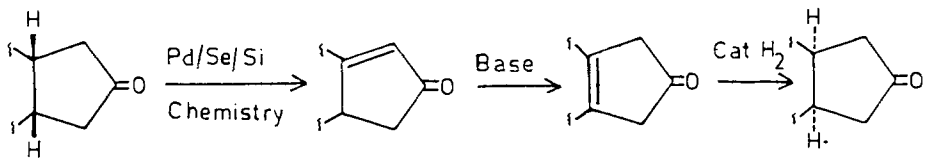
As eluded to above, the next important step towards the conquest of dodecahedrane was the appendage of two cyclopentane rings on 15 as in 4. A perusal of the available methods in literature for cyclopentannulation of olefins suggested the Greene methodology (Green and Depress 1979) of dichloroketene addition to olefins followed by regiospecific ring expansion to be superior to others as it would render strategic placement of the carbonyl group. For the exploratory studies, the oxa-tetraquinane 18 was utilised as it was readily obtained in large quantities. When oxa-tetraquinane 18 was treated with an excess of dichloroketene, generated *in situ*, by using trichloroacetylchloride and a Zn-Cu couple according to procedure of Bak and Brady (1979), a *bis*-dichloroketene adduct 19 was obtained. While the regiochemical assignment of 19 follows from its ^{1}H and ^{13}C NMR data, the *exo*-stereochemistry is based on the propensity of folded polyquinanes to react from the open convex face. The *bis*-adduct 19 was ring expanded using diazomethane in ether and the now redundant chlorine atoms were removed using $Zn/NH_4Cl/MeOH$ milieu (Noyori *et al* 1974) to give the hexaquinanedione 20 as shown in scheme 7.

Scheme 7



Even though *bis*-(cyclopentanone)annulation of 18 had been achieved, it could be successfully utilised for the synthesis of dodecahedrane only if the two newly appended cyclopentane rings could be projected within the cavity of the polyquinane framework. This required inversion of stereochemistry at four centres in 20 (marked with asterisks). This transformation was envisaged in a three step sequence as illustrated in scheme 8.

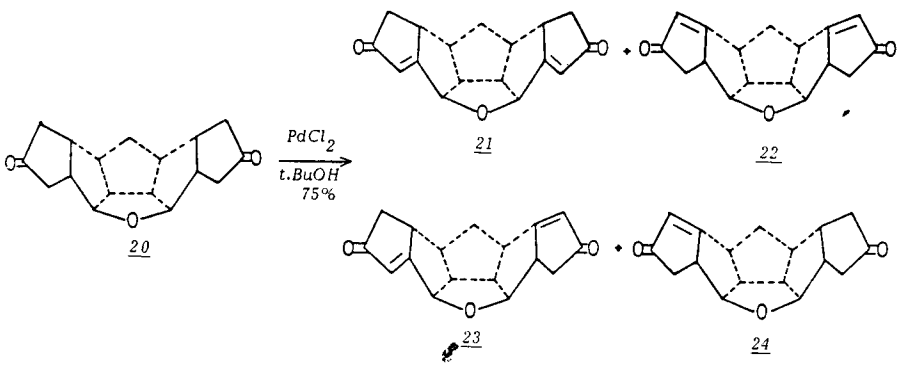
Scheme 8



Thus, the first step in the transformation was the introduction of double bonds in conjugation with the carbonyl groups. For this, any of the three general methods known viz., (i) the Reich procedure of α-phenylselenylation followed by dehydroselenation (Reich *et al* 1975; Reich 1979), (ii) the Saegusa procedure using Pd(II) mediated dehydrosilylation of an enolsilylether (Ito *et al* 1978) or (iii) the

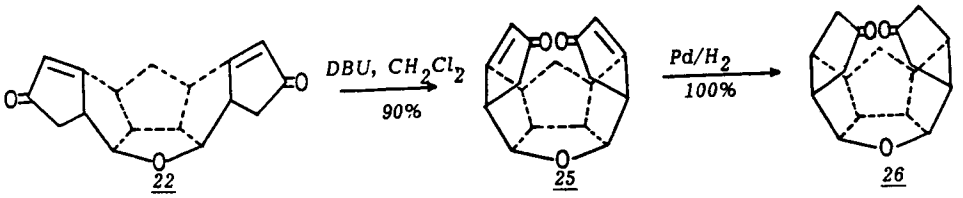
Mincionne procedure using $PdCl_2$ in refluxing t.BuOH to effect direct dehydrogenation (Mincionne *et al* 1977) could be utilised. While all three methods proved successful, the Mincionne procedure gave the best results. Reaction of hexaquinanedione 20 with $PdCl_2$ in refluxing *t*·BuOH transformed it into a mixture of *bis*-enones 21, 22, 23 and the monoenone 24 in approximately equal amounts as illustrated in scheme 9 (Mehta and Nair 1985a).

Scheme 9



The next task was the relocation of double bonds in *bis*-enones. As it is well known that α,β-unsaturated carbonyl compounds equilibrate with their β,γ-isomers in the presence of base, we decided to subject the *bis*-enones to this treatment. In order to avoid damage to the ether linkage, a mild base like DBU was chosen for the purpose. The *bis*-enone 22 under the influence of DBU isomerised to 25. The structure of 25 was arrived at through its ^{13}C NMR and 500 MHz ^1H NMR data. In the case of 22 the protons adjacent to ether linkage appeared as a doublet (J = 4·3 Hz), whereas in 25 they appeared as a doublet of a doublet ($J_1 = J_2$ = 5.3 Hz). Catalytic hydrogenation of 25 resulted in the projection of the two cyclopentanone units within the cavity, thus giving rise to 26. In this manner, the second stage in our approach to dodecahedrane, viz., *bis*-cyclopentanone annulation and ring inversion was successfully demonstrated on model oxatetraquinane 18, scheme 10.

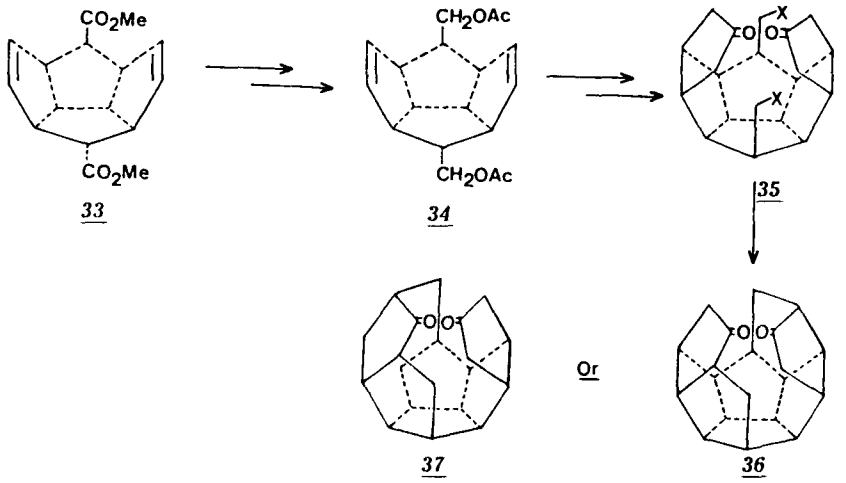
Scheme 10



With the experience of the above model studies, it was now the opportune time to aim at dodecahedrane itself. The *endo*, *endo*-diester 33 and the diacetate 34 derived from it appeared to be the most appropriate starting materials. The latter had the advantage of not being susceptible to epimerisation during the subsequent operations. Also, the molecular stitching plan (scheme 1) could be first tested with

35 which would only undergo a two-fold cyclisation to furnish an octaquinanedione 36 or 37, scheme 11.

Scheme 11

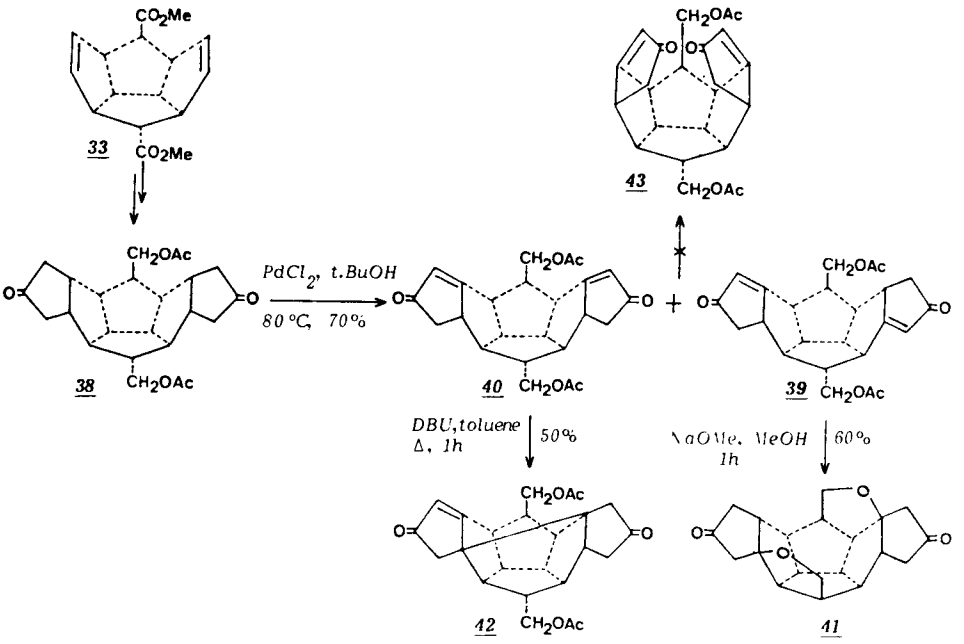


Thus, the diester 15 was routinely elaborated to diacetate and then *bis*-cyclopentannulated employing the dichloroketene addition methodology outlined earlier in this article, scheme 7. The resulting hexaquinanedione 38 was dehydrogenated to the *bis*-enones 39 and 40, using the $PdCl_2$-*t*-BuOH dehydrogenation procedure. Attempts were now directed to relocate the enone double bonds to the tetrasubstituted ring junction position in order to effect cyclopentane inversion. Towards this end, the *bis*-enone 39 of axial symmetry was exposed to sodiummethoxide in methanol. The exclusive product of this reaction turned out to be a C_{20}-dioxaoctaquinane 41 formed via intramolecular Michael addition of the *endo*-hydroxymethyl groups to the two enone moieties, scheme 12. The structure of 41 rests on its HRMS data (M^+ 326·150) and 400 MHz ^{1}H NMR spectrum, which exhibited diagnostic signals at δ 4·15–4·12 (2H, *dd*, J_1 = 2·4 Hz, J_2 = 9·6 Hz), 3·98–3·94 (2H, *dd*, J_1 = 6·6 Hz, J_2 = 9·6 Hz) due to HC–CH_2–O-type functionality.

In order to circumvent the deviation leading to 41, DBU was deployed as the non-nucleophilic base for the deconjugation of enone moieties in 40. However, in this case another type of intramolecular Michael addition intervened and the novel heptacyclic ene-dione 42 was obtained. The ^{1}H and ^{13}C NMR data are fully consonant with its structural formulation. Since the efforts to transform 39 and 40 to 43 were thwarted by unanticipated formation of 41 and 42, we were impelled to seek a different strategy to gain access to the key folded hexaquinane 2.

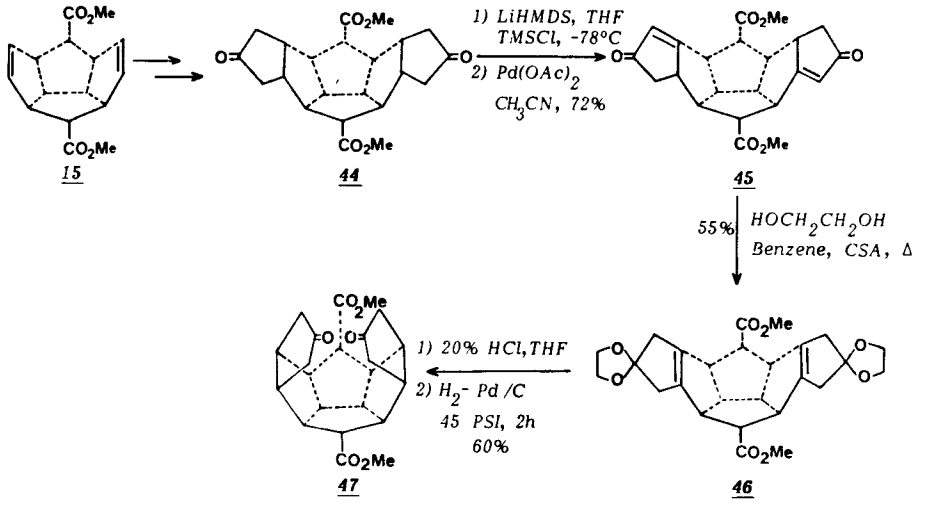
Believing that the inversion of the cyclopentenone rings in 39 and 40 was complicated by the presence of two *endo*-acetoxymethyl substituents protruding within the spherical cavity (cf. 22 → 25 change), we decided to operate on an *exo*, *exo*-derivative of the tetraquinane precursor. This option was expected to keep at bay any steric congestion within the developing sphere during the crucial ring inversion manoeuvre. However, provision was kept to project the *exo*-substituent into the *endo*-position at an appropriate stage to execute the molecular stitching

Scheme 12



plan (stage 3) as per scheme 1. Towards this objective, the *exo*, *exo*-diester 15, readily obtainable from the *endo*, *endo*-isomer through thermodynamic equilibration with methanolic sodiummethoxide was chosen as the starting tetraquinane derivative. The diester 15 was once again *bis*-cyclopentannulated via dichloroketene addition, diazomethane ring expansion and reductive dechlorination sequence to furnish the hexaquinanedione 44, scheme 13. The dione 44 was

Scheme 13



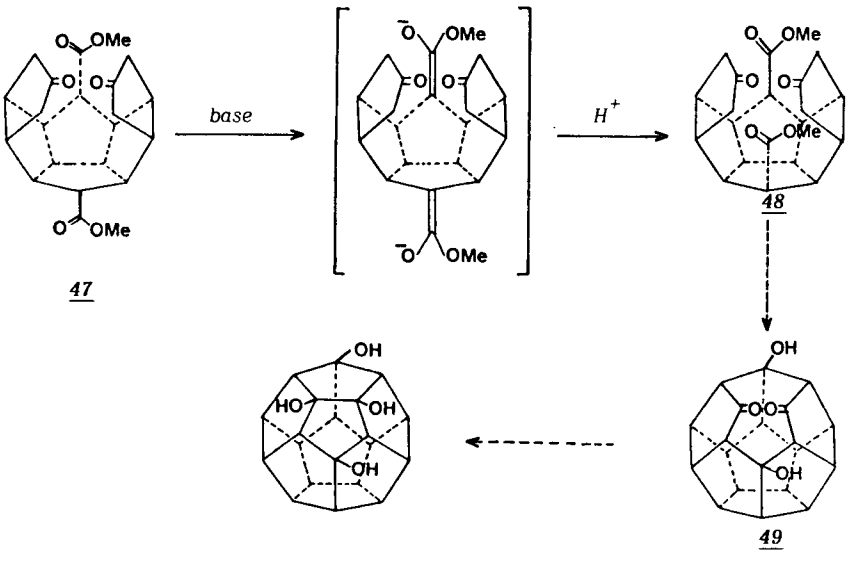
regioselectively transformed into a single *bis*-enone of axial symmetry following the Saegusa procedure (Ito *et al* 1978). When exposed to acid or base to relocate the enone moieties, the *bis*-enone 45 once again exhibited recalcitrant behaviour. After many exploratory attempts, we were most gratified to observe that 45 could be converted into *bis*-ketal 46 under carefully controlled acetalisation in the presence of camphorsulphonic acid. The 10 line ^{13}C NMR spectrum fully supported its structure and identified the location of two double bonds at the tetrasubstituted bridgehead position. Catalytic hydrogenation of 46 and deacetalisation under the mildly acidic conditions furnished the folded hexaquinanedione 47, scheme 13. The arrival at the long sought 47 was indicated by its 400 MHz ^{1}H NMR spectral parameters and 8 line ^{13}C NMR spectrum (δ 219·3, 175·8, 57·4, 55·6, 52·3, 49·4, 43·0, 40·6). The structure of this key penultimate precursor of dodecahedrane, by our approach was further secured through single crystal X-ray diffraction studies. With a reasonable supply of 47 at our disposal, we set about giving expression to the stage 3 of our plan, scheme 1.

Stage 3

The molecular stitching plan. End game en route to dodecahedrane

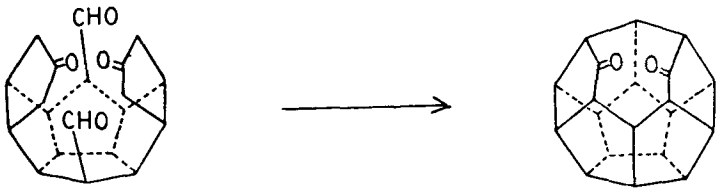
In order to orchestrate the intramolecular ring closure on to a secododecahedrane derivative, it was imperative that the ester groups of 47 be made to fall within the cavity. To achieve this, we proposed to exploit the propensity of the spheroidal systems towards protonation from the convex face. Thus, inversion of the two ester moieties in 47 was envisaged via deprotonation-kinetic protonation employing non-nucleophilic bases, scheme 14. The resulting 48, a surrogate for 2 (scheme 1) was simultaneously expected to result in a cascade of anion-induced ring closures leading to the secododecahedranediol-dione 49.

Scheme 14



Thus, 47 was exposed to a variety of bases (LDA, Li-HMDS, KH, *t*-BuOK-*t*-BuOH etc.) but the outcome was very disappointing. In a majority of these reactions, considerable loss of precious material occurred and no product could be firmly characterised. Consequently, we realised that the choice of diester functionality for effecting the four-fold anionic ring closure needed a change to a more electrophilic group. Presently we are in the process of preparing the hexacyclic diketodialdehyde 50 and hope that it will be possible to entice it into cyclisation to deliver the secododecahedranedione 51, scheme 15.

Scheme 15



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In summary, we have conceived a new, short approach to the $C_{20}H_{20}$ hydrocarbon sphere, dodecahedrane. To attain this formidable objective, a new synthesis of functionalised tetraquinanes based on photo-thermal olefin metathesis reaction has been developed. The Greene methodology has been successfully applied for the *bis*-cyclopentannulation of several tetraquinanes to furnish functionalised hexaquinanes. It has been possible to invert and project the newly appended cyclopentane rings into the spheroidal cavity. Thus, the advanced C_{20}-hexaquinane precursor of dodecahedrane 47 has been realised. Attempts to convert 47 to a secododecahedrane derivative *en route* to the target molecule 1 have so far not succeeded. However, firm ground work has been laid for making repeated assaults on the final objective, which has been appropriately referred to, as the 'Mount Everest of alicyclic chemistry' (Grubmuller 1979).

Acknowledgements

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