

## 1,2,3,4-Tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene: Diels–Alder Reactions and Applications of the Products Formed

Faiz Ahmed Khan,\* B. Prabhudas, and Jyotirmayee Dash

Kanpur (India), Department of Chemistry, Indian Institute of Technology

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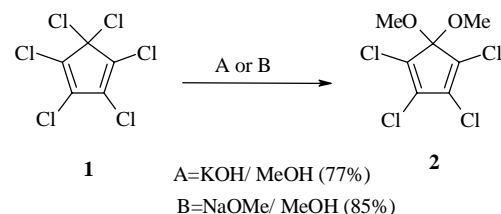
**Abstract.** Readily available 1,2,3,4-tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene (**2**) is an excellent cyclic diene for Diels–Alder reaction with a vast variety of dienophiles. The products so formed (norbornene derivatives) constitute important building blocks for the synthesis of diverse complex natural as well as non-natural products. Apart from very high *endo* selectivity associated with Diels–Alder reactions, there are several other fascinating features associated with these

bicyclic products which make them convenient entities in the synthesis of complex molecules. The most important is the rigid framework that act as a powerful template to provide high degree of selectivity and directional nature to various substituents. The proposed article is intended to focus on Diels–Alder reactions of **2** and the applications of norbornene derivatives in organic synthesis.

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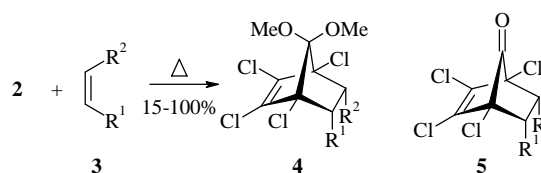
The preparation of 1,2,3,4-tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene (**2**) was first reported by Newcomer and McBee in 1949 [1a]. The addition of KOH–MeOH [1] or NaOMe–MeOH [2] to the easily available hexachlorocyclopentadiene (**1**) affords **2**, the yellow coloured liquid having sweet odour. This cyclic electron deficient diene **2** has been successfully utilized as an excellent reactant in numerous Diels–Alder reactions with a wide variety of dienophiles possessing both electron rich and electron deficient groups under mild conditions. Apart from high *endo* selectivity associated with the products so formed, the diene **2** can serve as masked cyclopentadienone, which is not a suitable candidate for the Diels–Alder reaction as it undergoes dimerisation.



### 1. Diels–Alder Reactions of 1,2,3,4-Tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene

Diels–Alder reaction is one of the most important and fundamental carbon–carbon bond forming reaction for the construction of six membered carbocycles. The Diels–Alder reaction

of **2** with maleic anhydride was first demonstrated by Newcomer and McBee [1]. Subsequently the remarkable reactivity of this diene **2** in Diels–Alder reactions with a variety of electron rich and electron deficient olefinic dienophiles **3** [3–8] was thoroughly investigated by McBee [3] and then by Hoch [4] and Jung, [5] exclusively giving rise to the *endo* adducts **4**. The adducts **4**, in majority of the cases, provide a convenient route to the synthesis of bicyclic bridged ketones **5** upon treatment with conc.  $\text{H}_2\text{SO}_4$  [3, 5, 7a] which are potential synthetic intermediates leading to diverse carbocyclic skeletons.

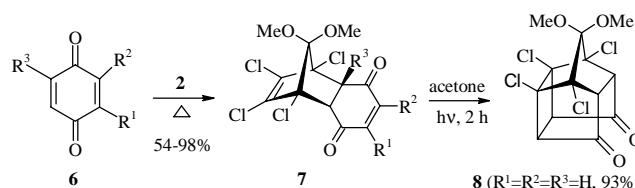


$\text{R}^1 = \text{H, Me, Hept, CO}_2\text{H, COMe, CO}_2\text{Me, Ph, CN, OEt, OAc, P(O)(\text{OMe})_2, \text{Cl, CH}_2\text{Hal (Hal = Cl, Br)}$

$\text{R}^2 = \text{H, Me, CH}_2\text{Cl, Cl}$

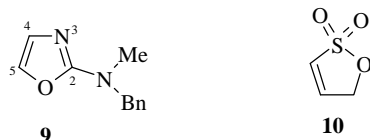
$\text{R}^1\text{--R}^2 = \text{C(O)--(CH}_2\text{)}_x\text{-- (x = 2, 3), Indene, Acenaphthalene}$

The [4+2] cycloaddition of **2** with quinones **6** proceeds smoothly giving rise to the *endo* adducts **7** [9]. However, **2** remains unreactive with chloranil and 2,5-dichloroquinone [9a]. The adduct **7a** photocyclized to give the cage compound **8** [9c].

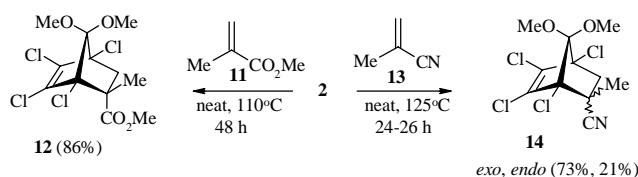


$\text{R}^1 = \text{H, Cl, OMe, } ^i\text{Pr; R}^2 = \text{H, Cl; R}^3 = \text{H, Me}$

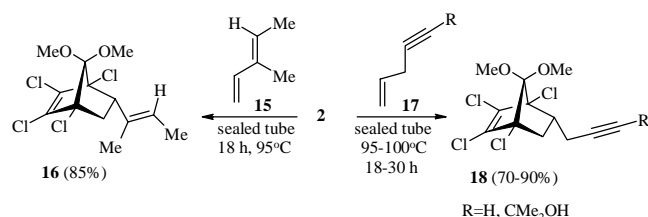
The addition of **2** with dienophiles **9** [10a] (across the C<sub>4</sub>-C<sub>5</sub> bond) and **10** [10b] was also reported to give exclusively the *endo* adducts.



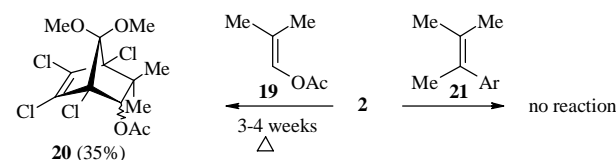
Reaction of **2** with methyl methacrylate **11** gave exclusive the *endo* adduct **12** whereas an *exo/endo* mixture (3.5:1) of adducts **14** were formed with methacrylonitrile **13** [11].



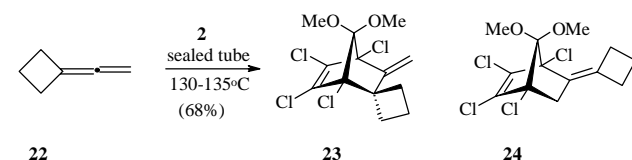
With conjugated 1,3-dienes, for example **15**, only the least hindered double bond of the dienophile reacts, [12a] whereas alkene is preferred over alkyne in case of allyl acetylenes **17** giving rise to adducts **16** and **18** [12b].



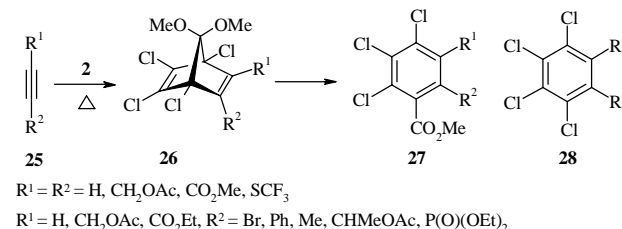
Although **2** is highly reactive with mono- and disubstituted olefinic dienophiles it is very unreactive with tri- or tetrasubstituted olefins [13]. The reaction of **2** with isobutenyl acetate **19** affords the adducts **20** in poor yields even when refluxed in neat for 3–4 weeks, whereas with tetrasubstituted ethylenic dienophile **21** the reaction fails [13a].



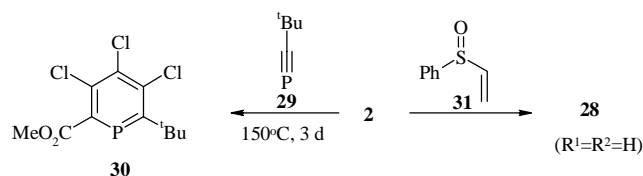
The reaction of **2** with allenic dienophile such as vinylidene cyclobutane **22** gave a mixture of 1:1 regioisomeric cycloadducts **23** and **24** [14].



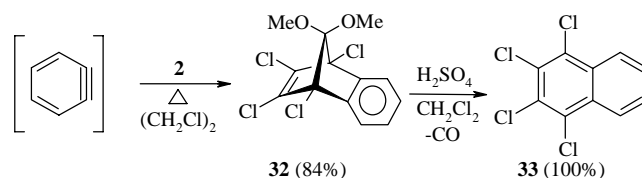
The initial Diels–Alder adducts **26** formed from **2** and acetylenic dienophiles **25** undergo aromatization either by retaining the bridge carbon leading to products **27** or by extrusion of dimethoxy carbene from bridgehead resulting in product **28** [15]. However Lemal *et al.* reported the isolation of some of the cycloadducts in pure form [15a].



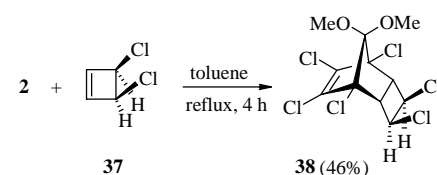
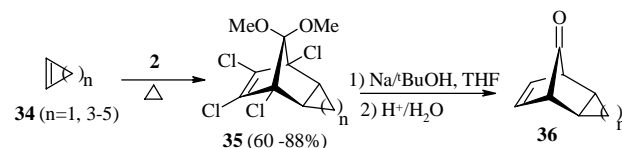
λ<sup>3</sup>-Phosphine **30** was obtained from the reaction of **2** and phosphalkyne **29** [15h]. The diene **2** reacts with phenyl vinyl sulfoxide **31** as acetylene equivalent to give tetrachloro benzene **28** (R<sup>1</sup> = R<sup>2</sup> = H) [15i].



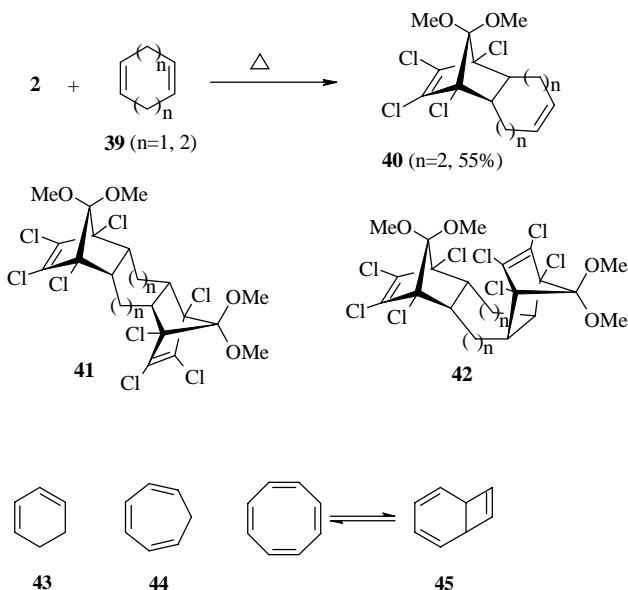
The cycloadduct **32** of **2** with benzyne was described to yield 1,2,3,4-tetrachloro-naphthalene **33** [16a] and 7-benzonorbornenone [16b] through simple manipulations.



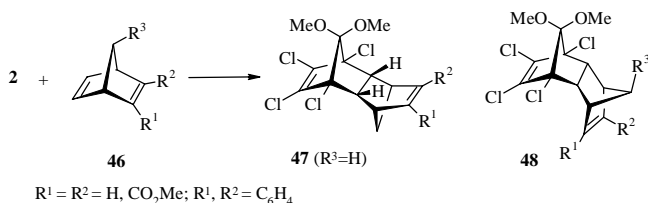
The Diels–Alder reaction of **2** with cyclic alkenes **34** were investigated to give the cycloadducts **35**, [5, 17, 18] which after dechlorination [19] and hydrolysis were converted to the bicyclic ketones **36**. The cycloadduct **38** was formed from the addition of **2** with cyclobutenic dienophiles such as **37** [20].



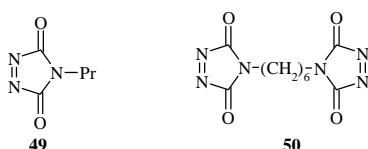
The non-conjugated cycloalkadienes **39** also serve as good dienophiles to furnish both mono- **40** and bisadducts **41** and **42** [21, 22]. Using excess of **2** in cycloaddition reaction with cyclooctadiene **39** ( $n = 2$ ), *syn* and *anti* isomers of *endo-endo* diadducts in a ratio of 1:4 were formed [22c,d]. The conjugated cyclohexadiene **43** was reported to yield *endo* mono adduct in high yield [23a]. The reaction of cycloheptatriene **44** with **2** affords both mono- and bisadducts [23b] whereas cyclooctatetraene reacts through its valence isomer **45** resulting in the formation of the bisadduct [24].



The Diels–Alder reaction of **2** with norbornadienes **46** without bridge substituents ( $R^3 = H$ ) proceeds regio- and stereospecifically with inverse electron demand to the less hindered *exo* face of **46** resulting in *endo-exo* series of **47** [25]. Whereas the 7-oxy substituted **46** ( $R^3 = OR$ ) furnish *endo-endo* cycloadducts **48** in a stereoselective manner [25a,b].

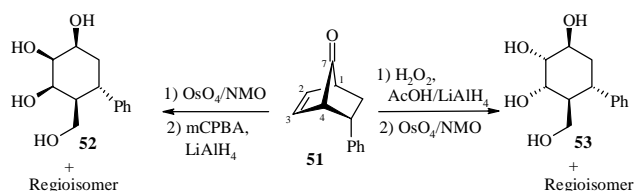


The heteroatomic dienophiles **49** and **50** also react with **2** resulting in mono- and bisadducts respectively in quantitative yields [26].

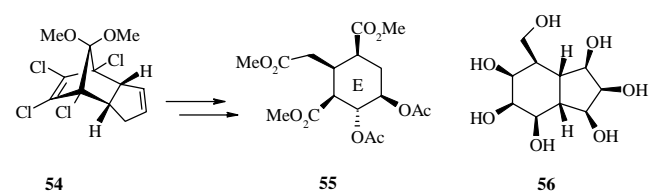


## 2. Application in the Synthesis of Natural Products and their Intermediates

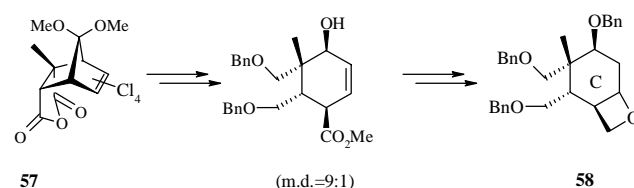
The norbornene skeleton, obtained from the reaction of **2** with a suitable dienophile [1–26] and adorned with 7-keto group (in the form of acetal),  $C_2$ – $C_3$  double bond and  $C_5$ – $C_6$  substituents, acts as a powerful template for the regio- and stereoselective synthesis of complex molecules. These functional groups actually provide the handle to convert norbornene derivative into desired structural entity through cleavage of appropriate skeletal bonds. For example, the bond between carbonyl carbon ( $C_7$ ) and bridgehead carbon ( $C_1$  or  $C_4$ ) in **51** (obtained from **4**,  $R^1 = Ph$ ,  $R^2 = H$ ) was broken by a two step procedure involving Baeyer–Villiger oxidation followed by  $LiAlH_4$  reduction to give cyclohexene derivatives **52** or **53** depending upon the sequence in which the two steps were executed, with as many as five contiguous stereocenters fixed [27]. The same approach was extended for the synthesis of tricyclic core of Pancratistatine and Narciclasine type alkaloids, [27] carbasugars [28] and Shikimic acid derivative [28].



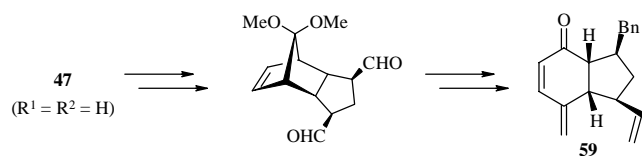
The highly functionalized *E*-ring **55** of Reserpine was elegantly synthesized by Mehta [29] from the adduct **54** of **2** with cyclopentadiene. By utilizing the same two-step procedure (Baeyer–Villiger oxidation and  $LiAlH_4$  reduction) for 7-keto cleavage, glycomimics like polyhydroxylated hydrindane **56** was conveniently prepared [30].



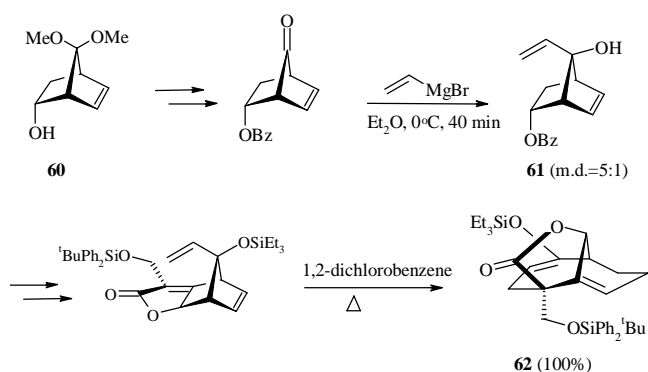
The C-ring fragment **58** of the antitumour agent, Taxol® was constructed in a stereocontrolled manner starting from citraconic anhydride adduct **57** [31].



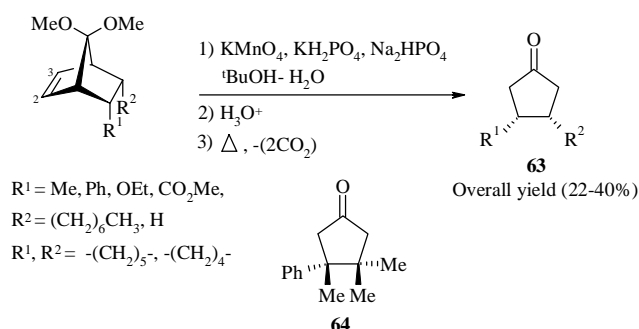
The doubtful structure **59** of ottelione A was unambiguously proved by Mehta *et al.* [32] by its synthesis starting from norbornadiene adduct **47**.



The carbobicyclic substructure of squalene synthase and farnesyl transferase inhibitors CP-225,917 and CP-263,114 were elegantly synthesized [33] from 2-hydroxy-7-norbornene acetal **60**. Interestingly, the compound **61** for the key step was obtained by predictable diastereofacial selectivity in vinylation step [34]. Subsequent manipulations furnished the required carbobicyclic substructure **62** of the CP-molecules.



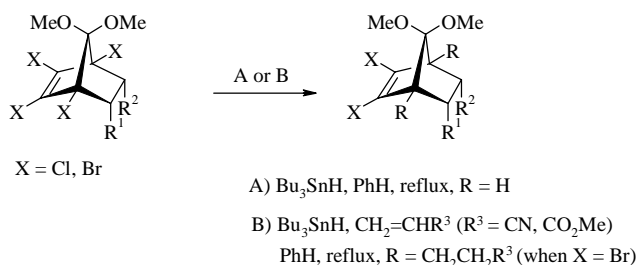
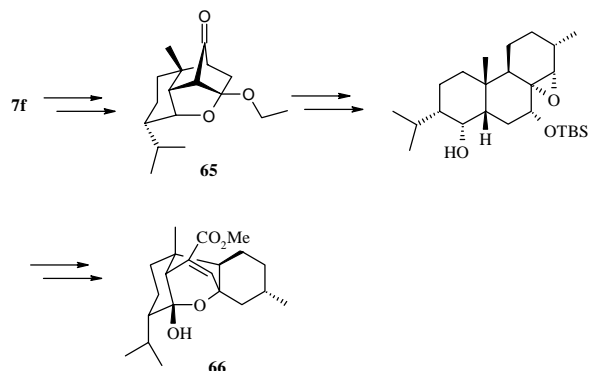
Extraction of five membered carbocycles **63** from 7-norbornene derivatives by the cleavage of C<sub>2</sub>–C<sub>3</sub> double bond was demonstrated by Jung *et al.* [5]. This methodology was applied in the synthesis of  $\beta$ -cuparenone **64** [13a].



Chatancin **66**, a molecule with an unusual oxygen-bridged dodecahydro phenanthrene skeleton and seven stereogenic centres succumbed to synthesis by Gössinger *et al.* [35]. The required intermediate **65** was synthesized from the adduct **7f** (R<sup>1</sup> = <sup>i</sup>Pr, R<sup>2</sup> = H, R<sup>3</sup> = Me).

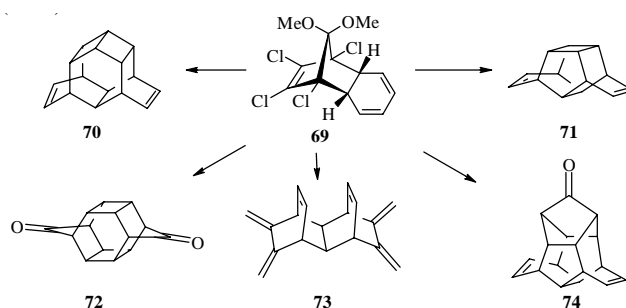
The selective utilization of halogens for bridgehead functionalization and partial reduction in these systems was demonstrated for the first time by Khan *et al.* [36].

The natural products Ikarugamycin [37a] was synthesized by Paquette starting from **67** employing oxy-Cope rearrangement as the key step [37b] leading to **68**, an advanced intermediate in the synthesis. The same strategy was used for Spinosyn-A, [37c] a related natural product.

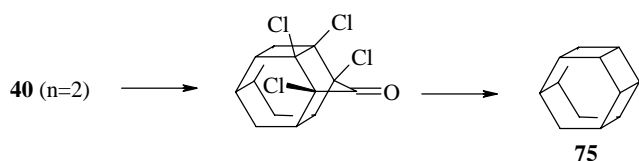


### 3. Application in the Synthesis of Unnatural Products

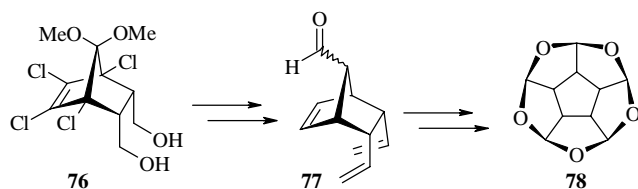
The aesthetically pleasing shape and unusual chemical reactivity of [n]-Prismanes with general formula (CH)<sub>2n</sub> and D<sub>nh</sub> symmetry has attracted many of synthetic chemist for its synthesis. The Diels–Alder adducts of the title diene **2** again serve as advantageous precursors for the construction of prismane analogues. The intermediate **69** [38b] obtained from benzoquinone adduct **7a** was transformed into various prismane analogues **70–72**, [21, 38] tetracyclic hexaene **73** [39] and a novel cage compound **74** [40].



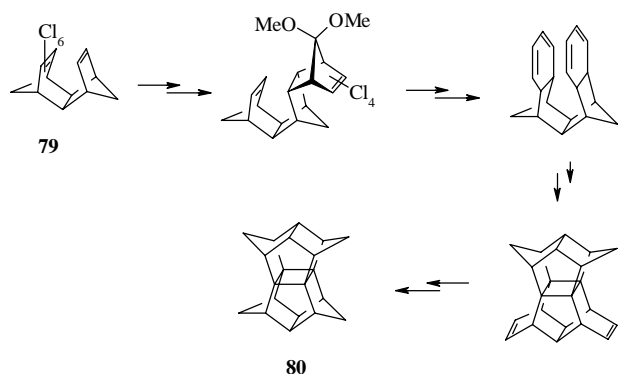
Quest for hexaprismane starting from cyclooctadiene adduct **40** ( $n=2$ ) resulted in the synthesis of seco-[6]-prismane **75** [41].



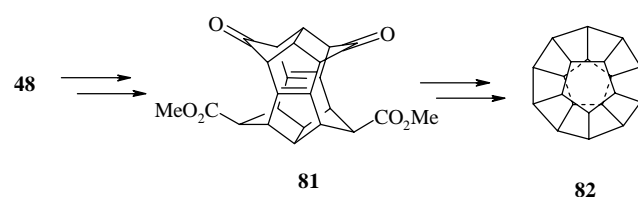
[ $n$ ]-Hetero-[ $n$ ]-peristylanes are related to the [ $n$ ]-peristylanes, where the methylene groups on the rim of the 'bowl' are replaced by heteroatoms. Pentaaxa[5]peristylane **78** was efficiently synthesized by Mehta *et al.* [42] in very few steps from **76**. Ozonolysis of the intermediate **77** triggered a facile cascade cyclization resulting in the formation of the oxabowl **78**.



Pagodane **80** is a  $C_{20}H_{20}$  polyquinane with highly complex and aesthetically appealing structure. Prinzbach *et al.* [43] achieved its synthesis starting from isodrin **79**.

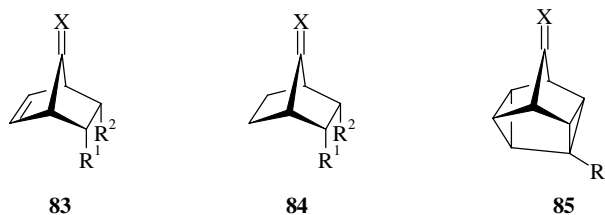


Dodecahedrane **82**, a  $C_{20}H_{20}$  polyquinane of  $I_h$  symmetry has been a major synthetic challenge for organic chemists. Prinzbach *et al.* [44] approached this problem *via* a functionalized Pagodane **81** which in turn was synthesized from the adduct **48**.



#### 4. Miscellaneous

The norbornyl derivatives **83–85** and few other related systems obtained from **2** have served as excellent probes for electronic control of  $\pi$ -facial selectivities by remote substituents ( $R^1, R^2$ ) during nucleophilic and electrophilic additions to trigonal center, a topic which has been the subject of intense debate and discussion in the recent past [34].



$X = O, CH_2, CMe_2$

In summary, the title diene **2** is an extremely versatile reagent for [4+2] cycloadditions with a variety dienophiles providing immense flexibility in the stereocontrolled synthesis of numerous densely functionalized natural and unnatural target molecules.

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Address for correspondence:

Dr. Faiz Ahmed Khan  
Department of Chemistry  
Indian Institute of Technology  
Kanpur-208 016, India  
Fax: 0091-512-590260  
e-Mail: faiz@iitk.ac.in