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GENERAL APPROACH FOR THE SYNTHESIS OF POLYQUINENES VIA THE WEISS REACTION[✠]

ASHOK K. GUPTA, XIAOYONG FU, JAMES P. SNYDER[†] and JAMES M. COOK[*]
[*] Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin 53201, U.S.A.
[†] Drug Design Group, Searle R&D, Skokie, IL 60077, U.S.A.

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1. INTRODUCTION

In 1968, Weiss and Edwards reported[1] that the reaction of two molecules of dimethyl 3-oxoglutarate **1** with one molecule of glyoxal **2** in slightly acidic (pH = 5) aqueous solution provided moderate but reproducible yields of tetramethyl *cis*-bicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate **3**, a substance which had been obtained previously by a much more involved procedure.[2] Acid catalyzed hydrolysis, followed by spontaneous decarboxylation of the resulting β-ketoacid functions gave *cis*-

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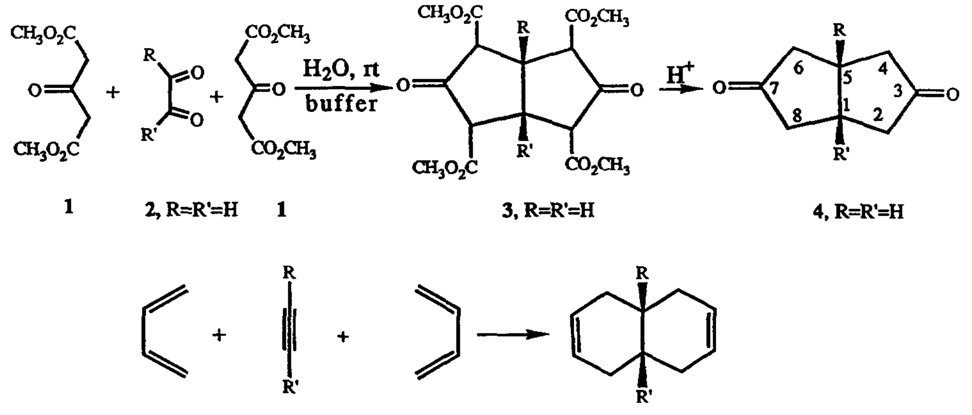
[✠] This paper is dedicated to the memory of Dr. Ulrich Weiss who passed away on July 15, 1989.



Scheme 1

bicyclo[3.3.0]octane-3,7-dione **4** (Scheme 1). The reaction of **1** with 1,2-dicarbonyl compounds other than **2** established[1] the generality of this process.[3a–d] For example, pyruvaldehyde and biacetyl gave the 1-monomethyl and 1,5-dimethyl analogs of **3**, respectively, while the use of alicyclic α-dicarbonyl compounds provided a simple one-pot procedure for the preparation of [*n*.3.3]-propellane derivatives.[1,3a,c] The potential of this condensation was greatly increased when the reaction of **1** with **2**[4] or **1** with other 1,2-dicarbonyl compounds was carried out in aqueous alkaline media.[4] This furnished the *cis*-bicyclo[3.3.0]octane-3,7-dione system **3** in excellent yield and generally as the sole reaction product. Simultaneously in Woodward's laboratory, Bertz observed the same phenomenon on heating **1** with **2** in sodium hydroxide/methanol.[5] A variety of [*n*.3.3]propellanediones and other 1,5-disubstituted *cis*-bicyclo[3.3.0]octane-3,7-diones were prepared in an alkaline medium.[3,4,6]

In a synthetic (not mechanistic) sense, the generation of the two five-membered rings from the reaction of **1** and **2** parallels the generation of two six-membered rings in the Diels–Alder reaction, as illustrated at the bottom of Scheme 1. Consequently, this facile generation of two polyquinane rings from aliphatic precursors prompted the investigation of the condensation with a variety of substrates in order to explore the scope of this process.

Close examination of the *cis*-bicyclo[3.3.0]octane-3,7-dione skeleton reveals that it comprises the basic component of all polyquinane natural and non-natural products. At least one retrosynthetic pathway will always be present in this series of compounds which will involve a *cis*-bicyclo[3.3.0]octane system. Consequently, an efficient general method for the synthesis of polyquinanes would constitute an approach in which the *cis*-bicyclo[3.3.0]octane unit is easily constructed and one in which the regiospecific introduction of substituents onto the molecule is readily accomplished. Moreover, the presence of oxo functions at positions-3 and -7 in the *cis*-bicyclo[3.3.0]octane framework renders this molecule a precursor for the preparation of polyquinenes,[7] and polyquinanes. Following this approach, a number of polyquinanes and polyquinenes have been prepared in our laboratories and include (Fig. 1): staurane-2,5,8,11-tetraene **7**[8] and the corresponding [5.5.5.5]fenestrane, staurane **12**, modhephene **9**[9], as well as tetracyclo[6.6.0.$0^{1,5}$.$0^{8,12}$]tetradecane **13** and the corresponding 3,6,10,13-tetraene **6**.[10] Furthermore, triquinacene **8**,[11,12] the related triquinane triene **5**,[13] the parent hydrocarbon **14**, and [3.3.3]propellane **11**,[3d] as well as many 1-substituted *cis*-bicyclo[3.3.0]octane-3,7-diones (see **10**) have been synthesized.

This method has also been employed for the synthesis of several polyquinane natural products including gymnomitrol,[14a] quadrone,[14b] isocomene,[14c] modhephene,[9] pentalenene,[14d] bifurcarenone,[14e] and loganin,[14f] as well as several non-natural products including semibullvalenes,[15] [5]peristylane[16] and [2_2]-(1,5)-cyclooctatetraeneophane.[17]

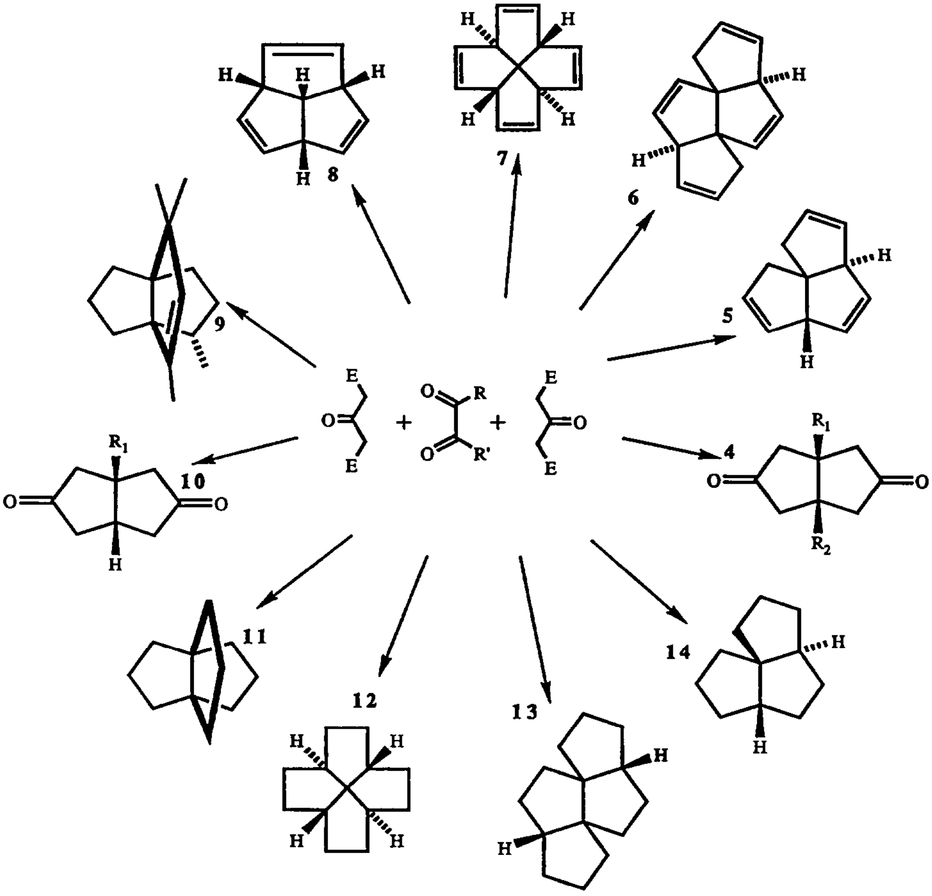


Fig 1 Polyquinanes and polyquinenes synthesized via the Weiss reaction

In order to test the validity of the general approach, efforts have recently centered on the synthesis of a number of polyquinenes of interest both in a computational and chemical sense. These targets are depicted in Fig. 2 and include: 10Π *cis*-tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodeca-1,3,5,7,9-pentaene **15**,[18] 14Π dicyclopenta[*a*,*e*]pentalene **16**, dicyclopenta[*a*,*d*]pentalene **17**,[19] pentaleno[2,1-*b*: 5,4-*b*′]diindole **18**,[20] 1,10-dimethyltricyclo[5.2.1.$0^{4,10}$]decane-2,5,8-triene **19**,[12] tetracyclo[5.5.2.$0^{1,8}$.$0^{4,8}$]tetradecane-2,5,13-triene **20**,[12] tetracyclo[11.5.2.$0^{1,8}$.$0^{4,8}$]eicosa-2,5,19-triene **21**,[21] tetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$]tridecanehexaene **22**[8,22] and tetracyclo[6.6.1.$0^{4,15}$.$0^{12,15}$]pentadecane-heptaene **23**.[22]

From the above discussions, it is clear that the most obvious attribute of this condensation is the facile construction of the *cis*-bicyclo[3.3.0]octane ring system In a single reaction, four carbon–carbon bonds and two rings are formed. Recently, Bertz has reported a method of synthetic analysis based upon graph theory.[23] Analysis of the Weiss reaction using this approach indicates that it is comparable to the Diels–Alder reaction for the rapid generation of molecular complexity in a single step.[23] Posner has referred to this process as a 3-component (3 + 2 + 3) coupling reaction and points out that an overall yield of 90% in the Weiss reaction can be viewed as an average yield of 97.5% for each of the new carbon–carbon bonds so formed.[24] It is important to note that only the *cis*-bicyclo[3.3.0]octane-3,7-dione stereoisomer is produced in the Weiss reaction. Examination of the mechanism of the condensation clearly indicates that a series of thermodynamic equilibria exist

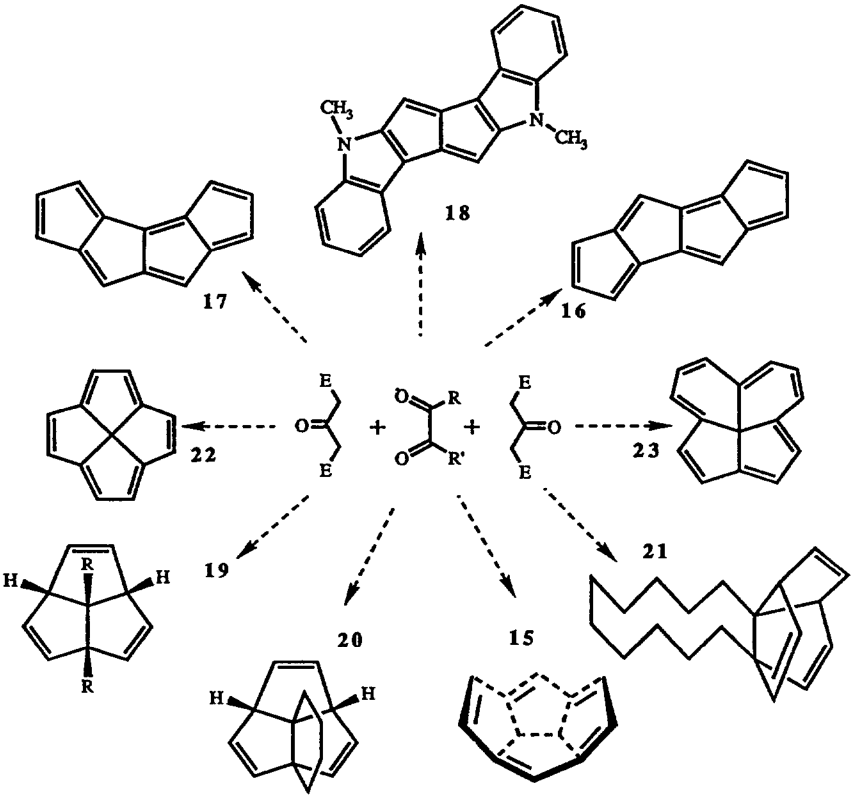


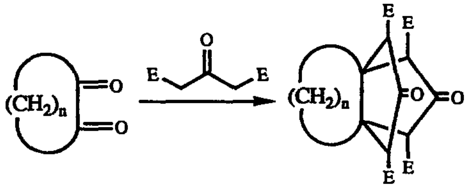
Fig 2 Polyquinenes of interest in synthetic and computational chemistry

during formation of the *cis*-bicyclo[3.3.0]octanedione system, as illustrated in reference 6. The stereochemical preference for the *cis* isomer in this condensation is not surprising, since the *cis* isomer of bicyclo[3.3.0]octane was shown by Barrett and Linstead to be more stable than the corresponding *trans* isomer by 6.1 kcal/mole.[25,26]

The ability to form multicyclic ring systems via the Weiss reaction has been used successfully for the synthesis of a wide range of [*n*.3.3]propellanes with $n > 3$. A survey of the reactants and yields employed in this process is illustrated in Table 1. Earlier the synthesis of [*n*.3.3]propellanediones with ring systems as large as twelve carbon atoms had been accomplished; the [10.3.3]propellanedione, for example, was obtained from cyclododecane-1,2-dione in 94% yield.[3a] Since large alicyclic 1,2-dicarbonyl compounds exhibit limited solubility in aqueous media, Ginsburg developed the preparation of the [22.3.3]propellanedione by a modification of the Weiss conditions in non-aqueous solution employing methanolic potassium hydroxide and benzene.[27] Sukenik has also utilized the same modification to obtain the [22.3.3]propellanedione (55% yield)[28] and Ginsburg has extended the series to include the [38.3.3]propellanedione.[29] The successful modification of the conditions of the Weiss reaction by Ginsburg[27] to include water insoluble substances further increases the versatility of this reaction.

The Weiss reaction has been shown to occur in a general fashion for a variety of 1,2-dicarbonyl compounds; 1,2-diketones, α-ketoaldehydes, and glyoxal all react with dimethyl 3-oxoglutarate to yield the corresponding *cis*-bicyclo[3.3.0]octanedione tetraesters. A survey of the reactants and yields for the preparation of aliphatic and aromatic substituted *cis*-bicyclo[3.3.0]octane-3,7-dione tetraesters is illustrated in Tables 2 and 3. The versatility of this reaction permits the simple and

Table 1. The preparation of [*n* 3.3] propellanediones via the Weiss reaction



1,2 Diketone	n	pH	Time	Yield	References
Cyclobutane 1,2-dione	2	5.6-6.8^a	8 h	0%^{c}	49
Cyclobutane 1,2-dione	2	8.3	8 h	0%^{c}	49
Dimethyl Squarate	2	5.6-6.8^a	24 h	No Rxn	3d
Cyclopentane 1,2-dione	3	6.6	4 d	45%	1,3d
Ninhydrin	3	8.3	72 h	60%	3b
Cyclohexane 1,2-dione	4	5.6-6.8^a	7 d	81%	1,3d,12
Phenanthrenequinone	4	>12^d	24 h	68%	56
Cyclooctane 1,2-dione	6	5.6-6.8^a	24 h	80%	3a
Cyclooct-5-ene 1,2-dione	6	8.3	24 h	>85%	57
Cyclododecane 1,2-dione	10	5.6-6.8^a	24 h	94%	3a
Cyclotetradecane 1,2-dione	12	5.6-6.8^a	3 d	70%^{b}	28
Cyclodocosane 1,2-dione	20	> 9	10 d	70%^{b}	27
Cyclotetracosane 1,2-dione	22	> 9	10 d	70%^{b}	28
Cyclotetracontane 1,2-dione	38	--	--	40%	29

[a] The citrate-phosphate buffer used in these reactions has an initial pH of 5.6, however, addition of MeOH to solubilize the starting diketones raises the pH to between 6.0 and 6.8.

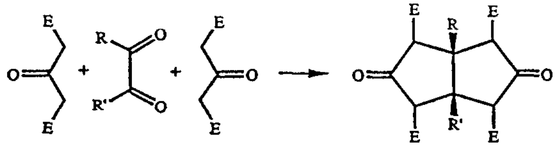
[b] These yields are of the corresponding propellanediones.

[c] No 1,2 adducts were formed in either of these reactions, instead hydrolysis and rearrangement of cyclobutane-1,2-dione occurred to form 1-hydroxy cyclopropane carboxylic acid

[d] NaOH/MeOH, Δ.

facile construction of monosubstituted and 1,5-disubstituted *cis*-bicyclo[3.3.0]octane-3,7-diones. Another important feature of this reaction is the production of bicyclo[3.3.0]octane systems rich in functionality. The diketotetraester formed in this process has handles built into it for substitution at the remaining positions. The substituents at positions C-1 and C-5 can be controlled through the choice of the dicarbonyl starting material. Both the tetraester and its hydrolysis product can be alkylated by standard procedures to introduce substituents at positions -2, -4, -6 and -8. Methods which will be discussed later offer potential for the regioselective introduction of substituents at positions -2 and -6 or positions -2 and -8. The carbonyl functions at positions -3 and -7 permit the introduction of substituents at the remaining two carbon atoms. More importantly, these carbonyl groups provide a means for the construction of more complex polyquinenes as mentioned. Once the appropriate functional groups have been incorporated into the molecule by one of the methods

Table 2 The preparation of aliphatic substituted 2,4,6,8-tetramethyl *cis*-bicyclo[3.3.0]octane-3,7-dione tetracarboxylates via the Weiss reaction



Dicarbonyl Compound	R,R'	Conditions	pH	Yield of 1:2 Adduct	References
Glyoxal	H,H	Aq. Buffer	5.3	15-30%	1,5
		Aq. Buffer	8.3	77%	4
		NaOH/MeOH,Δ	>12	60-75%	5,41
Methyl glyoxal	Me,H	Aq. Buffer	5.0	52%	1
		Aq. Buffer	8.4	80%	4
Biacetyl	Me,Me	Aq. Buffer	5.0	60%	1
		Aq. Buffer	8.3	70-90%	4,31
1,4-Dibromo-2,3-Butanedione	CH_2Br,CH_2Br	Aq. Buffer	5.6	0%	49
		Aq. Buffer	8.3	0%	49
2,3-Pentanedione	Et,Me	Aq. Buffer	8.3	75%	49
2,3-Hexanedione	Pr,Me	Aq. Buffer	8.3	70%	49
4,5-Dioxopentanoic acid	$CH_2CH_2CO_2H$,H	Aq. Buffer	6.8	80%	58
4,5-Dioxohexanoic acid	$CH_2CH_2CO_2H$,Me	Aq. Buffer	6.8	84%	14c,59
Ethyl 4,5-dioxo-hexanoic acid	$CH_2CH_2CO_2Et$,Me	Aq. Buffer	6.8	80%	59
Methyl-2,3-dioxobutanedionate	CO_2Me	Aq. Buffer	6.8	18%[a]	60
Ethyl 3-(Ethoxy carbonyl methyl)-4,5-dioxopentanoate	$CH_2(CH_2CO_2Et)_2$,H	Aq. Buffer	8.3	51%	6
3-Allyl-1,1-dioxo-5-hexene	$CH_2(CH{=}CH_2)_2$,H	Aq. Buffer	8.3	30%	49
1-(3'Cyclopentenyl)-1,2-ethanedione	C_5H_7,H	Aq. Buffer	5.6	78%	61
		Aq. Buffer	8.3	83-90%	61
1-(4'Cycloheptenyl)-1,2-ethanedione	C_7H_{11},H	Aq. Buffer	8.3	70%	6,62
Bis cyclopentyl-1,2-ethanedione	C_5H_9,C_5H_9	NaOH/MeOH,Δ	>12	12	49
Bis cyclohexyl-1,2-ethanedione	C_6H_{11},C_6H_{11}	NaOH/MeOH,Δ	>12	0%	63
Bis cyclopentenyl-1,2-ethanedione	C_5H_7,C_5H_7	NaOH/MeOH,Δ	>12	10	49
1-Phenyl-1,2-ethanedione	C_6H_5,H	Aq. Buffer	8.3	66%	3b
1-Phenyl-1,2-propanedione	C_6H_5,CH_3	Aq. Buffer	8.3	68%	49
		NaOH/MeOH,Δ	>12	50%	49

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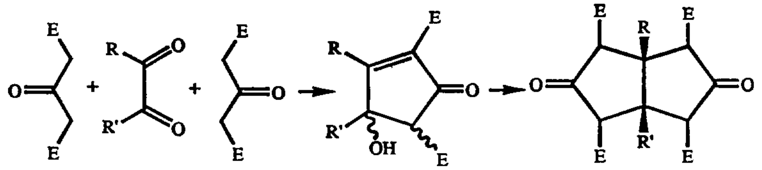
[a] The reported yield is of the hydrolysis product of the 1:2 adduct tetraester

Table 3 The formation of 1 : 1 and 1 : 2 adducts from the Weiss reation of dimethyl 3-oxoglutarate with 1,2-dicarbonyl compounds bearing bulky substituents executed in highly basic media ($NaOCH_3/CH_3OH$)



1:1 Adduct

Dicarbonyl Compound	R,R'	% Yield of 1:1 Adduct	Yield of 1:2 Adduct	References
Benzil	C_6H_5	70%	0%	3b
Phenanathrenequinone	σ,σ' biphenyl	68%	53%	56
2,2'-Pyridil	C_5H_4N	69%	0%	49
2,2'-Thenil	C_4H_3S	77%	0%	56
2,2'-Furil	C_4H_3O	52%	60%	64
Bis(cyclohexyl)ethane-1,2-dione	C_6H_{11}	61%	0%	63

discussed above, intramolecular carbon–carbon bond forming processes can yield an array of polyquinane ring systems.

2. STUDIES DIRECTED TOWARD THE SYNTHESIS OF *CIS*-TETRACYCLO[7.2.1.$0^{4,11}$.$0^{6,10}$]DODECA-3,5,7,9-TETRAENE (25) AND 10,11-DIMETHYL-*CIS*-TETRACYCLO[7.2.1.$0^{4,11}$.$0^{6,10}$]DODECA-3,5,7,9-TETRAENE (26)

Since the introduction of the 10Π annulene system by Vogel *et al.* in 1964,[30] the concept of maximizing $(4n+2)\Pi$ delocalization by imposing conformational rigidity has prompted investigation of the chemistry of non-benzenoid aromatic systems. In this connection polyquinenes **15** and **24** were studied earlier from a computational point of view.[31,32] According to ring current criteria, Jung[33] predicted that dicyclopenta[*cd*,*gh*]pentalene **24** would be aromatic; however, Binsch[34] proposed that **24** would behave as an antiaromatic species due to its second-order double-bond fixation. Nakajima *et al.* employed semi-empirical SCF-MO theory in conjunction with the variable bond length technique to arrive at the same conclusion.[35] Hess[32] and Garratt[36] have also studied the stability of systems such as **15** and **24**. Moreover, MNDO calculations from our laboratory[19] (Table 4) and MM2 computations from Paquette *et al.*[39] have described the increase in strain energy in going from **15** to **24** as substantial. Recently Glidewell and Lloyd have reported a study of the bond orders of **24** via MNDO calculations.[38] They conclude that **24** can be regarded either as a bis(ethylene-bridged)pentalene or as an ethenobridged[10]annulene, but all the double bonds are essentially isolated from one another. In other words **24** should behave as a highly reactive olefin with no sign of peripheral Π delocalization[38] in contrast to the earlier hypothesis of Platt (Fig. 3).[31]

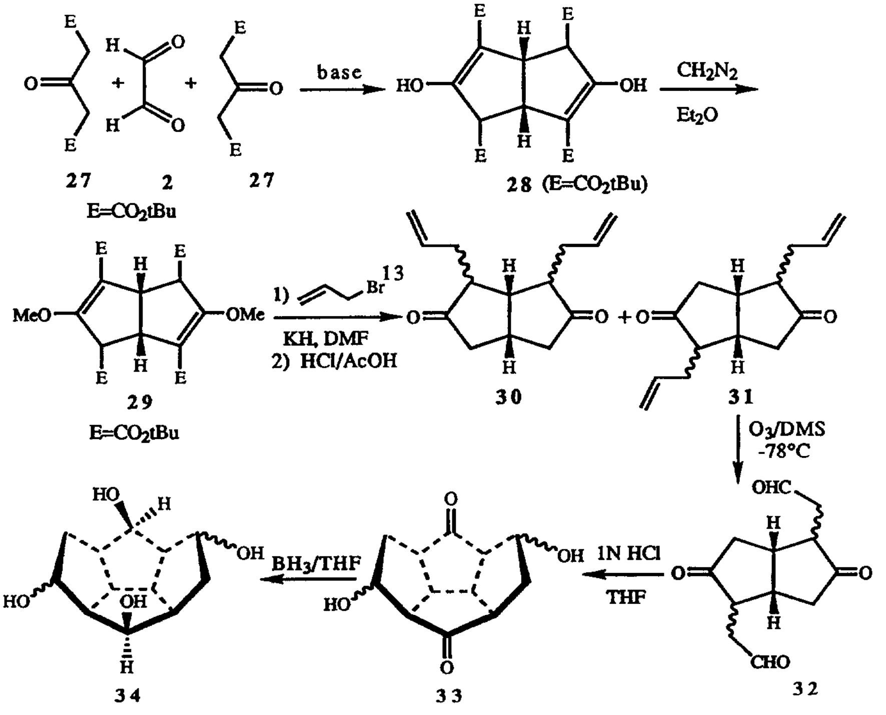
24 **15** **25a**, R=H **26a**, R=CH_3 **25b**, R=H **26b**, R=CH_3

Fig 3

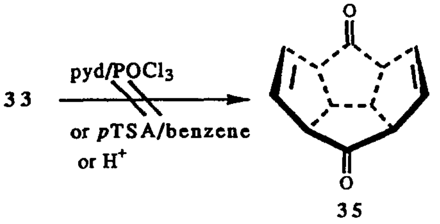
Table 4. MNDO-Calculated heats of formation[19]

	 25a	 25b	 15a	 15b	 24a planar represen- tation	24b nonplanar represen- tation
H_f (kcal/mole)	95.9	97.1	166.3	178.8	408.3	255.9
Total Energy (eV)	1672.4	1672.4	1641.0	1640.5	1602.2	1698.8
I.P. (eV)	8.9	8.8	8.0	8.5	8.5	8.5
no. πe	8	8	10	10	12	12
strain energy (kcal/mol)	56.7	56.7	108.2	-	-	-

Since the previously reported difference in the heat of formation between tetraene **25a** and isomeric olefin **25b** was approximately 1 kcal/mole,[19] a route to either of these olefins was considered a viable approach toward *cis*-tetracyclo[7.2.1.$0^{4,11}$.$0^{6,10}$]dodeca-1,3,5,7,9(12)-pentaene **15**. Outlined below are efforts directed toward the synthesis of either **25** or **26** which ultimately resulted in the synthesis and observation of the tetraene **25a** as a transient intermediate. The synthesis began with the 2,6-diallyl-*cis*-bicyclo[3.3.0]octane-3,7-dione **31** available from the Weiss reaction,[1] as illustrated in Scheme 2. In brief, di-*t*-butyl 3-oxoglutarate **27** and glyoxal **2** were converted into the bisenol **28**



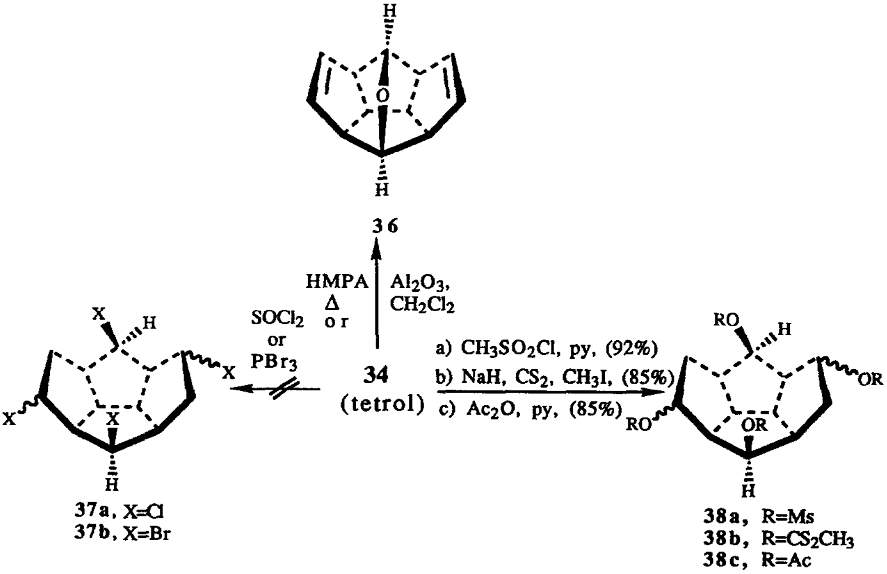
Scheme 2



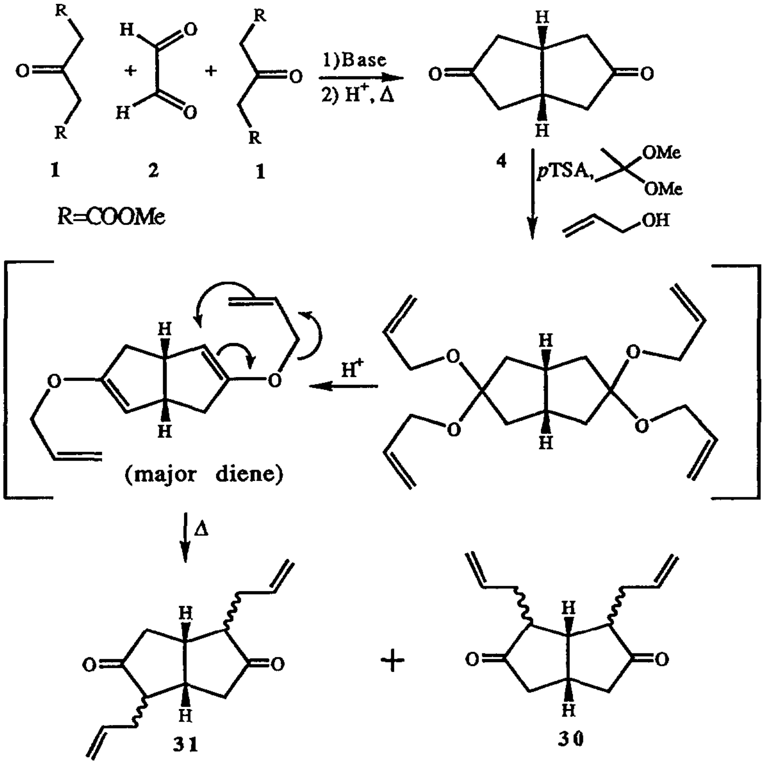
Scheme 3

in high yield under alkaline conditions. Conversion of **28** into the bisenol ether **29** was effected with diazomethane in excellent yield. Alkylation of the tetra-*t*-butyl ester **29** with allyl bromide was carried out in two separate steps, followed by hydrolysis. This gave a mixture of the 2,8-diallyl **30**- and 2,6-diallyl (**31**)-*cis*-bicyclo[3.3.0]octane-3,7-diones, in an overall yield greater than 90% from bisenol ether **28**. Separation of the 2,6-regioisomer **31** from **30** was followed by treatment of **31** with ozone to provide the dialdehyde **32** which underwent a facile bisaldol cyclization under carefully chosen conditions of high dilution.[19] This procedure provided the diketodiol **33** in 70% yield. All attempts to convert the diol **33** into the known dienedione **35**[39] (Scheme 3) under conditions of dehydration were unsuccessful. Either products of retro-aldol reactions[40] or unidentified oligomers which contained ether linkages were obtained.

At this stage the diketodiol **33** was treated with an electrophilic reducing agent (BH_3-THF) to provide the tetrol **34** in greater than 90% yield. The stereochemistry of the hydroxy groups was established as indicated earlier[19] and the mixture (9 : 1) of isomeric tetrols was employed as described below. When the tetrol **34** was heated in HMPA, analogous to the conditions employed for the synthesis of various triquinacenes,[11,12] only the tetracyclic ether **36** was isolated.[19] In an effort to convert the tetrol into an appropriately substituted precursor of tetraene **25**, the tetraquinane tetrol **34** was treated with PBr_3 or $SOCl_2$, under a variety of conditions, but neither **37a** nor **37b** was observed (Scheme 4), respectively. The tetrol (**34**) could, however, be converted into the tetramesylate **38a** (92%), tetraxanthate **38b** (85%) or tetraacetate **38c** (85%) under standard conditions, as illustrated in Scheme 4.



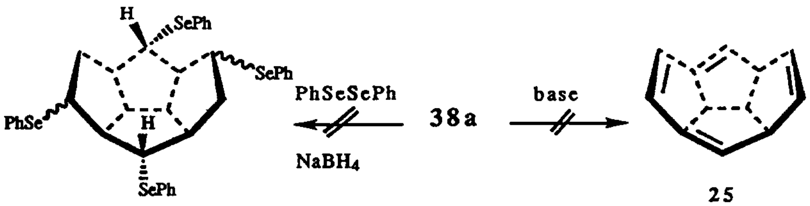
Scheme 4.



Scheme 5

Although the starting 2,6-diallyldione **31** could be prepared on a 15–20 gram scale, some of the problems associated with the route depicted in Scheme 2 are as follows: (1) the synthesis of large quantities of **27** is time consuming and its cost (Fluka) is prohibitively expensive; (2) the protection/deprotection steps render the sequence lengthy; (3) the route employs large quantities of diazomethane which should be avoided, if possible. For the above reasons a cheaper, shorter route to the 2,6-diallyl dione **31** was developed (Scheme 5). Since *cis*-bicyclo[3.3.0]octane-3,7-dione is available in kilogram quantities[41] from dimethyl 3-oxoglutarate **1** and glyoxal **2** the approach centered on allylation of this material via a Claisen rearrangement. When *cis*-bicyclo[3.3.0]octane-3,7-dione **4** was heated in toluene with an excess of allyl alcohol and dimethoxypropane in the presence of *para*-toluenesulfonic acid, an 80% yield of a mixture of 2,8-diallyl (**30**) and 2,6-diallyl (**31**)-*cis*-bicyclooctanediones was isolated.[42] The two diones were obtained in a ratio of 2 : 3 with the desired isomer predominating. This result was gratifying for the sequence was not only shorter than the route in Scheme 2 but employed the much less expensive **1**.

With a shorter preparation of 2,6-diallyl dione **31** in hand, efforts were redoubled toward the synthesis of tetraene **25**. The tetramesylate **38a** was treated with a variety of bases under conditions of E_2-elimination; however, only polymeric material was obtained. Moreover, stirring **38a** with alumina, analogous to the conditions of Deslongchamps (Scheme 6),[43] gave only the tetracyclic ether **36**, albeit in moderate yield. All efforts to convert **38a** into the tetraphenylseleno derivative **39** under the conditions of Jones *et al* [44] were also not successful. Attempted pyrolysis of tetraacetate **38c** under high vacuum in the presence or absence of diphenylisobenzofuran (DPIBF)[45] or to trap the tetraene **25** under conditions of E_2-elimination[46] were likewise unsuccessful. As a final resort the pyrolysis of tetraxanthate **38b** was pursued under a variety of conditions. Pyrolysis under high vacuum with or without the addition of DPIBF gave only black polymeric material. Pyrolysis of



39 (not observed)

25

Scheme 6

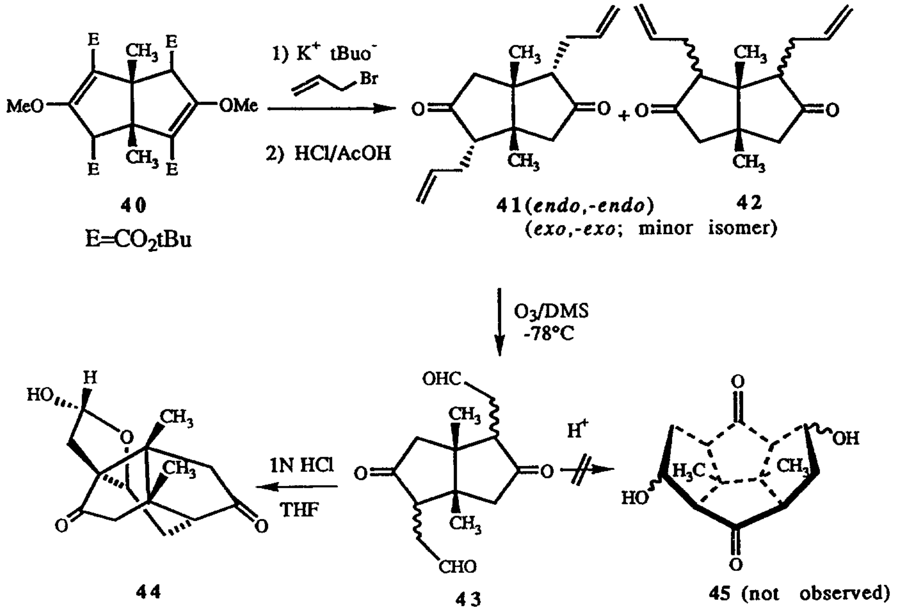
tetraxanthate **38b** in the mass spectrometer, however, gave an ion consistent with the structure of **25** as a transient intermediate.[47]

Although the four xanthate groups were removed, neither a trace of **25** nor a suitable Diels–Alder adduct with DPIBF was isolated. Although most reactions were carried out under an inert atmosphere, the inability to trap or isolate **25** may be due to the ability of the tetraene to selfcondense into polymeric material or to react with oxygen or moisture.

The synthesis of tetraene **25** in which the convex face was hindered to attack or prohibited from selfcondensation might provide a means in which to isolate a pentaene related to **15**. This approach has been employed successfully by Hafner during the synthesis of pentalenes stabilized by the presence of *t*-butyl substituents.[48]

Close examination of the structure of **25** indicated that substitution of methyl for hydrogen at positions -10 and -11 (see **26a**, **26b**) would not only retard selfcondensation, but would also provide a probe with which to monitor any anisotropy (upfield shift) due to Π delocalization. By taking advantage of the Weiss reaction, the two requisite methyl functions can be installed by replacing glyoxal with biacetyl with minimal departure from the previous route. The known bisenol ether **40**[12] was alkylated with allyl bromide in THF in the presence of potassium *t*-butoxide. The mixture of diallyl tetraesters was not separated or characterized, but rather the crude mixture of tetraesters was hydrolyzed and decarboxylated (HOAc/aqHCl/Δ). Since the 2,6-*endo*-*endo*-diallyl-1,5-dimethyl-*cis*-bicyclo[3.3.0]-octane-3,7-dione could now be synthesized on a preparative scale, attention turned to transformation of **41** into the 10,11-dimethyl-2,7-dihydroxy-*cis*-tetracyclo[7.2.1.0^{4,10}.0^{6,10}]-dodecane-5,12-dione **45**. Conversion of **41** into a mixture of stereoisomeric *exo*/*endo* bisaldehydes represented by **43** was accomplished via ozonolysis at −60°C in 98% yield. It was anticipated that the *endo*-*endo* diastereomer would predominate based upon previous results in this series.[12,49] The bisaldolization of **43** was effected under acidic conditions at high dilution to promote intramolecular reaction in similar fashion to the synthesis of diketodiol **33** (Scheme 2). Unfortunately, bisaldehyde **43** cyclized to provide the transannular product **44** rather than the desired 10,11-dimethyl diketodiol **45** (Scheme 7). This type of transannular cyclization was previously observed by Pattenden,[50] Paquette,[51] and during the synthesis of 1,10-dimethyl triquinacene.[12,49] In the latter case, evidence from X-ray crystallography indicates that methyl–methyl repulsion in the 1,5-dimethyl-*cis*-bicyclo[3.3.0]octane-3,7-dione skeleton causes a twist of the two cyclopentanoid units,[49] a result of which favors transannular cyclization. It is important to reiterate that aldol cyclization in the parent bisaldehyde **32** gave the desired bis-aldol **33** as the major product with only minor contamination from products of transannular cyclization.[52a] All attempts to effect equilibration of **44** into **43** under acidic or alkaline conditions were unsuccessful.

According to MNDO calculations (Table 4), the increase in the heat of formation in going from tetraene **25** to pentaene **15** is approximately 70 kcal/mole. Moreover, the increase in going from **15** to hexaene **24** is even greater. In addition, the increase in strain energy between tetraene **25** and pentaene **15** is 52 kcal/mole and would be expected to be larger for cyclopentapentalene **24**. Observation of the tetraene **25** under high vacuum in the mass spectrometer, but failure to isolate

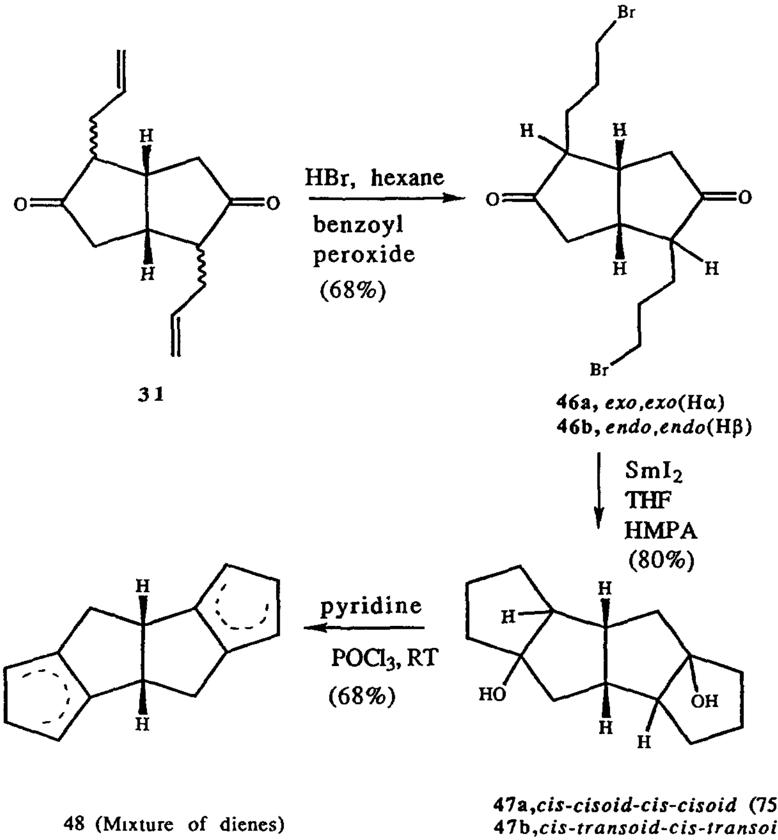


Scheme 7.

or trap (DPIBF) the compound illustrates the instability of this highly reactive olefinic system reminiscent of the properties of the related diene(*ii*).[53] This reactivity presumably would occur with either pentaene **15** or tetraene **25** in the presence of radicals or carbenium ions precluding a route toward hexaene **24** by either of these approaches, albeit the dianion chemistry pioneered by de Meijere toward acepentalene[54] might circumvent some of these difficulties. Even if Π delocalization in 10Π annulene **15** were to occur, the resonance energy ($\ll 36$ kcal/mole) gained from this overlap would not be enough to offset the increase in energy in going from **25** to **15** (70 kcal/mole). The preparation of tetraene **25** has also eluded Paquette *et al.*,[39] as well as Prinzbach in a related system.[55] Although the reactivity of **25** does not bear directly on the stability of **24**, examination of energy considerations via MNDO (Table 4) and the character of **25** described herein support the contention by Binsch,[34] Nakajima[35] and Glidewell *et al.*[38] that **15** and **24** should behave as highly reactive olefins rather than the delocalized Π systems of Platt[31] and Jung.[33]

3. PROGRESS TOWARD 14Π DICYCLOPENTA[*a*,*e*]PENTALENE (16) AND 14Π DICYCLOPENTA[*a*,*d*]PENTALENE (17)

Examination of the electronic character of the tetracyclic pentalenes **16** and **17** via a simple Hückel MO approach suggests that these molecules might exhibit aromatic character; however, quantum calculations indicate[32,35,65,66] that both **16** and **17** should possess very little resonance energy, and in fact, might be antiaromatic. In regard to this question, Hafner *et al.* have synthesized and characterized the hindered tetra-*t*-butyl derivative of **16**.[48] Interestingly, it was determined (NMR) that the double bonds in the tetra-*t*-butyl derivative of **16** were fixed, as predicted earlier by Nakajima *et al.*[65] In view of the above uncertainties, efforts in our laboratory have been directed toward the synthesis of **16** and **17**. As discussed above during the approach toward the 10Π annulene



31

46a, *exo,exo*(Hα)
46b, *endo,endo*(Hβ)

48 (Mixture of dienes)

47a, *cis-cisoid-cis-cisoid* (75)
47b, *cis-transoid-cis-transoid* (10)

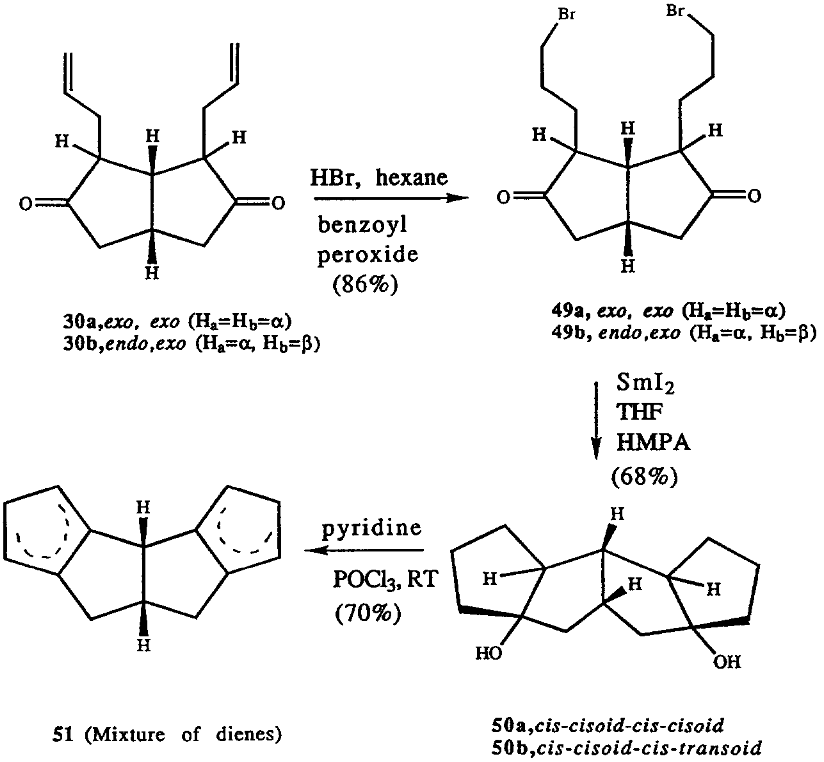
Scheme 8

15, the 2,8-diallyl and 2,6-diallyl-*cis*-bicyclo[3.3.0]octane-3,7-diones **30** and **31** were obtained in gram quantities from allyl alcohol and *cis*-bicyclo[3.3.0]octane-3,7-dione **4** via a Claisen rearrangement (Scheme 5).[42]

The anti-Markovnikov addition of hydrogen bromide to 2,6-regioisomer **31** gave 2,6-bis(3-bromopropyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione **46** as a mixture of diastereomers in yields ranging from 68 to 80%. Several approaches to effect the simultanous cyclization of the bromopropyl substituents with the carbonyl units in **46** to provide **47** via a carbanionic approach were envisaged. These were ineffective, consequently, the dibromo-dione **46** was reacted with samarium diiodide (HMPA-THF) via the conditions of Molander[67] to provide a mixture of the stereoisomeric tetracyclic diols **47a** and **47b** in an approximate ratio of 15 : 2. The overall yield of this process was 80% (Scheme 8).

Based on the successful conversion of diallyl dione **31** into perhydrodicyclopentapentalene **47**, the 2,8-diallyl dione **30** was reacted with HBr in the presence of peroxides. This process proceeded cleanly and in high yield (86%) to provide the two epimeric dibromides **49a** and **49b**. When this epimeric mixture of dibromides **49** was stirred with samarium diiodide at room temperature for several hours, the simultaneous cyclization of the two bromoalkyl substituents occurred to furnish the perhydrodicyclopenta[*a*,*d*]pentalene system **50** in 68% yield. The ratio of the two diastereomeric tetraquinanes **50a** and **50b** is at least 30 : 4 based on NMR spectroscopy (Scheme 9).[19,52a] A similar tetracycle has been prepared via the Weiss reaction by Keese and Schüttel.[52b]

Preliminary experiments have been carried out with regard to the removal of the hydroxyl groups from tetraquinane diol **47** to provide diene **48**. Although six isomeric dienes are possible, treatment



Scheme 9

of **47** with POCl$_3$ or (1,1,1,3,3,3-hexafluoro-2-phenyl-2-propoxyl) diphenylsulfurane[68] resulted in four isomeric dienes which were observed by gas chromatography and GC–mass spectroscopy. Since all four dienes were useful for the preparation of **16**, they were not separated. The analogous transformation was also effected with the mixture of diols represented by **50** to provide diene **51** (Scheme 9) as a mixture of olefinic isomers. Studies are currently underway to convert **48** and **51** into the 14Π-annulenes dicyclopenta[*a*,*e*]pentalene **16** and dicyclopenta[*a*,*d*]pentalene **17**, respectively.

4. SYNTHETIC APPROACH TO DIAZAPENTALENO[2,1-*b*:5,4-*b*′]DIINDOLES

Numerous attempts to isolate pentalene **52** by conventional synthetic methods over the last sixty years have been unsuccessful;[69] however, 1-methylpentalene was prepared and was observed to dimerize at −140°C.[70] The presence of bulky substituents in the pentalene framework appears to prevent dimerization. For example, the hexaphenyl,[71] bis(1,3-dimethylamino),[72] 1,3,5-tri-*t*-butyl[73] and benzoannulated pentalenes[74a] have been isolated and exhibit substantial stability.

A group of pentalenes studied less extensively include those wherein one or two heteroatoms have been incorporated into the pentalene skeleton.[75,76] One example in this category is 10-phenyldibenzo[*b*,*f*-1]azapentalene **54a** synthesized several years ago by Eisch and Abraham.[76] All attempts to prepare the parent dibenzo[*b*,*f*-1]azapentalene **54b** have been unsuccessful. Electron transfer reactions appear to be the origin of dimers formed in this series rather than the intermediate azapentalene **54b**.[77] Numerous radical anions and trianions related to pentalenes have been studied extensively,[78] but formation of dications in this series has, to date, eluded experimentalists. There is only one report in which a pentalene stabilized by heteroaromatic rings has been synthesized, the structure of which is represented by **55**.[79] LeGoff and Camp prepared the dipyrazolopentalene **55**,

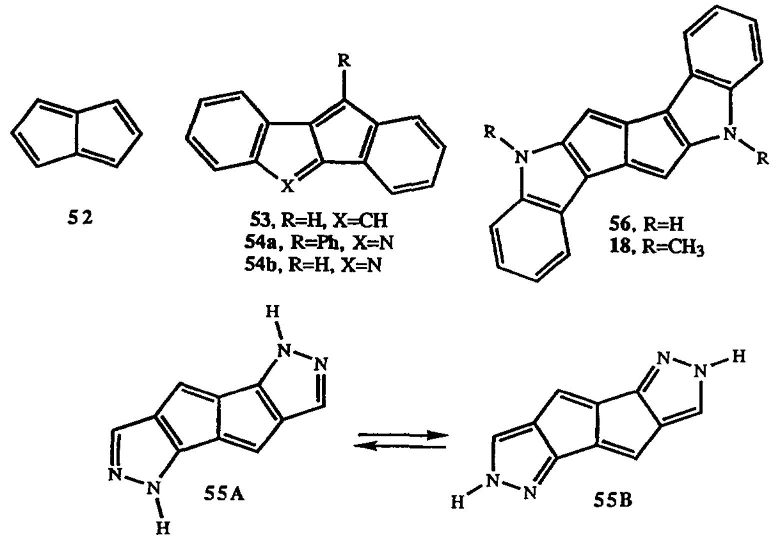
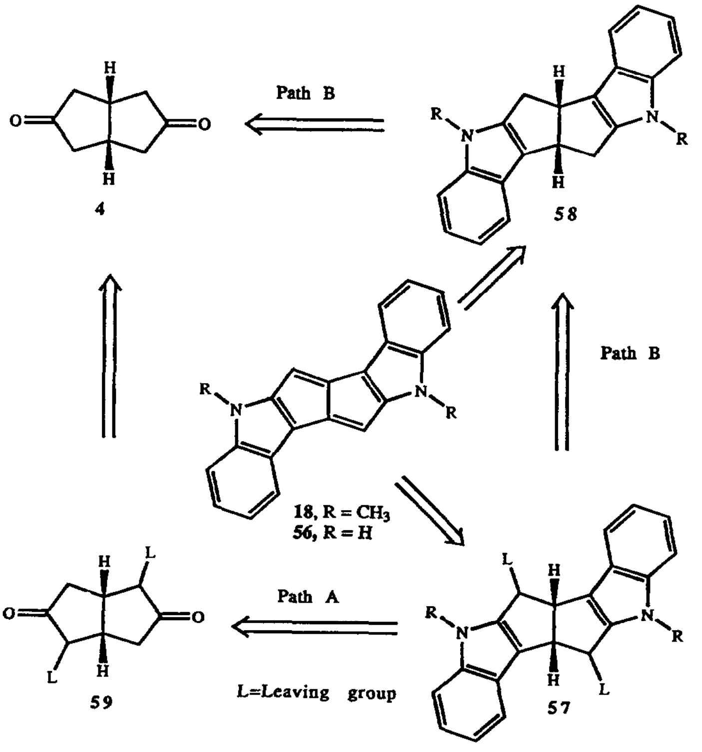


Fig 4

a heteroannulated analog of dibenzopentalene, the stability of which is presumably enhanced by the contribution of structures **55A** and **55B**.

In connection with a program directed toward the synthesis of cyclopentapentalenes,[19] it was of interest to synthesize either azapentalene **18** or **56**, both of which are diindole analogs of dibenzopentalene **53** (Fig. 4). As illustrated in Scheme 10, the bisindole substituted azapentalenes

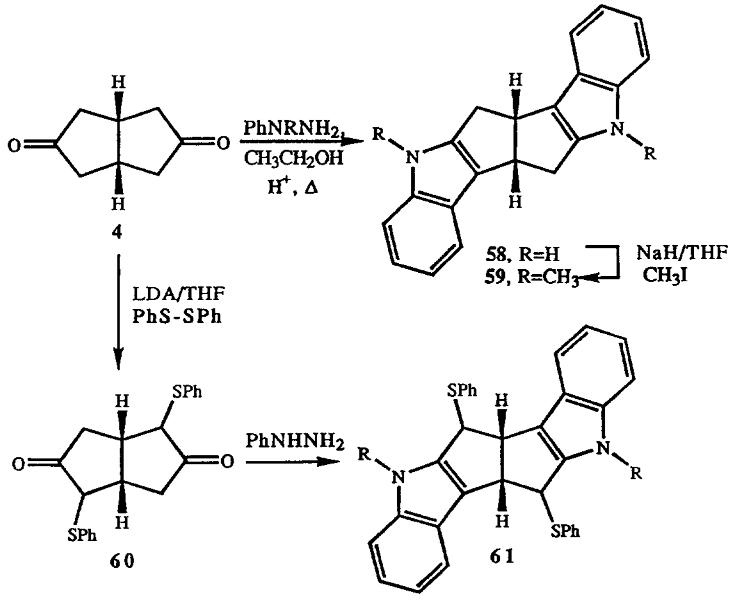


Scheme 10 Retrosynthetic analysis.

18 and **56** could arise from the loss of two molecules of LH from the suitably substituted dihydropentalene **57**. Two independent pathways were devised, one of which (path A) centered on the previous incorporation of the leaving groups into the *cis*-bicyclo[3.3.0]octane-3,7-dione unit (**4** → **59**)[79] followed by two simultaneous regiospecific Fischer indole cyclizations to furnish **57**. Path B involves a regiospecific bis Fischer indolization with the readily available *cis*-bicyclo[3.3.0]octane-3,7-dione **4**[1,41] to provide **58**, followed by introduction of the two leaving groups in a stereospecific manner.

The approach began, as noted, with **4** which is available on large scale from the Weiss reaction (Scheme 1).[1,41] The 2,6-bisphenylthio-*cis*-bicyclo[3.3.0]octane-3,7-dione **60** was originally prepared by the method of Bertz [5,80] It was later found that **60** could be obtained in an improved fashion by the method of Camp.[79] This involved treatment of **4** with LDA (10 M nBuLi was employed) at −78°C after which the dianion was quenched with diphenyldisulfide to give **60**. When bisphenyl sulfide **60** was heated with phenylhydrazine, under standard conditions of the Fischer indole cyclization,[81-83] a small amount of **61** was obtained, accompanied by several other compounds. Separation of this bisindole from the other components of the mixture (Scheme 11) proved difficult and this approach was abandoned in favor of that depicted in path B.

Analogous to previous work on the synthesis of bisindoles in our laboratory,[82,83] **4** was reacted with phenylhydrazine in the presence of a catalytic amount of hydrochloric acid. The bisindole **58** was isolated from this process in 20% yield as the sole identifiable material. Numerous reaction conditions (H_2SO_4, HOAc, polyphosphoric acid) were employed, none of which served to increase the yield of **58**. The bistosylhydrazone of **4** was also prepared[81,82] and subjected to Fischer indole cyclization; however, no increase in yield was realized. The mechanism of the Fischer indolization in regard to bisindole **58** involves two enehydrazine intermediates which simultaneously undergo [3,3]sigmatropic rearrangements, followed by the loss of ammonia to generate the tetrahydropentalenodiindole **58**.[81-83] When **58** was subjected to a variety of reagents to effect dehydrogenation [S, Se, Pd, DDQ, SeO_2, or MnO_2], only starting material was recovered. More vigorous conditions resulted in only products of decomposition and no evidence for the formation of pentalene **56** was

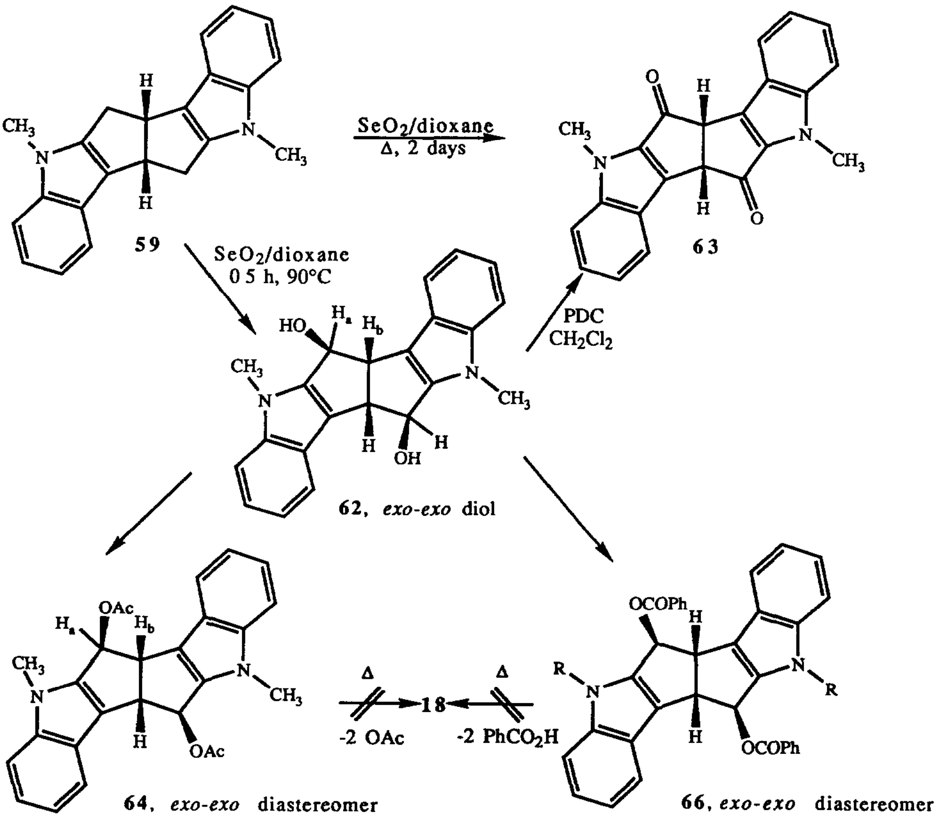


Scheme 11

observed. At this juncture it was decided to remove the influence of the two indole N–H groups on the stability of **56** by conversion into the bisdimethyl-tetrahydropentalene **59**. This was effected in 90% yield by treatment of **58** with sodium hydride and methyl iodide in tetrahydrofuran. A shorter route to **59** was developed by simply replacing phenylhydrazine with 1-methyl phenylhydrazine in the Fischer indole cyclization. This gave bis-(N-methyl)bisindole **59** in greater than 50% yield. Since six new bonds, two protecting groups (CH_3) and four rings were appended to the dione **4** in a one-pot reaction,^{24} no attempt to further improve the yield of **59** has been made. Again, when **59** was subjected to oxidation with a variety of dehydrogenating agents [Pd, S, Se, SO_2, MnO_2, $PdCl_2$, DDQ] similar to those employed with **58**, no evidence for the formation of azapentalene **18** was obtained. In these cases starting material or products of decomposition were observed (TLC). This is not surprising in regard to the high reactivity and reported antiaromatic character of pentalenes.$^{69-74,84}$

To functionalize the bisindole **59**, it was heated with selenium dioxide at 90°C to provide the *exo-exo*-diol **62** in 46% yield. A number of mono and dioxygenated by-products accompanied **62** in this process. Prolonged treatment of diol **59** with selenium dioxide in refluxing dioxane provided the diketone **63** in 56% yield.

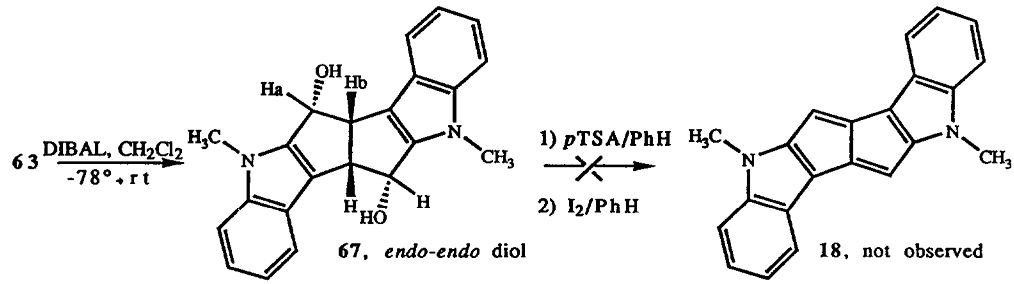
The diol **62** was also oxidized with PDC in dichloromethane to provide the diketone **63** in 90% yield, which confirmed the intermediacy of **62** on the pathway to **63** during oxidation with SeO_2. In order to attempt a *syn* elimination (pyrolysis), conversion of the diol **62** into the *exo-exo*-diacetate **64** or into the corresponding dibenzoate **66** was accomplished under standard conditions (Scheme 12). Thermally induced *syn* elimination of **64** or **66**, respectively, to provide pentalene **18** resulted



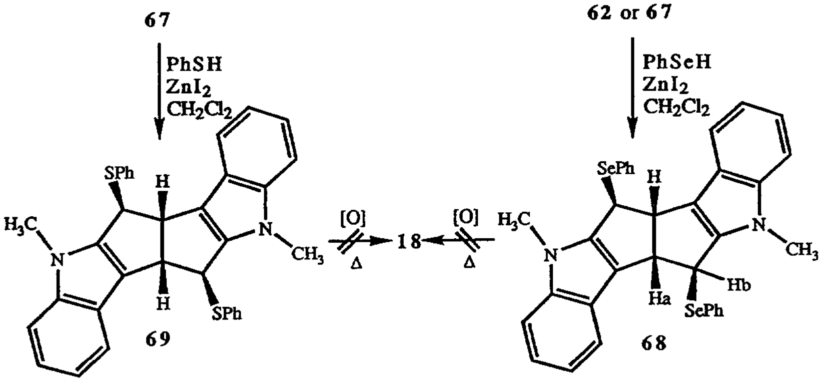
Scheme 12

in recovery of sublimed starting ester or tar like products of decomposition. However, pyrolysis of either diacetate **64** or dibenzoate **66** in the mass spectrometer (10^{-6} Torr) resulted in the observed loss of two molecules of acetic or benzoic acid, respectively, to provide an ion at 308 daltons. This corresponds to the mass required for the desired pentalene **18** and served as the base peak (100%) in the spectrum of diacetate **64** and an intense peak (70%) in the spectrum of the dibenzoate **66**. This ion was neither present in the mass spectrum of diol **62** nor of **67**. Experiments designed to convert the diol **62** into the bisdinitrobenzoate to provide better leaving groups for the *syn* elimination were unsuccessful and led only to products of decomposition or solvolysis. Treatment of dione **63** with diisobutylaluminum hydride in methylene chloride furnished the *endo-endo*-diol **67** in 95% yield. The stereochemistry of diol **67** is opposite to that of diol **62** (Scheme 13). When the *endo-endo*-diol **67** was treated with *o*-nitrophenyl selenocyanide,[85] a mixture of products was formed which lacked C_2 symmetry. However, it had been reported by Clarembeau *et al.* that hydroxyl groups which are suitably activated could be replaced by a phenylselenyl function via an S_N1 process.[86] Consequently, the *endo-endo*-diol **67** was stirred with benzeneselenol in dichloromethane in the presence of zinc iodide (Scheme 14) at room temperature to provide the *exo-exo*-bisphenylselenyl-*cis*-bicyclo[3.3.0]octane derivative **68** in 81% yield.

Initially **68** was treated with *meta*-chloroperbenzoic acid in dichloromethane. No evidence for either selenoxide or pentalene **18** formation was observed. These reactions either returned **68** or yielded black polymeric material. In an effort to isolate the bisphenylselenoxide intermediate, **68** was subjected to ozonolysis at low temperature. Neither the bisselenoxide nor pentalene **18** was isolated. Since the benzeneselenic acid which form during the elimination process might effect decomposition of **18**, the milder methods of oxidation reported by Davis[87] were explored. When **68**



Scheme 13



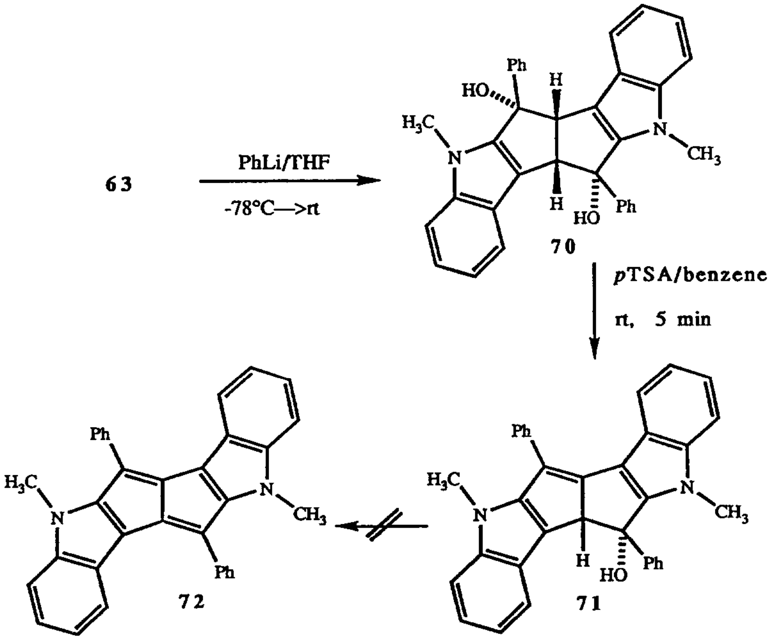
Scheme 14

was treated with Davis' reagent in the presence of ethylvinyl ether (benzeneselenic acid trap),[88] only tarry material or starting **68** were observed upon work-up.

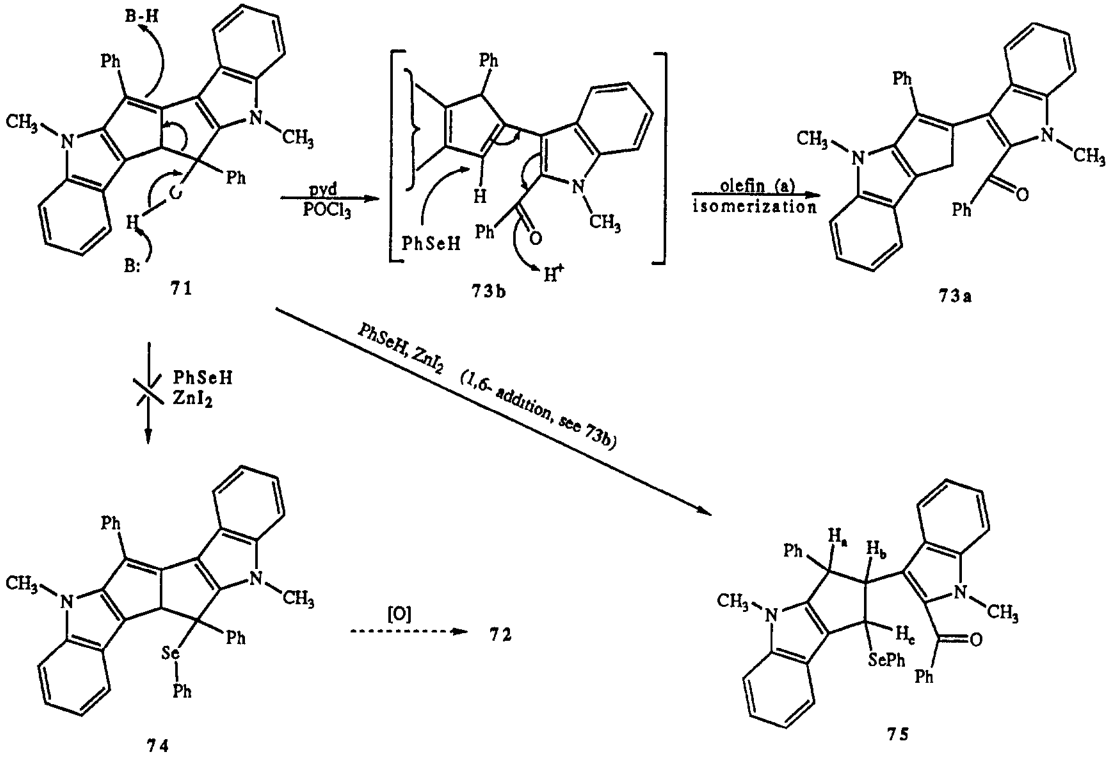
Since selenoxides are difficult to isolate and purify, attention turned to preparation of the corresponding bissulfoxide, although phenylselenoxides undergo *syn* elimination[89] at lower temperature than the corresponding bissulfoxides. The *endo-endo*-diol **67** was stirred with thiophenol in the presence of zinc iodide[90] to provide the *exo-exo*-bisphenylsulfinyl-*cis*-bicyclo[3.3.0]octane derivative **69** as a single diastereomer in 79% yield. This material was readily converted into a diastereomeric mixture of bissulfoxides on oxidation with MCPBA. When the mixture of *exo-exo*-bissulfoxides was treated [benzene (reflux), toluene (reflux), xylene (reflux)] in the presence or absence of agents to trap the benzenesulfenic acid (K_2CO_3; py; Et_3N), no evidence for the formation of **18** was observed. At 78°C only starting bissulfoxide was isolated. At temperatures greater than 100°C only decomposition material was observed. Attempts to execute the *syn* elimination between 78°–100°C yielded both the bissulfoxide and products of decomposition, moreover, no ion corresponding to the desired pentalene (308 da) was found in the mass spectrum of the bissulfoxide.

As noted earlier, the presence of bulky substituents on the pentalene framework retards the dimerization of these reactive olefins.[72–74] Analogous to the work of Hafner,[74a] Brand[91] and others, stabilization of the bisindole-substituted pentalene **18** was pursued by placement of phenyl substituents at positions -6 and -12 of **59**. A successful route via this approach toward diphenyl-dibenzo[*a*,*e*]pentalene had been earlier reported.[91] As outlined in Scheme 15, the 6,12-dioxobicyclo-octane dione **63** was stirred with phenyllithium in THF (−78°C → 25°C) to provide the 6,12-diphenyl-*endo-endo*-6,12-dihydroxybicyclooctane derivative **70** in 96% yield. This sequence not only gave the desired 6,12-*endo-endo*-diol, regiospecifically, but provided entry into the desired 6,12-diphenyl system with ease.[74,91] When diol **70** was stirred in benzene with *para*-toluenesulfonic acid (*p*TSA) in the presence of molecular sieves,[91] a red-colored solid was obtained in 83% yield, the structure of which was shown to be triene **71**.

Removal of the elements of water from triene **71** to provide pentalene **72** was attempted under a variety of conditions including *p*TSA/benzene (reflux), TFA (rt), Martins' reagent (−20°C → rt),



Scheme 15

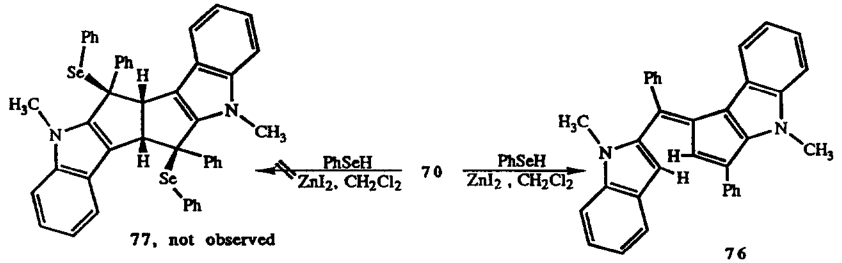


Scheme 16

Amberlite resin (CH_2Cl_2), etc. These reactions resulted in intractable mixtures with no evidence for the formation of diphenyl-bisindolopentalene **72**. Dehydration of **71** with $POCl_3$ in pyridine effected ring scission of the bicyclooctanediene framework to furnish the phenylketone **73a** which presumably arose via the intermediate triene **73b**, as illustrated in Scheme 16. Independent evidence for this mechanism was obtained when treatment of triene **71** with $POCl_3$/py or base provided the phenylketone **73a** in good yield. Ring scission to provide **73b**, followed by olefin isomerization would account for the formation of the phenylketone **73a**. Since triene **71** underwent ring fragmentation in the presence of base or decomposition on exposure to acid, it was decided to convert triene **71** into the phenylselenyl substituted triene **74**, a *syn* elimination of the corresponding selenoxide would presumably provide diphenyl-bisindolopentalene **72**. When **71** was reacted with benzeneselenol in the presence of zinc iodide[86] again a ring-cleaved material was obtained the structure of which has been proposed as **75**. None of the desired phenylselenyl triene **74** was observed or isolated The origin of **75** is not clear, for 1,6-addition of phenylselenol (ZnI_2) to the vinylogous α,β-unsaturated carbonyl intermediate **73b**[92] followed by tautomerization to regenerate the aromatic indole unit, would provide **75**. On the other hand, addition of the elements of phenylselenol across the vinylic double bond[93] via a free radical mechanism would also provide **75** (Scheme 16).

In a final attempt (Scheme 17) the diphenyldiol **70** was treated with phenylselenol in the presence of zinc iodide;[86] however, again ring-scission took place to provide the diene **76** rather than the bisphenylselenylperhydropentalene **77**. The structure of **76** was unambiguously assigned by single crystal X-ray analysis.[20]

In summary, a combination of the Weiss reaction[1] and the Fischer indole cyclization[81–83] was employed to execute a facile preparation of the tetrahydro-5,11-dihydropentaleno-[2,1-*b*·5,4-*b*′]diindoles **58** and **59**. The elimination of one molecule of water from **70** to provide triene **71** was



Scheme 17

successfully carried out, but further treatment yielded only the 2-phenylcyclopenta[*b*]indol-1-yl derivative **73a**. All attempts to effect the elimination of two molecules of LH via an E_2-elimination or *cis* (*syn*) elimination to provide azapentalenes **18** or **56** yielded only products of decomposition or ring-scission (see for example **73a**, **75** and **76**). However, in the mass spectrum of the *exo-exo*-diesters **64** and **66**, an intense peak corresponding to the ion for azapentalene **18** was clearly evident at 308 daltons and presumably arose from the desired *syn* elimination on heating. A similar ion (460 da) was not observed in the spectrum of the diphenyldiol **70** or the diphenylmonol **71** under conditions of EI or CI mass spectrometry. Since the diphenyldibenzopentalene has been prepared and isolated,[91] whereas the corresponding bisindole analog **72** has eluded synthesis (to date) under the analogous conditions, the bisindole units in **18** or **56** do not appear to provide the same stabilization as the benzene rings present in dibenzopentalenes.[74,91]

5. SYNTHESIS OF CENTROSUBSTITUTED TRIQUINACENES

The synthesis and chemistry of triquinacene **8** have been a topic of continuous interest since the molecule was first prepared by Woodward *et al.* in 1964.[94] A number of research groups have devised routes to this triquinane[11,94,95] as part of an approach towards dodecahedrane.[96] Moreover, de Meijere has detailed attempts to prepare the strained polyquinene, acepentalene, from **8** and has reported the preparation of dihydroacepentalenediide.[97]

Recently Serratosa *et al.*[98] have proposed an "aldol approach" to the synthesis of dodecahedrane related to the pericyclic route originally proposed for this molecule by Woodward,[94] Müller[99] and Jacobson.[95,100] Difficulties encountered in the reaction of the two triquinacene units in the desired fashion via their concave rather than convex faces have hampered previous attempts to execute this convergent, reflexive synthesis[101] via the pericyclic approach. Presumably this will pose difficulties in the related aldol approach.[98]

In keeping with our interest in the preparation of polyquinenes via the Weiss reaction, we utilized this approach for synthesis of triquinacene **8** and the centrosubstituted triquinacenes, 1,10-dimethyltriquinacene **19** ($R = CH_3$), 1,10-cyclohexanotriquinacene **20** and ellacene **21**. Of particular interest in regard to the present work is the unique topography of the tetracycles **20** and **21**. These molecules have embodied in their [4.3.3] and [10.3.3]propellane molecular structure,[102a] a six or twelve-membered ring which shields the convex face of the triquinane skeleton. This type of centrosubstituted triquinancene[102a,b] may prove to be useful in the pericyclic[94] and aldol[98] approaches to the spherically shaped dodecahedrane.

5.1. *Tricyclo*[5.2.1.$0^{4,10}$]*decane*-2,5,8-*triene* (**8**)

The initial route to triquinacene **8** via the Weiss reaction involved the monoalkylation of the highly symmetrical *cis*-bicyclo[3.3.0]octane-3,7-dione **4**. Numerous attempts to differentiate between the two five-membered rings of **4** have been reported in the synthesis of other polyquinanes.[103]

Previous attempts to monofunctionalize the symmetrical bicyclooctanedione unit **4** have employed multistep synthesis, protection–deprotection sequences accompanied by several recycle passes or alkylation reactions the yields of which have been only moderate.[103,104] In order to surmount this problem a new approach to the monoalkylation of **4** was recently developed which ultimately resulted in the synthesis of triquinacene **8** as well as centrosubstituted triquinacenes **19**, **20**, and **21**.[11,12,21]

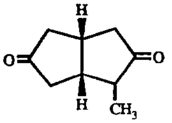
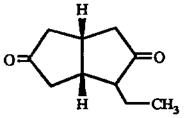
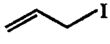
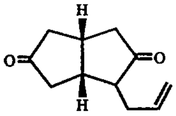
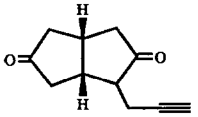
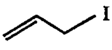
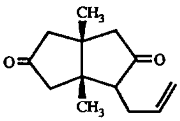
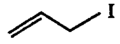
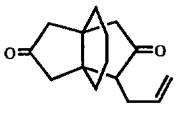
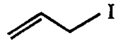
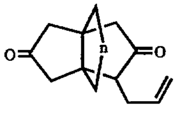
Attempts to monoalkylate **29a** (E = COOMe), available from the Weiss reaction (Scheme 2), at low temperatures with allyl iodide were successful but hydrolysis of the methyl ester groups of the allylated material resulted in the isolation of a number of products of incomplete hydrolysis.[52a] Evidently, attack of the electrophile occurred, as expected, from the convex face of **29a** and forced the methyl ester into the sterically congested cavity of the V-shaped molecule which retards the rate of hydrolysis of this ester function.[49,52a] However, the versatility of the Weiss reaction could be exploited at this juncture by substituting the *t*-butyl ester functions of bisenol tetraester **29b** (R′ = CO_2tBu) for those of the methyl ester analog **29a**. This replacement had profound effects on the regioselectivity of the monoalkylation process and provided a simple means by which the symmetry of the *cis*-bicyclo[3.3.0]octane-3,7-dione unit could be altered (see Table 5 for details). As illustrated earlier in Scheme 2, when glyoxal **2** was stirred with di-*t*-butyl 3-oxoglutarate **27** in alkaline solution, a 93% yield of tetra-*t*-butyl-*cis*-bicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate **28** was realized. Treatment of tetraester **28** with diazomethane resulted in the formation of the bisenol ether **29b** cleanly and in greater than 90% yield.

Monoalkylation of the tetramethyl tetraester **29a** (Scheme 18) with allyliodide and potassium hydride at low temperature (−58°C) gave a mixture of monoalkylated and dialkylated material. In contrast, monoalkylation of the tetra-*t*-butyl tetraester **29b** under analogous conditions gave the desired monoalkylated derivative **78** with high regioselectivity in 90% yield. The tetra-*t*-butyl ester functions are, therefore, extremely important in directing the reaction toward mono- rather than bisalkylation. Thus, **29b** was monoalkylated (−60 to −40°C) with potassium hydride/allyl iodide to provide **78** and the product was hydrolyzed to generate the monoallyl-3,7-dione **79** in 90% overall yield from **29b**. The monoallyl derivative was isolated as a mixture of *exo* (**79a**) and *endo* (**79b**) stereoisomers in a ratio of 3 : 1. The 2-allyl-*cis*-bicyclooctaenedione (**79a, b**) was stirred with ozone at −60°C in ethyl acetate, followed by addition of dimethyl sulfide (DMS)[105] to provide a stereoisomeric mixture of the corresponding aldehydes (**80a, b**) on large scale in 81% yield.

Examination of the geometry of both stereoisomeric diketodialdehydes **80a** and **80b** indicated that only the *endo* isomer (**80a**) could cyclize to provide the desired triquinacene skeleton. It was therefore decided to adopt reaction conditions which would permit equilibration of the *exo* isomer (**80a**) into the desired *endo* (**80b**) stereoisomer. Once the *endo* isomer **80a** cyclized, it was felt that triquinane **81** would not reopen readily in acidic solution due to the stability of the newly formed carbon–carbon single bond. The thermodynamic equilibrium (3 · 1) between the *exo* (**80a**) and *endo* (**80b**) isomers could re-establish and this process would continue until **80** was completely converted into the tricyclic system **81** (Scheme 18). In fact, the conversion of **80a,b** into **81** in THF in the presence of aqueous HCl (2N) took one week to go to completion but occurred in greater than 85% yield.[11,12]

Reduction of the two carbonyl groups present in **81a, b** under alkaline conditions ($NaBH_4$, CH_3OH) resulted in a retroaldol reaction to generate **80**, followed by reduction of the three carbonyl groups to provide the ring-opened triol. In contrast, Lewis acid mediated reduction of **81** with borane-THF resulted in the formation of the desired triols **82a** and **82b**, isolated as a mixture of stereoisomers in 93% yield. The mixture of triols **82a, b** was heated in refluxing HMPA for 48 hours to furnish an 80% yield of triquinacene **8**, accompanied by 8% of isotriquinacene.[106] Since isotriquinacene, the bridgehead olefinic isomer, is estimated by MM2 to be several kcal higher in energy as compared to **8**,[107] the mixture can be converted into **8** by stirring in a solution of methylene chloride/pentane in the presence of *p*-toluenesulfonic acid.[11,12,108] The disappearance of

Table 5. Tetra-*t*-butyltetraesters represented by monoalkylation of **29b** with electrophiles at low temperatures followed by hydrolysis-decarboxylation to provide monoalkylated *cis*-bicyclo[3.3.0]octane-3,7-diones

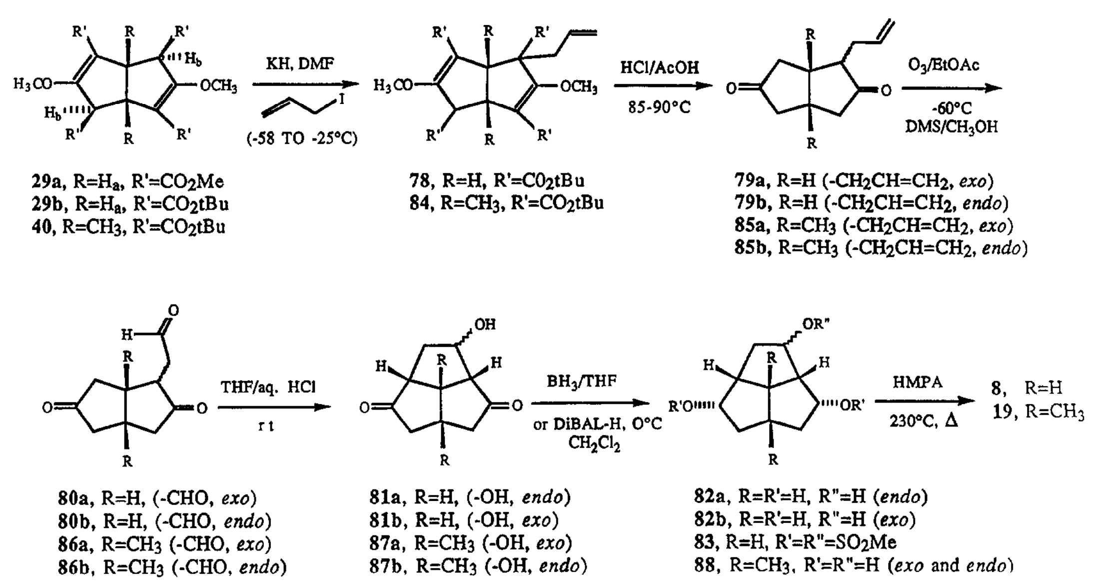
Electrophile	Product	Equivalents of Base	Reaction Time/Temp	Yields (%)
CH_3I		1.1	3hr, -60 to -50°C	82
CH_3CH_2I		1.1	3hr, -60 to -50°C	78
		3	5hr, -60 to -50°C	90
		2	4hr, -50 to -60°C	80
		2.6	7hr, -25°C	93
		2.2	7hr, -25°C	82
		2.3	6hr, -5°C	74

n=$(CH_2)_8$

isotriquinacene can be followed by capillary gas chromatography until the purity of **8** is greater than 99% negating the need for tedious distillation.[12]

5.2. 1,10-*Dimethyltricyclo*[5.2.1.0^{4,10}]*decane*-2,5,8-*triene* (**19**)

The versatility of the Weiss reaction for the construction of polyquinenes stimulated interest in the synthesis of 1,10-dimethyltriquinacene **19**. At the outset this synthesis might appear difficult for the methyl group as carbon-1 is located on a nonactivated position of the triquinacene framework. Moreover, the second methyl group (C-10) is cojoined at an activated position while two other activated carbon atoms remain encased in **19**. Dissection of **19** in a retrosynthetic sense, however, provided a simple approach related to that employed for the preparation of **8** (Scheme 18). When glyoxal **2**, was replaced by biacetyl in the Weiss reaction and stirred with di-*t*-butyl 3-oxoglutarate **27**, a 93% yield of the 1,5-dimethylated-*cis*-bicyclo[3.3.0]octane-3,7-dione tetraester was realized.[49] The bisenol was converted into the required bisenol ether **40** in excellent yield on treatment with ethereal diazomethane.[12]



Scheme 18

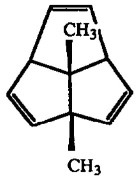
Alkylation of **40** at -25°C with allyl iodide/KH, followed by hydrolysis and decarboxylation gave 2-allyl-1,5-dimethyl-*cis*-bicyclo[3.3.0]octane-3,7-dione **85a, b** as a mixture of epimers (*exo*/*endo*, 2 : 3) in excellent yield. It was necessary to effect alkylation of **40** at higher temperatures in comparison to the alkylation of **29** in order to maximize the yield of **85**. Presumably, the 1,5-dimethyl functions in **40** retard the attack by electrophiles at positions -2 and -6. Conversion of the allyl groups of **85a, b** into the corresponding *exo* (**86a**) and *endo* (**86b**) aldehydes was accomplished via ozonolysis, according to published procedures,[12] again in yields greater than 90%. Because of the interaction between the methyl groups located at positions -1 and -5 and the aldehyde function at C-2, the *endo* isomer **86b** predominated in the mixture in a ratio of 3 : 2. Aldol cyclization of the mixture of aldehydes **86a, b** was carried out in THF in the presence of 4% aqueous HCl to provide the epimeric mixture of diketoalcohols represented by **87a, b**. The mixture of epimeric alcohols **87a** and **87b** was isolated in 70% yield, accompanied by another diketoalcohol (12%) the carbon skeleton of which is felt to be derived by aldolization of **86** in a transannular fashion.[12,49]

Treatment of **87a, b** with diisobutylaluminum hydride gave a mixture of epimeric triols **88** in 66% yield, although the yield of this step has not been maximized. The mixture of triols was then heated in HMPA at 230°C for 24 hours analogous to the conditions employed for the conversion of **82** into **8**. Careful extraction of the HMPA solution with pentane/water, followed by distillation at low temperature yielded 1,10-dimethyltriquinacene **19**, accompanied by a small quantity of an olefinic isomer. The relative stabilities of **19** and its olefinic isomers **89a, b** were assessed via a variety of force field methods.[109] As illustrated in Table 6, both bridgehead isomers **89a** and **89b** of **19** are higher in energy than **19**, consequently the mixture of dimethyltriquinancenes was stirred in the presence of *p*-toluenesulfonic acid in pentane/CH_2Cl_2. After three hours the olefinic isomers had disappeared and 1,10-dimethyltriquinacene **19** was isolated in pure form.

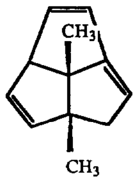
5.3. *Tetracyclo*[5.5.2.0^{1,8}.0^{4,8}]*tetradecane*-2,5,13-*triene* (**20**)

As pointed out earlier, the pericyclic approach to dodecahedrane has been hampered by the propensity of **8** to undergo reaction via the convex faces of the two reacting molecules rather than reaction between the desired concave faces For this reason a short synthesis of the centro-substituted[102b] triquinacene **20** was investigated. The construction of the [4.3.3]propellane frame-

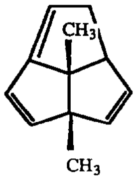
Table 6 Relative energy differences between dimethyl triquinancenes **19**, **89a** and **89b**



1 9



8 9 a



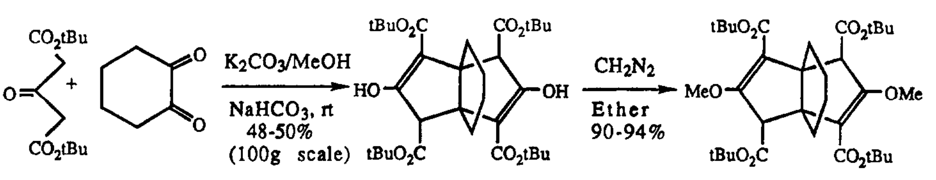
8 9 b

Method		Relative Δ E kcal/mole	 kcal/mole
MMPMI	0	7.6	8.0
MMPI	0	9.4	9.5
MM2	0	16.8	17.0

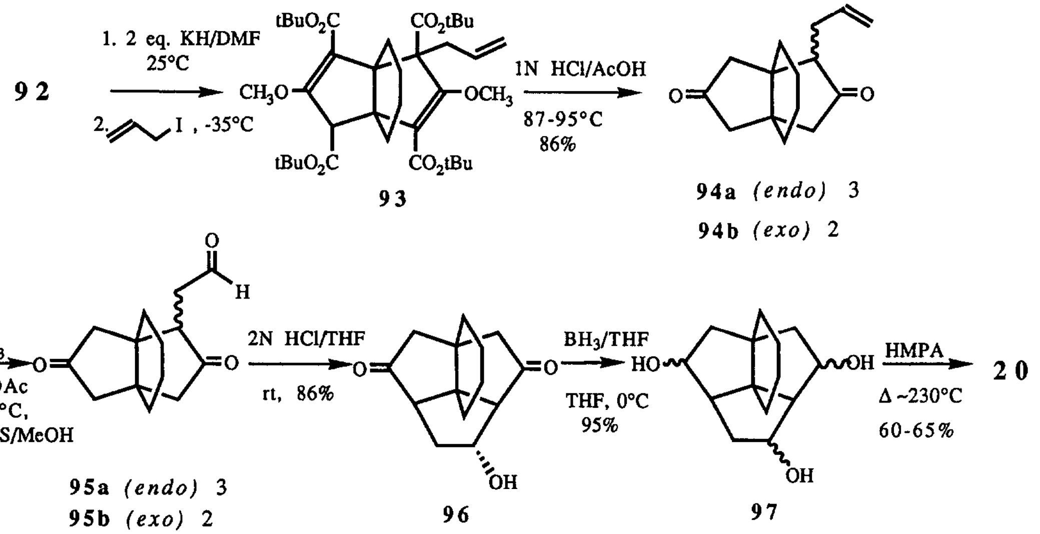
All three force field variations place the two bridgehead isomers considerably higher in energy than the symmetrical isomer and nearly isoelectronic amongst the pair The MM2 force field is not parameterized to accommodate the conjugated double bonds in the bridgehead olefinic isomers Consequently, the actual relative energy difference between **19** and the two bridgehead isomers **89a, b** is undoubtedly smaller

work contained in **20** began with the condensation of two equivalents of di-*t*-butyl 3-oxoglutarate **27** with cyclohexane-1,2-dione **90** in alkaline medium in a fashion similar to the preparation of [*n*.3.3]propellanes reported earlier (Scheme 19).[3d] Although the tetra-*t*-butylpropellanedione tetracarboxylate **91** precipitates from the medium in only 50% yield, the reaction can be scaled to above the one hundred gram level ; additional quantities of **91** remained in the mother liquor. The tetraester **91** exists in solution entirely as the bisenol tautomer and was isolated as a single symmetrical stereoisomer.

In order to protect the enolic hydroxyl functions of the bisenol **91**, it was converted into the bisenol ether **92** on treatment with ethereal diazomethane. The bisenol ether **92** was then stirred at 25°C with 2.2 equivalents of potassium hydride in DMF for one hour, followed by addition of allyl iodide (2.2 eq) at −35°C. Hydrolysis and decarboxylation of the intermediate tetraester **93** furnished the desired monoallyl[4.3.3]propellane dione **94** in 86% overall yield from **92**. Regiospecific monoalkylation had been effected in high yield. The monoallyl derivative **94** was isolated as a mixture of *endo* (**94a**) and *exo* (**94b**) stereoisomers in a ratio of 3 : 2 (GC and ^{13}C NMR). Conversion of the allyl group of **94** into the aldehyde function of **95** was accomplished by ozonolysis in 93% yield, according to published procedures.[12] Aldol cyclization of the mixture of aldehydes (**95a, b**) to provide triquinane **96** was executed under conditions of tautomeric equilibrium (2N HCl/THF) to permit the *exo* stereoisomer **95b** to epimerize to the *endo* diastereomer **95a**. Since the *endo* stereo-



Scheme 19



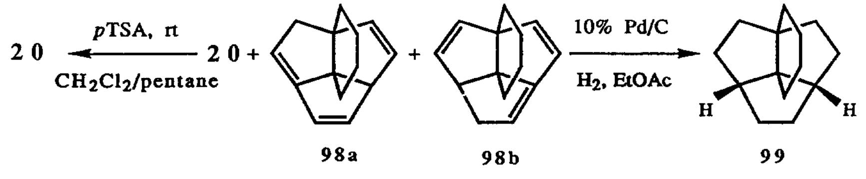
Scheme 20

isomer **95a** is the thermodynamically more stable epimer, cyclization to **96** occurred rapidly and in 86% yield.

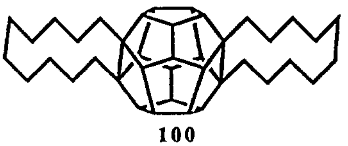
When diketomonol **96** was stirred in borane-THF (1N) at 0°C for 24 hours, a mixture of stereoisomeric triols represented by **97** was isolated in 95% yield (Scheme 20). These triols **97** were not separated but were heated in HMPA at 230–240°C for 20 hours under conditions analogous to those employed for the conversion of other polyols into polyquinenes.[11,12] This process furnished the propellane triquinacene **20** in 60–65% yield, accompanied by two minor olefinic isomers **98a** and **98b** (GC ratio 90 : 4 : 6). When the mixture of propellane triquinacenes (**20**, **98a, b**) was stirred in the presence of *para*-toluenesulfonic acid, the minor olefinic isomers **98a, b** disappeared and **20** was isolated in pure form (Scheme 21), analogous to the isomerizations with previous triquinacenes.[11,12] The carbon and proton NMR spectra of this unique molecule have been reported.[12] The mixture of olefinic isomers **20**, **98a** and **98b** could also be smoothly converted into the parent hydrocarbon **99** on catalytic hydrogenation. Further studies with this centrosubstituted triquinacene in regard to substituted dodecahedrane are underway at present and will be reported in due course.

5.4. *Tetracyclo*[11.5.2.$0^{2,13}$.$0^{2,16}$]*eicosa*-14,17,19-*triene*[(*ellacene*)**21**]

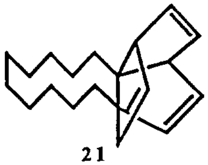
Examination of Dreiding models of centrosubstituted triquinacenes **19** and **20** indicated that the substituents on the convex faces of these molecules might not prohibit the undesired [2+2] cycloaddition reaction (see Gladysz *et al.*, reference 101). In this regard, the construction of 1,2,16,17-biscyclododecanododecahedrane **100** was envisaged from 1,10-cyclododecanotriquinacene (ellacene) **21** for the twelve membered ring would further shield the convex face of the triquinacene



Scheme 21



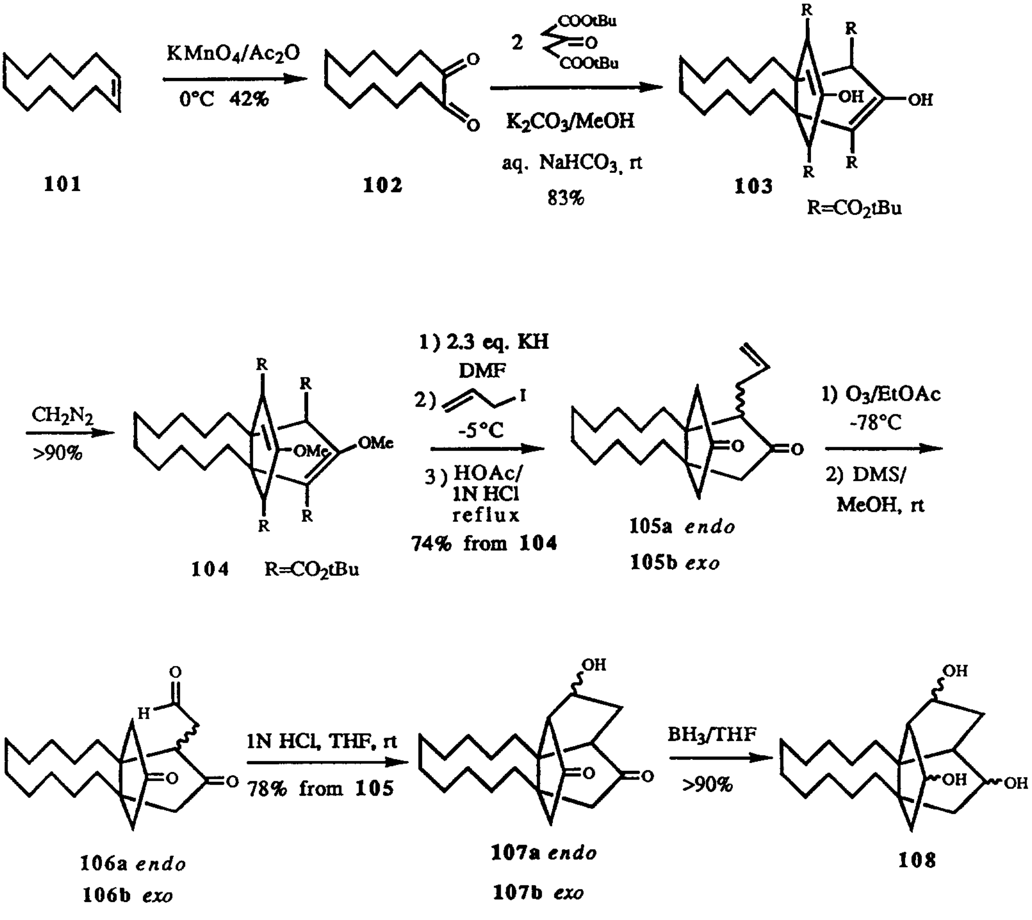
100



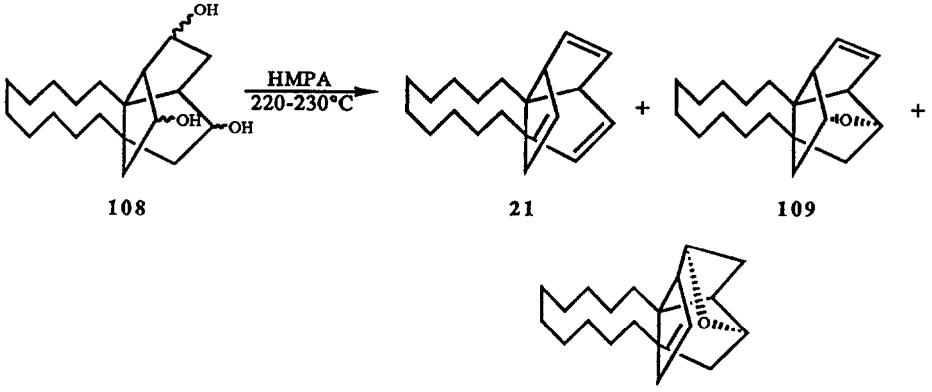
21

skeleton. Presumably, this would increase the opportunity for the two molecules of triene **21** to react in the desired concave–concave fashion required for the pericyclic approach.[94,95,99,100]

The synthesis of ellacene **21** began with the preparation[3a] of cyclododecane-1,2-dione **102** from **101** via the Sharpless procedure.[110] As illustrated in Scheme 22, the Weiss reaction of dione **102** with di-*t*-butyl 3-oxoglutarate gave the 1 : 2 adduct **103** and this material was converted into the bisenol ether **104** on treatment with diazomethane. The bisenol ether **104** was monoalkylated with allyl iodide at −5°C and then hydrolyzed to provide the monoallyl bicyclooctanedione **105** in 74% overall yield from **104**. Analogous to the route for triquinacene, **105** was oxidized to provide a mixture of epimeric aldehydes (**106a, b**) which were stirred under acidic conditions (aq. HCl/THF, rt) to provide the desired diketoalcohol **107** (78% from **105**) The monol was isolated as a 1 : 1 mixture of *endo* (**107a**) and *exo* (**107b**) stereoisomers the structures of which were confirmed by high resolution NMR spetroscopy by analogy to previous work.[12] The reduction of the mixture of **107a**



Scheme 22



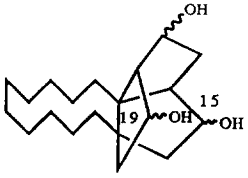
108 **21** **109**

110

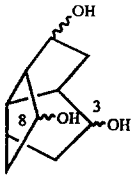
Scheme 23

and **107b** was carried out using the Lewis acid mediated sequence (THF/BH_3)[12] to provide a mixture of epimeric triols **108** in 90% yield. Examination of the mixture of triols by ^{13}C NMR spectroscopy indicated the presence of at least three diastereomers consonant with attack (BH_3) on the carbonyl groups from both the concave and convex faces of the *cis*-bicyclo[3.3.0]octane-3,7-dione unit. In contrast to the HMPA-mediated dehydration of perhydrotriquinacene triol and perhydrocyclohexanotriquinacene triol which yielded the desired trienes,[12] the HMPA/Δ sequence with triol **108** furnished only 10% yield of the desired ellacene **21**, accompanied by the two ethers **109** and **110** (30%). The structures of these ethers are depicted in Scheme 23 and were determined by 2D COSY NMR experiments.[21,111]

The formation of both *endo* and *exo* hydroxyl groups from the carbonyl reduction sequence (**107** → **108**) coupled with the buttressing effect of the twelve-membered ring, presumably, results in the formation of olefinic ethers **109** and **110** in preference to ellacene **21**. It is believed that the interaction with the twelve-membered ring has forced the cyclopentane rings closer together in the cavity of the concave triol of **108** as compared to **112**.[114] The buttressing effect in these systems was originally observed by Borden[112] in the case of 1,5-dimethyl-*cis*-bicyclo[3.3.0]octane-3,7-dione and subsequently by Yang *et al.* (**113**–**114**),[3a] as illustrated below. It is important to note that *cis*-bicyclo[3.3.0]octane-3,7-dione **4**, when heated under the conditions of Borden,[112] did not furnish any of the bisnoradamantyl alcohol related to **114a** or **114b**.



108



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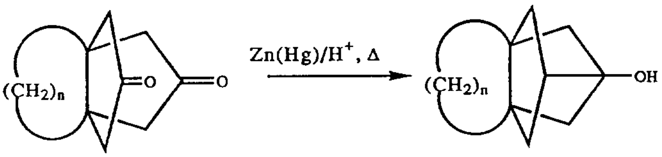
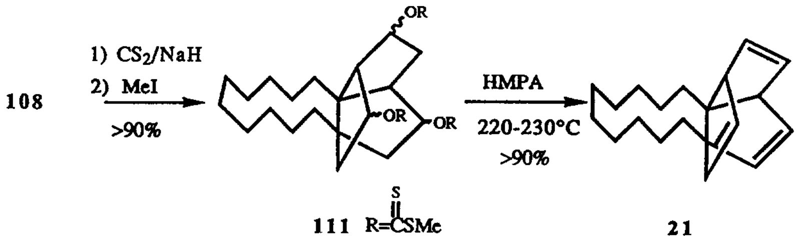


113a, n=6
113b, n=10

114a, n=6, 69%
114b, n=10, 70%



Scheme 24.

In order to circumvent the difficulty in transforming triol **108** to triene **21**, the Chugaev[113] approach was adopted and resulted in the synthesis of ellacene **21** in high yield.[21] Initial difficulties in the preparation of the trisxanthate **111** (Scheme 24) were overcome by replacing tetrahydrofuran with CS_2[113] in the reaction mixture. This process gave the trisxanthate in greater than 90% yield. Pyrolysis of the trisxanthate[112] as a solid was less than satisfactory; however heating **111** in HMPA at 220–230°C furnished ellacene **21** in 90% overall yield from **108**. These pyrolysis conditions are superior, as they limit intermolecular reactions which had previously resulted in some polymeric material when **111** was heated alone. It is conceivable that the Chugaev approach may be superior to the HMPA-mediated dehydration sequence for the synthesis of triquinacene,[12] as well as centro-substituted triquinacenes.

It is important to note that during the synthesis of triquinacene or cyclohexanotriquinacene **20** (Scheme 20), isomeric bridgehead olefins were observed from the HMPA-mediated dehydration sequence of the corresponding triols, although these isomeric trienes could be converted into the desired triquinacene with *para*-toluenesulfonic acid.[12] However, ellacene **21** was isolated as the single component of the *syn* elimination (trisxanthate) in HMPA (220–230°C). As expected from the C_s symmetry of **21**, three olefinic carbon signals were observed in the ^{13}C-NMR spectrum of the triene and five sets of signals were found in the ^{1}H-NMR spectrum of this centrosubstituted triquinacene.[21] Studies with **21** in regard to **100** are in progress.

6. COMPUTATIONAL AND CHEMICAL STUDIES DIRECTED TOWARD THE SYNTHESIS OF 12Π AND 14Π FENESTRANE ANNULENES (22) AND (23)

The tetrahedral nature of the tetracoordinate carbon atom was independently proposed by Van't Hoff and LeBel in 1874.[115] This hypothesis was based on the number of isomers for substituted methane, and has since been demonstrated by a number of spectroscopic methods. In practice, the exact tetrahedral bond angle of 109.47° is only observed when the four substituents of an sp^3 hybridized carbon atom are identical. In most organic molecules, slight deviations from this angle are observed; however, large deviations have been observed for strained organic compounds. For example, the bond angle of cyclopropane is 60° (in this case, it is believed the rehybridization occurs to produce orbitals which cannot be considered 'normal' sp^3 hybrids),[116] and one of the bond angles of 1,6-diaminocyclodecane dihydrochloride is 120°.[117]

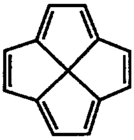
The deviation of tetracoordinate carbon from tetrahedral to square planar geometry has intrigued scientists for many years.[49,117–122] The first treatment of planar tetracoordinate carbon was reported in the early 1970s by Hoffmann and coworkers[118] based on the nature of planar methane. The electronic nature of planar methane is proposed to exhibit two normal carbon–hydrogen bonds, a single two electron three centered bond which uses only hydrogen electrons, and the remaining two valence electrons of carbon would reside in a *p* orbital perpendicular to the molecular plane. Many subsequent theoretical treatments have adopted this closed shell singlet model of a flattened sp^3 carbon.[119] However, relaxation of the wave function within the PRDDO-

GVB-CI framework suggests planar methane and simple alkyl derivatives to be a ground state open shell singlet; i.e., a biradical.[120] The Hoffmann species[118] in this context is a zwitterionic excited state.

Calculations have been carried out at various levels of sophistication to evaluate the energy difference between the planar and tetrahedral forms of methane.[118–120]

$$\Delta E = E_{(\text{planar})} - E_{(\text{tetrahedral})}$$

The energy differences which result lie in the range of 95 to 250 kcal/mol depending on the computational method and the flexibility of the wave function employed. The predicted ΔE can be lowered either by stabilization of the planar form or by destabilization of the tetrahedral form. Based on the closed shell, Π lone pair model of planar methane, Hoffmann[118] suggested that when a central carbon is fused in an annulene ring system, the planar form of the carbon would allow overlap of the lone-pair of electrons in the p_z orbital with the Π system of the annulene, thereby stabilizing the planar form (for example, **23**). This hypothesis has resulted in the suggestion that the molecules illustrated above might serve as candidates to house or stabilize the planar tetracoordinate form of carbon.[118,119,121,122] Because of the pronounced tendency of carbon atoms toward covalent bonding, the bridgehead double bonds in these structures can be imagined to exert a planarizing force on the adjacent σ-bonds to the central atom. Concomitant with the resulting strain localized to a large extent around the central atom, the Π-bonds of the annulene periphery should stabilize the electron pair of the developing 2*p* orbital. These two effects, the build-up of strain and the stabilization by Π-delocalization, Keese has suggested could result in structures which house a planoid tetracoordinate carbon atom.[121] The PRDDO-GVB approach agrees on this point. Certain π systems are predicted to favor a lowered, but still considerably energetic, closed shell ground state under the constraint of planar tetrahedral carbon.[120] In these cases, conjugative delocalization overwhelms the electron–electron repulsion primarily responsible for biradical formation.



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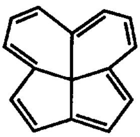
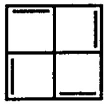


23



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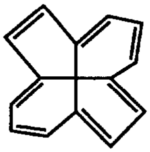


116

Keese[121] has examined a number of annulenes by HOMO calculations and the results are summarized in Table 7. The delocalization energy depends upon the annulene system and increases with ring size; however, the delocalization energy per double bond was largest for [12]annulene **22**. Consequently, Keese proposed that **22** would stabilize the planar form of carbon in preference to the other candidates. In **22**, the 2*p*-AO (atomic orbital) can interact only with one of the two degenerate MOs of the lowest antibonding set. Hence the highest occupied MOs of the tetracyclic *p*-system of **22** are exclusively localized in the surrounding *p*-system. The stabilization of the 2*p*-AO of the central atom is independent of the number of electrons in these two nonbonding MOs. This

Table 7 Delocalization energies of [n]annulenes with a planar central carbon atom

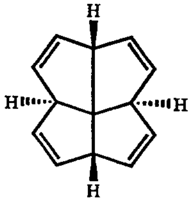
n-Value of the [n]annulene	Delocalization energy (β)	Delocalization energy (β) per peripheral double bond
8	1.657	0.414
10	1.950	0.39
12	2.646	0.44
14	2.939	0.418

suggests that the demand for electrons in the periphery of **22** could be adjusted by oxidation or reduction.

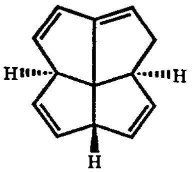
In response to Keese's predictions, Gleiter[122] and coworkers carried out MINDO/3 calculations on **22** and its corresponding dication and dianion. For the neutral species, it was found that the lowest energy structure is nonplanar and belongs to the point group D_2 ($\Delta H_f = 202.5$ kcal/mol). The two conformations bearing a planar central carbon atom were much higher in energy. The energy difference between the D_2 and D_{2h} structures was 49 1 kcal/mol. The D_{4h} triplet conformation was calculated to be 59.6 kcal/mol higher in energy than the D_2 structure. The results were interpreted to indicate that synthetic attempts toward **22** with a tetracoordinate central atom would lead at most to an energetically unfavorable ring system. Similar conclusions were drawn for structures **23** and **116**. Schleyer and coworkers confirmed the ground state nonplanarity of **22, 23** and **116** by means of MNDO calculations and furthermore predicted a pyramidal central carbon for **115**.[123] Both MINDO/3 and MNDO calculations indicate a reduction in energy between tetrahedral and planar forms for dianionic and dicationic **22**. Still, the estimated barriers to planarity, 45–70 kcal, are prohibitive. In spite of the theoretical evaluations, the unique topology of the [5.5.5.5] and [5.5.6.6]fenestranes coupled with the conflicting computational results in regard to annulenes **22** and **23** has prompted much interest in these systems.[6,8,11,49,123]

7. COMPUTATIONAL STUDIES WITH REGARD TO THE CONVERSION OF STAURANE-2,5,8,11-TETRAENE (7) INTO 12Π ANNULENE (22)[49]

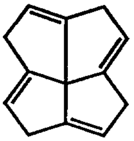
With the aid of force field calculations,[109] the strain energies and bond angle deformations of all *cis* [5.5.5.5]fenestrane tetraenes **7**, **117** and **118** have been determined. The relative energies of these olefinic isomers are depicted in Table 8. As expected, incorporation of bridgehead double bonds into the fenestrane system[12,22,121] induces additional strain into the molecule and results in a weakening of the σ bonds attached to the central carbon atom. Tetraene **7** was shown to be the most stable molecule of the three isomeric [5.5.5.5]fenestranes, as illustrated.



7



117



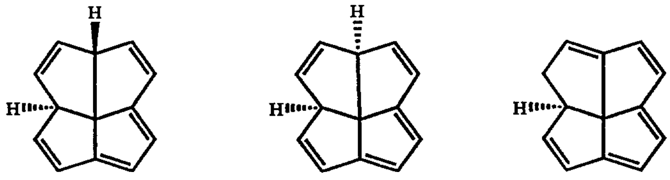
118

In order to access synthetic pathways in going from the stable tetraene **7** to the highly strained hexaene **22** the relative energies of three related isomeric [5.5.5.5]pentaenes were evaluated by

Table 8 Computational angles and energies for the [5 5.5 5]fenestrane tetraenes (**7**), (**117**) and (**118**)

fenestrane	C-C-C bond angles	Heat of formation kcal/mol	Strain energy* kcal/mol
7	117	70.4	0
117	n/a	75.1	4.7
118	139	112.6	42.2

* MNDO values with 7 taken as a reference point



	119	**120**	**121**
E (rel.) [kcal/mol]	0.0	62.1	4.8

Fig 5 Calculated relative energies of pentaenes **119–121**

molecular mechanics (MM2PI).[49,109,124] The Π force field has been parameterized for benzenoid aromatics and relatively unstrained conjugated olefins. Applying it to the highly strained structures discussed in this section brings the method to its limits. Consequently, quoted energy differences should be viewed as providing qualitative trends rather than quantitative predictions. Similar reservations apply to force-field optimized bond angles. Within this context the most stable pentaene is predicted to be **119** in which the [5.5.5.5]fenestrane system has the all *cis* configuration in agreement with Keese *et al.*[121] Although small deviations from tetrahedral geometry are predicted (118 1° vs 109.5°), the bond angles of the central carbon atom are near 109.5°. The olefinic isomer **120** with a *trans* bicyclo[3.3.0]octane subunit exhibited the highest degree of strain energy (62 kcal/mol higher) and housed a pyramidal central carbon atom with bond angles (C_1-C_{13}-C_7 and C_4-C_{13}-C_{10}) approaching 140°. In order to explore the possibility of migration of the double bond into conjugation (**120** vs **121**), the energy of pentaene **121** was optimized by MM2PI. This fenestrane **121** was found to be higher in energy by 4.8 kcal/mol than **119**, which suggests that isomerization toward the bridgehead position should not take place (Fig. 5). The increase in strain on incorporation of the third bridgehead double bond into the [5 5 5.5] system cannot be compensated by the resonance energy gained from additional overlap. It is, however, noteworthy that introduction of a third bridgehead double bond into **121** resulted in only a slight opening of the central bond angle (Table 9).

With the most stable individual species in mind, strain energy calculations were performed on the hydrocarbons **7**, **119** and **22** in regard to the following potential synthetic transformation.[119] Strain is defined by the difference between the heat of formation and the strainless heat of formation.[109] In the absence of physical measurement, the heat of formation depends upon the computational method employed. The results from two semi-empirical procedures and two Π force fields are summarized in Table 10.[124] Examination of the data in Table 10 suggests that in terms of strain energy, the transformation of tetraene **7** into pentaene **119** will cost 25–40 kcal/mole, and the **119** → **22** increment is similarly 30–40 kcal/mole If one assumes the best values in the Table to be

Table 9. Central carbon bond angles of the isomeric pentaenes (**119–121**)

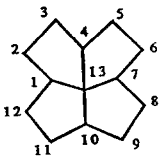
	Bond angle	119	120	121
	1-13-4	108.4	84.0	104.5
	4-13-7	104.7	83.3	101.4
	7-13-10	102.8	82.8	105.4
	10-13-1	104.8		105.6
	1-13-7	118.1	140 2	121.8
	4-13-10	118.1	140.2	118.7

Table 10 Strain energies (E_{strain}) and heats of formation (ΔH_f) calculated for [5.5.5.5]fenestrane polyenes

Method	E_{strain} (ΔH_f), kcal/mol		
	7	**119**	**22**
AM1[a]	19.5 (81.1)[e]	57.9 (134.9)[e]	95.0 (205.6)[e]
AM1/MNDO[b]	16.0 (77.6)[e]	40.3 (117.3)[e]	69.3 (179.9)[e]
MM2PI[c]	25.9 (82.3)	41.4 (114.3)	67.3 (177.9)
MMPI[d]	23.8 (82.4)	50.7 (126.3)	91.9 (202.5)
Average	21.3	47.6	81.5

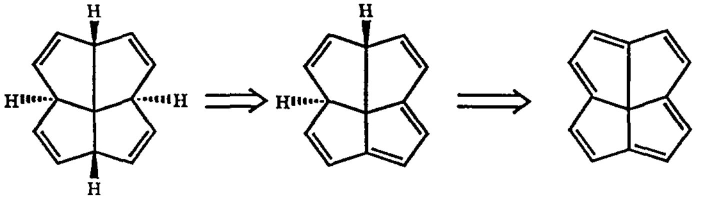
[a] Dewar, M. J. *et al.*, *J. Am. Chem. Soc.* **1985**, *107*, 3902, full geometry optimization

[b] MNDO values at AM1 optimized geometries

[c] Gajewski, J. J., Gilbert, K. E. version of MM2PI, full geometry optimization

[d] Allingers, N. PI program, full geometry optimization

[e] $\Delta H_{f(strainless)}$ = 61.6 (**7**), 77 (**119**), 110.6 kcal/mol (**22**) from S. W. Benson, Thermodynamical Kinetics, 2nd Edition, Wiley, New York, 1976



7 **119** **22**

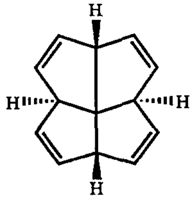
Scheme 25

AM1 energies, the corresponding increase in strain energy for the two steps is 38 and 37 kcal/mole, respectively.

From the above energies a potential synthetic route to the [5.5.5.5]fenestrane hexaene **22** from the stable tetraene **7** was studied computationally.[124] The approach involved the allylic bromination of staurane tetraene **7** to furnish either a dibromo or tetrabromo fenestrane tetraene (see Fig. 6). Either of these halosubstituted derivatives could potentially be debrominated or dehydrobrominated in a stepwise fashion to provide an intermediate pentaene on the pathway to annulene **22**. In this regard, the energies of the brominated [5.5.5.5]fenestrane polyenes were examined by MM2PI, and are presented in Fig. 6.

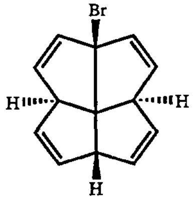
As illustrated, the strain energy of the bromosubstituted [5.5.5.5]fenestranes increases upon successive introduction of bromine atoms (see **122**–**129**). Much of this strain is due to the unfavorable *syn* 1,3-interactions with the bulky bromine atoms. An effort to minimize these interactions structurally results in an increase in the dihedral angle (ϕ) between the bridgehead substituent and in an opening of the central carbon–carbon bond angle. Some of the specific elements responsible for the strain in these systems are represented in Fig. 7.

Analysis of only two of the possible means for conversion of **7** into **22** via bromo intermediates is considered computationally here. The first begins with the allylic bromination of **7** with four molecules of N-bromosuccinamide (or $Br_2/h\nu$) to generate the 1,4,7,10-tetrabromo[5.5.5.5]fenestrane tetraene **126** (ΔE_{strain} = 23.6 kcal/mol). Phenyllithium or anion assisted removal of two bromine atoms via a *trans* elimination would generate the dibromo pentaene **129**. Once isolated and characterized, pentaene **129** could be reacted with potassium atoms under matrix isolation conditions to



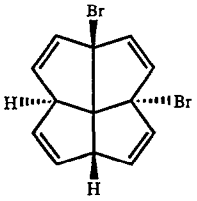
7

kcal/mol 25.9



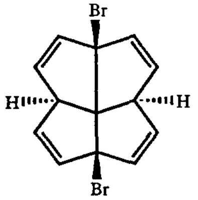
122

31.0



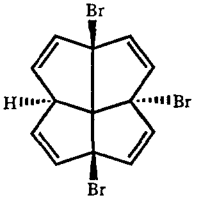
123

35.4



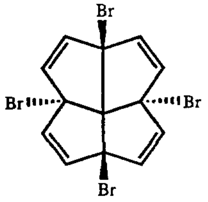
124

38.1



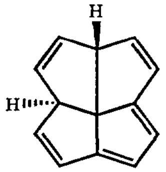
125

49.3



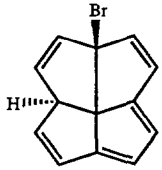
126

49.5



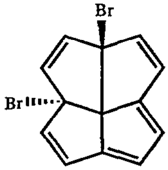
127

41.4



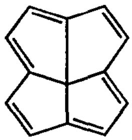
128

45.7



129

50.5



22

67.3

Fig 6 Calculated strain energies (MM2PI) for the brominated [5 5 5 5]fenestrane polyenes in kcal/mol

either observe spectroscopically the 12Π annulene **22** [ΔE_{strain} = 16.8 kcal/mol (30 kcal/mol AM1)] or the ensuing bond reorganization. An attractive feature of this pathway rests on the almost identical strain energies for **126** and the product **129** (MM2PI). Furthermore, Kuck *et al.*[125] have recently prepared a stable tetrabromo derivative of all *cis*-tetrabenzo-[5.5.5.5]fenestrane ('fenestrindan') related to **126**.

The second pathway, which is based on dehydrobromination reactions, begins with the reaction of tetraene **7** with two equivalents of N-bromosuccinamide to provide the dibromotetraene **123** (ΔE_{strain} = 9.5 kcal/mol). Since the strain energy of **123** was calculated (Fig. 6) to be considerably less than **126** (35.4 vs 49.3 kcal/mol), the latter route may prove easier to execute. The removal of the elements of hydrogen bromide from **123** with a hindered base (B:) to provide the monobromopentaene **128** [ΔE_{strain} = 10.3 kcal/mol (20 kcal/mol AM1)] is illustrated in Scheme 27. Again, pentaene **128** is more stable than its dibromo counterpart **129** by about 5 kcal/mol. As shown in Scheme 27, pentaene **128** would then have to be treated with a base to provide the desired 12Π annulene **22**[ΔE_{strain} = 21.6 kcal/mol (32 kcal/mol AM1)].

The data presented in Schemes 26 and 27 depict the increase in strain energy in going from **7** to **22** via two related pathways. There are advantages to both pathways, although the intermediate

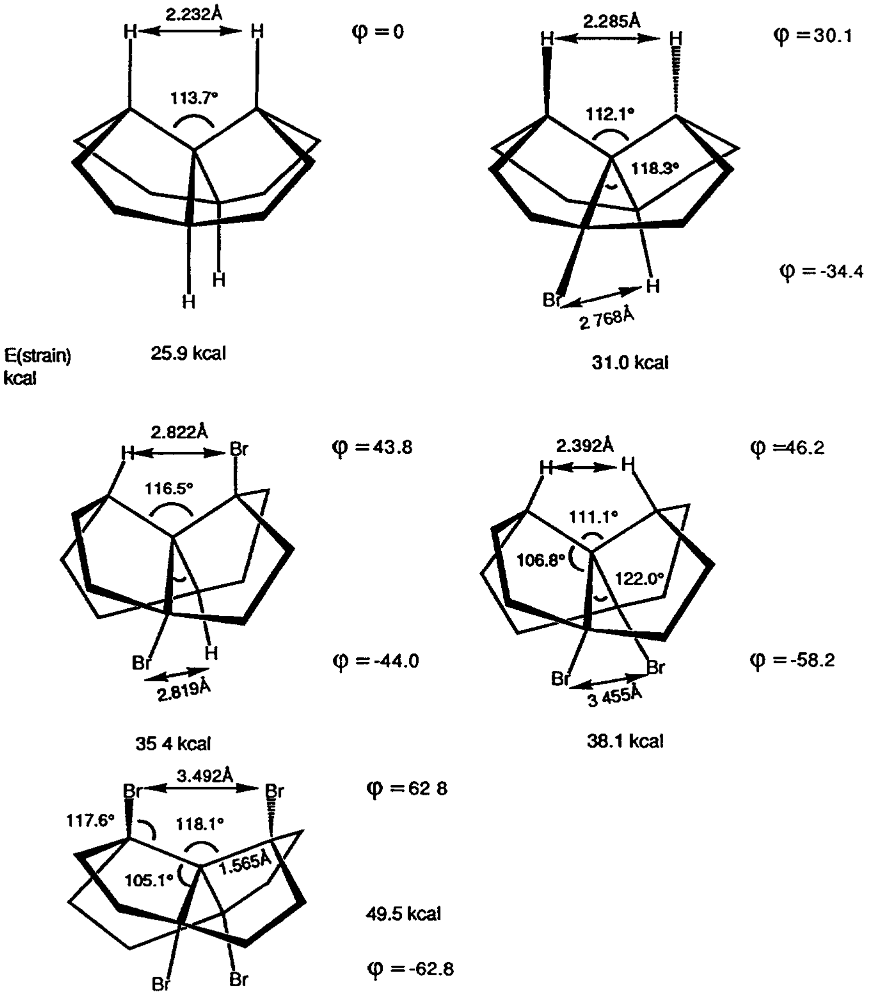
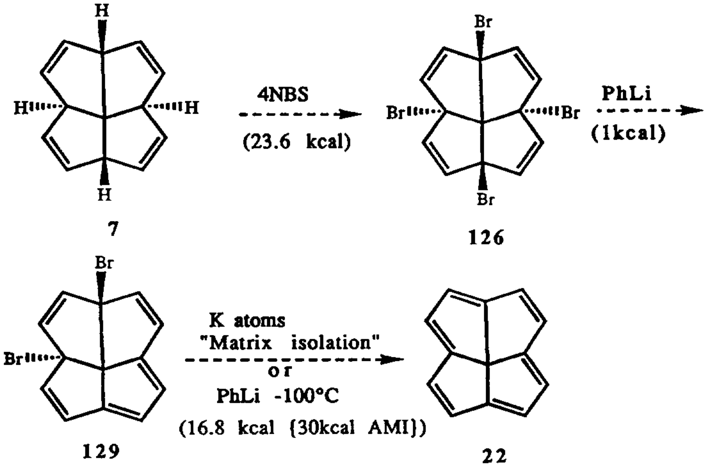
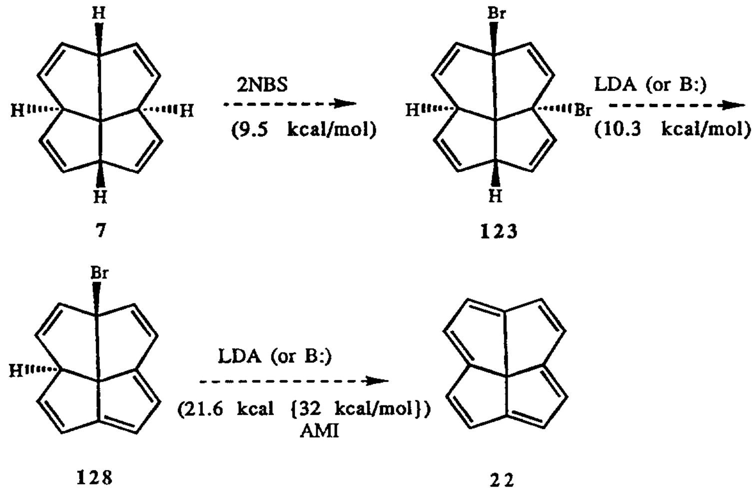


Fig 7 Geometric elements responsible for the strain build-up in the brominated [5.5 5 5]fenestrane polyenes



Scheme 26

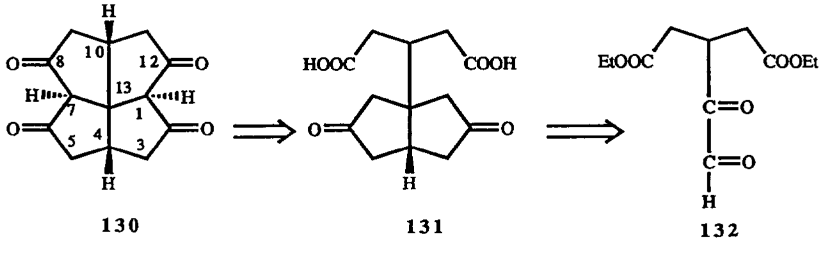


Scheme 27

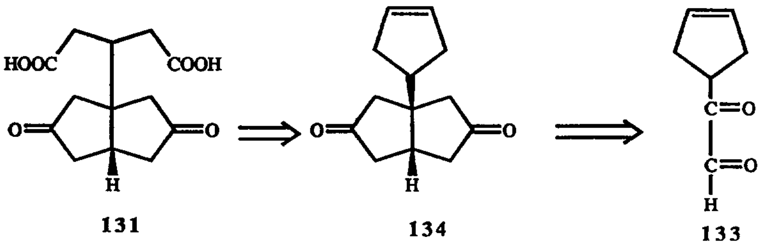
pentaenes **123** and **128** depicted in Scheme 27 certainly contain less strain energy than their dibromo counterparts (Scheme 26). As mentioned, the preparation of a stable, isolable tetrabenzotetrabromo[5.5.5.5]fenestrane tetraene by Kuck *et al.*[125] adds impetus to the routes outlined here This synthesis implies that reactions in this series with ΔEs less than that calculated for **7** → **126** (24 kcal/mol) may be within reach in a chemical sense.

8. SYNTHESIS OF [5.5.5.5]FENESTRANES

The first synthesis of a [5.5.5.5]fenestrane was reported by Mitschka *et al.* in 1978.[3d] The preparation of tetracyclo[5 5.1.0^{4,13}.0^{10,13}]tridecane-2,6,8,12-tetrone **130** was effected by the bis-acylation of the *cis*-bicyclo[3.3.0]octane-3,7-dione substituted diacid **131** which had been prepared by the Weiss reaction of glyoxal diethyl ester **132**.[3d] However, as reported earlier, success in the Weiss reaction is affected by the molecular volume[6,49,63] of the substituents attached to the 1,2-dicarbonyl compound (see Tables 1–3). This is due to steric congestion in the transition state from the diester groups of **132** during formation of the *cis*-fused bicyclo[3.3.0]system. Earlier, when α-ketoaldehyde **132** was stirred with dimethyl 3-oxoglutarate a 51% yield of the desired *cis*-bicyclo[3.3.0]octane-3,7-dione tetraester was realized.[3d] The yield of this process retarded preparation of staurane tetrone **130** on gram scale necessary for further transformations. This problem was circumvented by substitution of an alicyclic 1,2-dicarbonyl compound **133** for **132** in the Weiss condensation[8] and resulted in yields of the desired 1 : 2 adduct as high as 90% (Scheme 29). The



Scheme 28



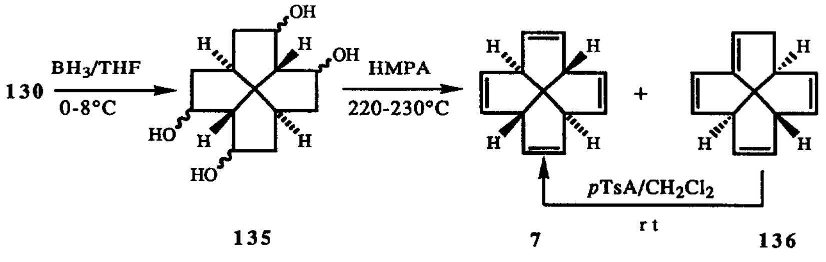
Scheme 29

1-(3-cyclopentenyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione **134** available via this route was readily converted into diacid **131** and the bisacylation sequence with **131** provided staurane tetrone **130**.

The lability of β-diketones in molecules such as **130**[40] prevented reduction of the carbonyl groups with nucleophilic reagents; however, reduction under Lewis acid mediated conditions (BH_3/THF) gave high yields of the staurane tetrol **135**, as reported. Elimination of four molecules of water from the tetrol was carried out by heating **135** in HMPA, analogous to earlier work from this laboratory.[11] This process gave the desired staurane-2,5,8,11-tetraene **7** accompanied by the bridgehead olefinic isomer **136** in an 80 : 20 ratio (Scheme 30).[8] As mentioned earlier, the bridgehead double bond in **136** renders this olefinic isomer to be an estimated 4.7 kcal/mol less stable species than staurane tetraene **7** (MM2PI). Though this is clearly an overestimate, it qualitatively parallels the synthetic result and predicts the direction of acid catalyzed double bond migration. Accordingly, the mixture was converted into the thermodynamically more stable **7** on exposure to *para*-toluenesulfonic acid in methylene chloride. It is conceivable that application of the Chugaev approach[21] developed during the synthesis of ellacene might provide **7** in an even simpler fashion. Catalytic reduction of **7** provided the all *cis*-[5.5.5.5]fenestrane staurane **12**, the synthesis of which had been reported by Keese via a different route.[120b,126] Tetracyclo[$5.5.1.0^{4,13}.0^{10,13}$]tridecane-2,5,8,11-tetraene **7** belongs to the D_{2d} point group. As a consequence of this symmetry, only three signals (δ 66.00, 66.36, 131.83 ppm) are observed in the ^{13}C-NMR spectrum of **7** and only two signals are found in the proton NMR spectrum [δ 3.48 (4H), 5.33 (8H) ppm] of this material.[8]

9. ALDOL APPROACH TOWARD [5.5.5.5]FENESTRANES

The lability of β-diketones in the [5.5.5.5]fenestrane system[40] and the successful execution of aldol chemistry in the synthesis of a number of other polyquinenes (see Scheme 31 for one example)[10,11] stimulated investigation of an aldol approach to these molecules. The key feature in the conversion of bisacetal **137** into tetraene **6** was the ability to trap the product of aldolization as the bisacetate **138**. This prevented ring-cleavage in tetraquinane **138** via retro-aldol processes.[10] However, when the dialdehyde **139**, which was available from **134** on ozonolysis, was stirred in 70% acetic acid in

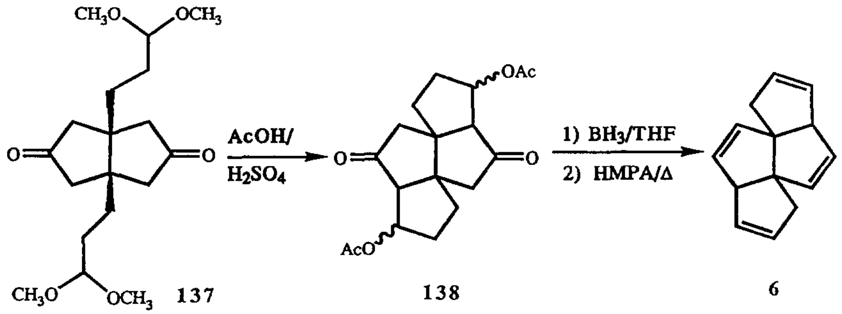


Scheme 30

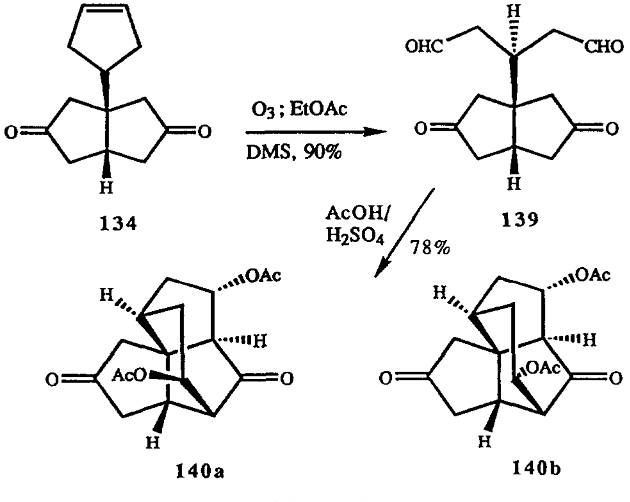
the presence of sulfuric acid for three days, followed by heating to 50–55°C, a 78% yield of the products of transannular cyclization **140a** and **140b** were isolated. The structures of the two diacetates were deduced from high resolution NMR experiments and later confirmed for **140b** by single crystal X-ray analysis.[61] Although this sequence was attempted under a variety of conditions,[10] none of the desired [5.5.5.5]fenestrane diacetate **141** was observed.

Since the two transannular diacetates **140a** and **140b** were felt to be thermodynamically less stable than the fenestrane derivative **141** (see references 6 and 61 for details), their origin arises from the irreversible kinetic trapping of the intermediate aldol as the acetate **140** (Scheme 33). The diketodialdehyde **139** can exist as two conformers (**139a** and **139b**) one of which experiences an unfavorable interaction between the bridgehead methine proton H_b and the proton labelled H_a, as illustrated for conformer **139a**. Presumably conformer **139b** is present at higher concentrations, and undergoes the transannular cyclization reaction to provide **140**. Examination of Dreiding models indicates that conformer **139b** cannot cyclize to the desired [5.5.5.5]fenestrane system **141**.[49]

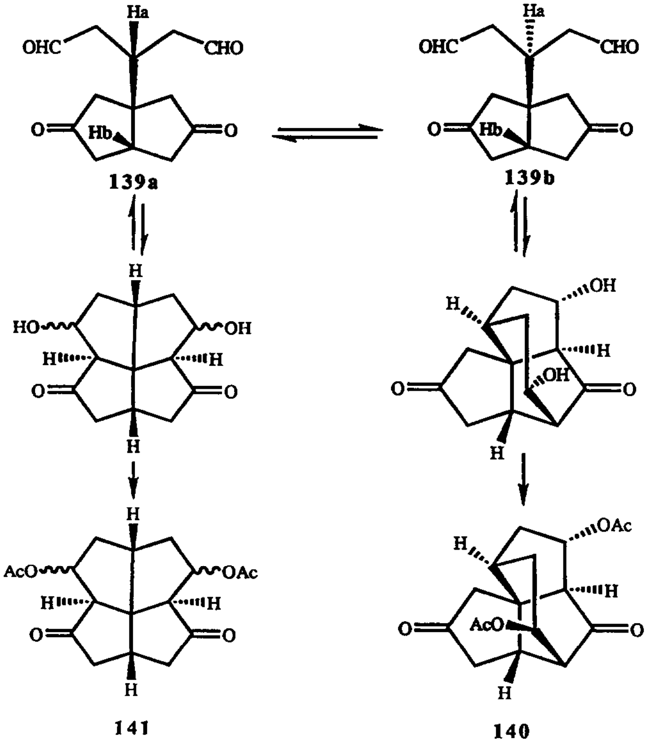
Based on the above analysis, the aldol cyclization of **139** was executed under equilibrating conditions developed during the synthesis of triquinacene.[11] The diketodialdehyde **139** was stirred in tetrahydrofuran in the presence of 4% aqueous HCl for fourteen days, and then quenched with excess acetic anhydride. After extensive flash chromatography the desired [5.5.5.5]fenestrane



Scheme 31



Scheme 32



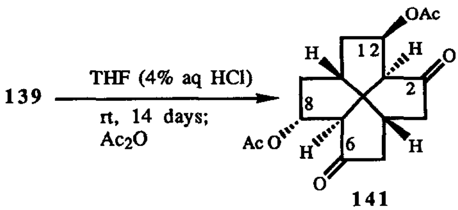
Scheme 33

diacetate was isolated.[22,49] The yield of diacetate **141** was 45% (NMR analysis) and it was accompanied in the reaction mixture by a symmetrical isomer (epimeric at either C-8 or C-12),[22,49] as well as the two transannular acetates **140a** and **140b**. The structure of the [5.5.5.5]fenestrane derivative **141** was assigned based on extensive 2D COSY as well as 1D NOE and NOESY NMR experiments.[127]

Formation of the all *cis* configuration at the ring junctures in **141** rather than the *cis-cis-cis-trans*-diastereomer was also in agreement with MM2 calculations,[109] as illustrated in Fig. 8. Examination of the energies of **142** and **143** indicates that the all *cis* diastereomer is more stable than **143** by 10 kcal/mol consequently, formation of **142** over **143** would be predicted under the conditions of equilibration. The all-*cis*-8α,12β-diacetoxytetracyclo[5.5.1.$0^{4,13}$.$0^{10,13}$]tridecane-2,6-dione can be converted into the desired staurane tetrol **135** on treatment with borane-THF analogous to published procedures.[10]

Steric energies (kcal/mol) 33.6 (all-*cis*) 43.6 (*cis-cis-cis-trans*)

Fig 8 MM2 optimized energies for the [5.5 5.5]fenestrane derivatives (**142**) and (**143**).

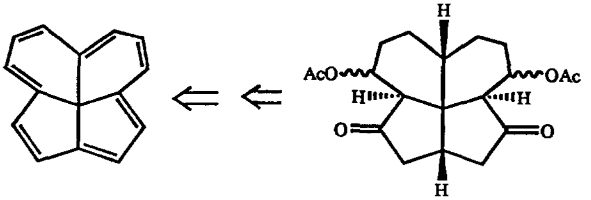


141

Scheme 34

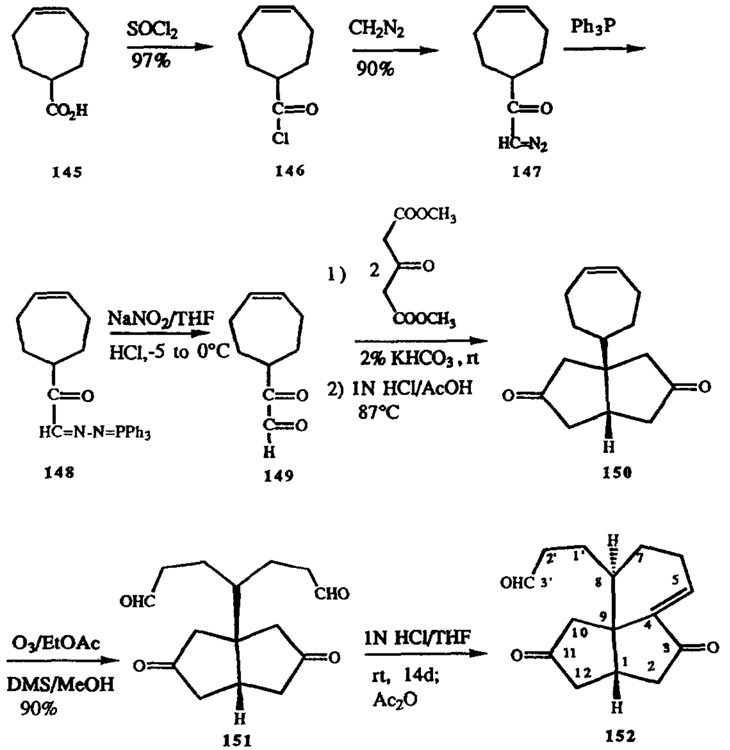
10. ALDOL APPROACH TOWARD THE [5.5.6.6]FENESTRANE SYSTEM

The successful synthesis of [5.5.5.5]fenestrane diacetate **141** encouraged the application of the aldol approach to the preparation of 2,8-diacetoxy-all-*cis*-tetracyclo$[7.5.1.0^{5,15}.0^{12,15}]$pentadecane-10,14-dione **144**, a potential intermediate on the pathway to the 14Π annulene **23**. The synthesis[128]



23 **144**

began with the preparation of 4-cycloheptene-1-carboxylic acid **145** on 200 gram scale via the modified[129] Stork enamine protocol.[130] As illustrated in Scheme 35, the carboxylic acid **145** was stirred with thionyl chloride to provide the acid chloride **146** in 97% yield. The diazoketone **147**, formed by reaction of **146** with diazomethane, was then treated with triphenyl phosphine to provide the desired phosphazine **147** as light yellow crystals. The phosphazine was stable for several months if kept in a desiccator under an atmosphere of nitrogen. The phosphazine was converted into the key 4-cycloheptene glyoxal **149**[6,49] by stirring with nitrous acid at temperatures between -5 and 0°C, according to the procedure of Bestmann.[131] The Weiss reaction of α-ketoaldehyde **149** with two equivalents of dimethyl 3-ketoglutarate **1** was carried out in 2% aqueous potassium bicarbonate solution (pH 8.3) at room temperature for seven days (yields 50–78%).[6] The 1 : 2 adduct which results from this process was transformed into the 1-(4′-(cycloheptenyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione **150** by hydrolysis of the ester functions (HCl/HOAc, 87°C) accompanied by decarboxylation. It has been found that the desired dione **150** can be routinely prepared in this sequence without purification of individual intermediates at an overall yield of greater than 40% from phosphazine **148**. Conversion of the double bond of **150** into the dialdehyde was accomplished in 90% yield by ozonolysis. The diketodialdehyde **151** obtained in this manner was directly subjected to an intramolecular aldol condensation under the conditions (aq. HCl/THF/rt ; Ac_2O) of equilibration analogous to those employed to prepare the [5.5.5.5]fenestrane diacetate **141**. Instead of isolation of the desired [5.5.6.6]fenestrane system **144**, the tricyclic diketoaldehyde **152** was obtained from the process as the major component (50% by GC analysis), accompanied by several other materials. None of the desired [5.5.6.6]fenestrane **144** was observed. The structure of tricyclic monoolefin **152** was deduced from high resolution NMR and mass spectroscopy. The presence of three carbonyl signals and two olefinic carbon atoms in the ^{13}C NMR spectrum of **152**, in addition to the aldehydic proton indicated the dissymmetry in the molecule. Moreover, the bridgehead proton at H_1 was found to be coupled to the four adjacent protons (CH_2-2 and CH_2-12) by cross peaks in the



Scheme 35

homonuclear 2D-COSY (500 MHz) NMR spectrum, a situation that is impossible in the products of transannular cyclization.

All attempts to convert **152** into the [5.5.6.6]fenestrane system **144** have failed, furthermore reactions at high temperatures did not provide **144**. It is felt that the configuration at C-8 is opposite to the required configuration in the all-*cis*-fenestrane system (see **141**) and consequently cannot cyclize to **144**. If this is the case the contrast in reactivity between the [5.5.5.5]fenestrane system (**139** → **141**) and the [5.5.6.6] system (**151** → **152**-‖ → **144**) can be understood. In the intermediate aldol to provide **140** or **141**, loss of water in the fused cyclopentane system is not favored, for the bridgehead double bond so formed is unstable in fused five membered rings (see **136** → **7**). Consequently, the aldol from the more stable **139b** (Scheme 32) forms reversibly and eventually results in the formation of the bisaldol from **139a**. The stability of the product in this case dictates the reaction pathway. However, in the [5.5.6.6] system, the aldol can lose water more readily, consequently, the more stable conformer will not equilibrate (as in **139b** → **139a**) but simply loses the elements of water to provide tricyclic monoolefin **152**. From examination of Dreiding models the configuration at C-8 (as shown) in **152** would prohibit reaction at C-10, moreover the added strain from the olefin at C_4-C_5 prevents transannular cyclization at C-2. Further work to explore an alternate route to the [5.5 6.6]fenestrane system is in progress and will be reported in due course.

11. SUMMARY

The Weiss reaction has been shown to be a versatile approach for the synthesis of polycyclopentanoid natural products[9,14] and non-natural products.[6–7,12,13,15–22,132] The presence of the two carbonyl moieties at positions -3 and -7 of the *cis*-bicyclo[3.3.0]octane-3,7-dione skeleton (**4**) have rendered this condensation a facile route to polyquinenes. As illustrated, the synthesis of staurane-2,5,8,11-tetraene **7**,[8] as well as a number of centrosubstituted triquinacenes including 1,10-dimethyltriquinacene **19**,[12] 1,10-cyclohexanotriquinacene **20**[12] and 1,10-cyclododecanotriquinacene (ellacene) **21**[21] have been completed via the Weiss reaction. On the other hand, the cup-shaped tetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodecatetraene **25** has been observed only as a transient intermediate. The inability to isolate or trap the tetraene attests to the instability of hexaene **15** and pentaene **24** in good agreement with MNDO calculations.[19] In this vein, the bisazacyclopentapentalene **56** could be observed as a transient intermediate on pyrolysis of the bisacetate **64** or bisbenzoate **66** in the mass spectrometer, but the antiaromatic pentalenes **18** or **56** could not be isolated.[20]

With respect to the conversion of staurane tetraene **7** into the 12Π annulene **22**, the energies of the intermediates along the two reaction coordinates were evaluated computationally. Moreover, a new 'aldol approach' for the construction of the [5.5.5.5]fenestrane system (see **141**) was executed successfully, but has not been extended, successfully, to the [5.5.6.6]fenestrane system (see **144**), to date.

It is important to point out that the modified conditions of Ginsburg[27,28] have increased the effectiveness of the Weiss reaction with respect to substrates which are only sparingly soluble in water. Additional studies of the Weiss reaction with regard to the synthesis of polyquinenes of computational and chemical interest are underway.

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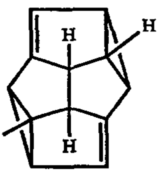
47 The molecular ion of the tetraxanthate **38b** under conditions of CI mass spectroscopy was observed at 155 daltons (100%) while under the conditions of EI spectroscopy (Δ) an ion was observed at 154 daltons (31%). The base peak in the latter spectrum was found at 155 daltons (100%) At present, formation of the biscyclopropyl derivative (i) in the mass spectrometer cannot be ruled out, however, construction of its framework with molecular models indicates prohibitive strain in relation to **25**



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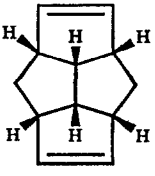

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