SYNTHETIC STUDIES ON CROSS-CONJUGATED OLEFINS AND THEIR APPLICATIONS IN CONSTRUCTION OF COMPLEX MOLECULAR SKELETONS

By

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I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

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List of publication arising from the thesis

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1. "[3]Dendralenes: synthesis, reactivity studies and employment in diversity oriented synthesis of complex polycyclic scaffolds", **Gonna Somu Naidu**, Rekha Singh and Sunil K. Ghosh, *Synlett* **2018**, *29*, 282-295.

2. "Tuning the stability and the reactivity of substituted [3]dendralenes for quick access to diverse copiously functionalized fused polycycles with step and atom economy", **Gonna Somu Naidu**, Rekha Singh, Mukesh Kumar and Sunil K. Ghosh, *J. Org. Chem.* **2017**, *82*, 3648-3658.

3. "Synthesis of highly functionalized [3]dendralenes and their Diels-Alder reaction displaying unexpected regioselectivity" **Gonna Somu Naidu**, Rekha Singh, Mukesh Kumar and Sunil K. Ghosh, *RSC Adv*. **2016**, *63*, 37136-37148.

4. "Synthesis of stable tri- and tetra-substituted [3]dendralenes with an allylsilane as integral component" Rekha Singh, **Gonna Somu Naidu**, Sunil K. Ghosh, *Proc. Natl. Acad. Sci., India, Sect. A Phys. Sci.* **2016**, *86*, 619-625.

Conferences

1. "Synthetic studies on cross-conjugated olefins and their applications in construction of complex molecular skeletons", **Gonna Somu Naidu** and Sunil K. Ghosh, ***RSM-2017***, St. Xavier's College, Mumbai, India.

2. "Quick access to highly substituted isoindole, cinnoline and decalin derivatives *via* acyclic substituted [3]dendralenes using DTDA sequence", **Gonna Somu Naidu**, Rekha Singh and Sunil K. Ghosh, ***ICOS21***, IIT Bombay, Mumbai, India.

3. "Demystifying the stability of substituted [3]dendralenes and their application for quick generation of complex molecular skeletons", **Gonna Somu Naidu**, Rekha Singh, Mukesh Kumar and Sunil K. Ghosh, ***ISMC-2016***, Bhabha Atomic Research Centre, Mumbai, India.

4. "Synthesis of highly fuctionalized stable [3]dendralenes and their Diels-Alder reactions with *N*-methylmaleimide", **Gonna Somu Naidu**, Rekha Singh and Sunil K. Ghosh, ***NDCS-2015***, BITS Pilani, Rajasthan, India.

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Dedicated to.....

MY Beloved Parents

&

Teachers

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CONTENTS

CHAPTER 3

Synthesis of Stable Tetrasubstituted [3]Dendralenes and Their Diels-Alder Reactions

CHAPTER 4

Engagement of [3]Dendralenes in Diversity-Oriented Diene Transmissive Diels-Alder Reaction for Construction of the Obscure Polycycles

SYNOPSIS

Synthetic Studies on Cross-Conjugated Olefins and Their Applications in Construction of Complex Molecular Skeletons

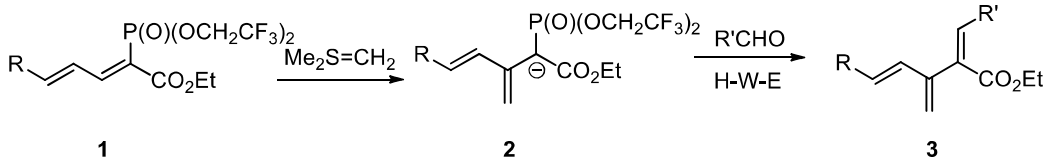
This thesis describes the synthesis of a new class of cross-conjugated olefins known as [3]dendralenes. It also entails about the structural features which govern the stability/reactivity of this kind of molecules. Besides, it forays upon the use of [3]dendralenes in conjunction with diversity oriented synthesis for the synthesis of complex polycycles. The content of this thesis has been divided into four chapters.

Chapter 1: Dendralenes: An Overview and Literature Methods of [3]Dendralene Synthesis

This chapter presents an overview of cross-conjugated olefins in general and [3]dendralenes in particular. Dendralenes[1] are a new class of olefins with tremendous potential, but have remained an uncharted territory for a long period primarily owing to their erratic stability and reactivity behavior. Since last one and half decade, this class has been a centre of attraction of material, theoretical and organic chemists because their properties are very different from the normal oligoenes. Besides, numerous bioactive natural products comprise of dendralenic core structures.[1a] From the synthetic point of view, [3]dendralenes are fascinating molecules because they possess a huge potential for the quick generation of complex multicyclic scaffolds when subjected to tandem Diels-Alder (D-A) reactions, also known as diene-transmissive Diels-Alder[2] (DTDA) sequence. Applications of dendralenes in various fields have been discussed in this chapter. Besides, it delineates the synthetic approaches of other research groups towards the synthesis of [3]dendralenes.

Chapter 2: Synthesis of Functionalized [3]Dendralenes: The Initial Attempts

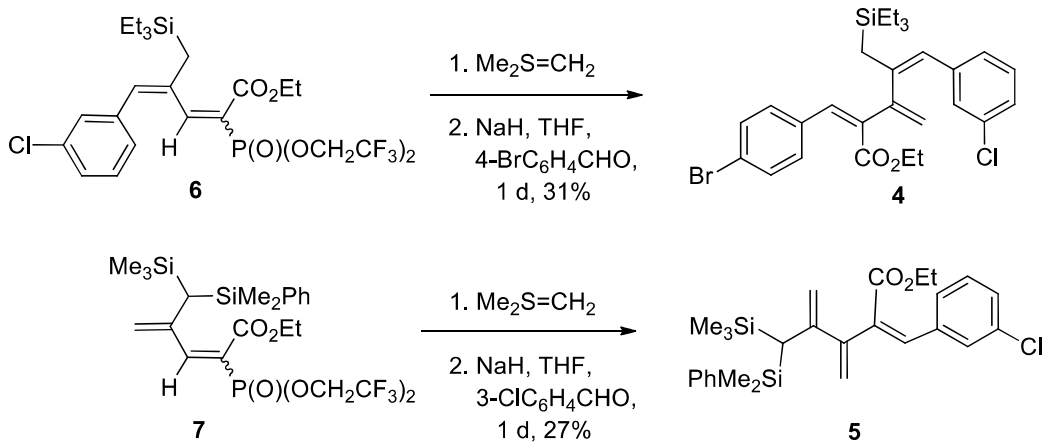
Under normal circumstances, dimethylsulfonium methylide reacts with aldehydes/ ketones, imines and activated olefins to give epoxide, aziridine and cyclopropane respectively.[3] But, in our group a novel olefination methodology was developed wherein activated olefins upon reaction with dimethylsulfonium methylide provide a new olefin.[4] When this reaction is performed with dienyl phosphonates **1**, a new diene **2** is obtained. This diene upon Horner–Wadsworth–Emmons (H-W-E) reaction provides [3]dendralene **3** (**Scheme 1**).



1 **2** **3**

Scheme 1 General synthesis of [3]dendralene

The ongoing work related to [3]dendralene synthesis in our group continually resulted in their formation only in transient forms which ultimately underwent *in situ* self cyclodimerization.[5] All the efforts to isolate these [3]dendralenes were unfruitful. This chapter is an extension of those initial efforts towards the synthesis of [3]dendralenes and attempts to trap them *via* Diels-Alder reactions by external additions of several dienophiles/dienes. Later stable mono, disilyl functionalized [3]dendralenes **4**, **5** were successfully synthesized from phosphonates **6** and **7** respectively *via* this sequential olefination methodology (**Scheme 2**).[6] These dendralenes did not participate in D–A reactions owing to their steric bulk.



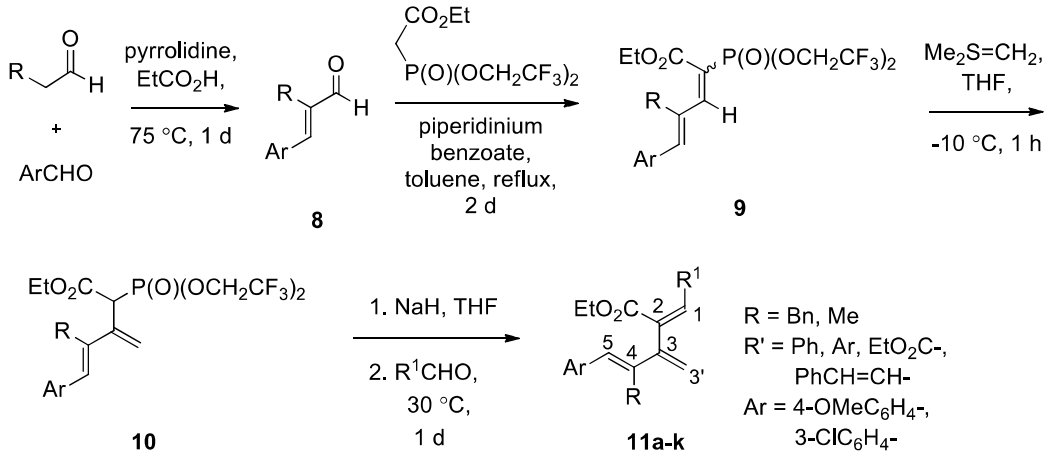
Scheme 2: Synthesis of silyl[3]dendralenes

Chapter 3: Synthesis of Stable Tetrasubstituted [3]Dendralenes and Their Diels-Alder Reactions

This chapter discusses synthesis of several stable [3]dendralenes with multiple substituents and a systematic study of their D-A reactions with respect to regio- and stereoselectivity.

Tetrasubstituted [3]dendralenes bearing a benzyl/methyl group at fourth position were synthesized as shown in **Scheme 3**. The conjugated aldehydes **8** were synthesized from aldol condensation of 3-phenylpropanal with *p*-anisaldehyde/3-chlorobenzaldehyde and propanal with *p*-anisaldehyde. Knoevenagel condensation of the resulting conjugated aldehydes **8** with ethyl bis-(2,2,2-trifluroethyl)-phosphonoacetate provided the desired dienic phosphonates **9**. The phosphonates **9** were treated with dimethylsulfonium methylide to afford the dienyl phosphonates **10**, which on treatment with NaH followed by reaction with various aldehydes furnished a library of 1,2,4,5-tetrasubstituted [3]dendralenes **11a-k** (Scheme 3).[7] All these dendralenes were stable towards D–A cyclodimerization at ambient temperatures. X-

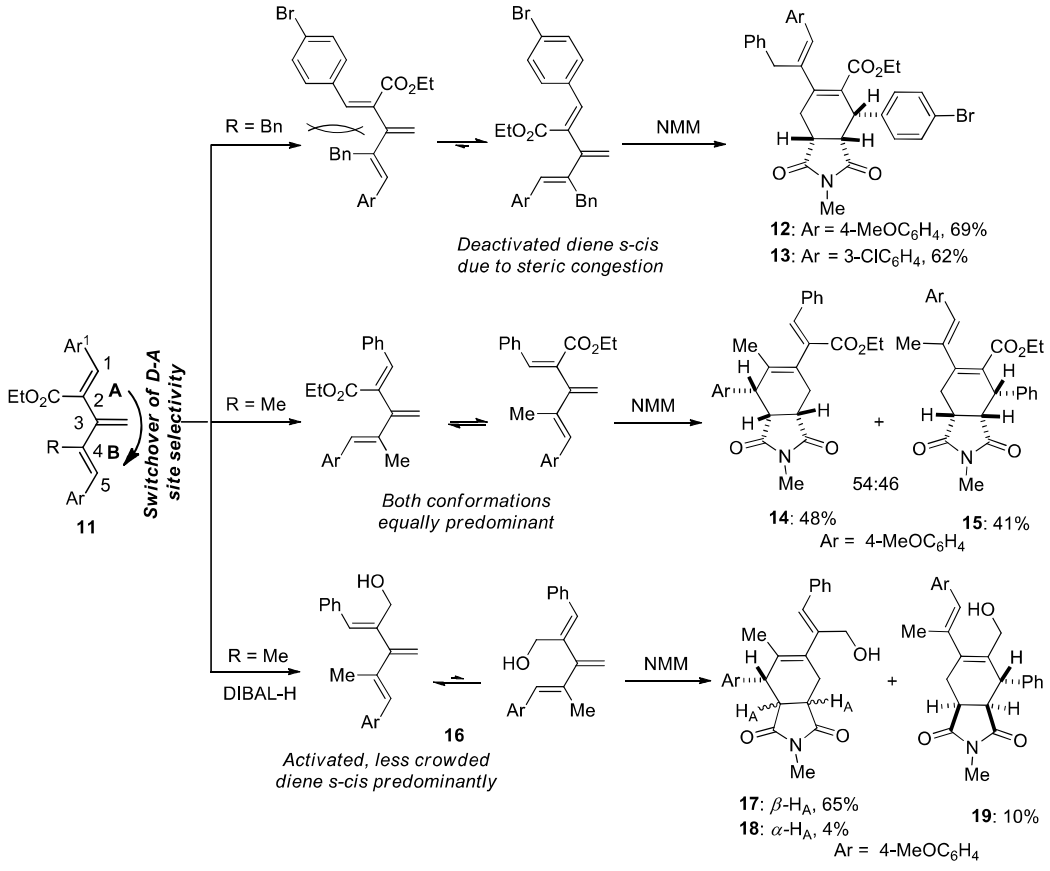
ray structure of one of these dendralenes disclosed that the diene component featuring double bonds at third and fourth position exists in *s-trans* conformation. This perhaps is due to the steric effect of benzyl substituent at fourth position which forces the diene to adopt D-A unreactive *s-trans* conformation thus imparting stability. Interestingly, all these [3]dendralenes **11** despite having extended conjugation at the termini were stable, contrary to Sherburn's conclusion which states that terminal conjugating substituents accelerate cyclodimerization whereas internal substituents have little effect on the dimerization reactivity.[8] This enhanced stability was rendered by the steric bulk of the internal substituents.



Scheme 3 Synthesis of tetra-substituted [3]dendralenes

After successful synthesis of the dendralenes, their reactivity for the D–A reaction with N-methylmaleimide (NMM) as a representative dienophile was examined (**Scheme 4**). From D-A reactions, it became apparent that steric effect outweighs electronic effects. An unexpected regioselectivity was obtained. When the fourth position substituent was benzyl group, diene '**A**' exclusively participated in D-A reaction to provide adducts **12** and **13** even though it appears electronically

deactivated (**Scheme 4**). When the fourth position substituent was a methyl group, both dienes '**A**' and **'B'** equally participated in D-A reaction to give adducts **14** and **15**. Reduction of ester functionality on dendralene **11** provided a new dendralene **16** with alcohol functionality. The D-A reaction of this dendralene **16** afforded adducts **17-19**, here surprisingly the diene '**B**' was predominantly involved in the reaction. The D-A reactions were highly *endo* selective. There was a switch over of site selectivity from diene '**A**' to diene '**B**' for the D–A reaction as the substituents on the [3]dendralenes were varied.[7]



Scheme 4 D–A reaction of [3]dendralenes

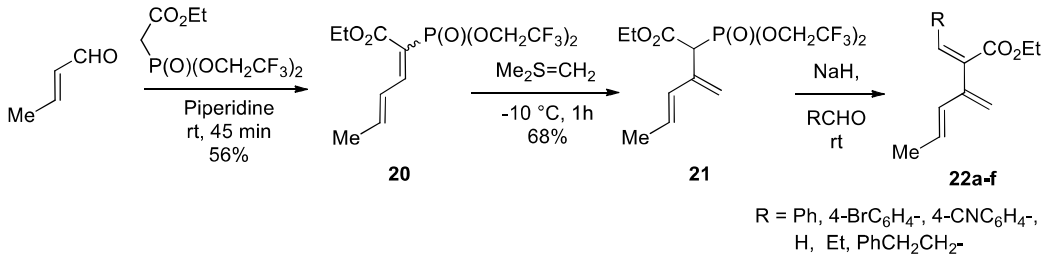
These first D-A adducts did not participate in a successive D-A owing to steric effect of the multiple functionalities which prevent the diene to adopt *s-cis* conformation which is imperative for its success.

Chapter 4: Engagement of [3]Dendralenes in Diversity-Oriented Diene Transmissive Diels-Alder Reaction for Construction of the Obscure Polycycles

The real potential of dendralenes from a synthetic chemistry point of view lies in their involvement in a diene transmissive Diels-Alder (DTDA) reactions as it results in formation of polycyclic compounds in a quick and efficient manner with step and atom economy. Besides, if DTDA is performed in a diversity oriented manner it would result in generation of a library of compounds. In chapter 3, [3]dendralenes with multiple substituents were synthesised successfully, but they could be engaged only in D–A reaction and not in a DTDA sequence. This shortcoming was due to the steric hindrance presented by the bulky functionalities on the D–A adducts. At this juncture, where the aim was to participate these dendralenes in a DTDA sequence, the need was to design these dendralenes in such a fashion, that they possess just right kind of reactivity and stability so that they are stable enough to be handled at the same time readily undergo a DTDA sequence. Hence, it was decided to have non-conjugating aliphatic groups at the terminal positions for enhancement of the stability and less bulky internal substituents for minimal steric congestion on the dendralenes.

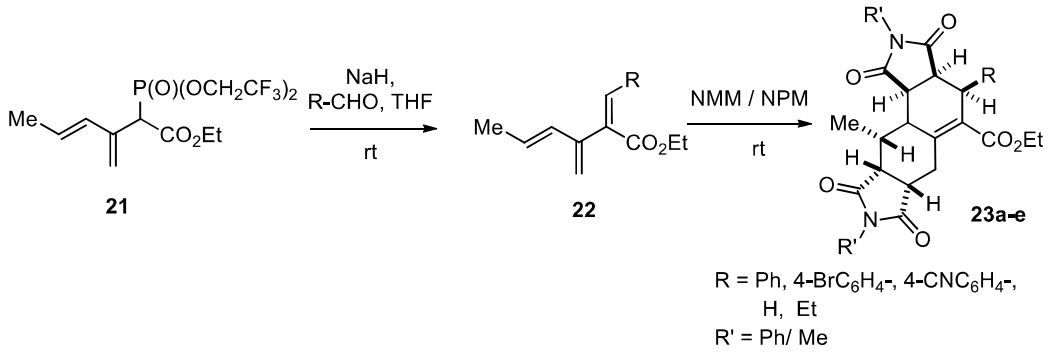
In this chapter, the synthesis of several such moderately stable dendralenes has been discussed. Also, it deals with the diversity oriented DTDA reaction of one such dendralene which resulted in generation of a small library of architecturally intriguing complex multicyclic compounds.

For this, the synthesis was begun with crotonaldehyde. Following the previously developed protocol as described in earlier chapters, the desired substituted [3]dendralenes **22a-f** were synthesized (**Scheme 5**). These dendralenes possessed one of the terminal substituents as a non-conjugating methyl group, which rendered stability to them. It was gratifying to note that all the dendralenes as anticipated were stable but to varying degrees.[9]



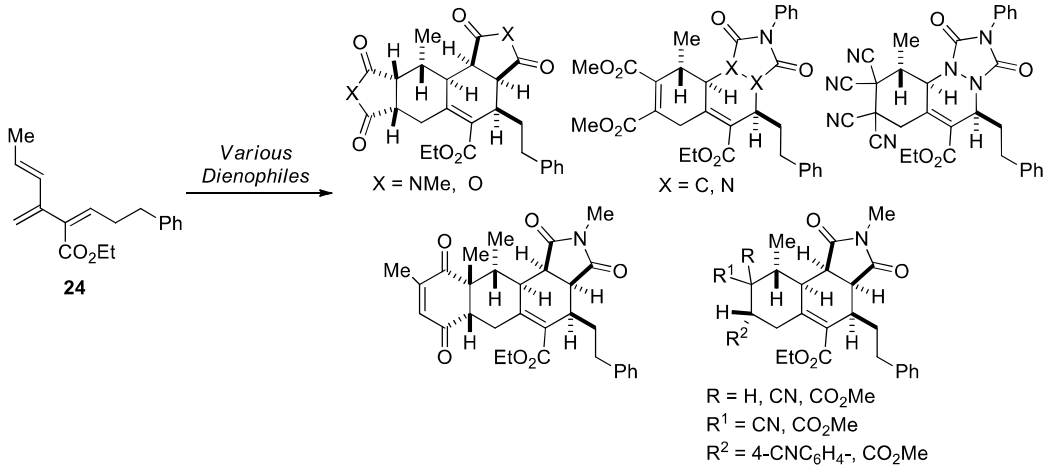
Scheme 5 Synthesis of [3]dendralenes

Subsequent to successful accomplishment of the synthesis of stable [3]dendralenes, they were engaged in the DTDA reactions. These dendralenes **22a-e** were reacted with 2 equiv of N-phenylmaleimide (NPM)/N-methylmaleimide (NMM), which provided the DTDA adducts **23a-e**, with high regio- and stereoselectivity (Scheme 6). X-ray crystallographic analysis divulged that both the consecutive D−A reactions were *endo* selective.[9]



Scheme 6 DTDA reactions of [3]dendralenes

To attain the structural diversity, focus was turned towards the relatively more stable dendralene **24**. The dendralene **24** was treated with various symmetric as well as unsymmetric dienophiles in tandem for quick generation of multicyclic complex scaffolds possessing core structures of isoindole, decalin and cinnoline featuring multiple functional groups and stereogenic centers with step and atom economy (Scheme 7).[9]



Scheme 7 Diversity oriented DTDA reactions with dendralene **24**

Hence, the full potential of [3]dendralenes was harnessed successfully by engaging them in DTDA reactions using two different dienophiles. The D-A reactions were facile, highly regio- and stereoselective and proceeded with *endo* selectivity. The DTDA sequences involved the generation of four new carbon-carbon bonds, two new rings and 3-7 stereogenic centers. A rapid generation of complexity along with functional and structural diversity took place from simple acyclic substrate.

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LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

CHAPTER 2

CHAPTER 3

CHAPTER 4

ABBREVIATIONS

b. p.	Boiling Point
m.p.	Melting Point
g	Gram
mg	Milligram
M	Molar
mmol	millimole
Hz	Hertz
mL	Milliliter
n-BuLi	*n*-Butyllithium
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPC	*N*,*N*-Diisopropylcarbodiimide
DIBAL	Diisobutylaluminum Hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
DCM	Dichloromethane
EtOH	Ethanol
EtOAc	Ethyl Acetate
LDA	Lithium Diisopropylamide

IR	Infrared
HRMS	High Resolution Mass Spectroscopy
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
COSY	Correlation Spectroscopy
ROESY	Rotating Frame Nuclear Overhauser Effect Spectroscopy
ppm	Parts Per Million
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl Chloride
TLC	Thin Layer Chromatography
NMM	*N*-Methylmaleimide
NPM	*N*-Phenylmaleimide
TCNE	Tetracyanoethylene
PTAD	4-Phenyl-1,2,4-triazole-3,5-dione
MA	Maleic Anhydride
DMAD	Dimethyl Acetylenedicarboxylate
DMBQ	2,6-Dimethyl-1,4-benzoquinone

CHAPTER 1

Dendralenes: An Overview and Literature Methods of [3]Dendralene Synthesis

1.1 Introduction

Olefins constitute vital synthons in organic chemistry for carbon–carbon bond formation and for generating complex organic structures as in olefin metathesis, olefin hydroformylation and Heck reaction both in laboratory and industry. These reactions establish the central role of olefins in modern synthetic organic chemistry. Olefins exhibit great structural diversity. Depending upon the type of connectivity of the ethylene units, conjugated polyenes can be catalogued into various classes[1] (**Figure 1.1**). Vicinal linkage gives rise to the linear polyenes **1** and annulenes **2,** whereas geminal linkage results in dendralenes **3**, and their cyclic counterparts the radialenes **4**. In addition to these four principal classes, fulvenes **5** are hybrid molecules that exhibit both vicinal and geminal connectivity whereas cumulenes **6**, comprise directly linked ethylene units wherein two or more C=C bonds share a common carbon atom.

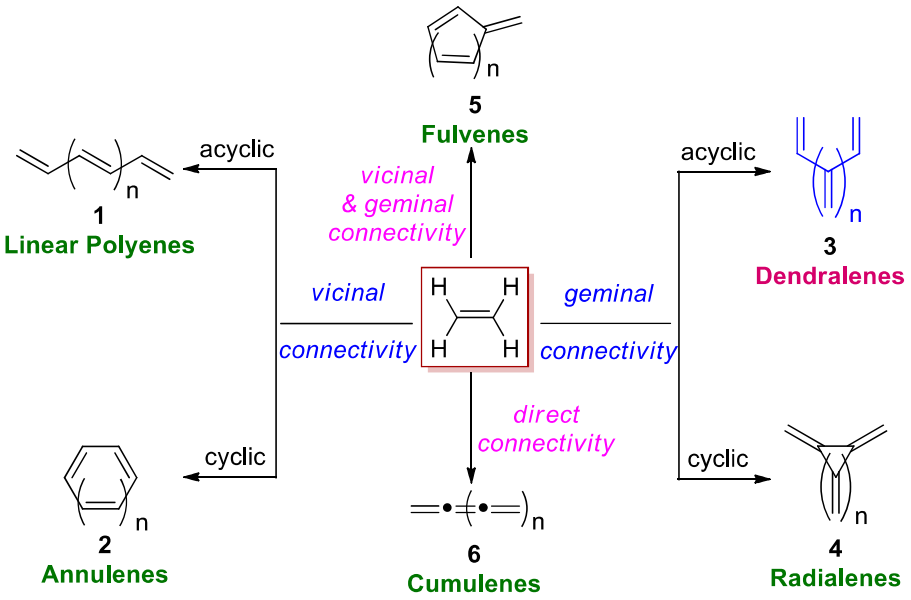


Figure 1.1 Classes of fundamental olefinic hydrocarbons

The linear polyenes **1** and annulenes **2** are common structural motifs in naturally occurring compounds and have been synthesised, studied extensively for industrial, commercial and academic interest. Besides, linear polyenes are found in many bioactive molecules such as beta carotenes, retinal I & II[2] and polyene macrolides.[3] Also, radialenes[4] **4,** fulvenes[5] **5** and cumulenes[6] **6** have been the subject of several reviews. However, the dendralenes[7] **3** have not been investigated comprehensively.

Dendralenes owe their name to Greek word 'dendron' (tree) because of their branched nature. These are a new class of cross-conjugated polyenes with [3]dendralene being the smallest member of the family. The higher analogs could be easily built by replacing the nonterminal hydrogen with a vinyl group. The nomenclature of these dendralenes involves placing the number of olefinic units in a square bracket prior to the word dendralene. Thus, [3]dendralene has three cross-conjugated olefinic units, [4]dendralene has four olefinic units and so on (**Figure 1.2**).

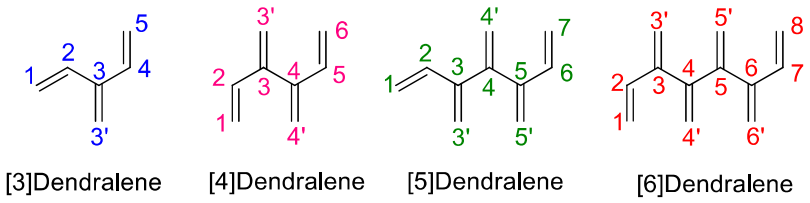


Figure 1.2 Nomenclature of the dendralenes

1.2 Importance of dendralenes

Despite being in existence in nature and the first synthesis reported in 1955, dendralenes remained a dormant class and did not gather the interest of organic chemists, chiefly owing to their unpredictable stability and reactivity. But over the past one and half decade, dendralenes have garnered the attention of researchers from various fields such as polymer chemistry,[8] material chemistry,[9] electrochemistry,[10]

and theoretical chemistry;[11] thus have gained prominence since they display unique properties contrary to the normal oligoenes. Besides, dendralenes are found in many bioactive natural products as their core structures (**Figure 1.3**).[12]

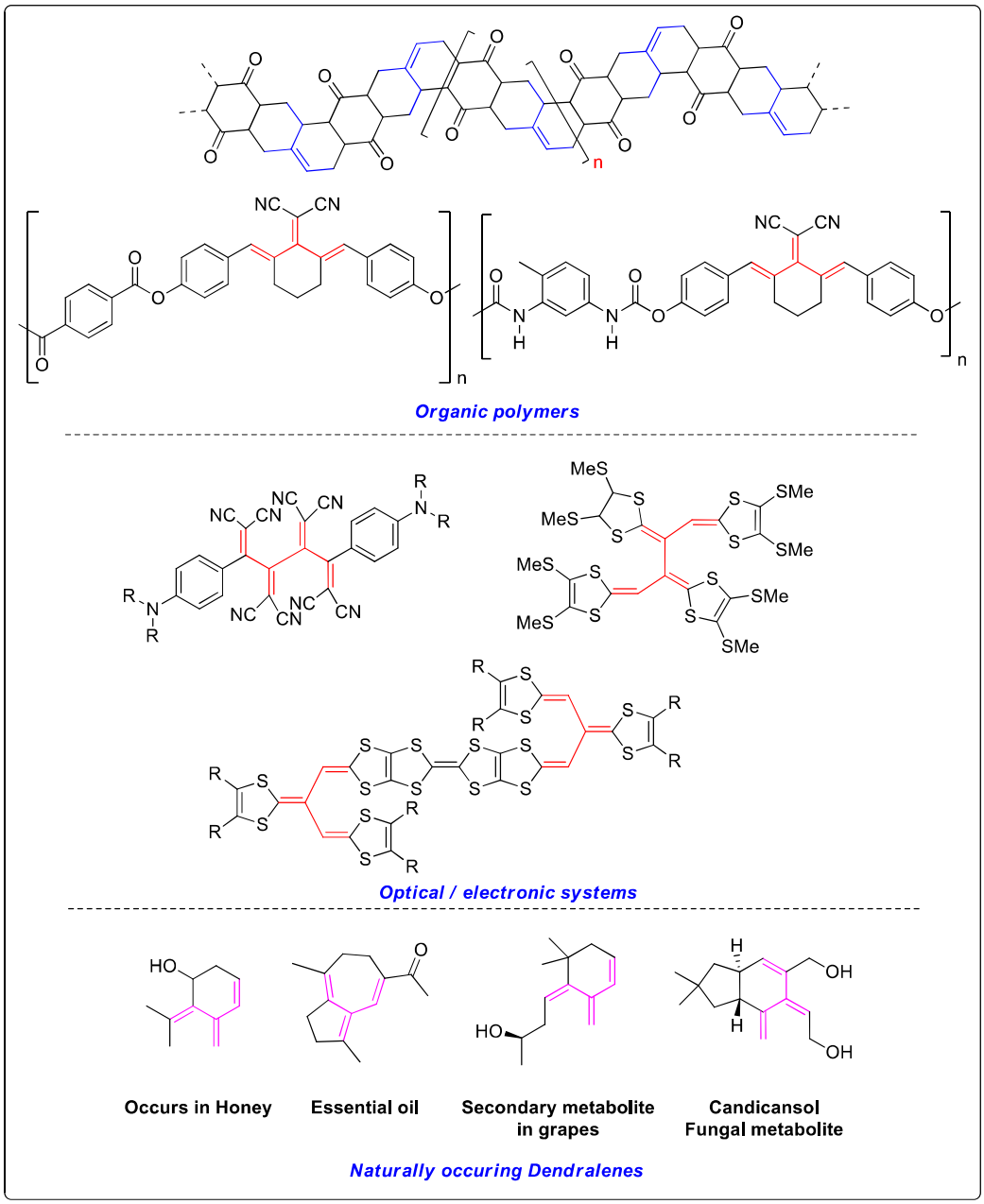
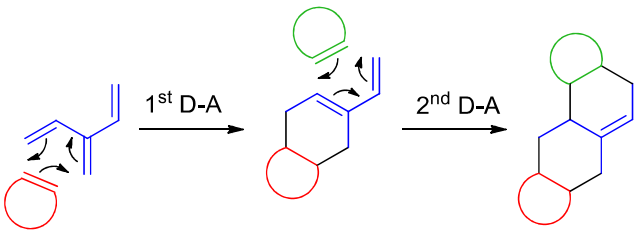


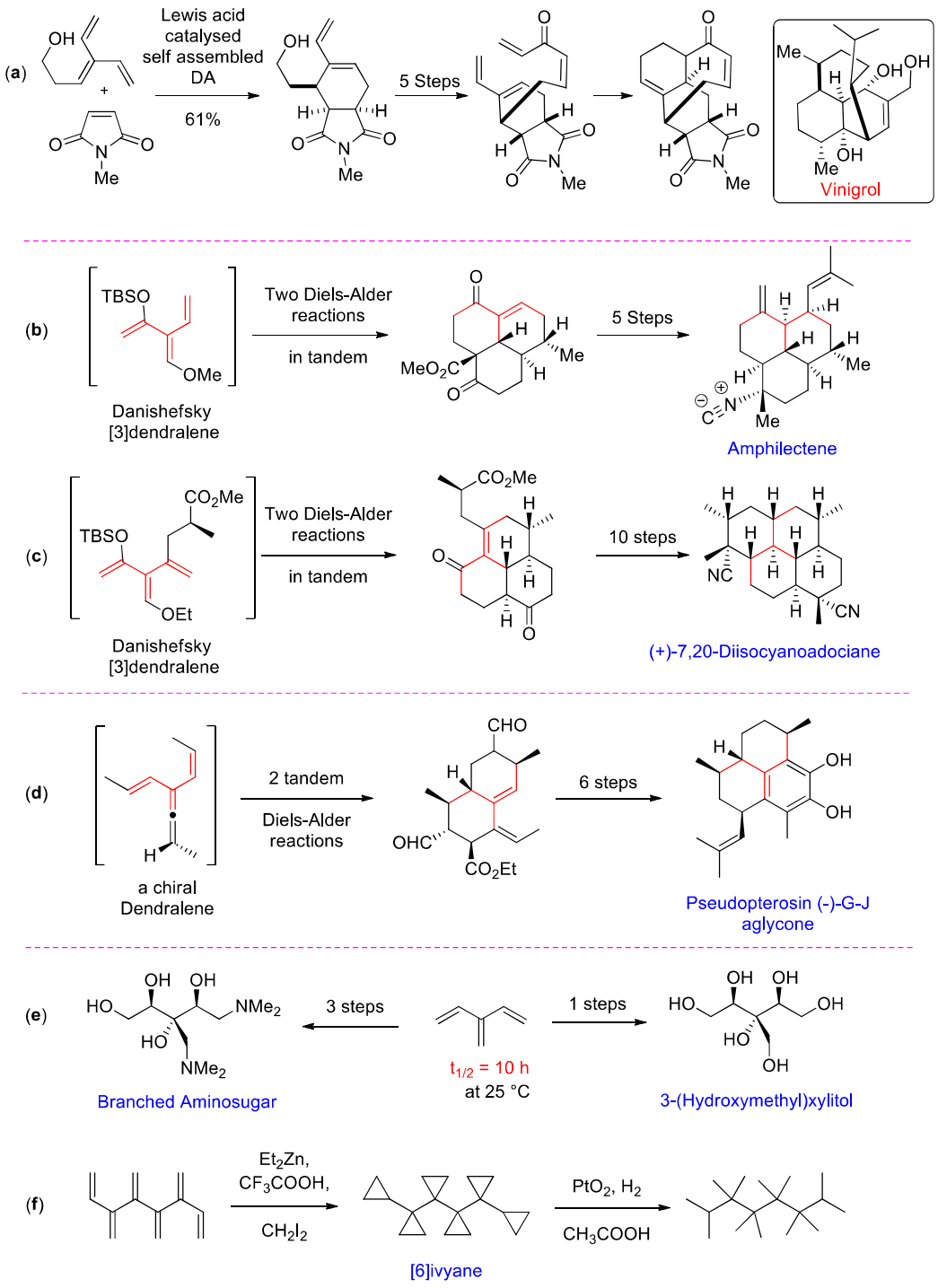
Figure 1.3 Importance of dendralenes in various fields

Fused carbo- and heterocyclic ring systems have intrigued synthetic organic chemists due to preponderance of such motifs in a plethora of bioactive compounds. Also, an efficient synthesis of such architecturally complex scaffolds is a daunting task and hence poses a challenge. In this regard, dendralenes are fascinating molecules because they possess a huge potential for the quick generation of complex multicyclic scaffolds in an atom economical manner by subjecting them to tandem Diels-Alder (D–A) reactions, also known as diene-transmissive D–A (DTDA) sequences.[13] A DTDA sequence involves the addition of a dienophile to [3]dendralene which provides a new semicyclic diene that may participate in a subsequent D–A reaction with a second dienophile (**Scheme 1.1**). Hence, the first addition lodges a new carbon-carbon double bond in conjugation with an existing double bond thus the first cycloaddition "transmits" diene to a new position, hence the name of the overall sequence. This sequence involves formation of four covalent bonds, as many as eight stereocenters and two new rings, in just two bond forming events.



Scheme 1.1 Diene transmissive Diels-Alder reaction

Dendralenes have served the role of important intermediates towards target oreinted formal or total synthesis of several natural products in step and atom economical manner *via* DTDA sequences (**Scheme 1.2**). Fallis and co-workers[14] have targeted the core structure of vinigrol, a trihydroxyditerpene from a monosubstituted



Scheme 1.2 Dendralenes in the target oriented synthesis of important compounds

[3]dendralene where they have employed the strategy of lewis acid catalysed self assembled D-A subsequently followed by another intramolecular D-A reaction (**Scheme 1.2 a**). Recently Shenvi has synthesized Danishefsky [3]dendralenes and used them for the synthesis of amphilectene, 7,20-diisocyanoadociane (a marine metabolite) with potent antimalarial activity (**Scheme 1.2 b,c**).[15,16] Also, Sherburn's group has performed the total synthesis of pseudopterosin (–)-G–J aglycone employing a diene-transmissive triple D-A cycloaddition strategy from 1,1-divinylallene, a chiral dendralene (**Scheme 1.2 d**).[17] They have also achieved the synthesis of branched aminosugars and 3-(hydroxymethyl)xylitol, a natural anti-diabetic from [3]dendralene (**Scheme 1.2 e**).[18] Another interesting application of dendralenes from this group is synthesis of ivyanes[19] (1,1-oligocyclopropanes) the strained hydrocarbon molecules, which have highest experimental heats of combustion thus could serve as additives for hybrid rocket fuels to boost their performance (**Scheme 1.2 f**).[20]

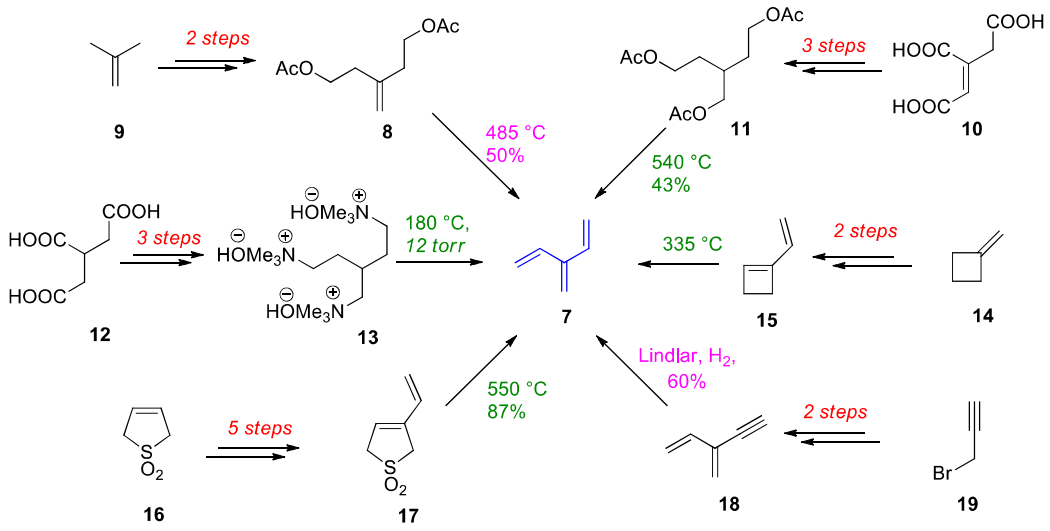
1.3 Synthetic approaches to [3]dendralene systems

Amongst the early synthetic studies on the dendralenes, a considerable number of processes have been described only for the preparation of [3]- and [4]dendralenes. Most of the preliminary preparative methods of dendralenes promulgate the formation of dendralenes but are not the efficient synthetic methods. The synthesis of these parent hydrocarbons was endeavoured by the classical methods of olefin synthesis such as β-elimination, acetate pyrolysis, Hofmann elimination and pericyclic reactions which often required harsh reaction conditions. The synthesis of the parent hydrocarbons by these methods however is of certain merit, but the preparation of

substituted dendralenes *via* these methods has limitation as they may be associated with side reactions under such severe reaction conditions.

In 1955, Blomquist and Verdol reported [3]dendralene **7** for the first time from diacetoxyalkene **8** which was synthesised in two steps from commercially available 2-methyl propene **9** (**Scheme 1.3**).[21] Heating of diacetoxyalkene **8** to 485 °C resulted in elimination of acetic acid to afford [3]dendralene **7** in 50% yield. Later that year, Bailey and Economy also reported [3]dendralene synthesis. Their method involved transformation of aconitic acid **10** to triacetate **11** in three steps and then this triacetate provided [3]dendralene **7** under Flash Vacuum Pyrolysis (FVP) conditions in 43% yield.[22] After 36 years, this strategy was recapitulated and optimised by Koeplinger and co-workers.[23] A three-fold Hoffman elimination of tri-ammonium salt **13** was employed to prepare [3]dendralene **7** again under FVP conditions by Martin and co-workers in 1980, though they didn't reveal the detailed experimental conditions and yield.[24] A little different approach to [3]dendralene was adopted by the Vdovin group. They converted methylenecyclobutane **14** into vinylcyclobutene **15** in two steps, which upon heating at 335 °C provided [3]dendralene **7** through a retro 4π electrocyclisation process.[25] In 1991 Cadogen and co-workers, presented yet another important route to [3]dendralene using 3-sulfolene as a masked butadiene unit which once again resorted to FVP conditions. 3-Sulfolene **16** was transformed to vinyl sulfolene **17** which is a stable, crystalline solid at room temperature in five steps. Heating of vinyl sulfolene **17** to 550 °C resulted in cheletropic elimination of SO_2 gas and provided [3]dendralene in 87% yield.[26] In another approach, Hopf and co-workers synthesised dienyne **18** from propargyl bromide **19** in two steps *via* a copper catalysed

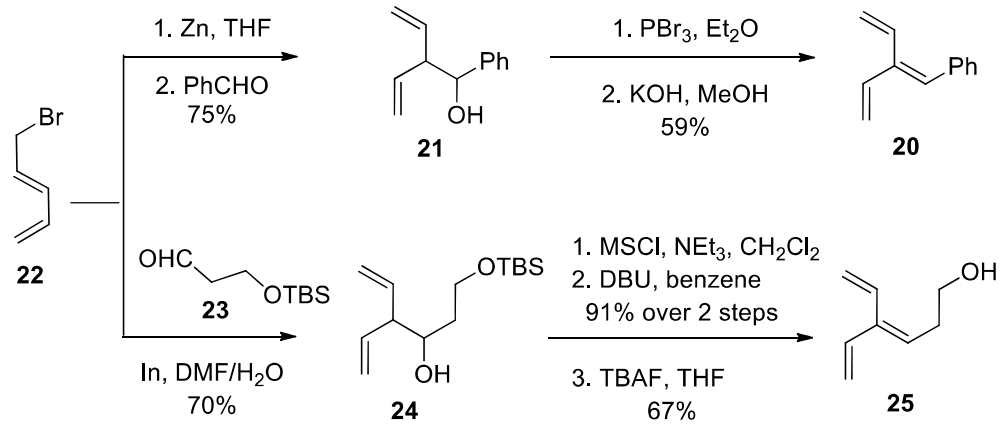
dimerisation/rearrangement sequence. Partial hydrogenation of this dienyne **18** using Lindlar's catalyst provided [3]dendralene in 60% yield.[27]



Scheme 1.3 Earlier synthetic approaches to [3]dendralene

In 1964, the Miginiacs reported the synthesis of 3'-phenyl[3]dendralene **20**.[28] They prepared alcohol **21** from the treatment of benzaldehyde with organozinc compound derived from 5-bromopenta-1,3-diene **22** (**Scheme 1.4**). Then, the resulting alcohol **21** was converted to bromide which upon base induced elimination of HBr afforded 3'-phenyl[3]dendralene **20** in 59% yield. Later, this approach was further improved by Fallis and co-workers (**Scheme 1.4**).[29,30] The 5-bromopenta-1,3-diene **22** reacted with indium for *in situ* generation of pentadienylindium, which was then treated with an aliphatic aldehyde **23** to provide the alcohol **24**. The alcohol **24** was dehydrated either through base-induced *β*-elimination of the corresponding mesylate[29] or under Mitsunobu conditions[30] to furnish 3'-substituted [3]dendralene **25** in good yield. The advantage of this methodology lies in the fact it allows a high degree of variability of aldehyde component thus holds a potential for the synthesis of various

3'-substituted [3]dendralenes. This Miginiac–Fallis method has been employed by other research groups to generate libraries of 3'-substituted [3]dendralenes.[31-33]



Scheme 1.4 Mono substituted [3]dendralenes from Pentadienyl nucleophiles

In 2000, Sherburn group has introduced direct cross-coupling reactions to synthesise [n]dendralenes.[34] Their group has capitalized on the potential of 3-sulfolene which is a masked 1,3-butadiene and was first reported by Cadogan group. They synthesized vinyl sulfolene **26** *via* Stille coupling of 3-iodosulfolene **27** and tributylvinylstannane **28**, which upon pyrolysis underwent cheletropic elimination of SO_2 at 450 °C and provided [3]dendralene **7** in 89% yield **(Scheme 1.5 a)**.[34] They have extended this strategy for the synthesis of [4]-, [5]-, [6]- and [8]dendralenes.

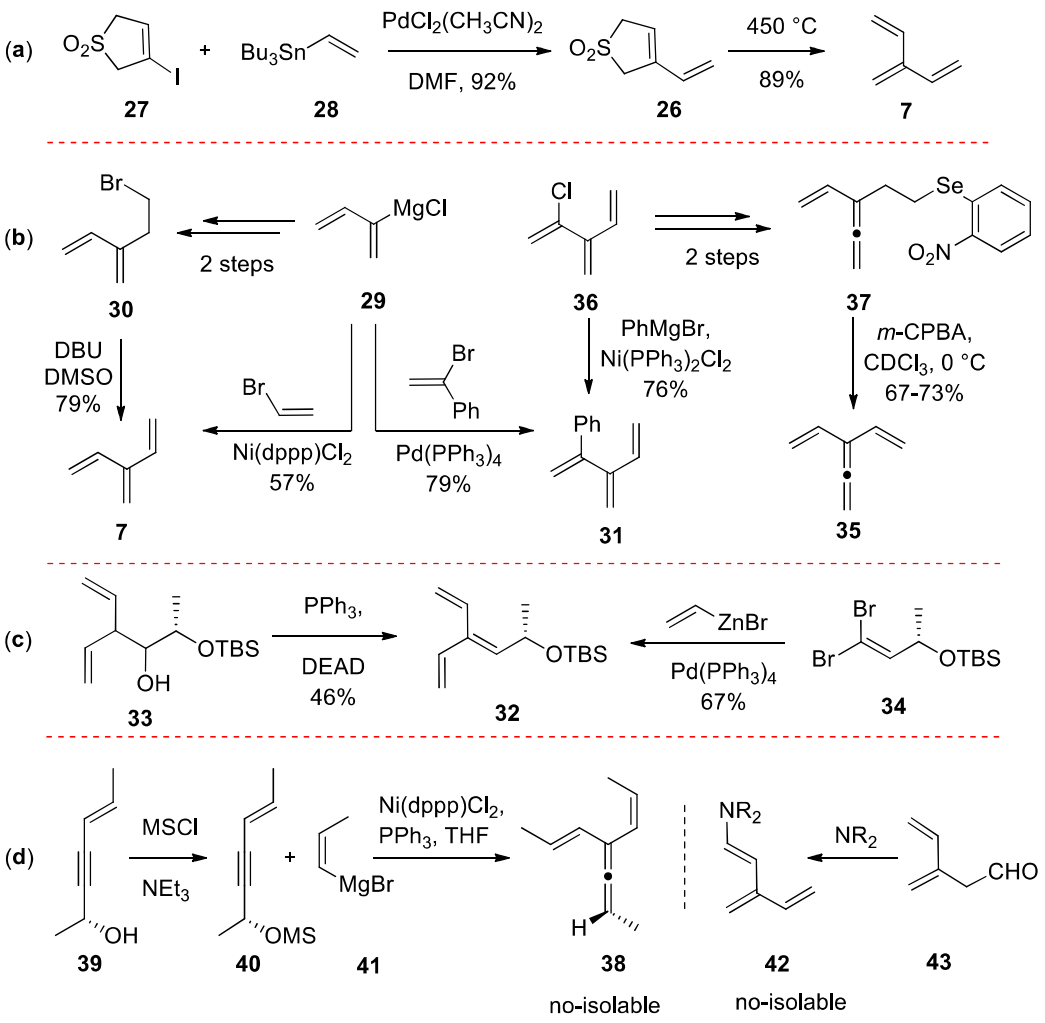
Although this strategy is very good but the drawback associated with it is that it requires a special apparatus to carry out flash vacuum pyrolysis and is not very safe as it sometimes implodes. To overcome the shortcomings of this method Sherburn group adopted another strategy which relies on Kumada and Negishi couplings which involve chloroprene Grignard reagent **29** a readily available starting material (**Scheme 1.5 b**). [3]Dendralene **7** could be readily obtained by the coupling of the chloroprene Grignard reagent **29** with vinyl bromide under nickel (0)-catalyzed conditions in

single step.[35] This strategy was extended for the synthesis of higher order [4]-[12]dendralenes.[35,36]

Although [3]dendralene could be easily synthesised but its isolation in concentrated form was a problem owing to its similar boiling point as that of THF which was used as a solvent. Thus, to override this problem Grignard reagent of chloroprene **29** was transformed to bromide **30** which on treatment with DBU eliminated HBr and yielded [3]dendralene **7** which could be isolated as a neat liquid in 79% yield.[37] Employing Kumada coupling they have also reported 2-substituted [3]dendralene **31** by varying the substitution pattern on the cross-coupling partners (**Scheme 1.5 b**).[38]

Besides, they synthesized a chiral 3'-substituted [3]dendralene **32** following two strategies. In the first one they carried out Mitsunobu dehydration of alcohol **33** a approach was originally adopted by Fallis and the second one a two-fold Negishi coupling of bromide **34** with vinyl zinc bromide (**Scheme 1.5 c**).[33]

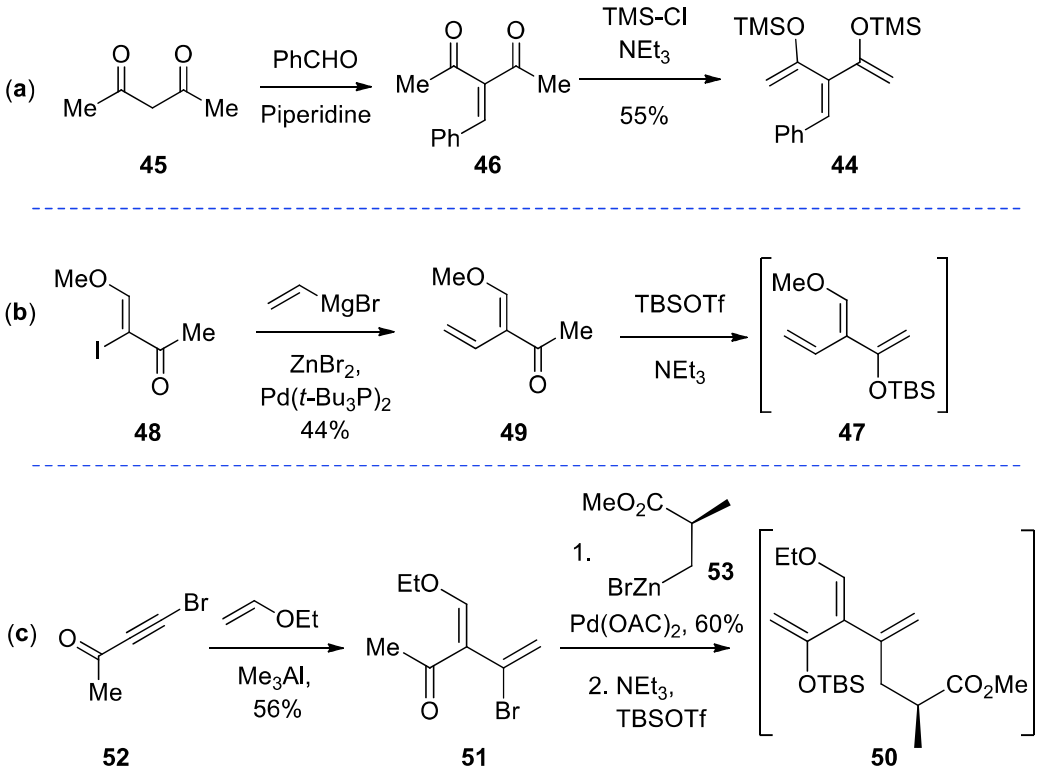
A new type of dendralene 1,1-divinylallene **35** was also reported by the same group for the first time, which was synthesised from 2-chloro[3]dendralene **36** in 3 steps via Greico-Sharpless elimination (**Scheme 1.5 b**).[39] Recently, chiral version of this new dendralene i.e. 1,1-divinylallene **38** was prepared from a chiral propargyl alcohol **39** *via* its mesylate derivative **40** which participated in Kumada cross-coupling with Grignard reagent **41** under Ni(0) catalyzed conditions (**Scheme 1.5 d**).[17] This dendralene **38** as mentioned earlier was utilised for the total synthesis of a pseudopterosin aglycone. Very recently their group has also synthesized amino dendralene **42** from condensation of dienal **43** and amine (1° or 2°).[40]



Scheme 1.5 Synthetic approaches to [3]dendralenes by Sherburn and co-workers

Most of these aforesaid methods yield unsubstituted or scantly substituted dendralenes. Only handful procedures are reported in the literature regarding the synthesis of dendralenes with multiple substituents. The first trisubstituted [3]dendralene **44** was reported by Tsuge and coworkers in 1983. The Knoevenagel condensation of 1,3-diketone **45** with benzaldehyde gave benzylidene derivative **46**. The diketo functionality of this benzylidene was transformed to enol silyl ethers to generate trisubstituted [3]dendralene **44** (**Scheme 1.6 a**).[13]

Later, Pronin and Shenvi in 2012 synthesized a "Danishefsky dendralene" **47** through a Negishi cross-coupling of vinyl megnasium bromide with a functionalized alkenyl iodide **48** followed by enol silyl ether formation of the ketone **49** (**Scheme 1.6 b**).[15] This dendralene after a series of transformations led to the total synthesis of a potent antimalarial amphilectene.

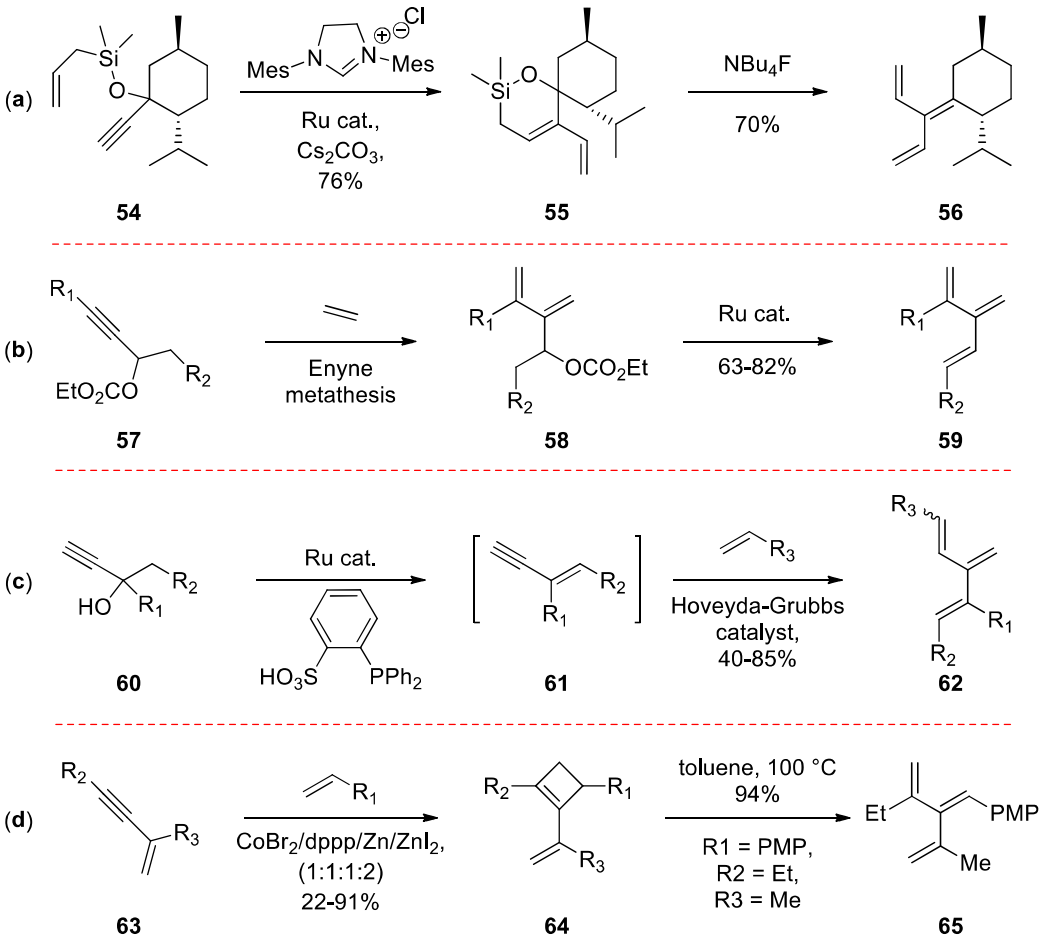


Scheme 1.6 Synthesis of [3]dendralenes *via* enolization as silyl ethers of ketones

In 2016, once again they followed the same approach to synthesise chiral tri substituted [3]dendralene **50**.[16] Diene **51** was obtained by coupling of the 4-bromo-2-butynone **52** with ethyl vinyl ether catalyzed by trimethylaluminum which involved cycloaddition and retroelectrocyclization. This diene **51** was coupled to zinc bromide **53** using catalytic palladium(II) acetate, and subsequently transformed to enol silyl ether to obtain chiral [3]dendralene **50** (**Scheme 1.6 c**).[16] This dendralene was then

employed for the total synthesis of (+)-7,20-diisocyanoadociane a marine metabolite with potent antimalarial activity.

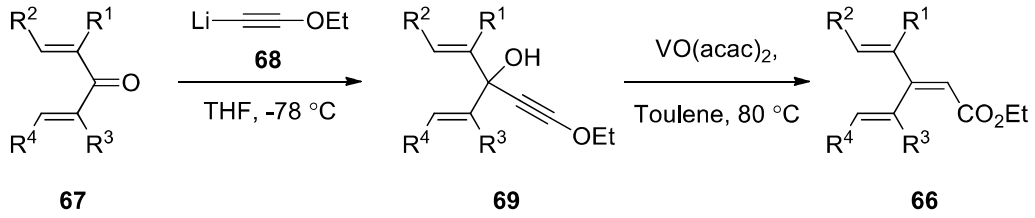
Yet another approach adopted by the researchers for the synthesis of dendralenes is enyne metathesis (**Scheme 1.7**).[41-45] Burneau and co-workers have synthesiszed dendralenes **56** and **59** following above strategy wherein the intermediate diene was subjected to elimination to obtain the desired dendralene.[41,42] In a converse approach they performed the elimination step first which was followed by enyne metathesis and thus yielded the dendralene **62**.[43]



Scheme 1.7 [3]Dendralenes *via* enyne metathesis

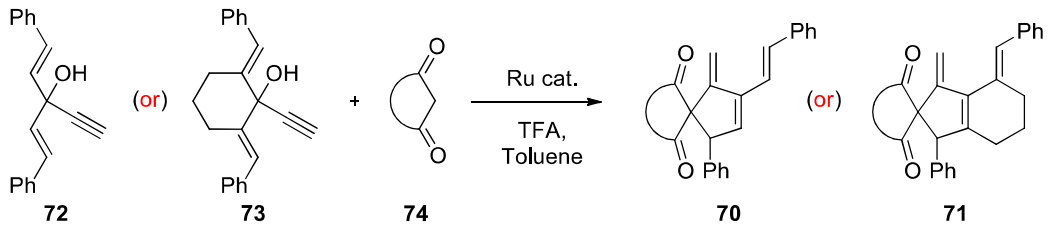
Along similar lines, Chang and co-workers reported an intramolecular ring-closing enyne metathesis to synthesise cyclic [3]dendralenes.[44] In another novel approach Ogoshi et al. synthesized cyclobutenes **64** *via* cobalt-catalyzed enyne metathesis. One of the cyclobutene was transformed to a trisubstituted [3]dendralene **65** by thermal electrocyclic ring-opening.[45] This methodology affords a modern, step-efficient manifestation of older methods that provided dendralenes from alkenyl cyclobutenes and involved lengthy sequences.

West and co-workers prepared penta substituted [3]dendralenes **66**.[46] They coupled α,α'-divinyl ketones **67** with lithium acetylide **68** to provide the propargyl alcohols **69** which were subsequently subjected to Meyer-Schuster rearrangement catalysed by [$VO(acac)_2$] to obtain the desired [3]dendralenes **66** (**Scheme 1.8**).



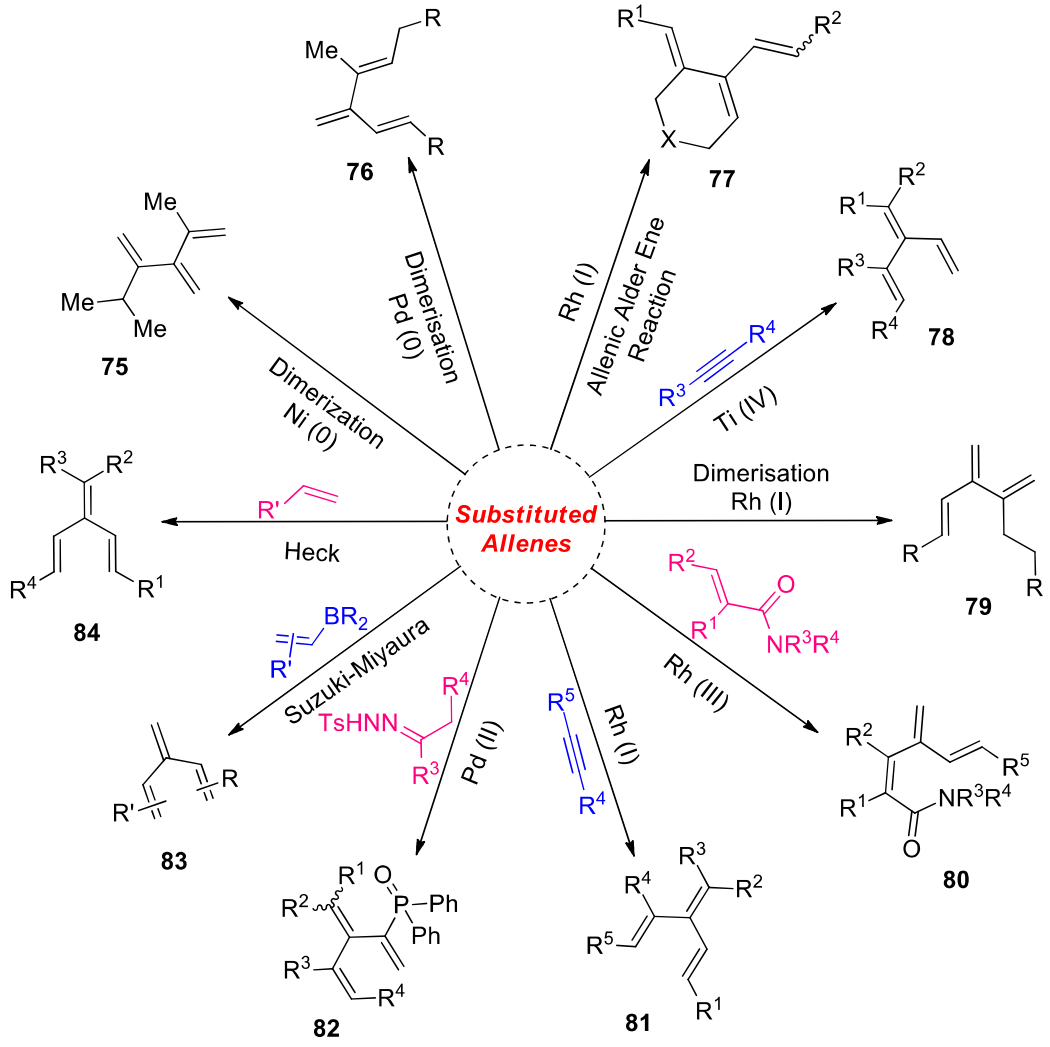
Scheme 1.8 [3]Dendralenes from dienones through Meyer-Schuster rearrangement

In yet another report Haak and coworkers performed synthesis of monocyclic and bicyclic [3]dendralenes **70**,**71** under ruthenium-catalyzed conditions from propargyl alcohols **72** and **73** on reaction with cyclic 1,3-diketone **74** (**Scheme 1.9**).[47]



Scheme 1.9 Ru(0)-catalyzed synthesis of cyclic [3]dendralenes

Allenes bearing various substituents have caught the attention of many researchers wherein they have been used as substrates under various metal catalysis conditions (Ni, Pd, Rh and Ti) to afford substituted [3]dendralenes (**Scheme 1.10**).[48-57] Some researchers synthesised [3]dendralene by dimerization of allenes under various metal catalysed conditions. In 1972, Englert and co-workers reported 2,4-di substituted [3]dendralene **75** *via* dimerization of allene under Ni(0) catalysed conditions.[48]



Scheme 1.10 Synthetic routes to substituted [3]dendralenes from substituted allenes

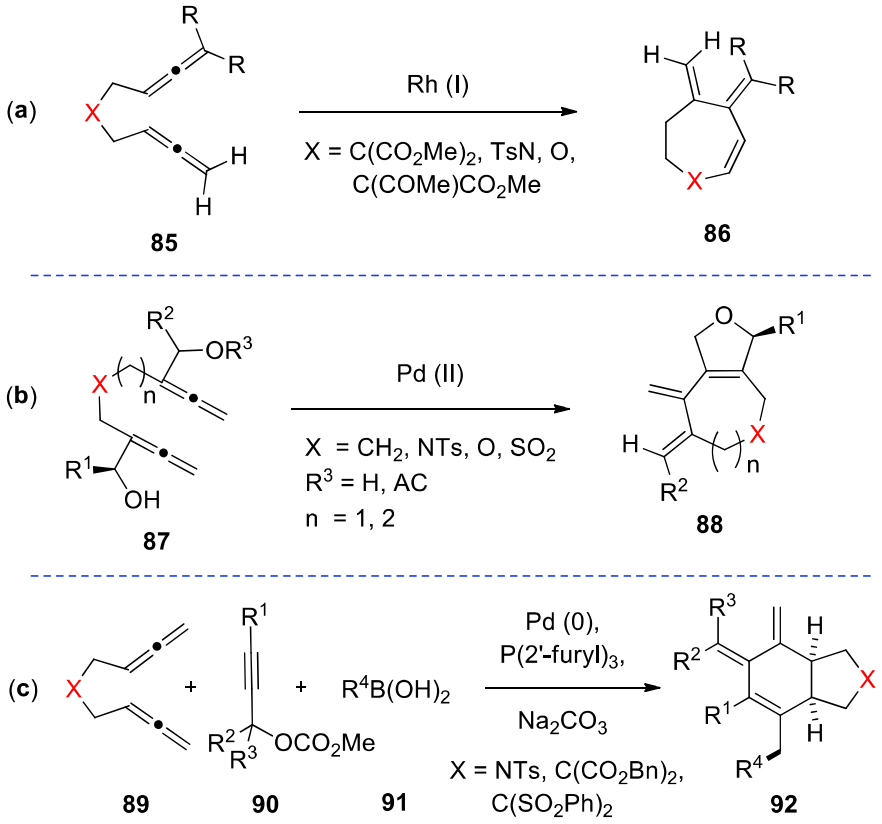
Later, Pasto and co-workers in 1985 while performing mechanistic study of the reactions of 1,1-dimethylallene with nickel(0) complexes once again synthesized few more dendralenes.[49] Subsequently in 1998, Yamaguchi and co-workers, synthesized tri substituted [3]dendralenes **76** *via* a palladium(0) mediated dimerization of substituted allenes.[50] On the other hand when Murakami and co-workers performed dimerization of same substituted allenes as used by Yamaguchi group by employing rhodium(I) catalysis, they obtained isomeric 1,4-di substituted [3]dendralenes **79**.[51]

In another approach, Brummond and coworkers reported a rhodium(I) catalyzed Alder Ene reaction for the synthesis of several carbo- and heterocyclic [3]dendralenes **77** featuring a variety of functional groups (**Scheme 1.10**).[52] In 2008 Micalizio and co-workers reported a titanium (IV) mediated cross-coupling of allenic alcohols with alkynes which resulted in the formation of trisubstituted [3]dendralenes **78**.[53] Of late C–H activation has gained popularity for the synthesis of dendralenes. In 2013, Glorius and coworkers followed Rhodium (III) catalyzed C–H activation strategy for the synthesis of a variety of diverse substituted [3]dendralenes **80** from allenyl carbinol carbonates and acrylamides.[54] In 2016, Tanaka and co-workers reported rhodium (I) catalysed dimerization of di- or tri substituted allenes with alkynes to afford substituted [3]dendralenes **81** through β-hydrogen elimination from the corresponding rhodacycles.[55] In the same year, Wu and co-workers synthesized phosphinyl [3]dendralenes **82** by coupling of allenylphosphine oxides with *N*-tosylhydrazones under palladium(II) catalysis conditions.[56]

Very recently (2017), Lipshutz and co-workers have reported a mild method for synthesis of highly functionalized [3]-[6]dendralenes through palladium catalysed coupling of substituted allenoates bearing various substitution patterns with a wide

range of boron and alkenyl nucleophiles under micellar conditions (**Scheme 1.10**).[57] Suzuki-Miyaura coupling led to formation of a range of fuctionalised [3]dendralenes **83** from the coupling of allenicbenzoates with alkenylboronates. Similarly, Heck coupling provided highly functionalised [3] dendralenes **84** from the reaction of π-allenyl systems with various activated olefins such as acrylates, acrylamides, styrenes, and other alkenes.

Ma and co-workers have reported synthesis of cyclic [3]dendralenes from cycloisomerization of bisallenes under both palladium(II) and rhodium(I) catalysed conditions (**Scheme 1.11**).[58-60] A rhodium(I) catalysed isomerisation of 1,5-diallenes **85** provided seven-membered cyclic [3]dendralenes **86**.[58]



Scheme 1.11 Synthesis of cyclic [3]dendralenes from bisallenes by Ma group

They have also performed the synthesis of 2,5-dihydrofuran-fused bicyclic dendralenes **88** from tandem double-cyclization reaction of 1,ω-bisallenols **87** under palladium(II)-catalysed conditions.[59] Subsequently, they carried out a palladium(0) catalysed three-component reaction of bisallenes **89**, propargylic carbonates **90** and boronic acids **91** to afford bicyclic [3]dendralenes **92**.[60]

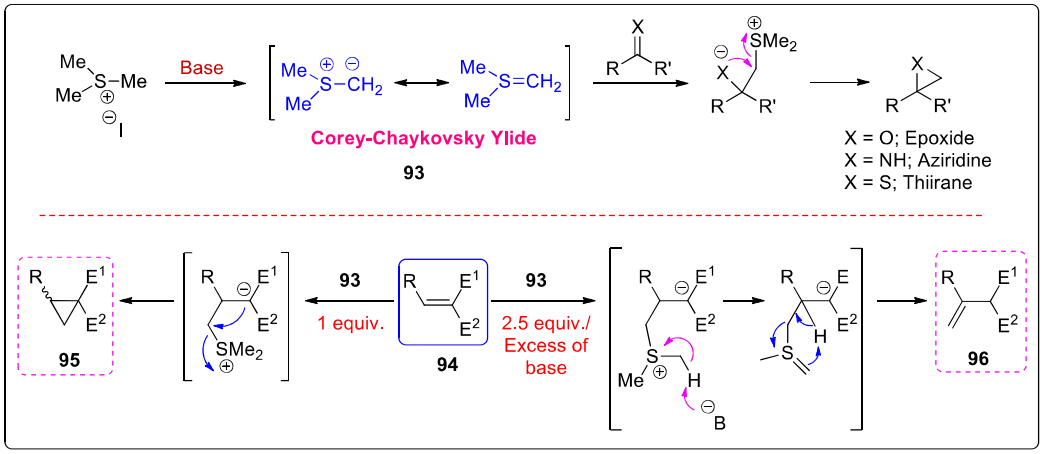
Thus, it is evident that over the years there is a gradual shift from lengthy and scope-limited isomerization and elimination-based strategies for the preparation of dendralenes, towards metal catalyzed direct formation of functionalized dendralene frameworks *via* carbon–carbon bond-forming reactions. Although several approaches for the synthesis of dendralenes have emerged but the aspect of stability/reactivity of the dendralenes is still elusive. The forthcoming chapters deal with our approach towards the synthesis of [3]dendralenes, hurdles encountered during their preparation, factors governing their stability/reactivity and finally their deployment in diversity oriented DTDA for the synthesis of architecturally intriguing polycyclic compounds with multiple functionalities.

CHAPTER 2

Synthesis of Functionalized [3]Dendralenes: The Initial Attempts

2.1 Introduction

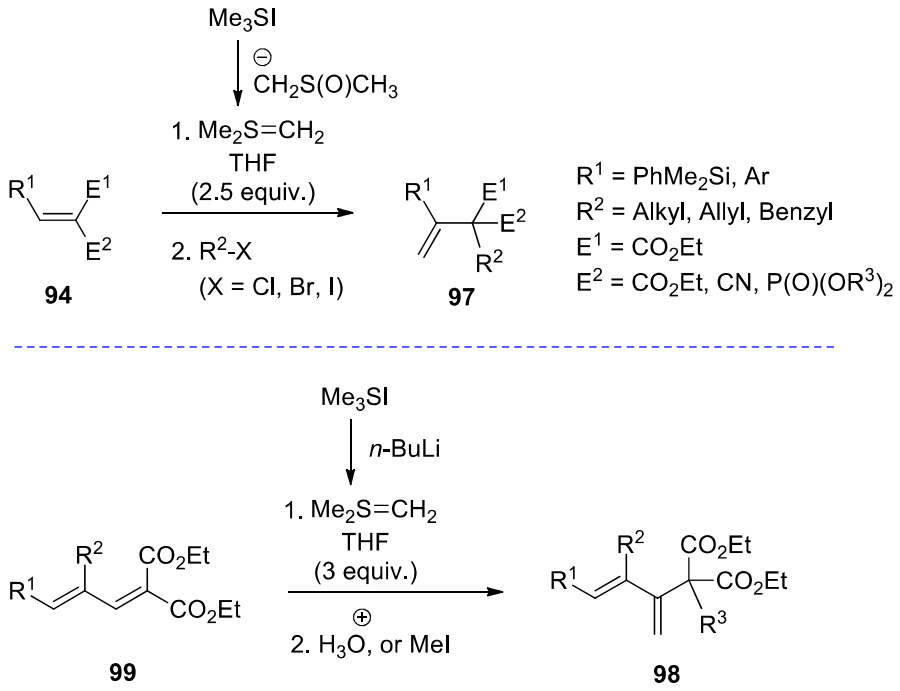
Over the years, the Corey–Chaykovsky reagent, dimethylsulfonium methylide (DMSM) **93**, is well-known to provide epoxide, aziridine and thiirane derivatives by an overall methylene insertion upon reaction with aldehydes/ketones, imines and thiocarbonyls respectively (**Scheme 2.1 top**).[61] Similarly, Michael acceptors **94** furnish cyclopropane derivatives **95** upon reaction with this ylide.[61] In 2003, a serendipitous olefination was recognized by our group along with cyclopropanation while performing reactions on various activated olefins with DMSM **93**.[62] It was found that, these activated olefins underwent a tandem ylide addition–eliminative olefination instead of the standard cyclopropanation in the presence of excess DMSM or a base. Later reaction conditions were optimized such that exclusively this olefinated product **96** was obtained (**Scheme 2.1 bottom**).



Scheme 2.1 Reactions of dimethylsulfonium methylide

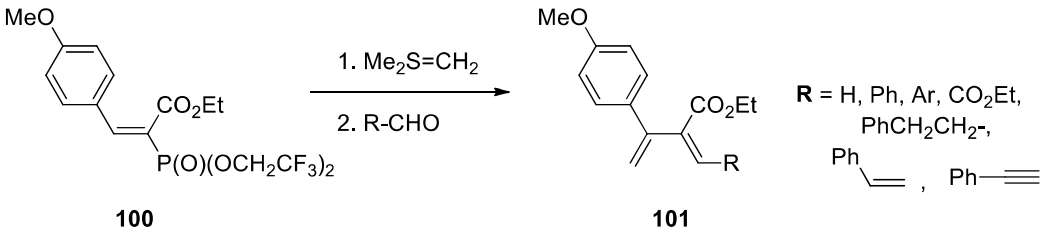
By using this olefination methodology, readily available activated olefins **94** were converted to synthetically valuable and scarce 1-substituted vinyl silanes and substituted styrene derivatives **97** (**Scheme 2.2 top**).[62,63] Later, the method of

generation of ylide **93** was improvised wherein *n*-butyllithium was employed instead of sodium dimsylate for the deprotonation from trimethylsulfonium iodide. Subsequently, this olefination methodology was employed for the synthesis of 1,3-butadien-2-ylmalonates **98** from 1,3-dienedioates **99** which feature extended conjugation. This reaction was highly regioselective wherein exclusively 1,4-addition took place (**Scheme 2.2 bottom**).[64]



Scheme 2.2 Olefination with dimethylsulfonium methylide

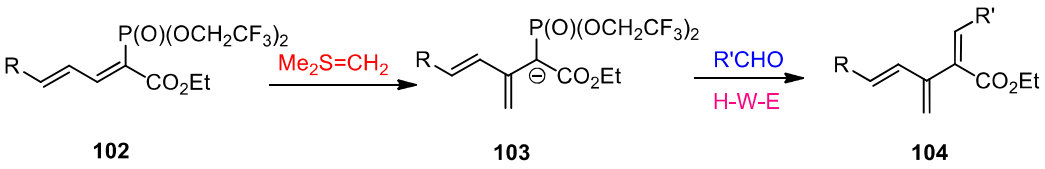
When this olefination methodology was extended to 2-arylmethylidene-2-phosphonoacetates **100,** subsequent to olefination when the reaction mixture was quenched with various aldehydes, Horner–Wadsworth–Emmons (H-W-E) olefination took place to furnish 1,2,3-trisubstituted dienes **101** with high stereoselectivity (**Scheme 2.3**).[65]



100 **101**

Scheme 2.3 Synthesis of tri-substituted dienes

On the basis of above results, the synthesis of [3]dendralenes was envisioned from a dienyl phosphonate **102** as illustrated in the **Scheme 2.4**. It was anticipated that subsequent to addition of dimethylsulfonium methylide **93**, the intermediate anion **103** upon reaction with an aldehyde would undergo H-W-E reaction to provide [3]dendralene **104**.

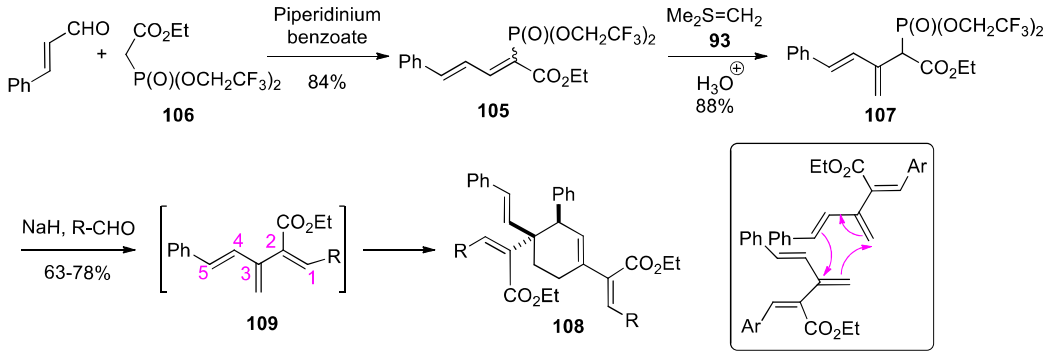


102 **103** **104**

Scheme 2.4 Proposed synthesis of [3]dendralenes

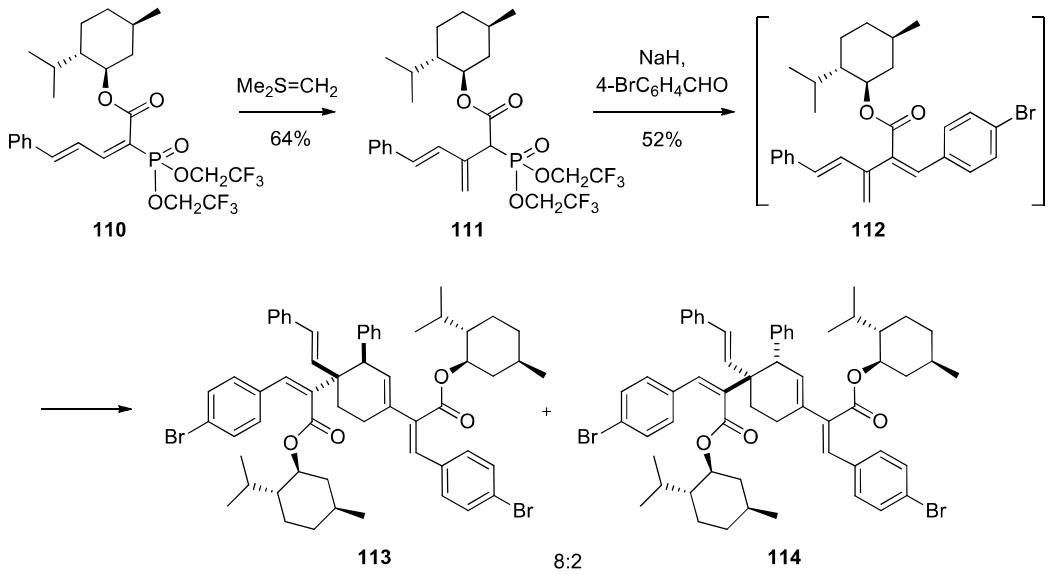
For this objective, 2-phenylethenylidene phosphonoacetate **105** was synthesized by Knoevenagel condensation of cinnamaldehyde with ethyl bis-(2,2,2-trifluroethyl) phosphonoacetate **106** (**Scheme 2.5**).[66] This phosphonoacetate **105** on treatment with 3 equiv of ylide **93** afforded the dienyl phosphonoacetate **107**, which on deprotonation with sodium hydride and reaction with various aromatic aldehydes surprisingly yielded dimerized [3]dendralene adducts **108** exclusively instead of the anticipated [3]dendralenes **109**. X-Ray crystal structure of one of these adducts **108** revealed that it was Diels–Alder (D–A) homodimerized product of the expected [3]dendralene **109**. Here one molecule of the dendralene acted as a diene and another

as a dienophile. Interestingly, the double bond at third position exclusively participated as the dienophile although it did not seemed as the most electronically deactivated one, and the diene encompassing double bonds at third and fourth positions acted as diene component.



Scheme 2.5 Synthesis of [3]dendralenes and their D–A self cyclodimerization

With the anticipation that an increase in steric bulk on the [3]dendralene would impede the homodimerization, the ethyl ester was replaced with a sterically demanding menthyl ester. Unfortunately the sequential double olefination of **110** with ylide **93** followed by H-W-E reaction with 4-bromobenzaldehyde once again did not provide the expected [3]dendralene **112**, instead two diastereoisomeric D–A homodimerization products **113** and **114** were obtained in a ratio of 8:2 in 52% yield (**Scheme 2.6**).[67]

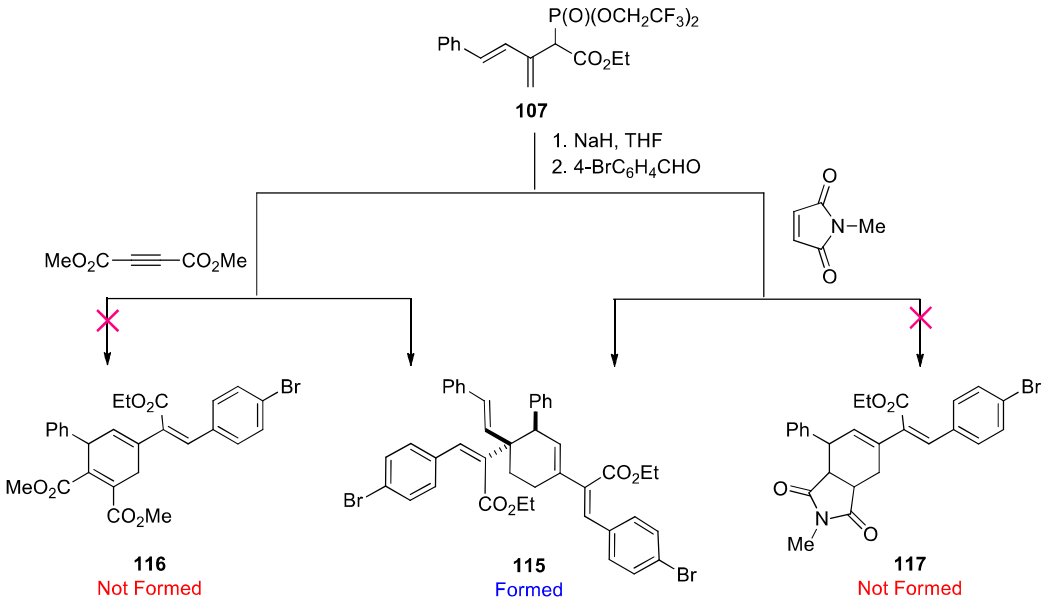


Scheme 2.6 Synthesis of a chiral [3]dendralene and its D–A cyclodimerization

2.2 Present work

Since the [3]dendralenes could not be isolated, it was decided to trap them in the reaction pot itself with the aid of an external dienophile or a diene. The diene constituted by the double bonds at third and fourth positions of the dendralenes **109** selectively participated in D–A homodimerization. It was therefore anticipated that in a similar fashion it would participate in D–A reaction with external dienophiles. For this purpose, dimethyl acetylenedicarboxylate (DMAD) was chosen as a dienophile. Subsequent to deprotonation of dienyl phosphonoacetate **107** by sodium hydride and H-W-E reaction with 4-bromobenzaldehyde, a solution of DMAD was added to the reaction pot at 0 °C after 30 min (**Scheme 2.7**). After 24 h stirring at room temperature, the usual self dimerized adduct **115** was only obtained with no trace of the desired cross D-A adduct **116** with DMAD. It was suspected that perhaps DMAD was unable to interrupt the self dimerization of the dendralene due to its relatively poor reactivity as a dienophile. Hence, the use of a more reactive dienophile like *N*-methylmaleimde

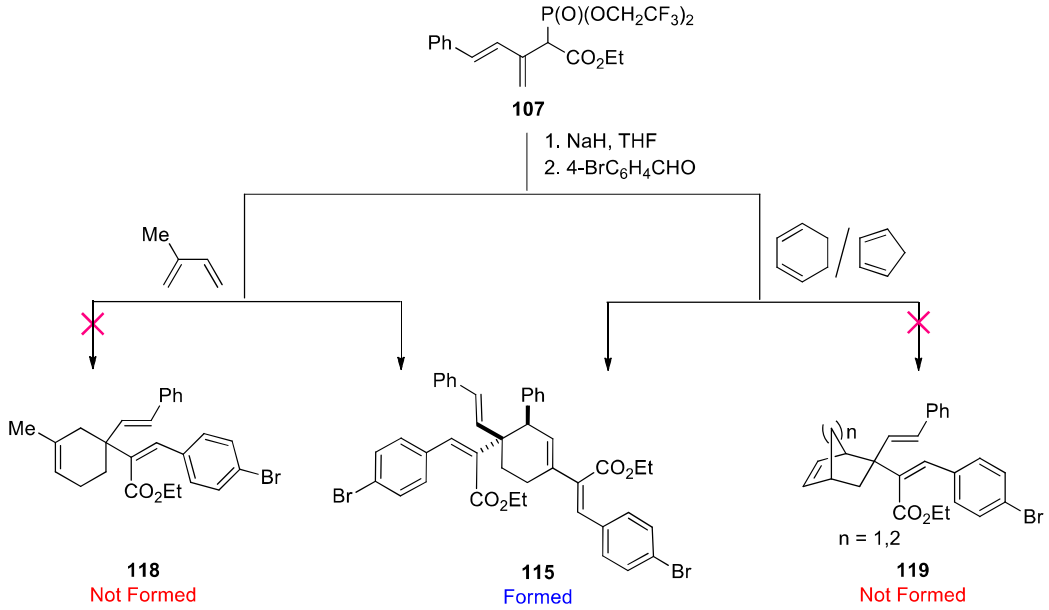
(NMM) was intended. Addition of excess NMM to reaction mixture at 0 °C after 30 min and overnight stirring at room temperature was of no avail, as once again the desired D–A adduct **117** was not obtained, merely self-dimerized adduct **115** was formed. Dimerization of the dendralene could not be circumvented by the addition of external dienophiles such as DMAD and NMM.



Scheme 2.7 Attempts to trap the [3]dendralene with dienophiles

Since the above experiments did not provide any fruitful result, attention was turned towards the reactive dienes such as isoprene, cyclohexadiene and cyclopentadiene. Here, it was anticipated that double bond at the third position of the dendralenes **109** which possesses a high dienophilic property as witnessed in the self dimerisation would readily react with above said dienes. Addition of isoprene along with 4-bromobenzaldehyde at 0 °C to the reaction pot containing the deprotonated **107** and further stirring for 17 h at room temperature once again was of no help. Replacement of isoprene with either cyclohexadiene or highly reactive

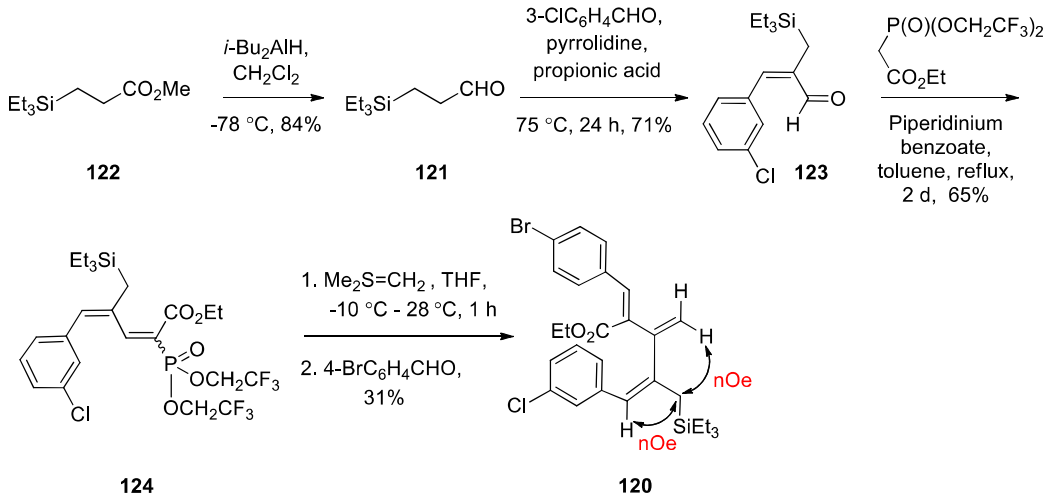
cyclopentadiene also did not succeed in trapping the dendralene to afford the desired D-A adducts **119**.



Scheme 2.8 Attempts to trap the [3]dendralene with dienes

The D-A cyclodimerization of [3]dendralene could not be averted either by using the reactive dienophiles or dienes. On careful inspection of D–A cyclodimerized products, it was found that during dimerization amongst the two diene's of dendralenes **109**, **112** the one which participated in D–A was not only electron rich but also had no substituent at fourth position hence no steric congestion, whereas the other one was deactivated as well as had a substituent at the second position. Hence, in order to curb the dimerization it was decided to introduce a bulky substituent at fourth position of dendralenes **109**. For this purpose, triethylsilyl group was chosen which would grant stable substituted [3]dendralene with an allylsilane as integral component of the dendralene system. The choice of triethylsilyl group was made because of its steric bulk as well as its ability to direct further reactions on the dendralene.

The synthesis of [3]dendralene **120** is depicted in **Scheme 2.9**.[68] The β-silyl propionaldehyde **121** wa**s** prepared in 84% yield by DIBAL-H reduction of silyl propionate **122** in dichloromethane at -78 °C. A selective aldol reaction of this aldehyde **121** with 3-chlorobenzaldehyde at 75 °C in presence of catalytic amount of pyrolidine and propanoic acid,[69] followed by dehydration furnished 2-silylmethyl substituted acrolein **123** in 71% yield. The ethenylidene phosphonoacetate **124** was obtained in 65% yield from the Knoevenagel condensation of unsaturated aldehyde **123** with ethyl bis-(2,2,2-trifluroethyl)phosphonoacetate in the presence of piperidinium benzoate in refluxing toluene, as an inseparable 1/1 mixture of two geometrical isomers of the double bond attached to phosphonate group as judged from ^{1}H NMR. When this phosphonate **124** was treated with dimethylsulfonium methylide generated *in situ* from Me_3SI and *n*-BuLi in THF, the desired olefination took place to provide the appropriately substituted butadien-2-ylphosphonoacetate which was reacted *in situ* with 4-bromobenzaldehyde under a H-W-E reaction conditions to give the desired tetrasubstituted [3]dendralene **120** in 31% yield. It was gratifying to note that the dendralene **120** was stable towards D-A cyclodimerization at ambient temperature. ^{1}H/^{1}H NOESY studies threw light on the conformational preference of this dendralene **120** (**Figure 2.1**). The diene featuring the double bonds at third and fourth positions was in *s-trans* conformation. This diene in our earlier dendralenes was acting as the diene component in self D-A reaction. The stability of dendralene **120** perhaps was due to D-A inert *s-trans* conformation of diene in consideration.



Scheme 2.9 Synthesis of silyl substituted [3]dendralene

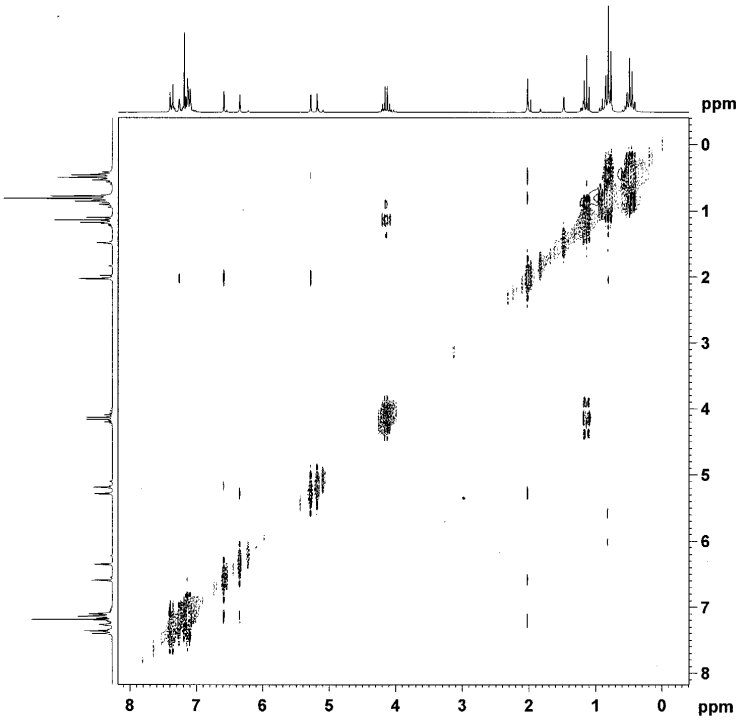
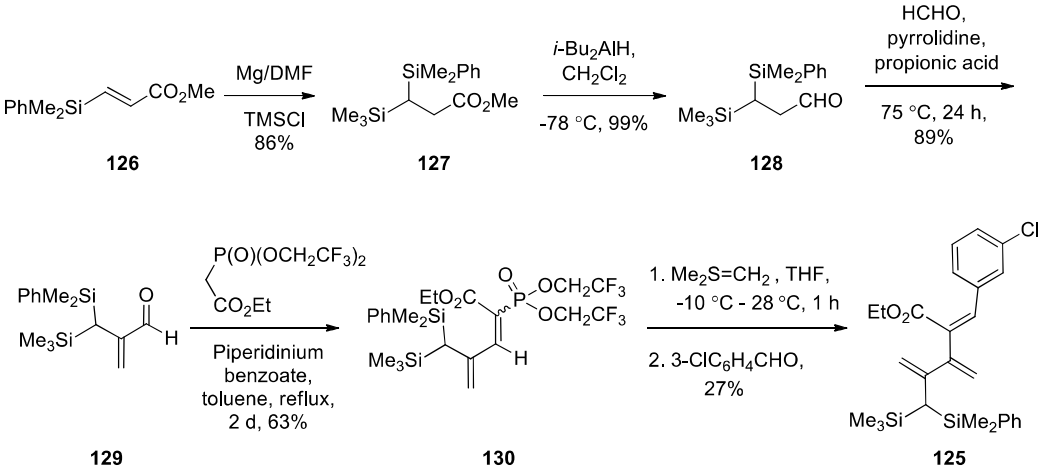


Figure 2.1 $^{1}H/^{1}H$ NOESY spectrum of dendralene **120**

After successful synthesis of monosilyl substituted [3]dendralene **120**, it was targeted to introduce a more functionalized and sterically demanding disilylmethyl

group at fourth position while removing substituent at fifth position to get a disilyl substituted [3]dendralene **125** (**Scheme 2.10**).[68] A Mg-mediated reductive silylation[70] of *β*-dimethyl(phenyl)silyl acrylate **126** using TMSCl in DMF at room temperature gave disilyl propionate **127** in 86% yield. This propionate **127** was then subjected to DIBAL-H reduction in dichloromethane at -78 °C to provide the aldehyde **128** in quantitative yield. This silylated propionaldehyde **128** upon a selective aldol condensation with formaldehyde in presence of catalytic amount of pyrolidine and propanoic acid at 75 °C, followed by dehydration provided 2-disilylmethyl substituted acrolein **129** in 89% yield. Knoevenagel condensation of this 2-substituted acrolein **129** with bis-(2,2,2-trifluroethyl)phosphonoacetate catalyzed by piperidinium benzoate under toluene reflux, furnished the desired ethenylidene phosphonoacetate **130** in 63% yield. The phosphonoacetate **130** was reacted with DMSM and subsequently was treated with 3-chlorobenzaldehyde wherein H-W-E took place to furnish desired [3]dendralene **125** in 27% yield. This dendralene was also stable towards D–A cyclodimerization at room temperature.



Scheme 2.10 Synthesis of disilyl substituted [3]dendralene

Later, D-A reaction was attempted with these dendralenes **120** and **125** using *N*-methylmaleimde as the dienophile, but it was not successful. This could probably be due to the steric bulk of the dendralenes.

2.3 Conclusion

In conclusion, stable and highly functionalized [3]dendralenes bearing silylmethyl functionality were successfully synthesized. The silyl functionality coerced the double bonds at third and fourth positions to attain D–A unfavoured *s-trans* conformation, thus drastically diminished the reactivity of these [3]dendralenes as regards to D–A cyclodimerization reactions hence imparted stability. These dendralenes unfortunately did not participate in the D–A reactions owing to their steric bulk.

2.4 Experimental section

2.4.1 General Details

All reactions were performed in oven-dried (120 ºC) or flame-dried glass apparatus under dry N_2 or argon atmosphere.

Solvent purification: The solvents were dried and distilled from the indicated drying agents. Benzene and toluene form sodium; tetrahydrofuran from sodium/benzophenone ketyl; DCM and DMF from CaH_2 and then stored over molecular sieves.

Reagents: All the aldehydes were purchased from Aldrich and were freshly distilled prior to use. NaH (60% in oil), *n*-BuLi (1.6 M in hexane) and Me_3SI were purchased from Aldrich.

NMR Study: ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 200, 500 and 800 MHz spectrometers. Spectra were referenced to residual chloroform (δ 7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C). Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (pentet), dd (doublet of doublets), dq (doublet of quartet) m (multiplet) and br (broad). Coupling constants (J) are reported in Hertz. For the interpretation of ^{1}H decouple ^{13}C spectrum, the number of expected carbons are provided in the parenthesis.

Mass Spectrometry: High-resolution mass spectrum was obtained using a high-resolution ESI-TOF mass spectrometer.

Elemental Analysis: Elemental analysis was performed on elementar 'vario MICRO cube' instrument.

IR Study: IR spectra were recorded on JASCO and Bruker FT IR spectrophotometers in NaCl cell or in KBr discs. Peaks are reported in cm^{-1}.

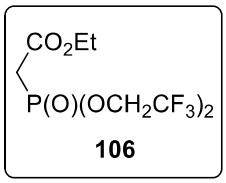
Melting Point: Melting points (mp) were determined on 'BUCHI M-560' instrument and are uncorrected.

TLC: Analytical thin-layer chromatography was carried out using Merck silica gel 60 F_{254} plates**.**

Column Chromatography: Column Chromatography was performed using Silica Gel 230-400 mesh obtained from Sisco Research Laboratories Pvt. Ltd.

2.4.2 General procedures and characterization data of products

Ethyl bis-(2,2,2-trifluroethyl) phosphonoacetate (106)

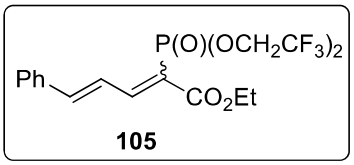


106

Phosphorus pentachloride (69.8 g, 334.8 mmol) was added portion wise to triethyl phosphonoacetate (25 g, 111.6 mmol) at 0 °C over a period of 20 minutes in a 250 ml round bottom flask fitted with KOH guard tube. After 10 minutes, the reaction mixture was heated to 75 °C for 4 days. Then excess of PCl_5 and the $POCl_3$ formed were removed under vacuum (0.1mm/Hg) at 45 °C over a period of 1 h to obtain crude oxychloro derivative. This crude product was diluted with 50 mL of dry benzene and cooled to 0 °C, to which 2,2,2-trifluroethanol (24.4 ml, 334.8 mmol) was added dropwise followed by addition of N,N-diisopropylethylamine (58 mL, 334.8 mmol) *via* dropping funnels. After stirring for 5 h the reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed thrice with water and concentrated on rotary evaporator. The residue was purified by vacuum distillation (0.1 mm/Hg at 120 °C bath temperature) to provide ethyl bis-(2,2,2-trifluroethyl) phosphonoacetate **106** (20 g, 54%).

R_f (hexane-EtOAc, 70:30) = 0.4; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.45 (dq, J = 8.5, 8.5 Hz, 4 H, 2 × OCH_2CF_3), 4.21 (q, J = 7.1 Hz, 2 H, CH_3CH_2O), 3.15 (d, J = 21.1 Hz, 2H, $COCH_2PO$), 1.28 (t, J = 7.1 Hz, 3 H, CH_3CH_2O) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.5 (d, J = 4.2 Hz), 122.3 (dq, J = 275.3, 8.4 Hz), 62.3 (dq, J = 38.0, 5.5 Hz), 61.9, 33.5 (d, J = 142.6 Hz), 13.4 ppm.

Ethyl 2-bis(2,2,2-trifluoroethyl)phophonato-5-phenyl-2,4-pentadienoate (105)



105

A solution of ethyl bis(2,2,2-trifluoroethyl)phosphonoaceatate (1.3 g, 4.0 mmol), cinnamaldehyde (0.5 mL, 4.0 mmol) and piperidinium benzoate (0.09 g, 0.4 mmol) in benzene (30 mL) was refluxed for 18 h in a Dean-Starke apparatus. The reaction mixture was cooled and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel to give phosphonoacetate **105** (1.5 g, 84%) as a mixture of *E*/*Z* isomers in the ratio 65:35. A small portion of the product was fractionated by chromatography to give pure (2*E*, 4*E*) and pure (2*Z*, 4*E*) isomers separately.

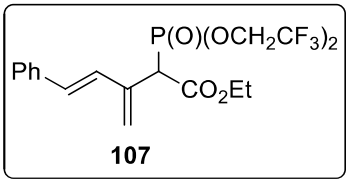
Ethyl (2*E*, 4*E*)-2-bis(2,2,2-trifluoroethyl)phophonato-5-phenyl-2,4-pentadienoate (*E*-105)

R_f (hexane-EtOAc, 80:20) = 0.3; IR (film): 3091, 3071, 3036, 2983, 2906, 1961, 1815, 1715, 1609, 1579, 1565, 1479, 1449, 1417, 1374, 1294, 1257, 1178, 1072, 963, 863, 750 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.90-8.20 (m , 1 H, PhCH=C*H*), 7.70 (dd, *J* = 22.8, 11.4 Hz, 1 H, PCCH), 7.50-7.53 (m, 2 H, Ph), 7.34-7.36 (m, 3 H, Ph), 7.12 (d, *J* = 15.2 Hz, 1 H, PhC*H*), 4.36-4.53 (m, 4 H, 2 × OCH_2CF_3), 4.29 (q, *J* = 7.0 Hz, 2 H, OCH_2CH_3), 1.33 (t, *J* = 7.0 Hz, 3 H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.0 (d, *J* = 15.1 Hz), 157.4, 148.7, 134.7, 130.1, 128.4 (2 C), 127.9 (2 C), 123.2 (d, *J* = 20.4 Hz), 122.4 (dq, *J* = 276, 8.8 Hz, 2 C, 2 × CF_3), 115.3 (d, *J* = 195 Hz), 61.9 (q, *J* = 37.6 Hz, 2 C, 2 × $POCH_2$), 60.8, 13.1 ppm.

Ethyl (2*Z*, 4*E*)-2-bis(2,2,2-trifluoroethyl)phophonato-5-phenyl-2,4-pentadienoate (*Z*-105)

R_f (hexane-EtOAc, 80:20) = 0.5; IR (film): ν_{max} = 3091, 3071, 3036, 1714, 1609, 1578, 1562, 1479, 1450, 1418, 1368, 1283, 1243, 1169, 1073, 963, 878, 751, 677 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.15 (dd, J = 49.4, 12 Hz, 1 H, PC=CH), 7.95-8.08 (m, 1 H, PhCHC*H*), 7.54-7.59 (m, 2 H, Ph), 7.36-7.39 (m, 3 H, Ph), 7.19 (d, J = 15.0 Hz, 1 H, PhC*H*), 4.38-4.57 (m, 4 H, 2 × OCH_2CF_3), 4.29 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 1.33 (t, J = 7.2 Hz, 3 H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.5 (d, J = 15.8 Hz), 158.67 (d, J = 8.1 Hz), 149.45, 134.9, 130.3, 128.6 (2 C), 128.1 (2 C), 123.3 (d, J = 5.0 Hz), 122.5 (dq, J = 276, 9.2 Hz, 2 C), 115.2 (d, J = 194 Hz), 62.1 (q, J = 38 Hz, 2 C, 2 × $POCH_2$), 61.3, 13.3 ppm.

Ethyl (4*E*)-2-bis(2,2,2-trifluoroethyl)phophonato-3-methylene-5-phenyl-4-pentenoate (107)

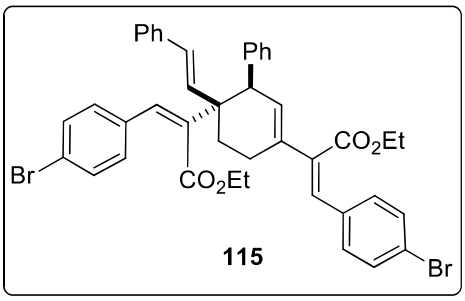


107

A solution of *n*-butyl lithium (1.5 M in hexane, 1.25 mL, 1.88 mmol) was added dropwise to a suspension of Me_3SI (0.384 g, 1.88 mmol) in THF (5 mL) at –10 °C. After 20 min at –10 °C, a solution of phosphonoacetate **105** (0.28 g, 0.62 mmol) in THF (4 mL) was slowly added to the reaction mixture and stirred for 1 h. The reaction mixture was allowed to warm up to 28 °C, diluted with water and extracted with ethyl acetate. The organic extract was concentrated on rotary evaporator and the residue was purified by column chromatography to give dienyl phosphonoacetate **107** (0.252 g, 88%).

R_f (hexane-EtOAc, 90:10) = 0.2; IR (film): ν_{max} = 3063, 2976, 2939, 1731, 1621, 1494, 1454, 1418, 1371, 1296, 1263, 1177, 1100, 1072, 1027, 962, 875, 844, 755, 698, 660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.30-7.49 (m, 5H, Ph), 6.87 (d, J = 16.2 Hz, 1 H, PhC*H*=CH), 6.72 (d, J = 16.2 Hz, 1 H, PhCH=C*H*), 5.66 (s, 1 H, CCH_AH_B), 5.64 (s, 1 H, CCH_AH_B), 4.23-4.61 (m, 7 H, 3 × OCH_2, PCH), 1.32 (t, J = 7.1 Hz, 3 H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.5, 136.2, 134.9 (d, J = 8 Hz), 129.9, 128.4 (2 C), 127.9 (2 C), 126.5 (2 C), 122.3 (dq, J = 276.0, 8.0 Hz, 2 C), 121.1 (d, J = 9.2 Hz), 62.6 (dq, J = 6.4, 42.9 Hz, OCH_2CF_3), 62.5 (dq, J = 6.6, 42.9 Hz, OCH_2CF_3), 62.2, 47.3 (d, J = 144.1 Hz, PC), 13.4 ppm.

(2Z,2'Z)-Diethyl 2,2'-((1*RS*,2*RS*)-2-((*E*)-styryl)-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2,5-diyl)bis(3-(4-bromophenyl)acrylate) (115)



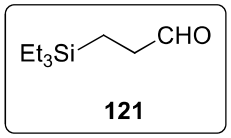
115

A solution of dienyl phosphonoacetate **107** (0.23 g, 0.5 mmol) and *p*-bromobenzaldehyde (0.143 g, 0.5 mmol) in THF (5 mL) was added to an oil free suspension of sodium hydride (0.012 g, 0.5 mmol) in THF (0.5 mL) at 0 °C. The reaction mixture was brought to room temperature (28 °C) and stirred for 5 h. The reaction mixture was evaporated under reduced pressure and the residue was purified by silica gel chromatography to give **115** (0.138 g, 72%) as a colorless solid.

mp: 175-176 °C (EtOAc/hexane); R_f (hexane-EtOAc, 90:10) = 0.46; IR (film): ν_{max} = 3025, 2981, 2936, 1714, 1627, 1599, 1587, 1487, 1215, 1074, 1010, 970, 874, 812,

760 and 705 cm^{-1}; ^1H NMR (800 MHz, $CDCl_3$): δ 7.45 (d, J = 8.0 Hz, 2 H, Ar), 7.43 (d, J = 8.0 Hz, 2 H, Ar), 7.25-7.31 (m, 8 H, Ph), 7.18-7.24 (m, 4 H, Ar, Ph), 7.10 (d, J = 8.0 Hz, 2 H, Ar), 6.58 (s, 1 H, ArC*H*), 6.35 (d, J = 16 Hz, 1 H, PhC*H*=CH), 6.31 (s, 1 H, ArC*H*), 6.18 (d, J = 16.8 Hz, 1 H, PhCH=C*H*), 6.02 (d, J = 3.2 Hz, 1 H, PhCHC*H*=C), 4.20-4.25 (m, 2 H, CO_2CH_2), 4.16-4.20 (m, 1 H, $CO_2CH_AH_B$), 4.11-4.16 (m, 1 H, $CO_2CH_AH_B$), 4.05-4.11 (m, 1 H, PhC*H*), 2.57-2.63 (m, 1 H, CCH_AH_B), 2.47-2.53 (m, 1 H, CCH_AH_B), 2.27 (t, J = 5.6 Hz, 2 H, HC=CCH_2), 1.18 (t, J = 7.2 Hz, 3 H, $CO_2CH_2CH_3$), 1.10 (t, J = 6.4 Hz, 3 H, $CO_2CH_2CH_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 169.3, 140.9, 140.1, 137.5, 137.4, 135.1, 134.8, 134.1, 132.7, 131.5 (2 C), 131.3 (2 C), 130.9, 130.8 (2 C), 130.5, 130.4, 129.7 (2 C), 129.4 (2 C), 128.4 (2 C), 127.6 (2 C), 127.3, 126.9, 126.1 (2 C), 125.4, 121.9, 121.7, 61.2, 60.9, 49.1, 47.1, 28.6, 23.1, 13.9, 13.8 ppm.

3-Triethylsilylpropanal (121)

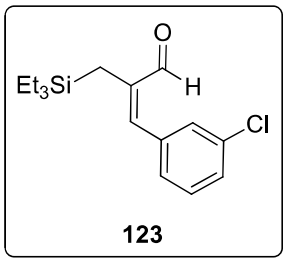


121

A solution of DIBAL-H (1 M in hexane, 4.85 mL, 4.85 mmol) was added dropwise to a solution ester **122** (0.89 g, 4.4 mmol) in dichloromethane (7 mL) at -78 ºC and the reaction mixture was stirred for 1 h at same temperature. The reaction mixture was then quenched with water, stirred for 10 min and dil. HCl was added till turbidity disappeared. The reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 25 mL). The organic layer was concentrated and the residue was purified by column chromatography to provide the aldehyde **121** (0.644 g, 84%) as a colorless liquid. R_f (hexane-EtOAc, 98:2) = 0.31; IR (film): ν_{max} = 2953, 2911, 2876,

2808, 2713, 1725, 1457, 1417, 1239, 1179, 1072, 1015, 912 and 733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.73 (t, J = 2.0 Hz, 1 H, CHO), 2.41-2.25 (m, 2 H, CH_2CHO), 0.92 (t, J = 7.8 Hz, 9 H, 3 × CH_3), 0.81- 0.70 (m, 2 H, SiCH_2CH_2), 0.52 (q, J = 8.0 Hz, 6 H, 3 × SiCH_2CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 203.2, 38.3, 7.2 (3 C), 3.0 (3 C), 2.9 ppm.

(*E*)-3-(3-Chlorophenyl)-2-[(triethylsilyl)methyl]acrylaldehyde (123)

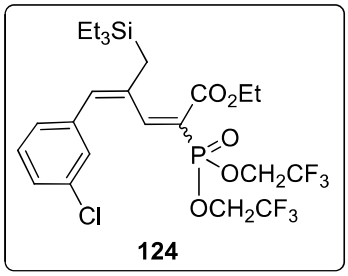


123

A solution of silyl aldehyde **121** (0.86 g, 4.95 mmol), 3-chlorobenzaldehyde (5.7 mL, 50 mmol), pyrrolidine (0.125 mL, 1.5 mmol) and propionic acid (0.115 mL, 1.5 mmol) was heated at 75 ºC for 1 d under argon atmosphere. Excess 3-chlorobenzaldehyde was distilled out under reduced pressure and the residue was purified by column chromatography to provide the unsaturated aldehyde **123** (1.0 g, 71%) as a pale yellow gum.

R_f (hexane-EtOAc, 90:10) = 0.6; IR (film): ν_{max} = 2952, 2910, 2875, 1684, 1616, 1592, 1562, 1471, 1416, 1240, 1201, 1154, 1092, 1016, 899, 804, 780, 726 and 686 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 9.51 (s, 1 H, CHO), 7.52 (s, 1 H, Ar), 7.39-7.32 (m, 3 H, Ar), 7.0 (s, 1 H, ArC*H*), 2.13 (s, 2 H, SiCH_2C), 0.87 (t, J = 8.0 Hz, 9.0 H, 3 × CH_3), 0.48 (q, J = 8.0 Hz, 6 H, 3 × SiCH_2CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.3, 144.2, 143.3, 137.5, 134.6, 129.8, 129.0, 128.8, 127.5, 11.1, 7.2 (3 C), 3.9 (3 C) ppm.

(*2E/Z,4E*)-Ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-5-(3-chlorophenyl)-4-(triethylsilylmethyl)penta-2,4-dienoate (124)

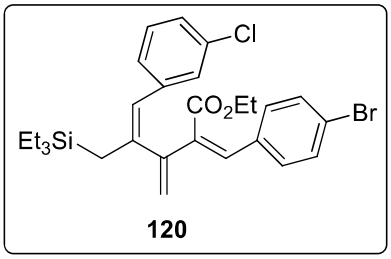


124

A solution of aldehyde **123** (0.51 g, 1.75 mmol), ethyl bis-(2,2,2-trifluroethyl)-phosphonoacetate (0.58 g, 1.75 mmol) and piperidinium benzoate (0.073 g, 0.35 mmol) in toluene (5 mL) was heated under reflux for 2 d in a flask fitted with Dean-Stark apparatus. The reaction mixture was then brought to room temperature, diluted with water and extracted with ethyl acetate. The organic extract was concentrated under the reduced pressure and the residue purified by column chromatography to give phosphonate **124** as 1:1 inseparable mixture of two *E/Z* isomers (0.68 g, 65%) as a brown colored viscous liquid.

R_f (hexane-EtOAc, 85:15) = 0.27; IR (film): ν_{max} = 3390, 2956, 2913, 2873, 2253, 1720, 1592, 1455, 1416, 1373, 1296, 1260, 1174, 1105, 1072, 1017, 963, 909, 778, 732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.74 (dd, J = 25.2, 1.2 Hz, 1 H, ArC*H*, 1st isomer), 7.49 (dd, J = 25.0, 0.8 Hz, 1 H, ArC*H*, 2nd isomer), 7.49-7.12 (m, 8 H, Ar, both isomers), 6.74 (d, J = 28.0 Hz, 1 H, P(O)CCH, 1st isomer), 6.49 (d, J = 19.8 Hz, P(O)CCH, 1 H, 2nd isomer), 4.51-4.28 (m, 12 H, 2 × OC*H*$_2$CH$_3$, 4 × OC*H*$_2$CF$_3$, both isomers), 2.18 ((s, 2 H, SiCH$_2$C,1st isomer), 2.02 (s, 2 H, SiCH$_2$C, 2nd isomer), 1.40 (t, J = 7.0 Hz, 6 H, 2 × OCH$_2$C*H*$_3$, both isomers), 1.12-0.95 (m, 9 H, SiCH$_2$C*H*$_3$, both isomers), 0.76-0.62 (m, 12 H, SiC*H*$_2$CH$_3$, both isomers) ppm; Anal. Calc. for $C_{24}H_{32}ClF_6O_5PSi$: C, 47.33; H, 5.30. Found: C, 47.06; H, 5.68.

(*2Z,4Z*)-Ethyl 2-(4-bromobenzylidene)-5-(3-chlorophenyl)-4-(triethylsilylmethyl)-3-methylenepent-4-enoate (120)



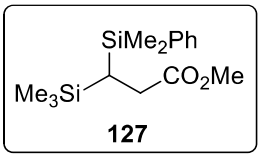
120

To a suspension of trimethylsulfonium iodide (0.493 g, 2.4 mmol) in THF (8 mL), *n*-BuLi (1.6 mL, 1.5 M, 2.4 mmol) was added dropwise at - 10 ºC under argon atmosphere and stirred for 20 min at the same temperature. Later a solution of phosphonate **124** (0.49 g, 0.8 mmol) in THF (5 mL) was cannulated and the reaction mixture was stirred for 1 h. To this reaction mixture 4-bromobenzaldehyde (0.185 g, 1.0 mmol) in THF (2 mL) was added and stirred for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was concentrated and column chromatography was done to obtain the dendralene **120** (0.134 g, 31%) as a pale yellow gum.

R_f (hexane-EtOAc, 90:10) = 0.7; IR (film): ν_{max} = 3019, 2954, 2909, 2875, 1716, 1592, 1559, 1541, 1507, 1488, 1473, 1417, 1376, 1215, 1074, 1043, 852, 757 and 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.45 (d, J = 8.4 Hz, 2 H, Ar), 7.40 (s, 1 H, Ar), 7.34-7.16 (m, 5 H, Ar), 6.66 (s, 1 H, ArC*H*), 6.42 (s, 1 H, ArC*H*), 5.35 (s, 1 H, C=CH_AH_B), 5.26 (s, 1 H, C=CH_AH_B), 4.22 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 2.09 (s, 2 H, SiCH_2C), 1.21 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3), 0.88 (t, J = 7.4 Hz, 9 H, 3 × SiCH$_2$CH_3), 0.57 (q, J = 8.0 Hz, 6 H, 3 × SiCH_2CH$_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.8, 150.2, 141.2, 140.0, 135.7, 134.4, 134.1, 131.8, 131.5 (2 C), 129.9 (2 C), 129.4, 128.6, 127.0,

126.6, 126.4, 122.4, 116.2, 61.2, 16.0, 13.9, 7.3 (3 C), 3.9 (3 C) ppm. Anal. Calc. for $C_{28}H_{34}BrClO_2Si$: C, 61.59; H, 6.28. Found: C, 61.95; H, 6.42.

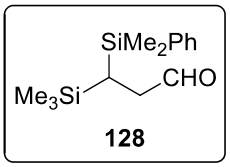
Methyl 3-(dimethyl(phenyl)silyl)-3-(trimethylsilyl)propanoate (127)



127

Trimethylsilyl chloride (9 mL, 71.0 mmol) was added to a suspension of Mg turnings (3.4 g, 142 gatom) in DMF (47 mL) and stirred for 15 minutes at RT. To this reaction mixture a solution of unsaturated ester **126** (2.6 g, 11.8 mmol) in DMF (12 mL) was added through a cannula. After 30 min reaction mixture was poured over saturated sodium bicarbonate solution and extracted with 15% ethyl acetate and hexane. The organic layer was concentrated to obtain the desired disilylated ester **127** (3.4 g, 86%). R_f (hexane-EtOAc, 95:5) = 0.7; IR (film): ν_{max} = 3069, 2999, 2952, 2898, 1739, 1428, 1348, 1252, 1204, 1050, 1032, 837 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.53-7.48 (m, 2 H, Ph), 7.36-7.31 (m, 3 H, Ph), 3.52 (s, 3 H, OCH_3), 2.38 (d, J = 6.6 Hz, 2 H, $COCH_2$), 0.76 (t, J = 6.6 Hz, 1 H, C*H*CH_2), 0.32 (s, 3 H, $SiCH_3$), 0.30 (s, 3 H, $SiCH_3$), -0.06 (s, 9 H, 3 × $SiCH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.1, 139.0, 133.8 (2 C), 129.0, 127.7 (2 C), 51.8, 30.7, 9.1, -0.5 (3 C), -1.4, -2.4 ppm

3-Dimethyl(phenyl)silyl-3-trimethylsilylpropanal (128)

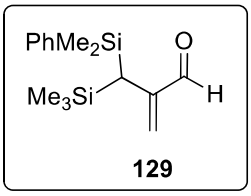


128

Following the procedure described for the preparation of **121**, a solution of ester **127** (0.71 g, 2.4 mmol) and DIBAL-H (1 M in hexane, 2.4 mL, 2.4 mmol) gave the aldehyde **128** (0.63 g, 99%) as a colorless thick liquid.

R_f (hexane-EtOAc, 98:2) = 0.4; IR (film): ν_{max} = 3068, 2954, 2898, 2812, 2713, 1722, 1643, 1427, 1251, 1112, 1056, 1021, 837, 732, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.59 (t, J = 1.2 Hz, 1 H, CHO), 7.51-7.45 (m, 2 H, Ph), 7.38-7.30 (m, 3 H, Ph), 2.52 (dd, J = 6.0, 1.4 Hz, 2 H, CH_2CHO), 0.84 (t, J = 6.0, 1 H, CHCH$_2$), 0.33 (s, 3 H, SiCH$_3$), 0.31 (s, 3 H, SiCH$_3$), -0.051 (s, 9 H, 3 × SiCH$_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 202, 138.9, 133.7 (2 C), 129.0, 127.8 (2 C), 40.9, 5.6, -0.32 (3 C), -1.38, -2.44 ppm.

2-[{(Dimethyl(phenyl)silyl}(trimethylsilyl)methyl]acrylaldehyde (129)



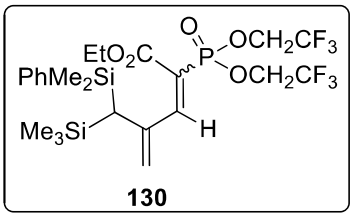
129

Following the procedure described for the preparation of **123**, disilyl aldehyde **128** (0.63 g, 2.4 mmol), formaldehyde (37% in water, 0.24 mL, 3.0 mmol), pyrrolidine (0.06 mL, 0.72 mmol) and propionic acid (0.054 mL, 0.72 mmol) in iso-propanol (0.25 mL) provided the conjugated aldehyde **129** (0.59 g, 89%) as a colorless gum.

R_f (hexane-EtOAc, 98:2) = 0.4; IR (film): ν_{max} = 3069, 2956, 2892, 2812, 2690, 2713, 1692, 1602, 1427, 1304, 1252, 1113, 1051, 836, 805,733, and 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.33(d, J = 0.4 Hz, 1 H, CHO), 7.49-7.45 (m, 2 H, Ph), 7.38-7.30 (m, 3 H, Ph), 6.03 (s, 1 H, C=CH_AH$_B$), 5.83 (d, J = 1.2 Hz, 1 H, C=CH$_A$$H_B$), 1.59 (s, 1 H, SiCH) 0.36 (s, 3 H, SiCH$_3$), 0.29 (s, 3 H, SiCH$_3$), -0.10 (s, 9 H, 3 × SiCH$_3$) ppm; ^{13}C

NMR (50 MHz, $CDCl_3$): δ 194.3, 150.3, 138.5, 133.8, 132.9, 129.0, 127.5, -0.4 (3 C), -1.8, -1.9 ppm.

(*2E/Z*)-Ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-4-[{(dimethyl(phenyl)silyl}(trimethylsilyl)] methylpenta-2,4-dienoate (130)

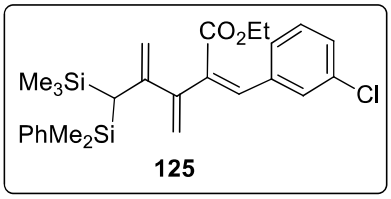


130

Following the procedure described for the preparation of **124**, aldehyde **129** (0.34 g, 1.23 mmol), ethyl bis-(2,2,2-trifluroethyl)-phosphonoacetate (0.41 g, 1.23 mmol) and piperdinium benzoate (0.05 g, 0.25 mmol) gave phosphonate **130** (0.46 g, 63%) as brown colored viscous liquid.

R_f (hexane-EtOAc, 85:15) = 0.5; IR (film): ν_{max} = 3071, 2959, 2902, 1727, 1597, 1455, 1427, 1373, 1297, 1259, 1217, 1172, 1105, 1070, 963, 838, 781, 735, 701 and 658 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.54-7.30 (m, 5 H, Ph), 6.90 (dd, J = 26.2, 0.6 Hz, 1 H, P(O)C=CH), 5.34 (d, J = 0.6 Hz, 1 H, C=CH_AH_B), 5.08 (s, 1 H, C=CH_AH_B), 4.44-4.28 (m, 6 H, OCH_2CH$_3$, 2 × CH_2CF_3), 1.36 (d, J = 1.6 Hz, 1 H, SiCH), 1.28 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 0.41 (s, 3 H, $SiCH_3$), 0.35 (s, 3 H, $SiCH_3$), -0.050 (s, 9 H, 3 × $SiCH_3$) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): 164.5 (d, J = 14.0 Hz), 154.3 (d, J = 6.5 Hz), 143.4 (d, J = 21.5 Hz), 138.4, 133.8 (2 C), 129.1, 127.6 (2 C), 122.3 (dq, J = 276.0, 9.5Hz, 2 C), 120.9, 119.6 (d, J = 184.5 Hz), 62.3 (dq, J = 38.0, 4.5 Hz, 2 C), 62.0, 25.6, 13.5, -0.4 (3 C), -2.1. -2.2 ppm; Anal. Calc. for $C_{23}H_{33}F_6O_5PSi_2$: C, 46.77; H, 5.63. Found: C, 47.01; H, 5.77.

(*2Z*)-Ethyl 2-(3-chlorobenzylidene)-4-[{(dimethyl(phenyl)silyl}(trimethylsilyl)methyl]-3-methylenepent-4-enoate (125)



125

Following the procedure described for the preparation of **120**, trimethylsulfonium iodide (0.218 g, 1.07 mmol), n-BuLi (0.67 mL, 1.6 M, 1.07 mmol), phosphonate **130** (0.21 g, 0.36 mmol) and 3-chlorobenzaldehyde (0.046 mL, 0.4mmol) gave the dendralene **125** (0.046 g, 27%) as a pale yellow gum.

R_f (hexane-EtOAc, 90:10) = 0.7; IR (film): ν_{max} = 2954, 2903, 1721, 1592, 1474, 1427, 1249, 1208, 1112, 1020, 837 and 736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.55-7.50 (m, 2 H, Ph), 7.35-7.30 (m, 3 H, Ph), 7.25-7.23 (m, 2 H, Ar), 7.19-7.14 (m, 2 H, Ar), 6.48 (s, 1 H, ArC*H*), 5.31 (s, 1 H, COCC=CH_AH_B), 5.21 (s, 2 H, COCC=CH_AH_B, SiCHC=CH_AH_B), 4.89 (s, 1 H, SiCHC=CH_AH_B), 4.14 (q, J = 7.0 Hz, 2 H, OCH_2CH$_3$), 1.63 (d, J = 2.2 Hz, 1 H, SiCH), 1.15 (t, J = 7.0 Hz, 3 H, OCH$_2$CH_3), 0.42 (s, 3 H, SiCH$_3$), 0.34 (s, 3 H, SiCH$_3$), - 0.06 (s, 9 H, 3 × SiCH$_3$) ppm; HRMS (ESI-TOF) m/z: Cacl. For $C_{27}H_{36}Cl_1O_2Si_2$: $(M + H)^+$, 483.1937; Found: $(M + H)^+$, 483.1952.

CHAPTER 3

Synthesis of Stable Tetrasubstituted [3]Dendralenes and Their Diels-Alder Reactions

3.1 Introduction

As discussed in **Chapter 2**, the initial [3]dendralenes prepared in our group were extremely unstable and underwent *in situ* Diels-Alder (D-A) cyclodimerization in the reaction pot itself, whereas the latter ones i.e. silyl functionalised [3]dendralenes although were stable towards the cyclodimerization, but could not participate in the D-A reaction owing to their high steric bulk. During this period, when our jugglery to optimize the reaction conditions to obtain moderately stable [3]dendralenes which could participate in D-A reaction was going on, Sherburn and co-workers reported studies regarding the stability and reactivity of various un/mono substituted dendralenes.[71,72] According to their report, odd dendralenes are more reactive in comparison to their even counterparts. This observation was corroborated by the DFT calculations. It suggested that even dendralenes are predominantly populated with D-A inert conformations wherein all the adjacent olefinic units are *s-trans* with respect to one another, with only a very small population of conformations possessing a D-A reactive *s-cis* component. On the contrary, the odd dendralenes possess a residual vinyl group, in addition to the *s-trans* butadiene units, which is free to adopt *s-cis* conformation with an adjacent olefinic unit, which results in a high population of D-A reactive *s-cis* conformation along with some amount of D-A inert *s-trans* conformation, thus conferring greater D-A reactivity, compared to their even counterparts (**Figure 3.1**). A more significant conclusion brought out in their study was that the conjugating terminal substituents (at C_1 or C_5) on [3]dendralenes accelerate the rate of D–A cyclodimerisation whereas the internal substituents (at C_2, C_3, and C_4) which have little effect on the dimerisation reactivity.[71,72]

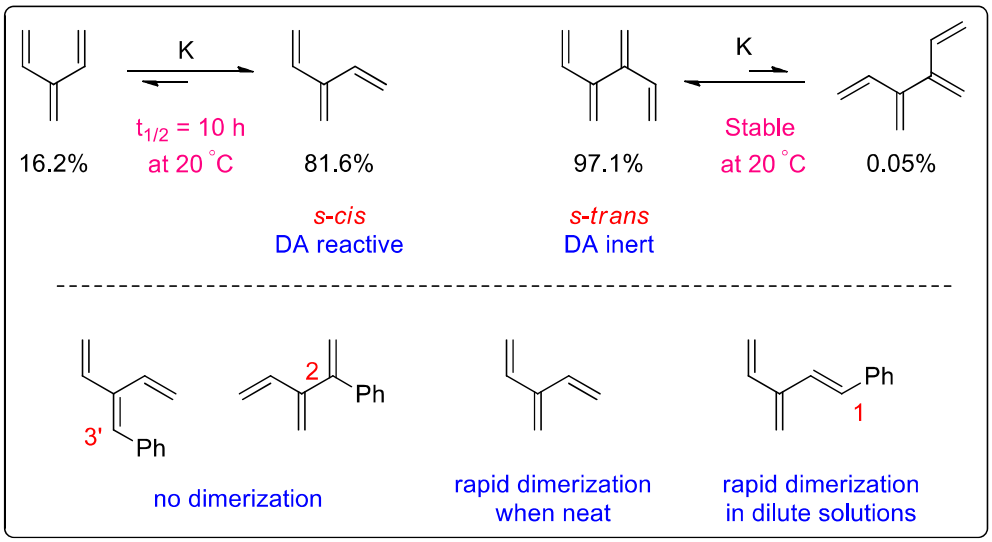


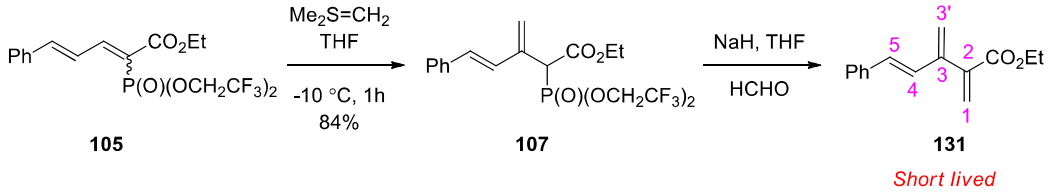
Figure 3.1 Conformational and substitution effect on stability of dendralenes

3.2 Present work

3.2.1 Synthesis of highly functionalized [3]dendralenes

In cognizance with the above facts, in order to accomplish the goal of synthesis of stable and functionalized [3]dendralenes which would participate in the D-A reactions, it was decided to exclude one of the terminal substituent on the earlier [3]dendralenes **109** (see **Scheme 2.5** in **Chapter 2**) to obtain 2,5-disubstituted [3]dendralene **131**. This dendralene **131** was synthesized from dienic phosphonate **105** following the olefination methodology described in **Chapter 2**. Phosphonate **105** was reacted with dimethylsulfonium methylide to provide 1,3-butadien-2-ylphosphonoacetate **107** in 84% yield. This phosphonoacetate upon deprotonation with NaH was reacted with formaldehyde to provide [3]dendralene **131** (**Scheme 3.1**).[73] This dendralene was extremely short lived and could be characterized only by ^{1}H NMR of the crude reaction mixture. Just after 15-20 minutes the dendralene underwent dimerization and polymerization as evidenced by ^{1}H NMR. This exemplified the dramatic effect of the

absence of a terminal conjugating substituent on the stability of the [3]dendralenes akin to Sherburn's observation.[72]

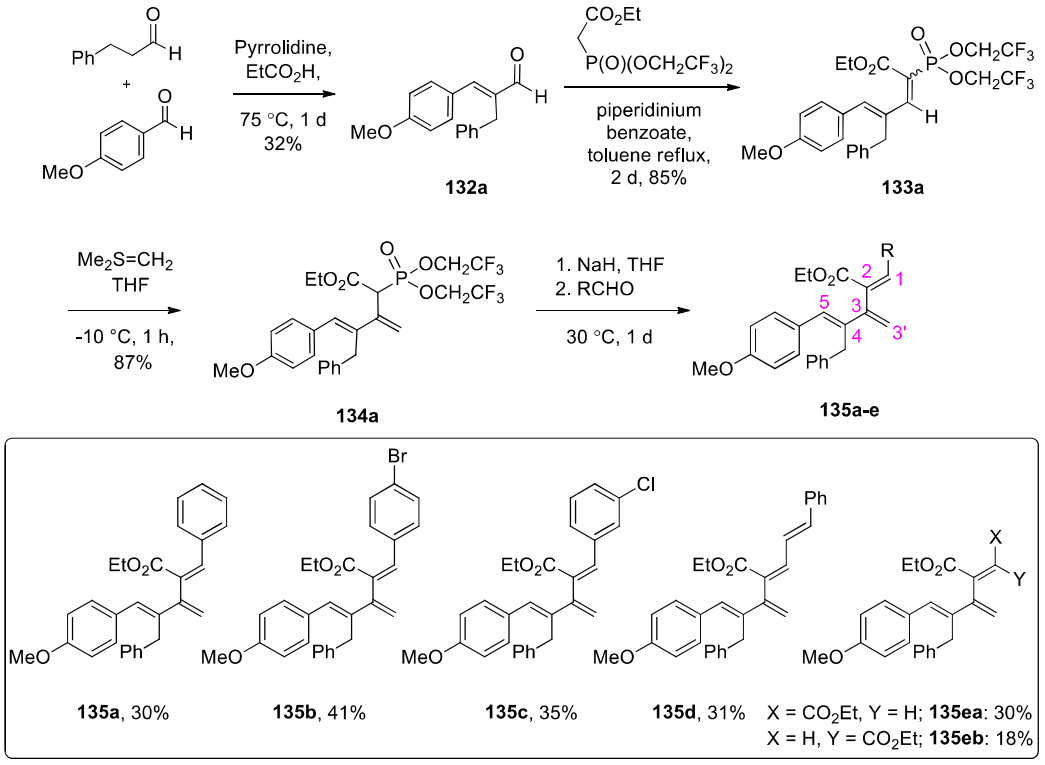


Scheme 3.1 Synthesis of 2,5-disubstituted [3]dendralene **131**

Owing to extremely short life, dendralene **131** could not be participated in the Diels-Alder reactions. Thus aim was to further enhance the stability of the [3]dendralenes such that they could be easily handled and participated in the Diels-Alder reactions. The silyl [3]dendralenes **120**, **125** prepared in **Chapter 2** were stable towards the cyclodimerization, but did not participate in D-A reaction owing to their high steric bulk. Hence, it was decided to replace the sterically bulkier silyl substituent with less bulky benzyl substituent at forth position of the [3]dendralene.

For the fulfillment of this objective, 3-phenylpropanal was reacted with 10 equiv. of *p*-anisaldehyde in the presence of catalytic amount of pyrrolidine and propionic acid[68] at 75 °C which provided α,β unsaturated aldehyde **132a** in 32% yield (**Scheme 3.2**). Knoevenagel condensation of aldehyde **132a** with ethyl bis-(2,2,2-trifluroethyl)-phosphonoacetate catalyzed by piperidinium benzoate in refluxing toluene furnished the desired dienyl phosphonate **133a** in 85% yield as an inseparable 1/1 mixture of two geometrical isomers of the double bond attached to phosphonate group as judged from ^{1}H NMR. When this phosphonate **133a** was reacted with dimethylsulfonium methylide generated using Me_3SI and *n*-BuLi in THF, the desired olefination took place to give the appropriately substituted butadien-2-

ylphosphonoacetate **134a** in 87% yield. This phosphonoacetate **134a** was then reacted with sodium hydride followed by benzaldehyde in THF at RT which provided the 1,2,4,5-tetrasubstituted [3]dendralene **135a** in 30% yield. Now the objective was to check the generality of this reaction hence the butadien-2-ylphosphonoacetate **134a** was reacted with a few more aldehydes under standard H-W-E conditions to obtain the desired 1,2,4,5-tetrasubstituted [3]dendralenes **135b-e** in moderate yields (**Scheme 3.2**). All the dendralenes were formed with high stereoselectivity except for the dendralene **135e** where ethyl glyoxalate was used as the aldehyde component.[73]



Scheme 3.2 Synthesis of tetra substituted [3]dendralenes

The dendralene **135e** was obtained as a separable mixture of *Z* and *E* diastereoisomers (**135ea**:**135eb**, 60:40) for the double bond generated from the H-W-E reactions. All

these dendralenes **135a-e** were stable towards D-A cyclodimerization at ambient temperature.

The structure of the dendralene **135a** was confirmed by single crystal X-ray crystallography (**Figure 3.2**) which also revealed its interesting conformational preferences in the solid state. The double bonds at first and third positions are in quasi *s-cis* conformation with a dihedral angle of 52.2°, whereas the double bonds at third and fourth positions are in *s-trans* conformation as was observed in case of silyl dendralene **120** in **Chapter 2**. This corroborated the DFT calculations[71] done by Sherburn *et al*. for the unsubstituted [3]dendralenes, wherein one dienic component exists predominantly as *s-cis* conformation and the other dienic unit as *s-trans* conformation. The present X-ray crystal structure of dendralene **135a** confirmed it for the first time.

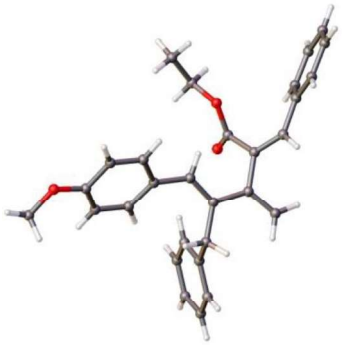
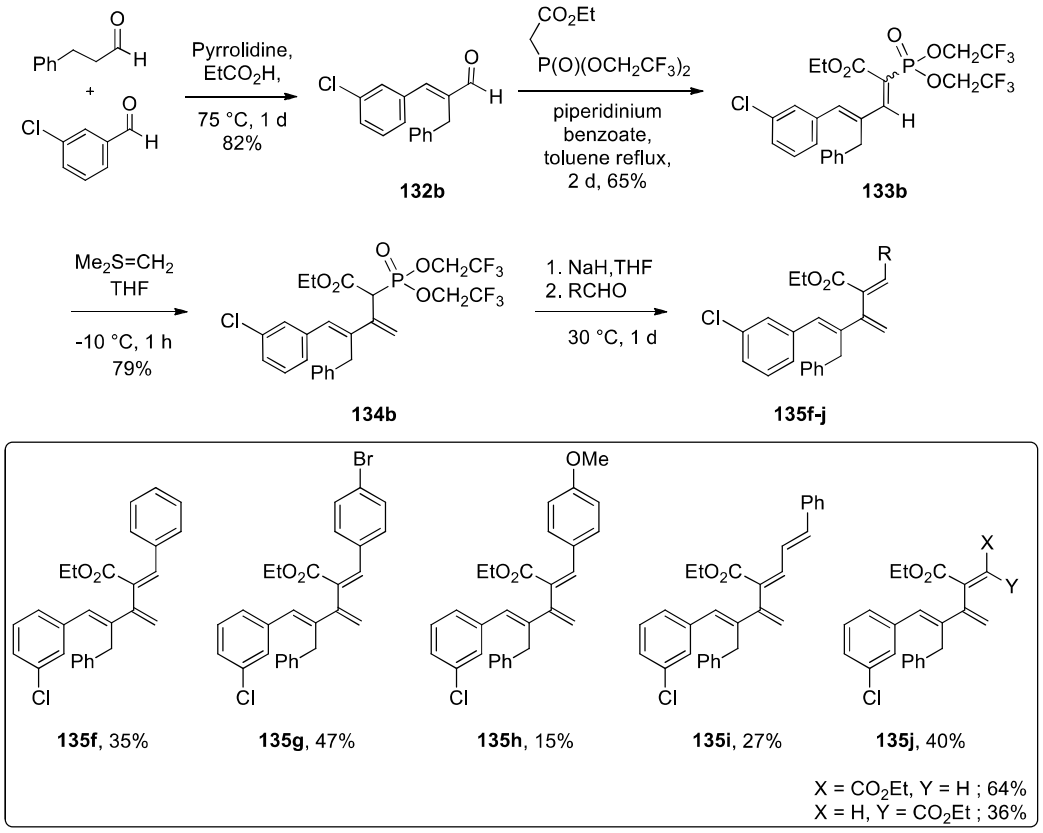


Figure 3.2 X-ray structure of **135a**

To examine the electronic effect of the terminal substituents on the stability of [3]dendralenes, it was decided to have a mildly electron withdrawing 3-chlorophenyl substituent at the fifth position. To achieve this, on the similar lines to aldehyde **132a**, 2-benzyl-3-(3-chlorophenyl) prop-2-enal **132b** was prepared by a selective aldol condensation of 3-phenylpropanal with 10 equiv. of 3-chlorobenzaldehyde in 82%

yield (**Scheme 3.3**). Once again, Knoevenagel condensation of this aldehyde **132b** with ethyl bis-(2,2,2-trifluroethyl)-phosphonoacetate furnished dienic phosphonate **133b** in 65% yield as an inseparable 6:4 mixture of *E*/*Z* isomers. This phosphonate **133b** was reacted with dimethylsulfonium methylide which provided butadien-2-ylphosphonoacetate **134b** in 79% yield. This phosphonoacetate **134b** subsequent to deprotonation with NaH was treated with different aldehydes which resulted in generation of another series of 1,2,4,5-tetrasubstituted [3]dendralenes (**135f-j**) in moderate yields.[73]

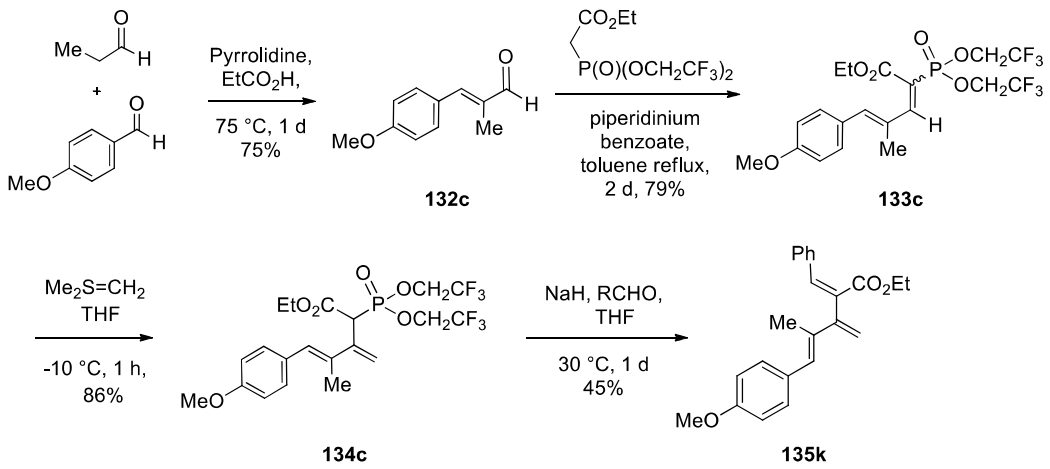


Scheme 3.3 Synthesis of tetra substituted [3]dendralenes

The stereoselectivity of the H-W-E reaction in all these cases once again was very high except for **135j** which was produced as an inseparable mixture of *Z*/*E* isomers in

a ratio of 64/36. Once again, these dendralenes are stable towards D-A cyclodimerization thus showing that change in electronic nature of the terminal substituents does not jeopardize their stabilities.

Moreover, it can be observed that as the substituent at fourth position was changed from silyl to benzyl there was no difference in the stability of these [3]dendralenes. In order to know the minimum size of this fourth position substituent, which would grant stability to the [3]dendralenes, it was aimed to reduce the size of this substituent even further to a methyl group. For this purpose, synthesis was started with the selective aldol condensation of propionaldehyde with *p*-anisaldehyde which provided prop-2-enal **132c** in 75% yield (**Scheme 3.4**). This aldehyde **132c** was converted to phosphonate **133c** as an inseparable 1/1 mixture of diastereoisomers by the Knoevenagel condensation with bis-(2,2,2-trifluroethyl)-phosphonoacetate catalyzed by piperidinium benzoate in refluxing toluene. Addition of dimethylsulfonium methylide to this phosphonate **133c** resulted in formation of butadien-2-ylphosphonoacetate **134c** in 86% yield. H-W-E reaction of this phosphonoacetate **134c** with benzaldehyde subsequent to deprotonation with sodium hydride furnished the desired [3]dendralene **135k** in 45% yield featuring a methyl group at fourth position. This dendralene **135k** also like the previous dendralenes **135a-j** was stable at room temperature. Thus one can observe that when the substituent at fourth position is a proton the dendralenes are extremely unstable but the moment this proton is replaced by a methyl group they are very stable at room temperature.[73]



Scheme 3.4 Synthesis of [3]dendralene **135k**

In earlier [3]dendralenes **109**, **112** (**Scheme 2.5**, **2.6** in **Chapter 2**)[66,67] there were two conjugating terminal substituents and one internal substituent at second position. None of these dendralenes could be isolated as they underwent D-A cyclodimerisation. In the present study, the [3]dendralene **131** had one conjugating terminal substituent at fifth position and one substituent at second position which was short lived. Whereas the [3]dendralenes **135a-k** had two conjugating terminal substituents and two substituents at the second and fourth positions and were stable. Contrary to Sherburn's conclusion which states that terminal conjugating substituents accelerate cyclodimerization whereas internal substituents have little effect on the dimerization reactivity[71,72] these dendralenes **135a-k** despite having two terminal conjugating substituents were highly stable and could be stored for long period in neat condition. This enhanced stability was rendered by the two substituents at the second and fourth positions. Hence, it was inferred that the internal substituents also have a discernible role in governing the stability of [3]dendralenes (**Figure 3.3**).

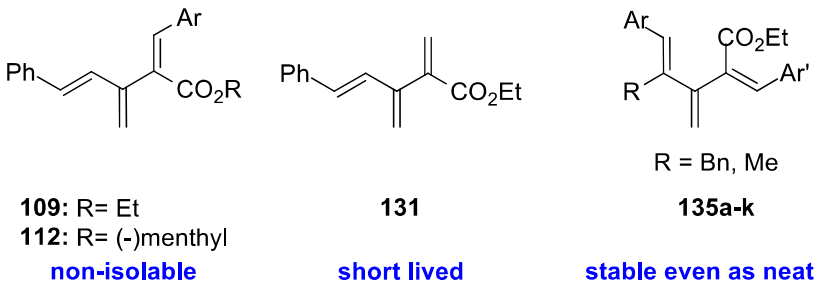
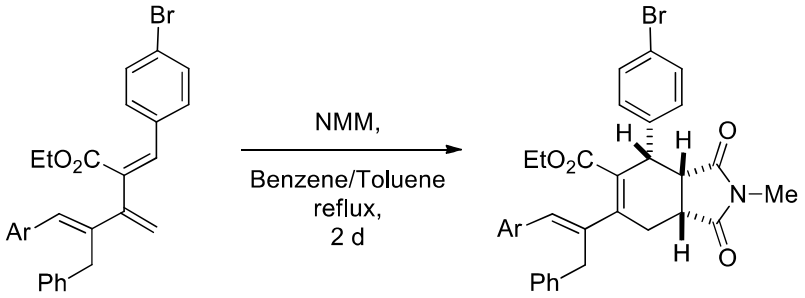


Figure 3.3 Stability of variously substituted [3]dendralenes

3.2.2 Diels-Alder reaction of substituted [3]dendralenes

After accomplishing the goal of synthesizing stable substituted [3]dendralenes **135a-k** it was next aimed to examine their reactivity for intermolecular D-A reaction with NMM as a representative dienophile. When dendralene **135b** was reacted with 1.0 molar equivalent of NMM in refluxing benzene, it furnished a mixture of stereoisomeric D-A adducts amongst which the major stereoisomer **136** (69%) was easily separated from the mixture whereas the minor isomers could not be identified (**Scheme 3.5**).[73] This major isomer **136** was found to be *endo*-isomer as confirmed by X-ray crystallography (**Figure 3.4**). It is noticeable that the D-A reaction had taken place at the diene incorporating double bonds at first and third positions thus indicating that these two double bonds exist in *s-cis* conformation in solution also as was observed in solid state by the X-ray structure of **135a** (**Figure 3.2**). It is noteworthy that the electronically rich diene constituted by double bonds at third and fourth positions was unable to participate in the D-A reaction owing to *s-trans* conformation that was preferred due to steric bulk of the benzyl group which results in high barrier of *s-trans* ⇆ *s-cis* interconversion. This allowed the electronically deactivated diene to participate in the D-A reaction.

In order to examine if the electronic effect from the terminal conjugating groups had any role to govern the stereo/regiochemical outcome of the D-A reaction, [3]dendralene **135g** was reacted with 1.0 molar equivalent of NMM in refluxing toluene which furnished a mixture of D-A adducts. From the mixture of products, the major diastereoisomer **137** was obtained in 62% yield (**Scheme 3.5**) as *endo*-isomer which was confirmed by single crystal X-ray crystallography (**Figure 3.4**).[73] The minor isomers could not be identified. Once again the D-A reaction took place at the diene incorporating double bonds at first and third positions thus indicating that these two double bonds exist in *s-cis* conformation in solution state. The electronic effect of substituent at fifth position aryl group was not observed because the diene incorporating double bonds at third and fourth positions comprising this substituent probably preferred *s-trans* conformation.



135 b, **g**

136: Ar = 4-$MeOC_6H_4$, 69%
137: Ar = 3-ClC_6H_4, 62%

Scheme 3.5 D-A reaction of [3]dendralenes **135b,g**

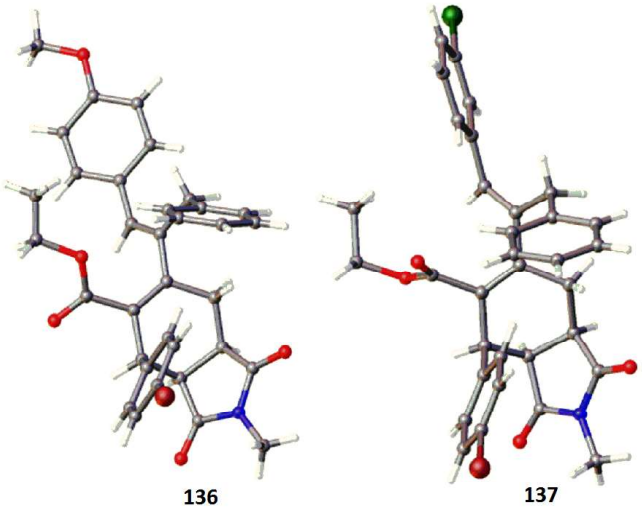
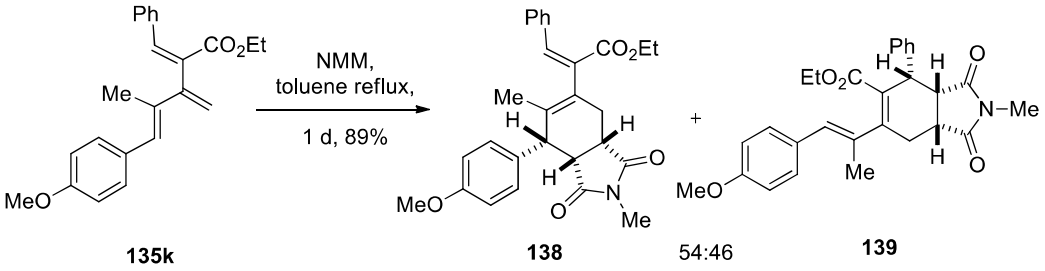


Figure 3.4 X-ray structures of **136**, **137**

To curb the steric effect, instead of 4-benzyl substituted [3]dendralene, 4-methyl substituted [3]dendralene **135k** was reacted with NMM which resulted in formation of regioisomeric adducts **138** and **139** in a ratio of 54:46, respectively (**Scheme 3.6**).[73] This suggested that in dendralene **135k** the steric hindrance was moderated thus both the dienes have almost equal preference for *s-cis* conformation and hence participated equally in the D-A reaction.



Scheme 3.6 D-A reaction of dendralene **135k**

The D-A adducts **138** and **139** could not be separated. Thus, their structural analysis was performed on a 54:46 mixture of the two regioisomers, where most of the signals

were clearly distinguishable in ^{1}H NMR spectrum. Firstly, the peaks were assigned with help of ^{1}H/^{1}H COSY interactions from the inseparable mixture. Then, the stereochemistry and regiochemistry of these products **138** and **139** was ascertained on the basis of ^{1}H/^{1}H ROESY interactions (for COSY and ROESY spectra and their analysis see the appendix at end of the chapter).

For isomer **138**, strong ROESY interactions between protons at δ 3.85 (ArC*H*) ↔ δ 7.08 (*ortho* H of Ar), and between δ 6.77 (PhC*H*) ↔ δ 7.40-7.31 (*ortho* H of Ph) indicated that diene component comprise of double bonds at third and fourth positions participated in the D-A reaction. The ROESY interaction between protons at δ 3.85 (ArC*H*) and δ 3.17-3.13 (NCOC*H*CH$_2$) further supported the *endo* addition of NMM (**Figure 3.5**).

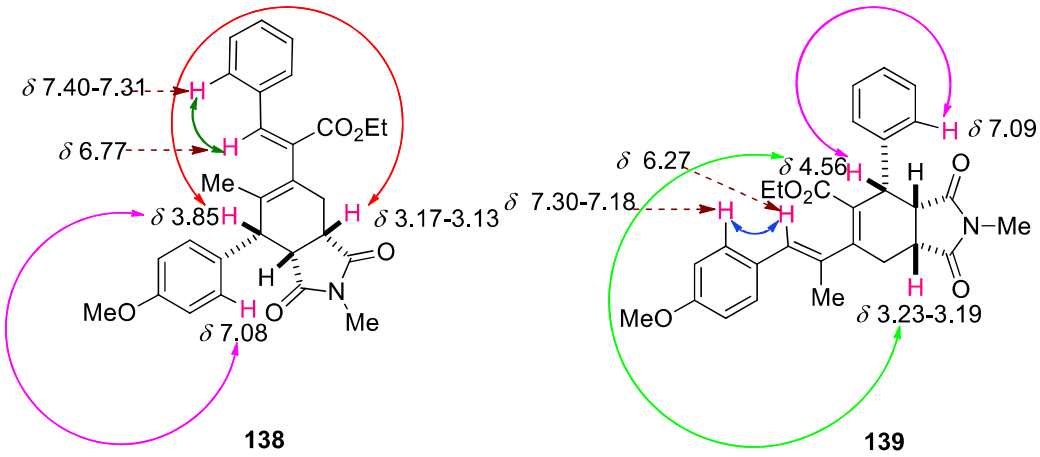
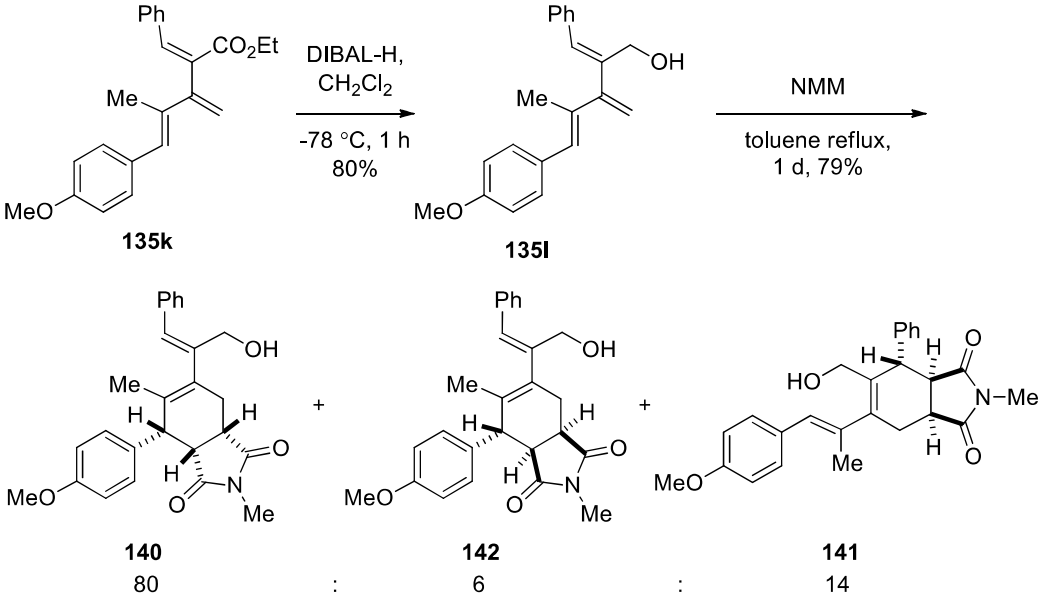


Figure 3.5 ^{1}H/^{1}H ROESY interactions of **138** and **139**

For isomer **139**, strong ROESY interactions between protons at δ 4.56 (PhC*H*) ↔ δ 7.09 (*ortho* H of Ph) and between δ 6.27 (ArC*H*) ↔ δ 7.30-7.18 (*ortho* H of Ar) indicated that diene component comprising of double bonds at first and third positions

participated in D-A reaction and interaction between protons at δ 4.56 (PhC*H*) $\leftrightarrow$ δ 3.23-3.19 (NCOC*H*CH_2) suggested the *endo* nature of the product (**Figure 3.5**).

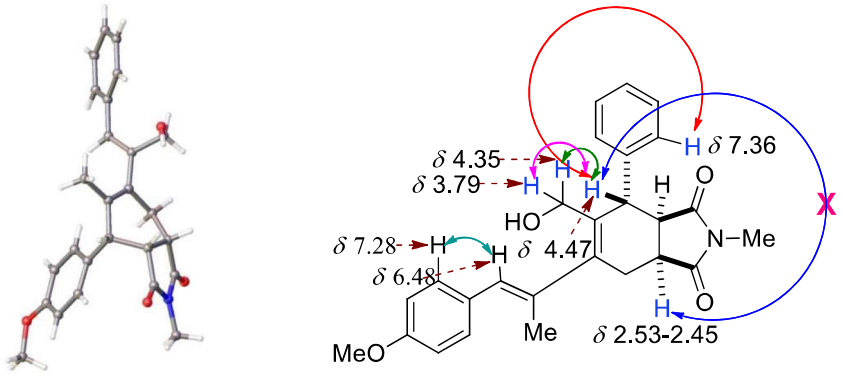
To address the electronic effect of the substituents on the D-A reaction, the ester functionality in the dendralene **135k** was reduced using DIBAL-H to obtain a new alcoholic [3]dendralene **135l** (**Scheme 3.7**). When **135l** was reacted with 1.0 molar equivalent of NMM in refluxing toluene, it furnished a mixture of three isomers **140**, **141** and **142** in a ratio of 80:14:6 respectively, from which all the individual isomers were separated by column chromatography.[73]



Scheme 3.7 D-A reaction of dendralene **135l**

The structure of **140** was established by single crystal X-ray crystallography (**Figure 3.6 a**). The structure of **142** was assigned by studying the ^{1}H NMR of **140** and **142**. Both the spectra showed similarity except that ArC*H* in **142** was a singlet thus suggesting *trans* relationship of the two protons *viz*. ArC*H* and ArCHC*H*. The structure of **141** was ascertained on the basis of ^{1}H/^{1}H COSY and ROESY interactions

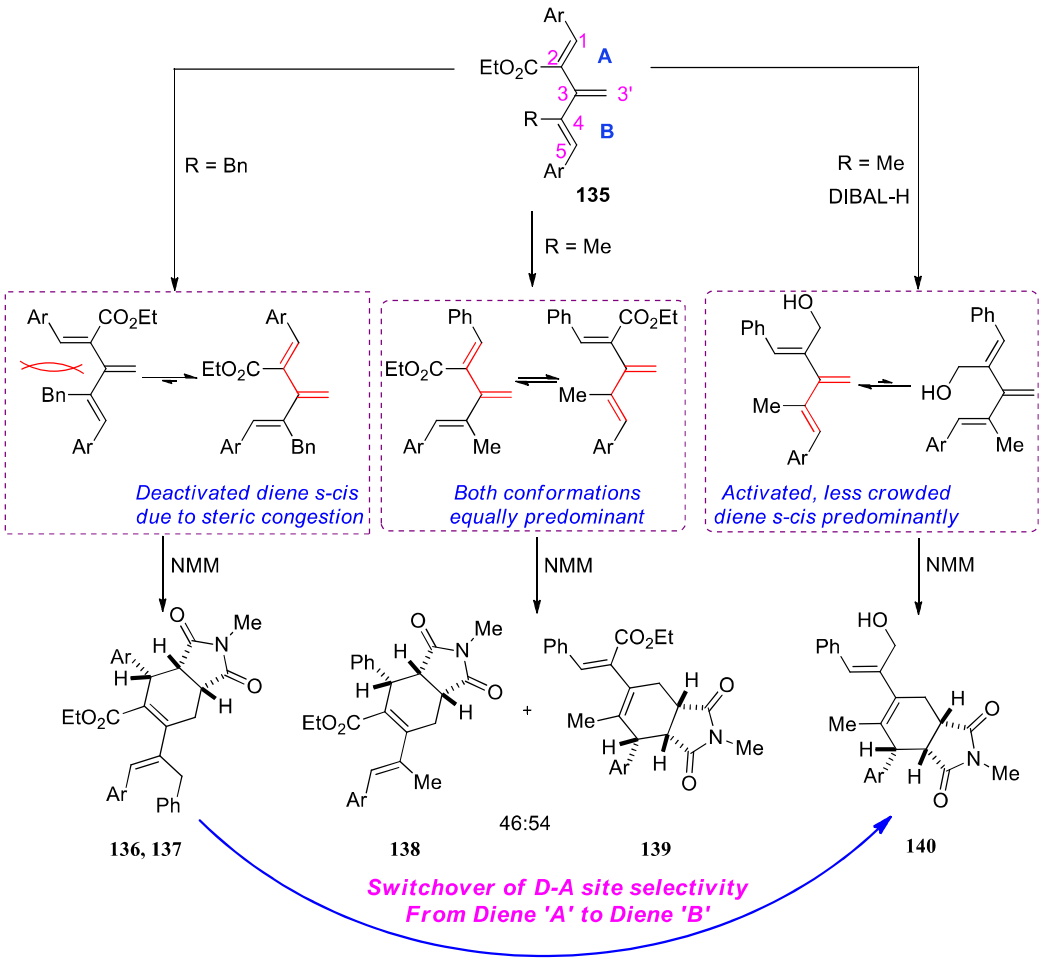
(For analysis see the appendix at end of the chapter). The positive ROESY interactions between protons at δ 4.47 (PhC*H*) ↔ δ 7.36 (*ortho* H of Ph), between δ 6.48 (ArC*H*) ↔ δ 7.28 (*ortho* H of Ar), between δ 4.47 (PhC*H*) ↔ 4.37(HOCH_AH_B), and between δ 4.47 (PhC*H*) ↔ δ 3.79 (HOCH_AH_B) were indicative of the depicted regiochemistry whereas the absence of ROESY interaction between protons at δ 4.47 (PhC*H*) ↔ δ 2.53-2.45 (NCOC*H*CH_2) suggested *exo* nature of the product (**Figure 3.6 b**). The main difference between structures **141** (**Figure 3.6 b**) and **139** (**Figure 3.5**) was the stereochemistry at the ring junction. In case of compound **139**, a positive ROESY peak due to *cis* disposition of protons at the ring junction and benzylic proton was observed. Therefore in case of compound **141**, on the basis of analogy from the absence of ROESY peak between protons at δ 4.47 (PhC*H*) ↔ δ 2.53-2.45 (NCOC*H*CH_2) it was concluded that the protons at ring junction are *trans* with respect to the benzylic proton. This apparently *exo* product **141** probably was not due to *exo*-mode D-A reaction but due to small amount of double bond isomerisation during heating which then underwent *endo*-selective D-A with NMM. No *endo*-isomer with this regioselectivity was found in the reaction mixture which suggested that the diene consisting of the double bond at first and third positions of dendralene **135l** (**Scheme 3.7**) preferred *s-trans* conformation. Thus the stereoselectivity i.e. *endo:exo* ratio (**140**:**142**) was 93:7, whereas the regioselectivity (**140**,**142**:**141**) was 86:14. It's interesting to note that diene encompassing double bonds at third and fourth positions predominantly participated in the D-A reaction.



a **b**

Figure 3.6 (a) X-ray structure of **140**; (b) ROESY interactions of **141**

In these D-A reactions, unexpected regioselectivity was observed. When the fourth position substituent was benzyl group, diene '**A**' exclusively participated in D-A reaction even though it appeared electronically deactivated. Both the dienes '**A**' and '**B**' equally participated in D-A reaction when the fourth position substituent was a methyl group. In case of dendralene **135l** surprisingly the diene '**B**' predominantly participated in the D-A reaction. There was a switchover of D-A site selectivity from diene '**A**' to diene '**B**' as the substituents on the [3]dendralenes were changed (**Scheme 3.8**).



Scheme 3.8 Effect of the substituent on D-A regioselectivity

Despite our repeated efforts, these Diels-Alder adducts **136**, **137**, **140** and the mixture of **138** and **139** did not undergo second D-A reaction with several dienophiles. This failure could be mainly attributed to the steric effects of the substituents which perhaps obstruct adoption of *s-cis* conformation of the dienic system in the D-A adducts which is a precondition for D-A reaction. The X-ray crystal structures of **136**, **137** and **140** also supported this fact where it is clearly seen that the diene component is in a *gauche* conformation with a dihedral angle ranging from 45-79°.

3.3 Conclusions

In conclusion, the goal of the synthesis of stable and highly functionalized [3]dendralenes was achieved. Substituents at second and third positions of [3]dendralenes drastically diminished their tendency for cyclodimerisation irrespective of their electronic nature thus grant stability. This was due to D-A unreactive *s-trans* conformation of the dienic components caused by the internal substituents. Steric effect outweighed electronic activation/deactivation in the D-A reactions to control the regioselectivity. There was a switch over of regioselectivity as the steric bulk of the internal groups changed. Regrettably none of these D-A adducts underwent a subsequent D-A reaction.

3.4 Experimental section

3.4.1 General Details: As described in **Chapter 2**

NMR study: ^{1}H NMR spectra were recorded on 200, 300, 500, 600 MHz and ^{13}C NMR spectra were recorded with 50, 75, 125, 150 MHz spectrometers using $CDCl_3$, C_6D_6, CD_3COCD_3 as the solvents. The spectra were referenced to residual chloroform (δ 7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C), partially deuterated acetone (δ 2.05 ppm, ^{1}H; 29.9, 206.7 ppm, ^{13}C), partially deuterated benzene (δ 7.16 ppm, ^{1}H; 128.4 ppm, ^{13}C). For the interpretation of ^{1}H decouple ^{13}C spectrum, the number of expected carbons are provided in the parenthesis.

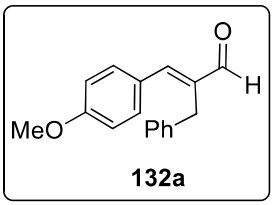
3.4.2 General procedures and characterization data of products

General procedure for aldehydes 132a-c

A solution of 3-phenylpropanal (3.2 mL, 24.3 mmol, 1 equiv), 4-methoxybenzaldehyde (29.5 mL, 243 mmol, 10 equiv), pyrrolidine (0.6 mL, 7.3

mmol, 0.3 equiv) and propionic acid (0.55 mL, 7.3 mmol, 0.3 equiv) were heated at 75 ºC for 24 h under argon atmosphere. Excess 4-methoxybenzaldehyde was distilled out and the residue was purified by column chromatography (petroleum ether-EtOAc; 95:5) to provide the aldehyde **132a** (1.96 g, 32%) as orange coloured viscous liquid. The same procedure was followed for the preparation of compounds **132b,c**.

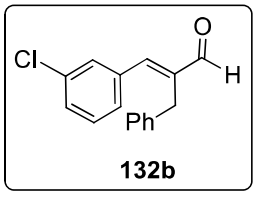
(*E*)-2-Benzyl-3-(4-methoxyphenyl)acrylaldehyde (**132a**)



132a

R_f (hexane-EtOAc, 90:10) = 0.35; IR ν_{max}: 3058, 3028, 3002, 2954, 2931, 2908, 2836, 2715, 2566, 1683, 1667, 1624, 1592, 1508, 1495, 1453, 1305, 1252, 1210, 1175, 1148, 1032, 956, 887, 828, 736, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.66 (s, 1 H, CHO), 7.46 (d, J = 9.0 Hz, 2 H, Ar), 7.44 (s, 1 H, ArC*H*), 7.27-7.19 (m, 5 H, Ph), 6.90 (d, J = 8.8 Hz, 2 H, Ar), 3.97 (s, 2 H, PhCH_2), 3.82 (s, 3 H, OCH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.9, 161.0, 151.5, 138.2, 137.9, 131.8 (2 C), 128.4 (2 C), 127.7 (2 C), 126.9, 126.0, 114.2 (2 C), 55.1, 30.1 ppm.

(*E*)-2-Benzyl-3-(3-chlrophenyl)acrylaldehyde (**132b**)

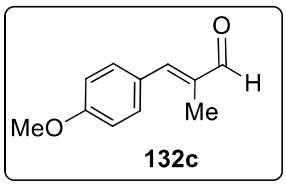


132b

Following the general procedure, isolated yield (1.36 g, 82%) as yellow coloured viscous liquid; R_f (hexane-EtOAc, 90:10) = 0.4; IR ν_{max}: 3083, 3061, 3027, 2927, 2826, 2717, 1682, 1627, 1599, 1561, 1494, 1474, 1453, 1394, 1206, 1142, 1077, 956,

890, 784, 737, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.68 (s, 1 H, CHO), 7.45-7.11 (m, 10 H, Ar, Ph, C=CH), 3.90 (s, 2 H, PhCH_2) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.7, 149.4, 141.7, 138.0, 136.1, 134.7, 130.0, 129.7, 129.5, 128.6 (2 C), 127.9 (2 C), 127.5, 126.3, 30.3 ppm.

(*E*)-3-(4-Methoxyphenyl)-2-methylacrylaldehyde (132c)



132c

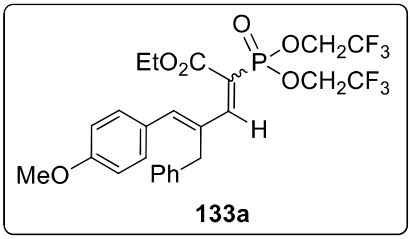
Following the general procedure, isolated yield (5.2 g, 75%) as yellow coloured viscous liquid; R_f (hexane-EtOAc, 80:20) = 0.48; IR ν_{max}: 3007, 2961, 2935, 2837, 2716, 1682, 1622, 1598, 1571, 1514, 1443, 1407, 1321, 1304, 1258, 1177, 1116, 1034, 1014, 763, 571, 562, 538 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.54 (s, 1 H, CHO), 7.53 (d, J = 8.4 Hz, 2 H, Ar), 7.19 (s, 1 H, ArC*H*), 6.97 (d, J = 8.4 Hz, 2 H, Ar), 3.86 (s, 3 H, OCH_3), 2.08 (s, 3 H, C=CCH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.3, 160.6, 149.7, 136.0, 131.9 (2 C), 127.8, 114.1 (2 C), 55.2, 10.7 ppm.

General procedure for phosphonates 133a-c

A solution of aldehyde **132a** (2.4 g, 9.5 mmol, 1 equiv), ethyl bis-(2,2,2-trifluroethyl)-phosphonoacetate (3.6 g, 9.5 mmol, 1 equiv) and piperdinium benzoate (0.39 g, 1.9 mmol, 0.2 equiv) in toluene (25 mL) was heated under reflux for 2 d in a flask fitted with Dean-Stark apparatus. The reaction mixture was then brought to room temperature, diluted with water and extracted with ethyl acetate. The organic extract was concentrated under the reduced pressure and the residue purified by column chromatography (petroleum ether-EtOAc; 85:15) to give phosphonate **133a** as

inseparable mixture of two *E/Z* isomers (3.15 g, 85%) as brown coloured viscous liquid. The same procedure was followed for the preparation of compounds **133b, c**.

(2*E*/*Z*,4*E*)-Ethyl 4-benzyl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-5-(4-methoxyphenyl)penta-2,4-dienoate (**133a**)

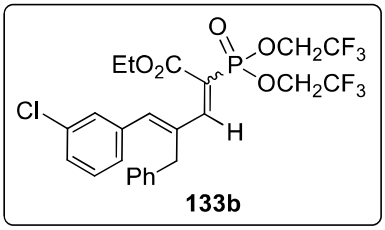


133a

R_f (hexane-EtOAc, 80:20) = 0.29; IR ν_{max}: 3063, 3028, 3002, 2970, 2939, 2907, 1720, 1605, 1579, 1508, 1496, 1455, 1419, 1296, 1251, 1175, 1104, 1071, 1032, 962 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, J =25.8 Hz, 1 H, ArC=CC*H*=C, 2*Z*), 7.40 (d, J = 25.8 Hz, 1 H, ArC=CC*H*=C, 2*E*), 7.29-7.12 (m, 14 H, Ph, Ar), 6.89 (d, J = 8.4 Hz, 2 H, Ar, 2*Z*), 6.87 (s, 1 H, ArC*H*, 2*Z*), 6.86 (d, J = 9.0 Hz, 2 H, Ar, 2*E*), 6.83 (s, 1 H, ArC*H*, 2*E*), 4.34-4.08 (m, 8 H, 2 × OCH_2CF_3), 4.24 (q, J = 7.2 Hz, 2 H, OCH_2CH_3, 2*Z*), 3.99 (q, J = 7.2 Hz, 2 H, OCH_2CH_3, 2*E*), 3.98 (s, 2 H, $PhCH_2$, 2*Z*), 3.82 (s, 3 H, OCH_3, 2*Z*). 3.80 (s, 3 H, OCH_3, 2*E*), 3.79 (s, 2 H, $PhCH_2$, 2*E*), 1.28 (d, J = 7.2 Hz, 3 H, OCH_2CH_3, 2*Z*), 1.09 (d, J = 7.2 Hz, 3 H, OCH_2CH_3, 2*E*) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 164.3 (d, J = 13.9 Hz, 2*Z*), 163.8 (d, J = 14.8 Hz, 2*E*), 160.1 (2 C), 156.1 (d, J = 6.3 Hz, 2*Z*), 154.8 (d, J = 7.2 Hz, 2*E*), 143.1 (2*Z*), 139.6 (2*Z*), 138.5 (2*E*), 138.0 (2*Z*), 133.5 (d, J = 19.9 Hz, 2*E*), 133.2 (d, J = 21.3 Hz, 2*Z*), 131.4 (2 C, 2*E*), 131.1 (2 C, 2*Z*), 128.9 (2 C, 2*E*), 128.4 (2 C, 2*Z*), 128.3 (3 C, 2*E*), 128.1 (2 C, 2*Z*), 127.8 (2*E*), 126.5 (2*E*), 126.3 (2*Z*), 122.4 (dq, J = 275.8, 9.7 Hz, 4 C), 120.6 (d, J = 186.4 Hz, 2*E*), 118.5 (d, J = 184.3 Hz, 2*Z*), 114.0 (2 C, 2*Z*), 113.8 (2 C, 2*E*), 62.3 (q, J = 37.9 Hz, 2 C, 2*Z*), 62.2 (q, J = 37.9 Hz, 2 C, 2*E*), 61.8 (2 C), 55.1 (2 C), 41.3

(2*E*), 34.8 (2*Z*), 13.6 (2*E*), 13.3 (2*Z*) ppm; Anal. Calc. for $C_{25}H_{25}F_6O_6P$: C, 53.01; H, 4.45. Found: C, 53.10; H, 4.20.

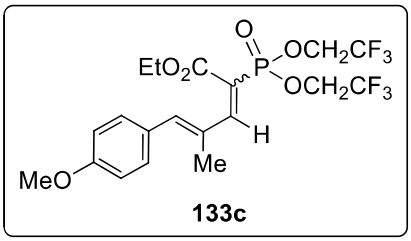
(2*E*/*Z*,4*E*)-Ethyl 4-benzyl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-5-(3-chlorophenyl)penta-2,4-dienoate (133b)



133b

Following the general procedure, inseparable mixture 60:40 of two *E/Z* isomers were isolated, yield (1.42 g, 65%) as brown coloured viscous liquid; R_f (hexane-EtOAc, 80:20) = 0.45; IR ν_{max}: 3064, 2982, 1723, 1594, 1495, 1454, 1419, 1374, 1173, 1070, 963, 879 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 25.5, 1.5 Hz, 1 H, ArCHCC*H*=C, 2*Z*), 7.36 (dd, *J* = 25.8, 1.2 Hz, 1 H, ArCHCC*H*=C, 2*E*), 7.30-7.05 (m, 18 H, Ar, Ph), 7.04 (s, 1 H, ArC*H*, 2*E*), 6.65 (s, 1 H, ArC*H*, 2*Z*), 4.35-4.12 (m, 10 H, 2 × OC$H_2$$CF_3$, OC$H_2$$CH_3$, 2*Z*), 4.08 (q, *J* = 7.2 Hz, 2 H, OC$H_2$$CH_3$, 2*E*), 3.91 (s, 2 H, PhCH_2, 2*E*), 3.76 (s, 2 H, PhCH_2, 2*Z*), 1.27 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3, 2*Z*), 1.15 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3, 2*E*) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1 (d, *J* = 13.6, 2*E*), 163.4 (d, *J* = 14.8, 2*Z*), 155.2 (d, *J* = 6.5, 2*E*), 154.7 (d, *J* = 6.8, 2*Z*), 139.0 (2*E*), 137.8 (2*E*), 137.6 (2*Z*), 137.4 (2*E*), 137.1 (2*Z*), 136.6 (d, *J* = 21.0, 2*E*), 135.0 (2*Z*), 134.4 (d, *J* = 19.1, 2*Z*), 129.9 (2*E*), 129.7 (2*Z*), 129.3, 129.1 (4 C), 128.6 (5 C), 128.3 (4 C), 127.6 (2*Z*), 127.1 (2*E*), 126.9 (2*Z*), 126.7 (2*E*), 123.3 (d, *J* = 185.6, 2*Z*), 122.4 (dq, *J* = 266.6, 9.3, 4 C), 121.3 (d, *J* = 183.6, 2*E*), 62.4 (q, *J* = 37.7, 4 C), 62.1 (2 C), 42.0 (2*Z*), 35.3 (2*E*), 13.7 (2*Z*), 13.6 (2*E*) ppm; Anal. Calc. for $C_{24}H_{22}ClF_6O_5P$: C, 50.50; H, 3.88. Found: C, 50.37; H, 3.59.

(2*E*/*Z*,4*E*)-Ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-5-(4-methoxyphenyl)-4-methylpenta-2,4-dienoate (133c)



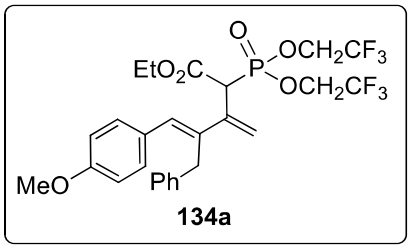
133c

Following the general procedure, inseparable mixture 1:1 of two E/Z isomers were isolated, yield (6.14 g, 79%) as brown coloured viscous liquid; R_f (hexane-EtOAc, 80:20) = 0.25; IR ν_{max} : 2965, 2937, 2909, 1720, 1606, 1578, 1509, 1305, 1258, 1175, 1101, 1071, 960 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, J = 26.4 Hz, 1 H, ArC=CCH=C, 2*Z*), 7.39 (d, J = 25.8 Hz, 1 H, ArC=CCH=C, 2*E*), 7.34 (d, J = 9.0 Hz, 2 H, Ar, 2*E*), 7.15 (d, J = 8.4 Hz, 2 H, Ar, 2*Z*), 6.94 (s, 1 H, ArC*H*, 2*E*), 6.92 (d, J = 9.0 Hz, 2 H, Ar, 2*E*), 6.89 (d, J = 8.4 Hz, 2 H, Ar, 2*Z*), 6.87 (s, 1 H, ArC*H*, 2*Z*), 4.46-4.37 (m, 8 H, 2 × OCH_2CF_3), 4.30 (q, J = 7.2 Hz, 4 H, OCH_2CH_3), 3.84 (s, 3 H, OCH_3, 2*E*), 3.82 (s, 3 H, OCH_3, 2*Z*), 2.04 (s, 3 H, C=CCH_3, 2*E*), 2.03 (s, 3 H, C=CCH_3, 2*Z*), 1.33 (t, J = 7.2 Hz, 6 H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1 (d, J = 13.2 Hz, 2*E*), 164.7 (d, J = 16.2 Hz, 2*Z*), 160.1 (2 C), 156.6 (d, J = 7.2 Hz, 2*E*), 152.1 (d, J = 7.1 Hz, 2*Z*), 144.3 (2*E*), 140.7 (2*Z*), 131.7 (4 C), 131.6 (2*Z*), 131.3 (2*E*), 128.5 (2*Z*), 128.3 (2*E*), 122.5 (dq, J = 266.4, 9.5 Hz, 4 C), 120.0 (d, J = 189.9 Hz, 2*Z*), 116.7 (d, J = 187.5 Hz, 2*E*), 114.0 (4 C), 62.5 (dq, J = 39.2, 3.6 Hz, 4 C), 62.0 (2 C), 55.2 (2 C), 15.6 (2 C), 13.7 (2 C) ppm; Anal. Calc. for $C_{19}H_{21}F_6O_6P$: C, 46.54; H, 4.32. Found: C, 46.48; H, 3.98.

General procedure for butadien-2-ylphosphonoacetate 134a-c

n-BuLi (0.89 mL, 1.6 M, 1.43 mmol, 3 equiv) was added drop wise to a stirred suspension of trimethylsulfonium iodide (0.29 g, 1.43 mmol, 3 equiv) in THF (10 mL) at -10 ºC under argon atmosphere and stirred for 20 min at the same temperature. Later, a solution of dienic phosphonate **133a** (0.27 g, 0.47 mmol, 1 equiv) in THF (5 mL) was cannulated into the reaction mixture and stirred for 1 h. The temperature of the reaction mixture was allowed to rise slowly to room temperature followed by dilution of the reaction mixture with water and extraction with ethyl acetate. The organic layer was concentrated and column chromatography (petroleum ether-EtOAc; 85:15) was done to obtain the diene **134a** (0.24 g, 87%) as pale yellow liquid. The same procedure was followed for the preparation of compounds **134b**,**c**.

(4*E*)-Ethyl 4-benzyl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-5-(4-methoxyphenyl)-3-methylene-4-pentenoate (134a)

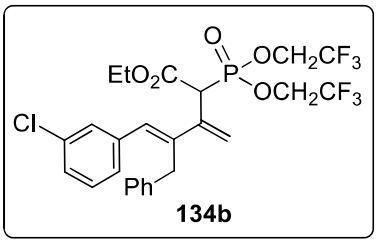


134a

R_f (hexane-EtOAc, 80:20) = 0.34; IR ν_{max}: 3058, 3024, 2969, 2938, 2911, 2840, 1729, 1649, 1602, 1574, 1542, 1510, 1456, 1417, 1369, 1299, 1258, 1173, 1104, 1070, 1032, 965, 878, 844, 699, 660 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.30-7.27 (m, 2 H, Ph), 7.21-7.20 (m, 5 H, Ph, Ar), 6.94 (s, 1 H, ArC*H*), 6.83 (d, *J* = 8.4 Hz, 2 H, Ar), 5.57 (d, *J* = 4.8 Hz, 1 H, C=CH_AH_B), 5.51 (d, *J* = 4.8 Hz, 1 H, C=CH_AH_B), 4.48-4.36 (m, 4 H, 2 × OCH_2CF_3), 4.34 (d, *J* = 24 Hz, 1 H, POCH), 4.17 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 3.95 (d, *J* = 16.8 Hz, 1 H, PhCH_AH_B), 3.88 (d, *J* = 16.8 Hz, 1 H,

PhCH$_A$$H_B$), 3.79 (s, 3 H, OCH$_3$), 1.22 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.1, 158.9, 139.2, 137.7, 135.6, 130.8, 129.9 (2 C), 129.2 (d, J = 9.4 Hz), 128.5 (2 C), 128.0 (2 C), 126.0, 122.8 (dq, J = 181.3, 9.1 Hz, 2 C), 119.8 (d, J = 8.5 Hz), 113.8 (2 C), 63.5-62.0 (m, 2 C), 62.3, 55.1 (2 C), 48.1 (d, J = 145.3 Hz), 34.6, 13.7 ppm; ^{31}P NMR (121.49 MHz, CDCl$_3$): δ 23.39 ppm; Anal. Calc. for $C_{26}H_{27}F_6O_6P$: C, 53.80; H, 4.69. Found: C, 53.98; H, 4.93.

(4*E*)-Ethyl 4-benzyl-2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-5-(3-chlorophenyl)-3-methylene-4-pentenoate (**134b**)

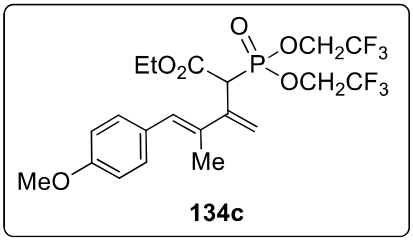


134b

Following the general procedure, isolated yield (0.18 g, 79%) as pale yellow liquid; R_f (hexane-EtOAc, 80:20) = 0.25; IR ν_{max}: 3063, 3028, 2968, 2932, 2878, 1734, 1718, 1603, 1594, 1560, 1497, 1472, 1456, 1417, 1297, 1264, 1170, 1100, 1070, 962 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 7.30-7.15 (m, 9 H, Ar, Ph), 6.92 (s, 1 H, ArCH), 5.64 (d, J = 4.8 Hz, 1 H, C=CH_AH$_B$), 5.58 (d, J = 5 Hz, 1 H, C=CH$_A$$H_B$), 4.50-4.06 (m, 5 H, 2 × OCH_2CF$_3$, POCH), 4.17 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 3.93 (d, J = 16.6 Hz, 1 H, PhCH_AH$_B$), 3.82 (d, J = 16.4 Hz, 1 H, PhCH$_A$$H_B$), 1.22 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (50 MHz, CDCl$_3$): δ 167.0 (d, J = 1.5 Hz), 138.8 (d, J = 6 Hz), 138.7, 138.6, 137.4 (d, J = 8 Hz), 134.2, 129.8, 129.7, 128.7, 128.6 (2 C), 128.0 (2 C), 127.5, 126.5, 126.3, 120.4 (dq, J = 276, 8 Hz, 2 C) 121.2 (d, J = 9 Hz), 62.8, (dq, J = 32, 6 Hz, 2 C), 62.5, 48.3 (d, J = 145 Hz), 34.6, 13.8 ppm; ^{31}P NMR (121.49

MHz, $CDCl_3$): δ 23.10 ppm; Anal. Calc. for $C_{25}H_{24}ClF_6O_5P$: C, 51.34; H, 4.14. Found: C, 51.37; H, 4.39.

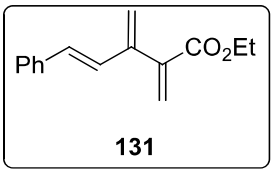
(4*E*)-Ethyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]-5-(4-methoxyphenyl)-4-methyl-3-methylene-4-pentenoate (134c)



134c

Following the general procedure, isolated yield (0.7 g, 86%) as pale yellow liquid; R_f (hexane-EtOAc, 80:20) = 0.3; IR ν_{max}: 2971, 2938, 2914, 2838, 1730, 1609, 1509, 1460, 1415, 1371, 1302, 1161, 1068, 1033, 960 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.21 (d, J = 8.4 Hz, 2 H, Ar), 6.89 (d, J = 8.4 Hz, 2 H, Ar), 6.64 (s, 1 H, ArC*H*), 5.60 (d, J = 4.8 Hz, 1 H, C=CH_AH_B), 5.59 (d, J = 6.0 Hz, 1 H, C=CH_AH_B), 4.51-4.35 (m, 4 H, 2 × OCH_2CF_3), 4.38 (d, J = 24 Hz, 1 H, POCH), 4.25 (q, J = 7.2 Hz, 1 H, OC$H_AH_BCH_3$), 4.24 (q, J = 7.2 Hz, 1 H, $OCH_AH_BCH_3$), 3.82 (s, 3 H, OCH_3), 2.04 (s, 3 H, C=CCH_3), 1.28 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 158.5, 139.4 (d, J = 8.2 Hz,), 134.2, 130.5 (2 C), 129.8, 128.0, 122.4 (dq, J = 270, 28 Hz, 2 C), 118.0 (d, J = 8.2 Hz), 113.5 (2 C), 62.6 (dq, J = 8.6, 24.7 Hz, 2 C), 62.4, 55.1, 48.1 (d, J = 144.4 Hz), 16.1, 13.8 ppm; ^{31}P NMR (121.49 MHz, C_6D_6): δ 23.71 ppm; Anal. Calc. for $C_{20}H_{23}F_6O_6P$: C, 47.63; H, 4.60. Found: C, 47.79; H, 4.85.

(*E*)-Ethyl 2,3-dimethylene-5-phenylpent-4-enoate (131)



131

A solution of diene **107** (0.29 g, 0.63 mmol), in THF (6 mL) was cannulated to a suspension of NaH (0.028 g, 55% in oil, 0.63 mmol) in THF (1 mL) at 0 ºC. After 15 min, formaldehyde gas was bubbled through this reaction mixture for 10 min. The reaction mixture was diluted with water and extracted with 20% EtOAc in hexanes. The organic extract was concentrated under reduced pressure to give **131**. Attempt to purify this material by chromatography was not successful due to degradation by dimerization and polymerization.

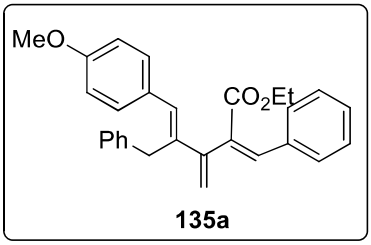
R_f (hexane-EtOAc, 95:5) = 0.5; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40-7.18 (m, 5H, Ph), 6.89 (d, J = 16.2 Hz, 1 H, PhC*H*), 6.38 (d, J = 1.2 Hz, 1 H, $EtCO_2C{=}CH_AH_B$), 6.36 (d, J = 16.2 Hz, 1 H, PhCH=C*H*), 5.75 (d, J = 1.2 Hz, 1H, $EtCO_2C{=}CH_AH_B$), 5.38 (s, 1 H, $PhCH{=}CHC{=}CH_AH_B$), 5.23 (s, 1 H, $PhCH{=}CHC{=}CH_AH_B$), 4.23 (q, J = 7.2 Hz, 2 H, OCH_2), 1.28 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm.

General procedure for [3]dendralenes 135a-k

A solution of butadien-2-ylphosphonoacetate **134a** (190 mg, 0.33 mmol, 1 equiv) in THF (5 mL) was cannulated to a suspension of sodium hydride (15 mg, 55% in oil, 0.33 mmol, 1 equiv) in THF (1 mL) under argon atmosphere and stirred for 5 min. Then freshly distilled benzaldehyde (0.034 mL, 0.33 mmol, 1 equiv) was added and stirred at room temperature for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was concentrated under the reduced pressure and purified by column chromatography (petroleum ether-EtOAc; 95:5) to

obtain the dendralene **135a** (42 mg, 30%) as white solid. The same procedure was followed for the preparation of dendralenes **135b-k**.

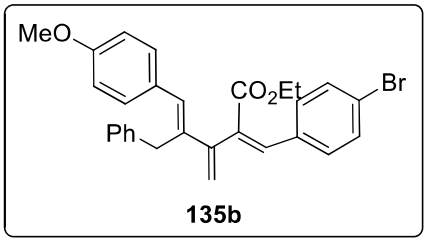
(2*Z*,4*E*)-Ethyl 4-benzyl-2-benzylidene-5-(4-methoxyphenyl)-3-methylenepent-4-enoate (**135a**)



135a

R_f (Benzene) = 0.85; mp 92-93 ºC; IR ν_{max}: 3081, 2959, 2923, 2855, 1715, 1604, 1573, 1508, 1494, 1463, 1455, 1370, 1304, 1256, 1210, 1175, 1095, 1029 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.35-7.23 (m, 12 H, Ar, 2 × Ph), 6.90 (s, 1 H, PhC*H*), 6.84 (s, 1 H, ArC*H*), 6.84 (d, J = 9.0 Hz, 2 H, Ar), 5.27 (s, 1 H, C=CH_AH_B), 5.24 (s, 1 H, C=CH_AH_B), 4.19 (q, 2 H, J = 7.2 Hz, OCH_2CH$_3$), 3.94 (s, 2 H, PhCH_2), 3.79 (s, 3 H, OCH_3), 1.16 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.0, 158.9, 148.7, 139.8, 136.4, 135.8, 135.7, 134.9, 132.4, 130.1 (2 C), 129.8, 128.7 (2 C), 128.6 (2 C), 128.5 (2 C), 128.4 (3 C), 126.1, 117.1, 113.9 (2 C), 61.1, 55.4, 35.5, 14.0 ppm; Anal. Calc. for $C_{29}H_{28}O_3$: C, 82.05; H, 6.65. Found: C, 82.26; H, 6.83. Recrystallization of compound **135a** from ethyl acetate/hexane gave crystals suitable for single crystal X-ray analysis.

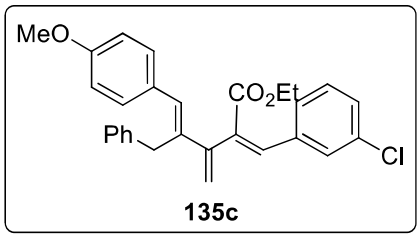
(2*Z*,4*E*)-Ethyl 2-(4-bromobenzylidene)-4-benzyl-5-(4-methoxyphenyl)-3-methylenepent-4-enoate (135b)



135b

Following the general procedure, isolated yield (43 mg, 41%) as pale yellow liquid; R_f (Benzene) = 0.75; IR ν_{max}: 2956, 2923, 2853, 1715, 1698, 1649, 1607, 1555, 1538, 1508, 1487, 1457, 1369, 1275, 1247, 1179, 1106, 1070, 1036 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.46 (d, 2 H, J = 8.4 Hz, Ar), 7.31-7.19 (m, 9 H, Ar, Ph), 6.85 (s, 1 H, 4-BrC_6H_4CH), 6.83 (d, J = 8.8 Hz, 2 H, Ar), 6.73 (s, 1 H, 4-$CH_3OC_6H_4CH$), 5.25 (s, 1 H, C=CH_AH_B), 5.24 (s, 1 H, C=CH_AH_B), 4.18 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.91 (s, 2 H, $PhCH_2$), 3.79 (s, 3 H, OCH_3), 1.17 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.6, 158.9, 148.6, 139.7, 136.6, 136.3, 134.6, 133.6, 132.5, 131.5 (2 C), 130.2 (2 C), 130.1 (2 C), 129.7, 128.6 (2 C), 128.5 (2 C), 126.1, 122.5, 117.4, 113.9 (2 C), 61.2, 55.3, 35.5, 14.1 ppm; Anal. Calc. for $C_{29}H_{27}BrO_3$: C, 69.19; H, 5.41. Found: C, 69.14; H, 5.57.

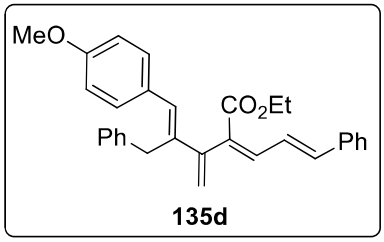
(2*Z*,4*E*)-Ethyl 2-(3-chlorobenzylidene)-4-benzyl-5-(4-methoxyphenyl)-3-methylenepent-4-enoate (135c)



135c

Following the general procedure, isolated yield (57 mg, 35%) as pale yellow liquid; R_f: (hexane-EtOAc, 95:5) = 0.4; IR ν_{max}: 3065, 2924, 2866, 2833, 1717, 1605, 1562, 1510, 1495, 1464, 1453, 1371, 1366, 1336, 1304, 1255, 1206, 1177, 1089, 1034 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.38-7.19 (m, 11 H, Ar), 6.87 (s, 1 H, 3-ClPhC*H*), 6.84 (d, J = 9.0 Hz, 2 H, 4-OCH_3*Ph*), 6.76 (s, 1 H, 4-OCH_3PhC*H*), 5.27 (s, 1 H, C=CH_AH_B), 5.26 (s, 1 H, C=CH_AH_B), 4.20 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.93 (s, 2 H, PhCH_2), 3.79 (s, 3 H, OCH_3), 1.18 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.5 158.9, 148.4, 139.7, 137.5, 137.3, 136.2, 134.3, 133.2, 132.5, 130.2 (2 C), 129.7, 129.6, 128.6 (3 C), 128.5 (2 C), 128.3, 126.7, 126.1, 117.5, 113.9 (2 C), 61.3, 55.4, 35.5, 14.0 ppm; Anal. Calc. for $C_{29}H_{27}ClO_3$: C, 75.89; H, 5.93. Found: C, 75.91; H, 5.93.

(2*Z*,4*E*)-Ethyl 2-[(*E*)-3-benzyl-4-(4-methoxyphenyl)buta-1,3-dien-2-yl]-5-phenylpenta-2,4-dienoate (135d)



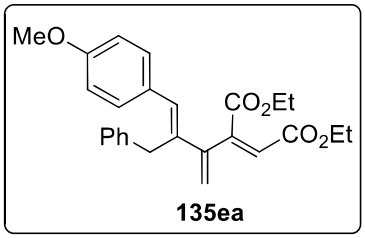
135d

Following the general procedure, isolated yield (43 mg, 31%) as yellow liquid; R_f (hexane-EtOAc, 90:10) = 0.53; IR ν_{max}: 3062, 3024, 2956, 2928, 2839, 1702, 1609, 1592, 1508, 1495, 1453, 1369, 1301, 1246, 1217, 1175, 1149, 1036, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (dd, J = 15.5, 11.5 Hz, 1 H, PhCH=C*H*CH=C), 7.51 (d, J = 7.0 Hz, 2 H, Ar), 7.38-7.17(m, 10 H, 2 × Ph), 6.81 (d, J = 9.0 Hz, 2 H, Ar), 6.80 (d, J = 15.5 Hz, 1 H, PhC*H*), 6.76 (s, 1 H, ArC*H*), 6.71 (d, J = 11.5 Hz, 1 H, PhCH=CHC*H*=C), 5.24 (s, 1 H, C=CH_AH_B), 5.17 (s, 1 H, C=CH_AH_B), 4.26 (q, J = 7

Hz, 2 H, OCH_2CH$_3$), 3.93 (s, 2 H, PhCH_2), 3.78 (s, 3 H, OCH$_3$), 1.29 (t, J = 7 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.1, 158.7, 149.0, 141.0, 140.0, 139.7, 136.6, 132.8, 131.6, 129.9 (2 C), 129.8, 128.6 (3 C), 128.5, 128.3 (2 C), 128.2 (2 C), 127.2 (2 C), 125.8, 125.5, 116.3, 113.7 (2 C), 60.5, 55.1, 34.8, 14.2 ppm; Anal. Calc. for $C_{31}H_{30}O_3$: C, 82.64; H, 6.71. Found: C, 82.63; H, 6.72.

Synthesis of 135ea/eb: Following the general procedure, a 6:4 mixture of *Z/E* isomers (^{1}H NMR) were isolated as colourless liquid. The individual isomers were separated by chromatography.

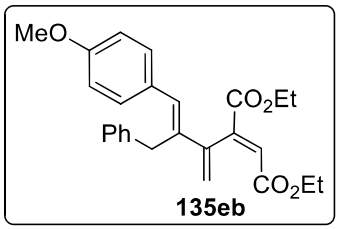
Diethyl 2-[(*E*)-3-benzyl-4-(4-methoxyphenyl)buta-1,3-dien-2-yl]maleate (**135ea**):



135ea

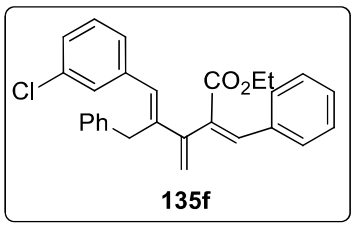
Isolated yield (55 mg, 30%); R_f (hexane-EtOAc, 80:20) = 0.54; IR ν_{max}: 3059, 2980, 2960, 2932, 2835, 1720, 1610, 1510, 1500, 1453, 1396, 1364, 1333, 1254, 1176, 1092, 1035 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29-7.25 (m, 4 H, Ar, Ph), 7.21-7.18 (m, 3 H, Ph), 6.86 (d, J = 9.0 Hz, 2 H, Ar), 6.77 (s, 1 H, ArCH), 6.00 (s, 1 H, CHCO$_2$Et), 5.30 (s, 1 H, C=CH_AH$_B$), 5.27 (s, 1 H, C=CH$_A$$H_B$), 4.31 (q, J = 7.0 Hz, 2 H, OCH_2CH$_3$), 4.22 (q, J = 7.0 Hz, 2 H, OCH_2CH$_3$), 3.85 (s, 2 H, PhCH_2), 3.80 (s, 3 H, OCH$_3$), 1.31 (t, 3 H, J = 7.0 Hz), 1.30 (t, J = 7.0 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.3, 164.9, 158.9, 148.7, 146.0, 139.0, 135.5, 133.0, 129.9 (2 C), 129.1, 128.4 (4 C), 126.0, 121.0, 120.1, 113.8 (2 C), 61.5, 60.9, 55.2, 35.5, 14.0, 13.9 ppm; Anal. Calc. for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 74.08; H, 6.82.

Diethyl 2-((*E*)-3-benzyl-4-(4-methoxyphenyl)buta-1,3-dien-2-yl)fumarate (135eb)



Isolated yield (33 mg, 18%); R_f (hexane-EtOAc, 80:20) = 0.52; IR ν_{max}: 3061, 2981, 2837, 1722, 1607, 1510, 1495, 1391, 1250, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.28-7.18 (m, 7 H, Ar, Ph), 6.77 (d, J = 8.8 Hz, 2 H, Ar), 6.41 (s, 1 H, ArC*H*), 5.93 (s, 1 H, C*H*CO_2Et), 5.39 (s, 1 H, C=CH_AH_B), 5.02 (s, 1 H, C=CH_AH_B), 4.37 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 4.16 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.76 (s, 3 H, OCH_3), 3.52 (s, 2 H, PhCH_2), 1.37 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.25 (t, J = 7.2 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.6, 165.2, 158.8, 147.1, 143.0, 138.7, 135.9, 129.9 (2 C), 129.8, 129.4 (2 C), 128.6, 128.3 (2 C), 126.4, 123.7, 118.3, 113.7 (2 C), 61.6, 60.9, 55.2, 45.6, 14.0 (2 C) ppm.

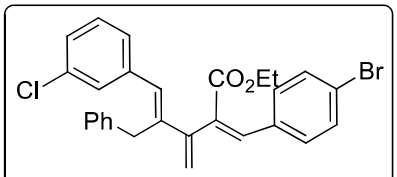
(2*Z*,4*E*)-Ethyl 4-benzyl-2-benzylidene-5-(3-chlorophenyl)-3-methylenepent-4-enoate (135f)



Following the general procedure, isolated yield (54 mg, 35%) as colourless liquid; R_f (hexane-EtOAc, 95:5) = 0.5; IR ν_{max}: 3060, 3026, 2981, 2959, 2871, 1716, 1636, 1589, 1556, 1490, 1476, 1453, 1373, 1213, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.18 (m, 14 H, Ar, 2×Ph), 6.88 (s, 1 H, PhC*H*), 6.83 (s, 1 H, ArC*H*), 5.33 (s, 1 H,

C=CH_AH$_B$), 5.29 (s, 1 H, C=CH$_A$$H_B$), 4.21 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 3.90 (s, 2 H, PhCH_2), 1.17 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 148.0, 139.6, 139.3, 139.0, 135.5, 135.3, 135.0, 134.2, 131.1, 129.6, 128.8, 128.5 (4 C), 128.4 (3 C), 128.3 (2 C), 127.2, 126.6, 126.2, 118.0, 61.1, 35.4, 13.9 ppm; Anal. Calc. for $C_{28}H_{25}ClO_2$: C, 78.40; H, 5.87. Found: C, 78.62; H, 6.12.

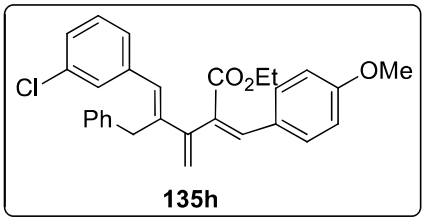
(2*Z*,4*E*)-Ethyl 2-(4-bromobenzylidene)-4-benzyl-5-(3-chlorophenyl)-3-methylenepent-4-enoate (135g)



135g

Following the general procedure, isolated yield (240 mg, 47%) as pale yellow liquid; R_f (hexane-EtOAc, 90:10) = 0.75; IR ν_{max}: 3061, 3026, 2979, 2926, 1720, 1591, 1561, 1486, 1453, 1371, 1343, 1302, 1276, 1211, 1073, 1046, 1010 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47 (d, J = 8.6 Hz, 2 H, Ar), 7.36-7.15 (m, 11 H, Ar, Ph), 6.82 (s, 1 H, ArCH), 6.70 (s, 1 H, ArCH), 5.29 (s, 1 H, C=CH_AH$_B$), 5.28 (s, 1 H, C=CH$_A$$H_B$), 4.18 (q, J = 7 Hz, 2 H, OCH_2CH$_3$), 3.87 (s, 2 H, PhCH_2), 1.17 (t, J = 7 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.4, 147.9, 139.4, 139.1, 138.9, 136.0, 134.4, 134.2, 133.7, 131.5 (2 C), 131.1, 130.1 (2 C), 129.6, 128.8, 128.5 (2 C), 128.4 (2 C), 127.3, 126.6, 126.2, 122.5, 118.2, 61.2, 35.4, 13.9 ppm; Anal. Calc. for $C_{28}H_{24}BrClO_2$: C, 66.22; H, 4.76. Found: C, 66.50; H, 4.92.

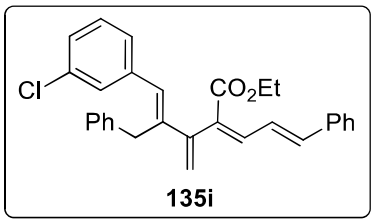
(2*Z*,4*E*)-Ethyl 2-(4-methoxybenzylidene)-4-benzyl-5-(3-chlorophenyl)-3-methylenepent-4-enoate (135h)



135h

Following the general procedure, isolated yield (28 mg, 15%) as colourless liquid; R_f (hexane-EtOAc, 95:5) = 0.28; IR ν_{max}: 3061, 3029, 2956, 2930, 2838, 1714, 1709, 1601, 1565, 1507, 1453, 1376, 1295, 1255, 1201, 1178, 1097, 962 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.17 (m, 11 H, Ar, Ph), 6.88 (d, J = 8.7 Hz, 2 H, Ar), 6.86 (s, 1 H, ArC*H*), 6.75 (s, 1 H, ArC*H*), 5.29 (s, 1 H, C=CH_AH_B), 5.26 (s, 1 H, C=CH_AH_B), 4.23 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 3.89 (s, 2 H, PhCH_2), 3.84 (s, 3 H, OCH_3), 1.21 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 159.8, 148.4, 139.7, 139.3, 139.1, 134.8, 134.2, 133.1, 132.2, 140.0, 130.3 (2 C), 129.6, 128.8, 128.5 (2 C), 128.4 (2 C), 127.2, 126.6, 126.1, 117.6, 113.8 (2 C), 61.0, 55.3, 35.4, 14.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{28}ClO_3$ 459.1721; Found 459.1723.

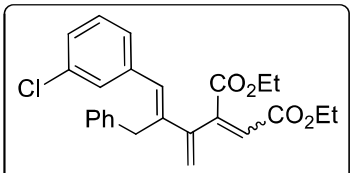
(2*Z*,4*E*)-Ethyl 2-[(*E*)-3-benzyl-4-(3-chlorophenyl)buta-1,3-dien-2-yl]-5-phenylpenta-2,4-dienoate (135i)



135i

Following the general procedure, isolated yield (37 mg, 27%) as yellow liquid; R_f (hexane-EtOAc, 95:5) = 0.54; IR ν_{max}: 3058, 3027, 2979, 2929, 2869, 1705, 1615, 1592, 1561, 1496, 1476, 1447, 1367, 1317, 1304, 1221, 1206, 1159, 1150, 1096, 1045, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (dd, J = 15.6, 11.4 Hz, 1 H, PhCH=C*H*CH), 7.53-7.50 (m, 2 H, Ar), 7.39-7.11 (m, 12 H, Ar, 2 × Ph), 6.82 (d, J = 15.6 Hz, 1 H, PhC*H*=CHCH), 6.73 (s, 1 H, ArC*H*), 6.70 (dd, J = 11.4, 0.9 Hz, 1 H, PhCH=CHC*H*=C), 5.31 (s, 1 H, C=CH_AH_B), 5.23 (s, 1 H, C=CH_AH_B), 4.27 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 3.89 (s, 2 H, PhCH_2), 1.31 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 148.6, 141.5, 140.2, 139.8, 139.6, 139.2, 136.6, 134.2, 132.3, 130.4, 129.5, 128.8 (4 C), 128.5 (2 C), 128.2 (2 C), 127.3 (2 C), 127.1, 126.6, 126.1, 125.4, 117.7, 60.7, 34.8, 14.3 ppm; Anal. Calc. for $C_{30}H_{27}ClO_2$: C, 79.19; H, 5.98. Found: C, 79.25; H, 5.80.

Diethyl 2-[(*E*)-3-benzyl-4-(3-chlorophenyl)buta-1,3-dien-2-yl]maleate (135j)

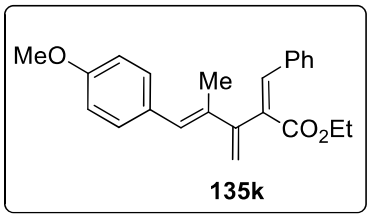


135j

Following the general procedure, isolated yield (54 mg, 40%) as colourless liquid. The product was contaminated with 36% of diethyl 2-[(*E*)-3-benzyl-4-(3-chlorophenyl)buta-1,3-dien-2-yl]fumarate and could not be separated. R_f (hexane-EtOAc, 95:5) = 0.26; IR ν_{max}: 3063, 3026, 2979, 2934, 2906, 2871, 1723, 1615, 1591, 1562, 1241, 1182, 1100, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34-7.14 (m, 18 H, Ar, Ph), 6.75 (s, 1 H, ArC*H*, *Z*), 6.40 (s, 1 H, ArC*H*, *E*), 5.99 (s, 1 H, CHCO$_2$Et, *Z*), 5.91 (s, 1 H, CHCO$_2$Et, *E*), 5.44 (s, 1 H, C=CH_AH_B, *E*), 5.35 (s, 1 H, C=CH_AH_B, *Z*),

5.30 (s, 1 H, C=CH$_A$*H*$_B$, *Z*), 5.06 (s, 1 H, C=CH$_A$*H*$_B$, *E*), 4.40 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$, *E*), 4.33 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$, *Z*), 4.24 (q, *J* = 7.0Hz, 2 H, OC*H*$_2$CH$_3$, *Z*), 4.19 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$, *E*), 3.81 (s, 2 H, PhC*H*$_2$, *Z*), 3.58 (s, 2 H, PhC*H*$_2$, *E*), 1.39 (t, *J* = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$, *E*), 1.33 (t, *J* = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$, *Z*), 1.32 (t, *J* = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$, *Z*), 1.28 (t, *J* = 7.0 Hz, 3 H, OCH$_2$C*H*$_3$, *E*) ppm; ^{13}C NMR (125 MHz, CDCl$_3$): δ 167.3 (*E*), 167.2 (*Z*), 164.9 (*E*), 164.8 (*Z*), 148.3 (*Z*), 146.9 (*E*), 145.4 (*Z*), 142.4 (*E*), 139.9 (*E*), 138.9 (*Z*), 138.5 (*Z*), 138.4 (*Z*), 138.0 (*E*), 137.7 (*E*), 134.3 (*Z*), 134.1 (*E*), 131.8 (*Z*), 129.6 (*E*), 129.4 (2 C, *Z*), 128.9 (*E*), 128.8 (*Z*), 128.6 (*E*), 128.5 (4 C), 127.4 (*Z*), 127.2 (*E*), 126.6 (*Z*), 126.5 (*E*), 126.3 (*Z*), 123.9 (*E*), 121.1 (*Z*), 121.0 (*E*), 118.5 (*E*), 61.6 (2 C), 61.0 (2 C), 45.5 (*E*), 35.6 (*Z*), 14.1 (2 C), 14.0 (2 C) ppm; Anal. Calc. for $C_{25}H_{25}ClO_4$: C, 70.67; H, 5.93. Found: C, 70.80; H, 5.98.

(2*Z*,4*E*)-Ethyl 2-benzylidene-5-(4-methoxyphenyl)-4-methyl-3-methylenepent-4-enoate (**135k**)

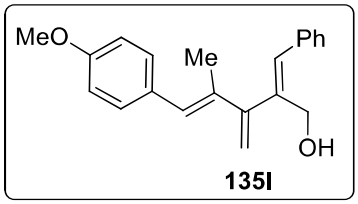


135k

Following the general procedure, isolated yield (100 mg, 45%) as colourless liquid; R_f (hexane-EtOAc, 95:5) = 0.42; IR ν_{max}: 3070, 3036, 2364, 2326, 1962, 1812, 1717, 1611, 1509, 1479, 1251, 1214, 1177, 1036 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) : δ 7.36-7.26 (m, 7 H, Ar, Ph), 6.91 (d, *J* = 8.4 Hz, 2 H, Ar), 6.85 (s, 1 H, PhC*H*), 6.62 (s, 1 H, ArC*H*), 5.37 (s, 1 H, C=C*H*$_A$H$_B$), 5.32 (s, 1 H, C=CH$_A$*H*$_B$), 4.22 (q, *J* = 6.9 Hz, 2 H, OC*H*$_2$CH$_3$), 3.84 (s, 3 H, OCH$_3$), 2.13 (s, 3 H, C=CCH$_3$), 1.17 (t, *J* = 6.9 Hz, 3 H,

OCH_2CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 158.3, 150.5, 135.6, 135.5, 134.7, 130.4 (2 C), 129.7, 128.5 (2 C), 128.3 (4 C), 115.3, 113.6 (2 C), 61.0, 55.3, 17.0, 13.9 ppm; Anal. Calc. for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.52; H, 6.89.

(2*Z*,4*E*)-2-Benzylidene-5-(4-methoxyphenyl)-4-methyl-3-methylenepent-4-en-1-ol (135l)



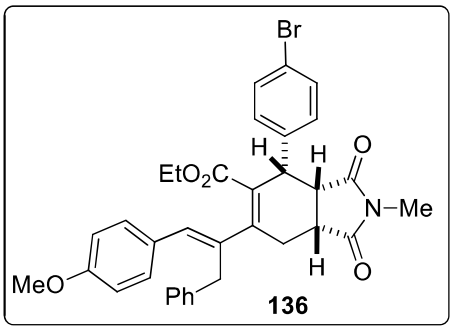
135l

To a solution of dendralene **135k** (151 mg, 0.43 mmol) in dichloromethane (10 mL), DIBAL-H (1.74 mL, 1.0 M in cyclohexane, 1.73 mmol) was added at -78 °C under the argon atmosphere and the solution was stirred for 1 h at the same temperature. The temperature of the reaction mixture was raised to 0 ºC, stirred for another 1 h and finally allowed to attain room temperature. The reaction mixture was quenched with dil HCl and extracted with dichloromethane. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography (petroleum ether-EtOAc; 90:10) to obtain the dendralene **135l** (105 mg, 80%) as colourless liquid.

R_f (hexane-EtOAc, 80:20) = 0.4; IR ν_{max}: 3426, 3058, 3034, 2951, 2933, 2838, 1607, 1511, 1480, 1441, 1303, 1248, 1177, 1034 cm^{-1}; ^1H NMR (300 MHz, CD_3COCD_3): δ 7.49 (d, J = 7.5 Hz, 2 H, Ph), 7.37-7.25 (m, 5 H, Ar, Ph), 6.90 (d, J = 8.7 Hz, 2 H, Ar), 6.64 (s, 1 H, PhC*H*), 6.53 (s, 1 H, ArC*H*), 5.27 (s, 1 H, C=CH_AH_B), 5.24 (s, 1 H, C=CH_AH_B), 4.36 (d, J = 5.4 Hz, 2 H, CH_2OH), 3.89 (t, J = 5.4 Hz, 1 H, CH_2OH), 3.78 (s, 3 H, OCH_3), 2.05 (s, 3 H, C=CCH_3) ppm; ^{13}C NMR (75 MHz, CD_3COCD_3): δ

155.6, 143.2, 138.3, 136.8, 132.8, 131.6 (2 C), 130.3 (3 C), 129.3 (3 C), 128.3, 114.7 (2 C), 113.6 (2 C), 60.3, 55.8, 17.6 ppm; Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.15; H, 7.32.

(3a*SR*,4*SR*,7a*RS*)-Ethyl 4-(4-bromophenyl)-2,3,3a,4,7,7a-hexahydro-6-[(*E*)-1-(4-methoxyphenyl]-3-phenylprop-1-en-2-yl)-2-methyl-1,3-dioxo-1*H*-isoindole-5-carboxylate (136)



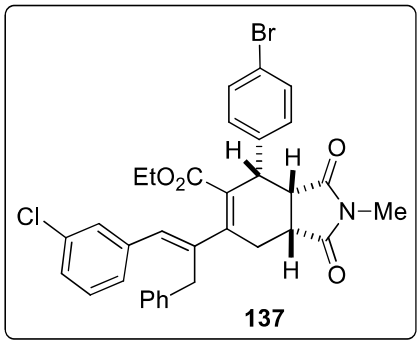
136

A solution of dendralene **135b** (60 mg, 0.12 mmol, 1 equiv) and NMM (14 mg, 0.12 mmol, 1 equiv) in benzene (3 mL) was heated under reflux for 3 d. The reaction mixture was then concentrated on rotary evaporator and the residue was filtered through a small silica gel column to obtain the D-A adducts (57 mg, 78%) which on careful chromatography on silica gel provided the major adduct **136** (50 mg, 69%) as a white solid.

R_f (hexane-EtOAc, 70:30) = 0.36; mp 119 °C; IR ν_{max}: 3062, 3023, 2979, 2954, 2932, 2838, 1775, 1702, 1606, 1510, 1488, 1434, 1380, 1281, 1253, 1220, 1178, 1122, 1075, 1025, 1008, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.5 Hz, 2 H, Ar), 7.29-7.23 (m, 5 H, Ph), 7.19 (d, J = 8.0 Hz, 2 H, Ar), 6.90 (d, 2 H, J = 8.5 Hz, Ar), 6.63 (d, J = 8.5 Hz, 2 H, Ar), 6.45 (s, 1 H, ArC*H*), 4.46 (d, J = 7.5 Hz, 1 H, ArC*H*CH), 4.10 (q, J = 7.5 Hz, 1 H, $OCH_AH_BCH_3$), 4.09 (q, J = 7.5 Hz, 1 H, $OCH_AH_BCH_3$), 4.06 (d, J = 15.0 Hz, 1 H, $PhCH_AH_B$), 3.83 (d, J = 17.0 Hz, 1 H,

$PhCH_AH_B$), 3.81 (s, 3 H, OCH_3), 3.07 (t, J = 7.5 Hz, 1 H, ArCHC*H*), 2.72-2.67 (m, 1 H, COC*H*CH_AH_B), 2.65 (dd, J = 18.5, 6 Hz, 1 H, $COCHCH_AH_{B)}$, 2.53 (dd, J = 18.5, 10.5 Hz, 1 H, $COCHCH_AH_B$), 2.40 (s, 3 H, NCH_3), 1.16 (t, J = 7.5 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.7, 177.0, 167.2, 158.8, 150.1, 140.4, 138.6, 135.1, 131.4 (2 C), 130.3 (2 C), 130.1 (2 C), 129.5 (2 C), 129.2, 128.4 (3 C), 127.7, 126.6, 121.5, 113.9 (2 C), 60.9, 55.3, 45.1, 41.9, 37.6, 37.0, 28.7, 24.0, 14.1 ppm; Anal. Calc. for $C_{34}H_{32}BrNO_5$: C, 66.45; H, 5.25; N, 2.28. Found: C, 66.28; H, 5.39; N, 2.05. Recrystallization of compound **136** from ethylacetate/hexane gave crystals suitable for single crystal X-ray analysis.

(3a*SR*,4*SR*,7a*RS*)-Ethyl 4-(4-bromophenyl)-6-[(*E*)-1-(3-chlorophenyl)-3-phenylprop-1-en-2-yl]-2,3,3a,4,7,7a-hexahydro-2-methyl-1,3-dioxo-1*H*-isoindole-5-carboxylate (**137**)

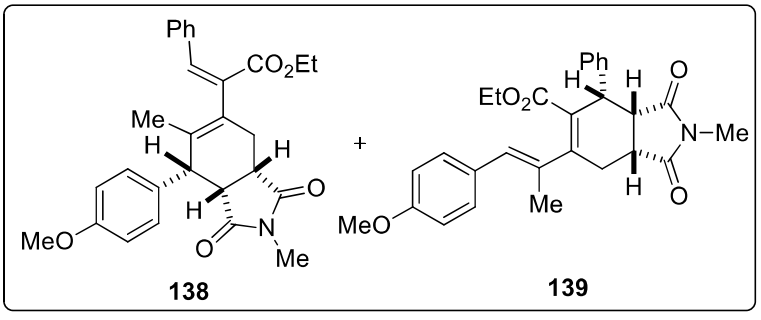


137

A solution of dendralene **135g** (155 mg, 0.3 mmol, 1 equiv) and NMM (34 mg, 0.3 mmol, 1 equiv) in toluene (5 mL) was heated under reflux for 2 d. The reaction mixture was then concentrated on rotary evaporator and the residue was filtered through a small silica gel column to obtain the D-A adducts (148 mg, 78%) which on careful chromatography on silica gel provided the major adduct **137** (118 mg, 62%) as a white solid.

R_f (hexane-EtOAc, 80:20) = 0.16; mp 140-141 °C; IR ν_{max}: 3024, 2977, 2929, 2849, 1778, 1703, 1591, 1562, 1486, 1434, 1382, 1276, 1220, 1124, 1074, 1047, 1010 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.37-7.19 (m, 11 H, Ar, Ph), 6.64 (d, J = 8.4 Hz, 2 H, Ar), 6.44 (s, 1H, ArC*H*), 4.49 (d, J = 7.2 Hz, 1 H, ArC*H*CH), 4.14 (q, J = 7.2 Hz, 1H, OCH_ACH$_B$CH$_3$), 4.13 (q, J = 7.0 Hz, 1H, OCH$_A$CH_BCH$_3$), 4.05 (d, J = 15.4 Hz, 1 H, PhCH_ACH$_B$), 3.84 (d, J = 14.6 Hz, 1 H, PhCH$_A$CH_B), 3.08 (t, J = 7.6 Hz, 1 H, ArCHC*H*), 2.75-2.46 (m, 3 H, COCHCH$_2$), 2.42 (s, 3 H, NCH$_3$), 1.20 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 178.6, 176.9, 166.6, 149.9, 143.6, 138.4, 138.1, 135.0, 134.3, 131.4 (2 C), 130.2 (2 C), 129.7, 129.6 (2 C), 128.8, 128.6, 128.5 (2 C), 127.3, 126.9, 126.8, 126.2, 121.5, 61.0, 45.0, 41.7, 37.4, 37.1, 28.9, 24.0, 14.1 ppm; Anal. Calc. for $C_{33}H_{29}BrClNO_4$: C, 64.04; H, 4.72; N, 2.26. Found: C, 64.13; H, 4.77; N, 2.09. Recrystallization of compound **137** from ethanol gave crystals suitable for single crystal X-ray analysis.

(2*Z*)-Ethyl 2-((3a*RS*,4*RS*,7a*SR*)-2,3,3a,4,7,7a-hexahydro-4-(4-methoxyphenyl)-2,5-dimethyl-1,3-dioxo-1*H*-isoindol-6-yl)-3-phenylacrylate (138) and (3a*SR*,4*SR*,7a*RS*)-Ethyl 2,3,3a,4,7,7a-hexahydro-6-[(*E*)-1-(4-methoxyphenyl)prop-1-en-2-yl]-2-methyl-1,3-dioxo-4-phenyl-1*H*-isoindole-5-carboxylate (139)



138 **139**

A solution of dendralene **135k** (126 mg, 0.36 mmol, 1 equiv) and NMM (41 mg, 0.36 mmol, 1 equiv) in toluene (3 mL) was heated under reflux for 1 d. The reaction mixture was then concentrated on rotary evaporator and chromatographed to obtain the D-A adducts as an inseparable 54:46 mixture of **138**/**139** (149 mg, 89%).

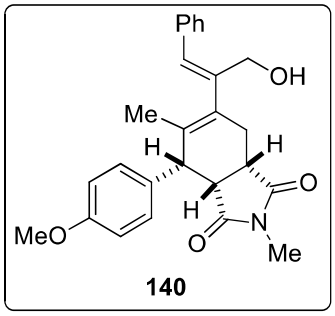
R_f (hexane-EtOAc, 70:30) = 0.3; IR ν_{max}: 3023, 2981, 2940, 2906, 2837, 1780, 1713, 1696, 1610, 1511, 1437, 1382, 1255, 1175, 1035, 760,697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.31 (m, 5 H, Ph, **138**), 7.30-7.18 (m, 5 H, Ar, Ph, **139**), 7.09 (d, J = 7.0 Hz, 2 H, Ph, **139**), 7.08 (d, J = 8.5 Hz, 2 H, Ar, **138**), 6.92 (d, J = 8.5 Hz, 2 H, Ar, **139**), 6.81 (d, J = 9.0 Hz, 2 H, Ar, **138**), 6.77 (s, 1 H, PhC*H*, **138**), 6.27 (s, 1 H, ArC*H*, **139**), 4.56 (d, J = 7.5 Hz, 1 H, PhC*H*, **139**), 4.21 (q, J = 7.0 Hz, 2 H, OCH_2CH$_3$, **138**), 4.03 (q, J = 7.0 Hz, 1 H, OCH_2CH$_3$, **139**), 3.85 (d, J = 5.0 Hz, 1 H, ArC*H*, **138**), 3.85 (s, 3 H, OCH$_3$, **139**), 3.79 (s, 3 H, OCH$_3$, **138**), 3.39 (t, J = 8.0 Hz, 1 H, PhCHC*H*, **139**), 3.33 (t, J = 9.0 Hz, 1 H, ArCHC*H*, **138**), 3.23-3.15 (m, 3 H, COC*H*CH_AH$_B$, **139**, COC*H*CH$_2$, **138**), 3.08-2.98 (m, 1 H, COCHCH_AH$_B$, **138**), 2.82 (dd, J = 20.0, 12.0 Hz, 1 H, COCHCH$_A$$H_B$, **139**), 2.73 (dd, J = 18.0, 11.5 Hz, 1 H, COCHCH$_A$$H_B$, **138**), 2.47 (s, NCH$_3$, 3 H, **138**), 2.40 (s, 3 H, NCH$_3$, **139**), 2.15 (d, J = 0.5 Hz, 3 H, C=CCH$_3$, **139**), 1.81 (s, 3 H, C=CCH$_3$, **138**), 1.19 (t, J = 7.0 Hz, 3 H, OCH$_2$CH_3, **138**), 1.09 (t, J = 7.0 Hz, 3 H, OCH$_2$CH_3, **139**) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 179.5 (**138**), 179.0 (**139**), 178.0 (**138**), 177.2 (**139**), 168.1 (**138**), 167.7 (**139**), 158.9 (**138**), 158.4 (**139**), 150.6 (**139**), 137.6 (**138**), 136.8 (**139**), 136.6 (**138**), 135.5 (**138**), 134.6 (**138**), 134.3 (**138**), 130.1 (2 C), 130.0 (2 C), 129.9, 129.8, 128.6 (3 C), 128.4 (4 C), 128.3, 128.2 (2 C), 127.6, 127.0, 125.9, 113.7 (2 C, **138**), 113.6 (2 C, **139**), 61.0 (**138**) , 60.6 (**139**), 55.2 (**139**), 55.1 (**138**), 46.2 (**139**), 45.2 (**138**), 45.1 (**138**), 42.0 (**139**), 37.5 (**139**), 37.4 (**138**), 29.7 (**139**), 26.6 (**139**), 25.9 (**139**), 23.9 (**138**), 23.8 (**139**), 20.3

(**138**), 17.4 (**139**), 13.8 (**138**) ppm; Anal. Calc. for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.36; N, 3.05. Found: C, 73.07; H, 6.56; N, 3.07.

Synthesis of compounds 140, 141 and 142

A solution of dendralene **135l** (48 mg, 0.16 mmol, 1 equiv) and NMM (21 mg, 0.19 mmol, 1.2 equiv) in toluene (3 mL) was heated under reflux for 1 d. The reaction mixture was then concentrated on rotary evaporator and the residue on careful chromatography on silica gel provided D-A adducts **140** (52 mg, 65%) as white solid, **141**(8 mg, 10%) as foam and **145** (3 mg, 4%) as gummy solid (Combined yield: 79%).

(3a*RS*,4*RS*,7a*SR*)-3a,4,7,7a-Tetrahydro-6-[(*Z*)-1-hydroxy-3-phenylprop-2-en-2-yl]-4-(4-methoxyphenyl)-2,5-dimethyl-2*H*-isoindole-1,3-dione (**140**)

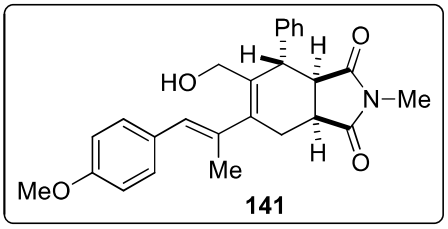


140

R_f (hexane-EtOAc, 60:40) = 0.21; mp 117-118 °C; IR ν_{max}: 3443, 3059, 3021, 2936, 2906, 2853, 2840, 1777, 1694, 1610, 1507, 1434, 1386, 1249, 1178, 1135, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39-7.36 (m, 2 H, Ph), 7.30-7.28 (m, 3 H, Ph), 7.07 (d, J = 8.5 Hz, 2 H, Ar), 6.78 (d, J = 8.5 Hz, 2 H, Ar), 6.48 (s, 1 H, PhC*H*), 4.53 (d, J = 12.5 Hz, 1 H, CH_AH$_B$OH), 4.49 (d, J = 12.5 Hz, 1 H, CH$_A$$H_B$OH), 3.82 (d, J = 7.0 Hz, 1 H, ArC*H*CH), 3.75 (s, 3 H, OCH_3), 3.31 (t, J = 8.5 Hz, 1 H, ArCHC*H*), 3.19-3.14 (m, 1 H, COC*H*CH_2), 3.02 (d, J = 18.0 Hz, 1 H, COCHCH_AH$_B$), 2.73 (dd, J = 18.0, 11.5 Hz, 2 H, COCHCH$_A$$H_B$), 2.45 (s, 3 H, NCH_3), 1.80 (s, 3H, C=CCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.9, 178.2, 158.8, 141.3, 136.3, 132.4, 132.0,

130.6, 130.0 (2 C), 129.0, 128.7 (2 C), 128.3 (2 C), 127.2, 113.7 (2 C), 60.3, 55.1, 46.0, 45.2, 37.3, 25.7, 23.8, 20.2 ppm. Recrystallization of compound **140** from ethylacetate/hexane gave crystals suitable for single crystal X-ray analysis.

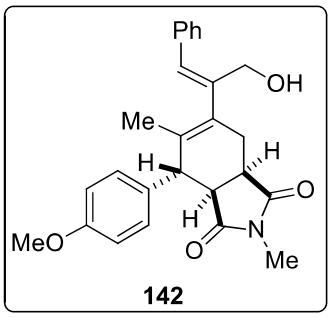
(3a*RS*,4*SR*,7a*SR*)-3a,4,7,7a-Tetrahydro-5-(hydroxymethyl)-6-[(*E*)-1-(4-methoxyphenyl) prop-1-en-2-yl]-2-methyl-4-phenyl-2*H*-isoindole-1,3-dione (**141**)



141

R_f (hexane-EtOAc, 60:40) = 0.17; IR ν_{max}: 3457, 3035, 2925, 2854, 1700, 1510, 1434, 1251, 1034 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 7.36 (d, J = 7.5 Hz, 2 H, Ph), 7.28 (d, J = 8.5 Hz, 2 H, Ar), 7.17 (t, J = 7.5 Hz, 2 H, Ph), 7.07 (t, J = 7.5 Hz, 1 H, Ph), 6.94 (d, J = 8.5, 2 H, Ar), 6.48 (s, 1 H, ArC*H*), 4.47 (d, J = 7 Hz, 1 H, PhC*H*), 4.35 (d, J = 12 Hz, 1 H, CH_ACH_BOH), 3.79 (dd, J = 12, 2 Hz, 1 H, CH$_A$CH_BOH), 3.46 (s, 3 H, OCH_3), 3.18 (m, 2 H, COCHCH_AH$_B$, CH_2OH), 3.02 (t, J = 7.5 Hz, 1 H, PhCHC*H*), 2.53-2.45 (m, 2 H, COC*H*CH$_A$*H*$_B$), 2.39 (s, 3 H, NCH_3), 1.96 (s, 3 H, C=CCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.6, 177.9, 158.3, 140.3, 137.4, 135.6, 132.1, 130.1 (2 C), 129.6, 128.9 (2 C), 128.4 (2 C), 127.8, 127.5, 113.6 (2 C), 62.2, 55.2, 45.4, 41.8, 37.4, 25.3, 23.7, 17.8 ppm; Anal. Calc. for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.60; H, 6.67; N, 3.26.

(3a*SR*,4*RS*,7a*RS*)-3a,4,7,7a-Tetrahydro-6-[(*Z*)-1-hydroxy-3-phenylprop-2-en-2-yl]-4-(4-methoxyphenyl)-2,5-dimethyl-2*H*-isoindole-1,3-dione (**142**)



142

R_f (hexane-EtOAc, 60:40) = 0.4; IR ν_{max}: 3498, 3019, 2932, 1774, 1697, 1610, 1510, 1441, 1250, 1034, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.25 (m, 7 H, Ar, Ph), 6.91 (d, J = 8.5 Hz, 2 H, Ar), 6.34 (s, 1 H, PhC*H*), 4.39 (d, J = 13.5 Hz, 1 H, CH_AH$_B$OH), 4.37 (d, J = 13.0 Hz, 1 H, CH$_A$$H_B$OH), 4.13 (s, 1 H, ArC*H*), 3.81 (s, 3 H, OCH_3), 3.40 (d, J = 8.5 Hz, 1 H, ArCH*CH*), 3.12 (t, J = 8.0 Hz, 1 H, COCHCH_AH$_B$), 3.01 (s, 3 H, NCH_3), 2.70 (d, J = 15.5 Hz, 1 H, COCHCH$_A$$H_B$), 2.44-2.39 (m, 1 H, COC*H*CH$_2$), 1.92 (d, J = 2.0 Hz, 3 H, C=CCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.8, 179.4, 158.3, 140.7, 136.2, 134.1, 133.5, 131.3, 130.7, 128.8 (2 C), 128.3 (2 C), 128.2 (2 C), 127.2, 114.3 (2 C), 59.7, 55.2, 47.1, 45.7, 39.6, 28.1, 25.1, 21.0 ppm.

3.5 Appendix

3.5.1 X-ray crystallographic studies

Single crystal X-ray diffraction data were collected on Agilent Supernova system equipped with a microfocus Cu-source (λ = 1.5418 Å) and a Titan CCD detector. The crystals were separated, coated with paraffin oil and mounted on a loop for X-ray diffraction data collection at specified temperature. The data reduction and analysis were carried out with CrysAlisPro software suit. Analytical absorption correction using a multifaceted crystal model based on expressions derived by Clark & Reid[74] and as implemented in the CrysAlisPro software suit was carried out for both the crystals. The structures were solved by direct method using Shelxs and refined using

Shelxl softwares[75] using Olex2 interface.[76] All the nonhydrogen atoms were refined anisotropically and hydrogens were generated at their idealized positions and refined isotropically according to riding model.

3.5.2 X-ray Crystallographic Data (Table 3.1)

Compounds	**135a**	**136**	**137**	**140**
Formula	$C_{29}H_{28}O_3$	$C_{34}H_{32}BrNO_5$	$C_{33}H_{29}BrClNO_4$	$C_{26}H_{27}NO_4$
Formula Wt	424.51	614.51	618.93	417.48
Crystal System	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space Group	$P2_1/n$	$P2_1/c$	Pbca	$P2_1/c$
T,K	293	293	150.15	293(2)
Z	4	4	8	4
a, Å	10.4846(6)	13.0988(11)	10.4479(2)	14.7213(14)
b, Å	15.8614(8)	27.6314(14)	20.6292(3)	12.0482(10)
c, Å	14.7350(8)	8.4212(5)	27.0817(4)	13.0935(10)
α, deg	90	90	90	90
β, deg	99.128(5)	93.631(7)	90	109.305(11)
γ, deg	90	90	90	90
V, $Å^3$	2419.4(2)	3041.8(4)	5836.97(16)	2191.8(4)
$\rho_{calc,}$ mg/mm^3	1.165	1.342	1.409	1.265
μ, m/mm^{-1}	0.585	2.179	3.072	0.683
θ range, deg	4.123-69.930	3.199-70.246	4.29-72.13	3.181-70.164
GOF (F^2)	1.041	1.049	1.045	1.053
$R_1{}^a$ ($wR_2{}^b$), %	0.0464 (0.1220)	0.0787 (0.2324)	0.0430 (0.1152)	0.0524 (0.1452)

3.5.3 X-ray Crystal Structures (50% ellipsoid contour percent probability):

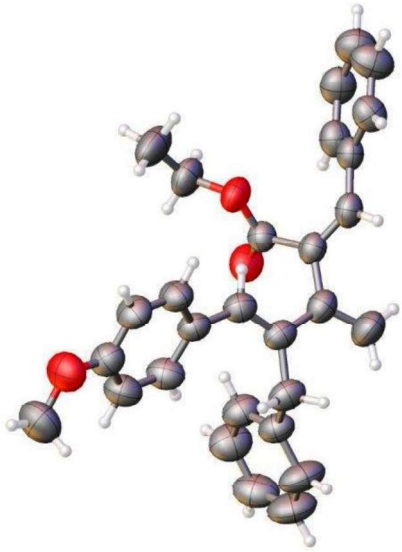


Figure S3.1: X-ray structure of **135a**, CCDC No. **1427878**

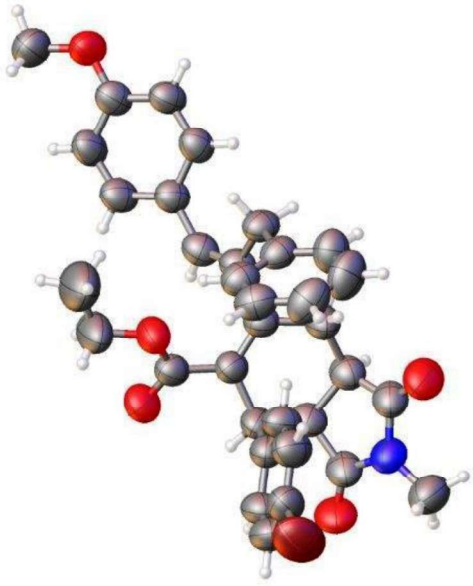


Figure S3.2: X-ray structure of **136**, CCDC No. **1427914**

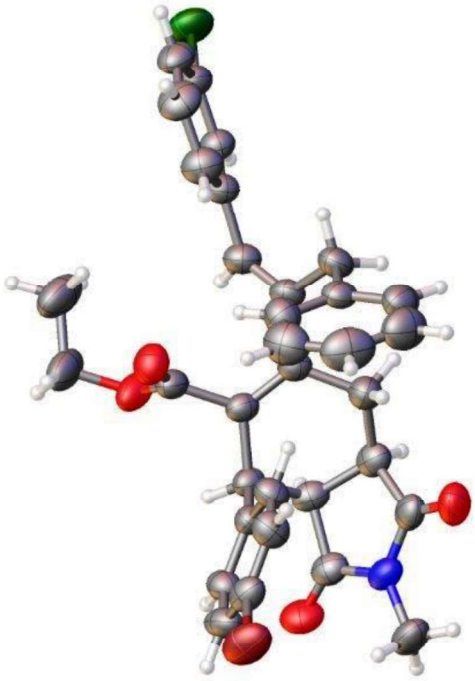


Figure S3.3: X-ray structure of **137**, CCDC No. **1427900**

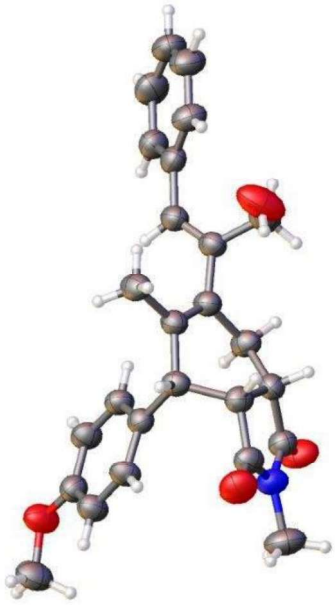


Figure S3.4: X-ray structure of **140**, CCDC No. **142791**

3.5.4 NMR spectra

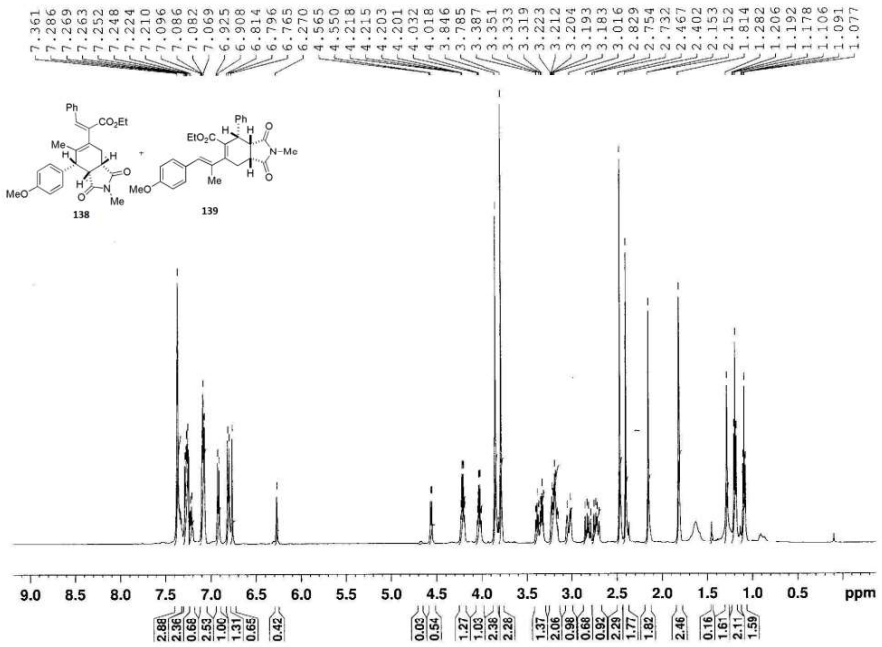


Figure S3.5: ^{1}H NMR spectrum of **138** and **139**

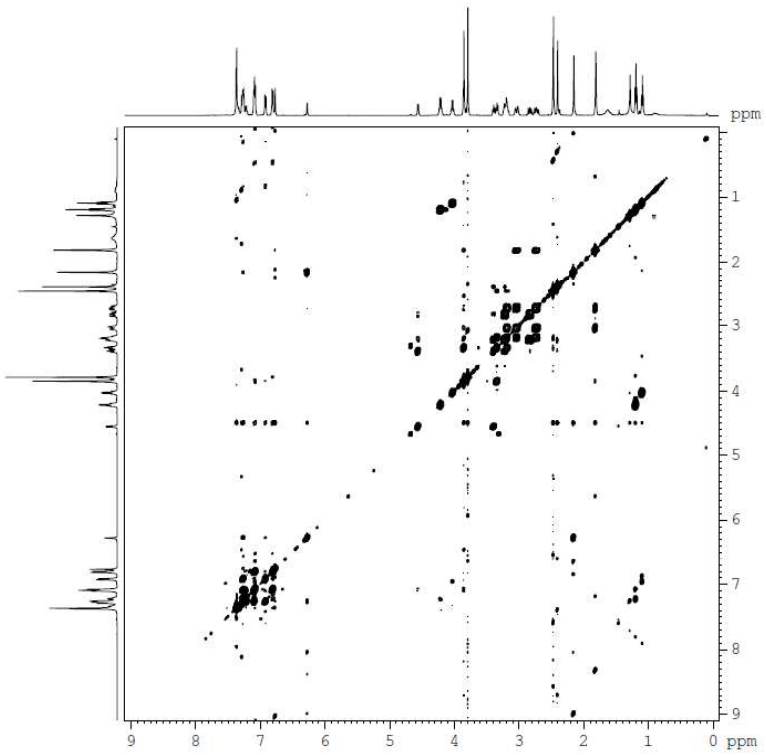


Figure S3.6: ^{1}H/^{1}H COSY spectrum of **138** and **139**

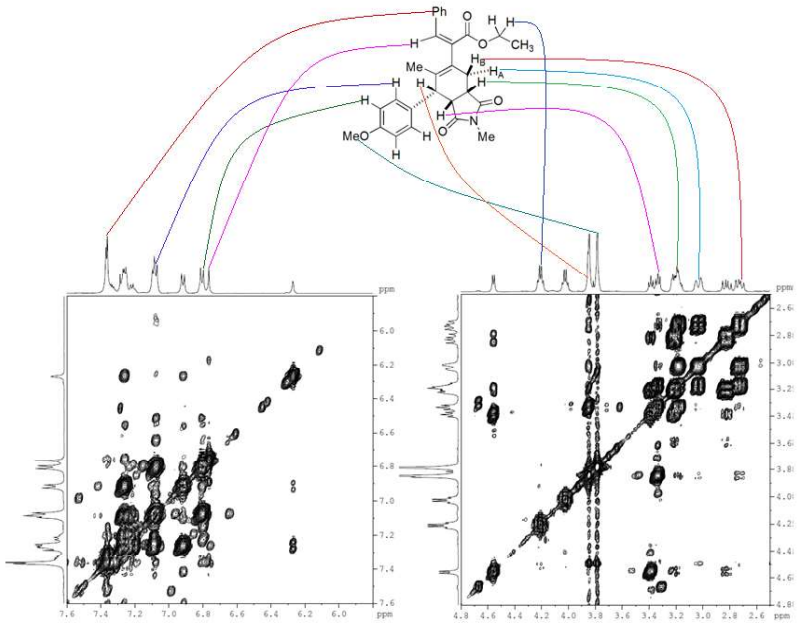


Figure S3.7: Expansions of $^{1}H/^{1}H$ COSY spectrum for the interpretation of peaks of **138**; Unmarked peaks belong to the other regioisomer **139**

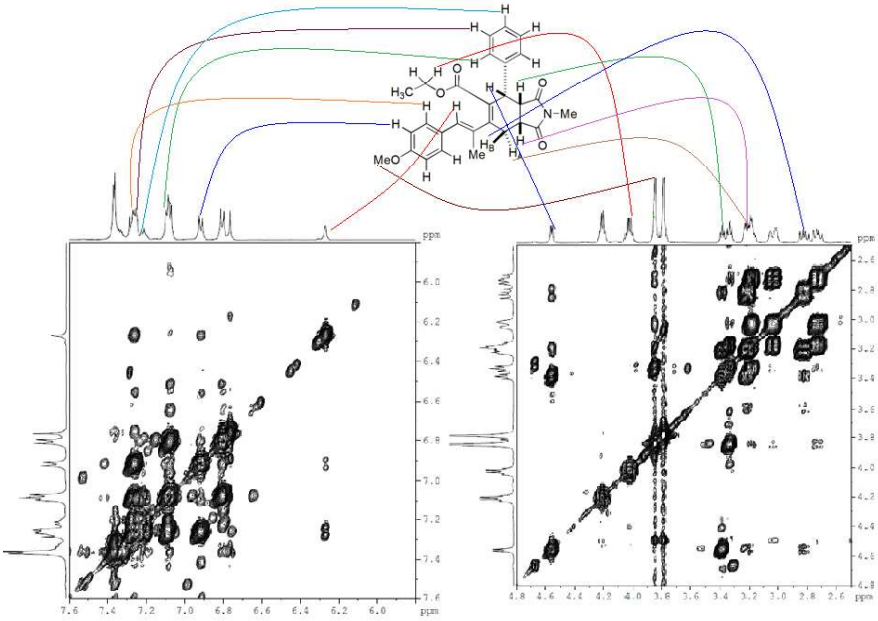


Figure S3.8: Expansions of $^{1}H/^{1}H$ COSY spectrum for the interpretation of peaks of **139**; Unmarked peaks belong to the other regioisomer **138**

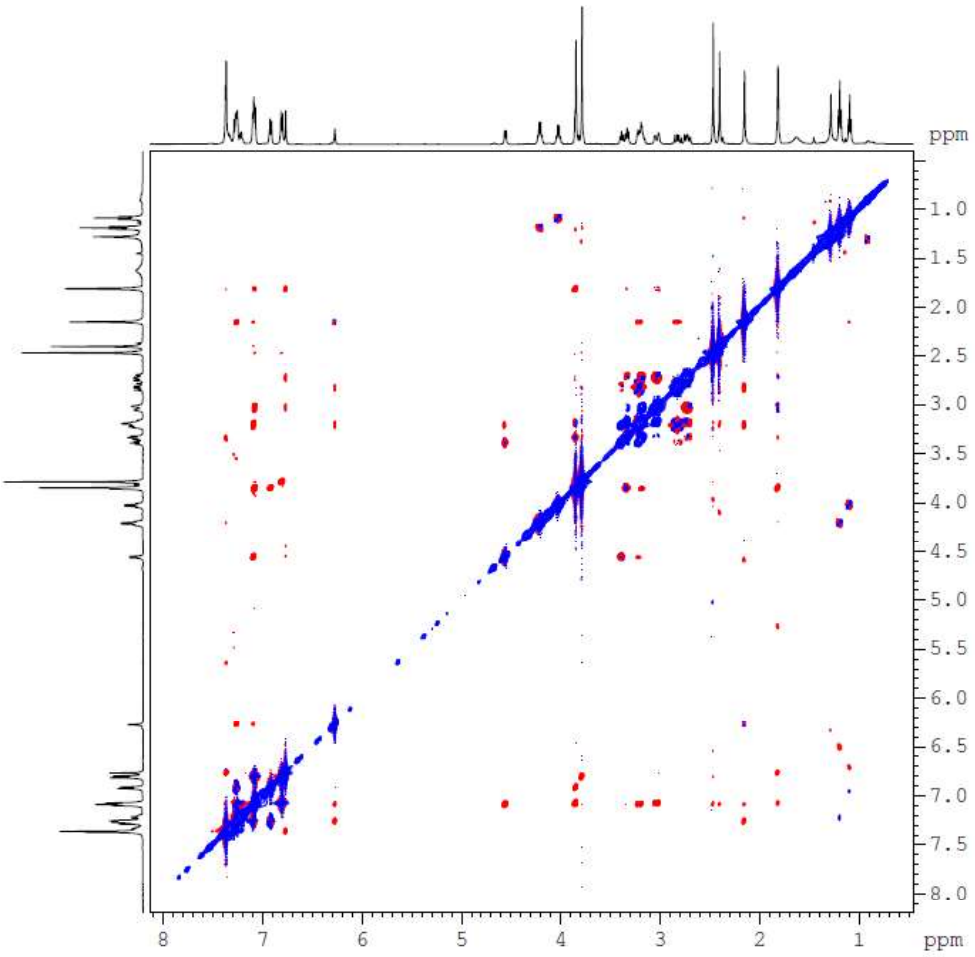


Figure S3.9: $^{1}H/^{1}H$ ROESY spectrum of **138** and **139**

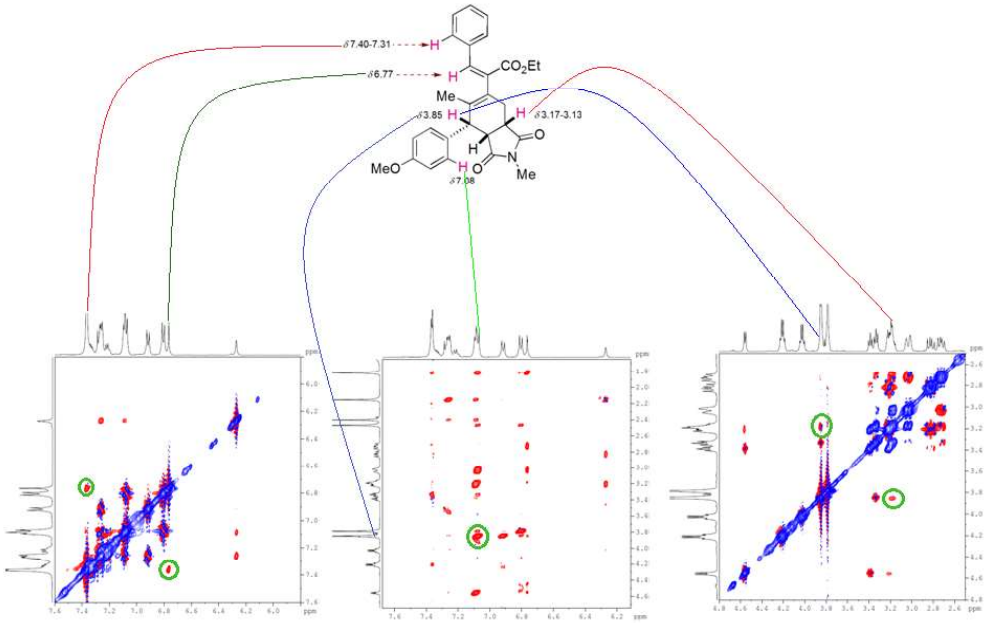


Figure S3.10: Expansions of $^{1}H/^{1}H$ ROESY for the assignment of stereo and regiochemistry of **138**

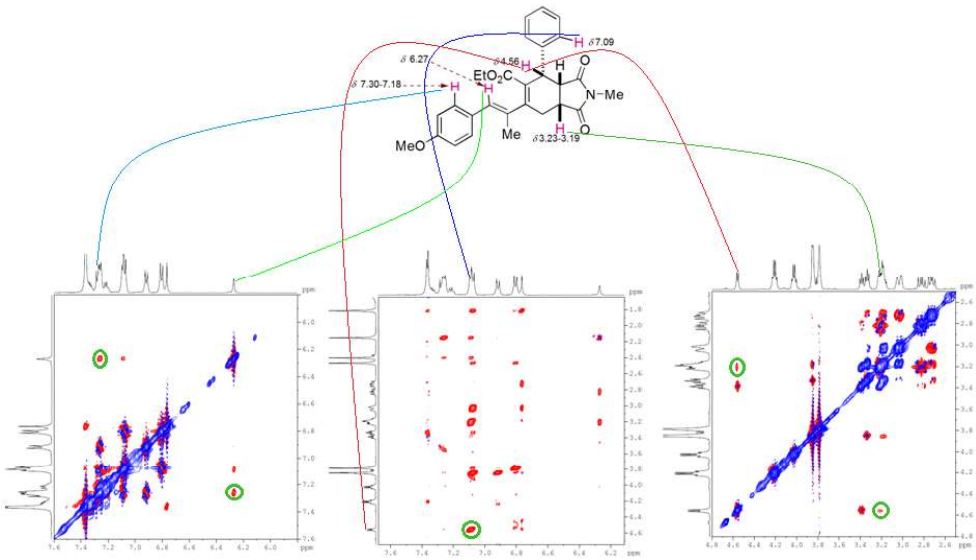


Figure S3.11: Expansions of $^{1}H/^{1}H$ ROESY for the assignment of stereo and regiochemistry of **139**

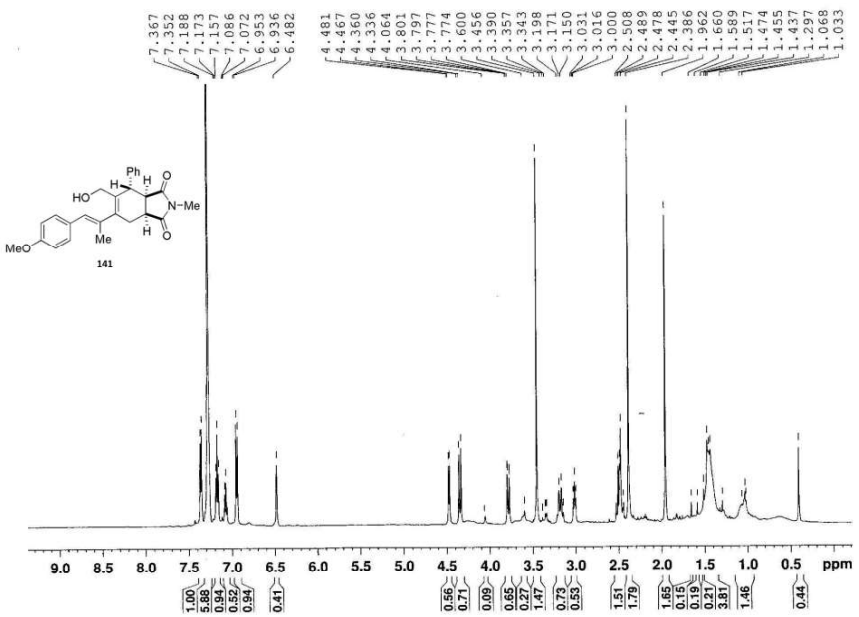


Figure S3.12: 1H NMR Spectrum of **141**

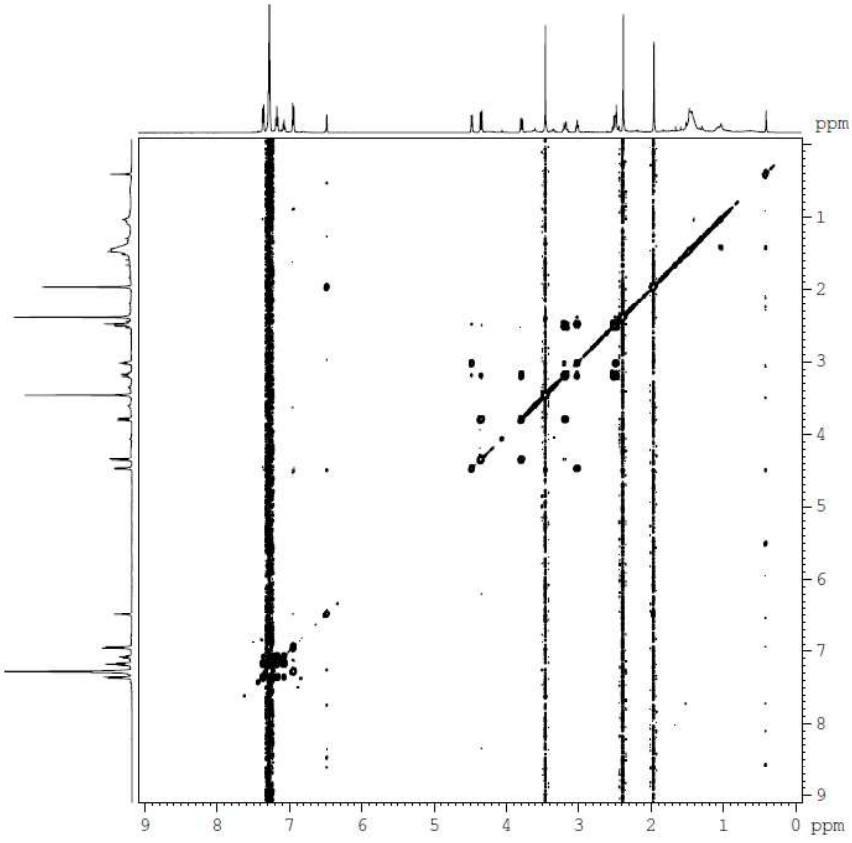


Figure S3.13 $^{1}H/^{1}H$ COSY spectrum of **141**

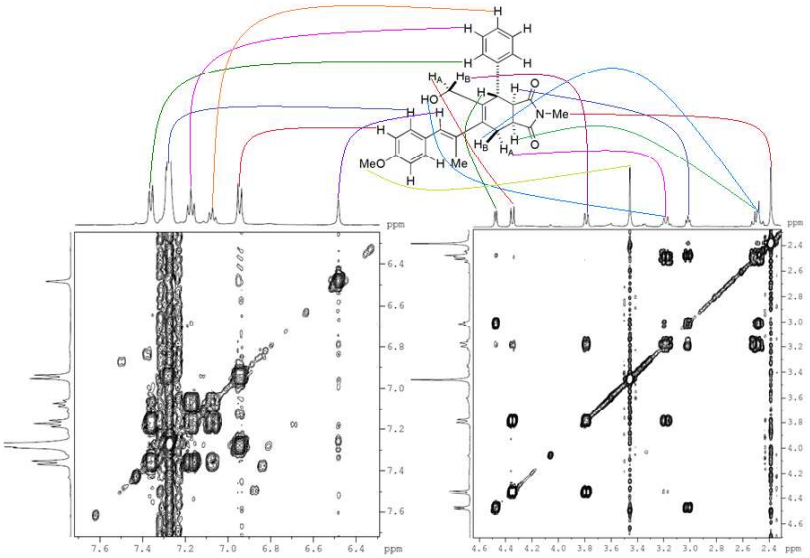


Figure S3.14: Expansions of $^{1}H/^{1}H$ COSY spectrum for the interpretation of peaks of **141**

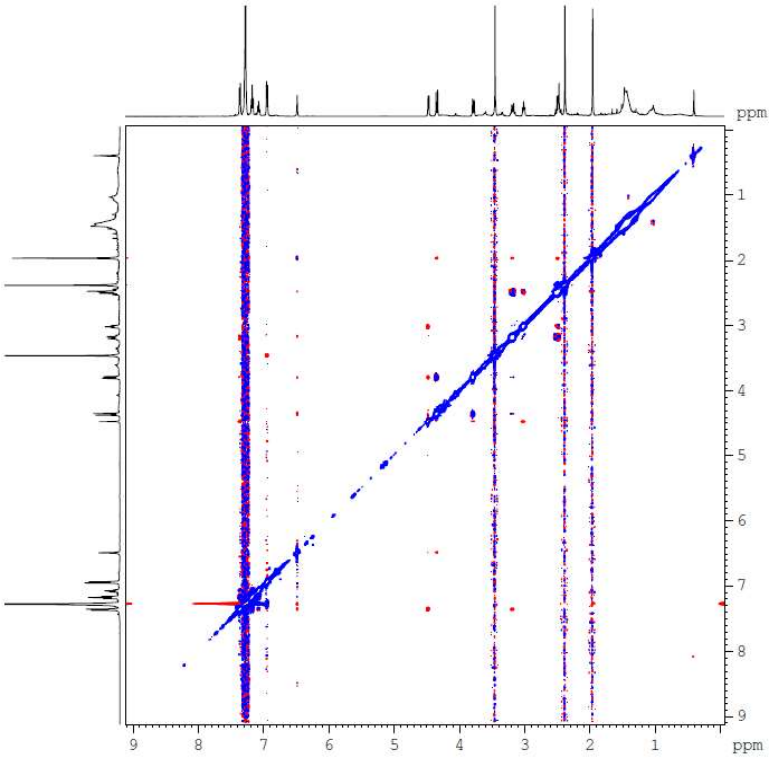


Figure S3.15: $^{1}H/^{1}H$ ROESY spectrum of **141**

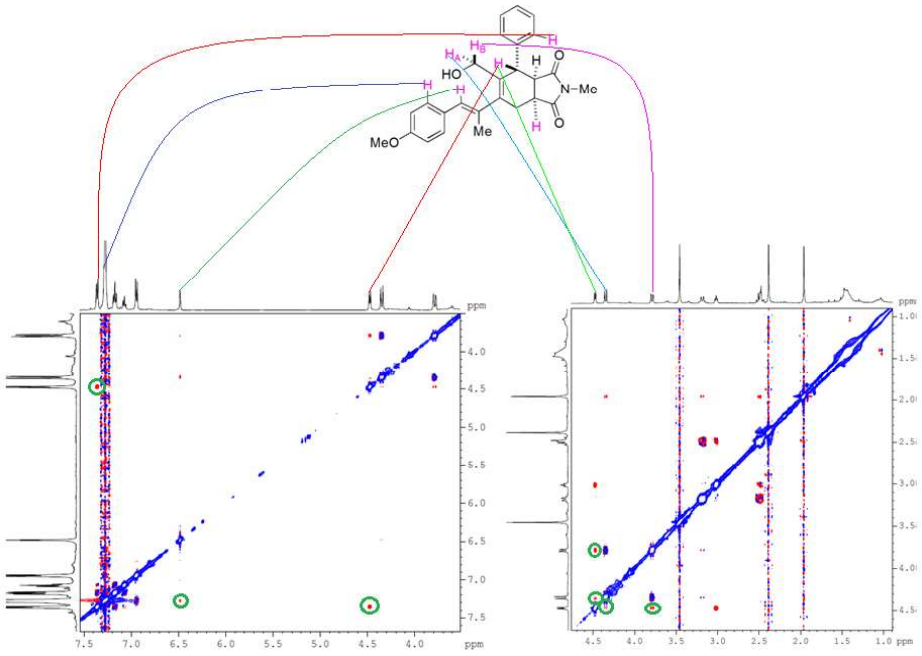


Figure S3.16: Expansions of $^{1}H/^{1}H$ ROESY for the assignment of stereo and regiochemistry of **141**

CHAPTER 4

Engagement of [3]Dendralenes in Diversity-Oriented Diene Transmissive Diels-Alder Reaction for Construction of the Obscure Polycycles

4.1 Introduction

Small bioactive molecules are regarded as powerful tools for biological studies since they interact with bio-macromolecules like proteins and consequentially exert specific effects.[77-79] Deliberate and selective use of small molecules for modulation of biological functions strengthens the fields of medicinal chemistry and chemical genetics.[80-82] Identification of such novel molecules capable of specific interactions with bio-macromolecules present a considerable challenge. When the biological target is well defined and understood the rational designing of bioactive molecules is feasible. However, for less understood cases, or when a novel mode of binding is involved, rational designing is not possible. Here high-throughput screening of small-molecule libraries can provide an effective solution.[83] The most important feature of these libraries is, their composition with regard to the chemical structures included within them.[84] Since the bioactivity of a given molecule is inherently related to its chemical structure; the greater degree of structural variation of compounds within a library would result in broad range of bioactivities across the library.[85-87]

The molecules comprising these libraries can be naturally existing or chemically synthesized. Umpteen number of naturally existing biologically relevant secondary metabolites display specific and exquisite biological activities and have been used in medicine as drugs and provide lead compounds.[88-90] But isolation, identification and purification of bioactive compounds from natural resources is quite a tedious process and also the quantities obtained are abysmal.[91] Thus, in order to have large number of compounds in sufficient quantities for screening, deliberate chemical synthesis is the most efficient approach. Hence, to cater to this potential need "*diversity-oriented synthesis*" (DOS) has been developed.[84,92,93] It forays into efficient

synthesis of collection of natural product like and/or drug-like molecules with diverse skeletal structures, since it is the skeletal nature which confers the desired bioactivity to a compound. The term "diversity-oriented synthesis" was coined by Stuart Schreiber in the year 2000.[94]

In target oriented synthesis (TOS) a target structure is broken down rationally into simpler starting materials and building blocks through retro synthetic analysis and these building blocks are then combined in a "convergent" fashion to achieve the target. Unlike the TOS which is convergent in nature, the strategy behind the DOS is divergent, where a small number of simple and similar compounds are transformed into many distinct structures. Direct application of retrosynthetic analysis is not feasible in case of DOS and forward synthetic analysis is needed. Thus starting materials and intermediates must be chosen with a view to diverse reactivity at a later point in the synthetic sequence. DOS pathways employ complexity-generating reactions to quickly build up molecular scaffolds (**Figure 4.1**).[93]

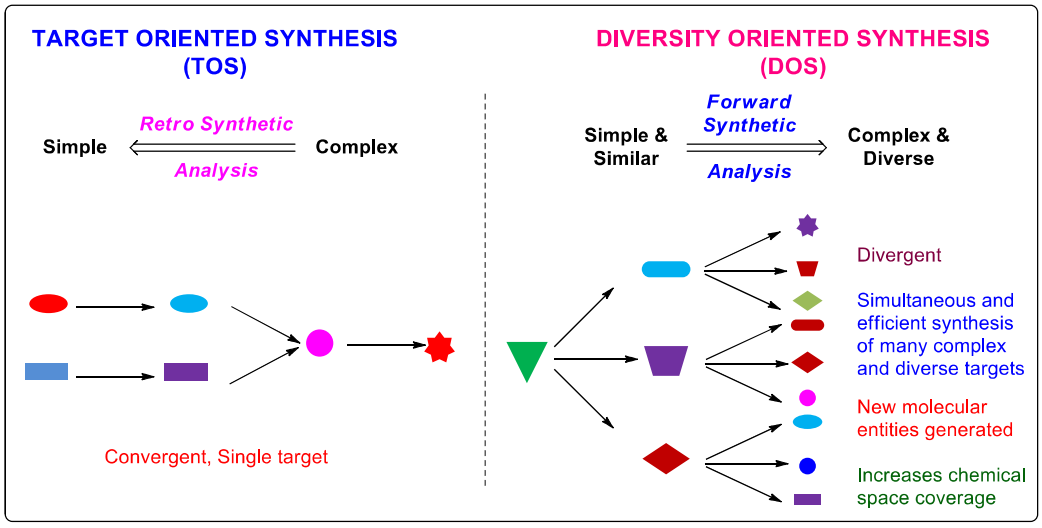


Figure 4.1 TOS *vs* DOS

Apart from meeting the needs of synthesis of small molecule collections exhibiting a spectrum of bioactivities for generation of lead in drug discovery, DOS also holds such a promise for the identification of novel compounds with a desired physicochemical property such as catalysts, synthetic reagents or biological probes. In this regard, dendralenes are splendid contenders for rapid generation of structural complexity with step and atom economy owing to their propensity to get engaged in diene transmissive Diels-Alder (DTDA) sequences. Thus, DOS and [3]dendralenes synergistically upon appropriate selection of dienophiles, open gateway to a gamut of compounds with complex and diverse architecture (**Figure 4.2**).

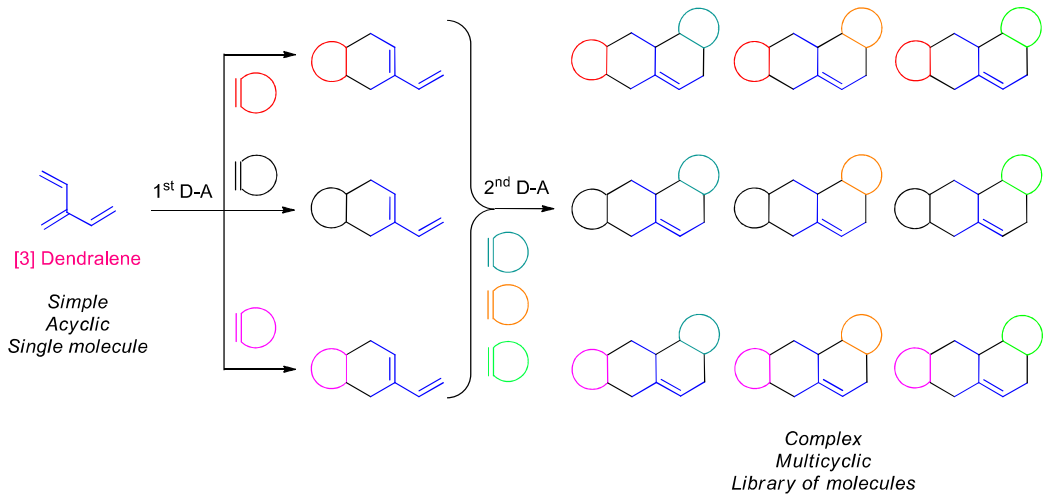
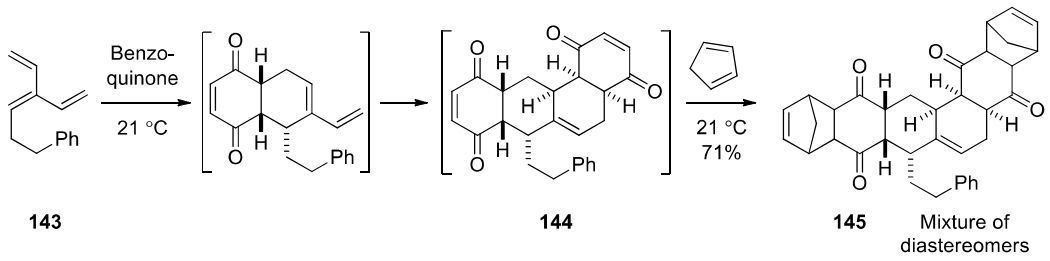


Figure 4.2 Diversity oriented synthesis with [3]dendralenes

4.2 DTDA reactions of other research groups

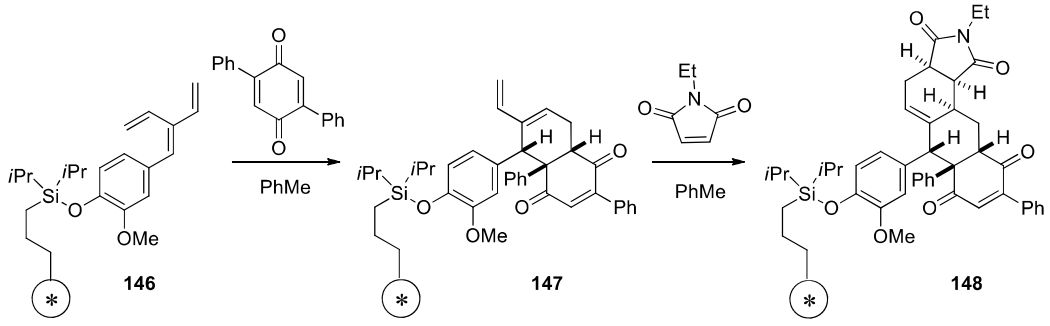
Many research groups have performed DTDA reactions with unsubstituted [3]dendralenes to achieve structural complexity.[21,22,95] Fallis and co-workers have performed many DTDA sequences with 3' monosubstituted [3]dendralenes and shown how multicyclic frameworks can be generated *via* tandem cycloadditions.[14,29,30,96] In one of their examples, the 3'-substituted dendralene **143** was treated with *p*-

benzoquinone to provide tetracyclic scaffold **144** which upon subsequent addition of cyclopentadiene furnished octacyclic complex molecule **145** as a mixture of diastereomers (**Scheme 4.1**).[30] Thus one-pot reaction quickly generated four new rings *via* the combination of five molecules.



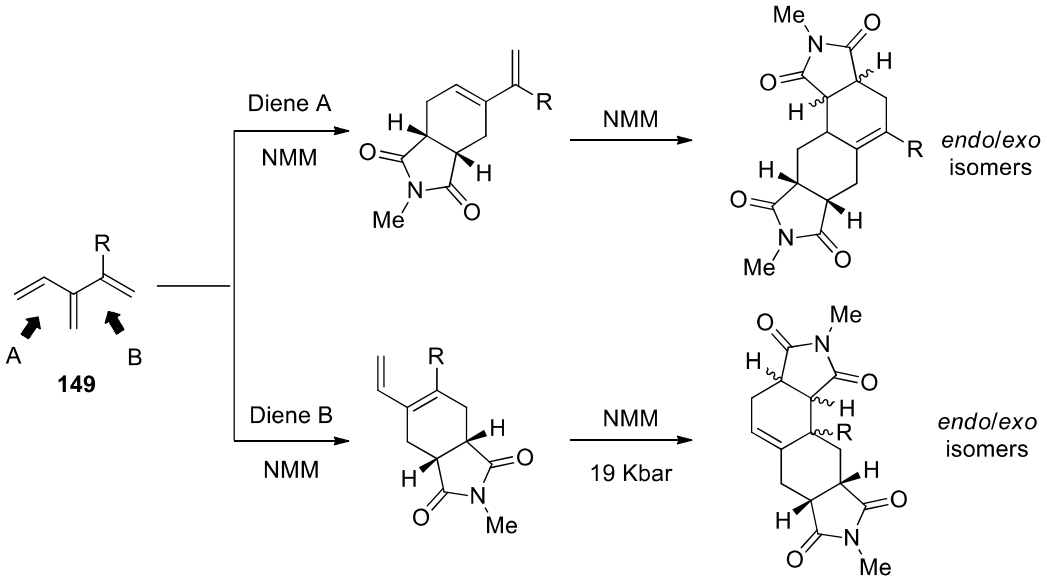
Scheme 4.1 DTDA sequence of [3]dendralene by Fallis *et al.*

By utilizing the methodology of Fallis, Schreiber and co-workers have synthesised 3'-monosubstituted [3]dendralenes on solid support and employed them in diversity oriented synthesis to prepare a library of polycyclic compounds *via* DTDA sequences.[31] When tri- or tetrasubstituted dienophiles were used for the first D-A reaction, the first D-A adduct could be isolated and treated with a different dienophile. A representative example is shown in **Scheme 4.2**. The solid supported [3]dendralene **146** was subjected to a DTDA sequence using 2,5-diphenyl benzoquinone and N-ethylmaleimide to prepare complex scaffold **148**.



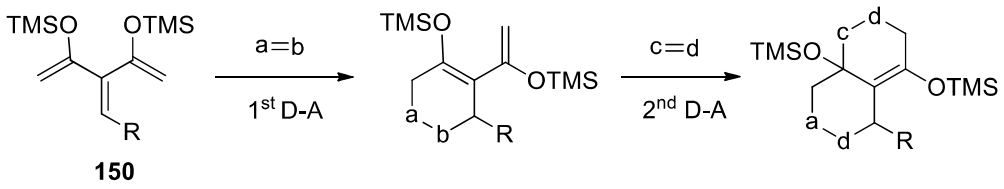
Scheme 4.2 Schreiber and co-workers approach to DOS on solid support

On the basis of above examples, Sherburn and coworkers have synthesized chiral 3'-monosubstituted [3]dendralene and used it for the generation of enantiomerically pure cycloadducts.[33] Apart from this, their group has reported the DTDA reactions of some mono and unsubstituted [3]dendralenes.[17,37-40] In case of 3'-monosubstituted [3]dendralenes, since both the dienic systems are identical there is no regioselectivity issue. But, in case of unsymmertically substituted [3]dendralene D-A reactions may result in formation of regioisomers. This was the case when DTDA reaction was performed on 2-substituted [3]dendralenes **149** both the dienes '**A**' and '**B**' participated in the D-A reaction in variable ratios and provided mixture of four regio- and stereoisomers (**Scheme 4.3**).[38]



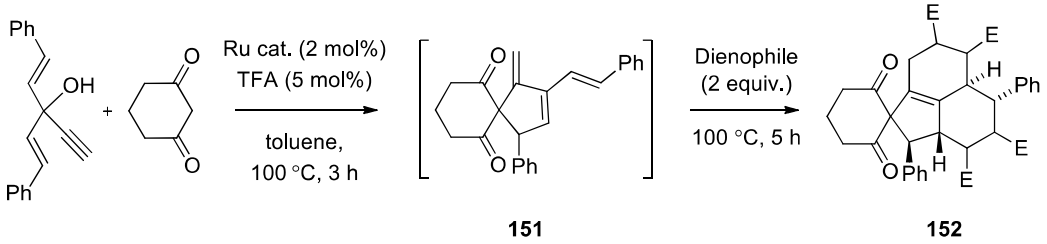
Scheme 4.3 DTDA reaction of unsymmetric [3]dendralenes by Sherburn's group

Researchers of all these groups performed DTDA reactions either with unsubstituted or with monosubstituted [3]dendralenes. Tsuge *et al*. had reported DTDA reaction of enol ether-type 2, 3',4 trisubstituted symmetric [3]dendralenes **150** thus once again did not face regioselectivity issue (**Scheme 4.4**). [13,97]



Scheme 4.4 DTDA reactions of Tsuge and coworkers

As discussed in **Chapter 1** (**Scheme 1.2**)**,** Shenvi *et al*. have synthesized Danishefsky [3]dendralene and used it for the synthesis of antimalarial compounds by employing DTDA reaction.[15,16] Lately Haak has reported DTDA with cyclic trisubstituted [3]dendralenes **151** for the synthesis of polycyclic compounds **152** with a single dienophile (**Scheme 4.5**).[47a]



Scheme 4.5 DTDA reactions of Haak *et al*.

Although above mentioned research groups have performed DTDA with various [3]dendralenes, except Schreiber none of the groups used it towards diversity oriented synthesis, and he did on the solid support.

4.3 Present work

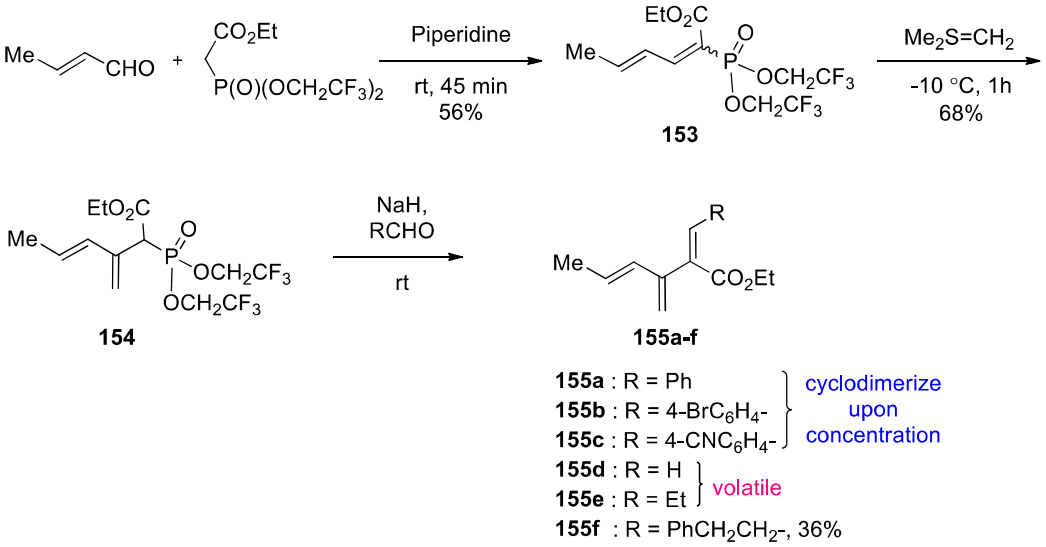
The full potential of the dendralenes in organic synthesis can be derived only when they are engaged in the DTDA sequence preferably using two different dienophiles which would result in rapid generation of complex scaffold bearing multiple stereogenic centres in a quick and efficient manner with step and atom economy. Our

earlier dendralenes were extremely unstable (**109** and **112**),[66,67] later stable [3]dendralenes (**120** and **125**) were synthesized but they did not undergo D-A reaction due to bulky silyl functionality (**Chapter 2**).[68] Dendralenes **135a-k** prepared in **Chapter 3** were slightly more reactive than silyl dendralenes; they did participate in the first D-A reaction but did not undergo second D-A reaction once again due to the bulk of the substituents.[73] Thus in order to make dendralenes participate in a DTDA sequence, the reactivity of the two dienic systems in [3]dendralene must be astutely differentiated; also the reactivity and the stability of the dendralenes must be fine tuned to maintain a subtle balance of the two. An insight of conformational preferences and activation/deactivation of the dienes by the presence of the functional groups at various positions would assist in designing the quintessential dendralene structures and eventually culminate to a successful DTDA. Also as mentioned above that DOS and [3]dendralenes synergistically upon appropriate selection of dienophiles, open gateway to a gamut of compounds with complex and diverse architecture.

From earlier chapters it was found that conjugating terminal substituents accelerate the rate of D-A cyclodimerization of [3]dendralenes. However, substitution at both second and fourth positions significantly enhanced the stability of the [3]dendralenes, but steric bulk impedes the second D-A reaction. Hence, dendralenes had to be tailored in such a fashion that they bore aliphatic groups at the terminal positions for enhancement of the stability at the same time there was minimal steric congestion of the internal substituents which would allow a facile DTDA reaction.

For the achievement of this goal, synthesis was started with Knoevenagel condensation of crotonaldehyde and ethyl bis-(2,2,2-trifluroethyl)-phosphonoacetate in the presence of piperidine which furnished the desired dienyl phosphonate **153**

(56%) as a mixture of two geometrical diastereoisomers (72:28) arising from the double bond attached to phosphonate group as judged from ^{1}H NMR (**Scheme 4.6**). When the phosphonate **153** was reacted with dimethylsulfonium methylide, the desired olefination took place to provide the substituted butadien-2-ylphosphonoacetate **154** as a pale yellow liquid in 68% yield. This phosphonoacetate **154** was then treated with sodium hydride in THF followed by various aldehydes under standard H-W-E conditions which furnished the desired substituted [3]dendralenes (**155a-f**) (**Scheme 4.6**) with one of the terminal substituent as a non-conjugating methyl group, which would render stability to these dendralenes. All the dendralenes as anticipated were stable but to varying degrees.

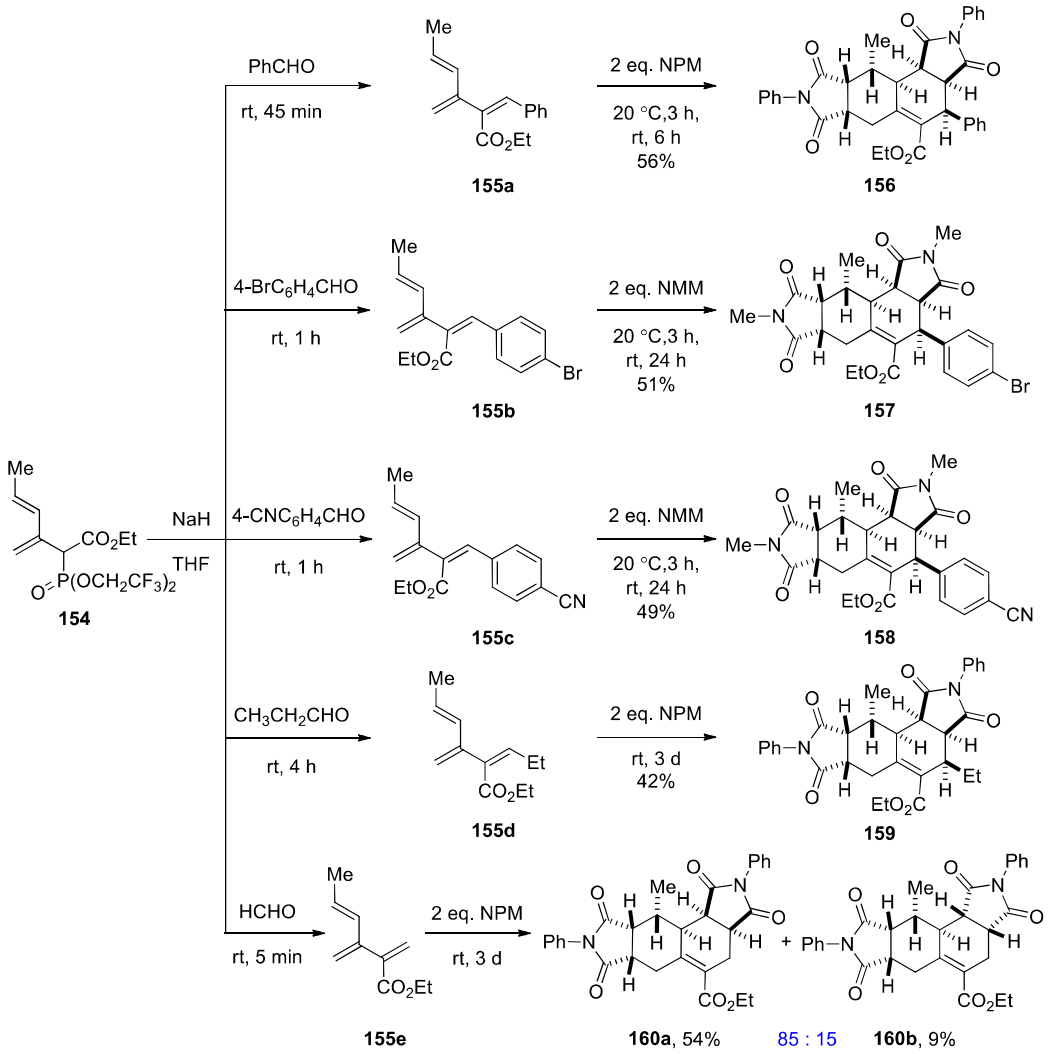


Scheme 4.6 Synthesis of [3]dendralenes

The dendralenes **155a-c** were stable in dilute solutions but were prone to D-A cyclodimerization upon concentration. The dendralenes **155d-f** were stable even in concentrated solutions but dendralenes **155d** and **155e** were volatile. Owing to these difficulties, dendralenes **155a-e** could not be directly characterized hence were

subjected directly to DTDA sequence after isolation in solution from the reaction. The dendralene **155f** was obtained in 36% yield as a colorless liquid.[98]

After the synthesis of stable [3]dendralenes, aim was to engage them in the DTDA reactions. Dendralenes **155a**, **155d** and **155e** were reacted with 2 equivalents of *N*-phenylmaleimide (NPM) whereas dendralenes **155b** and **155c** were reacted with 2 equivalents of *N*-methylmaleimide (NMM) to obtain the DTDA adducts **156-160** as depicted in **Scheme 4.7**.[98]



Scheme 4.7 DTDA reactions of [3]dendralenes

A single diastereoisomer was obtained in all the cases with high regio and stereoselectivity except in the case of adduct **160** where two diastereoisomeric products (**160a**, **160b**) were obtained in a ratio of 85:15. The structures of adducts **156-158**, **160a** were ascertained by single crystal X-ray crystallography (**Figure 4.3**). These structures revealed that both the consecutive D-A reactions were *endo* selective. The minor isomer **160b** was the *exo* isomer resulting from the second D-A reaction. The formation of this isomer resulted since there was no substituent at the first position of dendralene **155e**. This exemplified the role of substituents in governing the stereoselectivity of the D-A reactions. The stereochemistry of the adduct **159** was assigned on the basis of analogy of the other adducts.

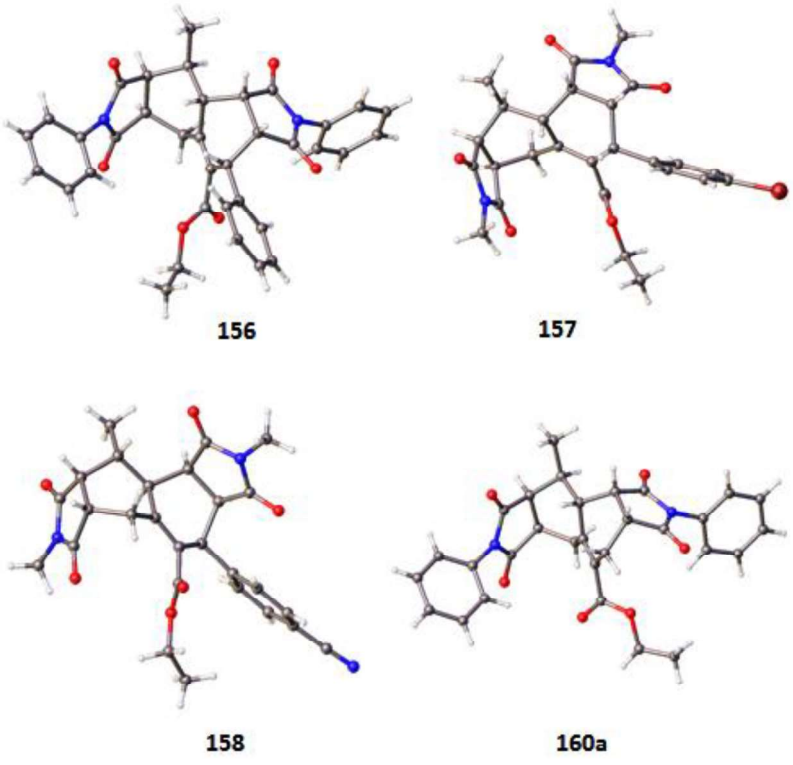
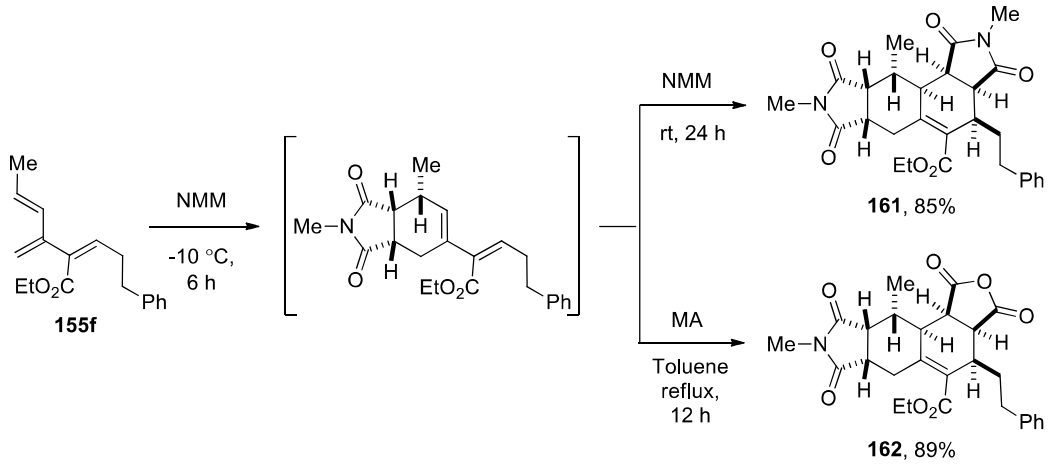


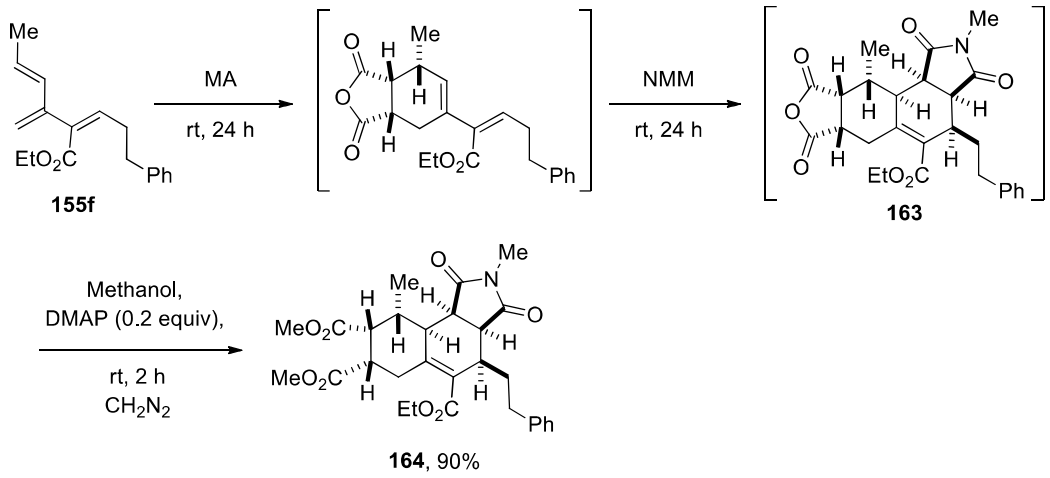
Figure 4.3 X-ray structures of **156**, **157**, **158** and **160a**

Subsequent to successful DTDA reactions of relatively less stable or volatile [3]dendralenes with same dienophile, for enhancement of structural diversity attention was turned towards the more stable dendralene **155f**. At the outset, this dendralene **155f** was reacted with two equivalents of NMM which afforded DTDA adduct **161** in 85% yield (**Scheme 4.8**).[98] For augmentation of structural diversity, it was decided to perform the DTDA reaction of this dendralene with two different dienophiles in tandem. Thus, dendralene **155f** was reacted with NMM at -10 °C followed by maleic anhydride (MA) in refluxing toluene to provide the adduct **162** (89%) as the sole product (**Scheme 4.8**).

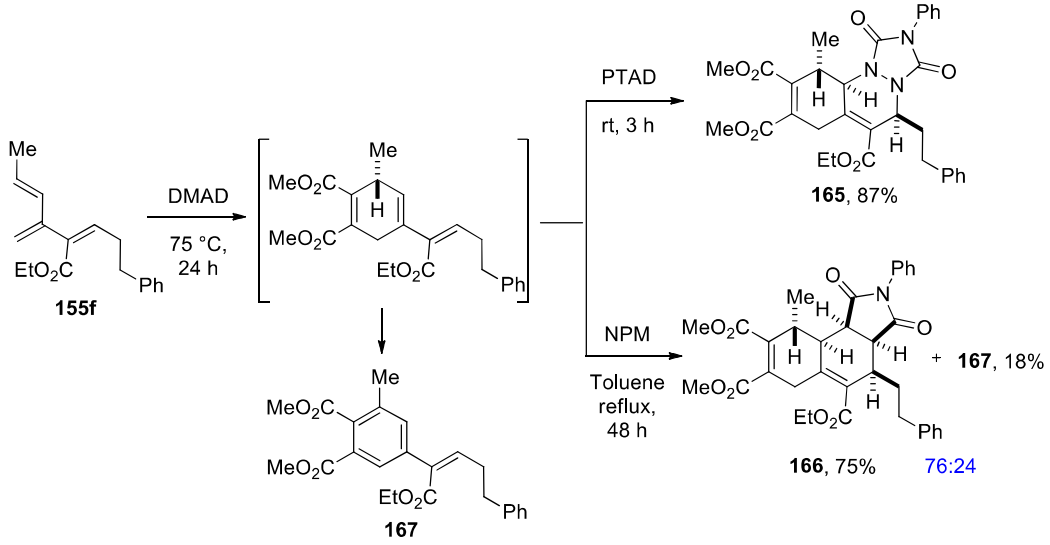


Scheme 4.8 DTDA reaction with NMM and MA

Conversely, dendralene **155f** upon reaction with MA followed by NMM gave the DTDA adduct **163**. This adduct subsequent to reaction with methanol and esterification with diazomethane afforded the dimethyl ester **164** in 90% yield (**Scheme 4.9**).[98]



Scheme 4.9 DTDA reaction with MA and NMM

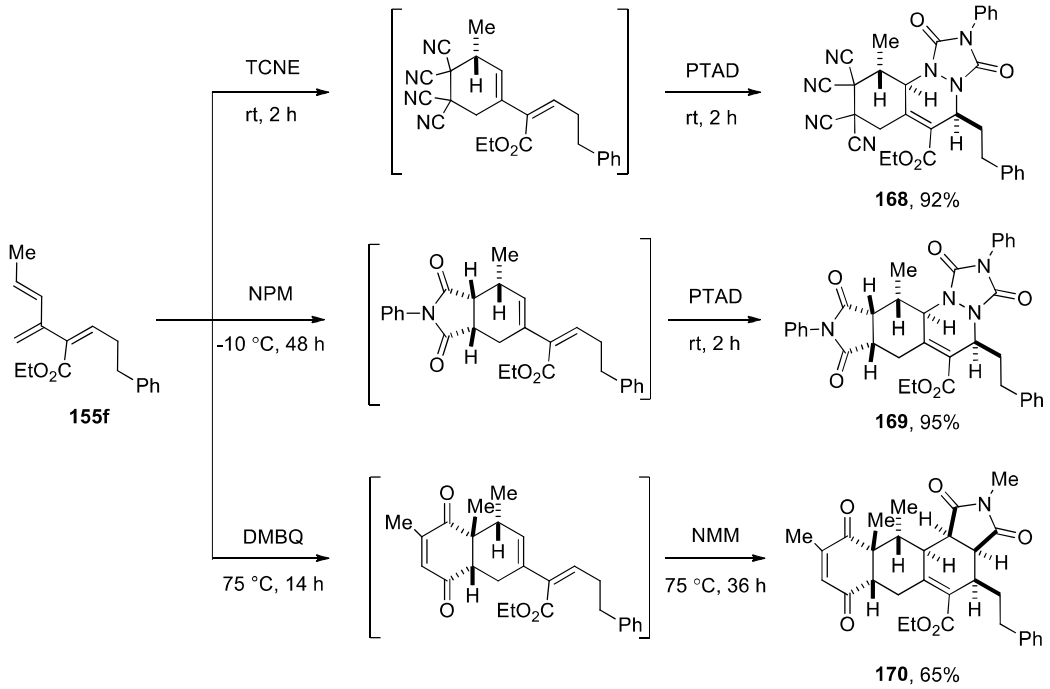


Scheme 4.10 DTDA reaction with DMAD and PTAD/NPM

Further, [3]dendralene **155f** was treated with dimethyl acetylenedicarboxylate (DMAD) at 75 °C followed by 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) at ambient temperature to grant the cinnoline derivative **165** in 87% yield (**Scheme 4.10**). Besides this, dendralene **155f** upon reaction with DMAD at 75 °C and subsequently with NPM in refluxing toluene furnished the isoindole derivative **166** in 75% yield. It was

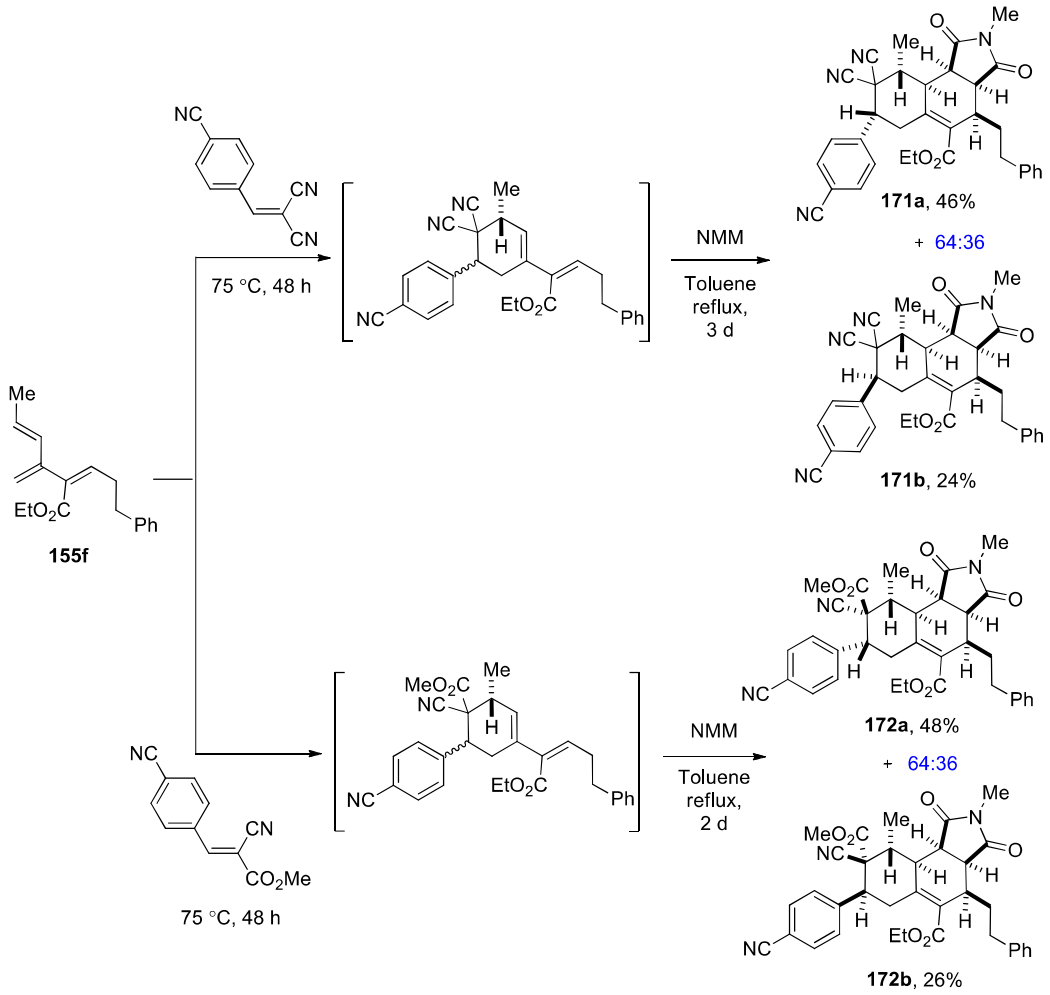
associated with a small but variable amount of byproduct **167** (ca. 18%) formed due to the aromatization of the first D-A adduct (**Scheme 4.10**).[98]

With this there was enhancement of certain amount of diversity. Furthermore, tetracyanoethylene (TCNE) and PTAD sequentially reacted smoothly with dendralene **155f** at ambient temperature to provide yet another cinnoline derivative possessing tetracyano functionality **168** in 92% yield (**Scheme 4.11**). In addition to this, NPM and PTAD on sequential reaction with dendralene **155f** at -10 °C and ambient temperature, respectively, afforded a hybrid of cinnoline and isoindole derivative **169** in 95% yield. In order to incorporate more diversity, **155f** was reacted with 2,6-dimethyl-1,4-benzoquinone (DMBQ) followed by NMM in toluene at 75 °C which provided isoindole derivative **170** featuring dione functionality in 65% yield.[98]



Scheme 4.11 DTDA reactions of dendralene **155f**

In attempt to increment the diversity further, it was intended to explore the DTDA reaction with unsymmetrical dienophiles. To accomplish this endeavour, **155f** was subjected to reaction with 2-(4-cyanobenzylidene)malononitrile (CBMN) or (*E*)-methyl 2-cyano-3-(4-cyanophenyl)acrylate (MCCA) at 75 °C followed by reaction with NMM in refluxing toluene (**Scheme 4.12**).



Scheme 4.12 DTDA reaction of **155f** with unsymmetric dienophiles

In both the cases a mixture of diastereoisomeric adducts in a ratio of 64:36 was obtained. Adducts **171a** (46%) and **171b** (24%) were obtained from reaction with 2-(4-cyanobenzylidene)malononitrile and their structures were ascertained by single

crystal X-ray crystallography (**Figure 4.4**). Adducts **172a** (48%) and **172b** (26%) were obtained from reaction with (*E*)-methyl 2-cyano-3-(4-cyanophenyl)acrylate and the structure of adduct **172b** was confirmed by single crystal X-ray crystallography (**Figure 4.4**). The stereochemistry of **172a** was assigned on the basis of analogy with **171a**. The diastereoisomers in both of these cases had resulted due to *endo*/*exo* approach of the dienophile during first D-A reaction. Nonetheless, both the reactions were highly regioselective and no other regioisomeric products were detected.[98]

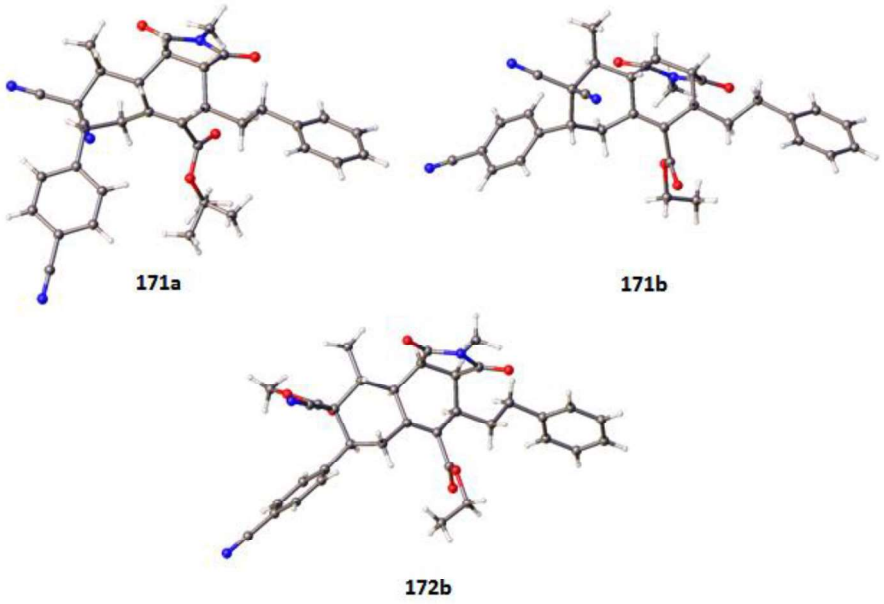
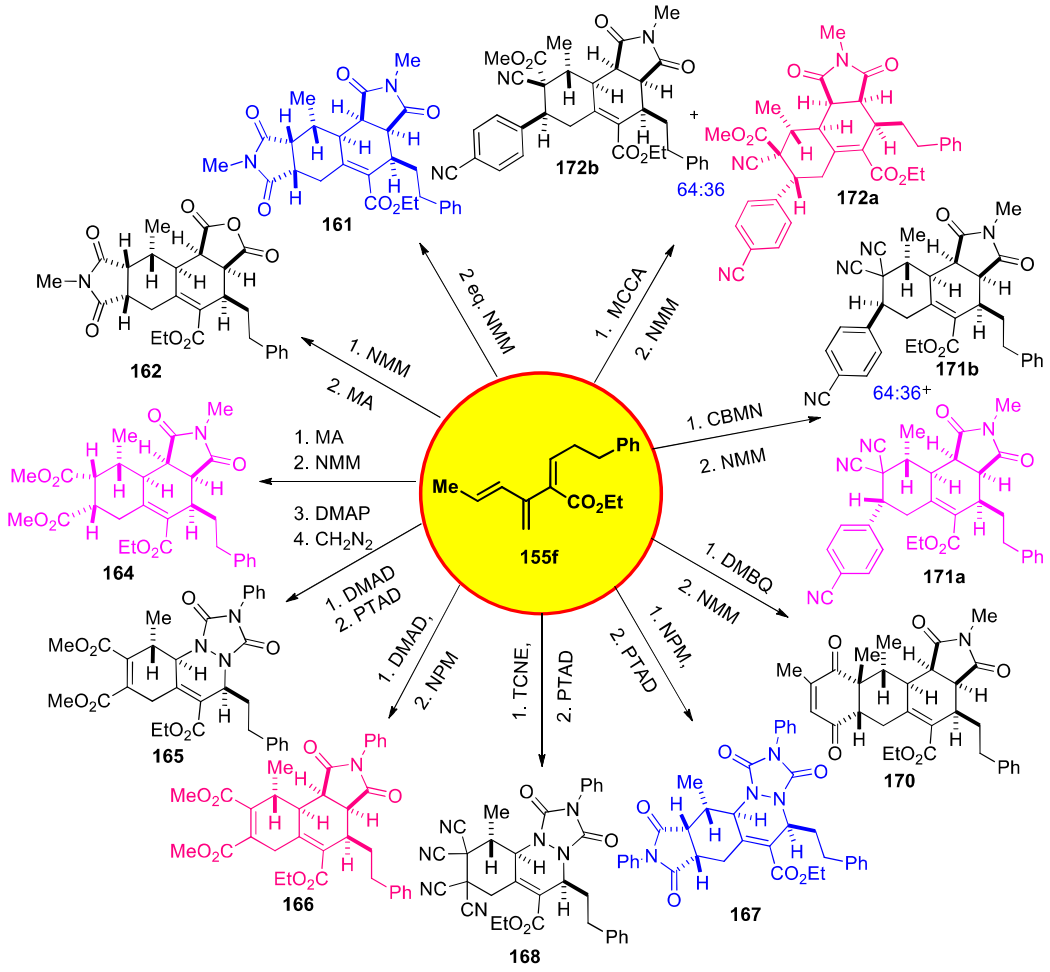


Figure 4.4 X-ray structures of **171a**, **171b** and **172b**

The stereochemistry of adducts **160**, **162**, **164-166 and 168-170** was assigned on the basis of analogy to adducts **156-158, 160a** and **171a**. This was further supported by $^{1}H/^{1}H$ COSY and ROESY correlation of **165**, **166** and **168** (For COSY and ROESY spectra, see appendix at the end of the chapter).

To this end, it can be seen that after encounter with initial stumbling blocks, eventually the way for the engagement of amply substituted [3]dendralenes in DTDA

sequences could be paved. Also, tangible amount of diversity and complexity along with selectivity could be embodied in these adducts. Thus a small but diverse repository of complex molecules could be generated from a trivial acyclic molecule (**Scheme 4.13**).



Scheme 4.13 Diversity oriented DTDA reactions with dendralene **155f**

4.4 Rationale for stability/reactivity of [3]dendralenes

Now it can be rationalized how the attributes and position of the substituents govern the stability and reactivity of the [3]dendralenes (**Figure 4.5**). Dendralenes with both the terminal conjugating aromatic functional groups rapidly cyclodimerize, whereas

when just single terminal aromatic substituent is present the dendralene is short lived but isolable. Amongst the two terminal groups when one is non-conjugating aliphatic and the other one is conjugating aromatic the dendralenes are stable in dilute solutions but undergo cyclodimerization upon concentration. Dendralenes bearing both the terminal groups as non-conjugating aliphatic groups are stable even in concentrated solutions. Also it is noteworthy that in the case of dendralenes possessing both terminal groups as conjugating functional groups, the presence of internal groups renders the stability to them and they are stable even as neat compounds since the active diene is forced to adopt a *s-trans* conformation due to steric congestion.

With regard to the DTDA neither too reactive nor too stable dendralenes are appropriate (**Figure 4.5**), since the former undergo cyclodimerization readily whereas the latter just undergo first D-A but do not undergo second D-A on account of non-coplanarity of the dienic system caused by steric congestion. The most suitable candidates for the DTDA are the dendralenes with moderate stability and reactivity.

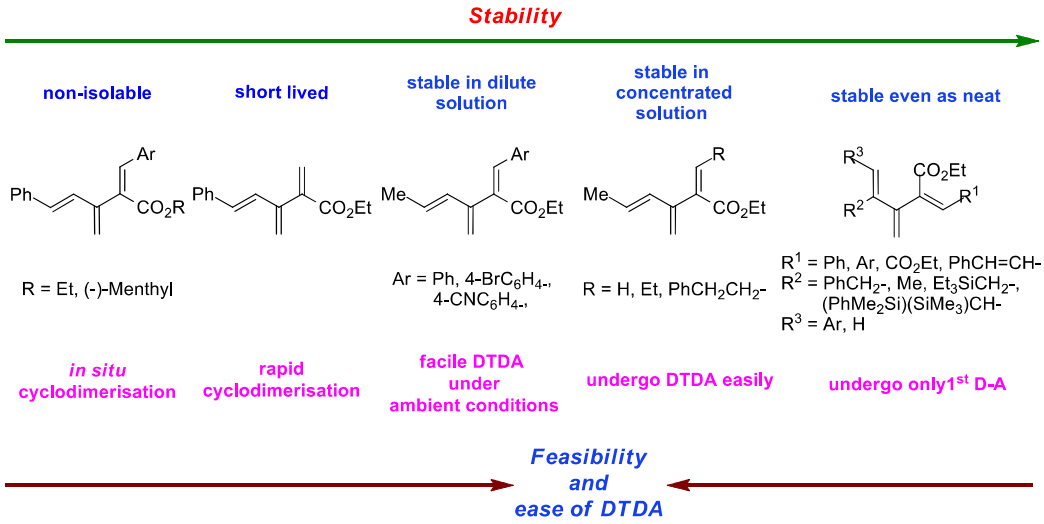


Figure 4.5 Substituent effect on the stability and DTDA reactivity of [3]dendralenes

4.5 Conclusions

To summarize, stable acyclic trisubstituted [3]dendralenes were synthesized. Their stability and reactivity was tuned by making a judicious choice of the position and the nature of the functional groups. These dendralenes were allowed to participate in the DTDA sequence by employing several symmetrical as well as unsymmetrical dienophiles for the diversity oriented synthesis of multicyclic complex scaffolds possessing several functional groups and multiple stereogenic centers. Thus the full potential of [3]dendralenes was tapped successfully by engaging them in DTDA reactions using two different dienophiles. The D-A reactions were facile, highly regio, stereoselective and proceeded with *endo* selectivity. The DTDA sequences involved the generation of four new carbon-carbon bonds, two new rings and 3-7 stereogenic centers. A rapid generation of complexity along with functional and structural diversity took place from simple acyclic substrate. The process was associated with step, atom economy and involved mild reaction conditions. The compounds synthesized resemble the cores of several bioactive natural products hence could serve as promising candidates for biological studies. Correlation between the stability, reactivity and attributes of the substituents of the [3]dendralenes could be deduced for the achievement of a successful DTDA reaction with desired level of selectivities.

4.6 Experimental section

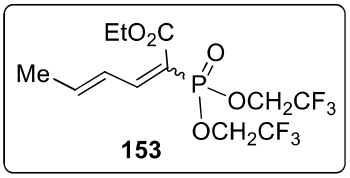
4.6.1 General Details: As described in **Chapter 2**

NMR Study: ^{1}H NMR spectra were recorded on 500 MHz and ^{13}C NMR spectra were recorded with 125 MHz spectrometer using $CDCl_3$ and C_6D_6 as the solvents. The spectra were referenced to residual chloroform (δ 7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C) and

partially deuterated benzene (δ 7.16 ppm, ^{1}H; 128.4 ppm, ^{13}C). For the interpretation of ^{1}H decouple ^{13}C spectrum, the number of expected carbons are provided in the parenthesis.

4.6.2 Procedures and characterization data of products

(2*E*/*Z*,4*E*)-Ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)hexa-2,4-dienoate (153)



153

To a solution of ethyl bis-(2,2,2-trifluroethyl)-phosphonoacetate (1.0 g, 3.01 mmol, 1 equiv) in benzene (2 mL), freshly distilled piperdine (0.074 mL, 0.75 mmol, 0.25 equiv) was added followed by dropwise addition of freshly distilled crotonaldehyde (0.275 mL, 3.31 mmol, 1.1 equiv) over a period of 5 min. The reaction mixture was stirred for 1 h at ambient temperature and then quenched with water. The reaction was extracted with 20% EtOAc in petroleum ether, the organic extract was concentrated under the reduced pressure and the residue purified by column chromatography (petroleum ether-EtOAc; 85:15) to give product **153** as mixture of two *E/Z* isomers (0.65 g, 56%) in a ratio of 72:28 as brown a coloured liquid.

(2*E*,4*E*)-Ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)hexa-2,4-dienoate (*E*-153)

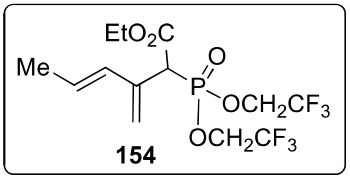
IR (film): ν_{max} = 2980, 2917, 1718, 1632, 1579, 1419, 1375, 1174, 928, 735 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (dd, J = 24.0, 11.5 Hz, 1 H, P(O)CCH), 7.29 (dd, J = 15.0, 13.5 Hz, 1 H, CH_3CHCH), 6.50 (dq, J = 13.5, 6.5 Hz, 1 H, CH_3CHCH), 4.49-4.31 (m, 4 H, 2 × OCH_2CF_3), 4.27 (q, J = 7.5 Hz, 2 H, OCH_2CH_3), 1.97 (d, J = 7.0 Hz, 3 H, CH_3CH), 1.31 (t, J = 7.0 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$):

δ 163.4 (d, J = 16.1 Hz), 158.4 (d, J = 6.6 Hz), 150.2, 128.2 (d, J = 20.9 Hz), 122.6 (dq, J = 276.0, 9.5 Hz, 2 C), 114.8 (d, J = 195.5 Hz), 62.5 (dq, J = 38.0, 4.75 Hz, 2 C), 61.4 , 19.3, 13.8 ppm; Anal. Calcd for $C_{12}H_{15}F_6O_5P$: C, 37.51; H, 3.94. Found: C, 37.77; H, 3.88.

(2*Z*,4*E*)-Ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)hexa-2,4-dienoate (*Z*-153)

IR (film): ν_{max} = 2981, 2919, 1714, 1632, 1574, 1288, 1246, 1172, 1071, 963 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (dd, J = 49.0, 11.5 Hz, 1 H, P(O)CCH), 7.30 (dd, J = 14.5, 13.5 Hz, 1 H, CH_3CHCH), 6.54 (dq, J = 14.5, 7.0 Hz, 1 H, CH_3CHCH), 4.51-4.35 (m, 4 H, 2 × OCH_2CF_3), 4.26 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 1.98 (d, J = 6.5 Hz, 3 H, CH_3CH), 1.31 (t, J = 6.5 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.9 (d, J = 16.1 Hz), 159.6 (d, J = 8.5 Hz), 150.8, 128.1 (d, J = 5.7 Hz), 122.6 (dq, J = 276.0, 8.5 Hz, 2 C), 114.2 (d, J = 192.5 Hz), 62.4 (dq, J = 38.0, 4.7 Hz, 2 C), 61.7, 19.4, 13.9 ppm; Anal. Calcd for $C_{12}H_{15}F_6O_5P$: C, 37.51; H, 3.94. Found: C, 37.69; H, 4.08.

(*E*)-Ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)-3-methylenehex-4-enoate (154)



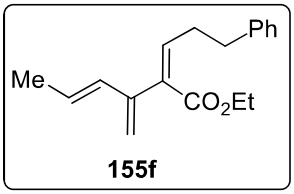
154

n-BuLi (1.6 mL, 1.6 M, 2.54 mmol, 3 equiv) was added dropwise to a stirred suspension of trimethylsulfonium iodide (518 mg, 2.54 mmol, 3 equiv) in THF (15 mL) at -10 ºC under argon atmosphere and stirred for 20 min at the same temperature. Later, a solution of dienoate **153** (325 mg, 0.85 mmol, 1 equiv) in THF (5 mL) was cannulated into the reaction mixture and stirred for 1 h. The temperature of the

reaction mixture was allowed to rise slowly to room temperature followed by dilution of the reaction mixture with water and extraction with 50% EtOAc in petroleum ether. The organic layer was concentrated and the residue was purified by column chromatography (petroleum ether-EtOAc; 85:15) to obtain the diene **154** (0.23 g, 68%) as pale yellow liquid.

IR (film): ν_{max} = 2972, 2941, 2922, 1731, 1452, 1419, 1371, 1297, 1263, 1173, 1073,962, 877 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 5.89 (d, J = 15.5 Hz, 1 H, CH_3CHCH), 5.53 (dq, J = 15.5, 7.0 Hz, 1 H, CH_3CHCH), 5.49 (d, J = 5.5 Hz, 1 H, CCH_AH_B), 5.09 (d, J = 5.5 Hz, 1 H, CCH_AH_B), 4.25-3.95 (m, 4 H, 2 × OCH_2CF_3), 4.03 (d, J = 23.5 Hz, 1 H, P(O)CH), 3.87-3.77 (m, 2 H, OCH_2CH_3), 1.46 (d, J = 7.0 Hz, 3 H, CH_3CHCH), 0.81 (t, J = 7.5 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4 (d, J = 1.9 Hz), 135.9 (d, J = 9.5 Hz), 131.8 (d, J = 5.6 Hz), 127.6, 123.6 (dq, J = 276.0, 5.7 Hz), 123.5 (dq, J = 276.0, 5.6 Hz), 119.3 (d, J = 9.5 Hz), 63.3 (dq, J = 38.0, 5.7 Hz), 63.2 (dq, J = 37.0, 5.8 Hz), 62.5, 48.3 (d, J = 143.2 Hz), 18.3, 14.0 ppm; Anal. Calcd for $C_{13}H_{17}F_6O_5P$: C, 39.21; H, 4.30. Found: C, 39.49; H, 4.12.

(2*Z*,4*E*)-Ethyl 3-methylene-2-(3-phenylpropylidene)hex-4-enoate (155f)



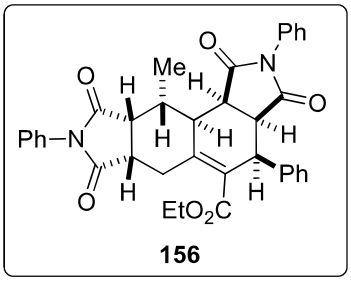
155f

A solution of diene **154** (691 mg, 1.74 mmol, 1 equiv) in THF (10 mL) was cannulated to a suspension of sodium hydride (84 mg, 55% in oil, 1.74 mmol, 1 equiv) in THF (1 mL) under argon atmosphere and stirred for 5 min. Then freshly distilled 3-phenylpropionaldehyde (0.23 mL, 1.74 mmol, 1 equiv) was added and stirred at room

temperature for 6 h. The reaction mixture was diluted with water and extracted with 20% EtOAc in petroleum ether. The organic layer was concentrated under the reduced pressure and the residue was purified by column chromatography (petroleum ether-EtOAc; 98:2) to obtain the dendralene **155f** (170 mg, 36%) as colourless liquid.

IR (film): ν_{max} = 3027, 2980, 2932, 2856, 1715, 1634, 1602, 1495, 1453, 1368, 1213, 1096, 1030, 964, 893, 748, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2 H, Ph), 7.24-7.16 (m, 3 H, Ph), 6.10 (dd, J = 16.0, 1.0 Hz, 1 H, CH_3CHCH), 6.02 (t, J = 7.0 Hz, 1 H, $PhCH_2CH_2CH$), 5.57 (dq, J = 15.5, 7.0 Hz, 1 H, CH_3CHCH), 5.04 (s, 1 H, CCH_AH_B), 4.93 (d, J = 1.5 Hz, 1 H, CCH_AH_B), 4.19 (q, J = 7.5 Hz, 2 H, OCH_2CH_3), 2.82-2.73 (m, 4 H, $PhCH_2CH_2$), 1.73 (dd, J = 6.5, 1.5 Hz, 3 H, CH_3CH), 1.25 (t, J = 7.5 Hz, 3 H, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 145.6, 141.3, 141.2, 134.2, 131.8, 128.5 (2 C), 128.4, 128.3, 128.2, 125.9, 115.2, 60.4, 35.4, 31.1, 18.1, 14.2 ppm; Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.90; H, 8.42.

(3a*SR*,4*SR*,6a*SR*,9a*RS*,10*RS*,10a*SR*,10b*RS*)-Ethyl 10-methyl-1,3,7,9-tetraoxo-2,4,8-triphenyl-1,2,3,3a,4,6,6a,7,8,9,9a,10,10a,10b-tetradecahydroisoindolo[5,6-e]isoindole-5 carboxylate (156)



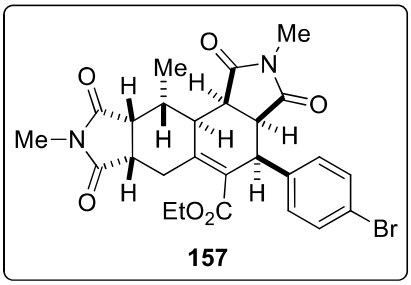
156

A solution of diene **154** (240 mg, 0.6 mmol, 1 equiv) in THF (7 mL) was cannulated to a suspension of sodium hydride (30 mg, 55% in oil, 0.6 mmol, 1 equiv) in THF (1

mL) under argon atmosphere and stirred for 5 min. Then freshly distilled benzaldehyde (0.06 mL, 0.6 mmol, 1 equiv) was added and stirred at room temperature for 45 min. The reaction mixture was diluted with water and extracted with benzene (3 × 10 mL). The organic layer was concentrated under the reduced pressure to 5 mL volume and to this NPM (214 mg, 1.2 mmol, 2 equiv) was added and stirred at 20 °C for 3 h and then stirred at room temperature for additional 6 h. The product was precipitated out of the solution on its own as a white solid. The reaction mixture was filtered to obtain the DTDA adduct **156** (197 mg, 56%). The product was purified by recrystallization from dichloromethane which provided crystals suitable for single crystal X-ray analysis.

mp 283-284 °C; IR (film): ν_{max} = 2980, 2965, 1770, 1702, 1596, 1495, 1457, 1390, 1327, 1306, 1262, 1196, 1165, 786, 763,728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.43 (m, 4 H), 7.42-7.37 (m, 2 H), 7.33-7.25 (m, 3 H), 7.24-7.17 (m, 6 H), 3.99 (dq, J = 11.0, 7.0 Hz, 1 H), 3.83-3.74 (m, 2 H), 3.58 (dd, J = 9.0, 5.0 Hz, 1 H), 3.44 (t, J = 8.0 Hz, 1 H), 3.38- 3.24 (m, 3 H), 3.21 (d, J = 15.0 Hz, 1 H), 2.68 (d, J = 15.5 Hz, 1 H), 2.22 (d, J = 9.0 Hz, 1 H), 1.64 (d, J = 6.5 Hz, 3 H), 0.89 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 177.1, 175.2, 174.3, 166.4, 139.1, 136.6, 133.0, 131.7, 131.6, 129.5 (2 C), 129.2 (2 C), 129.1 (2 C), 128.8, 128.7, 128.0 (2 C), 127.6, 126.7 (2 C), 126.3 (2 C), 60.9, 46.1, 44.6, 44.4, 40.9, 40.7, 39.9, 29.4, 27.5, 15.8, 13.6 ppm; Anal. Calcd for $C_{36}H_{32}N_2O_6$: C, 73.45; H, 5.48; N, 4.76. Found: C, 73.19; H, 5.44; N, 4.81.

(3a*SR*,4*SR*,6a*SR*,9a*RS*,10*RS*,10a*SR*,10b*RS*)-Ethyl4-(4-bromophenyl)-2,8,10-trimethyl-1,3,7,9-tetraoxo-1,2,3,3a,4,6,6a,7,8,9,9a,10,10a,10b tetradecahydroisoindolo[5,6-e]isoindole-5-carboxylate (157)



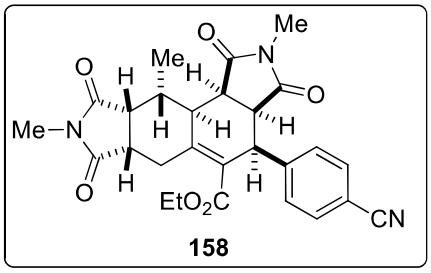
157

A solution of diene **154** (188 mg, 0.47 mmol, 1 equiv) in THF (5 mL) was cannulated to a suspension of sodium hydride (23 mg, 55% in oil, 0.47 mmol, 1 equiv) in THF (1 mL) under argon atmosphere and stirred for 5 min. Then 4-bromobenzaldehyde (87 mg, 0.47 mmol, 1 equiv) was added, stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with benzene (3 × 10 mL). The organic layer was concentrated under the reduced pressure to 3 mL volume and to this NMM (104 mg, 0.94 mmol, 2 equiv) was added and stirred at 20 °C for 3 h and then stirred at room temperature for another 1 d. The reaction mixture was concentrated and the residue was chromatographed to obtain the DTDA adduct **15**7 (130 mg, 51%) as a white solid. The product was crystallized from dichloromethane and ethyl acetate to obtain suitable crystals for single crystal X-ray analysis.

mp 232 °C*;* IR (film): ν_{max} = 2979, 2939, 1773, 1697, 1491, 1434, 1382, 1298, 1287, 1209, 1075, 1012, 915, 789, 752,730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 8.5 Hz, 2 H), 6.99 (d, J = 8.5 Hz, 2 H), 3.95 (dq, J = 10.5, 7.5 Hz ,1 H), 3.79 (dq, J = 10.5, 7.5 Hz, 1 H), 3.68-3.63 (m, 1 H), 3.38 (dd, J = 8.5, 5.0 Hz, 1 H), 3.25 (t, J = 8.0 Hz, 1 H), 3.22-3.16 (m, 2 H), 3.16-3.11 (m, 1 H), 3.09 (d, J = 16.0 Hz, 1 H), 2.94 (s, 3 H), 2.90 (s, 3 H), 2.56-2.47 (m, 1 H), 1.95 (dd, J = 12.5, 5.0 Hz, 1 H), 1.58 (d, J = 6.0

Hz, 3 H), 0.91 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 178.0, 175.9, 175.2, 166.2, 140.0, 136.1, 131.8, 131.0 (2 C), 130.9 (2 C), 121.5, 60.9, 45.6, 44.0, 43.3, 40.6, 40.1, 39.6, 29.1, 26.7, 25.0, 24.9, 15.9, 13.6 ppm; Anal. Calcd for $C_{26}H_{27}BrN_2O_6$: C, 57.47; H, 5.01; N, 5.16. Found: C, 57.63; H, 4.88; N, 5.33.

(3a*SR*,4*SR*,6a*SR*,9a*RS*,10*RS*,10a*SR*,10b*R*S)-Ethyl 4-(4-cyanophenyl)-2,8,10-trimethyl-1,3,7,9-tetraoxo-1,2,3,3a,4,6,6a,7,8,9,9a,10,10a,10b-tetradecahydroisoindolo[5,6-e]isoindole-5-carboxylate (158)

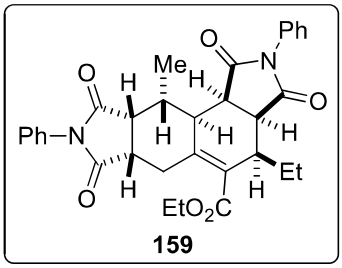


158

A solution of diene **154** (155 mg, 0.39 mmol, 1 equiv) in THF (5 mL) was cannulated to a suspension of sodium hydride (20 mg, 55% in oil, 0.39 mmol, 1 equiv) in THF (1 mL) under argon atmosphere and stirred for 5 min. Then 4-cyanobenzaldehyde (51 mg, 0.39 mmol, 1 equiv) was added, stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with benzene (3 × 10 mL). The organic layer was concentrated under the reduced pressure to 3 mL volume and to this NMM (87 mg, 0.78 mmol, 2 equiv) was added and stirred at 20 °C for 3 h and then stirred at room temperature for another 1 d. The reaction mixture was concentrated and purified by column chromatograpy to obtain the DTDA adduct **158** (93 mg, 49%) as a gummy solid. The product was crystallized from ethyl acetate to obtain suitable crystals for single crystal X-ray analysis.

mp 265-266 °C; IR (film): ν_{max} = 3021, 2924, 2850, 2229, 1773, 1698, 1610, 1507, 1435, 1383, 1298, 1216, 1126, 1072, 1022, 858, 828, 755, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 8.0 Hz, 2 H), 7.23 (d, J = 8.5 Hz, 2 H), 3.93 (dq, J = 11.0, 7.0 Hz ,1 H), 3.75 (dq, J = 11.0, 7.5 Hz ,1 H), 3.74-3.70 (m, 1 H), 3.40 (dd, J = 9.0, 5.5 Hz, 1 H), 3.27 (dd, J = 8.5, 8.0 Hz, 1 H), 3.21- 3.10 (m, 4 H), 2.92 (s, 3 H), 2.89 (s, 3 H), 2.53-2.45 (m, 1 H), 1.95 (ddd, J = 12.5, 5.5, 3.0 Hz, 1 H), 1.57 (d, J = 7.0 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.4, 177.9, 175.6, 174.9, 165.9, 142.7, 141.1, 131.6 (2 C), 130.9, 130.2 (2 C), 118.6, 111.3, 61.0, 45.3, 43.9, 43.7, 40.4, 40.3, 39.6, 29.1, 26.6, 25.0, 24.9, 15.9, 13.6 ppm; Anal. Calcd for $C_{27}H_{27}N_3O_6$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.36; H, 5.20; N, 8.37.

(3a*SR*,4*RS*,6a*SR*,9a*RS*,10*RS*,10a*SR*,10b*RS*)-Ethyl 4-ethyl-10-methyl-1,3,7,9-tetraoxo-2,8-diphenyl-1,2,3,3a,4,6,6a,7,8,9,9a,10,10a,10b tetradecahydroisoindolo[5,6-e]isoindole-5-carboxylate (159)



159

A solution of diene **154** (190 mg, 0.5 mmol, 1 equiv) in THF (5 mL) was cannulated to a suspension of sodium hydride (22 mg, 55% in oil, 0.5 mmol, 1 equiv) in THF (1 mL) under argon atmosphere and stirred for 5 min. Then freshly distilled propionaldehyde (0.07 mL, 1 mmol, 2 equiv) was added and stirred at room temperature for 4 h. The reaction mixture was diluted with water and extracted with benzene (3 × 10 mL). The organic layer was concentrated under the reduced pressure

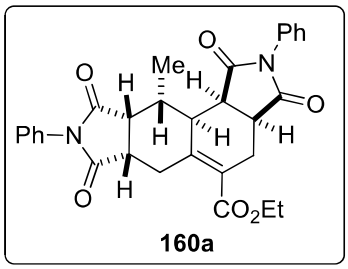
to 5 mL volume and to this NPM (173 mg, 1 mmol, 2 equiv) was added and stirred at room temperature for 3 d. The reaction mixture was then concentrated and the residue was purified by chromatography to obtain DTDA adduct **159** (113 mg, 42%) as white solid. mp 209-210 °C; IR (film): ν_{max} = 2969, 2937, 2878, 1774, 1708, 1597, 1500, 1456, 1384, 1311, 1255, 1184, 1095, 913, 786, 756, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.49-7.42 (m, 4 H), 7.41-7.35 (m, 2 H), 7.23-7.18 (m, 4 H), 4.32-4.19 (m, 2 H), 3.48 (dd, *J* = 8.5, 5.0 Hz, 1 H), 3.35-3.21 (m, 3 H), 3.20-3.10 (m, 1 H), 2.99 (d, *J* = 14.5 Hz, 1 H), 2.49-2.41 (m, 1 H), 2.39-2.31 (m, 1 H), 2.14 (dd, *J* = 12.5, 4.5 Hz, 1 H), 2.09-1.93 (m, 2 H), 1.62 (d, *J* = 6.5 Hz, 3 H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.09 (t, *J* = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 177.1, 175.8, 174.9, 166.5, 136.9, 133.5, 131.8, 131.7, 129.2 (2 C), 129.1 (2 C), 128.7, 128.6, 126.7 (2 C), 126.4 (2 C), 61.2, 44.4, 42.4, 41.2, 41.0, 40.5, 40.0, 28.80, 27.3, 20.7, 16.0, 14.2, 12.5 ppm; Anal. Calcd for $C_{32}H_{32}N_2O_6$: C, 71.09; H, 5.97; N, 5.18. Found: C, 70.90; H, 6.06; N, 5.46.

Ethyl 10-methyl-1,3,7,9-tetraoxo-2,8-diphenyl-1,2,3,3a,4,6,6a,7,8,9,9a,10,10a,10b-tetradecahydroisoindolo[5,6-e]isoindole-5-carboxylate (160)

A solution of diene **154** (180 mg, 0.45 mmol, 1 equiv) in THF (5 mL) was cannulated to a suspension of sodium hydride (22 mg, 55% in oil, 0.45 mmol, 1 equiv) in THF (1 mL) under argon atmosphere and stirred for 5 min. Then formaldehyde gas was bubbled through the reaction mixture for 5 minutes. The reaction mixture was then filtered to remove the excess paraformaldehyde. To this filtrate NPM (156 mg, 0.9 mmol, 2 equiv) was added and reaction mixture was stirred for 3 d. The reaction mixture was concentrated and the residue was purified by chromatography to provide isomeric DTDA adducts **160a** (124 mg, 54%) as white solid and **160b** (22 mg, 9%) as

white foam in a ratio of 85:15. The major adduct **160a** was recrystallized from dichloromethane and ethyl acetate to obtain crystals suitable for single crystal X-ray analysis.

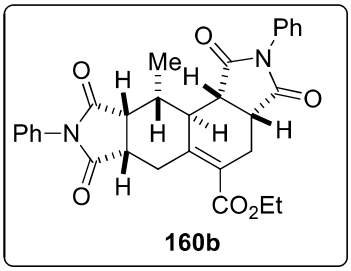
(3a*SR*,6a*SR*,9a*RS*,10*RS*,10a*SR*,10b*RS*)-Ethyl 10-methyl-1,3,7,9-tetraoxo-2,8-diphenyl-1,2,3,3a,4,6,6a,7,8,9,9a,10,10a,10b-tetradecahydroisoindolo[5,6-e]isoindole-5-carboxylate (160a)



160a

mp 278 °C; IR (film): ν_{max} = 3020, 2984, 2931, 1775, 1711, 1598, 1500, 1444, 1384, 1298, 1216, 1183,755, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.47-7.41 (m, 4 H), 7.41-7.35 (m, 2 H), 7.14-7.09 (m, 4 H), 4.28-4.17 (m, 2 H), 4.08 (dd, *J* = 15.0, 1.0 Hz, 1 H), 3.49 (dd, *J* = 9.0, 5.5 Hz, 1 H), 3.41 (d, *J* = 15.5 Hz, 1 H), 3.36-3.28 (m, 2 H), 3.25 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.16-3.06 (m, 1 H), 2.49-2.40 (m, 1 H), 2.22 (ddd, *J* = 13.5, 6.0, 4.0 Hz, 1 H), 2.11 (dd, *J* = 12.5, 5.0 Hz, 1 H), 1.61 (d, *J* = 7.0 Hz, 3 H), 1.30 (t, *J* = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 177.5, 177.0, 175.9, 165.4, 147.2, 131.7, 131.6, 129.2 (4 C), 128.9, 128.7, 127.4, 126.5 (2 C), 126.3 (2 C), 61.1, 44.0, 42.4, 39.9, 39.85, 39.8, 29.0, 26.7, 26.4, 16.1, 14.2 ppm; Anal. Calcd for $C_{30}H_{28}N_2O_6$: C, 70.30; H, 5.51; N, 5.47. Found: C, 70.66; H, 5.19; N, 5.53.

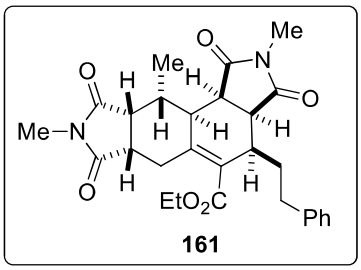
(3a*RS*,6a*SR*,9a*RS*,10*RS*,10a*SR*,10b*SR*)-Ethyl 10-methyl-1,3,7,9-tetraoxo-2,8-diphenyl-1,2,3,3a,4,6,6a,7,8,9,9a,10,10a,10b-tetradecahydroisoindolo[5,6-e]isoindole-5-carboxylate (160b)



160b

IR (film): ν_{max} = 3019, 2979, 2927, 1774, 1712, 1633, 1598, 1499, 1455, 1386, 1242, 1196, 1180,754, 693 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51-7.35 (m, 6 H), 7.31-7.24 (m, 2 H), 7.13-7.08 (m, 2 H), 4.25 (q, J = 7.0 Hz, 2 H), 4.10 (dd, J = 15.5, 6.5 Hz, 1 H), 3.62 (dd, J = 8.5, 6.5 Hz, 1 H), 3.46 (d, J = 15.5 Hz, 1 H), 3.40 (t, J = 8.5 Hz, 1 H), 3.09-2.92 (m, 2 H), 2.58 (dd, J = 11.5, 10.0 Hz, 1 H), 2.37-2.28 (m, 1 H), 2.22 (t, J = 14.5 Hz, 1 H), 2.08 (dd, J = 13.0, 6.0 Hz, 1 H), 1.62 (d, J = 6.0 Hz, 3 H), 1.31 (t, J = 7.5 Hz, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.5, 176.9, 176.8, 176.0, 165.7, 148.4, 131.7, 131.5, 129.2 (2 C), 129.1 (2 C), 128.9, 128.7, 126.5 (2 C), 126.4 (2 C), 125.8, 61.1, 46.1, 45.3, 40.1, 39.5, 39.3, 29.9, 26.7, 26.0, 17.0, 14.2 ppm; Anal. Calcd for $C_{30}H_{28}N_2O_6$: C, 70.30; H, 5.51; N, 5.47. Found: C, 70.20; H, 5.65; N, 5.09.

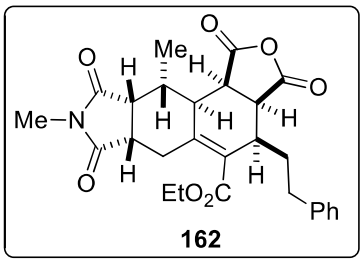
(3a*SR*,4*RS*,6a*SR*,9a*RS*,10*RS*,10a*SR*,10b*RS*)-Ethyl 2,8,10-trimethyl-1,3,7,9-tetraoxo-4-phenethyl-1,2,3,3a,4,6,6a,7,8,9,9a,10,10a,10b-tetradecahydroisoindolo[5,6-e]isoindole-5-carboxylate (161)



161

To dendralene **155f** (13 mg, 0.048 mmol, 1 equiv), NMM (1.07 mL, 0.09 M in toluene, 0.096 mmol, 2 equiv) was added and stirred at -10 ºC for 6 h. Later the reaction mixture was allowed to attain rt and stirred for 1 d. The reaction was then concentrated on rotary evaporator and the residue was purified by column chromatography to obtain the DTDA adduct **161** (20 mg, 85%) as a colourless gum. IR (film): ν_{max} = 3024, 2979, 2938, 2851, 1772, 1696, 1435, 1383, 1286, 1210, 1126, 1031, 753, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.30-7.24 (m, 2 H), 7.21-7.16 (m, 3 H), 4.24-4.10 (m, 2 H), 3.27 (dd, J = 8.5, 5.5 Hz, 1 H), 3.20-3.12 (m, 2 H), 3.12-3.02 (m, 2 H), 2.94 (s, 3 H), 2.93-2.82 (m, 2 H), 2.89 (s, 3 H), 2.63 (ddd, J = 14.5, 9.5, 6.0 Hz, 1 H), 2.34-2.10 (m, 4 H), 1.83 (dd, J = 12.0, 4.0 Hz, 1 H), 1.55 (d, J = 6.5 Hz, 3 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.3, 178.1, 176.7, 175.9, 166.4, 141.3, 137.4, 132.6, 128.5 (2 C), 128.4 (2 C), 126.0, 61.0, 44.1, 42.5, 41.1, 40.5, 39.8, 37.4, 33.8, 29.4, 28.5, 26.3, 24.8, 24.7, 16.0, 14.1 ppm; Anal. Calcd for $C_{28}H_{32}N_2O_6$: C, 68.28; H, 6.55; N, 5.69. Found: C, 68.02; H, 6.42; N, 5.90.

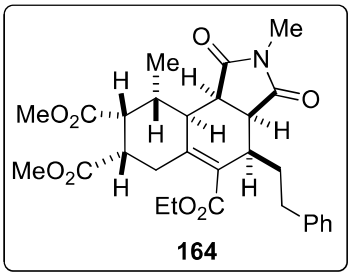
(3a*SR*,4*RS*,6a*SR*,9a*RS*,10*RS*,10a*SR*,10b*RS*)-Ethyl 8,10-dimethyl-1,3,7,9-tetraoxo-4-phenethyl-3,3a,4,6,6a,7,8,9,9a,10,10a,10b-dodecahydro-1*H*-isobenzofuro[4,5-f]isoindole-5-carboxylate (162)



162

A solution of dendralene **155f** (17 mg, 0.063 mmol, 2 equiv) and NMM (0.35 mL, 0.09 M in toluene, 0.031 mmol, 1 equiv) in toulene (1 mL) was stirred at -10 ºC for 6 h. The reaction mixture was then concentrated on rotary evaporator and the residue was fast filtered through a small silica gel column to obtain first D-A adduct free from excess dendralene **155f**. Later a solution of this first D-A adduct and maleic anhydride (3 mg, 0.031 mmol) in dry toluene (1 mL) was heated under reflux for 12 h. Then the reaction mixture was concentrated under reduced pressure and a white gummy solid was obtained. This solid was washed with dry 10% EtOAC in hexane to obtain desired pure DTDA adduct **162** (13 mg, 89%) as white foam. IR (film): ν_{max} = 3027, 2922, 2851, 1851, 1775, 1697, 1495, 1434, 1383, 1301, 1279, 1258, 1204, 1128, 1095, 1070, 1019, 1003, 986, 914, 843, 791cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2 H), 7.23-7.15 (m, 3 H), 4.30-4.14 (m, 2 H), 3.57 (dd, J = 9.0, 5.5 Hz, 1 H), 3.43 (dd, J = 9.0, 6.5 Hz, 1 H), 3.19 (br t, J = 8.0 Hz, 1 H), 3.10 (dd, J = 10.0, 5.0 Hz, 1 H), 3.04 (d, J = 15.0 Hz, 1 H), 2.96-2.88 (m, 1 H), 2.95 (s, 3 H), 2.81 (dt, J = 14.0, 8.0 Hz, 1 H), 2.65 (ddd, J = 14.0, 9.0, 6.0 Hz, 1 H), 2.37 (dd, J = 7.5, 3.0 Hz, 1 H), 2.36-2.29 (m, 1 H), 2.29-2.16 (m, 2 H), 1.86 (dd, J = 12.5, 5.0 Hz, 1 H), 1.54 (d, J = 6.5 Hz, 3 H), 1.31 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0, 177.8, 170.7, 169.4, 165.7, 140.7, 138.1, 133.2, 128.6 (2 C), 128.4 (2 C), 126.3, 61.4, 43.8, 43.4, 42.7, 40.0, 39.6, 36.7, 33.5, 29.1, 28.4, 26.4, 24.9, 15.9, 14.1 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{29}NNaO_7$ 502.1836; Found 502.1836.

(3a*SR*,4*RS*,7*SR*,8*RS*,9*RS*,9a*SR*,9b*RS*)-5-Ethyl 7,8-dimethyl 2,9-dimethyl-1,3-dioxo-4-phenethyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[e]isoindole-5,7,8-tricarboxylate (164)



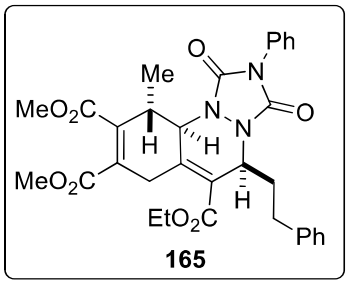
164

A solution of dendralene **155f** (14 mg, 0.052 mmol, 1 equiv) and maleic anhydride (6 mg, 0.062 mmol, 1.2 equiv) in toluene (1 mL) was stirred at rt under inert atmosphere for 1 d. Then NMM (0.575 mL, 0.09 M in toluene, 0.052 mmol, 1 equiv) was added to the reaction mixture and stirred for additional 1 d. Later the solvent was removed under reduced pressure to obtain the crude DTDA adduct **163**. A solution of this crude adduct and DMAP (2 mg, 0.01 mmol, 0.2 equiv) in anhydrous methanol (2 mL) was stirred for 2 h. The reaction mixture was then concentrated and extracted with ethyl acetate (3 × 5 mL). The organic layer was then concentrated and the residue obtained was treated with an ethereal solution of diazomethane to obtain the triester **164**. This solution was once again concentrated and the residue was purified by chromatography to obtain pure **164** (24 mg, 90%) as colourless gum.

IR (film): ν_{max} = 3026, 2953, 2928, 2850, 1769, 1695, 1495, 1454, 1436, 1384, 1287, 1202, 1174, 1117, 1030, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2 H), 7.25-7.16 (m, 3 H), 4.21-4.10 (m, 2 H), 3.70 (s, 3 H), 3.64 (s, 3 H), 3.24-3.15 (m, 3 H), 3.12 (dd, J = 7.5, 4.0 Hz, 1 H), 2.96 (ddd, J = 13.0, 10.5, 6.0 Hz, 1 H), 2.92- 2.86 (m, 1 H), 2.89 (s, 3 H), 2.83 (dd, J = 13.0, 2.5 Hz, 1 H), 2.63 (ddd, J = 14.0, 10.5, 5.5 Hz, 1 H), 2.55 (ddd, J = 17.5, 6.0, 2.5 Hz, 1 H), 2.51-2.44 (m, 1 H), 2.29-2.18 (m, 2 H),

2.13-2.03 (m, 1 H), 1.23 (t, J = 7.5 Hz, 3 H), 1.19 (d, J = 6.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.5, 176.1, 173.4, 172.3, 167.2, 141.7, 140.2, 129.0, 128.5 (2 C), 128.4 (2 C), 125.9, 60.5, 52.0, 51.4, 46.2, 42.9, 42.8, 41.7, 40.6, 37.6, 34.0, 31.4, 29.7, 25.5, 24.6, 18.1, 14.2 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{35}NNaO_8$ 548.2255; Found 548.2255.

(5*SR*,10*SR*,10a*RS*)-6-Ethyl 8,9-dimethyl 10-methyl-1,3-dioxo-5-phenethyl-2-phenyl-2,3,5,7,10,10a-hexahydro-1*H*-[1,2,4]triazolo[1,2-a]cinnoline-6,8,9-tricarboxylate (165)



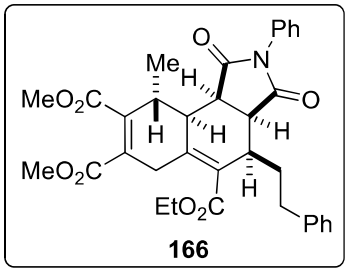
165

A solution of dendralene **155f** (15 mg, 0.055 mmol, 1 equiv) and DMAD (0.01 mL, 0.066 mmol, 1.2 equiv) in toulene (1 mL) was stirred at 75 ºC under inert atmosphere for 1 d. Then the reaction mixture brought to room temperature, PTAD (10 mg, 0.055 mmol, 1 equiv) was added and stirred for 3 h. Later the solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain the desired DTDA adduct **165** (28 mg, 87%) as white foam.

IR (film): ν_{max} = 3026, 2981, 2952, 2920, 2850, 1770, 1714, 1650, 1601, 1503, 1433, 1270, 1174, 1093, 1031, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.45 (m, 4 H), 7.41-7.36 (m, 1 H), 7.31-7.23 (m, 4 H), 7.22-7.17 (m, 1 H), 5.22 (d, J = 9.5 Hz, 1 H), 4.63 (dd, J = 19.5, 2.0 Hz, 1 H), 4.49 (d, J = 10.0 Hz, 1 H), 4.20 (q, J = 7.5 Hz, 1 H), 4.19 (q, J = 7.0 Hz, 1 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.17 (dd, J = 19.5, 1.5 Hz, 1 H),

3.08-2.98 (m, 1 H), 2.91-2.74 (m, 2 H), 2.39-2.28 (m, 1 H), 2.10-1.98 (m, 1 H), 1.38 (d, J = 7.0 Hz, 3 H), 1.24 (t, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 165.4, 164.1, 152.6, 148.5, 142.7, 141.5, 140.4, 131.4, 129.1 (2 C), 128.5 (2 C), 128.4 (2 C), 128.2, 127.7, 126.2, 125.4 (2 C), 124.7, 61.6, 59.2, 52.5, 52.4, 51.6, 43.3, 36.1, 32.0, 31.4, 16.5, 14.0 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{33}N_3NaO_8$ 610.2160; Found 610.2159.

(3a*SR*,4*RS*,9*RS*,9a*SR*,9b*RS*)-5-Ethyl 7,8-dimethyl 9-methyl-1,3-dioxo-4-phenethyl-2-phenyl-2,3,3a,4,6,9,9a,9b-octahydro-1*H*-benzo[e]isoindole-5,7,8-tricarboxylate (166)



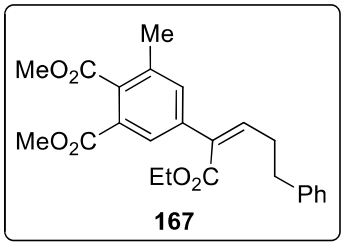
166

A solution of dendralene **155f** (18 mg, 0.066 mmol, 1 equiv) and DMAD (0.01 mL, 0.08 mmol, 1.2 equiv) in toulene (1 mL) was stirred at 75 ºC under inert atmosphere for 1 d. Then NPM (14 mg, 0.08 mmol, 1.2 equiv) was added to the reaction mixture which was refluxed for 2 d. Later the solvent was removed under reduced pressure and the residue was purified by column chromatography to obtained desired DTDA adduct **166** (29 mg, 75%) as white foam along with some amount of aromatized product **167** (5 mg, 18%) as colourless viscous liquid in a ratio of 76:24.

IR (film): ν_{max} = 3025, 2978, 2952, 2932, 2854, 1772, 1712, 1640, 1599, 1499, 1455, 1435, 1387, 1273, 1193, 1094, 1029, 753 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.41 (m, 2 H), 7.40-7.35 (m, 1 H), 7.31-7.26 (m, 2 H), 7.26-7.17 (m, 5H), 4.31-4.19

(m, 2 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 3.72 (d, J = 18.0 Hz, 1 H), 3.69-3.62 (m, 1 H), 3.45 (dd, J = 8.5, 5.5 Hz, 1 H), 3.40 (dd, J = 8.5, 6.0 Hz, 1 H), 2.97 (ddd, J = 14.0, 9.5, 6.0 Hz, 1 H), 2.78 (dd, J = 18.0, 2.5 Hz, 1 H), 2.71 (ddd, J = 14.5, 8.0, 4.5 Hz, 1 H), 2.55-2.46 (m, 1 H), 2.45-2.35 (m, 1 H), 2.31-2.22 (m, 1 H), 2.18 (br t, J = 7.0 Hz, 1 H), 1.34 (d, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.9, 175.0, 168.0, 166.8, 165.8, 145.9, 141.3, 138.9, 131.7, 130.0, 129.1 (2 C), 128.7, 128.5 (4 C), 128.3, 126.8 (2 C), 126.0, 61.1, 52.3, 52.1, 43.6, 42.9, 42.2, 38.3, 33.9, 32.2, 29.5, 28.3, 15.8, 14.1 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{35}NNaO_8$ 608.2255; Found 608.2251.

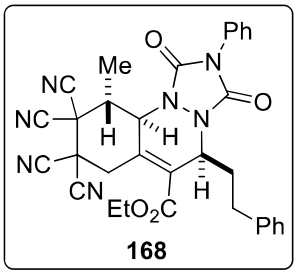
(*Z*)-Dimethyl 5-(1-ethoxy-1-oxo-5-phenylpent-2-en-2-yl)-3-methylphthalate (167)



167

IR (film): ν_{max} = 2985, 2955, 2942, 2909, 1739, 1605, 1440, 1373, 1243, 1095, 1047, 916, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 1.0 Hz, 1 H), 7.35-7.28 (m, 3 H), 7.25-7.19 (m, 3 H), 6.25 (t, J = 6.5 Hz, 1 H), 4.27 (q, J = 7.5 Hz, 2 H), 3.94 (s, 3 H), 3.89 (s, 3 H), 2.88-2.78 (m, 4 H), 2.34 (s, 3 H), 1.29 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 166.2 (2 C), 141.6, 141.0, 139.2, 135.6, 134.2, 133.3, 128.5 (3 C), 128.4 (3 C), 126.6, 126.1, 61.0, 52.5 (2 C), 35.3, 31.8, 19.1, 14.2 ppm; HRMS (ESI-TOF)m/z: $[M + Na]^+$ Calcd for $C_{24}H_{26}NaO_6$ 433.1622; Found 433.1623.

(5S*R*,10*SR*,10a*RS*)-Ethyl 8,8,9,9-tetracyano-10-methyl-1,3-dioxo-5-phenethyl-2-phenyl-2,3,5,7,8,9,10,10a-octahydro-1*H*-[1,2,4]triazolo[1,2-a]cinnoline-6-carboxylate (168)

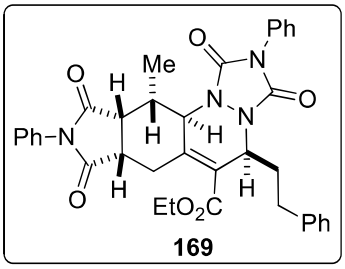


168

A solution of dendralene **155f** (13 mg, 0.048 mmol, 1 equiv) and tetracyano ethylene (8 mg, 0.057 mmol, 1.2 equiv) in toulene (1 mL) was stirred at ambient temperature for 2 h, later PTAD (10 mg, 0.057 mmol, 1.2 equiv) was added and stirred for another 2 h. Later the solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain desired DTDA adduct **168** (25 mg, 92%) as white powder.

mp 109 °C; IR (film): ν_{max} = 2984, 2956, 2926, 2254, 1777, 1719, 1600, 1503, 1454, 1422, 1282, 1257, 1029, 912, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.55-7.48 (m, 4 H), 7.47-7.41 (m, 1 H), 7.33-7.27 (m, 2 H), 7.25-7.17 (m, 3 H), 5.36-5.29 (m, 1 H), 4.88 (d, J = 14.5 Hz, 1 H), 4.76 (d, J = 4.5 Hz, 1 H), 4.34 (dq, J = 10.5, 7.5 Hz, 1 H), 4.27 (dq, J = 10.5, 7.5 Hz, 1 H), 4.14 (dq, J = 7.5, 5.5 Hz), 2.85 (d, J = 14.0 Hz, 1 H), 2.85-2.75 (m, 2 H), 2.24-2.14 (m, 1 H), 2.14-2.0 (m, 1 H), 1.66 (d, J = 7.5 Hz, 3 H), 1.31 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7, 154.1, 149.6, 139.8, 135.7, 130.4, 129.4 (2 C), 129.1, 128.8, 128.7 (2 C), 128.3 (2 C), 126.6, 125.3 (2 C), 110.6, 110.3, 109.8, 109.4, 63.0, 57.6, 52.8, 44.0, 41.2, 38.3, 36.0, 33.7, 32.4, 14.0, 11.8 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{28}N_7O_4$ 574.2197; Found 574.2192.

(5*SR*,7a*SR*,10a*RS*,11*SR*,11a*RS*)-Ethyl 11-methyl-1,3,8,10-tetraoxo-5-phenethyl-2,9-diphenyl-1,2,3,5,7,7a,8,9,10,10a,11,11a-dodecahydropyrrolo[3,4-g][1,2,4]triazolo[1,2-a]cinnoline-6-carboxylate (169)



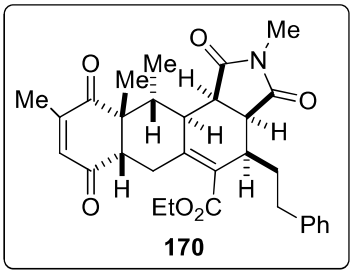
169

A solution of dendralene **155f** (13 mg, 0.048 mmol, 1 equiv) and NPM (0.415 mL, 0.12 M in toluene, 0.048 mmol, 1 equiv) in toulene (0.5 mL) was stirred at at -10 ºC for 2 d. Later the reaction mixture was allowed to attain room temperature followed by addition of PTAD (10 mg, 0.057 mmol, 1.2 equiv) and once again stirred for 2 h. Later the solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain the desired DTDA adduct **169** (28 mg, 95%) as white solid.

mp 93-98 °C; IR (film): ν_{max} = 3064, 3026, 2978, 2934, 1771, 1715, 1649, 1600, 1501, 1455, 1421, 1378, 1262, 1243, 1179, 1141, 1029, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.55-7.46 (m, 6 H), 7.44-7.38 (m, 2 H), 7.32-7.26 (m, 4 H), 7.23-7.18 (m, 3 H), 5.26 (t, J = 5.5 Hz, 1 H), 4.35-4.23 (m, 2 H), 4.20 (s, 1 H), 3.88 (dd, J = 13.0, 8.0 Hz, 1 H), 3.60 (q, J = 8.5 Hz, 1 H), 3.44 (quint d, J = 7.5, 3.5 Hz, 1 H), 3.23 (dd, J = 9.0, 6.5 Hz, 1 H), 2.82-2.69 (m, 2 H), 2.22 (dd, J = 12.5, 12.0 Hz, 1 H), 2.18-2.05 (m, 2 H), 1.49 (d, J = 7.5 Hz, 3 H), 1.32 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.5, 175.6, 164.2, 154.9, 149.5, 141.9, 140.3, 131.6, 131.0, 129.2 (2 C), 129.1 (2 C), 128.7, 128.6 (2 C), 128.3, 128.2 (2 C), 126.3, 126.2 (2 C), 125.7, 125.4 (2

C), 62.6, 61.8, 51.9, 42.3, 42.2, 39.0, 35.4, 31.9, 26.3, 18.2, 14.1 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}N_4O_6$ 619.2551; Found 619.2553.

(3a*SR*,4*RS*,6a*SR*,10a*RS*,11*RS*,11a*SR*,11b*RS*)-Ethyl 2,9,10a,11-tetramethyl-1,3,7,10-tetraoxo-4-phenethyl-2,3,3a,4,6,6a,7,10,10a,11,11a,11b-dodecahydro-1*H*-naphtho[2,3-e]isoindole-5-carboxylate (170)



170

A solution of dendralene **155f** (15 mg, 0.055 mmol, 1 equiv) and 2,6-dimethyl-1,4-benzoquinone (9 mg, 0.066 mmol, 1.2 equiv) in toulene (1 mL) was stirred at 75 ºC for 14 h. To this reaction mixture NMM (7.5 mg, 0.066 mmol, 1.2 equiv) was added and stirred at the same temperature for another 36 h. Later the solvent was removed under reduced pressure and the residue was purified by column chromatography to obtain the desired DTDA adduct **170** (18 mg, 65%) as pale yellow foam.

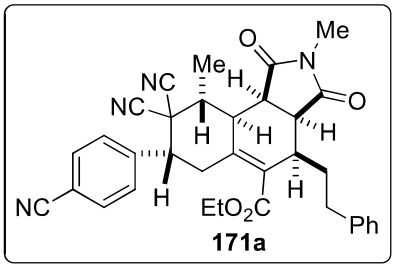
IR (film): ν_{max} = 3025, 2980, 2936, 2869, 1771, 1695, 1631, 1495, 1436, 1383, 1286, 1218, 1196, 1122, 1099, 1029, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.32-7.24 (m, 2 H), 7.23-7.15 (m, 3 H), 6.50 (s, 1 H), 4.17-4.03 (m, 2 H), 3.28 (dd, J = 8.5, 5.0 Hz, 1 H), 3.19 (dd, J = 8.0, 7.0 Hz, 1 H), 2.88 (s, 3 H), 2.87-2.79 (m, 2 H), 2.70-2.58 (m, 2 H), 2.58-2.52 (m, 2 H), 2.38-2.29 (m, 1 H), 2.28-2.10 (m, 3 H), 1.94 (s, 3 H), 1.39 (s, 3 H), 1.37 (d, J = 7.0 Hz, 3 H), 1.20 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.6, 199.9, 177.2, 175.9, 166.7, 150.5, 141.4, 138.8, 135.8, 131.4, 128.4 (4 C), 126.0, 60.8, 54.6, 49.6, 43.4, 41.9, 41.7, 37.9, 37.0, 34.0, 29.5, 28.5, 26.3, 24.6,

16.4, 14.1, 13.2 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{35}NNaO_6$ 540.2357; Found 540.2353.

Ethyl 8,8-dicyano-7-(4-cyanophenyl)-2,9-dimethyl-1,3-dioxo-4-phenethyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[e]isoindole-5-carboxylate (171)

A solution of dendralene **155f** (16 mg, 0.06 mmol, 1 equiv) and 2-(4-cyanobenzylidene)malononitrile (11 mg, 0.06 mmol, 1 equiv) in toulene (1 mL) was stirred at 75 ºC for 2 d. This was followed by addition of NMM (8 mg, 0.07 mmol, 1.2 equiv) and the reaction mixture was refluxed for 3 d. Later the reaction mixture was then concentrated on rotary evaporator and the residue upon careful chromatography provided the isomeric DTDA adducts **171a** (15 mg, 46%) as white solid, **171b** (8 mg, 24 %) as white solid (Combined yield: 70%) in a ratio of 64:36. Recrystallization of major adduct **171a** from 30% ethyl acetate in hexane and minor adduct **171b** from chloroform gave crystals suitable for single crystal X-ray analysis.

(3a*SR*,4*RS*,7*RS*,9*RS*,9a*SR*,9b*RS*)-Ethyl 8,8-dicyano-7-(4-cyanophenyl)-2,9-dimethyl-1,3-dioxo-4-phenethyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[e]isoindole-5-carboxylate (171a)

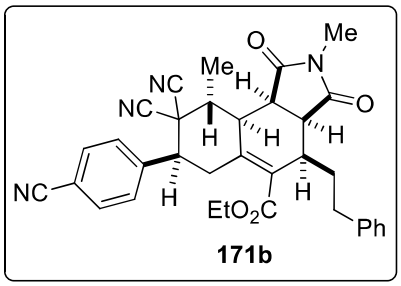


171a

mp 203 °C; IR (film): ν_{max} = 3025, 2979, 2935, 2864, 2231, 1772, 1696, 1610, 1495, 1438, 1385, 1369, 1315, 1288, 1129, 1098, 1017, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.5 Hz, 2 H), 7.62 (d, J = 8.0 Hz, 2 H), 7.34-7.28 (m, 2 H),

7.25-7.19 (m, 3 H), 4.19-4.08 (m, 2 H), 3.79 (dq, *J* = 9.5, 6.5 Hz, 1 H), 3.50 (dd, *J* = 11.5, 6.0 Hz, 1 H), 3.31 (dd, *J* = 8.0, 7.0 Hz, 1 H), 3.26 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.10 (ddd, *J* = 18.0, 11.5, 2.5 Hz, 1 H), 3.03-2.89 (m, 1 H), 2.94 (s, 3 H), 2.76 (dd, *J* = 18.5, 6.0 Hz, 1 H), 2.68 (ddd, *J* = 15.0, 8.5, 4.0 Hz, 1 H), 2.53-2.44 (m, 1 H), 2.33-3.20 (m, 2 H), 2.18-2.08 (m, 1 H), 1.55 (d, *J* = 6.5 Hz, 3 H), 1.20 (t, *J* = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 175.1, 166.3, 142.6, 141.0, 135.6, 132.9 (2 C), 132.1, 129.0 (2 C), 128.6 (2 C), 128.4 (2 C), 126.2, 118.1, 114.3, 113.3, 112.2, 61.2, 46.3, 45.4, 42.8, 42.4, 40.5, 38.2, 37.9, 33.8, 30.4, 29.4, 24.9, 17.3, 14.2 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{32}N_4NaO_4$ 583.2316; Found 583.2316.

(3a*SR*,4*RS*,7*SR*,9*RS*,9a*SR*,9b*RS*)-Ethyl 8,8-dicyano-7-(4-cyanophenyl)-2,9-dimethyl-1,3-dioxo-4-phenethyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[e]isoindole-5-carboxylate (171b)



171b

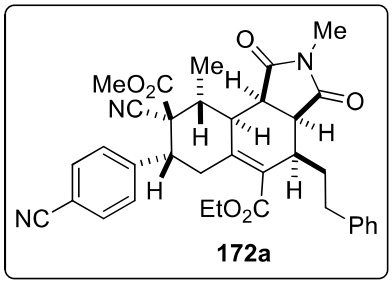
mp 233 °C; IR (film): ν_{max} = 3026, 2978, 2927, 2854, 2231, 1771, 1697, 1609, 1495, 1438, 1384, 1289, 1233, 1121, 1018, 838, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.5 Hz, 2 H), 7.36-7.30 (m, 2 H), 7.26-7.21 (m, 3 H), 4.14 (q, *J* = 7.5 Hz, 2 H), 3.66-3.54 (m, 2 H), 3.39 (dd, *J* = 8.0, 5.0 Hz, 1 H), 3.35 (dd, *J* = 8.0, 6.5 Hz, 1 H), 3.02-2.92 (m, 1 H), 2.96 (s, 3 H), 2.80 (dd, *J* = 14.5, 4.0 Hz, 1 H), 2.71 (ddd, *J* = 15.5, 10.0, 6.0 Hz, 1 H), 2.63 (br t, *J* =14.5 Hz, 1 H), 2.57-2.49 (m, 1 H), 2.38-2.26 (m, 2 H), 2.25-2.16 (m, 1 H), 1.62 (d, *J* = 6.0 Hz, 3 H),

1.20 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.5, 175.2, 166.3, 142.7, 141.0, 137.2, 133.0 (2 C), 132.2, 128.8 (2 C), 128.6 (2 C), 128.4 (2 C), 126.2, 118.0, 114.8, 113.7, 113.4, 61.3, 48.4, 44.2, 42.2, 41.2, 39.2, 37.8, 35.5, 33.8, 29.4, 28.8, 24.9, 15.7, 14.1 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{32}N_4NaO_4$ 583.2316; Found 583.2311.

5-Ethyl 8-methyl 8-cyano-7-(4-cyanophenyl)-2,9-dimethyl-1,3-dioxo-4-phenethyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[e]isoindole-5,8-dicarboxylate (172)

A solution of dendralene **155f** (23 mg, 0.085 mmol, 1 equiv) and (*E*)-methyl 2-cyano-3-(4-cyanophenyl)acrylate (18 mg, 0.085 mmol, 1 equiv) in toulene (1 mL) was stirred at 75 ºC for 2 d. This was followed by addition of NMM (12 mg, 0.1 mmol, 1.2 equiv) and the reaction mixture was refluxed for additional 2d. Later the reaction mixture was then concentrated and the residue upon careful chromatography provided the isomeric DTDA adducts **172a** (24 mg, 48%) as white foam, **172b** (13 mg, 26%) as white solid (Combined yield: 74%) in a ratio of 64:36. Recrystallization of minor adduct **172b** from ethyl acetate gave crystals suitable for single crystal X-ray analysis.

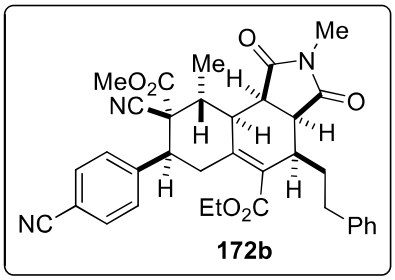
(3a*SR*,4*RS*,7*RS*,8*SR*,9*RS*,9a*SR*,9b*RS*)-5-Ethyl 8-methyl 8-cyano-7-(4-cyanophenyl)-2,9-dimethyl-1,3-dioxo-4-phenethyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[e]isoindole-5,8-dicarboxylate (172a)



172a

IR (film): ν_{max} = 3025, 2958, 2933, 2858, 2230, 1771, 1744, 1695, 1609, 1436, 1385, 1289, 1255, 1202, 1116, 1095, 1031, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.5 Hz, 2 H), 7.52 (d, J = 8.5 Hz, 2 H), 7.34-7.29 (m, 2 H), 7.27-7.19 (m, 3 H), 4.12 (q, J = 7.5 Hz, 2 H), 3.81 (dq, J = 9.5,7.0 Hz, 1 H), 3.56 (s, 3 H), 3.54 (dd, J = 12.5, 6.0 Hz, 1 H), 3.29 (dd, J = 8.0, 7.0 Hz, 1 H), 3.24 (dd, J = 8.5, 4.0 Hz, 1 H), 3.08 (ddd, J = 18.0, 12.5, 3.0 Hz, 1 H), 3.02-2.91 (m, 1 H), 2.95 (s, 3 H), 2.76-2.63 (m, 2 H), 2.55-2.46 (m, 1 H), 2.34-2.20 (m, 2 H), 2.18-2.07 (m, 1 H), 1.22 (d, J = 6.5 Hz, 3 H), 1.18 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0, 175.4, 167.8, 166.6, 144.1, 141.2, 137.3, 132.5 (2 C), 131.1, 128.9 (2 C), 128.5 (2 C), 128.4 (2 C), 126.1, 118.3, 115.9, 112.4, 60.9, 57.3, 53.4, 45.7, 42.8, 42.6, 41.0, 37.8, 37.0, 33.9, 31.3, 29.6, 24.8, 16.6, 14.2 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{35}N_3NaO_6$ 616.2418; Found 616.2420.

(3a*SR*4*RS*,7*SR*,8*RS*,9*RS*,9a*SR*,9b*RS*)-5-Ethyl 8-methyl 8-cyano-7-(4-cyanophenyl)-2,9-dimethyl-1,3-dioxo-4-phenethyl-2,3,3a,4,6,7,8,9,9a,9b-decahydro-1*H*-benzo[e]isoindole-5,8-dicarboxylate (172b)



172b

mp 225 °C; IR (film): ν_{max} = 3024, 2956, 2918, 2850, 2230, 1770, 1737, 1696, 1609, 1436, 1384, 1288, 1242, 1120, 1106, 1019, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 8.0 Hz, 2 H), 7.34-7.29 (m, 2 H), 7.28-7.19 (m, 5 H), 4.11 (q, J = 7.0 Hz, 2 H), 3.86 (s, 3 H), 3.62-3.53 (m, 2 H), 3.29 (ABq, $\Delta\nu_{AB}$ = 8.4 Hz, J_{AB} = 7.5 Hz, 2 H),

2.99 (ddd, J = 16.5, 10.5, 6.0 Hz, 1 H), 2.95 (s, 3 H), 2.77-2.64 (m, 3 H), 2.55-2.46 (m, 2 H), 2.36-2.26 (m, 1 H), 2.24-2.15 (m, 1 H), 1.39 (d, J = 6.5 Hz, 3 H), 1.17 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 175.7, 169.2, 166.7, 144.4, 141.3, 140.1, 132.6 (2 C), 130.0, 128.6 (2 C), 128.5 (2 C), 128.4 (2 C), 126.1, 118.3, 117.8, 112.4, 61.1, 55.4, 53.7, 46.4, 42.0, 41.0, 37.9, 37.5, 36.8, 33.9, 29.6, 28.9, 24.8, 14.6, 14.2 ppm; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{35}N_3NaO_6$ 616.2418; Found 616.2426.

4.7 Appendix

4.7.1 X-ray Crystallographic Studies: As described in **Chapter 3**

4.7.2 X-ray Crystallographic Data (Table 4.1)

Compound	**156**	**157**	**158**	**160a**
Formula	$C_{36}H_{32}N_2O_6$	$C_{26}H_{27}N_2O_6Br$	$C_{27}H_{27}N_3O_6$	$C_{30}H_{28}N_2O_6$
Formula Wt	588.63	543.40	489.51	512.54
Crystal System	monoclinic	monoclinic	monoclinic	monoclinic
Space Group	C2/c	$P2_1/c$	$P2_1/c$	$P2_1/c$
T, K	293	293	293(2)	293
Z	8	4	4	4
a, Å	19.5031(3)	15.9993(7)	16.7281(4)	12.5019(14)
b, Å	16.6971(2)	10.8867(5)	10.2986(17)	21.1909(18)
c, Å	20.1118(3)	16.1051(9)	16.3055(4)	10.0757(15)
α, deg	90	90	90	90

β, deg	109.9234(18)	114.970(6)	116.342(3)	95.255(13)
γ, deg	90	90	90	90
V, $Å^3$	6157.31(18)	2543.0(2)	2517.35(11)	2658.1(5)
$\rho_{calc,}$ mg/mm^3	1.270	1.419	1.292	1.281
μ, m/mm^{-1}	0.705	2.568	0.761	0.735
2θ range, deg	7.16- 146.61	6.094- 146.604	5.896-146.58	7.1 - 147.226
GOF (F^2)	1.147	1.033	1.069	1.049
R_1 (wR_2), %	0.0855	0.0598	0.0552	0.1018
	(0.2583)	(0.1557)	(0.1552)	(0.2996)

4.7.2 X-ray Crystallographic Data (Table 4.2)

Compound	**171a**	**171b**	**172b**
Formula	$C_{34}H_{32}N_4O_4$	$C_{34}H_{32}N_4O_4$	$C_{35}H_{35}N_3O_6$
Formula Wt	560.63	560.63	593.66
Crystal System	triclinic	monoclinic	triclinic
Space Group	P-1	I2/a	P-1
T, K	293	293	293(2)
Z	2	8	2
a, Å	11.2044(7)	19.1282(4)	10.7283(3)
b, Å	11.5815(6)	12.2400(2)	11.4578(4)
c, Å	12.9947(8)	25.3264(5)	14.3942(3)
α, deg	75.244(5)	90	97.385(2)
β, deg	88.540(5)	97.9603(18)	97.614(2)
γ, deg	67.453(5)	90	113.028(3)

V, $Å^3$	1501.08(16)	5872.5(2)	1582.16(8)
ρ_{calc}, mg/mm^3	1.240	1.268	1.246
μ, m/mm^{-1}	0.664	0.679	0.697
2θ range, deg	7.058 -146.504	7.048 - 146.612	6.32 - 146.688
GOF (F^2)	1.099	1.046	1.044
R_1 (wR_2), %	0.0883	0.0480	0.0546
	(0.2712)	(0.1302)	(0.1443)

4.7.3 X-ray Crystal Structures

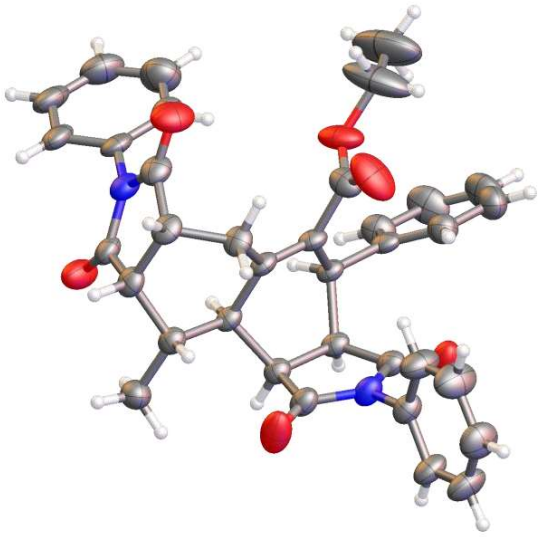


Figure S4.1: X-ray structure of **156**, (CCDC No. **1526486**). Ellipsoids show 50% probability levels.

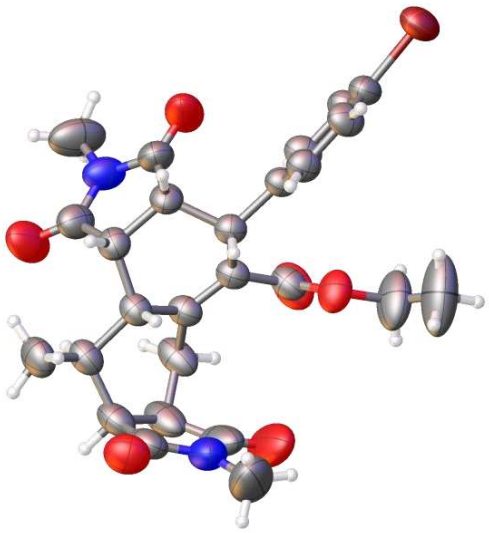


Figure S4.2: X-ray structure of **157**, (CCDC No. **1526489**). Ellipsoids show 50% probability levels.

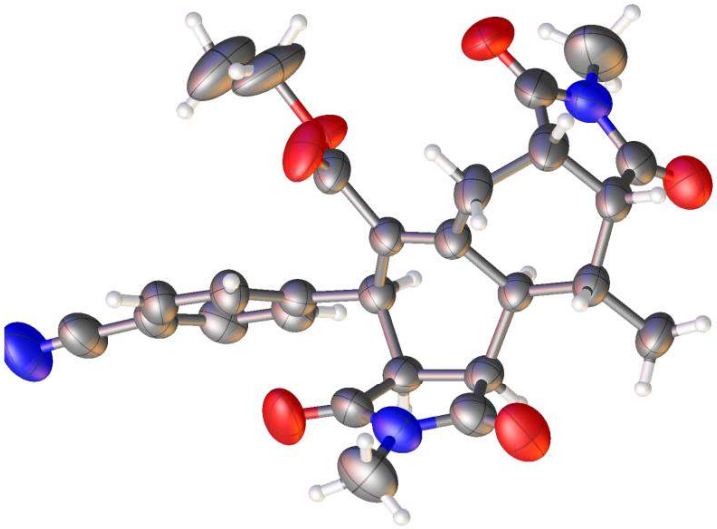


Figure S4.3: X-ray structure of **158**, (CCDC No. **1526487**). Ellipsoids show 50% probability levels.

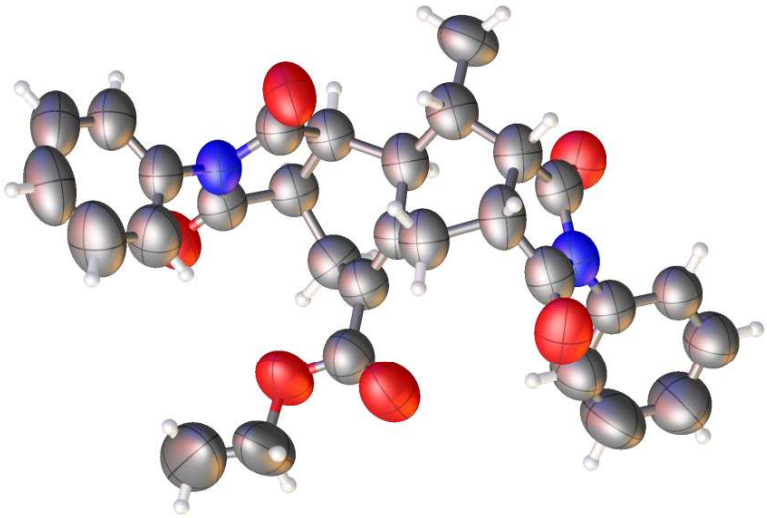


Figure S4.4: X-ray structure of **160a**, (CCDC No. **1526488**). Ellipsoids show 50% probability levels.

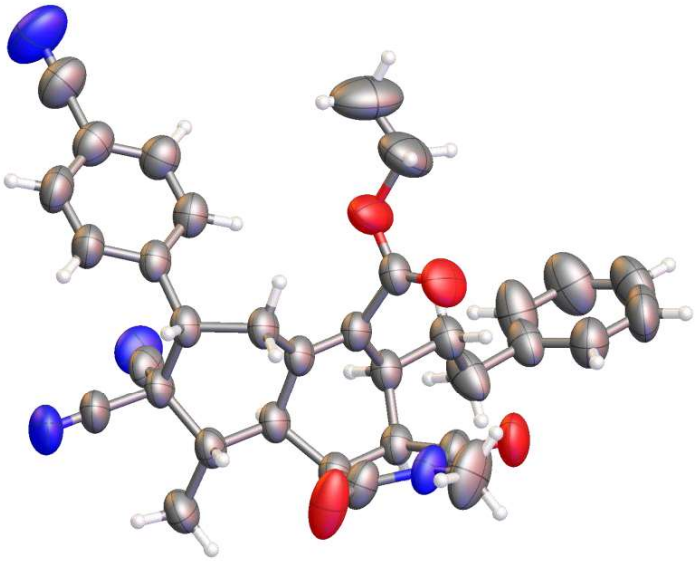


Figure S4.5: X-ray structure of **171a**, (CCDC No. **1526490**). Ellipsoids show 50% probability levels.

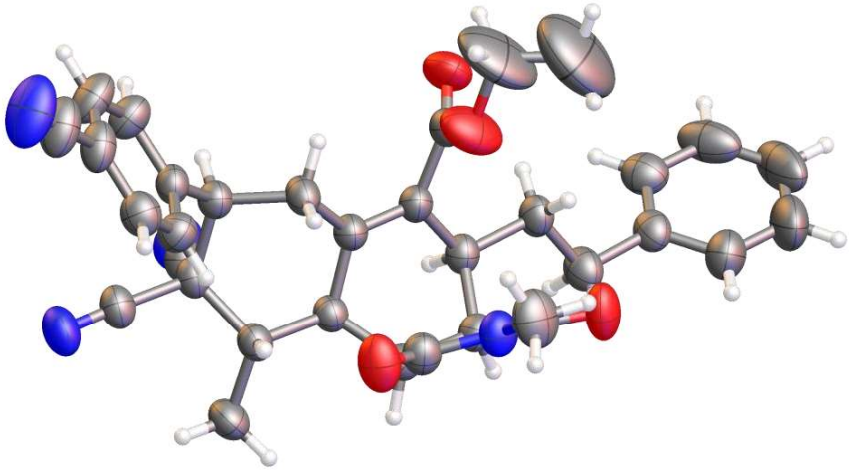


Figure S4.6: X-ray structure of **171b**, (CCDC No. **1526491**). Ellipsoids show 50% probability levels.

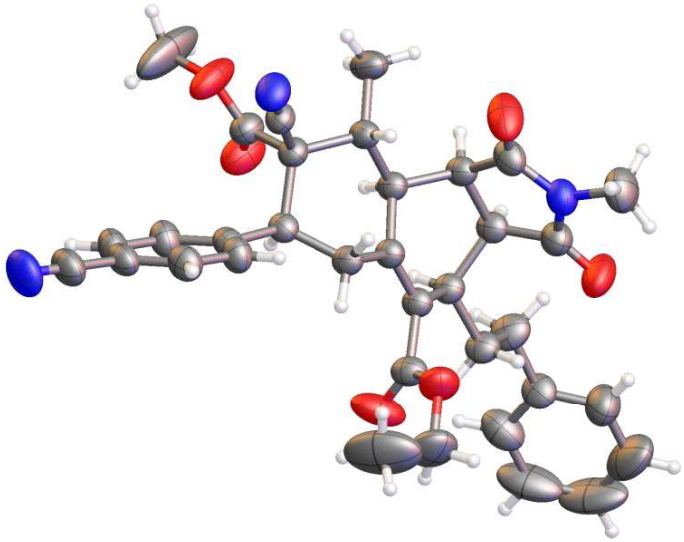


Figure S4.7: X-ray structure of **172b**, (CCDC No. **1526492**). Ellipsoids show 50% probability levels.

4.7.4 NMR spectra

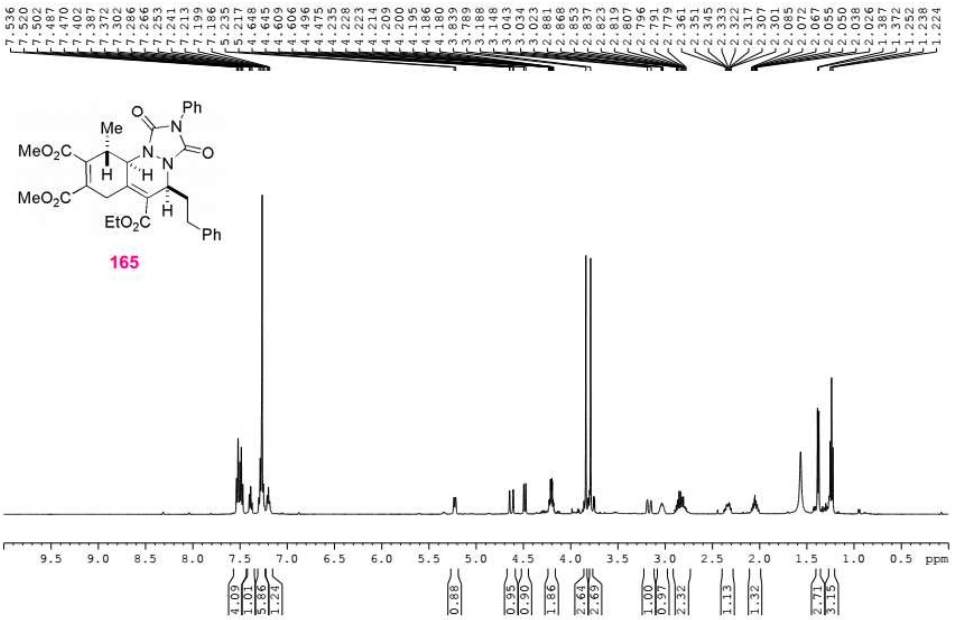


Figure S4.8: ^{1}H NMR spectrum of **165**

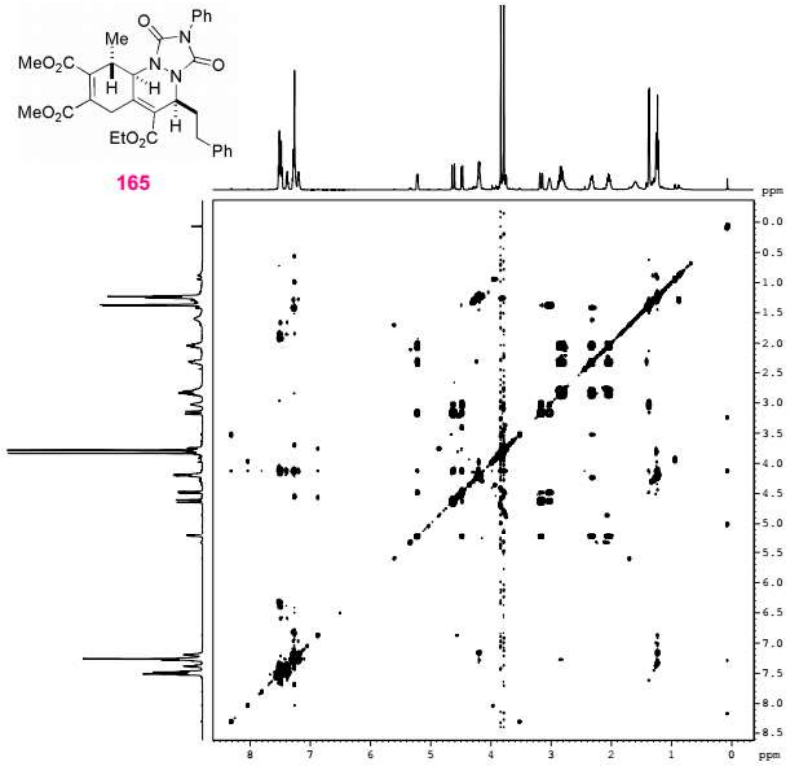


Figure S4.9: ^{1}H/^{1}H COSY spectrum of **165**

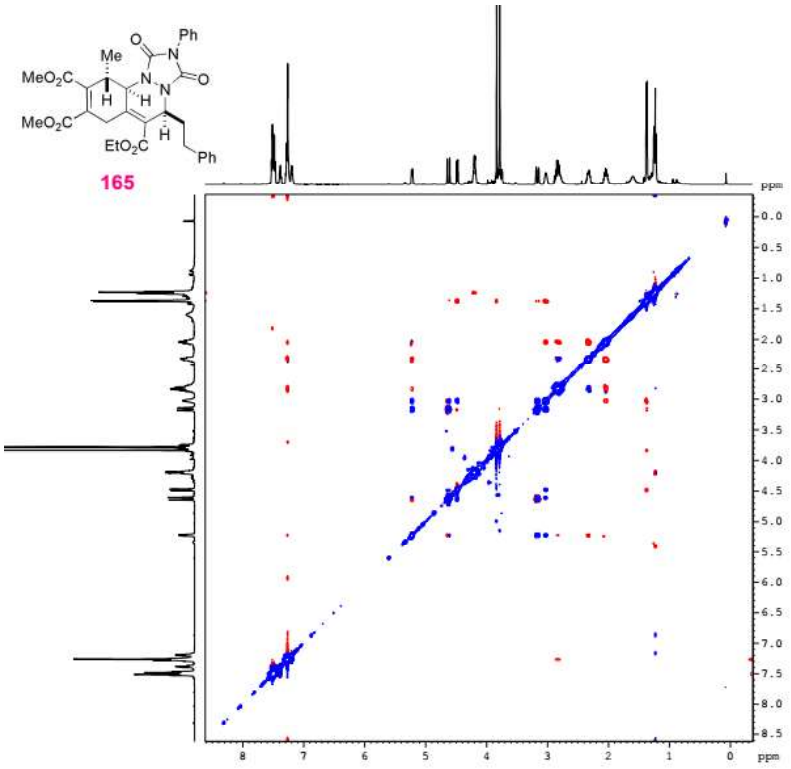


Figure S4.10: $^{1}H/^{1}H$ ROESY spectrum of **165**

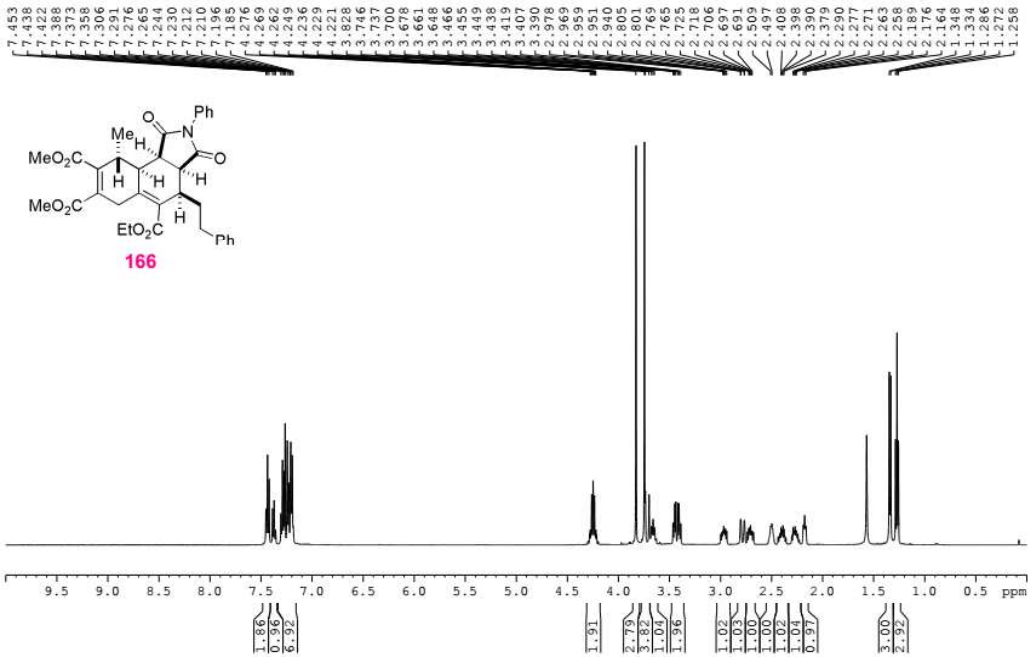


Figure S4.11: ^{1}H NMR spectrum of **166**

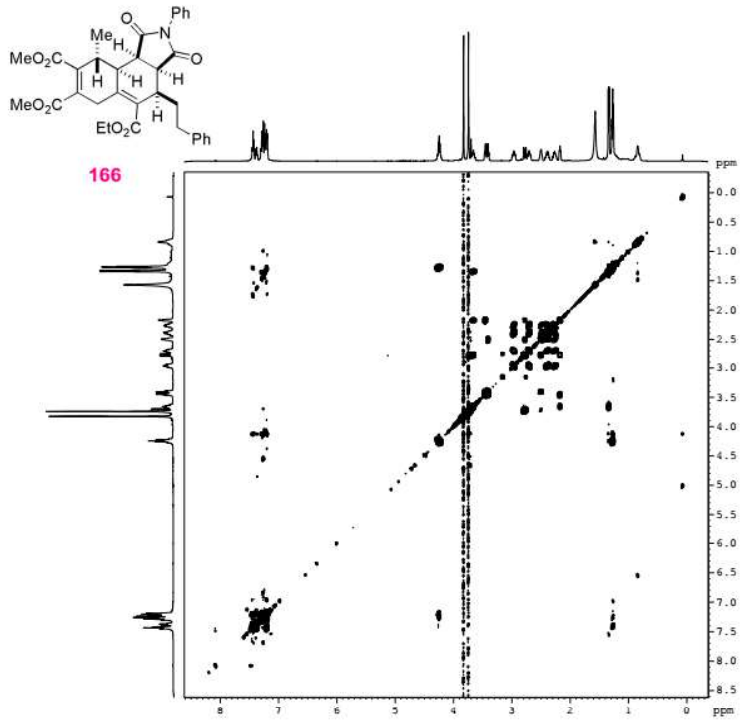


Figure S4.12: $^{1}H/^{1}H$ COSY spectrum of **166**

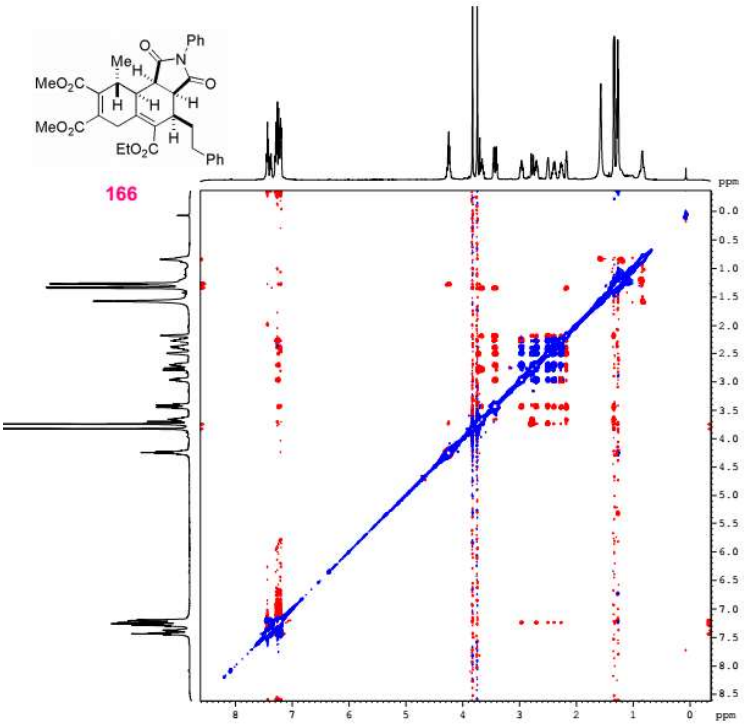


Figure S4.13: $^{1}H/^{1}H$ ROESY spectrum of **166**

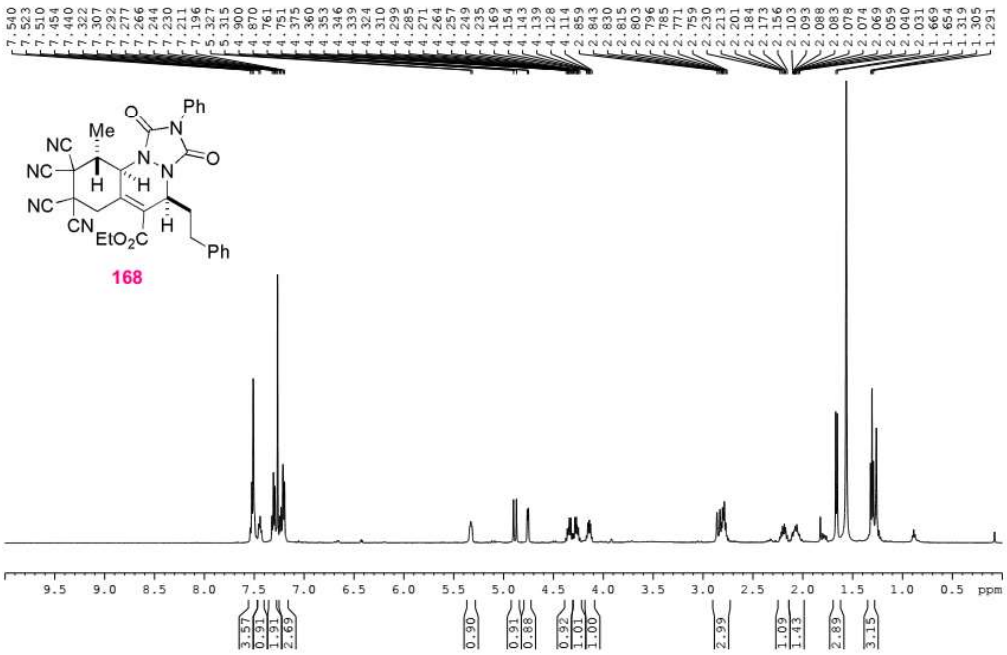


Figure S4.14: ^{1}H NMR spectrum of **168**

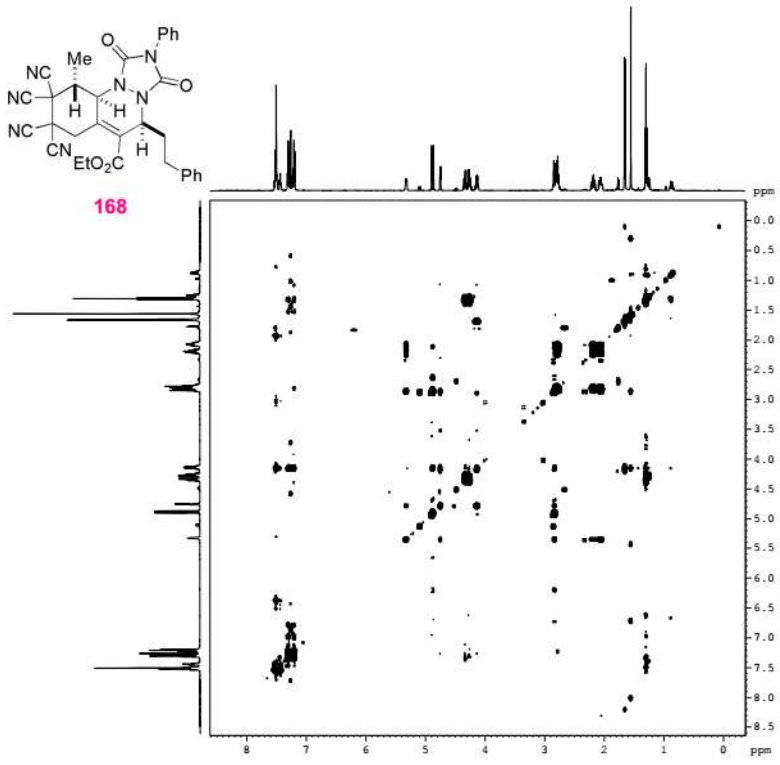


Figure S4.15: ^{1}H/^{1}H COSY spectrum of **168**

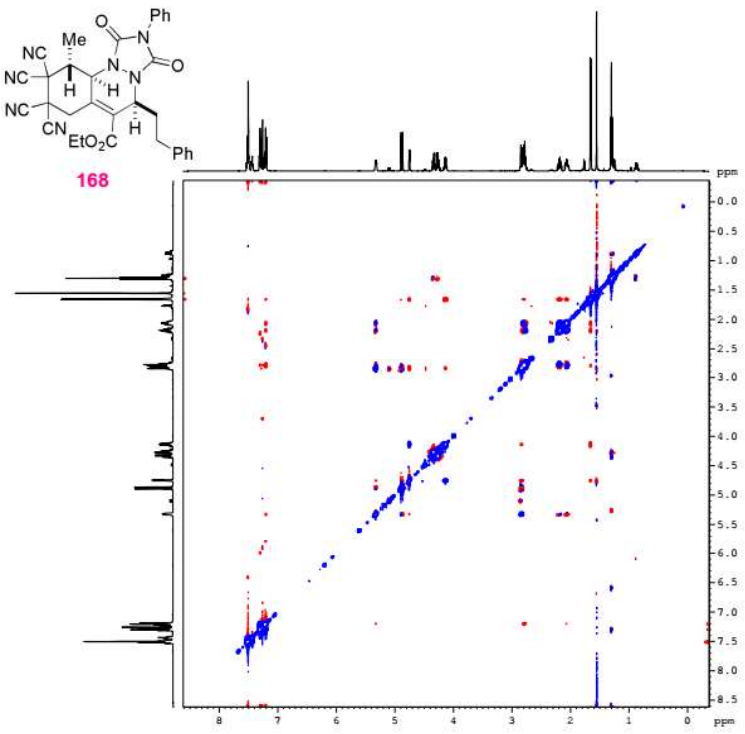


Figure S4.16: $^{1}H/^{1}H$ ROESY spectrum of **168**

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