General Synthesis and New Applications of Dendralenes

A thesis submitted in fulfillment of the requirements for admission to the degree of

Doctor of Philosophy

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Declaration

Except where specific acknowledgements of others are made, the work described in this thesis was carried out by the author during the period of May 2014 to July 2019 in the Research School of Chemistry of the Australian National University, Australia, under the supervision of Professor Mick Sherburn. The material presented has not been submitted for any other degree and is less than 100,000 words in length.

Josemon George

22nd MAY 2020
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Publications and Presentations

This thesis is submitted in publication format.

The following list details the publications and presentations that have resulted from the author’s research during his candidature for the Degree of Doctor of Philosophy:

Publications:


Poster Presentations:


Oral Presentations:

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<td>%</td>
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<tr>
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<td>Diels–Alder</td>
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<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
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<td>nuclear Overhauser and exchange spectroscopy</td>
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<tr>
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<td>t</td>
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</tr>
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<td>temperature</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
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Abstract

The objectives of the research work carried out and presented in this thesis are to develop a better understanding of chemical reactivity and to devise improved synthetic methods by following the principles of the ‘ideal synthesis’. Described herein are three projects based on generating molecular complexity from commercially available, structurally simple starting materials in a step-, atom-economical fashion. Dendralenes, which are acyclic, cross-conjugated hydrocarbons, provide the focus of this research. Dendralenes are important building blocks in synthetic organic chemistry as they undergo diene transmissive Diels–Alder (DTDA) reaction sequences with a range of dienophiles to generate all carbon and heteroatom-containing multi-cyclic complex frameworks. Chapter 1 provides an overall introduction to subsequent chapters of this thesis.

Chapter 2 outlines the first general synthetic route to substituted [3]dendralenes, via twofold Negishi cross-couplings of dibromomethylenes with alkenyl zinc reagents. The requisite dibromomethylenes are synthesised from the corresponding aldehydes using the Ramirez dibromomethylation reaction. We report herein subsequently the first stereoselective synthesis of substituted dendralenes by a catalyst-controlled sequential twofold Negishi cross-coupling of dibromomethylenes with different nucleophilic coupling partners. This strategy makes it possible to synthesise both geometrical isomers of substituted [3]dendralenes. The versatility of these compounds in further chemistry is highlighted by their use in both DTDA cycloaddition sequences and domino 6π-electrocyclisation sequences.

Chapter 3 explores the Diels–Alder reactions between substituted [3]dendralenes and in situ generated benzyne as dienophiles to generate 2-vinyl-1,4-dihyronaphthalenes. Both substituted and unsubstituted benzyne were found to react well with substituted [3]dendralenes. The products of the first Diels–Alder reaction were shown to react with different dienophiles to generate aromatic-ring-containing, multicyclic complex molecules. The DTDA reaction sequences can be performed in one pot, avoiding work up and
purification of the intermediate semicyclic diene. It is also shown that this chemistry can be utilised to rapidly generate the tetracyclic framework of 7-arylangucyclines, a new “hybrid drug” structure.

**Chapter 4** investigates the organocatalysed, enantioselective Diels–Alder reactions of substituted [3]dendralenes. A high level of regio-, diastereo- and enantioselectivity was observed. The substrate-controlled second Diels–Alder reaction on these enantioenriched substrates was also performed to obtain enantiopure, complex polycyclic compounds.

The work to be described in this thesis has been published in three papers, for which the following introduction provides further context.
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Chapter One:

Introduction
1 Introduction

1.1 General Introduction

Hydrocarbon chemistry is a branch of chemistry that focuses on compounds that are comprised exclusively of carbon and hydrogen. Hydrocarbons can be broadly classified into saturated and unsaturated depending upon the types of chemical bonds present within the molecule. Hydrocarbons with only $\sigma$-bonds within the molecular structure are known as alkanes. The presence of double bonds and triple bonds within the molecular structure make them alkenes and alkynes, respectively. Historically, hydrocarbons served as a source of energy (fuels). As of today, they are the main source of synthetic products from plastics to pharmaceuticals.¹

Alkenes are more reactive than alkanes due to the presence of a $\pi$-bond. Four fundamental classes of hydrocarbons are possible with alternating C=C and C–C bonds (Figure 1). They are through-conjugated, acyclic structures, known as polyenes and their cyclic counterpart, annulenes. The other two fundamental classes of hydrocarbons are cross-conjugated. The acyclic structures are known as dendralenes and the cyclic ones are called radialenes. Whereas both polyenes and annulenes have been studied in detail, the synthetic community generally ignored exploring the synthetic benefits of cross-conjugated hydrocarbons. Dendralenes, first reported in the 1950s, were described as unstable, which explains why they were not studied further by synthetic chemists.²

![Figure 1: Four fundamental classes of hydrocarbons containing alternating C=C and C–C bonds.](image)

What makes dendralenes important in synthetic organic chemistry is their ability to participate as multiple dienes in Diels–Alder reaction sequences to generate multicyclic, complex structures. Thus, [3]dendralene, the lowest member of the dendralene family, 1 can react with a dienophile to yield the cyclic structure 2 in a
Diels–Alder (DA) reaction. The semicyclic diene unit of 2 can participate in a second Diels–Alder reaction with same or a different dienophile to generate bicyclic structure 3 (Scheme 1).²

Scheme 1: A diene-transmissive Diels–Alder reaction sequence of [3]dendralene

The parent [3]dendralene was first synthesised independently by Blomquist and Bailey in 1955.³⁴ Blomquist synthesised the parent [3]dendralene 1 in 26% yield by thermal elimination of acetic acid from diacetoxyalkene 4.³ Another method from Blomquist by pyrolysis of 1,2-bis(acetoxymethyl)cyclobutane 5 generated [3]dendralene in 12% yield.⁵ The synthesis by Bailey involved the thermal elimination of acetic acid from the triacetate 6 and a 43% yield of [3]dendralene was obtained (Scheme 2).⁴ Both groups observed and reported that [3]dendralene is unstable and tends to undergo dimerisation and polymerisation.


The parent [3]dendralene syntheses by Blomquist and Bailey depended on conditions such as gas phase pyrolysis and this most likely contributed in the low overall yield for the dendralene. Additionally, access to dendralene precursors 4, 5 and 6 required multi-step syntheses. Despite these factors, both the groups showed the synthetic potential of [3]dendralene by Diels–Alder reaction sequences.³⁵
In 1991, Cadogan and co-workers demonstrated a new route to [3]dendralene 1 through chelotropic elimination of SO$_2$ from a sulfolene 12, serving as a masked dendralene (Scheme 3). However, this route required a five-step synthesis to access the key intermediate 12. 

![Scheme 3: [3]Dendralene synthesis by Cadogan](image)

The Sherburn group later improved the Cadogan’s dendralene synthesis by introducing the cross-coupling strategy to access the sulfolene 12 through the group’s seminal publication in 2000 (Scheme 4).

![Scheme 4: Sherburn’s cross-coupling strategy to access masked [3]dendralene](image)

The Sherburn group further expanded the scope of this masked dendralene methodology to access higher members of the family, specifically [4], [5], [6] and [8]dendralenes for the first time (Scheme 5).
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Scheme 5: Sherburn’s synthesis of [3], [4], [5], [6] and [8] dendralenes from sulfolene precursors

This work showed that the dendralenes were not as unstable as the original publications indicated. This discovery led the group to develop a direct approach for dendralene synthesis, which avoided the protection of butadiene groups as 3-sulfolenes. Hence, the most efficient and practical synthetic route to parent dendralenes involves cross-coupling reactions and avoids issues of lengthy reaction sequences, low yields and harsh reaction conditions. So far, the Sherburn group has accessed up to [12] dendralenes by the cross-coupling strategy (Scheme 6A, 6B).
Scheme 6A: Parent dendralene synthesis based on cross-coupling strategies by the Sherburn group
Even though the approach shown in Scheme 6A allows [3]dendralene to be prepared easily and in good yields, the dendralene is not obtained solvent-free. The solvent used for the reaction, THF, has a similar boiling point to dendralene and co-distills with the product. To overcome this issue, a solvent-free synthesis of [3]dendralene 1 was developed. The key step of dehydrobromination was performed in high boiling DMSO as solvent in the presence of DBU as the base (Scheme 7).\textsuperscript{10}
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Even though the parent [3]dendralene was synthesised and its double Diels–Alder reactions were demonstrated in the 1950’s, many years passed before the field was developed further, through important contributions by Tsuge’s group. Tsuge and coworkers developed the first synthetic methods to access substituted [3]dendralenes and studied their Diels–Alder reactions. Tsuge developed various methods based on condensation, cross-coupling and nucleophilic substitution reactions to access the substituted [3]dendralenes. It was Tsuge, who coined the term “diene-transmissive Diels–Alder” (DTDA), to describe the synthetic potential of dendralenes (Scheme 8).¹¹-¹⁴

Scheme 7: Practical synthesis of [3]dendralene by Sherburn

Scheme 8: Tsuge and coworkers synthetic routes to substituted [3]dendralenes
Another major contribution toward substituted [3]dendralenes was reported by Fallis. The Fallis group deployed an indium-mediated $\gamma$-pentadienylation of aldehydes, e.g. cinnamaldehyde 60 to generate secondary alcohols such as 61 and employed subsequent water elimination under Mitsunobu type conditions to generate the dendralenes such as 62 (Scheme 9).$^{15}$

![Scheme 9: Fallis’ synthesis of substituted [3]dendralenes](image)

Recently, Shenvi demonstrated the use of a “Danishefsky-type” [3]dendralene (prepared through silyl enol ether formation, as pioneered by Tsuge) toward the total synthesis of a natural product, amphilectene 66 (Scheme 10).$^{16}$ The key step involved is the intermolecular, ambient temperature DA reaction between dendralene 63 and methyl ester dienophile 64, followed by hydrolysis of the adduct to the cross-conjugated enone and a subsequent intramolecular DA reaction, generating the tricycle 65.

![Scheme 10: Shenvi’s amphilectene synthesis using a Danishefsky dendralene](image)

The developments in the field of dendralene chemistry mainly from Tsuge and more recently from the Fallis and the Sherburn groups inspired various research groups across the world. There has recently been an upsurge in publications describing the development of substituted [3]dendralene syntheses. The recent developments in this field are dominated by the deployment of metal-based catalytic methods. In 2009, the Ma group showed the Pd(0)-catalysed three-component reaction of bisallenes 67, propargylic carbonates 68 and boronic acids 69 to generate bicyclic [3]dendralenes 70 (Scheme 11).$^{17}$
In 2015, Haak and co-workers reported a synthesis of spirocyclic [3]dendralenes e.g. 73 from unsaturated alcohols 71 and 1,3-diketones 72, catalysed by a cyclopentadienone ruthenium complex. The reaction mechanism involves ruthenium(0)-mediated dehydration of the alkyne 71 to yield the intermediate ruthenium complex and subsequent addition of the nucleophile 72 to generate the spirocyclic dendralene 73 (Scheme 12).\textsuperscript{18}

The Glorius group demonstrated the Rh(III)-catalysed, alkenyl C–H activation of activated amides such as 74 and subsequent cross-coupling with allenyl carbinal carbonate such as 75 to generate substituted [3]dendralenes such as 76. This methodology provided dendralene derivatives that are unsubstituted at the C3 position for majority of the examples, and C–H activation required an amide directing group on the alkene which is retained in the product (Scheme 13).\textsuperscript{19}

Scheme 11: Bicyclic [3]dendralene synthesis by Ma

Scheme 12: Haak’s spirocyclic [3]dendralene synthesis
Tanaka and co-workers showed that cationic Rh(I) compounds catalyse the cross-coupling of di- or trisubstituted allenes \(78\) and alkynes \(77\) to yield the corresponding substituted [3]dendralenes \(79\). This methodology was successful in yielding highly substituted [3]dendralenes, however substituent variation was demonstrated on just one C=C unit of the dendralene. (Scheme 14).\(^{20}\)

Lipshutz showed palladium-catalysed cross-coupling of allenoates under Suzuki-Miyaura/ Mizoroki-Heck conditions to yield substituted [3]dendralenes such as \(82\) and \(85\), respectively. This methodology, however, required multi-step synthesis of the allenoates and coupling partners. Most of the examples shown had at least one alkene unit unsubstituted and otherwise the dendralenes were symmetrically substituted (Scheme 15).\(^ {21}\)
Bäckvall and co-workers demonstrated palladium-catalysed allenic C–H bond oxidation to synthesise various substituted [3]dendralenes. Here, an activating group was required on the alkene and most of the examples had symmetrical substitution on the 3’-position of the [3]dendralene (Scheme 16).22

Fananas-Mastral demonstrated the synthesis of borylated [3]dendralenes such as 91 via copper-catalysed allylboration of alkynes. This methodology, however, left the dendralene unsubstituted on two C=C units (Scheme 17).23
All the above-mentioned synthetic efforts show the importance of cross-conjugated hydrocarbons, dendralenes and an ever-increasing interest of the chemical community to explore their synthetic potential. These synthetic methods show elegant methods from various groups. While most of these efforts investigated and discovered new synthetic routes to dendralenes, none of these methods can be considered as an efficient and synthetically useful generalised method. Lengthy synthesis, requirements of activating groups, overall yields and lack of substituent variation possible on the dendralenes are some of the limitations of these methods. Above all, surprisingly, none of these methods discussed the stereoselective synthesis of substituted [3]dendralenes. Lack of an efficient, wide scope general method prevented the diene transmissive Diels–Alder reaction sequences of dendralenes beyond those involving the widely-reported simple dienophiles such as N-methylmaleimide (NMM), N-phenylmaleimide (NPM), benzoquinone etc. In other words, most of these studies invested much effort toward the synthesis of the dendralenes and repeatedly demonstrated abundantly the same Diels–Alder reaction with frequently used dienophiles.

Considering these facts, we devised a new synthetic route to address the drawbacks associated with the existing routes. The key objectives were to develop a simple method to access substituted [3]dendralenes that uses commercially available, cheap starting materials, air stable reagents and avoids the formation of unstable intermediates and harsh reaction conditions.

The Sherburn group has previously shown the successful synthesis of a chiral [3]dendralene through twofold Stille/Negishi cross-coupling strategy. This method was, however, not generalised on a wide variety of substrates and it involves two steps starting from commercially available aldehyde 92. Ramirez dibromomethylenation of an aldehyde provides a dibromoolefin 93 and subsequent twofold Negishi cross-coupling with nucleophilic coupling partners yields the desired [3]dendralene 94 under mild reaction conditions (Scheme 18).

![Scheme 18: Our synthetic route to substituted [3]dendralenes](image-url)
Introduction

Of particular interest in generalising this method are the following benefits.

- The starting materials are cheap and readily available.
- No unstable intermediates are involved and no special functionality/directing groups are required on the substrates.
- Above all, this method can be successfully applied to make the never before reported stereoselective synthesis of the dendralenes by sequential cross-coupling of the dibromoolefin.

This method worked well on all the variations with respect to the nucleophilic and electrophilic coupling partners and substituted [3]dendralenes were isolated in yields up to 85%. The methodology worked well in the presence of electron rich aromatic, electron poor aromatic, carbocyclic and heterocyclic, alkyl, alkenyl and alkynyl substrates. Altogether 24 examples of symmetrically coupled, multi-substituted [3]dendralenes were prepared through this method (Figure 2).

![Figure 2: Representative examples of substituted [3]dendralenes from the new method](image)

It was next envisaged that [3]dendralenes could be stereoselectively synthesised by the sequential cross-coupling of the dibromoalkenes with different nucleophilic coupling partners. Based on the seminal report from Negishi for the stereoselective cross-coupling of alkyl nucleophile and monobromodiens, that proceed with either clean...
retention or inversion of configuration, we thought of generating both the diastereomers of the dendralene by using the new method.\textsuperscript{25-26} Initially it was thought that both the diastereomeric dendralenes could be generated from the same monobromodiene by using the retention catalyst and inversion catalyst. Our initial efforts to selectively generate dendralenic diastereomers from the same monobromodiene were unsuccessful as one of the two catalysts always yielded non-selective reactions. It was thought at this stage to synthesise both the monobromodienes 96 and 98 by trans-selective cross coupling of the dibromoolefin 95 with each of the nucleophiles of interest and subsequently perform the second cross-coupling reaction, whereby retention or inversion of stereochemistry would be governed by the catalyst used (Scheme 19). This approach was found to be successful in selectively synthesising the dendralenic diastereomers 97 and 99. Synthesising overall 10 pairs of geometrical isomers in yields up to 91\% and $E/Z$ ratio up to 95\% further proved the generality of the method.

![Scheme 19: Representative stereoselective syntheses of geometrical isomers of substituted [3]dendralenes.](image)

The power of this new methodology was finally shown by synthesising stereoselective [4]dendralene 100 and subjecting it to triene-transmissive twofold 6$\pi$-electrocyclisation sequence to generate the bicyclic [3]dendralene 102 in a single operation (Scheme 20).

1.2 Diene Transmissive Diels–Alder (DTDA) Reactions–Common Introduction to Chapter-2 and Chapter-3

The most striking feature that renders the acyclic, cross-conjugated hydrocarbons, dendralenes, important in synthetic organic chemistry is their capacity to undergo diene-transmissive Diels–Alder (DTDA) reaction sequences as shown in Scheme 1. The DTDA sequence involves two successive DA reactions and it leads to four new covalent bonds, two new rings and up to eight stereocentres. This most atom and step-economical transformation is the basis of the research described in Chapters 3 and 4 of this thesis.

It was Tsuge who coined the term “diene-transmissive Diels–Alder” and explored the DTDA reaction sequences of various substituted [3]dendralenes with reactive dienophiles such as dimethylacetylene dicarboxylate (DMAD), N-methylmaleimide (NMM), N-phenyltriazolinedione (PTAD).11-14, 27 Tsuge deserves the credit for the first use of a hetero-dienophile in DTDA reaction sequences (Scheme 21).28
Cadogan and co-workers made a major breakthrough achievement in DTDA reactions by isolating the mono adduct from the first DA reaction between the parent [3]dendralene and various dienophiles such as quinone, PTAD, DMAD and maleimide. Also Cadogan demonstrated the reaction of these monoadducts with a second dienophile, which increases the complexity of the final product.

The Fallis group performed DTDA reactions of 3'-substituted [3]dendralenes with reactive dienophiles such as benzoquinone and N-phenylmaleimide (NPM). Fallis and co-workers performed the first intramolecular/intermolecular DTDA sequences, involving dendralene 108 to generate oxygen rich “nor-triterpenoid” molecule 111 (Scheme 22).

The Sherburn group demonstrated chemo-, regio-, and stereoselective intermolecular DTDA reaction sequences of a chiral [3]dendralene 112 to generate enantiomerically enriched polycyclic complex structure 117 (Scheme 23). It is noteworthy to mention the seminal work from the Sherburn group toward the synthesis of pseudopterosin G-J aglycone from the key intermediate, a substituted [3]dendra-2-allene. A cleverly orchestrated diene-transmissive triple Diels–Alder reaction sequence made it possible to synthesise the complex target structure in just 11 steps from commercially available starting materials.
Scheme 23: Enantiomerically enriched polycyclic scaffolds by Sherburn

The recently developed new synthetic routes to substituted dendralenes by Ghosh, Fananas-Mastral, Tanaka and Glorius groups revealed DTDA sequences with NMM, NPM, benzoquinone, tetracyanoethylene (TCNE) and DMAD as dienophile.\textsuperscript{19-20, 23, 32}

The methodological studies reported in Chapter 3 and Chapter 4 explore the use of previously unreported benzyne DA reactions of dendralenes, and rarely reported enantioselective DA reactions of dendralenes, respectively.

1.3 Diene-Transmissive Diels–Alder Sequences with Benzyne

Recent literature contains a large volume of work demonstrating the synthesis of dendralenes and their synthetic potential.\textsuperscript{2, 33} However, most of this work has employed stable dienophiles such as \textit{N}-methylmaleimide (NMM), \textit{N}-phenylmaleimide (NPM), dimethylacetylenedicarboxylate (DMAD), benzoquinone etc. Chapter 2 of this thesis has already discussed a short and efficient synthetic route to substituted dendralenes. Having such a powerful, easy method to access substituted dendralenes in hand, the prospect of examining previously unexplored research in the field of DTDA sequences of dendralenes was possible. Attempts to move into unexplored
areas of synthetic chemistry led us to the field of benzynes, which are reactive and non-isolable dienophiles.

Evidence for the existence of benzyne 119 was obtained by J. D. Roberts, who showed that, when chlorobenzene-1-14C 118 was reacted with potassium amide, equal amounts aniline-1-14C 120 and aniline-2-14C 121 were produced (Scheme 24).  

\[
\begin{align*}
\text{ClH} & \quad \text{KNH}_2 \quad \text{NH}_3(0) \\
\rightarrow & \quad \text{119} \\
\rightarrow & \quad \text{14NH}_2 + \text{14NH}_2
\end{align*}
\]

**Scheme 24:** J. D. Robert’s experiments with benzyne

Benzynes are highly reactive intermediates and can be generated in situ by various methods mainly based on 1,2-elimination strategies. The exceptional reactivity of benzyne stems from its unusually low-lying LUMO. This feature makes it useful for bond-forming reactions such as nucleophilic additions, [4+2] cycloadditions, [2+2] cycloadditions, σ-bond insertion reactions, etc. The reactivity of benzynes has been utilised in more than 75 natural product syntheses and the majority involve [4+2] cycloadditions. Furans are used in most [4+2] cycloaddition reactions of benzynes, with acyclic dienes very sparsely reported in the literature. Early reports of [4+2] cycloadditions of acyclic dienes and benzyne were accompanied by competing [2+2] cycloadditions and ene reactions. In 1969, Levin showed that benzyne 119, generated from the corresponding benzene diazonium-2-carboxylate 122 reacted with trans,trans-2,4-hexadiene 123 and yielded the respective [4+2] cycloaddition and ene reaction products 125 and 126 respectively (Scheme 25).

\[
\begin{align*}
\text{122} & \quad \triangle \quad [\text{119}] \\
& \quad + \quad \text{123} \\
& \quad \text{1,2-dichloroethane} \quad 84^\circ \text{C} \\
& \quad 74\% \quad \rightarrow \quad \text{125} \\
& \quad \text{6}\% \quad \rightarrow \quad \text{126}
\end{align*}
\]

**Scheme 25:** Levin and co-workers’ cycloaddition reaction of benzyne and an acyclic diene.
Waali showed in 1975 that benzyne 119 reacted with trans-1,3-pentadiene 127 yielding a mixture of the corresponding [4+2] cycloaddition product 128 and [2+2] cycloaddition product 129. When the diene was replaced by cis-1,3-pentadiene 130, the [2+2] product 131 was obtained exclusively (Scheme 26).\(^{38}\)

\[\text{Scheme 26: Cycloaddition reaction of benzyne and acyclic dienes by Waali.}\]

Angerbauer observed a successful [4+2] cycloaddition reaction between benzyne 119 and (E,E)-1,4-diacetoxy-1,3-butadiene 132 to give adduct 133 in 53% yield.

Interestingly, this was the only example reported in the paper (Scheme 27).\(^{39}\)

\[\text{Scheme 27: [4+2] cycloaddition reaction of benzyne by Angerbauer.}\]

Recently, Lautens and co-workers demonstrated successful DA reactions of multi-substituted dienes with benzyne, with products obtained in isolated yields of up to 86% (Scheme 28).\(^{40}\)
Scheme 28: 1, 4-Dihydronaphthalene synthesis by Lautens.

Following the publication of Lautens’ method, the Chen group also used 1,4-disubstituted dienes to synthesise the corresponding DA adducts.\textsuperscript{41} There are also several reports of intramolecular arynes DA reactions of acyclic dienes. Contributions from Buszek, Smith, Danheiser and Suzuki are summarised in Scheme 29.\textsuperscript{42-45}

Scheme 29: IMDA reactions of benzyne and acyclic dienes.

The absence of literature precedent for Diels–Alder reactions between benzyne and dendralenes provides the aim of the research work carried out and described in Chapter 3. The work described in this thesis shows that substituted [3]dendralenes \textsuperscript{145} undergo a single DA reaction with \textit{in situ} generated benzyne \textsuperscript{119} from precursor \textsuperscript{144} to generate 2-vinyl-1,4-dihydronaphthalenes \textsuperscript{146}. The product of this first DA
reaction reacts with a second dienophile 147 to generate carbo- and hetero-annelated tetralins 148 (Scheme 30). Moreover, this three component DTDA reaction sequence between the benzyne, substituted [3]dendralene and second dienophile, generates condensed multicyclic compounds of relevance to medicinal chemistry.

Scheme 30: DTDA reaction sequences involving benzyne as the 1st dienophile

We thought of deploying benzyne for the first DA event by considering three points. Firstly, mild benzyne generation methods would allow us to perform reactions at ambient temperature and pressure. Secondly, since both benzyne and substituted [3]dendralenes are reactive components for DA reactions, we postulated that the first cycloaddition might happen under the conditions of benzyne generation. Thirdly, if the mono DA adduct is not a very reactive diene and doesn’t undergo further cycloaddition with benzyne, then it could be isolated and used as a common scaffold for further DA reactions with various dienophiles. Our studies were performed with four symmetric benzyne precursors as shown in Figure 3.

Figure 3: Benzyne precursors employed for the study

The optimisation studies revealed that benzo-TMS-triflate 144 and 151 are the most promising benzyne precursors with respect to the overall conversion of the starting material and the yield of the isolated mono adduct. Double DA adduct formation occurred to a minor extent and this allowed us to use a different dienophile for the
second DA reaction. We next focussed on to getting both the reactions in the same flask without isolation of the mono adducts (Scheme 31). The one-pot reactions were successful in generating the corresponding double adducts in yields up to 63%.

**Scheme 31**: One-pot DTDA reaction sequences involving benzyne.

Substituted [3]dendralenes with various electronic and steric properties reacted well under the optimised reaction conditions to yield annelated tetralins in good yields. The second cycloaddition was found to have excellent π-diastereofacial selectivity and endo-selectivity with NMM as the second dienophile (Figure 4).

**Figure 4**: Representative examples of one-pot double DA adducts

In summary, Diels–Alder reactions between substituted [3]dendralenes and benzyne was demonstrated for the first time. A second DA reaction with various dienophiles constructed multi-cyclic, complex structures in good yield and excellent π-diastereofacial selectivity. The DTDA reaction sequences could be performed in one-pot to show the robustness of this method to make multi-cyclic compounds in high atom- and step-economy.
1.4 Diene-Transmissive Enantioselective Diels-Alder Reactions and Sequences Involving Substituted Dendralenes

Enantioselective synthesis of chiral molecules is one of the major objectives and central foci in chemical synthesis. Many total syntheses of natural products reported in the last century depended on metal-based chiral catalysts and chiral auxiliaries. Toward the end of the last century, methods based on metal-free, small organic molecule based catalysts became a core focus of research in many labs across the globe and these efforts laid the foundation of a new type catalysis called organocatalysis. Organocatalysis is the acceleration of chemical reactions by small organic molecules. These organic catalysts are generally stable in air and water and do not lead to metal contamination of the products. Despite the advantages of organocatalysis over other modes of catalysis, its applications were previously found sporadically in the literature. In the last two decades, however, many reactions catalysed by small organic molecules have been reported. Enantioselective cycloadditions, aldol reactions, alkylations, asymmetric conjugate additions, α-halogenations of carbonyl compounds, allylations of aldehydes, Mannich reactions, etc. have been achieved by organocatalysis.\(^{46, 47}\)

The recent advancement in the field of asymmetric organocatalysis was ignited mainly by the rediscovery of proline-based enamine catalysis by List, and MacMillan’s work on imidazolidinone-based iminium catalysis (Scheme 32 and 33).\(^{48-50}\)

**Scheme 32:** Proline catalysed asymmetric aldol and Mannich reactions by List
The enantioselective Diels–Alder reaction is a powerful method for the construction of chiral cyclohexene frameworks. This venerable reaction is deployed as a key step toward the synthesis of many a natural products.\textsuperscript{51} MacMillan and co-workers reported the first organocatalysed, enantioselective Diels–Alder reaction of dienes with $\alpha,\beta$-unsaturated aldehydes and ketones.\textsuperscript{50, 52} Chiral imidazolidinone \textbf{168} was used as the catalyst, which functions by LUMO-lowering iminium formation with the carbonyl compound.

![Scheme 33](image)

\textbf{Scheme 33:} Iminium catalysed asymmetric DA reactions by MacMillan

MacMillan and co-workers demonstrated the short and efficient synthesis of the marine metabolite solanapyrone D \textbf{177} via organocatalysed, enantioselective Type I IMDA reaction (Scheme 34).\textsuperscript{53}

![Scheme 34](image)

\textbf{Scheme 34:} Catalytic enantioselective synthesis of solanapyrone D by MacMillan.

Following these seminal publications on organocatalysed Diels–Alder reactions by MacMillan in the early 2000s, there was an avalanche of research activity in this field and various organocatalysts were introduced. Ishihara demonstrated that a
diammonium salt of binaphthyldiamine 179 can catalyse the enantioselective Diels–Alder reaction of substituted \( \alpha,\beta \)-unsaturated aldehydes to generate the adducts with \( ees \) up to 94\% (Scheme 35). 54

\[
\text{Scheme 35: Organocatalysed DA reactions by Ishihara}
\]

Maruoka and co-workers further expanded the scope of the work carried out by Ishihara by introducing the substituted binaphthyl catalyst 182. Maruoka also employed a variety of substitutents at the \( \alpha \) position of the \( \alpha,\beta \)-unsaturated aldehydes (Scheme 36). 55

\[
\text{Scheme 36: Enatioselective DA reaction of \( \alpha \)-substituted acroleins by Maruoka.}
\]

Hayashi and co-workers introduced an \( exo \)-selective Diels–Alder reaction of \( \alpha,\beta \)-unsaturated aldehydes catalysed by diarylprolinol silyl ether 185 in the presence of an acid (Scheme 37). 56
Recently, Hayashi demonstrated that the catalyst 185 could also be used for the DA reactions of $\alpha$-substituted acroleins. Ogilvie and co-workers showed that a hydrazide-derived organocatalyst could be employed for the Diels–Alder reaction of the $\alpha,\beta$-unsaturated aldehyde and dienes. The organocatalysed, enantioselective DA reactions described so far demonstrate that various catalysts have been developed to promote these reactions. When it comes to diene structure variation, however, cyclopentadiene and substituted butadienes are used in most of this work. The commonly used dienes are shown in the Figure 5. Considering the fact that the importance of dendralenes as multiple dienes is increasing in the synthetic community, it is surprising that none of the above-mentioned studies used these cross-conjugated hydrocarbons.

**Scheme 37: Asymmetric DA reaction by Hayashi**

![Scheme 37: Asymmetric DA reaction by Hayashi](image)

**Figure 5: Dienes used by various groups in organocatalysed DA reactions**
There are only two publications so far discussing enantioselective DTDA sequences of dendralenes and both these papers emerged from the Sherburn lab. Enantioselective DA reaction of the parent [3]dendralene 1 with an \(\alpha,\beta\)-unsaturated ester used a modified Corey oxazaborolidinium catalyst 189 (Scheme 38), and MacMillan’s imidazolidinone organocatalyst 192 was used to induce organocatalytic cascades of the parent dendralenes with \(\alpha,\beta\)-unsaturated aldehydes (Scheme 39).\(^{10, 59}\) The third chapter of this thesis explores the enantioselective DTDA sequences of substituted [3]dendralenes for the first time.

**Scheme 38:** Enantioselective DA reaction of [3]dendralene in the presence of a modified Corey oxazaborolidinium catalyst.

In this study, [3]dendralenes having various substitution patterns, including symmetrically and unsymmetrically-substituted [3]dendralenes were employed, and acrolein was used as the dienophile. MacMillan’s first generation imidazolidinone was used as organocatalyst.\(^{50}\) This methodology demonstrates the generation of complex, cyclic, enantio-enriched molecules through atom and step-economical chemical transformations.
Under the optimised reaction conditions, it was observed that the mono Diels–Alder reaction between the substituted [3]dendralene and acrolein regio- and diastereoselectively gave monoadducts in yields up to 72% and $ers$ up to 99%. The best results were observed when an electron rich aromatic substituent was present in the 3’ position. Conversely, the electron withdrawing $p$-nitrophenyl substituent, and weakly electron-donating alkyl substituents failed to give the product under the optimised reaction conditions. Evidently, the reactions were too slow to be synthetically useful, which is a common issue with organocatalysed reactions. One surprising outcome of this study was the reversal of regioselectivity of first cycloaddition relative to the parent [3]dendralene 1. Next a substrate controlled DA reaction was investigated between the monoadducts and the dienophiles NMM, PTAD and benzoquinone. The second DA reaction was found to be diastereoselective and yielded annulated, functional group-rich, chiral $\Delta^{(9)}$-octalin building blocks through one pot operations in excellent yield (Figure 6).

![Chemical structures](image)

**Figure 6**: Enantioselective DTDA sequences of substituted [3]dendralenes with two different dienophiles

In summary, substituted [3]dendralenes have thus been used to generate chiral, $\Delta^{(9)}$-octalin structures through organocatalysed, chemo-, regio-, diastereo- and enantioselective Diels–Alder reaction sequences. The entire operations are carried out in a one pot manner to show the power of this methodology to deliver enantioenriched complex structures from simple, acyclic starting materials, i.e. dendralenes. Ultimately, the successful synthesis of otherwise difficult chiral $\Delta^{(9)}$-octalin structures are synthesised by applying the principles of green chemistry and ideal synthesis.
References

Introduction

Chapter Two:

A General Synthesis of Dendralenes
2 A General Synthesis of Dendralenes

Prelude

The work was published in the journal *Chemical Science*. The other authors listed on the manuscript are Michael S. Sherburn and Jas S. Ward. Jas S. Ward obtained the X-ray crystallographic studies upon samples provided by myself. The project, and the draft manuscript, was conceived and evolved in collaboration with Professor Michael S. Sherburn. All of the experimental work was conducted by myself. Austin F. Smith, Maryne Dubois and Tegan O’Brien were involved in the preliminary experiments and are acknowledged in the manuscript.

Dendralenes are one of the four fundamental classes of hydrocarbons made of conjugated C=C units. They are acyclic, branched and cross-conjugated hydrocarbons. What makes dendralenes valuable in synthetic organic chemistry is their ability to undergo diene transmissive Diels–Alder (DTDA) reaction sequences to produce complex polycyclic scaffolds. This chapter discloses a new synthetic method to generate substituted [3]dendralenes from substituted dibromo-olefins via twofold Negishi cross-coupling reactions. The dibromo-olefin can be accessed from the respective aldehyde through the use of the Ramirez dibromo-olefination reaction.

We demonstrate the first stereoselective synthesis of dendralenes through the use of two successive cross-couplings of a 1,1-dibromoalkene with different alkenyl coupling partners. The first cross-coupling yields the monobromo diene and the second cross-coupling yields the unsymmetrical dendralene. This stereoselective dendralene synthesis is made possible by the catalyst-controlled stereoretentive or stereoinvertive reaction pathway in the second cross-coupling.
To show the robustness of this method, we synthesised twenty five examples of unsymmetrically substituted [3]dendralenes and three examples of unsymmetrically substituted [4]dendralenes with very high selectivity. The power of this chemistry is highlighted by the use of these compounds in both DTDA reaction sequences and domino 6π-electrocyclisation reactions.
Chemical breaking investigations primarily from the Tsuge milligrams to tens of grams dendralene have now been synthesized on scales of hundreds of value of dendralenes, and the urgent need for better syntheses. perceived to be unmanageable.

introduction

In hydrocarbons comprising carbon atoms that are sp\(^2\) hybridized, the absence or presence of chain bifurcations and rings permit four fundamental structural families to be designed (Fig. 1). Dendralenes are the acyclic, branched class of structures that, until the turn of this century, were widely recognized, numerous publications focusing on dendralene methods to access them, renders the recent contributions significant. Nonetheless, these existing methods are limited, in that they permit the synthesis of heavily restricted subsets of structures. Furthermore, none of these existing approaches permit the stereoselective preparation of dendralenes. Herein, we introduce a direct method for acyclic branched oligo-alkene synthesis that (a) tolerates a wider variety of substituent types; (b) permits greater diversity in the number of substituents; (c) represents the first stereoselective synthesis of dendralenes, whilst also being shorter in step count than existing methods.

The new approach permits the synthesis of dendralenes bearing the most common substituents (alkyl, cycloalkyl, alkynyl, alkenyl, and heteroaryl groups) in only two or three steps from commercially-available aldehydes through a robust sequence involving Ramirez dibromomethylenation\(^{12}\) and Negishi cross-coupling\(^{13}\) reactions (Fig. 2).

Building upon the foundations of previous, narrow-scope cross-coupling methods for dendralene synthesis, and ground-breaking work from the Negishi laboratory,\(^{14,15}\) we establish a method that is unparalleled in its ability to generate dendralenic structural variety. Until now, no published dendralene preparation has addressed the diastereoselective synthesis of internally-substituted systems. This is a challenging and unsolved problem since it requires the stereoselective preparation of a tri-substituted C=C bond, whereupon two non-equivalent (but very similar) alkényl-substituents are attached to the same carbon. We provide solutions that are of broad scope, allowing selective access to both E- and Z-diastereomers of an internally-substituted dendralene from the same 1,1-dibromomethane precursor.

A general synthesis of dendralenes\(^{†}\)

Josemon George, Jas S. Ward and Michael S. Sherburn

† Electronic supplementary information (ESI) available: CCDC 191054, 191055, 191056, 191057, 191058 and 191059. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc03976g

The first general synthetic approach to substituted [3]- and higher dendralenes is reported. Fifty-one monosubstituted and 1,1-dibromomethanes with alkeny/zinc reagents, and exploits both substrate- and catalyst-controlled aspects of chemo-, regio- and stereoselectivity in the two C(sp\(^{2}\))-C(sp\(^{2}\)) bond forming steps. The value of the new hydrocarbons in rapid structural complexity generation is demonstrated through their deployment in unprecedented diene- and triene-transmissive pericyclic reaction sequences.

Dendralenes are useful building blocks for the swit

Fig 1. Hydrocarbon design with sp\(^2\) carbons, the unique synthetic value of dendralenes, and the urgent need for better syntheses.

The rapid expansion of chemical interest in dendralenes, combined with the paucity of synthetic structures that, until the turn of this century, were widely recognized, numerous publications focusing on dendralene methods to access them, renders the recent contributions significant. Nonetheless, these existing methods are limited, in that they permit the synthesis of heavily restricted subsets of structures. Furthermore, none of these existing approaches permit the stereoselective preparation of dendralenes. Herein, we introduce a direct method for acyclic branched oligo-alkene synthesis that (a) tolerates a wider variety of substituent types; (b) permits greater diversity in the number of substituents; (c) represents the first stereoselective synthesis of dendralenes, whilst also being shorter in step count than existing methods.

The new approach permits the synthesis of dendralenes bearing the most common substituents (alkyl, cycloalkyl, alkynyl, alkenyl, and heteroaryl groups) in only two or three steps from commercially-available aldehydes through a robust sequence involving Ramirez dibromomethylenation\(^{12}\) and Negishi cross-coupling\(^{13}\) reactions (Fig. 2).

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The first group of [3]dendralenes reported here lack stereogenicity about the central C=C bond. Thus, 1,1-dibromoalkenes 1 undergo twofold Negishi C(sp$^2$)–C(sp$^2$) coupling with unsubstituted and substituted alkylzinc bromides to furnish dendralenic products 2, where the two newly introduced alkyl substituents are the same. Table 1 depicts 23 examples of twofold cross-couplings between 13 different 1,1-dibromoalkenes 1 and four different alkyl nucleophiles, to demonstrate the broad scope of this lynchpin strategy.

The twofold Negishi cross-coupling protocol works well with vinylzinc bromide and its alkyl and aryl-substituted congeners, to access mono- to penta-substituted [3]dendralenes 2a–w with substitution at all possible sites on the dendralene framework. Substituents incorporated at the central methylene position of the [3]dendralene (substituents colored blue in Table 1) include acyclic and cyclic primary and secondary alkyl-groups, carbocyclic and heterocyclic aromatic groups of diverse electronic characteristics, and alkenyl- and alkynyl-substituents. While several (pre)catalysts were effective, [PdCl$_2$(dppf)] was superior for twofold cross-coupling.

To achieve the first diastereoselective synthesis of dendralenes, we envisioned two successive cross-couplings of a 1,1-dibromoalkene 1 with different alkenylzinc reagents. It is well established that aldehyde-derived 1,1-dibromoalkenes undergo chemo- and regio-selective single cross-coupling with an alkenyl nucleophile to replace the bromine trans to the carbon-based substituent (Table 2, 1/3). In our hands, [Pd(PPh$_3$)$_4$] was the most consistent performer in the trans-selective mono-coupling of 1,1-dibromomethanes (1 $\rightarrow$ 3). A little fine-tuning of the reaction was needed for each substrate (e.g., stoichiometry of coupling partners, temperature) for optimal results. The ESI† contains 18 examples involving seven different 1,1-dibromomethanes 1 and four different alkenyl nucleophiles.

Negishi reported that cross-couplings of the resulting (1Z)-2-bromo-1,3-dienes 3 with methyl-, ethyl-, n-butyl- or phenylzinc bromide proceed with retention$^{12}$ of configuration at the sp$^2$C initially carrying the bromine trans to the carbon-based substituent (Table 2). We are delighted to report that the same ligand also brings about Pd(0)-catalyzed stereo-retentive cross-couplings of (1Z)-2-bromo-1,3-dienes with alkenyl nucleophiles to permit the first stereoselective dendralene synthesis (Table 2, 3 $\rightarrow$ 4).

Consistent with the results of the Negishi group with non-olefinic nucleophiles,$^{12}$ we find that alkylzinc bromides
exhibit wide scope in Pd(0)/t-Bu₃P-catalyzed stereo-retentive couplings involving (1Z)-2-bromo-1,3-butadienes. Inconsistent with Negishi’s findings, however, are couplings of alkyl-substituted systems (Table 2, 3/4, R = alkyl), which generally give mixtures of E and Z-diastereomers in the second cross-coupling (see ESI† for details). Fortuitously, these substrates work well in cross-couplings with [PdCl₂(dppf)] as pre-catalyst, which proceed with stereochemical inversion16,20 (Table 3, 3/4).

Overall, the sequence involving Pd(0)/t-Bu₃P-catalyzed stereo-retentive cross-coupling (Table 2) has broader scope than the alternative stereo-invertive pathway with [PdCl₂(dppf)] pre-catalyst (Table 3). Nineteen [3]dendralenes, prepared through stereo-retentive couplings, are depicted in Table 2. Collectively, Tables 2 and 3 describe the stereoselective synthesis of ten pairs of E and Z-diastereomers of dendralenes. Operationally, each pair of diastereomers is synthesized through a complementary pair of sequences (i.e. 1/3/4) in which the order of addition of the two non-equivalent alkenyl-zinc bromides is reversed. As shown in Scheme 1, the two couplings can be performed in the same flask, through successive additions of two pairs of catalysts and reagents. Thus, the previously unsolved problem of stereo-selective dendralene synthesis is reduced to the simple task of (a) selecting whether a stereo-retentive or -invertive pathway is required, and (b) performing two cross-couplings with two different alkenyl-zinc reagents.

The geometry of every stereogenic dendralene (Tables 2 and 3) was assigned by NOE experiments, with two X-ray crystal structures supporting these assignments. The molecular structures of 4e-Z and 4l-Z (Table 2) exhibit essentially in plane conformations of the longest through-conjugated segment of each structure, namely 1,6-diphenyl-1,3-hexadien-5-yne and 1,6-diphenyl-1,3,5-butatriene, respectively. Both structures carry isopropenyl substituents, which are skewed at angles of 78° and 82° out of plane.
A General Synthesis of Dendralenes

As described in the introduction, the most important feature of dendralenes is their participation in diene-transmissive Diels–Alder (DTDA) sequences to form octalin. The present work significantly extends the scope of the DTDA process since, as we demonstrate here for the first time in Scheme 2, geometrical isomers of [3]dendralenes give different constitutional isomers of twofold cycloadducts.

Thus, each diastereomeric [3]dendralene 4a-Z and 4a-E reacts with the dienophile N-methylmaleimide (NMM, 5) with complete selectivity for the 1,3-butadiene site that lacks the inside-1,1-butadiene Z substitutent. Substrate 4a-Z gives semicyclic diene 8, which reacts on, in situ, with a second NMM molecule to furnish 1-methyl-Δ[9]-octalin 7 as the major product. The semicyclic diene 8 derived from diastereomeric dendralene 4a-E undergoes a second NMM cycloaddition under high pressure conditions to form 10-methyl-Δ[10]-octalin 9, possessing an angular methyl substituent. Octalin and decalin ring systems are extremely common structural motifs in natural products and medicinal agents.

The 48 dendralenes depicted in Tables 1–3 conclusively demonstrate the broad scope of this method for substituted [3]dendralene synthesis. Scheme 3 shows that the same approach permits the first stereoselective synthesis of a substituted [4]dendralene 10a-Z, by simply deploying 2-[1,3-butadienyl]zinc bromide as a coupling partner (see the ESI† for two more examples).

The freshly minted Z-configuration of the trisubstituted C-C unit of [4]dendralene 10a-Z is essential for the first twofold, triene transmissive 6–4π-electrocyclization sequence (10a-Z → 11 → 12). The execution of a pair of electrocyclizations in this interconnected manner is without precedent. Several variations upon this original theme can be envisaged, which has potential for development into a broad scope, new method for step economic polycycle synthesis.

Conclusions

In conclusion, the first broad-spectrum synthesis of substituted dendralenes has been demonstrated, and unprecedented domino sequences for polycycle construction proven. [3]Dendralenes bearing from one to five alkyl, cycloalkyl, alkenyl, allyl, vinyl, and heteroaryl substituents have been prepared. Substitution at every conceivable position on the [3]dendralene framework has been realized. The previously unsolved problem of diastereoselective synthesis of internally-substituted systems has been solved. The method has been shown to work also with [4]dendralenes. Importantly, the approach represents the first general synthesis of dendralenic structures with extended C=C and C=C through-conjugation, as evidenced by the preparation of 23 new compounds containing this feature. We venture that the findings described herein, when combined with the strategies recently introduced for the preparation of the unsubstituted higher [n]dendralenes \(n = 5-12\), will permit the chemical synthesis of any conceivable dendralenic structure in short order, and lead to new applications in step economic total syntheses.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references


Supporting Information

A General Synthesis of Dendralenes

(Josemon George, Jas S. Ward, and Michael S. Sherburn)
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Analyses of the Widest Scope Substituted [3]Dendralene Syntheses


A General Synthesis of Dendralenes


**Synthesis of Stereodefined Borylated Dendralenes through Copper-Catalyzed Allylboration of Alkynes**:  
Additional Findings on Retention/Inversion Experiments

A stepwise inversion pathway was proposed (Scheme S1), driven by the minimization of steric strain in the initial oxidative insertion product S1. Thus, rearrangement through putative cis-alkenylidene-substituted π-allylpalladium complex S2 to the σ-alkyl/palladium complex S3, which after σ-bond rotation would generate the trans-alkenylidene-substituted π-allylpalladium complex S4 (and/or σ-alkyl/palladium complex S5). Evidently, for clean inversion, this process would have to be faster than transmetalation-reductive elimination of the initial oxidative insertion product S1/S2.

Scheme S1:

The Negishi group came to the following general conclusions regarding the inversion pathway: (a) it only works for alkyl aldehyde precursors, and (b) the reaction is successful irrespective of the nature of the nucleophile. Our results with alkenyl-zinc bromide nucleophiles (the Negishi work includes one example with vinyl-zinc bromide) are not fully consistent with these findings, in that the para-methoxybenzaldehyde-derived dibromoalkene works well (see main manuscript, Table 3, 4o-E/Z). Additionally, in our hands several reactions of alkyl-substituted aldehydes gave mixtures of diastereomers with Pd(0)/t-Bu₃P (Scheme S2, these are referred to in the main manuscript in the paragraph above Table 3).
A General Synthesis of Dendralenes

Scheme S2

Four other substrates gave clean retention of stereochemistry with \([\text{Pd(dppf)Cl}_2]\) (Scheme S3)

Scheme S3
General Methods

NMR Spectroscopy

$^1$H NMR spectra were recorded at 700, 600 and 400 MHz using a Bruker AVANCE 700, AVANCE 600, AVANCE 400 and Varian 400-MR spectrometer, as indicated. Residual solvent peaks were used as an internal reference for $^1$H NMR spectra (CDCl$_3$ δ 7.26 ppm, CD$_2$OD δ 3.31 ppm, (CD$_3$)$_2$SO δ 2.50 ppm, CD$_2$CN δ 1.94 ppm, CD$_2$Cl$_2$ δ 5.32 ppm, C$_6$D$_6$ δ 7.16 ppm). Coupling constants ($J$) are quoted to the nearest 0.1 Hz. The assignment of proton signals was assisted by COSY, HSQC and HMBC experiments. $^{13}$C NMR spectra were recorded at 100 MHz and 175 MHz using a Bruker AVANCE 400 or Bruker AVANCE 700 spectrometer respectively. Solvent peaks were used as an internal reference for $^{13}$C NMR spectra (CDCl$_3$ δ 77.16 ppm, CD$_2$OD δ 49.0 ppm, (CD$_3$)$_2$SO δ 39.52 ppm, CD$_3$CN δ 1.32 ppm). Assignment of carbon signals was assisted by HSQC and HMBC experiments. NOE spectra were recorded at 400 MHz using Varian 400-MR spectrometer. The following abbreviations (or combinations thereof) are used to denote $^1$H NMR multiplicities: s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplet, t = triplet, m = multiplet.

Infrared Spectroscopy

IR spectra were recorded on a Perkin–Elmer UATR Two spectrometer as a thin film or solid.

Mass Spectrometry

Low-resolution EI mass spectra were recorded on a Finnigan Polaris Q ion trap mass spectrometer using electron impact (EI+) ionization mode at 70 eV. High-resolution EI mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. Low-resolution ESI mass spectra were recorded on a ZMD Micromass spectrometer with Waters Alliance 2690 HPLC. High-resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) mass spectrometer.

Melting Points

Melting points were measured on a Stanford Research Systems Optimelt Automated Melting Point System and are uncorrected.
X-ray Crystallography

Single crystal X-ray data was collected on a SuperNova (Dual Source) diffractometer using a SuperNova (Cu) X-ray radiation source. Crystallographic structures were solved using CryoAlis PRO.

Experimental Procedures, Reagents, Chromatography and Glassware

Reactions were conducted under a positive pressure of dry nitrogen in oven dried glassware and at room temperature, unless specified otherwise. Anhydrous solvents were either obtained from commercial sources or dried according to the procedure outlined by Grubbs and co-workers.\(^2\) Commercially available chemicals were used as purchased, or where specified, purified by standard techniques. Analytical thin-layer chromatography was conducted with aluminum-backed silica gel 60 F\(_{254}\) (0.2 mm) plates supplied by Merck, and visualized using UV fluorescence (\(\lambda_{\text{max}} = 254\) nm), or developed using KMnO\(_4\) or p-anisaldehyde or phosphomolybdic acid followed by heating. Flash chromatography employed Merck Kieselgel 60 silica gel (230–400 mesh). AgNO\(_3\) coated silica TLC plates were prepared according to the procedure by Caspi and co-workers.\(^3\) AgNO\(_3\) impregnated silica gel was prepared as per the reported procedure by Mizaikoff and co-workers.\(^5\) Solvent compositions are given in (v/v). PS 40–60 °C refers to petroleum spirits, boiling point fraction 40–60 °C. Grignard reagents were prepared from the corresponding halides as per the general procedure by Cook and co-workers.\(^4\) Grignard reagent concentration was determined by the method detailed by Love and Jones.\(^5\) Pd\(_2\)(dba)-CHCl\(_3\) was prepared according the procedure reported by Ananikov and co-workers.\(^6\) PdCl\(_2\)(dppf)-toluene was prepared according to a procedure reported by Brandsma and co-workers.\(^7\)

Synthesis of 1,1-Dibromoalkenes

(2,2-Dibromovinyl)benzene (1a)

\[
\begin{align*}
\text{O} & \quad \text{CBrz} \quad \text{PPh}_3 \quad \text{CH}_2\text{Cl}_2 \quad 0 \degree \text{C, 2h} \quad \text{Br} \quad \text{Br} \\
& \quad \text{1a}
\end{align*}
\]

(2,2-Dibromovinyl)benzene 1a was prepared according to the reported procedure by Kim and co-workers from benzaldehyde (4.00 g, 37.7 mmol) as a colourless oil (7.12 g, 27.2 mmol, 72%) and the characterization data is consistent with the literature.\(^8\) R\(_f\) = 0.63 (5% EtOAc in PS 40–60);
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$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 – 7.51 (m, 2H), 7.49 (s, 1H), 7.41 – 7.31 (m, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.0 (CH), 135.5 (Cq), 128.7 (CH), 128.6 (2×CH), 128.5 (2×CH), 89.8 (Cq) ppm; IR (thin film): $v_{\text{max}}$ = 3056, 3023, 1948, 1885, 1595, 1493, 1444 cm$^{-1}$; LRMS: (El+): m/z (%): 264 ([M(81$^{18}$Br$_2$]+•, 59), 262 ([M(81$^{79}$Br$^{18}$Br]+•, 100), 260 ([M(81$^{79}$Br$_2$]+•, 53), 102 ([M–Br]+•), 100); HRMS (EI+): calculated for C$_8$H$_6$81$^{18}$Br$_2$: 263.8795; found: 263.8796; calculated for C$_8$H$_6$81$^{79}$Br$^{18}$Br: 261.8816; found: 261.8817; calculated for C$_8$H$_6$81$^{79}$Br$_2$: 259.8836; found: 259.8839.

1-(2,2-Dibromovinyl)-4-methylbenzene (1b)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47 – 7.42 (m, 3H), 7.18 (d, $J$ = 8.0 Hz, 2H), 2.35 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.8 (Cq), 136.9 (CH), 132.5 (Cq), 129.0 (2×CH), 128.5 (2×CH), 88.73 (Cq), 21.5 (CH$_3$) ppm; IR (thin film): $v_{\text{max}}$ = 3023, 2918, 1905, 1610, 1598, 1508 cm$^{-1}$; LRMS: (El+): m/z (%): 278 ([M(81$^{18}$Br$_2$]+•, 52), 276 ([M(81$^{79}$Br$^{18}$Br]+•, 100), 274 ([M(81$^{79}$Br$_2$]+•, 52), 197 ([M(81$^{79}$Br$^{18}$Br]+•, 15), 195 ([M(81$^{79}$Br$^{18}$Br]+•, 14), 116 ([M–Br]+•), 76); HRMS (EI+): calculated for C$_9$H$_8$81$^{18}$Br$_2$: 277.8952; found: 277.8959; calculated for C$_9$H$_8$81$^{79}$Br$^{18}$Br: 275.8972; found: 275.8976; calculated for C$_9$H$_8$81$^{79}$Br$_2$: 273.8993; found: 273.8995.

1-(2,2-Dibromovinyl)-4-methoxybenzene (1c)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47 – 7.42 (m, 3H), 7.18 (d, $J$ = 8.0 Hz, 2H), 2.35 (s, 3H) ppm; IR (thin film): $v_{\text{max}}$ = 3023, 2918, 1905, 1610, 1598, 1508 cm$^{-1}$; LRMS: (El+): m/z (%): 278 ([M(81$^{18}$Br$_2$]+•, 52), 276 ([M(81$^{79}$Br$^{18}$Br]+•, 100), 274 ([M(81$^{79}$Br$_2$]+•, 52), 197 ([M(81$^{79}$Br$^{18}$Br]+•, 15), 195 ([M(81$^{79}$Br$^{18}$Br]+•, 14), 116 ([M–Br]+•), 76); HRMS (EI+): calculated for C$_9$H$_8$81$^{18}$Br$_2$: 277.8952; found: 277.8959; calculated for C$_9$H$_8$81$^{79}$Br$^{18}$Br: 275.8972; found: 275.8976; calculated for C$_9$H$_8$81$^{79}$Br$_2$: 273.8993; found: 273.8995.
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10% EtOAc in PS 40–60); m.p. 36 – 38 °C (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.51 (d, J = 8.9 Hz, 2H), 7.41 (s, 1H), 6.89 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 159.8 (Cq), 136.4 (CH), 130.0 (2 × CH), 128.0 (Cq), 113.9 (2 × CH), 87.4 (Cq), 55.5 (CH₃) ppm; IR (thin film): v max = 3005, 2956, 2835, 1605, 1508 cm⁻¹; LRMS: (EI⁺): m/z (%): 294 ([M(²⁹Br₂)]⁺, 29), 292 ([M(²⁹Br²⁷Br)]⁺, 100), 290 ([M(²⁷Br₂)]⁺, 50), 277 ([M(²⁹Br²⁷Br)-CH₃]⁺, 29), 132 ([M–Br₂]⁺), 45; HRMS (EI⁺): calculated for C₉H₈O²⁹Br₂: 293.8901; found: 293.8902; calculated for C₉H₈O²⁷Br⁸¹Br: 291.8921; found: 291.8916; calculated for C₉H₈O²⁷Br₂: 289.8942; found: 289.8934.

5-(2,2-Dibromovinyl)-1,2,3-trimethoxybenzene (1d)

5-(2,2-Dibromovinyl)-1,2,3-trimethoxybenzene (1d) was prepared according to the reported procedure by Doddi and co-workers from 3,4,5-trimethoxybenzaldehyde (5.00 g, 25.5 mmol) as a pale brown solid (7.80 g, 22.2 mmol, 87%) and the characterization data is consistent with the literature [11].

IR (thin film): v max = 2997, 2936, 2830, 1576, 1506 cm⁻¹; LRMS: (EI⁺): m/z (%): 354 ([M(²⁹Br₂)]⁺, 53), 352 ([M(²⁹Br²⁷Br)]⁺, 100), 350 ([M(²⁷Br₂)]⁺, 50), 339 ([M(²⁷Br)-CH₃]⁺, 43), 337 ([M(²⁹Br²⁷Br)-CH₃]⁺, 43), 335 ([M(²⁷Br₂)-CH₃]⁺, 43), 177 ([M–CH₂Br₂]⁺, 28); HRMS (EI⁺): calculated for C₁₁H₁₂O₃²⁹Br₂: 353.9112; found: 353.9120; calculated for C₁₁H₁₂O₃²⁷Br⁸¹Br: 351.9133; found: 351.9132; calculated for C₁₁H₁₂O₃²⁷Br₂: 349.9153; found: 349.9153.

1-(2,2-Dibromovinyl)-4-nitrobenzene (1e)

5-(2,2-Dibromovinyl)-1,2,3-trimethoxybenzene (1d)

1-(2,2-Dibromovinyl)-4-nitrobenzene (1e)

S10
1-(2,2-Dibromovinyl)-4-nitrobenzene 1e was prepared according to the reported procedure by Doddi and co-workers from 4-nitrobenzaldehyde (3.00 g, 19.9 mmol) as a yellow solid (5.12 g, 16.7 mmol, 84%) and the characterization data is consistent with the literature.\textsuperscript{[6]-[8], [11, 12]} $R_f = 0.45$ (10% EtOAc in PS 40–60); m.p. 104 – 106 °C (CH\textsubscript{2}Cl\textsubscript{2}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 8.23 (d, $J = 8.8$ Hz, 2H), 7.70 (d, $J = 8.8$ Hz, 2H), 7.56 (s, 1H) ppm; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 147.4 (Cq), 141.6 (Cq), 135.1 (CH), 129.3 (2×CH), 123.9 (2×CH), 94.3 (Cq) ppm; IR (thin film): $v_{\text{max}}$ = 3102, 3077, 2443, 1929, 1589, 1506 cm\textsuperscript{-1}; LRMS: (EI\textsuperscript{+}): m/z (%): 309 ([M(2×Br)]\textsuperscript{+}•, 50), 307 ([M(2×79Br)]\textsuperscript{+}•, 100), 305 ([M(2×79Br)]\textsuperscript{+}•, 50); HRMS (EI\textsuperscript{+}): calculated for C\textsubscript{8}H\textsubscript{5}NO\textsubscript{2}81Br\textsubscript{2}: 308.8646; found: 308.8639; calculated for C\textsubscript{8}H\textsubscript{5}NO\textsubscript{2}79Br\textsubscript{2}: 306.8667; found: 306.8657; calculated for C\textsubscript{8}H\textsubscript{5}NO\textsubscript{2}79Br\textsubscript{2}: 304.8687; found: 304.8688.

1,1-Dibromohept-1-ene (1f)

Adapted from the literature procedure by Ramirez and co-workers.\textsuperscript{[13]} To a stirred solution of Hexanal (1.00 g, 9.98 mmol) and PPh\textsubscript{3} (6.28 g, 24.0 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (40 mL) at 0 °C was added a solution of CBr\textsubscript{4} (3.97 g, 12.0 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) over 10 minutes. After stirring at 0 °C for 4h, TLC analysis showed a colourless oil as the resulting slurry was stirred with 50 mL petroleum ether for 30 minutes and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to the dibromide 1f as a colourless oil (1.26 g, 4.92 mmol, 49%). $R_f = 0.61$ (100% PS 40–60); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 6.39 (t, $J = 7.2$ Hz, 1H), 2.09 (q, $J = 7.2$ Hz, 2H), 1.49 – 1.20 (m, 6H), 0.90 (t, $J = 6.6$ Hz, 3H) ppm; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 139.1 (CH), 88.6 (Cq), 33.1 (CH\textsubscript{2}), 31.4 (CH\textsubscript{2}), 27.6 (CH\textsubscript{2}), 22.6 (CH\textsubscript{2}), 14.1 (CH\textsubscript{3}) ppm; IR (thin film): $v_{\text{max}}$ = 2956, 2926, 2857, 1621 cm\textsuperscript{-1}; LRMS: (EI\textsuperscript{+}): m/z (%): 258 ([M(81Br)]\textsuperscript{+}•, 40), 256 ([M(81Br)]\textsuperscript{+}•, 35), 254 ([M(79Br)]\textsuperscript{+}•, 30), 198 ([M(81Br)–C\textsubscript{5}H\textsubscript{11}]\textsuperscript{+}•, 50), 95 (100); HRMS (EI\textsuperscript{+}): calculated for C\textsubscript{7}H\textsubscript{12}81Br\textsubscript{2}: 257.9265; found: 257.9268; calculated for C\textsubscript{7}H\textsubscript{12}79Br\textsubscript{2}: 255.9285; found: 255.9285; calculated for C\textsubscript{7}H\textsubscript{12}79Br\textsubscript{2}: 253.9306; found: 253.9302.
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1,1-Dibromododec-1-ene (1g)

Adapted from the literature procedure by Ramirez and co-workers.[13] To a stirred solution of undecanal (5.00 g, 29.4 mmol) and PPh₃ (18.5 g, 70.5 mmol) in CH₂Cl₂ (200 mL) at 0 °C was added a solution of CBr₄ (11.7 g, 35.2 mmol) in CH₂Cl₂ (50 mL) over 10 minutes. After stirring at 0 °C for 1 h, TLC analysis showed reaction completion. CH₂Cl₂ was removed under reduced pressure and the resulting slurry was stirred with 250 mL PS 40–60 for 30 minutes and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give the dibromide 1g as a colourless oil (4.02 g, 12.3 mmol, 42%). Rf = 0.65 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 6.39 (t, J = 7.3 Hz, 1H), 2.09 (q, J = 7.3 Hz, 2H), 1.51–1.17 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 139.1 (CH), 88.6 (Cq), 33.2 (CH₂), 32.1 (CH₂), 29.7 (CH₂), 29.7 (CH₂), 29.5 (CH₂), 29.5 (CH₂), 28.0 (CH₂), 22.9 (CH₂), 14.3 (CH₂) ppm; IR (thin film): v_max = 2922, 2853, 1623, 1464 cm⁻¹; LRMS: (EI⁺): m/z (%): 328 ([M(⁸¹Br₂]+•, 3), 326 ([M(⁸¹Br⁷⁹Br]+•, 8), 324 ([M(⁷⁹Br₂]+•, 3), 201 ([M(⁸¹Br₂-C₉H₁₉]+•, 26), 199 ([M(⁸¹Br⁷⁹Br-C₉H₁₉]+•, 63), 197 ([M(⁷⁹Br₂-C₉H₁₉]+•, 26), 95 (100); HRMS (EI⁺): calculated for C₁₂H₂₂⁸¹Br₂: 328.0047; found: 328.0049; calculated for C₁₂H₂₂⁷⁹Br₂Br: 326.0068; found: 326.0071; calculated for C₁₂H₂₂⁷⁹Br₂: 324.0088; found: 324.0092.

(2,2-Dibromovinyl)cyclohexane (1h)

(2,2-Dibromovinyl)cyclohexane 1h was prepared according to the reported procedure by Hosomi and co-workers from cyclohexane carbaldehyde (3.00 g, 26.7 mmol) as a colourless liquid (6.15 g, 22.9 mmol, 86%) and the characterization data is consistent with the literature.[14] Rf = 0.56 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 6.23 (d, J = 9.2 Hz, 1H), 2.44–2.10 (m, 1H), 1.89–1.57 (m, 5H), 1.44–0.86 (m, 5H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 143.9 (CH), 87.1 (Cq), 42.6 (CH₂), 31.4 (2×CH₃), 25.9 (CH₃), 25.6 (2×CH₂) ppm; IR (thin film): ν_max = 2923, 2850, 1603, 1447 cm⁻¹; LRMS: (EI⁺): m/z (%): 270 ([M(⁸¹Br₂]+•, 42), 268 ([M(⁸¹Br⁷⁹Br]+•, 100), S12
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266 ([M(79Br)79]+, 58), 82 ([M–C2HBr2]–, 100); HRMS (EI+): calculated for C8H8Br2: 269.9265; found: 269.9272; calculated for C8H779Br81: 267.9285; found: 267.9297; calculated for C8H779Br2: 265.9306; found: 265.9313.

(4,4-Dibromobut-3-en-1-yl)benzene (1i)

(4,4-Dibromobut-3-en-1-yl)benzene 1i was prepared according to the reported procedure by Doi and co-workers from 3-phenylpropanal (5.00 g, 37.3 mmol) as a pale brown oil (7.62 g, 26.3 mmol, 70%); [11a, 15] Rf = 0.63 (5% EtOAc in PS 40–60); 1H NMR (400 MHz, CDCl3) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 6.42 (t, J = 7.2 Hz, 1H), 2.74 (t, J = 7.7 Hz, 2H), 2.42 (q, J = 7.2 Hz, 2H) ppm; 13C NMR (100 MHz, CDCl3) δ 140.7 (Cq), 137.8 (CH), 128.7 (2 × CH), 128.5 (2 × CH), 126.4 (CH), 89.6 (Cq), 137.8 (CH), 128.7 (2 × CH), 128.5 (2 × CH), 126.4 (CH), 89.6 (Cq), 34.8 (CH2), 34.0 (CH2) ppm; IR (thin film): νmax = 3026, 2924, 2857, 1782, 1603, 1495 cm−1; LRMS: (EI+): m/z (%): 292 ([M(81Br)81]+, 1), 290 ([M(81Br79Br)+], 2), 288 ([M(81Br)79]+, 1), 211 ([M(81Br79Br)+], 33), 209 ([M(81Br81Br)+], 33), 91 ([M–C3H3Br2]–, 100); HRMS (EI+): calculated for C10H881Br2: 291.9108; found: 291.9104; calculated for C10H881Br79Br: 289.9129; found: 289.9120; calculated for C10H879Br2: 287.9149; found: 287.9148.

(E)-(4,4-Dibromobuta-1,3-dien-1-yl)benzene (1j)

(E)-(4,4-Dibromobuta-1,3-dien-1-yl)benzene 1j was prepared according to the reported procedure by Doddi and co-workers from trans-cinnamaldehyde (5.00 g, 37.8 mmol) as a white solid (8.94 g, 31.0 mmol, 82%) and the characterization data is consistent with the literature. [6, 11a, 16] Rf = 0.60 (5% EtOAc in PS 40–60); m.p. 50 – 52 °C (CH2Cl2); 1H NMR (400 MHz, CDCl3) δ 7.52 – 7.42 (m, 2H), 7.38 – 7.27 (m, 3H), 7.10 (d, J = 9.6 Hz, 1H), 6.86 – 6.65 (m, 2H) ppm;
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$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.3 (CH), 136.5 (Cq), 135.8 (CH), 128.9 (2$\times$CH), 128.8 (CH), 127.0 (2$\times$CH), 125.4 (CH), 91.4 (Cq) ppm; IR (thin film): $\nu_{max}$ = 3030, 3015, 1704, 1557, 1484 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 290 ([M($^{81}$Br$_2$)]$^+$, 35), 288 ([M($^{81}$Br$^{79}$Br)]$^+$, 68), 286 ([M($^{79}$Br)]$^+$, 37), 128 ([M–Br$_2$]$^+$, 100); HRMS (EI$^+$): calculated for C$_{10}$H$_8^{81}$Br$_2$: 289.8952; found: 289.8965; calculated for C$_{10}$H$_8^{81}$Br$^{79}$Br: 287.8972; found: 287.8979; calculated for C$_{10}$H$_8^{79}$Br$_2$: 285.8993; found: 285.8991.

(4,4-Dibromobut-3-en-1-yn-1-yl)benzene (1k)

(4,4-Dibromobut-3-en-1-yn-1-yl)benzene 1k was prepared according to the reported procedure by Negishi and co-workers from phenylacetylene (2.00 g, 19.6 mmol) as a colourless oil (3.55 g, 12.4 mmol, 63% from phenylacetylene) and the characterization data is consistent with the literature.$^{[17]}$ $R_f$ = 0.60 (5% EtOAc in PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53 – 7.47 (m, 2H), 7.39 – 7.30 (m, 3H), 6.78 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 131.7 (2$\times$CH), 129.2 (CH), 128.6 (2$\times$CH), 122.6 (Cq), 119.8 (CH), 101.9 (Cq), 97.3 (Cq), 86.3 (Cq) ppm; IR (thin film): $\nu_{max}$ = 3054, 3017, 2200, 1570, 1487 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 288 ([M($^{81}$Br$_2$)]$^+$, 39), 286 ([M($^{81}$Br$^{79}$Br)]$^+$, 71), 284 ([M($^{79}$Br)]$^+$, 126 ([M–Br$_2$]$^+$, 100); HRMS (EI$^+$): calculated for C$_{10}$H$_6^{81}$Br$_2$: 287.8795; found: 287.8809; calculated for C$_{10}$H$_6^{81}$Br$^{79}$Br: 285.8816; found: 285.8822; calculated for C$_{10}$H$_6^{79}$Br$_2$: 283.8836; found: 283.8832.

3-(2,2-Dibromovinyl)-1-tosyl-1H-indole (1l)

3-(2,2-Dibromovinyl)-1-tosyl-1H-indole 1l was prepared over two steps from indole-3-carboxaldehyde according to the reported procedure by Katsumura and co-workers from indole-3-carboxaldehyde (2.00 g, 13.8 mmol) as a white solid (4.52 g, 9.93 mmol, 72% over two steps) and the data is consistent with the literature.$^{[18]}$ $^{[19]}$ $R_f$ = 0.56 (30% EtOAc in PS 40–60);
m.p. 129 – 132 °C (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.59 – 7.47 (m, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 2.35 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 145.5 (Cq), 135.1 (Cq), 134.2 (Cq), 130.2 (2× CH), 129.6 (Cq), 127.1 (2× CH), 127.0 (CH), 125.6 (CH), 125.1 (CH), 123.8 (CH), 119.0 (CH), 117.5 (Cq), 113.8 (CH), 90.5 (Cq), 21.8 (CH₃) ppm; IR (thin film): v max = 3157, 2923, 1592, 1537, 1446 cm⁻¹; LRMS: (EI⁺): m/z (%): 457 ([M(81Br₂]+•, 43), 455 ([M(81Br₇9Br]+•, 70), 453 ([M(79Br₂]+•, 43), 140 ([M – C₇H₇O₂SBr₂]+•, 70); HRMS (EI⁺): calculated for C₁₇H₁₃NO₂S₈₁Br₂: 456.8993; found: 456.8992; calculated for C₁₇H₁₃NO₂S₇₉Br₂Br: 454.9013; found: 454.9016; calculated for C₁₇H₁₃NO₂S₇₉Br₂: 452.9034; found: 452.9039.

2-(2,2-Dibromovinyl)-5-methylfuran (1m)

2-(2,2-Dibromovinyl)-5-methylfuran 1m was prepared according to the reported procedure by Mikami and co-workers from 5-methylfuraldehyde (2.60 g, 23.6 mmol) as a colourless liquid (4.53 g, 17.0 mmol, 72%) and the characterization data is consistent with the literature.[²⁰] B r = 0.42 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 7.32 (s, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.05 (d, J = 2.8 Hz, 1H), 2.28 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 152.9 (Cq), 148.6 (Cq), 126.6 (CH), 112.9 (CH), 108.1 (CH), 85.4 (Cq), 13.8 (CH₃) ppm; IR (thin film): v max = 3028, 2921, 1586, 1520 cm⁻¹; LRMS: (EI⁺): m/z (%): 268 ([M(8¹Br₂]⁺, 50), 266 ([M(8¹Br₇₉Br]⁺, 100), 264 ([M(7⁹Br₂]⁺, 50), 106 ([M – Br₂]⁺, 50); HRMS (EI⁺): calculated for C₇H₆O₃Br₂: 267.8744; found: 267.8741; calculated for C₇H₆O³¹Br₇₉Br: 265.8765; found: 265.8759; calculated for C₈H₆O³¹Br₂: 263.8785; found: 263.8785.
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**Standard Procedure A**

A solution of 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (5.0 mol %) and the dibromo olefin (1.0 mol equiv) in THF (50 mL/g dibromide precursor) was purged with N\textsubscript{2} for 5 minutes. After cooling to 0 °C, ZnBr\textsubscript{2} (4.0 mol equiv, 1.10 – 1.25 M solution in THF) was added, followed by dropwise addition of the Grignard reagent (3.0 mol equiv, 0.40 – 0.85 M solution in THF) over 15 minutes. The resulting heterogeneous reaction mixture was brought to room temperature and stirred for 16h, until the reaction was complete by \textsuperscript{1}H NMR spectroscopic analysis. Saturated aqueous NH\textsubscript{4}Cl (5 mL/g dibromide precursor) was added, the reaction mixture was filtered through Celite then the filtrate was diluted with CH\textsubscript{2}Cl\textsubscript{2} (50 mL/g dibromide precursor) and water (100 mL/g dibromide precursor). The aqueous and organic layers were separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (10 mL/g dibromide precursor × 3). The combined organic layers were washed with saturated brine (20 mL/g dibromide precursor), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure.

(2-Vinylbuta-1,3-dien-1-yl)benzene (2a)

Following **Standard Procedure A**, the reaction mixture containing dibromide 1a (3.40 g, 13.0 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.535 g, 0.649 mmol), ZnBr\textsubscript{2} solution in THF (47.2 mL, 1.10 M, 51.9 mmol) and vinyl magnesium bromide (32.5 mL, 1.20 M, 38.9 mmol) in THF (170 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (120 g SiO\textsubscript{2}, PS 40–60) gave dendralene 2a as a colourless liquid (1.48 g, 9.47 mmol, 73%). R\textsubscript{f} = 0.48 (100% PS 40–60); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.42 – 7.30
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(4H), 7.28 – 7.20 (m, 1H), 6.71 (dd, J = 17.8, 11.1 Hz, 1H), 6.65 (s, 1H), 6.56 (dd, J = 17.2, 10.7 Hz, 1H), 5.55 (d, J = 17.2 Hz, 1H), 5.46 (d, J = 17.7 Hz, 1H), 5.36 (d, J = 11.1 Hz, 1H), 5.22 (d, J = 10.9 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.1 (Cq), 138.0 (CH), 137.2 (Cq), 133.7 (CH), 129.8 (2× CH), 129.7 (CH), 128.2 (2× CH), 127.3 (CH), 118.5 (CH$_2$), 116.2 (CH$_2$) ppm; IR (thin film): $v_{max} = 3085, 3007, 2955, 1830, 1605, 1491$ cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 156 ([M]$^+$, 66), 141 ([M–CH$_3$]$^+$, 86), 128 ([M–2×CH$_2$]$^+$, 100), 115 ([M–C$_3$H$_6$]$^+$, 66); HRMS (EI$^+$): calculated for C$_{12}$H$_{12}$: 156.0939; found: 156.0939.

1-Methyl-4-(2-vinylbuta-1,3-dien-1-yl)benzene (2b)

Following **Standard Procedure A**, the reaction mixture containing dibromide 1b (1.04 g, 3.77 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (132 mg, 0.181 mmol), ZnBr$_2$ solution in THF (11.2 mL, 1.29 M, 14.5 mmol) and vinyl magnesium bromide (16.9 mL, 0.64 M, 10.9 mmol) in THF (50 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (40 g SiO$_2$, PS 40–60) gave dendralene 2b as a colourless liquid (0.46 g, 2.68 mmol, 71%). R$_f$ = 0.44 (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.27 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.71 (dd, J = 17.8, 11.1 Hz, 1H), 6.62 (s, 1H), 6.55 (dd, J = 17.3, 10.7 Hz, 1H), 5.52 (dd, J = 17.2, 1.5 Hz, 1H), 5.44 (dd, J = 17.7, 1.2 Hz, 1H), 5.34 (d, J = 11.1 Hz, 1H), 5.19 (dd, J = 10.7, 1.6 Hz, 1H), 2.36 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.1 (CH), 137.4 (Cq), 137.1 (Cq), 134.4 (Cq), 133.8 (CH), 129.8 (2× CH), 129.7 (CH), 129.0 (2× CH), 118.2 (CH$_2$), 21.4 (CH$_3$) ppm; IR (thin film): $v_{max}$ = 3085, 3005, 1604, 1507 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 170 ([M]$^+$, 27), 155 ([M–CH$_3$]$^+$, 100), 142 ([M–2×CH$_2$]$^+$, 23), 128 ([M–C$_3$H$_6$]$^+$, 30), 115 ([M–C$_4$H$_7$]$^+$, 27); HRMS (EI$^+$): calculated for C$_{13}$H$_{14}$: 170.1096; found: 170.1089.

Br Br
\[ \text{MgBr} \]

Br

\[ \text{ZnBr}_2 \]

PdCl$_2$(dppf)-PhMe

THF

0 °C – 23 °C, 16h

1b

2b
1-Methoxy-4-(2-vinylbuta-1,3-dien-1-yl)benzene (2c)

Following Standard Procedure A, the reaction mixture containing dibromide 1c (3.00 g, 10.3 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.423 g, 0.514 mmol), ZnBr₂ solution in THF (36.1 mL, 1.14 M, 41.1 mmol) and vinyl magnesium bromide (35.8 mL, 0.86 M, 30.8 mmol) in THF (150 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (90 g SiO₂, 3% EtOAc in PS 40–60) gave dendralene 2c as a colourless liquid (1.46 g, 7.84 mmol, 76%). \( R_f = 0.5 \) (5% EtOAc in PS 40–60); ¹H NMR (400 MHz, CDCl₃) \( \delta 7.33 \ (d, J = 8.3 \text{ Hz}, 2H), 6.88 \ (d, J = 8.3 \text{ Hz}, 2H), 6.70 \ (dd, J = 17.8, 11.1 \text{ Hz}, 1H), 6.60 \ (s, 1H), 6.54 \ (dd, J = 17.2, 10.7 \text{ Hz}, 1H), 5.51 \ (d, J = 17.2 \text{ Hz}, 1H), 5.44 \ (d, J = 17.8 \text{ Hz}, 1H), 5.35 \ (d, J = 11.1 \text{ Hz}, 1H), 5.18 \ (d, J = 10.7 \text{ Hz}, 1H), 3.83 \ (s, 3H) \text{ ppm}; \) ¹³C NMR (100 MHz, CDCl₃) \( \delta 158.9 \ (C_{q}), 138.2 \ (CH), 136.6 \ (C_{q}), 133.8 \ (CH), 131.2 \ (2\times CH), 129.9 \ (C_{q}), 129.4 \ (CH), 118.0 \ (CH₂), 115.5 \ (CH₂), 113.7 \ (2\times CH₂), 55.4 \ (CH₃) \text{ ppm}; IR (thin film): \( v_{\text{max}} = 3086, 3003, 2835, 1601, 1506 \text{ cm}^{-1}; \) LRMS: (EI⁺): m/z (%): 186 ([M⁺]+•, 100), 155 ([M⁻CH₃O⁺]+•, 62); HRMS (EI⁺): calculated for C₁₃H₁₄O: 186.1045; found: 186.1044.

1,2,3-Trimethoxy-5-(2-vinylbuta-1,3-dien-1-yl)benzene (2d)

Following Standard Procedure A, the reaction mixture containing dibromide 1d (3.00 g, 8.52 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.351 g, 0.426 mmol), ZnBr₂ solution in THF (30.0 mL, 1.14 M, 34.1 mmol) and vinyl magnesium bromide (31.2 mL, 0.82 M, 25.6 mmol) in THF (150 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (90 g SiO₂, 12% EtOAc in PS 40–60) gave dendralene 2d as a colourless liquid (1.30 g, 5.28 mmol, 62%). \( R_f = 0.42 \) (20% EtOAc in PS 40–60); ¹H NMR (400 MHz, CDCl₃) \( \delta 6.72 \ (dd, J = 17.6, 10.8 \text{ Hz}, 1H), 6.61 \ (s, 2H), 6.59 - 6.47 \ (m, 2H), 5.52 \text{ ppm} \).
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(dd, J = 16.8, 1.2 Hz, 1H), 5.45 (dd, J = 17.6, 1.6 Hz, 1H), 5.37 (dt, J = 10.8, 1.6 Hz, 1H), 5.20 (dd, J = 10.4, 1.2 Hz, 1H, 3.86 (s, 3H), 3.85 (s, 6H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.0 (2×Cq), 138.0 (CH), 137.8 (Cq), 137.6 (Cq), 133.8 (CH), 132.8 (Cq), 129.6 (CH), 118.5 (CH$_2$), 116.2 (CH$_2$), 107.1 (2-CH), 61.1 (CH), 56.2 (2-CH$_2$) ppm; IR (thin film): $\nu$$_{max}$ = 2937, 2835, 1584, 1503 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 246 ([M]+•, 49), 215 ([M$-$CH$_3$O]+•, 100), 184 ([M$-$2×CH$_3$O]+•, 22); HRMS (EI$^+$): calculated for C$_{15}$H$_{18}$O$_3$: 246.1256; found: 246.1259.

1-Nitro-4-(2-vinylbuta-1,3-dien-1-yl)benzene (2e)

Following Standard Procedure A, the reaction mixture containing dibromide 1e (3.00 g, 9.77 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.403 g, 0.489 mmol), ZnBr$_2$ solution in THF (43.9 mL, 0.89 M, 39.1 mmol) and vinyl magnesium bromide (39.0 mL, 0.75 M, 29.3 mmol) in THF (150 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (90 g SiO$_2$, 1% EtOAc in PS 40–60) gave dendralene 2e as a yellow liquid (0.913 g, 4.54 mmol, 46%). R$_f$ = 0.58 (5% EtOAc in PS 40–60); $^1$H NMR (400 MHz, C$_6$D$_6$) δ 7.79 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.36 (dd, J = 17.4, 11.1 Hz, 2H), 6.22 (s, 1H), 5.44 (dd, J = 17.2, 1.4 Hz, 1H), 5.31 (dd, J = 17.7, 1.3 Hz, 1H), 5.15 (d, J = 11.2, Hz, 1H), 5.11 (dd, J = 10.7, 1.3 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, C$_6$D$_6$) δ 146.7 (Cq), 143.3 (Cq), 141.2 (Cq), 137.7 (CH), 132.8 (CH), 130.1 (2-CH), 127.6 (CH), 123.5 (2-CH$_2$), 120.4 (CH$_2$), 117.9 (CH$_2$) ppm; IR (thin film): $\nu$$_{max}$ = 3088, 3009, 2447, 1591, 1511 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 201 ([M]+•, 70), 155 ([M$-$NO$_2$]+•, 61), 153 (100); HRMS (EI$^+$): calculated for C$_{12}$H$_7$NO$_2$: 201.0790; found: 201.0787.

3-Vinylnona-1,3-diene (2f)

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Following **Standard Procedure A**, the reaction mixture containing dibromide **1f** (1.02 g, 3.98 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (142 mg, 0.195 mmol), ZnBr$_2$ solution in THF (12.1 mL, 1.29 M, 15.6 mmol) and vinyl magnesium bromide (18.7 mL, 0.64 M, 11.9 mmol) in THF (50 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (80 g SiO$_2$, PS 40–60) gave dendralene **2f** as a colourless liquid (0.51 g, 3.33 mmol, 85%). $R_f = 0.81$ (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.49 (dd, $J = 18.3$, 10.6 Hz, 1H), 6.40 (dd, $J = 17.3$, 10.7 Hz, 1H), 5.63 (t, $J = 7.6$ Hz, 1H), 5.26 (d, $J = 16.5$ Hz, 3H), 5.02 (dd, $J = 10.7$, 1.4 Hz, 1H), 2.20 (q, $J = 7.5$ Hz, 2H), 1.48 – 1.18 (m, 6H), 0.89 (t, $J = 6.9$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.2 (CH), 137.0 (Cq), 133.2 (CH), 132.3 (CH), 117.1 (CH$_2$), 113.7 (CH$_2$), 31.7 (CH$_2$), 29.5 (CH$_2$), 28.4 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_2$) ppm; IR (thin film): $v_{\text{max}}$ = 3088, 2957, 2924, 2856, 1627 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 150 ([M$^+$•]$, 60), 121 ([M–CH$_3$CH$_2$]$^+$, 70), 79 (100); HRMS (EI$^+$): calculated for C$_{11}$H$_{18}$: 150.1409; found: 150.1413.

3-Vinyltetradeca-1,3-diene (2g)

Following **Standard Procedure A**, the reaction mixture containing dibromide **1g** (1.50 g, 4.60 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.19 g, 0.23 mmol), ZnBr$_2$ solution in THF (16.3 mL, 1.13 M, 18.4 mmol) and vinyl magnesium bromide (18.4 mL, 0.75 M, 13.8 mmol) in THF (75 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (45 g SiO$_2$, PS 40–60) gave dendralene **2g** as a colourless liquid (0.653 g, 2.96 mmol, 64%). $R_f = 0.61$ (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.49 (dd, $J = 18.3$, 10.6 Hz, 1H), 6.40 (dd, $J = 17.4$, 10.7 Hz, 1H), 5.63 (t, $J = 7.6$ Hz, 1H), 5.31 – 5.23 (m, 3H), 5.02 (dd, $J = 10.7$, 1.2 Hz, 1H), 2.20 (q, $J = 7.4$ Hz, 2H), 1.43 – 1.19 (m, 16H), 0.88 (t, $J = 6.8$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.1 (CH), 136.9 (Cq), 133.2 (CH), 132.3 (CH), 117.1 (CH$_2$), 113.7 (CH$_2$), 32.1 (CH$_2$), 29.8 (CH$_2$), 29.7 (2×CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 28.5 (CH$_2$), 22.9 (CH$_2$), 14.3 (CH$_2$) ppm; IR (thin film): $v_{\text{max}}$ = 2982, 2853, 1679 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 220 ([M$^+$••]$, 10), 149 ([M–C$_3$H$_7$]$^+$, 5), 135 ([M–C$_6$H$_5$]$^+$, 11), 105 ([M–C$_7$H$_{15}$]$^+$, 3).
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121 ([M–C₆H₄]⁺, 28), 107 ([M–C₅H₇]⁺, 38), 93 ([M–C₅H₈]⁺, 76), 79 ([M–C₆H₉]⁺, 100); HRMS (EI⁺): calculated for C₉H₁₂: 220.2191; found: 220.2188.

(2-Vinylbuta-1,3-dien-1-yl)cyclohexane (2h)

Following **Standard Procedure A**, the reaction mixture containing dibromide 1h (3.00 g, 11.2 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.461 g, 0.560 mmol), ZnBr₂ solution in THF (39.3 mL, 1.14 M, 44.8 mmol) and vinyl magnesium bromide (41 mL, 0.82 M, 33.6 mmol) in THF (150 mL) was stirred at 23 °C for 16h. Purification by flash column chromatography (90 g SiO₂, PS 40–60) gave dendralene 2h as a colourless liquid (1.48 g, 9.12 mmol, 81%). Rf = 0.72 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 6.51 (dd, J = 17.6, 11.2 Hz, 1H), 6.38 (dd, J = 17.3, 10.7 Hz, 1H), 5.46 (d, J = 9.6 Hz, 1H), 5.33 – 5.17 (m, 3H), 5.02 (d, J = 10.7 Hz, 1H), 2.51 – 2.32 (m, 1H), 1.81 – 1.57 (m, 5H), 1.41 – 0.98 (m, 5H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 138.7 (CH), 138.2 (CH), 135.3 (Cq), 132.5 (CH), 116.8 (CH₂), 113.9 (CH₂), 37.2 (CH), 33.2 (2×CH₃), 26.2 (CH₃), 26.0 (2×CH₂) ppm; IR (thin film): v max = 3087, 2923, 2850, 1628 cm⁻¹; LRMS: (EI⁺): m/z (%): 162 ([M⁺], 31), 147 ([M–CH₃]⁺, 12), 133 ([M–C₆H₄]⁺, 26), 79 (100); HRMS (EI⁺): calculated for C₁₂H₁₈: 162.1409; found: 162.1410.

(4-Vinylhexa-3,5-dien-1-yl)benzene (2i)

Following **Standard Procedure A**, the reaction mixture containing dibromide 1i (3.00 g, 10.3 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.426 g, 0.517 mmol), ZnBr₂ solution in THF (34.5 mL, 1.20 M, 41.4 mmol) and vinyl magnesium bromide (36.1 mL, 0.86 M, 31.0 mmol) in THF (150 mL) was stirred at 23 °C for 16h. After work up, purification by
flash column chromatography (90 g SiO$_2$, 100% PS 40–60) gave dendralene 2i as a pale yellow liquid (1.56 g, 8.47 mmol, 82%). $R_f$ = 0.44 (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 – 7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 6.57 – 6.32 (m, 2H), 5.68 (t, $J$ = 7.5 Hz, 1H), 5.32 – 5.21 (m, 3H), 5.05 (dd, $J$ = 10.4, 1.6 Hz, 1H), 2.77 – 2.70 (m, 2H), 2.55 (q, $J$ = 7.6 Hz, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.9 (Cq), 138.0 (CH), 137.7 (Cq), 132.1 (CH), 131.6 (CH), 128.6 (2×CH), 128.5 (2×CH), 126.0 (CH), 117.6 (CH$_2$), 114.2 (CH$_2$), 36.0 (CH$_2$), 30.4 (CH$_2$) ppm; IR (thin film): $v_{\text{max}}$ = 3086, 3026, 2924, 2856, 1603 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 184 ([M]+•, 10), 169 ([M–CH$_3$]+•, 12), 155 ([M–C$_2$H$_5$]+•, 12), 91 ([M–C$_7$H$_9$]+•, 100), 77 ([M–C$_8$H$_{11}$]+•, 35); HRMS (EI$^+$): calculated for C$_{14}$H$_{16}$: 184.1252; found: 184.1251.

(\textit{E})-(4-Vinylhexa-1,3,5-trien-1-yl)benzene (2j)

Following Standard Procedure A, the reaction mixture containing dibromide 1j (3.00 g, 10.4 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.429 g, 0.521 mmol), ZnBr$_2$ solution in THF (36.6 mL, 1.14 M, 41.7 mmol) and vinyl magnesium bromide (36.3 mL, 0.86 M, 31.3 mmol) in THF (150 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (90 g SiO$_2$, 100% PS 40–60) gave dendralene 2j as a colourless liquid (1.22 g, 6.69 mmol, 64%). $R_f$ = 0.32 (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43 (d, $J$ = 7.8 Hz, 2H), 7.32 (t, $J$ = 7.6 Hz, 2H), 7.29 – 7.18 (m, 2H), 6.78 – 6.58 (m, 2H), 6.50 (dd, $J$ = 17.4, 10.8 Hz, 1H), 6.37 (d, $J$ = 11.4 Hz, 1H), 5.50 – 5.34 (m, 3H), 5.16 (d, $J$ = 10.8 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.2 (Cq), 137.9 (CH), 137.6 (Cq), 134.2 (CH), 132.0 (CH), 130.7 (CH), 128.8 (2×CH), 127.8 (CH), 126.7 (2×CH), 125.5 (CH), 119.1 (CH$_2$), 115.4 (CH$_2$) ppm; IR (thin film): $v_{\text{max}}$ = 3083, 3031, 3002, 1812, 1602 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 182 ([M]+•, 62), 167 ([M–CH$_3$]+•, 100), 141 ([M–C$_2$H$_5$]+•, 29); HRMS (EI$^+$): calculated for C$_{14}$H$_{14}$: 182.1096; found: 182.1095.
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(4-Vinylhexa-3,5-dien-1-yn-1-yl)benzene (2k)

Following Standard Procedure A, the reaction mixture containing dibromide 1k (1.00 g, 3.49 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.140 g, 0.175 mmol), ZnBr₂ solution in THF (12.7 mL, 1.10 M, 14.0 mmol) and vinyl magnesium bromide (19.1 mL, 0.55 M, 10.5 mmol) in THF (50 mL) was heated under reflux for 4h. After work up, purification by flash column chromatography (30 g SiO₂, 100% PS 40–60) gave dendralene 2k as a pale yellow liquid (0.398 g, 2.21 mmol, 63%). Rf = 0.50 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.42 (m, 2H), 7.37–7.28 (m, 3H), 6.96 (dd, J = 17.6, 11.2 Hz, 1H), 6.52 (dd, J = 17.2, 10.8 Hz, 1H), 5.88 (s, 1H), 5.65 (d, J = 17.6 Hz, 1H), 5.56 (d, J = 17.2 Hz, 1H), 5.43 (d, J = 11.2 Hz, 1H), 5.25 (d, J = 10.8 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 146.8 (Cq), 135.0 (CH), 133.2 (CH), 131.6 (2×CH), 128.5 (2×CH), 128.4 (CH), 123.7 (Cq), 118.7 (CH₂), 117.2 (CH₂), 108.6 (CH), 97.6 (Cq), 87.8 (Cq) ppm; IR (thin film): νmax = 3086, 3010, 2198, 1830, 1612, 1597 cm⁻¹; LRMS: (EI⁺): m/z (%): 180 ([M]+•, 100), 165 ([M – CH₃]+•, 60), 152 ([M – C₂H₄]+•, 38); HRMS (EI⁺): calculated for C₁₄H₁₂: 180.0939; found: 180.0939.

1-Tosyl-3-(2-vinylbuta-1,3-dien-1-yl)-1H-indole (2l)

Following Standard Procedure A, the reaction mixture containing dibromide 1l (650 mg, 1.43 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (60 mg, 0.0714 mmol), ZnBr₂ solution in THF (5.0 mL, 1.14 M, 5.71 mmol) and vinyl magnesium bromide (5.2 mL, 0.82 M, 4.28 mmol) in THF (35 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (20 g SiO₂, 3% EtOAc in PS 40–60) gave dendralene 2l as a pale yellow liquid (383 mg, 1.10 mmol, 77%). Rf = 0.33 (10% EtOAc in PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.48 (s, 1H), 4.09 (t, J = 7.6 Hz, 2H), 2.07 (s, 3H), 1.83 (s, 3H), 1.56 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 0.99 (t, J = 7.6 Hz, 3H).
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7.38 – 7.31 (m, 1H), 7.29 – 7.20 (m, 3H), 6.72 (dd, J = 18.0, 11.2 Hz, 1H), 6.63 – 6.53 (m, 2H), 5.59 – 5.49 (m, 2H), 5.46 (d, J = 11.2 Hz, 1H), 5.24 (dd, J = 10.8, 1.2 Hz, 1H), 2.34 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 145.2 (Cq), 139.3 (Cq), 137.5 (CH), 135.2 (Cq), 134.8 (Cq), 133.6 (CH), 130.8 (Cq), 130.0 (2 × CH), 127.0 (2 × CH), 125.2 (CH), 125.2 (CH), 123.5 (CH), 119.8 (CH), 119.2 (Cq), 119.1 (CH), 118.2 (CH), 116.5 (CH\(_2\)), 113.8 (CH), 21.7 (CH\(_3\)) ppm; IR (thin film): \(v_{\text{max}}\) = 3005, 2923, 1740, 1596, 1446 cm\(^{-1}\); LRMS: (EI\(^+\)) m/z (%): 349 ([M]\(^+\), 100), 295 ([M–C\(_4\)H\(_6\)]\(^+\), 23); HRMS (EI\(^+\)): calculated for C\(_{21}\)H\(_{19}\)NO\(_2\)S: 349.1137; found: 349.1136.

2-Methyl-5-(2-vinylbuta-1,3-dien-1-yl)furan (2m)

Following Standard Procedure A, the reaction mixture containing dibromide 1m (3.00 g, 11.3 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.465 g, 0.564 mmol), ZnBr\(_2\) solution in THF (37.6 mL, 1.2 M, 45.1 mmol) and vinyl magnesium bromide (39.4 mL, 0.86 M, 33.8 mmol) in THF (150 mL) was heated under reflux for 16 h. After work up, purification by flash column chromatography (90 g SiO\(_2\), 100% PS 40–60) gave dendralene 2m as a yellow liquid (1.25 g, 7.80 mmol, 69%). \(R_f\) = 0.40 (100% PS 40–60); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.07 (dd, J = 17.7, 11.1 Hz, 1H), 6.52 (dd, J = 17.2, 10.8 Hz, 1H), 6.34 – 6.27 (m, 2H), 6.02 (d, J = 2.7 Hz, 1H), 5.54 – 5.39 (m, 2H), 5.35 (d, J = 11.1 Hz, 1H), 5.15 (dd, J = 10.7, 1.3 Hz, 1H), 2.33 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 152.9 (Cq), 151.7 (Cq), 137.2 (CH), 134.0 (Cq), 133.8 (CH), 117.6 (CH\(_2\)), 116.9 (CH), 115.4 (CH\(_2\)), 113.0 (CH), 108.1 (CH), 14.0 (CH\(_3\)) ppm; IR (thin film): \(v_{\text{max}}\) = 3088, 2921, 1577, 1521 cm\(^{-1}\); LRMS: (EI\(^+\)) m/z (%): 160 ([M]\(^+\), 88), 145 ([M–CH\(_3\)]\(^+\), 23), 117 ([M–C\(_4\)H\(_6\)]\(^+\), 100); 91 ([M–C\(_3\)H\(_3\)]\(^+\), 36) HRMS (EI\(^+\)): calculated for C\(_{11}\)H\(_{12}\)O: 160.0888; found: 160.0888.
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1-Methoxy-4-(3-methyl-2-(prop-1-en-2-yl)buta-1,3-dien-1-yl)benzene (2n)

Following **Standard Procedure A**, the reaction mixture containing dibromide 1c (500 mg, 1.7 mmol), 1,1′-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (71 mg, 0.086 mmol), ZnBr$_2$ solution in THF (6.0 mL, 1.14 M, 6.85 mmol) and isopropenyl magnesium bromide (9.2 mL, 0.56 M, 5.14 mmol) in THF (25 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (15 g SiO$_2$, 1.5% EtOAc in PS 40–60) gave dendralene 2n as a colourless liquid (251 mg, 1.18 mmol, 69%). $R_f$ = 0.73 (5% EtOAc in PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J$ = 8.8 Hz, 2H), 6.83 (d, $J$ = 8.8 Hz, 2H), 6.38 (s, 1H), 5.23 (s, 1H), 5.17 (s, 1H), 5.04 (s, 1H), 4.86 (s, 1H), 3.81 (s, 3H), 2.02 (s, 3H), 1.89 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.6 (Cq), 143.7 (Cq), 143.3 (Cq), 143.2 (Cq), 130.5 (2 × C), 130.2 (Cq), 124.1 (CH), 116.6 (CH$_3$), 114.9 (CH$_2$), 113.7 (2 × CH), 55.4 (CH$_3$), 23.2 (CH$_3$), 21.0 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}}$ = 3079, 2950, 2836, 1599, 1509 cm$^{-1}$; LRMS: (EI+): m/z (%): 214 ([M]+, 27), 199 ([M–CH$_3$]+, 100), 184 ([M–2×CH$_3$]+, 17), 158 ([M–C$_4$H$_8$]+, 17); HRMS (EI+): calculated for C$_{15}$H$_{18}$O: 214.1358; found: 214.1358.

1,2,3-Trimethoxy-5-(3-methyl-2-(prop-1-en-2-yl)buta-1,3-dien-1-yl)benzene (2o)

Following **Standard Procedure A**, the reaction mixture containing dibromide 1d (1.00 g, 2.84 mmol), 1,1′-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (117 mg, 0.142 mmol), ZnBr$_2$ solution in THF (9.2 mL, 1.23 M, 11.4 mmol) and isopropenyl magnesium bromide (16.7 mL, 0.51 M, 8.52 mmol) in THF (10 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (40 g SiO$_2$, 10% EtOAc in PS 40–60) gave dendralene 2o as a
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pale yellow solid (0.64 g, 2.33 mmol, 82%). Rf = 0.34 (10% EtOAc in PS 40–60); m.p. 50 – 52 °C (CH₂Cl₂); 1H NMR (400 MHz, CDCl₃) δ 6.85 (s, 2H), 6.35 (s, 1H), 5.29 (s, 1H), 5.22 (s, 1H), 5.08 (s, 1H), 4.91 (s, 1H), 3.85 (s, 3H), 3.84 (s, 6H), 2.03 (s, 3H), 1.92 (s, 3H) ppm; 13C NMR (100 MHz, CDCl₃) δ 152.9 (2×Cq), 144.6 (Cq), 144.1 (Cq), 143.0 (Cq), 137.3 (Cq), 132.9 (Cq), 124.5 (CH), 116.6 (CH₂), 115.7 (CH₂), 106.5 (2×CH), 61.1 (CH₃), 56.1 (2×CH₃), 23.3 (CH₃), 21.0 (CH₃) ppm; IR (thin film): νmax = 2997, 2939, 2834, 1573, 1504 cm⁻¹; LRMS: (EI⁺): m/z (%): 274 ([M]⁺, 60), 259 ([M–CH₃]⁺, 42), 243 ([M–CH₃O]⁺, 100), 212 ([M–2×CH₃O]⁺, 18); HRMS (EI⁺): calculated for C₁₇H₂₂O₃: 274.1569; found: 274.1567.

(E)-(5-Methyl-4-(prop-1-en-2-yl)hexa-1,3,5-trien-1-yl)benzene (2p)

Following Standard Procedure A, the reaction mixture containing dibromide 1j (1.00 g, 3.47 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (143 mg, 0.174 mmol), ZnBr₂ solution in THF (11.3 mL, 1.23 M, 13.9 mmol) and isopropenyl magnesium bromide (18.6 mL, 0.56 M, 10.4 mmol) in THF (50 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (40 g SiO₂, 100% PS 40–60) gave dendralene 2p as a colourless liquid (0.51 g, 2.42 mmol, 70%). Rf = 0.38 (100% PS 40–60); 1H NMR (400 MHz, CDCl₃) δ 7.40 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.04 (dd, J = 15.6, 11.2 Hz, 1H), 6.63 (d, J = 15.6 Hz, 1H), 6.29 (d, J = 11.2 Hz, 1H), 5.27 (s, 1H), 5.13 (s, 1H), 5.05 (s, 1H), 4.81 (s, 1H), 1.98 (s, 3H), 1.91 (s, 3H) ppm; 13C NMR (100 MHz, CDCl₃) δ 146.9 (Cq), 143.2 (Cq), 141.8 (Cq), 137.9 (Cq), 133.0 (CH), 128.7 (2×CH), 127.5 (CH), 127.4 (CH), 126.6 (2×CH), 125.4 (CH), 116.2 (CH₂), 115.8 (CH₂), 24.0 (CH₃), 20.5 (CH₃) ppm; IR (thin film): νmax = 3081, 3032, 2969, 1799, 1637, 1600 cm⁻¹; LRMS: (EI⁺): m/z (%): 210 ([M]⁺, 83), 195 ([M–CH₃]⁺, 100), 180 ([M–2×CH₃]⁺, 23); HRMS (EI⁺): calculated for C₁₈H₁₄O₂: 210.1409; found: 210.1408.

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(5-Methyl-4-(prop-1-en-2-yl)hexa-3,5-dien-1-yn-1-yl)benzene (2q)

Following Standard Procedure A, the reaction mixture containing dibromide 1k (200 mg, 0.70 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (29 mg, 0.035 mmol), ZnBr₂ solution in THF (1.9 mL, 1.48 M, 2.8 mmol) and isopropenyl magnesium bromide (3.5 mL, 0.60 M, 2.1 mmol) in THF (10 mL) was stirred at 66 °C for 4h. After work up, purification by flash column chromatography (8 g AgNO₃-impregnated silica, 100% PS 40–60) gave dendralene 2q as a colourless liquid (58 mg, 0.28 mmol, 40%). R_f = 0.30 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.38 (m, 2H), 7.34 – 7.27 (m, 3H), 5.76 (s, 1H), 5.24 (s, 1H), 5.21 (s, 1H), 5.11 (s, 1H), 4.90 (s, 1H), 1.98 (s, 3H), 1.95 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 156.4 (Cq), 143.1 (Cq), 141.3 (Cq), 131.5 (2×CH), 128.4 (2×CH), 128.1 (CH), 124.1 (Cq), 117.7 (CH₂), 115.9 (CH₂), 105.1 (CH), 95.4 (Cq), 88.6 (Cq), 23.0 (CH₃), 20.3 (CH₃) ppm; IR (thin film): ν_{max} = 3079, 2970, 1598 cm⁻¹; LRMS: (EI⁺): m/z (%): 208 ([M]+•, 46), 193 ([M–CH₃]+•, 40), 178 ([M–2×CH₃]+•, 100); HRMS (EI⁺): calculated for C₁₆H₁₆: 208.1252; found: 208.1255.

2-Methyl-5-(3-methyl-2-(prop-1-en-2-yl)buta-1,3-dien-1-yl)furan (2r)

Following Standard Procedure A, the reaction mixture containing dibromide 1m (2.30 g, 8.65 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.356 g, 0.432 mmol), ZnBr₂ solution in THF (28.1 mL, 1.23 M, 34.6 mmol) and isopropenyl magnesium bromide (46.3 mL, 0.56 M, 26.0 mmol) in THF (115 mL) was stirred at 66 °C for 16h. After work up, purification by flash column chromatography (70 g SiO₂, 100% PS 40–60) and further by AgNO₃-impregnated silica gave dendralene 2r as a colourless liquid (0.653 g, 3.47 mmol, 40%).
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R_f = 0.38 (100% PS 40–60); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.48 (s, 1H), 6.31 (s, 1H), 5.99 (s, 1H), 5.23 (s, 1H), 5.16 (s, 1H), 5.03 (s, 1H), 4.83 (s, 1H), 2.30 (s, 3H), 2.00 (s, 3H), 1.91 (s, 3H) ppm; \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 151.5 (Cq), 151.4 (Cq), 143.9 (Cq), 142.1 (Cq), 141.9 (Cq), 115.6 (CH\(_2\)), 115.4 (CH\(_2\)), 110.2 (CH), 108.2 (CH), 22.2 (CH\(_3\)), 20.5 (CH\(_3\)), 13.8 (CH\(_3\)) ppm; IR (thin film): \(v_{\text{max}}\) = 3078, 2967, 2947, 1642, 1603, 1526 cm\(^{-1}\); LRMS: (EI\(^+\)): m/z (%): 188 ([M\(^+\)], 100), 173 ([M – CH\(_3\)]\(^+\), 46), 158 ([M – 2×CH\(_3\)]\(^+\), 14); HRMS (EI\(^+\)): calculated for C\(_{13}\)H\(_{16}\)O: 188.1201; found: 188.1202.

1,2,3-Trimethoxy-5-(4-methyl-2-{2-methylprop-1-en-1-yl}penta-1,3-dien-1-yl)benzene (2s)

Following Standard Procedure A, the reaction mixture containing dibromide 1d (200 mg, 0.568 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (23 mg, 0.028 mmol), ZnBr\(_2\) solution in THF (1.9 mL, 1.23 M, 2.27 mmol) and isobutenyl magnesium bromide (3.9 mL, 0.44 M, 1.70 mmol) in THF (10 mL) was stirred at 23 °C for 16 h. After work up, purification by flash column chromatography (5 g SiO\(_2\), 5% EtOAc in PS 40–60) gave dendralene 2s as a colourless liquid (133 mg, 0.440 mmol, 77%). R_f = 0.40 (20% EtOAc in PS 40–60); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.70 (s, 2H), 6.18 (s, 1H), 6.00 (s, 1H), 5.82 (s, 1H), 3.85 (s, 3H), 3.83 (s, 6H), 1.84 (s, 3H), 1.83 (s, 3H), 1.62 (s, 3H) ppm; \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 152.8 (2×Cq), 136.8 (Cq), 136.8 (Cq), 136.1 (Cq), 134.6 (Cq), 134.0 (Cq), 129.2 (CH), 128.6 (CH), 124.7 (CH), 106.2 (2×CH\(_3\)), 61.0 (CH\(_2\)), 56.0 (2×CH\(_3\)), 27.1 (CH\(_3\)), 26.0 (CH\(_3\)), 19.8 (CH\(_3\)), 19.7 (CH\(_3\)) ppm; IR (thin film): \(v_{\text{max}}\) = 2962, 2928, 2908, 1570, 1504 cm\(^{-1}\); LRMS: (EI\(^+\)): m/z (%): 302 ([M\(^+\)], 100), 287 ([M–CH\(_3\)]\(^+\), 51), 272 ([M–2×CH\(_3\)]\(^+\), 11); HRMS (EI\(^+\)): calculated for C\(_{19}\)H\(_{26}\)O\(_3\): 302.1882; found: 302.1891.
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1-Methoxy-4-(4-methyl-2-(2-methylprop-1-en-1-yl)penta-1,3-dien-1-yl)benzene (2t)

Following Standard Procedure A, the reaction mixture containing dibromide 1c (200 mg, 0.685 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (28 mg, 0.034 mmol), ZnBr₂ solution in THF (2.8 mL, 1.22 M, 3.43 mmol) and isobutenyl magnesium bromide (6.2 mL, 0.44 M, 2.74 mmol) in THF (10 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (5 g SiO₂, 1% EtOAc in PS 40 – 60) gave dendralene 2t as a colourless liquid (115 mg, 0.475 mmol, 69%). Rf = 0.51 (5% EtOAc in PS 40 – 60); ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.20 (s, 1H), 5.95 (s, 1H), 5.83 (s, 1H), 3.81 (s, 3H), 1.83 (s, 3H), 1.83 (s, 3H), 1.81 (s, 3H), 1.59 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 158.2 (Cq), 135.8 (Cq), 135.4 (Cq), 133.9 (Cq), 131.3 (Cq), 130.3 (2×CH), 129.1 (CH), 128.9 (CH), 124.6 (CH), 113.6 (2×CH), 55.4 (CH₃), 27.1 (CH₃), 26.1 (CH₃), 19.8 (CH₃), 19.7 (CH₃) ppm; IR (thin film): v max = 2964, 2907, 2852, 1605, 1506 cm⁻¹; LRMS: (EI⁺): m/z (%): 242 ([M⁺]⁺, 100), 227 ([M–CH₃]⁺, 91), 212 ([M–2×CH₃]⁺, 20); HRMS (EI⁺): calculated for C₁₇H₂₂O: 242.1671; found: 242.1671.

(E)-(6-Methyl-4-(2-methylprop-1-en-1-yl)hepta-1,3,5-trien-1-yl)benzene (2u)

Following Standard Procedure A, the reaction mixture containing dibromide 1j (200 mg, 0.694 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (29 mg, 0.035 mmol), ZnBr₂ solution in THF (2.3 mL, 1.23 M, 2.78 mmol) and isobutenyl magnesium bromide (4.7 mL, 0.44 M, 2.08 mmol) in THF (10 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (5 g SiO₂, 100% PS 40 – 60) gave dendralene 2u as a colourless liquid.
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((1E,4E)-3-((E)-3-Phenylallylidene)penta-1,4-diene-1,5-diyl)dibenzene (2v)

Following Standard Procedure A, the reaction mixture containing dibromide 1j (400 mg, 1.4 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (57 mg, 0.07 mmol), ZnBr₂ solution in THF (4.6 mL, 1.22 M, 5.56 mmol) and styrenyl magnesium bromide (7.2 mL, 0.58 M, 4.17 mmol) in THF (20 mL) was heated under reflux for 14h. After work up, purification by flash column chromatography (15 g SiO₂, 0.5% EtOAc in PS 40–60) gave 2v as a white solid (330 mg, 0.99 mmol, 71%). R₆ = 0.38 (5% EtOAc in PS 40–60); m.p. 93 – 95 °C (hexane: EtOAc, 8:2); ¹H NMR (700 MHz, CD₃CN) δ 7.64 (d, J = 7.4 Hz, 2H), 7.58 – 7.46 (m, 5H), 7.44 – 7.20 (m, 10H), 7.14 (d, J = 16.1 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 6.78 (d, J = 15.4 Hz, 1H), 6.67 (d, J = 11.9 Hz, 1H) ppm; ¹³C NMR (175 MHz, CD₃CN) δ 138.6 (Cq), 138.6 (Cq), 138.0 (Cq), 135.2 (CH), 133.7 (CH), 131.8 (CH), 131.1 (CH), 130.3 (CH), 129.7 (2×CH), 129.7 (2×CH), 129.6 (2×CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.7 (2×CH), 127.6 (2×CH), 127.5 (2×CH), 126.5 (CH), 124.9 (CH) ppm; IR (thin film): vₘₐₓ = 3057, 3026, 1595 cm⁻¹; LRMS: (EI⁺): m/z (%): 334 ([M]⁺, 100), 243 ([M–C₆H₅]⁺, 76); HRMS (EI⁺): calculated for C₂₆H₂₂: 334.1722; found: 334.1724.
Following Standard Procedure A, the reaction mixture containing dibromide 1c (1.00 g, 3.43 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (0.14 g, 0.17 mmol), ZnBr₂ solution in THF (13.9 mL, 1.23 M, 17.1 mmol) and styrenyl magnesium bromide (34.3 mL, 0.40 M, 13.7 mmol) in THF (50 mL) was heated under reflux for 4 h. After work up, purification by flash column chromatography (30 g SiO₂, 1% EtOAc in PS 40–60) and recrystallization from hexane:CH₂Cl₂ (9:1) gave 2w as a white solid (0.88 g, 2.60 mmol, 76%).

Rf = 0.38 (5% EtOAc in PS 40–60); m.p. 105 – 107 °C (hexane:CH₂Cl₂ 9:1); ¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.41 – 7.31 (m, 6H), 7.30 – 7.22 (m, 2H), 7.18 (d, J = 16.4 Hz, 1H), 7.05 (d, J = 15.6 Hz, 1H), 6.95 – 6.89 (m, 3H), 6.86 (d, J = 16.4 Hz, 1H), 6.80 (s, 1H), 3.84 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 159.3 (Cq), 137.8 (Cq), 137.7 (Cq), 135.9 (Cq), 132.6 (CH), 131.4 (2×CH), 130.8 (CH), 130.6 (CH), 130.4 (Cq), 129.9 (CH), 128.9 (2×CH), 128.8 (2×CH), 127.8 (CH), 127.7 (CH), 126.7 (2×CH), 126.7 (2×CH), 126.6 (CH), 114.0 (2×CH), 55.5 (CH₃) ppm; IR (thin film): νmax = 3057, 3024, 2989, 2837, 1597 cm⁻¹; LRMS: (El⁺): m/z (%): 338 ([M]+, 100), 247 ([M–C₅H₇]+, 38); HRMS (El⁺): calculated for C₂₅H₂₂O: 338.1671; found: 338.1668.
Synthesis of Monobromodienes by \(E\)-Selective Single Cross-Coupling

**Standard Procedure B:**

A solution of \(\text{Pd}([\text{PPh}_3]_4)\) (3.0 - 4.0 mol%) and dibromo olefin (1.0 mol equiv) in THF (20 mL/g dibromo olefin) was purged with \(\text{N}_2\) for 5 minutes. The reaction mixture was cooled to 0 °C and \(\text{ZnBr}_2\) (0.90 - 3.0 mol equiv, 1.10 - 1.48 M solution in THF) was added, followed by dropwise addition of Grignard reagent (0.75 - 2.0 mol equiv, 0.31 - 0.86 M solution in THF) over 5 minutes. The resulting heterogeneous reaction mixture was warmed to room temperature and stirred until complete by \(^1\text{H} \text{NMR/TLC analysis}\.\) Saturated aqueous \(\text{NH}_4\text{Cl}\) (5 mL/g dibromo olefin) was added, the reaction mixture was filtered through a pad of Celite and the filtrate was diluted with \(\text{CH}_2\text{Cl}_2\) (25 mL/g dibromo olefin) and water (50 mL/g dibromo olefin). The aqueous and organic layers were separated and the aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (10 mL/g dibromo olefin \(\times\) 3). The combined organic layers were washed with saturated brine (20 mL/g dibromo olefin), dried over \(\text{Na}_2\text{SO}_4\) and concentrated under reduced pressure.

\((Z)-1-(2\text{-Bromobuta-1,3-dien-1-yl})-4\text{-methoxybenzene (3a)}\)

Following **Standard Procedure B**, the reaction mixture containing dibromide 1c (1.00 g, 3.43 mmol), \(\text{Pd}([\text{PPh}_3]_4)\) (0.12 g, 0.103 mmol) \(\text{ZnBr}_2\) solution in THF (4.5 mL, 1.14 M in THF, 5.14 mmol) and vinyl magnesium bromide (5.0 mL, 0.82 M in THF, 4.11 mmol) in THF (20 mL) was stirred at 40 °C for 2h. After work up, purification by flash column chromatography (25 g SiO\(_2\), 1% EtOAc in PS 40–60) gave monobromodiene 3a as a white solid (0.736 g, 3.07 mmol, 90%). \(R_f = 0.33\text{ (5% EtOAc in PS 40–60); m.p. 51 – 52 °C (hexane:EtOAc, 9:1); \(^1\text{H} \text{NMR (400 MHz, CDCl}_3\)}\) \(\delta\) 7.70 (d, \(J = 8.8\) Hz, 2H), 6.99 – 6.82 (m, 3H), 6.49 (dd, \(J = 16.0, 10.4\) Hz, 1H), 5.68 (s, 1H).
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(d, J = 16.0 Hz, 1H), 5.28 (d, J = 10.4 Hz, 1H), 3.84 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.7 (Cq), 137.4 (CH), 132.0 (CH), 131.3 (2×CH), 128.2 (Cq), 122.1 (Cq), 118.1 (CH$_2$), 113.8 (2×CH), 55.4 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}}$ = 3003, 2965, 2839, 1591, 1505 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 240 ([M($^81$Br)]$^{+\cdot}$, 26), 238 ([M($^79$Br)]$^{+\cdot}$, 26), 159 ([M-Br]$^{+\cdot}$, 60), 144 ([M-CH$_3$Br]$^{+\cdot}$, 86), 128 ([M-OCH$_3$Br]$^{+\cdot}$, 38), 115 (100); HRMS (EI$^+$): calculated for C$_{11}$H$_{11}$O$^81$Br: 239.9973; found: 239.9961; calculated for C$_{11}$H$_{11}$O$^79$Br: 237.9997.

(Z)-1-(2-Bromo-3-methylbuta-1,3-dien-1-yl)-4-methoxybenzene (3b)

Following Standard Procedure B, the reaction mixture containing dibromide 1c (1.50 g, 5.14 mmol), Pd(PPh$_3$)$_4$ (0.180 g, 0.154 mmol) ZnBr$_2$ (4.1 mL, 1.14 M in THF, 4.62 mmol) and isopropenyl magnesium bromide (6.9 mL, 0.56 M in THF, 3.85 mmol) in THF (30 mL) was stirred at 23 °C for 4h. After work up, purification by flash column chromatography (45 g SiO$_2$, 1% EtOAc in PS 40–60) gave monobromodiene 3b as a pale yellow liquid (0.650 g, 2.57 mmol, 50%). $R_f$ = 0.41 (5% EtOAc in PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.63 (d, $J$ = 8.8 Hz, 2H), 7.00 (s, 1H), 6.91 (d, $J$ = 8.8 Hz, 2H), 5.63 (s, 1H), 5.22 (s, 1H), 3.84 (s, 3H), 2.13 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.4 (Cq), 142.0 (Cq), 131.2 (2×CH), 128.9 (Cq), 128.5 (CH), 124.7 (Cq), 118.8 (CH$_2$), 113.6 (2×CH), 55.4 (CH$_3$), 21.5 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}}$ = 3000, 2953, 2835, 1601, 1507 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 254 ([M($^81$Br)]$^{+\cdot}$, 16), 252 ([M($^79$Br)]$^{+\cdot}$, 16), 239 ([M($^81$Br)-CH$_3$]$^{+\cdot}$, 14), 237 ([M($^79$Br)-CH$_3$]$^{+\cdot}$, 14), 173 ([M-Br]$^{+\cdot}$, 46), 158 ([M-CH$_3$Br]$^{+\cdot}$, 100); HRMS (EI$^+$): calculated for C$_{12}$H$_{13}$O$^81$Br: 254.0129; found: 254.0124; calculated for C$_{12}$H$_{13}$O$^79$Br: 252.0150; found: 252.0151.
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1-((1Z,3E)-2-Bromo-4-phenylbuta-1,3-dien-1-yl)-4-methoxybenzene (3c)

Following Standard Procedure B, the reaction mixture containing dibromide 1c (1.00 g, 3.43 mmol), Pd(PPh₃)₄ (0.119 g, 0.103 mmol) ZnBr₂ (8.4 mL, 1.23 M in THF, 10.3 mmol) and styrenyl magnesium bromide (17.1 mL, 0.40 M in THF, 6.85 mmol) in THF (20 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (25 g SiO₂, 1% EtOAc in PS 40–60) gave monobromodiene 3c as a pale yellow solid (0.92 g, 2.93 mmol, 85%). Rᶠ = 0.26 (1% EtOAc in PS 40–60); m.p. 124 – 126 °C (hexane:EtOAc, 9:1); 'H NMR (400 MHz, (CD₃)₂SO) δ 7.76 (d, J = 9.2 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H), 7.42 – 7.35 (m, 3H), 7.33 – 7.25 (m, 2H), 7.01 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 15.2 Hz, 1H), 3.80 (s, 3H) ppm; ¹³C NMR (100 MHz, (CD₃)₂SO) δ 159.4 (Cq), 136.2 (Cq), 132.4 (CH), 132.0 (CH), 131.0 (2 × CH), 129.8 (CH), 128.9 (2 × CH), 128.1 (CH), 127.8 (Cq), 126.9 (2 × CH), 120.6 (Cq), 113.9 (2 × CH), 55.3 (CH₃) ppm; IR (thin film): v_max = 3008, 2837, 1599, 1578, 1505 cm⁻¹; LRMS: (EI⁺): m/z (%): 316 ([M+Br]⁺, 46), 314 ([M⁻Br]⁺, 46), 313 ([M⁻Br₂]⁺, 81), 204 ([M⁻OCH₃Br]⁺, 36); HRMS (EI⁺): calculated for C₁₇H₁₅OBr: 316.0286; found: 316.0276; calculated for C₁₇H₁₅O⁻Br: 314.0306; found: 314.0310.

(Z)-1-((2-Bromo-4-methylpenta-1,3-dien-1-yl)-4-methoxybenzene (3d)

Following Standard Procedure B, the reaction mixture containing dibromide 1c (1.00 g, 3.43 mmol), Pd(PPh₃)₄ (0.119 g, 0.103 mmol) ZnBr₂ (7.0 mL, 1.22 M in THF, 8.56 mmol) and isobutenyl magnesium bromide (13.6 mL, 0.44 M in THF, 6.00 mmol) in THF (20 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (30 g SiO₂, 1%
EtOAc in PS 40–60) gave monobromodiene 3d as a colourless liquid (0.654 g, 2.45 mmol, 71%).

\[ \text{EtOAc in PS 40–60} \]

\[ S_{35} \]

\[ \text{gave monobromodiene 3d as a colourless liquid (0.654 g, 2.45 mmol, 71%).} \]

\[ R_f = 0.42 (5% \text{ EtOAc in PS 40–60}); ^1H \text{ NMR (400 MHz, CDCl}_3\delta 7.62 (d, } J = 8.8 \text{ Hz, 2H), 6.91 (d, } J = 8.8 \text{ Hz, 2H), 6.63 (s, 1H), 5.95 (s, 1H), 3.83 (s, 3H), 1.89 (d, } J = 0.8 \text{ Hz, 3H), 1.86 (d, } J = 1.2 \text{ Hz, 3H) ppm; } ^{13}C \text{ NMR (100 MHz, CDCl}_3\delta 159.3 (\text{Cq}), 137.9 (\text{Cq}), 130.5 (2\times \text{CH}), 129.5 (\text{CH}), 128.6 (\text{Cq}), 121.9 (\text{Cq}), 113.7 (2\times \text{CH}), 55.4 (\text{CH}_3), 19.7 (\text{CH}_3) \text{ ppm; IR (thin film): } v_{\text{max}} = 2966, 2932, 2835, 1606, 1508 \text{ cm}^{-1}; \text{ LRMS: (EI}^+)\text{ m/z (%): 268 ([M}^{81}\text{Br}]+•, 29), 266 ([M}^{79}\text{Br}]+•, 29), 253 ([M}^{81}\text{Br}–\text{CH}_3]+•, 13), 251 ([M}^{79}\text{Br}–\text{CH}_3]+•, 13), 187 ([M–Br]$, 22), 172 ([M–CH}_2\text{Br}]$, 100); HRMS (EI$^+$): calculated for C$_{13}$H$_{15}$O$_{81}$Br: 268.0286; found: 268.0287; calculated for C$_{13}$H$_{15}$O$_{79}$Br: 266.0306; found: 266.0305.}

\[ ((1E,3Z)-4-\text{Bromohexa-1,3,5-trien-1-yl)benzene (3e}) \]

\[ \begin{align*}
\text{Br} & \quad \text{ZnBr$_2$} \\
\text{Br} & \quad \text{Pd(PPh$_3$)$_4$} \\
\text{ZnBr$_2$} & \quad \text{THF} \\
\text{Br} & \quad \text{0 °C – 23 °C, 2h} \\
\text{O} & \quad \text{Pd(PPh$_3$)$_4$} \\
\text{MgBr} & \quad \text{THF} \\
\text{Br} & \quad \text{0 °C – 23 °C, 2h} \\
\text{O} & \quad \text{Pd(PPh$_3$)$_4$}
\end{align*} \]

\[ \text{Following Standard Procedure B, the reaction mixture containing dibromide 1j (500 mg, 1.74} \]

\[ \text{mmol), Pd(PPh$_3$)$_4$ (80 mg, 0.069 mmol) ZnBr$_2$ (3.5 mL, 1.48 M in THF, 5.21 mmol) and vinyl} \]

\[ \text{magnesium bromide (4.4 mL, 0.86 M in THF, 3.82 mmol) in THF (10 mL) was stirred at 23 °C for} \]

\[ \text{2h. After work up, purification by flash column chromatography (15 g SiO$_2$, 100% PS 40–60) gave} \]

\[ \text{monobromodiene 3e as a white solid (325 mg, 1.38 mmol, 79%).} \]

\[ R_f = 0.37 (100% \text{ PS 40–60); m.p. 64 – 68 °C (CH}_2\text{Cl}_2); ^1H \text{ NMR (400 MHz, CDCl}_3\delta 7.51 (d, } J = 8.0 \text{ Hz, 2H), 7.37 (t, } J = 7.4 \text{ Hz, 2H), 7.3 – 7.22 (m, 2H), 6.80 (d, } J = 15.6 \text{ Hz, 1H), 6.70 (d, } J = 10.4 \text{ Hz, 1H), 6.46 (dd, } J = 16.2, 10.4 \text{ Hz, 1H), 5.70 (d, } J = 16.2 \text{ Hz, 1H), 5.31 (d, } J = 10.4 \text{ Hz, 1H) ppm; } ^{13}C \text{ NMR (100 MHz, CDCl}_3\delta 137.0 (\text{Cq}), 136.8 (\text{CH}), 136.1 (\text{CH}), 132.7 (\text{CH}), 128.9 (2\times \text{CH}), 128.5 (\text{CH}), 127.0 (2\times \text{CH}), 126.7 (\text{CH}), 126.1 (\text{Cq}), 119.0 (\text{CH}_2) \text{ ppm; IR (thin film): } v_{\text{max}} = 3032, 2917, 1824, 1599 \text{ cm}^{-1}; \text{ LRMS: (EI}^+)\text{ m/z (%): 236 ([M}^{81}\text{Br}]$), 26), 234 ([M}^{79}\text{Br}]$, 26), 155 ([M–Br]$^+$, 100), 154 ([M–HBr]$^+$, 30); HRMS (EI$^+$): calculated for C$_{13}$H$_{11}$O$_{79}$Br: 236.0024; found: 236.0020; calculated for C$_{13}$H$_{11}$O$_{81}$Br: 234.0044; found: 234.0050.} \]
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((1E,3Z)-4-Bromo-5-methylhexa-1,3,5-triene-1-yl)benzene (3f)

Following Standard Procedure B, the reaction mixture containing dibromide 1j (2.00 g, 6.94 mmol), Pd(PPh$_3$)$_4$ (241 mg, 0.208 mmol), ZnBr$_2$ (9.0 mL, 1.23 M in THF, 11.1 mmol) and isopropenyl magnesium bromide (14.9 mL, 0.56 M in THF, 8.33 mmol) in THF (40 mL) was stirred at 23 °C for 4 h. After work up, purification by flash column chromatography (50 g SiO$_2$, 100% PS 40–60) gave monobromodiene 3f as a white solid (1.41 g, 5.66 mmol, 82%).

R$_f$ = 0.38 (100% PS 40–60); m.p. 68–69 °C (hexane); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 (d, $J$ = 7.2 Hz, 2H), 7.35 (t, $J$ = 7.4 Hz, 2H), 7.30–7.24 (m, 2H), 6.80 (d, $J$ = 16.0 Hz, 1H), 6.74 (d, $J$ = 10.4 Hz, 1H), 5.64 (s, 1H), 5.22 (s, 1H), 2.09 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 140.8 (Cq), 137.1 (Cq), 136.6 (CH), 129.2 (CH), 128.9 (2×CH), 128.4 (CH), 127.8 (Cq), 127.8 (CH), 127.0 (2×CH), 119.5 (CH$_2$), 21.1 (CH$_3$) ppm; IR (thin film): $v_{max}$ = 3037, 2956, 1792, 1598 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 250 ([M+(81Br)]$^+$, 31), 248 ([M+(79Br)]$^+$, 31), 169 ([M–Br]$^+$, 100), 154 ([M–CH$_3$Br]$^+$, 73); HRMS (EI$^+$): calculated for C$_{13}$H$_{13}$81Br: 250.0180; found: 250.0188; calculated for C$_{13}$H$_{13}$79Br: 248.0201; found: 248.0203.

((1E,3Z,5E)-3-Bromo-hexa-1,3,5-triene-1,6-diyl) dibenzene (3g)

Following Standard Procedure B, the reaction mixture containing dibromide 1j (500 mg, 1.74 mmol), Pd(PPh$_3$)$_4$ (60 mg, 0.052 mmol), ZnBr$_2$ (3.3 mL, 1.22 M in THF, 4.0 mmol) and styrenyl magnesium bromide (4.8 mL, 0.58 M in THF, 2.78 mmol) in THF (10 mL) was stirred at 23 °C for 4 h. After work up, purification by flash column chromatography (5 g SiO$_2$, 100% PS 40–60) gave...
monobromodiene 3g as a pale yellow solid (398 mg, 1.28 mmol, 74%). \( R_f = 0.23 \) (100% PS 40–60); m.p. 142 – 144 °C (hexane:CH\(_2\)Cl\(_2\), 9:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.56 – 7.48 (m, 4H), 7.42 – 7.36 (m, 4H), 7.36 – 7.27 (m, 3H), 7.07 (d, \( J = 15.1 \) Hz, 1H), 6.90 (d, \( J = 15.1 \) Hz, 1H), 6.83 (d, \( J = 11.2 \) Hz, 1H), 6.80 (d, \( J = 6.8 \) Hz, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 137.1 (Cq), 136.7 (Cq), 136.3 (CH), 133.9 (CH), 132.7 (CH), 128.9 (4\( \times \)CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.1 (2\( \times \)CH), 127.0 (2\( \times \)CH), 127.0 (2\( \times \)CH) ppm.

Following **Standard Procedure B**, the reaction mixture containing dibromide 1j (500 mg, 1.74 mmol), Pd(PPh\(_3\))\(_4\) (60 mg, 0.052 mmol) ZnBr\(_2\) (3.6 mL, 1.22 M in THF, 4.34 mmol) and isobutenyl magnesium bromide (7.5 mL, 0.44 M in THF, 3.30 mmol) in THF (10 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (15 g SiO\(_2\), 100% PS 40–60) gave monobromodiene 3h as a colourless liquid (195 mg, 0.741 mmol, 43%).

\( R_f = 0.29 \) (100% PS 40–60); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.49 (d, \( J = 7.4 \) Hz, 2H), 7.36 (t, \( J = 7.5 \) Hz, 2H), 7.31 – 7.24 (m, 1H), 7.14 (dd, \( J = 15.7, 10.2 \) Hz, 1H), 6.73 (d, \( J = 15.7 \) Hz, 1H), 6.43 (d, \( J = 10.2 \) Hz, 1H), 5.95 (s, 1H), 1.92 (s, 3H), 1.88 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 138.9 (Cq), 137.3 (Cq), 134.7 (CH), 130.3 (CH), 128.8 (2\( \times \)CH), 128.1 (CH), 127.3 (CH), 126.8 (2\( \times \)CH), 126.6 (CH), 123.3 (Cq), 26.3 (CH\(_3\)), 20.0 (CH\(_3\)) ppm; IR (thin film): \( \nu_{\text{max}} \) = 3035, 2970, 2909, 1633 cm\(^{-1}\); LRMS: (El\(^+\)): m/z (%): 264 ([M\(^{81}\)Br])\(^+\), 61), 262 ([M\(^{79}\)Br])\(^+\), 61), 183 ([M–Br])\(^+\), 100), 168 ([M–CH\(_3\)Br])\(^+\), 95), 153 ([M–CH\(_3\)CH\(_2\)Br])\(^+\), 47); HRMS (El\(^+\)): calculated for C\(_{14}\)H\(_{15}\)\(^{81}\)Br: 264.0337; found: 264.0349; calculated for C\(_{14}\)H\(_{15}\)\(^{79}\)Br: 262.0357; found: 262.0358.
(Z)-(4-Bromohexa-3,5-dien-1-yn-1-yl)benzene (3i)

Following Standard Procedure B, the reaction mixture containing dibromide 1k (510 mg, 1.78 mmol), Pd(PPh₃)₄ (62 mg, 0.054 mmol) ZnBr₂ (2.2 mL, 1.23 M in THF, 2.68 mmol) and vinyl magnesium bromide (3.0 mL, 0.71 M in THF, 2.14 mmol) in THF (10 mL) was stirred at 23 °C for 3 h. After work up, purification by flash column chromatography (15 g SiO₂, 100% PS 40–60) gave monobromodiene 3i as a pale yellow liquid (320 mg, 1.37 mmol, 77%). R_f = 0.20 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 7.59 – 7.48 (m, 2H), 7.41 – 7.30 (m, 3H), 6.45 (dd, J = 16.4, 10.4 Hz, 1H), 6.33 (s, 1H), 5.74 (d, J = 16.4 Hz, 1H), 5.40 (d, J = 10.4 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 135.0 (CH), 134.8 (Cq), 131.8 (2 × CH), 128.9 (CH), 128.5 (2 × CH), 123.1 (Cq), 121.8 (CH₂), 114.1 (CH), 99.2 (Cq), 87.6 (Cq) ppm; IR (thin film): ν_max = 3054, 3001, 2193, 1613, 1597, 1568 cm⁻¹; LRMS: (EI⁺): m/z (%): 234 ([M(81Br)]⁺, 63), 232 ([M(79Br)]⁺, 63), 153 ([M–Br]⁺, 76), 152 ([M–HBr]⁺, 100), 151 ([M–HBrH]⁺, 43); HRMS (EI⁺): calculated for C₁₂H₉Br: 233.9867; found: 233.9860; calculated for C₁₂H₉Br: 231.9888; found: 231.9888.

(Z)-(4-Bromo-5-methylhexa-3,5-dien-1-yn-1-yl)benzene (3j)

Following Standard Procedure B, the reaction mixture containing dibromide 1k (970 mg, 3.40 mmol), Pd(PPh₃)₄ (118 mg, 0.102 mmol) ZnBr₂ (4.1 mL, 1.23 M in THF, 5.09 mmol) and isopropenyl magnesium bromide (8.0 mL, 0.51 M in THF, 4.07 mmol) in THF (20 mL) was stirred at 23 °C for 4 h. After work up, purification by flash column chromatography (25 g SiO₂, 100% PS 40–60) gave monobromodiene 3j as a pale yellow liquid (675 mg, 2.73 mmol, 81%).
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Rf = 0.28 (100% PS 40–60); 1H NMR (400 MHz, CDCl3) δ 7.58 – 7.48 (m, 2H), 7.36 – 7.31 (m, 3H), 6.39 (s, 1H), 5.68 (s, 1H), 5.29 (s, 1H), 2.06 (s, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 140.2 (Cq), 136.4 (Cq), 131.8 (2×CH), 128.8 (CH), 128.5 (2×CH), 123.2 (Cq), 121.5 (CH2), 111.4 (CH), 98.5 (Cq), 88.1 (Cq), 20.5 (CH3) ppm; IR (thin film): νmax = 3025, 2923, 2197, 1599 cm−1; LRMS: (EI+): m/z (%): 248 ([M(81Br)+•], 31), 246 ([M(79Br)+•], 31), 167 ([M–Br]+•, 90), 166 ([M–HBr]+•, 36), 165 ([M–HBrH]+•, 100), 152 ([M–CH3Br]+•, 70), 126 ([M–C6H5Br]+•, 13); HRMS (EI+): calculated for C13H1181Br: 248.0024; found: 248.0024; calculated for C13H1179Br: 246.0044; found: 246.0043.

((1E,3Z)-3-Bromohexa-1,3-dien-5-ynes-1,6-diyl)dibenzene (3k)

Following Standard Procedure B, the reaction mixture containing dibromide 1k (460 mg, 1.61 mmol), Pd(PPh3)4 (56 mg, 0.048 mmol) ZnBr2 (3.7 mL, 1.22 M in THF, 4.50 mmol) and styrenyl magnesium bromide (6.4 mL, 0.58 M in THF, 3.70 mmol) in THF (10 mL) was stirred at 23 °C for 2h. After work up, purification by flash column chromatography (10 g SiO2, 100% PS 40–60) gave monobromodiene 3k as a white solid (438 mg, 1.42 mmol, 88%). Rf = 0.25 (100% PS 40–60); m.p. 139 – 141 °C (hexane:CH2Cl2, 9:1); 1H NMR (400 MHz, CDCl3) δ 7.60 – 7.52 (m, 2H), 7.49 (d, J = 7.3 Hz, 2H), 7.43 – 7.27 (m, 6H), 7.10 (d, J = 14.8 Hz, 1H), 6.87 (d, J = 14.8 Hz, 1H), 6.41 (s, 1H) ppm; 13C NMR (100 MHz, CDCl3) δ 136.7 (CH), 136.1 (Cq), 134.3 (Cq), 131.8 (2×CH), 129.0 (2×CH), 128.9 (CH), 128.8 (CH), 128.5 (2×CH), 127.4 (2×CH), 126.7 (CH), 123.2 (Cq), 113.5 (CH), 99.6 (Cq), 88.4 (Cq) ppm; IR (thin film): νmax = 3050, 3024, 2190, 1595, 1573, 1554 cm−1; LRMS: (EI+): m/z (%): 310 ([M+81Br]+•, 16), 308 ([M+79Br]+•, 16), 229 ([M–Br]+•, 100), 152 ([M–C6H5Br]+•, 86); HRMS (EI+): calculated for C18H1381Br: 310.0180; found: 310.0180; calculated for C18H1379Br: 308.0201; found: 308.0204.
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(\textit{Z})-(4-Bromo-6-methyhepta-3,5-dien-1-yn-1-yl)benzene (3l)

Following Standard Procedure B, the reaction mixture containing dibromide 1k (410 mg, 1.43 mmol), Pd(PPh3)4 (50 mg, 0.0430 mmol) ZnBr2 (2.9 mL, 1.22 M in THF, 3.58 mmol) and isobutylmagnesium bromide (5.7 mL, 0.50 M in THF, 2.87 mmol) in THF (10 mL) was stirred at 23 °C for 3h. After work up, purification by flash column chromatography (20 g SiO2, 100% PS 40–60) gave monobromodiene 3l as a colourless liquid (230 mg, 0.881 mmol, 62%). \( R_f = 0.27 \) (100% PS 40–60); \( ^1 \text{H} \) NMR (400 MHz, CDCl3) \( \delta \) 7.54 – 7.45 (m, 2H), 7.36 – 7.29 (m, 3H), 6.10 (s, 1H), 5.93 (brs, 1H), 1.91 (d, \( J = 1.2 \) Hz, 3H), 1.86 (d, \( J = 1.2 \) Hz, 3H) ppm; \( ^{13} \text{C} \) NMR (100 MHz, CDCl3) \( \delta \) 140.7 (Cq), 132.1 (Cq), 131.7 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 125.7 (CH), 123.3 (Cq), 112.4 (CH), 96.3 (Cq), 87.6 (Cq), 26.5 (CH₃), 20.0 (CH₃) ppm; IR (thin film): \( \nu_{\text{max}} = 2971, 2909, 2198, 1633 \text{ cm}^{-1} \); LRMS: (EI+): m/z (%): 262 ([M(\text{81Br})]^{+}\cdot, 21), 260 ([M(\text{79Br})]^{+}\cdot, 21), 181 ([M–Br]^{+}\cdot, 34), 166 ([M–CH₃Br]^{+}\cdot, 72), 165 ([M–CH₃HBr]^{+}\cdot, 100); HRMS (EI+): calculated for C₁₄H₁₃\text{81Br}: 262.0180; found: 262.0177; calculated for C₁₄H₁₃\text{79Br}: 260.0204; found: 260.0204.

(\textit{Z})-(2-Bromobuta-1,3-dien-1-yl)cyclohexane (3m)

Following Standard Procedure B, the reaction mixture containing dibromide 1h (960 mg, 3.58 mmol), Pd(PPh3)₄ (124 mg, 0.107 mmol) ZnBr₂ (6.2 mL, 1.22 M in THF, 7.52 mmol) and vinylmagnesium bromide (7.2 mL, 0.50 M in THF, 3.58 mmol) in THF (20 mL) was stirred at 23 °C for 3h. After work up, purification by flash column chromatography (30 g AgNO₃ impregnated silica, 1% EtOAc in PS 40–60) gave monobromodiene 3m as a colourless liquid (506 mg, 2.35 mmol, 66%). \( R_f = 0.56 \) (100% PS 40–60); \( ^1 \text{H} \) NMR (400 MHz, CDCl3) \( \delta \) 6.28 (dd, \( J = 16.3, 10.5 \) Hz, 1H),
Following **Standard Procedure B**, the reaction mixture containing dibromide 1h (920 mg, 3.43 mmol), Pd(PPh₃)₄ (119 mg, 0.103 mmol) ZnBr₂ (6.5 mL, 1.22 M in THF, 7.90 mmol) and isopropenyl magnesium bromide (11.9 mL, 0.46 M in THF, 5.50 mmol) in THF (20 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (25 g AgNO₃ impregnated silica, 100% PS 40–60) gave monobromodiene 3n as a colourless liquid (536 mg, 2.34 mmol, 68%). Rf = 0.63 (100% PS 40–60); H NMR (400 MHz, CDCl₃) δ 5.82 (d, J = 8.8 Hz, 1H), 5.46 (s, 1H), 5.08 (s, 1H), 2.65 – 2.44 (m, 1H), 1.98 (s, 3H), 1.85 – 1.58 (m, 5H), 1.44 – 1.02 (m, 5H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 141.1 (Cq), 136.5 (CH), 125.8 (Cq), 117.8 (CH₂), 41.6 (CH), 32.0 (2×CH₂), 26.1 (CH₂), 21.2 (CH₃) ppm; IR (thin film): v_max = 2924, 2850, 1624, 1605 cm⁻¹; LRMS: (EI⁺): m/z (%): 230 ([M⁺Br]⁺, 30), 228 ([M⁺(Br⁻)]⁺, 30), 215 ([M⁺(Br⁻)⁻]⁻, 8), 213 ([M⁺(Br⁻)⁺]⁺, 8), 149 ([M⁺Br⁻]⁺, 74), 120 ([M⁺CH₃Br⁻]⁺, 11), 32 (100); HRMS (EI⁺): calculated for C₁₁H₁₇Br: 230.0493; found: 230.0496; calculated for C₁₁H₁₇Br: 228.0514; found: 228.0514.

(Z)-3-Bromotetradeca-1,3-diene (3o)
Following **Standard Procedure B**, the reaction mixture containing dibromide 1g (677 mg, 2.08 mmol), Pd(PPh$_3$)$_4$ (72 mg, 0.062 mmol) ZnBr$_2$ (3.9 mL, 1.22 M in THF, 4.80 mmol) and vinyl magnesium bromide (4.7 mL, 0.75 M in THF, 3.53 mmol) in THF (15 mL) was stirred at 23 °C for 4h. After work up, purification by flash column chromatography (20 g AgNO$_3$ impregnated silica, 100% PS 40–60) gave monobromodiene 3o as a colourless liquid (260 mg, 0.951 mmol, 46%).

$\text{RF} = 0.60$ (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.31 (dd, $J = 16.3$, 10.4 Hz, 1H), 5.98 (t, $J = 7.2$ Hz, 1H), 5.53 (d, $J = 10.4$ Hz, 1H), 5.15 (d, $J = 16.4$ Hz, 1H), 2.31 (q, $J = 7.3$ Hz, 2H), 1.50 – 1.09 (m, 16H), 0.88 (t, $J = 6.8$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 136.0 (CH), 135.4 (CH), 125.9 (Cq), 117.1 (Cq), 117.2 (CH$_2$), 32.1 (CH$_2$), 31.7 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.4 (CH$_2$), 28.5 (CH$_2$), 22.9 (CH$_2$), 14.3 (CH$_3$) ppm; IR (thin film): $\nu_{max}$ = 2955, 2923, 2853, 1632 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 274 ([M(81Br)]$^+$, 12), 272 ([M(79Br)]$^+$, 12), 193 ([M–Br]$^+$), 81 (100); HRMS (EI$^+$): calculated for C$_{14}$H$_{25}$81Br: 274.1119; found: 274.1123; calculated for C$_{14}$H$_{25}$79Br: 272.1140; found: 272.1149.

Following **Standard Procedure B**, the reaction mixture containing dibromide 1g (780 mg, 2.39 mmol), Pd(PPh$_3$)$_4$ (83 mg, 0.072 mmol) ZnBr$_2$ (3.9 mL, 1.22 M in THF, 4.78 mmol) and isopropenyl magnesium bromide (6.8 mL, 0.49 M in THF, 3.35 mmol) in THF (15 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (25 g AgNO$_3$ impregnated silica, 100% PS 40–60) gave monobromodiene 3p as a colourless liquid (382 mg, 1.33 mmol, 55%). $\text{RF} = 0.60$ (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.01 (t, $J = 6.8$ Hz, 1H), 5.46 (s, 1H), 5.08 (s, 1H), 2.31 (q, $J = 7.2$ Hz, 2H), 1.99 (s, 3H), 1.51 – 1.17 (m, 16H), 0.87 (t, $J = 6.8$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.0 (Cq), 131.6 (CH), 127.7 (Cq), 117.6 (CH$_2$), 32.6 (CH$_3$), 32.1 (CH$_2$), 29.8 (CH$_3$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.5 (2×CH$_2$), 28.6 (CH$_2$), 22.9 (CH$_2$), 21.2 (CH$_3$), 14.3(CH$_3$) ppm; IR (thin film): $\nu_{max}$ = 2922, 2853, 1625, 1606 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 288 ([M(81Br)]$^+$, 20), 286 ([M(79Br)]$^+$, 20), 207 ([M–Br]$^+$, 10), 79 (100); HRMS (EI$^+$): calculated for C$_{15}$H$_{27}$81Br: 288.1276; found: 288.1267; calculated for C$_{15}$H$_{27}$79Br: 286.1296; found: 286.1297.

(Z)-3-Bromo-2-methyltetradeca-1,3-diene (3p)
(Z)-1-(2-Bromobuta-1,3-dien-1-yl)-4-nitrobenzene (3q)

Following Standard Procedure B, the reaction mixture containing dibromide 1e (850 mg, 2.77 mmol), Pd(PPh₃)₄ (96 mg, 0.083 mmol) ZnBr₂ (4.5 mL, 1.22 M in THF, 5.54 mmol) and vinyl magnesium bromide (5.2 mL, 0.75 M in THF, 3.88 mmol) in THF (20 mL) was stirred at 23 °C for 5h. After work up, purification by flash column chromatography (30 g SiO₂, 1% EtOAc in PS 40–60) gave monobromodiene 3q as a pale yellow fluffy solid (449 mg, 1.77 mmol, 64%).

R_f = 0.33 (5% EtOAc in PS 40–60); 'H NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.03 (s, 1H), 6.53 (dd, J = 16.2, 10.4 Hz, 1H), 5.85 (d, J = 16.2 Hz, 1H), 5.48 (d, J = 10.4 Hz, 1H) ppm; IR (thin film): ν_max = 3101, 3082, 2924, 1831, 1590, 1504 cm⁻¹; LRMS: (EI⁺): m/z (%): 255 ([M(81Br)]⁺•), 4), 253 ([M(79Br)]⁺•), 4), 174 ([M−Br]⁺•), 4), 128 ([M−NO₂Br]⁺•), 100); HRMS (EI⁺): calculated for C₁₀H₈NO₂₈₁Br: 254.9718; found: 254.9716; calculated for C₁₀H₈NO₂₇₉Br: 252.9738; found: 252.9738.

(13C NMR (100 MHz, CDCl₃) δ 147.2 (Cq), 142.2 (Cq), 136.7 (CH), 130.3 (2×CH), 130.1 (CH), 127.7 (Cq), 123.6 (2×CH), 121.7 (CH₂) ppm; IR (thin film): ν_max = 3101, 3082, 2924, 1831, 1590, 1504 cm⁻¹; LRMS: (EI⁺): m/z (%): 255 ([M(81Br)]⁺•), 4), 253 ([M(79Br)]⁺•), 4), 174 ([M−Br]⁺•), 4), 128 ([M−NO₂Br]⁺•), 100); HRMS (EI⁺): calculated for C₁₀H₈NO₂₈₁Br: 254.9718; found: 254.9716; calculated for C₁₀H₈NO₂₇₉Br: 252.9738; found: 252.9738.

Following Standard Procedure B, the reaction mixture containing dibromide 1m (230 mg, 0.865 mmol), Pd(PPh₃)₄ (30 mg, 0.026 mmol) ZnBr₂ (1.1 mL, 1.23 M in THF, 1.30 mmol) and isopropenyl magnesium bromide (1.85 mL, 0.56 M in THF, 1.04 mmol) in THF (5 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (10 g SiO₂, 100% PS 40–60) gave monobromodiene 3r as a colourless liquid (145 mg, 0.638 mmol, 74%).
A General Synthesis of Dendralenes

Stereoselective Synthesis of Dendralenes

Standard Procedure C: Second Cross-Coupling with Pd(0)/t-Bu3P (Retention)

A solution of Pd₂(dba)₃·CHCl₃ (3.0 – 4.0 mol%), t-Bu₃P·HBF₄ (6.0 – 8.0 mol%) and monobromodiene (1.0 mol equiv) in THF (50 mL/g monobromodiene precursor) was purged with N₂ for 5 minutes. The reaction mixture was cooled to 0 °C and ZnBr₂ (4.0 mol equiv, 1.22 – 1.23 M solution in THF) was added, followed by dropwise addition of the Grignard reagent (3.0 mol equiv, 0.44 – 0.70 M solution in THF) dropwise over 5 minutes. The resulting heterogeneous reaction mixture was warmed to room temperature and stirred for 16h until complete by ¹H NMR analysis. Saturated aqueous NH₄Cl (5 mL/g monobromodiene precursor) was added, the reaction mixture was filtered through a pad of Celite, then the filtrate was diluted with CH₂Cl₂ (50 mL/g monobromodiene precursor) and water (100 mL/g monobromodiene precursor). The aqueous and organic layers were separated and the aqueous layer was extracted with CH₂Cl₂ (10 mL/g monobromodiene precursor × 3). The combined organic layers were washed with saturated brine (20 mL/g monobromodiene precursor), dried over Na₂SO₄ and concentrated under reduced pressure.
(E)-(5-Methyl-4-vinylhexa-3,5-dien-1-yn-1-yl)benzene (4a-E)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3j (75 mg, 0.303 mmol), Pd(dba)_3·CHCl_3 (11 mg, 0.011 mmol), t-Bu_P•HBF_4 (6 mg, 0.021 mmol) ZnBr_2 (1.0 mL, 1.23 M in THF, 1.21 mmol) and vinyl magnesium bromide (1.3 mL, 0.68 M in THF, 0.910 mmol) in THF (4 mL) was stirred at 23 °C for 3h. After work up, purification by flash column chromatography (3 g SiO_2, 100% PS 40–60) gave dendralene 4a-E as a colourless liquid (38 mg, 0.196 mmol, 65%, >95% retention). R_f = 0.49 (100% PS 40–60); ^1H NMR (400 MHz, CDCl_3) δ 7.49 – 7.42 (m, 2H), 7.38 – 7.27 (m, 3H), 6.91 (dd, J = 17.6, 10.8 Hz, 1H), 5.75 (s, 1H), 5.56 (d, J = 17.6 Hz, 1H), 5.45 (d, J = 10.8 Hz, 1H), 5.13 (s, 1H), 5.10 (s, 1H), 1.96 (s, 3H) ppm; ^13C NMR (100 MHz, CDCl_3) δ 152.0 (Cq), 142.9 (Cq), 133.5 (CH), 131.6 (2×CH), 128.5 (2×CH), 128.3 (CH), 123.7 (Cq), 120.0 (CH_2), 116.3 (CH_2), 107.4 (CH), 96.5 (Cq), 87.6 (Cq), 22.4 (CH_3) ppm; IR (thin film): \( \nu_{\text{max}} \) = 3052, 2924, 2853, 1597, 1488 cm\(^{-1}\); LRMS: (EI\(^+\)): m/z (%): 194 ([M]+•, 48), 179 ([M–CH_3]+•, 49), 178 ([M–CH_4]+•, 100); HRMS (EI\(^+\)): calculated for C_{15}H_{14}: 194.1096; found: 194.1091.

(Z)-(5-Methyl-4-vinylhexa-3,5-dien-1-yn-1-yl)benzene (4a-Z)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3i (75 mg, 0.322 mmol), Pd(dba)_3·CHCl_3 (13 mg, 0.013 mmol), t-Bu_P•HBF_4 (8 mg, 0.026 mmol) ZnBr_2 (1.1 mL, 1.23 M in THF, 1.29 mmol) and isopropenyl magnesium bromide (1.9 mL, 0.51 M in THF, 0.965 mmol) in THF (4 mL) was stirred at 23 °C for 16h. After work up, purification by flash...
column chromatography (3 g SiO$_2$, 100% PS 40–60) gave dendralene 4a-Z as a colourless liquid (45 mg, 0.232 mmol, 72%, >95% retention). $R_f$ = 0.44 (100% PS 40–60). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.45 – 7.36 (m, 2H), 7.33 – 7.27 (m, 3H), 6.41 (dd, $J$ = 17.4, 10.7 Hz, 1H), 5.69 (s, 1H), 5.28 (s, 1H), 5.21 (d, $J$ = 10.6 Hz, 1H), 4.94 (s, 1H), 2.01 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.3 (Cq), 141.2 (Cq), 137.2 (CH), 131.5 (2×CH), 128.4 (2×CH), 128.2 (CH), 123.9 (Cq), 117.8 (CH$_2$), 116.2 (CH$_2$), 108.7 (CH), 96.2 (Cq), 88.2 (Cq), 22.6 (CH$_3$) ppm; IR (thin film): $\nu_{max}$ = 3080, 2969, 2918, 2192, 1722, 1682, 1599 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 194 ([M$^+$], 44), 193 ([M–H$^-$], 24), 179 ([M–CH$_3$]$^-$, 47), 178 ([M–CH$_3$]$^-$, 100); HRMS (EI$^+$): calculated for C$_{15}$H$_{14}$: 194.1096; found: 194.1097.

(E)-(6-Methyl-4-vinylhepta-3,5-dien-1-yn-1-yl)benzene (4b-E)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3l (65 mg, 0.250 mmol), Pd$_2$(dba)$_3$-CHCl$_3$ (10 mg, 0.010 mmol), t-Bu$_3$P•HBF$_4$ (6 mg, 0.020 mmol) ZnBr$_2$ (0.82 mL, 1.22 M in THF, 0.996 mmol) and vinyl magnesium bromide (1.1 mL, 0.70 M in THF, 0.747 mmol) in THF (3.5 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (3 g SiO$_2$, 100% PS 40–60) gave dendralene 4b-E as a colourless liquid (36 mg, 0.173 mmol, 69%, >95% retention). $R_f$ = 0.33 (100% PS 40–60). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 – 7.44 (m, 2H), 7.36 – 7.28 (m, 3H), 7.12 (dd, $J$ = 17.6, 10.8 Hz, 1H), 5.86 (d, $J$ = 1.2 Hz, 1H), 5.62 (s, 1H), 5.41 (dd, $J$ = 17.6, 1.6 Hz, 1H), 5.28 (dt, $J$ = 10.8, 1.6 Hz, 1H), 1.87 (d, $J$ = 1.2 Hz, 3H), 1.78 (d, $J$ = 1.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.9 (Cq), 138.4 (Cq), 135.3 (CH), 131.5 (2×CH), 128.5 (2×CH), 128.2 (CH), 123.8 (Cq), 122.0 (CH), 117.8 (CH$_2$), 110.0 (CH), 96.8 (Cq), 87.4 (Cq), 26.5 (CH$_3$), 20.0 (CH$_3$) ppm; IR (thin film): $\nu_{max}$ = 2969, 2910, 2190, 1597 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 208 ([M$^+$], 33), 193 ([M–CH$_3$]$^-$, 50), 178 ([M–2×CH$_3$]$^-$, 100), 165 ([M–C$_3$H$_7$]$^-$, 57); HRMS (EI$^+$): calculated for C$_{16}$H$_{16}$: 208.1252; found: 208.1251.
(Z)-(6-Methyl-4-vinylhepta-3,5-dien-1-yn-1-yl)benzene (4b-Z)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3i (60 mg, 0.26 mmol), Pd(dba)$_2$-CHCl$_3$ (11 mg, 0.010 mmol), t-Bu$_3$P•HBF$_4$ (6 mg, 0.021 mmol) ZnBr$_2$ (0.84 mL, 1.23 M in THF, 1.03 mmol) and isobutenyl magnesium bromide (1.8 mL, 0.44 M in THF, 0.772 mmol) in THF (3 mL) was stirred at 23 °C for 4h. After work up, purification by flash column chromatography (3 g SiO$_2$, 100% PS 40–60) gave dendralene 4b-Z as a pale yellow liquid (35 mg, 0.168 mmol, 65%, >90% retention). $R_f$ = 0.30 (100% PS 40–60);

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42 – 7.37 (m, 2H), 7.35 – 7.27 (m, 3H), 6.45 (dd, $J = 17.2, 10.4$ Hz, 1H), 5.85 (s, 1H), 5.75 (s, 1H), 5.33 (d, $J = 10.4$ Hz, 1H), 1.93 (s, 3H), 1.72 (s, 3H) ppm;

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.7 (Cq), 139.4 (Cq), 138.5 (CH), 131.5 (2×CH), 128.5 (2×CH), 128.1 (CH), 124.0 (Cq), 119.7 (CH), 117.2 (CH$_2$), 110.5 (CH), 96.5 (Cq), 89.2 (Cq), 26.1 (CH$_3$), 20.8 (CH$_3$) ppm; $\nu_{as}$ = 3005, 2969, 2909, 2190, 1822, 1661, 1597 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 208 ([M]+, 39), 193 ([M–CH$_3$]+, 49), 178 ([M–2×CH$_3$]+, 100); HRMS (EI$^+$): calculated for C$_{16}$H$_{16}$: 208.1252; found: 208.1249.

(E)-(6-Methyl-4-(prop-1-en-2-yl)hepta-3,5-dien-1-yn-1-yl)benzene (4c-E)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3j (52 mg, 0.21 mmol), Pd(dba)$_2$-CHCl$_3$ (9 mg, 0.0084 mmol), t-Bu$_3$P•HBF$_4$ (5 mg, 0.017 mmol), ZnBr$_2$ (0.68 mL, 1.23 M in THF, 0.842 mmol) and isobutenyl magnesium bromide (1.4 mL, 0.44 M in THF,
0.631 mmol) in THF (3 mL) was stirred at 23 °C for 3h. After work up, purification by flash column chromatography (3 g SiO$_2$, 100% PS 40–60) gave dendralene 4c-E as a colourless liquid (27 mg, 0.121 mmol, 58%, >95% retention). R$_f$ = 0.33 (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.35 (m, 2H), 7.34 – 7.27 (m, 3H), 5.88 (s, 1H), 5.85 (s, 1H), 5.19 (s, 1H), 5.07 (s, 1H), 1.96 (s, 3H), 1.91 (d, $J$ = 1.6 Hz, 3H), 1.68 (d, $J$ = 1.2 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 150.6 (Cq), 142.8 (Cq), 138.1 (Cq), 131.4 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 124.2 (Cq), 121.8 (CH), 117.0 (CH$_2$), 107.0 (CH), 95.7 (Cq), 89.5 (Cq), 25.9 (CH$_3$), 20.4 (CH$_3$), 20.4 (CH$_3$) ppm; IR (thin film): $v_{max}$ = 3076, 2970, 2928, 1598 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 222 ([M$^+$]+•, 65), 207 ([M–CH$_3$]+•, 82), 192 ([M–2×CH$_3$]+•, 100); HRMS (EI$^+$): calculated for C$_{17}$H$_{18}$: 222.1409; found: 222.1406.

(Z)-(6-Methyl-4-(prop-1-en-2-yl)hepta-3,5-dien-1-ynyl)benzene (4c-Z)

Following **Standard Procedure C**, the reaction mixture containing monobromodiene 3l (70 mg, 0.268 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (11 mg, 0.0107 mmol), t-Bu$_3$P•HBF$_4$ (6 mg, 0.021 mmol) ZnBr$_2$ (0.88 mL, 1.22 M in THF, 1.07 mmol) and isopropenyl magnesium bromide (1.6 mL, 0.49 M in THF, 0.804 mmol) in THF (3.5 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (3 g SiO$_2$, 100% PS 40–60) gave dendralene 4c-Z as a colourless liquid (42 mg, 0.189 mmol, 70%, >90% retention). R$_f$ = 0.29 (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.39 (m, 2H), 7.38 – 7.24 (m, 3H), 5.83 (s, 1H), 5.61 (s, 1H), 5.20 (s, 1H), 5.18 (s, 1H), 2.11 (s, 3H), 1.86 (s, 3H), 1.84 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.6 (Cq), 143.9 (Cq), 137.6 (Cq), 131.3 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 125.9 (CH), 124.2 (Cq), 116.6 (CH$_2$), 107.5 (CH), 95.1 (Cq), 89.1 (Cq), 27.1 (CH$_3$), 22.7 (CH$_3$), 19.7 (CH$_3$) ppm; IR (thin film): $v_{max}$ = 3079, 2969, 2911, 2190, 1684, 1598 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 222 ([M$^+$]+•, 63), 207 ([M–CH$_3$]+•, 85), 192 ([M–2×CH$_3$]+•, 100); HRMS (EI$^+$): calculated for C$_{17}$H$_{18}$: 222.1409; found: 222.1410.
A General Synthesis of Dendralenes

((1E,3E)-3-Vinylhexa-1,3-dien-5-ynediyl)dibenzene (4d-E)

Following Standard Procedure C, vinyl magnesium bromide (0.97 mL, 0.70 M in THF, 0.68 mmol), Pd(dba)$_2$-CHCl$_3$ (9 mg, 0.009 mmol), t-Bu$_3$P•HBF$_4$ (5 mg, 0.018 mmol) and ZnBr$_2$ (0.74 mL, 1.22 M in THF, 0.906 mmol) at −20 °C and brought the reaction mixture to 23 °C and stirred for 16h. After work up, purification by flash column chromatography (3 g SiO$_2$, 0.5% EtOAc in PS 40–60) gave dendralene 4d-E as a pale yellow solid (35 mg, 0.137 mmol, 60%, >95% selective retention). $R_f$ = 0.50 (5% EtOAc in PS 40–60); m.p. 64–68 °C (CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51 – 7.43 (m, 4H), 7.39 – 7.30 (m, 5H), 7.30 – 7.24 (m, 1H), 6.99 (dd, $J = 17.7, 11.1$ Hz, 1H), 6.92 (s, 2H), 5.99 (s, 1H), 5.75 (dd, $J = 17.7, 0.8$ Hz, 1H), 5.51 (d, $J = 11.2$ Hz, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.6 (Cq), 137.2 (Cq), 133.4 (CH), 131.8 (CH), 131.6 (2×CH), 128.9 (2×CH), 128.5 (2×CH), 128.4 (CH), 128.2 (CH), 127.0 (CH), 126.9 (2×CH), 123.7 (Cq), 119.2 (CH$_2$), 108.6 (CH), 98.2 (Cq), 88.3 (Cq) ppm; IR (thin film): $\nu_{max}$ = 3052, 3024, 2923, 2186, 1595 cm$^{-1}$; LRMS: (EI$^+$): $m/z$ (%): 256 ([M]$^+$, 100), 255 ([M–H]$^+$, 69), 242 ([M–CH$_3$]$^+$, 17), 229 ([M–CH$_2$CH$_2$]$^+$, 14), 179 ([M–C$_6$H$_5$]$^+$, 17); HRMS (EI$^+$): calculated for C$_{20}$H$_{16}$: 256.1252; found: 256.1251.

((1E,3Z)-3-Vinylhexa-1,3-dien-5-ynediyl)dibenzene (4d-Z)

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Following **Standard Procedure C**, the reaction mixture containing monobromodiene 3i (63 mg, 0.27 mmol), \( \text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 \) (11 mg, 0.011 mmol), \( t\text{-Bu}_3\text{P} \cdot \text{HBF}_4 \) (6 mg, 0.022 mmol) \( \text{ZnBr}_2 \) (0.88 mL, 1.23 M in THF, 1.08 mmol) and styrenyl magnesium bromide (1.4 mL, 0.58 M in THF, 0.811 mmol) in THF (4.0 mL) was stirred at 23 °C for 16h. After work up, purification by reverse phase HPLC (Phenomenex Luna 5u C18(2), 100 A, 250×10 mm, eluting with 15% water/MeCN, \( R_f = 9.6 \)) gave dendralene 4d-Z as a colourless liquid (35 mg, 0.14 mmol, 51%, >85% selective retention). \( R_f = 0.50 \) (5% EtOAc in PS 40–60); 1H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.57–7.49 (m, 4H), 7.45 (d, \( J = 16.4 \text{ Hz} \), 1H), 7.42–7.33 (m, 5H), 7.33–7.26 (m, 1H), 7.02 (d, \( J = 16.4 \text{ Hz} \), 1H), 6.66 (dd, \( J = 17.2, 10.8 \text{ Hz} \), 1H), 5.95 (s, 1H), 5.64 (dd, \( J = 17.2, 0.8 \text{ Hz} \), 1H) ppm; 13C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 146.7 (Cq), 137.3 (Cq), 135.3 (CH), 133.0 (CH), 131.5 (2×CH), 128.9 (2×CH), 128.6 (2×CH), 128.4 (CH), 128.3 (CH), 127.0 (2×CH), 125.4 (CH), 123.7 (Cq), 117.5 (CH\(_2\)), 108.4 (CH), 98.3 (Cq), 88.2 (Cq) ppm; IR (thin film): \( \nu_{\text{max}} \) = 3079, 3058, 3027, 2923, 2852, 2185, 1597 cm\(^{-1}\); LRMS: (EI\( ^+ \)): m/z (%): 256 ([M]\(^+\), 77), 255 ([M–H]\(^+\), 84), 242 ([M–CH\(_3\)]\(^+\), 19), 241 ([M–CH\(_3\)]\(^+\), 100), 229 ([M–CH\(_3\)CH\(_2\)]\(^+\), 17), 179 ([M–C\(_6\)H\(_5\)]\(^+\), 42); HRMS (EI\( ^+ \)): calculated for C\(_{20}\)H\(_{16}\): 256.1252; found: 256.1254.

$$\text{BrZnBr}_2 \quad \text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 \quad t\text{-Bu}_3\text{P} \cdot \text{HBF}_4 \quad \text{THF} \quad 0 \text{ °C} \to 23 \text{ °C, 16h}$$

(\( 1E,3E \)-3-(Prop-1-en-2-yl)hexa-1,3-dien-5-yn-1,6-diyl)dibenzene (4e-E)

Following **Standard Procedure C**, the reaction mixture containing monobromodiene 3j (71 mg, 0.287 mmol), \( \text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 \) (12 mg, 0.0115 mmol), \( t\text{-Bu}_3\text{P} \cdot \text{HBF}_4 \) (7 mg, 0.023 mmol) \( \text{ZnBr}_2 \) (0.94 mL, 1.22 M in THF, 1.15 mmol) and styrenyl magnesium bromide (1.5 mL, 0.58 M in THF, 0.862 mmol) in THF (4 mL) was stirred at 23 °C for 16h. After work up, purification by reverse phase HPLC (Phenomenex Luna 5u C18(2), 100A, 250×10 mm, eluting with 15% water/MeCN, \( R_f = 19 \text{ min} \)) gave dendralene 4e-E as a colourless liquid (35 mg, 0.13 mmol, 45%, >95% retention). \( R_f = 0.34 \) (5% EtOAc in PS 40–60);
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\[^{1}\text{H} \text{NMR (400 MHz, CDCl}_3\}] \delta 7.39 – 7.28 (m, 4H), 7.24 – 7.05 (m, 7H), 6.71 (d, J = 16.4 Hz, 1H), 5.61 (s, 1H), 5.02 (s, 1H), 4.96 (s, 1H), 1.85 (s, 3H) ppm; \[^{13}\text{C} \text{NMR (100 MHz, CDCl}_3\}] \delta 152.3 (\text{Cq}), 143.6 (\text{Cq}), 137.4 (\text{Cq}), 134.3 (\text{CH}), 131.5 (2\times \text{CH}), 128.9 (2\times \text{CH}), 128.5 (2\times \text{CH}), 128.3 (\text{CH}), 128.2 (\text{CH}), 127.0 (2\times \text{CH}), 125.6 (\text{CH}), 123.8 (\text{Cq}), 116.3 (\text{CH}_2), 107.5 (\text{CH}), 97.3 (\text{Cq}), 87.9 (\text{Cq}), 23.0 (\text{CH}_3) ppm; \text{IR (thin film): } \nu_{\text{max}} = 3078, 3026, 2187, 2919, 1596 \text{ cm}^{-1}; \text{LRMS: (EI}^+)\text{: m/z (%): 270 ([M}^{+}\text{]), 89), 269 ([M-H}^{+}\text{]), 54), 255 ([M-CH}_3}^{+}\text{], 100); HRMS (EI}^+)\text{: calculated for } \text{C}_21\text{H}_18: 270.1409; \text{found: 270.1411.}

((1E,3Z)-3-(\text{Prop-1-en-2-yl})\text{hexa-1,3-dien-5-yne-1,6-diyl})\text{dibenzene (4e-Z)}

Following Standard Procedure C, the reaction mixture containing monobromodiene 3k (70 mg, 0.226 mmol), Pd\(_2\)(dba)\(_3\) • CHCl\(_3\) (9 mg, 0.0091 mmol), t-Bu\(_3\)P • HBF\(_4\) (5 mg, 0.018 mmol) ZnBr\(_2\) (0.74 mL, 1.22 M in THF, 0.906 mmol) and isopropenyl magnesium bromide (1.3 mL, 0.51 M in THF, 0.679 mmol) in THF (3.5 mL) was stirred at 23 °C for 4h. After work up, purification by flash column chromatography (3 g SiO\(_2\), 0.5% EtOAc in PS 40 – 60) gave dendralene 4e-Z as a pale yellow solid (43 mg, 0.16 mmol, 70%, >95% retention). R\(_f\) = 0.61 (5% EtOAc in PS 40 – 60); m.p. 77 – 79 °C (hexane:EtOAc, 8:2); \[^{1}\text{H} \text{NMR (400 MHz, CDCl}_3\}] \delta 7.62 – 7.42 (m, 4H), 7.42 – 7.21 (m, 6H), 6.88 (d, J = 16.0 Hz, 1H), 6.73 (d, J = 16.0 Hz, 1H), 5.83 (s, 1H), 5.39 (s, 1H), 5.03 (s, 1H), 2.12 (s, 3H) ppm; \[^{13}\text{C} \text{NMR (100 MHz, CDCl}_3\}] \delta 154.5 (\text{Cq}), 141.7 (\text{Cq}), 137.1 (\text{Cq}), 132.5 (\text{CH}), 131.5 (2\times \text{CH}), 129.3 (\text{CH}), 128.8 (2\times \text{CH}), 128.4 (2\times \text{CH}), 128.2 (\text{CH}), 128.1 (\text{CH}), 126.9 (2\times \text{CH}), 124.0 (\text{Cq}), 116.3 (\text{CH}_2), 108.8 (\text{CH}), 96.9 (\text{Cq}), 88.8 (\text{Cq}), 22.8 (\text{CH}_3) ppm; \text{IR (thin film): } \nu_{\text{max}} = 3057, 3022, 2967, 1640, 1594 \text{ cm}^{-1}; \text{LRMS: (EI}^+)\text{: m/z (%): 270 ([M}^{+}\text{]), 91), 269 ([M-H}^{+}\text{], 50), 255 ([M-CH}_3}^{+}\text{], 100); HRMS (EI}^+)\text{: calculated for } \text{C}_21\text{H}_18: 270.1409; \text{found: 270.1410.}
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Following Standard Procedure C, the reaction mixture containing monobromodiene 3f (105 mg, 0.421 mmol), Pd(dba)\(_2\)-CHCl\(_3\) (15 mg, 0.015 mmol), t-Bu\(_3\)P•HBF\(_4\) (9 mg, 0.030 mmol) ZnBr\(_2\) (1.70 mL, 1.48 M in THF, 2.53 mmol) and vinyl magnesium bromide (2.50 mL, 0.85 M in THF, 2.11 mmol) in THF (6 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (5 g SiO\(_2\), 100% PS 40–60) gave dendrale 4f-\(E\) as a colourless liquid (65 mg, 0.331 mmol, 79%, >95% retention). R\(_f\) = 0.38 (100% PS 40–60);

\(\text{\(\delta\}}\) 7.42 (d, \(J = 7.6\) Hz, 2H), 7.32 (t, \(J = 7.6\) Hz, 2H), 7.28 – 7.18 (m, 2H), 6.69 – 6.56 (m, 2H), 6.35 (d, \(J = 11.2\) Hz, 1H), 5.45 (dd, \(J = 10.8, 1.6\) Hz, 1H), 5.30 (dd, \(J = 17.6, 1.6\) Hz, 1H), 5.09 (s, 1H), 5.07 (s, 1H), 1.99 (s, 3H) ppm; \(\text{\(\delta\}}\) 143.8 (Cq), 141.9 (Cq), 137.8 (Cq), 133.7 (CH), 133.2 (CH), 128.8 (2×CH), 127.9 (CH), 127.7 (CH), 126.6 (2×CH), 126.3 (CH), 119.8 (CH\(_2\)), 115.4 (CH\(_2\)), 21.6 (CH\(_3\)) ppm; \(v_{\text{max}}\) = 3079, 3033, 2997, 1796, 1601 cm\(^{-1}\); LRMS: (EI\(^+\)); m/z (%): 196 ([M]+, 68), 181 ([M–C\(_3\)H\(_5\)])\(^+\), 100, 167 ([M–C\(_3\)H\(_5\)])\(^+\), 155 ([M–C\(_3\)H\(_5\)])\(^+\), 21); HRMS (EI\(^+\)): calculated for C\(_{15}\)H\(_{16}\)C\(_3\)H\(_5\): 196.1252; found: 196.1251.

\((\text{\(1E,3Z\})\)-5-Methyl-4-vinylhexa-1,3,5-trien-1-yl\)benzene (4f-Z)

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S52
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Following **Standard Procedure C**, the reaction mixture containing monobromodiene 3e (106 mg, 0.451 mmol), Pd(dba)$_2$-CHCl$_3$ (14 mg, 0.0135 mmol), t-Bu$_3$P•HBF$_4$ (8 mg, 0.03 mmol) ZnBr$_2$ (1.5 mL, 1.48 M in THF, 2.25 mmol) and isopropenyl magnesium bromide (3.1 mL, 0.59 M in THF, 1.80 mmol) in THF (6 mL) was stirred at 23 °C for 5h. After work up, purification by flash column chromatography (5 g SiO$_2$, 100% PS 40–60) gave dendralene 4f-Z as a colourless liquid (65 mg, 0.331 mmol, 73%, >86% retention). $R_f$ = 0.38 (100% PS 40–60);

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.40 (d, $J$ = 7.6 Hz, 2H), 7.31 (t, $J$ = 7.6 Hz, 2H), 7.21 (t, $J$ = 7.3 Hz, 1H), 7.02 (dd, $J$ = 15.6, 11.1 Hz, 1H), 6.60 (d, $J$ = 15.6 Hz, 1H), 6.39 (dd, $J$ = 17.3, 10.5 Hz, 1H), 6.18 (d, $J$ = 11.1 Hz, 1H), 5.29 (s, 1H), 5.25 (d, $J$ = 17.3 Hz, 1H), 5.12 (d, $J$ = 10.5 Hz, 1H), 4.84 (s, 1H), 1.93 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 145.4 (Cq), 141.6 (Cq), 138.3 (CH), 137.7 (Cq), 133.3 (CH), 129.9 (CH), 128.7 (2×CH), 127.7 (CH), 126.5 (2×CH), 116.4 (CH$_2$), 115.4 (CH$_2$), 23.6 (CH$_3$) ppm; $v_{\text{max}}$ = 3081, 3029, 3000, 2969, 1809, 1643, 1599 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 196 ([M]+•, 90), 181 ([M−CH$_3$]+•, 100), 166 ([M−CH$_2$CH$_2$H]+•, 55), 165 ([M−C$_2$H$_7$]+•, 68) 155 ([M−C$_3$H$_5$]+•, 21); HRMS (EI$^+$): calculated for C$_{15}$H$_{16}$: 196.1252; found: 196.1254.

1-Methoxy-4-((E)-3-methyl-2-((E)-styryl)buta-1,3-dien-1-yl)benzene (4g-E)

Following **Standard Procedure C**, the reaction mixture containing monobromodiene 3b (90 mg, 0.36 mmol), Pd(dba)$_2$-CHCl$_3$ (15 mg, 0.014 mmol), t-Bu$_3$P•HBF$_4$ (8 mg, 0.03 mmol) ZnBr$_2$ (1.2 mL, 1.22 M in THF, 1.42 mmol) and styrenyl magnesium bromide (1.9 mL, 0.56 M in THF, 1.07 mmol) in THF (5 mL) was stirred at 23 °C for 16h. After work up, purification by reverse phase HPLC (Phenomenex Luna 5u C18(2) 100A 250×10 mm, eluting with 15% water/McCN, $t_r$ = 14.9 min) gave dendralene 4g-E as a colourless liquid (30 mg, 0.109 mmol, 30%, >90% retention). $R_f$ = 0.49 (5% EtOAc in PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, $J$ = 7.2 Hz, 2H), 7.36 – 7.29 (m, 4H), 7.27 – 7.21 (m, 1H), 7.11 (d, $J$ = 16.4 Hz, 1H), 6.90 (d, $J$ = 8.4 Hz, 2H), 6.66 (d, $J$ = 16.4 Hz, 1H), 6.54 (s, 1H), 5.14 (s, 2H), 3.84 (s, 3H), 2.04 (s, 3H) ppm;
Following **Standard Procedure C**, the reaction mixture containing monobromodiene 3c (200 mg, 0.634 mmol), Pd\(_2\)(dba)\(_3\)•CHCl\(_3\) (26 mg, 0.025 mmol), \(\text{t-Bu}_3\text{P} \cdot \text{HBF}_4\) (15 mg, 0.051 mmol) ZnBr\(_2\) (2.1 mL, 1.23 M in THF, 2.54 mmol) and isopropenyl magnesium bromide (3.7 mL, 0.51 M in THF, 1.90 mmol) in THF (10 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (8 g SiO\(_2\), 1% EtOAc in PS 40–60) gave dendralene 4g-Z as a colourless solid (160 mg, 0.579 mmol, 91%, >95% retention). R\(_f\) = 0.36 (5% EtOAc in PS 40–60); m.p. 79 – 82 °C (hexane:CH\(_2\)Cl\(_2\), 9:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.52 (d, \(J = 8.5\) Hz, 2H), 7.44 (d, \(J = 7.6\) Hz, 2H), 7.32 (t, \(J = 7.6\) Hz, 2H), 7.25 – 7.18 (m, 1H), 6.91 (d, \(J = 15.8\) Hz, 1H), 6.86 (d, \(J = 8.5\) Hz, 2H), 6.60 (d, \(J = 15.8\) Hz, 1H), 6.40 (s, 1H), 5.38 (s, 1H), 5.00 (s, 1H), 3.82 (s, 1H), 1.97 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.9 (Cq), 142.7 (Cq), 141.5 (Cq), 137.9 (Cq), 132.7 (CH), 130.5 (2×CH), 129.9 (Cq), 129.3 (CH), 128.8 (CH), 128.7 (2×CH), 127.3 (CH), 126.5 (2×CH), 116.8 (CH\(_2\)), 113.9 (2×CH), 55.4 (CH\(_3\)), 22.8 (CH\(_3\)) ppm; IR (thin film): \(\nu_{max}\) = 3081, 3012, 2959, 2835, 1601, 1507 cm\(^{-1}\); LRMS: (EI\(^+\)): m/z (%): 276 ([M]\(^+\), 75), 261 ([M-CH\(_3\)]\(^+\), 45), 246 ([M-2×CH\(_3\)]\(^+\), 15), 121 (100); HRMS (EI\(^+\)): calculated for C\(_{20}\)H\(_{20}\)O: 276.1514; found: 276.1516.
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1-Methoxy-4-((Z)-4-methyl-2-((E)-styryl)penta-1,3-dien-1-yl)benzene (4h-Z)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3c (60 mg, 0.19 mmol), Pd$_2$(dba)$_3$-CHCl$_3$ (6 mg, 0.0057 mmol), t-Bu$_3$P•HBF$_4$ (4 mg, 0.013 mmol) ZnBr$_2$ (0.62 mL, 1.23 M in THF, 0.761 mmol) and isobutenyl magnesium bromide (1.3 mL, 0.44 M in THF) in THF (3 mL) was stirred at 23 °C for 4h. After workup, purification by flash column chromatography (3 g SiO$_2$, 2% EtOAc in PS 40–60) gave dendralene 4h-Z as a white solid (52 mg, 0.179 mmol, 94%, >95% retention). R$_f$ = 0.46 (5% EtOAc in PS 40–60); m.p. 74–78 °C (hexane); $^1$H NMR (400 MHz, (CD$_3$)$_2$SO) δ 7.50–7.46 (m, 4H), 7.33 (t, J = 7.6 Hz, 2H), 7.24–7.20 (m, 1H), 7.05 (d, J = 16.0 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.64 (s, 1H), 6.46 (d, J = 16.0 Hz, 1H), 5.93 (s, 1H), 3.77 (s, 3H), 1.92 (d, J = 1.2 Hz, 3H), 1.44 (d, J = 0.8 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, (CD$_3$)$_2$SO) δ 158.3 (Cq), 137.4 (Cq), 136.5 (Cq), 135.2 (Cq), 133.1 (Cq), 131.4 (CH), 130.2 (2×CH), 130.1 (Cq), 128.7 (2×CH), 128.1 (CH), 127.1 (CH), 126.2 (2×CH), 120.7 (CH), 113.8 (2×CH), 55.1 (CH$_3$), 25.1 (CH$_3$), 19.4 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}}$ = 3022, 2930, 1599, 1505 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 290 ([M$^+$]$, 100$; HRMS (EI$^+$): calculated for C$_{21}$H$_{22}$O: 290.1671; found: 290.1674.

1-Methoxy-4-((1E,3E)-4-phenyl-2-vinylbuta-1,3-dien-1-yl)benzene (4i-E)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3c (50 mg, 0.16 mmol), Pd$_2$(dba)$_3$-CHCl$_3$ (5 mg, 0.005 mmol), t-Bu$_3$P•HBF$_4$ (3 mg, 0.0095 mmol) ZnBr$_2$ (0.77 mL, 1.23 M in THF, 0.952 mmol) and vinyl magnesium bromide (1.2 mL, 0.68 M in THF) was stirred at 0–66 °C for 8h. After workup, purification by flash column chromatography (3 g SiO$_2$, 5% EtOAc in PS 40–60) gave dendralene 4i-E as a white solid (26 mg, 0.086 mmol, 58%, >95% retention). R$_f$ = 0.46 (5% EtOAc in PS 40–60); m.p. 89–91 °C (hexane); $^1$H NMR (400 MHz, (CD$_3$)$_2$SO) δ 7.50–7.46 (m, 4H), 7.33 (t, J = 7.6 Hz, 2H), 7.24–7.20 (m, 1H), 7.05 (d, J = 16.0 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.64 (s, 1H), 6.46 (d, J = 16.0 Hz, 1H), 5.93 (s, 1H), 3.77 (s, 3H), 1.92 (d, J = 1.2 Hz, 3H), 1.44 (d, J = 0.8 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, (CD$_3$)$_2$SO) δ 158.3 (Cq), 137.4 (Cq), 136.5 (Cq), 135.2 (Cq), 133.1 (Cq), 131.4 (CH), 130.2 (2×CH), 130.1 (Cq), 128.7 (2×CH), 128.1 (CH), 127.1 (CH), 126.2 (2×CH), 120.7 (CH), 113.8 (2×CH), 55.1 (CH$_3$), 25.1 (CH$_3$), 19.4 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}}$ = 3022, 2930, 1599, 1505 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 290 ([M$^+$]$, 100$; HRMS (EI$^+$): calculated for C$_{21}$H$_{22}$O: 290.1671; found: 290.1674.
mmol) in THF (2.5 mL) was stirred at 66 °C for 8h. After work up, purification by flash column chromatography (3 g SiO2, 1.5% EtOAc in PS 40–60) gave dendralene 4i-E as a colourless liquid (30 mg, 0.114 mmol, 72%, >95% retention). \( R_f = 0.43 \) (5% EtOAc in PS 40–60); 
\(^1^H\) NMR (400 MHz, CDCl₃) \( \delta \) 7.46 (d, \( J = 7.5 \text{ Hz}, 2\text{H} \)), 7.40 – 7.29 (m, 4H), 7.29 – 7.19 (m, 1H), 6.99 – 6.82 (m, 4H), 6.75 (dd, \( J = 17.9, 11.2 \text{ Hz}, 1\text{H} \)), 6.70 (s, 1H), 5.51 (dd, \( J = 17.8, 1.5 \text{ Hz}, 1\text{H} \)), 5.43 (d, \( J = 11.1 \text{ Hz}, 1\text{H} \)), 3.83 (s, 3H) ppm; 
\(^{13}^C\) NMR (100 MHz, CDCl₃) \( \delta \) 158.9 (Cq), 137.8 (Cq), 136.3 (Cq), 134.4 (CH), 131.2 (2×CH), 130.6 (CH), 130.2 (CH), 130.1 (Cq), 129.7 (CH), 128.8 (2×CH), 127.5 (CH), 126.6 (2×CH), 118.6 (CH₂), 113.8 (2×CH), 54.4 (CH₂) ppm; IR (thin film): \( \nu_{max} = 3026, 2929, 2835, 1701, 1602, 1507 \text{ cm}^{-1} \); LRMS: (EI⁺): m/z (%): 262 ([M]+•, 100), 247 ([M–CH₃]+•, 13), 231 ([M–OCH₃]+•, 17); HRMS (EI⁺): calculated for C₁₉H₁₈O: 262.1358; found: 262.1360.

Following Standard Procedure C, the reaction mixture containing monobromodiene 3f (92 mg, 0.37 mmol), Pd₂(dba)₃•CHCl₃ (12 mg, 0.011 mmol), t-Bu₃P•HBF₄ (78 mg, 0.026 mmol) ZnBr₂ (1.2 mL, 1.23 M in THF, 1.48 mmol) and isobutenyl magnesium bromide (2.5 mL, 0.44 M in THF, 1.11 mmol) in THF (5 mL) was stirred at 23 °C for 4h. After work up, purification by flash column chromatography (3 g SiO₂, 100% PS 40–60) gave dendralene 4j-E as a colourless liquid (50 mg, 0.223 mmol, 60%, >90% retention). \( R_f = 0.44 \) (100% PS 40–60); \(^1^H\) NMR (400 MHz, CDCl₃) \( \delta \) 7.44 – 7.36 (m, 2H), 7.36 – 7.27 (m, 2H), 7.25 – 7.17 (m, 1H), 6.92 (dd, \( J = 15.6, 10.8 \text{ Hz}, 1\text{H} \)), 6.65 (d, \( J = 15.6 \text{ Hz}, 1\text{H} \)), 6.39 (d, \( J = 10.8 \text{ Hz}, 1\text{H} \)), 5.81 (s, 1H), 5.11 (d, \( J = 2.0 \text{ Hz}, 1\text{H} \)), 5.00 (s, 1H), 2.00 (s, 3H), 1.93 (d, \( J = 1.4 \text{ Hz}, 3\text{H} \)), 1.54 (d, \( J = 1.1 \text{ Hz}, 3\text{H} \) ppm); 
\(^{13}^C\) NMR (100 MHz, CDCl₃) \( \delta \) 143.3 (Cq), 140.8 (Cq), 138.1 (Cq), 136.9 (Cq), 132.8 (CH), 128.7 (2×CH), 128.1 (CH), 127.5 (CH), 127.2 (CH), 126.4 (2×CH), 121.9 (CH), 115.3 (CH₂), 25.5 (CH₃), 20.6 (CH₃), 19.7 (CH₃) ppm; IR (thin film): \( \nu_{max} = 3030, 2968, 2910, 2855, 1789, 1601 \text{ cm}^{-1} \); LRMS: (EI⁺): m/z (%):
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(E)-2-Methyl-3-vinyltetradeca-1,3-diene (4k-E)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3p (70 mg, 0.244 mmol), Pd₂(dba)₃–CHCl₃ (10 mg, 0.010 mmol), t-Bu₃P•HBF₄ (6 mg, 0.019 mmol) ZnBr₂ (1.0 mL, 1.22 M in THF, 1.22 mmol) and vinyl magnesium bromide (1.4 mL, 0.70 M in THF, 0.975 mmol) in THF (4 mL) was stirred at 66 °C for 16 h. After work up, purification by flash column chromatography (3 g SiO₂, 100% PS 40–60) gave dendralene 4k-E as a colourless liquid (34 mg, 0.145 mmol, 60%, >90% retention). Rₛ = 0.67 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 6.46 (dd, J = 17.6, 11.2 Hz, 1H), 5.53 (t, J = 7.5 Hz, 1H), 5.25 (d, J = 11.2 Hz, 1H), 5.16 (dd, J = 17.6, 2.0 Hz, 1H), 4.94 (s, 1H), 4.91 (s, 1H), 2.18 (q, J = 7.4 Hz, 2H), 1.89 (s, 3H), 1.50 – 1.18 (m, 16H), 0.88 (t, J = 6.6 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 144.8 (Cq), 140.7 (Cq), 132.9 (CH), 130.2 (CH), 117.4 (CH₂), 113.7 (CH₂), 32.1 (CH₂), 30.0 (CH₂), 29.8 (2×CH₂), 29.7 (CH₂), 29.5 (CH₂), 28.6 (CH₂), 22.9 (CH₂), 22.2 (CH₃), 14.3 (CH₃) ppm; IR (thin film): νmax = 2955, 2923, 2853, 1631, 1456 cm⁻¹; LRMS: (EI⁺): m/z (%): 234 ([M]⁺, 8), 219 ([M–CH₃]⁺, 8), 79 (100); HRMS (EI⁺): calculated for C₁₇H₃₀: 234.2348; found: 234.2356.

((1E,3Z,5E)-3-(Prop-1-en-2-yl)hexa-1,3,5-triene-1,6-diyl)dibenzene (4l-Z)
Following Standard Procedure C, the reaction mixture containing monobromodiene 3g (200 mg, 0.643 mmol), Pd\(_2\)(dba)\(_3\)-CHCl\(_3\) (27 mg, 0.026 mmol), i-But$_3$P-HBF\(_4\) (15 mg, 0.051 mmol) ZnBr\(_2\) (2.1 mL, 1.22 M in THF, 2.57 mmol) and isopropenyl magnesium bromide (3.8 mL, 0.51 M in THF, 1.93 mmol) in THF (10 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (6 g SiO$_2$, 0.75% EtOAc in PS 40–60) gave dendralene 4l-Z as a yellow solid (125 mg, 0.459 mmol, 71%, >90% retention). R$_f$ = 0.53 (5% EtOAc in PS 40–60); m.p. 141 – 143 °C (hexane:CH$_2$Cl$_2$, 8:2); \(^1\)H NMR (400 MHz, CDCl$_3$) \(\delta\) 7.48 – 7.40 (m, 4H), 7.36 – 7.29 (m, 4H), 7.25 – 7.19 (m, 2H), 7.08 (dd, \(J = 15.6\), 11.2 Hz, 1H), 6.84 (d, \(J = 16.0\) Hz, 1H), 6.63 (d, \(J = 15.6\) Hz, 1H), 6.58 (d, \(J = 16.0\) Hz, 1H), 6.32 (d, \(J = 11.2\) Hz, 1H), 5.37 (s, 1H), 4.92 (s, 1H), 2.01 (s, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl$_3$) \(\delta\) 145.4 (Cq), 141.9 (Cq), 137.8 (Cq), 137.7 (Cq), 133.2 (CH), 130.6 (CH), 130.5 (CH), 130.2 (CH), 128.8 (4\(\times\)CH), 127.7 (CH), 127.5 (CH), 126.7 (CH), 126.7 (2\(\times\)CH), 126.6 (2\(\times\)CH), 116.6 (CH$_2$), 23.9 (CH$_3$) ppm; IR (thin film): \(v_{\text{max}}\) = 3058, 3022, 2961, 2936, 1880, 1813, 1593 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 272 ([M$^+$]+, 100), 257 ([M–CH$_3$]+, 17); HRMS (EI$^+$): calculated for C$_{21}$H$_{20}$: 272.1565; found: 272.1566.

Standard Procedure D: Second Cross-Coupling with PdCl$_2$(dppf)-Toluene (Inversion)

\[
\begin{align*}
\text{R}^1 & \text{Br} \quad \rightarrow \quad \text{R}^2 \\
\text{ZnBr}_2 & \text{PdCl}_2\text{(dppf)}\text{-tol} \\
0 \text{ °C – 23 °C, 16h} & \text{THF} \\
\text{R}^1 & \text{MgBr} \\
\text{R}^2 & \text{R}^1
\end{align*}
\]

1,1'-Bis(diphenylphosphino)ferrocene palladium(II) chloride•toluene (3 – 5 mol%) and monobromodiene (1.0 mol equiv) in THF (50 mL/g monobromodiene precursor) was purged with N$_2$ for 5 minutes. The reaction mixture was cooled to 0 °C, ZnBr$_2$ (4.0 – 10.0 mol equiv, 0.96 – 1.23 M solution in THF) was added, followed by dropwise addition of the Grignard reagent (3.0 – 8.0 mol equiv, 0.46 – 0.86 M solution in THF) over 5 minutes. The resulting heterogeneous reaction mixture was warmed to room temperature and stirred for 16h until complete by \(^1\)H NMR analysis. Saturated aqueous NH$_4$Cl (5 mL/g monobromodiene precursor) was added, the reaction mixture was filtered through a pad of Celite, then the filtrate was diluted with CH$_2$Cl$_2$ (50 mL/g monobromodiene precursor) and water (100 mL/g monobromodiene precursor). The aqueous and organic layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (10 mL/g...
monobromodiene precursor $\times 3$. The combined organic layer was washed with saturated brine (20 mL/g monobromodiene precursor), dried over Na$_2$SO$_4$ and concentrated under reduced pressure.

**(E)-(3-Methyl-2-vinylbuta-1,3-dien-1-yl)cyclohexane (4m-E)**

Following **Standard Procedure D**, the reaction mixture containing monobromodiene 3m (67 mg, 0.31 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (10 mg, 0.013 mmol) ZnBr$_2$ (1.1 mL, 1.09 M in THF, 1.25 mmol) and isopropenyl magnesium bromide (2.0 mL, 0.46 M in THF, 0.934 mmol) in THF (3.5 mL) was stirred at 23 °C for 4h. After work up, purification by flash column chromatography (3 g SiO$_2$, 100% PS 40–60) gave dendralene 4m-E as a colourless liquid (31 mg, 0.18 mmol, 57%, >95% inversion). $R_f = 0.63$ (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.48 (dd, $J = 17.6, 10.8$ Hz, 1H), 5.34 (d, $J = 9.2$ Hz, 1H), 5.23 (d, $J = 10.8$ Hz, 1H), 5.18 (dd, $J = 17.6, 2.0$ Hz, 1H), 4.94 (s, 1H), 4.90 (s, 1H), 2.57 – 2.26 (m, 1H), 1.88 (s, 3H), 1.79 – 1.58 (m, 5H), 1.40 – 1.00 (m, 5H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.8 (Cq), 139.1 (Cq), 135.8 (CH), 133.1 (CH), 117.1 (CH$_2$), 113.9 (CH$_2$), 37.3 (CH), 33.4 ($2 \times$CH$_2$), 26.2 (CH$_3$), 26.0 ($2 \times$CH$_2$), 22.2 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}}$ = 3084, 2922, 2850, 1630 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 176 ([M$^+$]$,^+$, 31), 161 ([M–CH$_3$]$^+$, 41), 147 ([M–CH$_3$CH$_2$]$^+$, 30), 91 (100); HRMS (EI$^+$): calculated for C$_{13}$H$_{20}$: 176.1565; found: 176.1569.

**(Z)-(3-Methyl-2-vinylbuta-1,3-dien-1-yl)cyclohexane (4m-Z)**

Following **Standard Procedure D**, the reaction mixture containing monobromodiene 3n (110 mg, 0.48 mmol), 1,1'-bis(diphenyolphosphino)ferrocene palladium(II) chloride-toluene (20 mg, 0.024 mmol), ZnBr$_2$ (3.0 mL, 0.96 M in THF, 2.88 mmol) and vinyl magnesium bromide (3.2 mL, 0.75 M in THF, 2.40 mmol) in THF (5.5 mL) was stirred at 23 °C for 16h. After work up,
purification by flash column chromatography (4 g SiO$_2$, 100% PS 40–60) gave dendralene 4m-Z as a colourless liquid (35 mg, 0.199 mmol, 41%, >95% inversion). R$_f$ = 0.71 (100% PS 40–60);

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.30 (dd, $J$ = 17.6, 10.8 Hz, 1H), 5.24 (d, $J$ = 10.0 Hz, 1H), 5.12 (s, 1H), 5.06 (d, $J$ = 17.6 Hz, 1H), 4.95 (d, $J$ = 10.8 Hz, 1H), 4.69 (s, 1H), 2.30 – 2.16 (m, 1H), 1.84 (s, 3H), 1.75 – 1.55 (m, 5H), 1.33 – 1.00 (m, 5H) ppm;

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 142.1 (Cq), 141.5 (Cq), 139.1 (CH), 137.7 (CH), 114.8 (CH$_2$), 113.0 (CH$_2$), 38.1 (CH), 33.4 (2 × CH$_2$), 26.2 (CH$_2$), 25.9 (2 × CH$_2$), 23.7 (CH$_3$) ppm;

IR (thin film): $\nu_{\text{max}}$ = 2922, 2850, 1726, 1448 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 176 ([M]$^+$, 31), 161 ([M – CH$_3$]$^+$, 44), 147 ([M – CH$_3$CH$_2$]$^+$, 20), 91 (100); HRMS (EI$^+$): calculated for C$_{13}$H$_{20}$: 176.1565; found: 176.1569.

(E)-2-Methyl-3-vinyldodeca-1,3-diene (4k-E)

Following Standard Procedure D, the reaction mixture containing monobromodiene 3o (100 mg, 0.366 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (9 mg, 0.015 mmol) ZnBr$_2$ (1.5 mL, 1.22 M in THF, 1.83 mmol) and isopropenyl magnesium bromide (3.2 mL, 0.46 M in THF, 1.46 mmol) in THF (5.0 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (5 g SiO$_2$, 100% PS 40–60) gave dendralene 4k-E as a colourless liquid (70 mg, 0.30 mmol, 82%, >95% inversion). R$_f$ = 0.67 (100% PS 40–60);

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.46 (dd, $J$ = 17.6, 11.2 Hz, 1H), 5.53 (t, $J$ = 7.5 Hz, 1H), 5.25 (d, $J$ = 11.2 Hz, 1H), 5.16 (dd, $J$ = 17.6, 2.0 Hz, 1H), 4.94 (s, 1H), 4.91 (s, 1H), 2.18 (q, $J$ = 7.4 Hz, 2H), 1.89 (s, 3H), 1.50 – 1.18 (m, 16H), 0.88 (t, $J$ = 6.6 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.8 (Cq), 140.7 (Cq), 132.9 (CH), 130.2 (CH), 117.4 (CH$_2$), 113.7 (CH$_2$), 32.1 (CH$_2$), 30.0 (CH$_2$), 29.8 (2 × CH$_2$), 29.7 (CH$_2$), 29.5 (CH$_2$), 28.6 (CH$_2$), 22.9 (CH$_2$), 22.2 (CH$_2$), 14.3 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}}$ = 2955, 2923, 2853, 1631, 1456 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 234 ([M]$^+$, 8), 219 ([M – CH$_3$]$^+$, 8), 79 (100); HRMS (EI$^+$): calculated for C$_{17}$H$_{32}$: 234.2348; found: 234.2356.
Following **Standard Procedure D**, the reaction mixture containing monobromodiene 3p (110 mg, 0.383 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (13 mg, 0.015 mmol) ZnBr₂ (3.1 mL, 1.22 M in THF, 3.83 mmol) and vinyl magnesium bromide (4.1 mL, 0.75 M in THF, 3.06 mmol) in THF (5.5 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (6 g SiO₂, 100% PS 40–60) gave dendralene 4k-Z as a colourless liquid (62 mg, 0.26 mmol, 69%, >95% inversion). Rf = 0.67 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 6.29 (dd, J = 17.2, 10.4 Hz, 1H), 5.42 (t, J = 7.5 Hz, 1H), 5.14 (s, 1H), 5.06 (d, J = 17.2 Hz, 1H), 4.95 (d, J = 10.4 Hz, 1H), 4.69 (s, 1H), 2.08 (q, J = 7.3 Hz, 2H), 1.85 (s, 3H), 1.26 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 143.3 (Cq), 141.9 (Cq), 138.9 (CH), 132.1 (CH), 115.0 (CH₂), 112.8 (CH₂), 32.1 (CH₂), 30.0 (CH₂), 29.8 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.1 (CH₂), 23.3 (CH₂), 22.9 (CH₂), 14.3 (CH₃) ppm; IR (thin film): v max = 2956, 2922, 2853, 1804, 1624 cm⁻¹; LRMS: (EI⁺): m/z (%): 234 ([M⁺]⁺, 6), 219 ([M-CH₃]⁺, 6), 79 (100); HRMS (EI⁺): calculated for C₁₇H₃₀: 234.2348; found: 234.2351.

**((Z)-2-Methyl-3-vinyltetradeca-1,3-diene (4k-Z))**

Following **Standard Procedure D**, the reaction mixture containing monobromodiene 3p (110 mg, 0.383 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (13 mg, 0.015 mmol) ZnBr₂ (3.1 mL, 1.22 M in THF, 3.83 mmol) and vinyl magnesium bromide (4.1 mL, 0.75 M in THF, 3.06 mmol) in THF (5.5 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (6 g SiO₂, 100% PS 40–60) gave dendralene 4k-Z as a colourless liquid (62 mg, 0.26 mmol, 69%, >95% inversion). Rf = 0.67 (100% PS 40–60); ¹H NMR (400 MHz, CDCl₃) δ 6.29 (dd, J = 17.2, 10.4 Hz, 1H), 5.42 (t, J = 7.5 Hz, 1H), 5.14 (s, 1H), 5.06 (d, J = 17.2 Hz, 1H), 4.95 (d, J = 10.4 Hz, 1H), 4.69 (s, 1H), 2.08 (q, J = 7.3 Hz, 2H), 1.85 (s, 3H), 1.26 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 143.3 (Cq), 141.9 (Cq), 138.9 (CH), 132.1 (CH), 115.0 (CH₂), 112.8 (CH₂), 32.1 (CH₂), 30.0 (CH₂), 29.8 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.1 (CH₂), 23.3 (CH₂), 22.9 (CH₂), 14.3 (CH₃) ppm; IR (thin film): v max = 2956, 2922, 2853, 1804, 1624 cm⁻¹; LRMS: (EI⁺): m/z (%): 234 ([M⁺]⁺, 6), 219 ([M-CH₃]⁺, 6), 79 (100); HRMS (EI⁺): calculated for C₁₇H₃₀: 234.2348; found: 234.2351.

**((E)-1-Methoxy-4-(3-methyl-2-vinylbuta-1,3-dien-1-yl)benzene (4n-E))**

Following **Standard Procedure D**, isopropenyl magnesium bromide (12.8 mL, 0.56 M in THF, 7.19 mmol) was added to the reaction mixture containing monobromodiene 3a (430 mg, 1.80 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II) chloride-toluene (74 mg, 0.09 mmol) and ZnBr₂ (7.9 mL, 1.14 M in THF, 8.99 mmol) at −78 °C. The reaction mixture was warmed to 23 °C and continued stirring for 16h. After work up, purification by flash column chromatography
(15 g SiO$_2$, 1% EtOAc in PS 40–60) gave dendralene 4n-$E$ as a colourless liquid (266 mg, 1.33 mmol, 74%, >95% inversion). $R_f$ = 0.51 (5% EtOAc in PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.29 ($d, J = 8.8$ Hz, 2H), 6.87 ($d, J = 8.8$ Hz, 2H), 6.46 ($s, 1H$), 5.34 ($s, 1H$), 5.09 ($s, 1H$), 5.07 ($s, 1H$), 3.82 ($s, 3H$), 1.98 ($s, 3H$) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.6 (Cq), 145.4 (Cq) 141.3 (Cq), 133.7 (CH), 131.1 (2×CH), 130.1 (Cq), 127.4 (CH), 118.8 (CH$_2$), 115.2 (CH$_2$), 113.6 (2×CH), 55.4 (CH$_3$), 22.4 (CH$_3$) ppm; IR (thin film): $\nu$ _max_ = 2952, 2835, 1605, 1508 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 200 ([M]+•, 64), 199 ([M–H]+•, 25), 185 ([M–CH$_3$]+•, 100); HRMS (EI$^+$): calculated for C$_{14}$H$_{16}$O: 200.1201; found: 200.1204.

(3Z)-1-Methoxy-4-(3-methyl-2-vinylbuta-1,3-dien-1-yl)benzene (4n-$Z$)

Following Standard Procedure D, the reaction mixture containing monobromodiene 3b (90 mg, 0.356 mmol), 1,1’-bis(diphenylphosphino)ferrocene palladium(II) chloride (15 mg, 0.018 mmol) and vinyl magnesium bromide (2.5 mL, 0.86 M in THF) was stirred at 23 °C 16h. After work up, purification by flash column chromatography (3 g SiO$_2$, 1% EtOAc in PS 40–60) gave dendralene 4n-$Z$ as a colourless liquid (40 mg, 0.20 mmol, 56%, >95% inversion). $R_f$ = 0.56 (5% EtOAc in PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.47 ($d, J = 8.8$ Hz, 2H), 6.84 ($d, J = 8.8$ Hz, 2H), 6.46 ($d, J = 16.8$, 10.4 Hz, 1H), 6.26 ($s, 1H$), 5.33 – 5.22 (m, 2H), 5.08 ($d, J = 10.4$ Hz, 1H), 4.91 ($s, 1H$), 3.81 ($s, 3H$), 1.90 ($s, 3H$) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.8 (Cq), 142.0 (Cq), 141.6 (Cq), 140.2 (CH), 130.4 (2×CH), 129.7 (Cq), 128.8 (CH), 116.5 (CH$_2$), 114.0 (CH$_2$), 113.8 (2×CH), 55.4 (CH$_3$), 22.6 (CH$_3$) ppm; IR (thin film): $\nu$ _max_ = 3078, 3002, 2961, 2835, 1595, 1507 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 200 ([M]$,^+$, 41), 185 ([M–CH$_3$]$,^+$, 100), 170 ([M–2×CH$_3$]$,^+$, 29), 154 ([M–OCH$_3$CH$_3$]$,^+$, 21); HRMS (EI$^+$): calculated for C$_{14}$H$_{16}$O: 200.1201; found: 200.1199.
A General Synthesis of Dendralenes

One flask synthesis of the geometrical isomers

Following Standard Procedure B, the reaction mixture containing dibromide 1k (154 mg, 0.539 mmol), Pd(PPh₃)₄ (19 mg, 0.016 mmol) ZnBr₂ (0.67 mL, 1.23 M in THF, 0.808 mmol) and isopropenyl magnesium bromide (1.3 mL, 0.49 M in THF, 0.646 mmol) in THF (10 mL) was stirred at 23 °C for 4 h. To the above reaction mixture, Pd₂(dba)₃-CHCl₃ (22 mg, 0.022 mmol), t-Bu₃P•HBF₄ (13 mg, 0.043 mmol) ZnBr₂ (1.7 mL, 1.23 M in THF, 2.15 mmol) and vinyl magnesium bromide (2.3 mL, 0.70 M in THF, 1.62 mmol) were added at 0 °C and the reaction mixture was stirred at 23 °C for 16 h. After work up, purification by flash column chromatography (10 g SiO₂, 100% PS 40–60) gave dendralene 4a-E as a pale yellow liquid (75 mg, 0.39 mmol, 72%, isomer ratio 95:5).

Following Standard Procedure B, the reaction mixture containing dibromide 1k (110 mg, 0.385 mmol), Pd(PPh₃)₄ (13 mg, 0.012 mmol) ZnBr₂ (0.47 mL, 1.22 M in THF, 0.577 mmol) and vinyl magnesium bromide (0.63 mL, 0.73 M in THF, 0.462 mmol) in THF (10 mL) was stirred at 23 °C for 4 h. To the above reaction mixture, Pd₂(dba)₃-CHCl₃ (12 mg, 0.12 mmol), t-Bu₃P•HBF₄ (8 mg, 0.027 mmol) ZnBr₂ (1.3 mL, 1.22 M in THF, 1.54 mmol) and isopropenyl magnesium bromide (2.3 mL, 0.51 M in THF, 1.15 mmol) were added at 0 °C and stirred for the reaction mixture at 23 °C for 16 h. After work up, purification by flash column chromatography (10 g SiO₂, 100% PS 40–60) gave monobromodiene 4a-Z as a pale yellow liquid (50 mg, 0.257 mmol, 67%, isomer ratio 90:10).
A General Synthesis of Dendralenes

((1E,3Z)-5-Methylene-4-(prop-1-en-2-yl)hepta-1,3,6-trien-1-yl)benzene (10a-Z)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3f (80 mg, 0.321 mmol), Pd2(dba)3-CHCl3 (13 mg, 0.013 mmol), t-Bu3P•HBF4 (8 mg, 0.026 mmol) ZnBr2 (1.0 mL, 1.23 M in THF, 1.28 mmol) and chloroprene grignard reagent (1.3 mL, 0.75 M in THF, 0.963 mmol) in THF (4 mL) was stirred at 23 °C for 16h. After work up, purification by flash column chromatography (3 g SiO2, 100% PS 40–60) gave dendralene 10a-Z as a colourless liquid (53 mg, 0.24 mmol, 74%, >95% retention). Rf = 0.36 (100% PS 40–60);

1H NMR (400 MHz, (CD3)2CO) δ 7.41 (d, J = 7.2 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.28 – 7.16 (m, 1H), 6.91 (dd, J = 15.6, 10.8 Hz, 2H), 6.74 (d, J = 15.6 Hz, 1H), 6.65 – 6.54 (m, 2H), 5.56 (s, 1H), 5.15 – 5.00 (m, 5H), 2.05 (s, 3H) ppm; 13C NMR (100 MHz, (CD3)2CO) δ 146.7 (Cq), 142.9 (Cq), 142.6 (Cq), 138.9 (CH), 138.5 (Cq), 134.4 (CH), 129.5 (2×CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.2 (2×CH), 120.1 (CH2), 117.0 (CH2), 116.4 (CH2), 20.4 (CH3) ppm; IR (thin film): v_{max} = 3083, 3033, 2980, 1944, 1795, 1591 cm\(^{-1}\); LRMS: (EI\(^+\)): m/z (%): 222 ([M\(^+\)], 100), 207 ([M–CH3\(^+\)], 63), 192 ([M–CH2CH3\(^+\)], 30); HRMS (EI\(^+\)): calculated for C17H18: 222.1409; found: 222.1408.

(Z)-(5-Methylene-4-vinylhepta-3,6-dien-1-yn-1-yl)benzene (10b-Z)

Following Standard Procedure C, the reaction mixture containing monobromodiene 3i (55 mg, 0.236 mmol), Pd2(dba)3-CHCl3 (10 mg, 0.0094 mmol), t-Bu3P•HBF4 (6 mg, 0.019 mmol) ZnBr2

S64
(0.77 mL, 1.23 M in THF, 0.94 mmol) and chloroprene grignard reagent (0.94 mL, 0.75 M in THF, 0.71 mmol) in THF (3 mL) was stirred at 0 °C for 3 h. After work up, purification by flash column chromatography (3 g SiO2, 100% PS 40–60) gave dendralene 10b-Z as a colourless liquid (33 mg, 0.160 mmol, 68%, >95% retention). Rf = 0.58 (5% EtOAc in PS 40–60); 1H NMR (400 MHz, (CD3)2CO) δ 7.39 – 7.30 (m, 5H), 6.62 (dd, J = 17.2, 10.4 Hz, 1H), 6.54 (dd, J = 16.8, 11.2 Hz, 1H), 6.03 (s, 1H), 5.26 (d, J = 17.2 Hz, 1H), 5.20 (d, J = 10.4 Hz, 1H), 5.12 (s, 1H), 5.11 – 5.07 (m, 2H) ppm; 13C NMR (100 MHz, (CD3)2CO) δ 151.6 (Cq), 145.0 (Cq), 138.3 (CH), 137.5 (CH), 132.1 (2×CH), 129.4 (2×CH), 129.2 (CH), 124.5 (Cq), 119.6 (CH2), 118.5 (CH2), 116.6 (CH2), 112.0 (CH), 96.8 (Cq), 88.7 (Cq) ppm; IR (thin film): νmax = 3089, 3006, 2193, 1822, 1595 cm−1; LRMS: (EI+): m/z (%): 206 ([M]+•, 50), 205 ([M–H]+•, 100), 191 ([M–CH3]+•, 100), 179 ([M–C2H5]+•, 31), 165 ([M–C3H7]+•, 84), 152 ([M–C4H6]+•, 46); HRMS (EI+): calculated for C16H14: 206.1096; found: 206.1090.

Following Standard Procedure C, the reaction mixture containing monobromodiene 3j (55 mg, 0.223 mmol), Pd2(dba)3•CHCl3 (9 mg, 0.009 mmol), t-Bu3P•HBF4 (5 mg, 0.018 mmol) ZnBr2 (0.72 mL, 1.23 M in THF, 0.890 mmol) and chloroprene grignard reagent (0.89 mL, 0.75 M in THF, 0.668 mmol) in THF (3 mL) was stirred at 0 °C for 2 h. After work up, purification by flash column chromatography (3 g SiO2, 100% PS 40–60) gave dendralene 10c-Z as a pale yellow liquid (38 mg, 0.17 mmol, 77%, >95% retention). Rf = 0.24 (100% PS 40–60); 1H NMR (400 MHz, C6D6) δ 7.45 (dd, J = 8.0, 1.6 Hz, 2H), 7.02 – 6.90 (m, 3H), 6.43 (dd, J = 17.2, 10.4 Hz, 1H), 5.95 (s, 1H), 5.34 (s, 1H), 5.28 (s, 1H), 5.23 (d, J = 17.2 Hz, 1H), 5.15 (s, 1H), 5.06 (d, J = 10.4 Hz, 1H), 4.97 (s, 1H), 1.72 (s, 3H) ppm; 13C NMR (100 MHz, C6D6) δ 152.2 (Cq), 146.3 (Cq), 141.5 (Cq), 137.5 (CH), 131.8 (2×CH), 128.6 (2×CH), 128.2 (CH), 124.6 (Cq), 119.2 (CH2), 118.4 (CH2), 116.3 (CH2), 108.4 (CH), 96.5 (Cq), 89.1 (Cq), 19.8 (CH3) ppm; IR (thin film): νmax = 3088, 2971, 2913, 1593, 1488 cm−1; LRMS: (EI+): m/z (%): 220 ([M]+•, 31), 219 ([M–H]+•, 219).
100), 205 ([M–CH$_3$]$^+$, 56), 191 ([M–C$_2$H$_5$]$^+$, 47), 179 ([M–C$_3$H$_7$]$^+$, 22), 165 ([M–C$_4$H$_9$]$^+$, 36);
HRMS (EI$^+$): calculated for C$_{17}$H$_{18}$: 220.1252; found: 220.1252.


[4]dendralene 10a-Z (16 mg, 0.072 mmol) was dissolved in 0.5 mL toluene-$_d^8$ and heated under reflux for 24h. The reaction completion was confirmed by $^1$H NMR spectroscopic analysis. The reaction mixture was concentrated under reduced pressure and purification by flash column chromatography (3 g SiO$_2$, 100% PS 40–60) gave the bicyclic [3]dendralene 12 as a colourless liquid (15 mg, 0.067 mmol, 94%). R$_f$ =0.25 (100% PS 40–60); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.35 – 7.27 (m, 2H), 7.24 – 7.15 (m, 3H), 6.61 (d, $J$ = 9.9 Hz, 1H), 5.82 (d, $J$ = 9.8 Hz, 1H), 5.46 (s, 1H), 3.54 (s, 1H), 2.66 (dd, $J$ = 13.7, 5.3 Hz, 1H), 2.41 – 2.28 (m, 1H), 2.27 – 2.04 (m, 4H), 1.94 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 145.9 (Cq), 133.1 (Cq), 130.5 (Cq), 130.1 (CH), 128.5 (2×CH), 127.7 (2×CH), 126.3 (CH), 125.8 (Cq), 123.9 (CH), 119.0 (CH), 42.7 (CH), 40.1 (CH$_2$), 30.6 (CH$_2$), 22.3 (CH$_2$), 18.7 (CH$_3$) ppm; IR (thin film): $v_{max}$ = 3028, 2924, 2851, 1602 cm$^{-1}$; LRMS: (EI$^+$): m/z (%): 222 ([M]$^+$, 100), 207 ([M–CH$_3$]$^+$, 63), 129 ([M–C$_4$H$_9$CH$_3$]$^+$, 29); HRMS (EI$^+$): calculated for C$_{17}$H$_{18}$: 222.1409; found: 222.1408.
A General Synthesis of Dendralenes


(3aR,6aR,6aS,9aS,10aR,10bS)-2,5,8-trimethyl-6-(phenylethynyl)-3a,4,6a,9a,10,10a,10b-octahydropseudoindole[5,6-e]isoindole-1,3,7,9(2H,8H)-tetraone (7)

[3]dendralene 4a-Z (14 mg, 0.07 mmol) and NMM 5 (20 mg, 0.18 mmol) were dissolved in 0.5 mL CDCl₃ containing tiny crystals of BHT and K₂CO₃ and the reaction mixture was heated under reflux for 16h. The reaction completion was confirmed by ¹H NMR spectroscopic analysis. The solvent was distilled off to afford the crude material as a mixture of diastereomers (dr = 67:33).

The major adduct 7 was isolated using 40% EtOAc in PS 40–60 as a white solid (16 mg, 0.04 mmol, 53%). Rᵣ = 0.23 (50% EtOAc in PS 40–60); m.p. 211 – 216 °C (recrystallized by slow diffusion method from CH₂Cl₂ and diethyl ether); ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.16 (m, 5H), 4.19 (d, 3.7 Hz, 1H), 3.63 (q, 3.1 Hz, 1H), 3.13 (p, 3.7 Hz, 2H), 2.94 (s, 3H), 2.73 (m, 6H); 2.76 (m, 2H), 2.76 (m, 2H), 2.20 (d, 3.7 Hz, 1H), 1.82 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 181.1 (Cq), 179.4 (Cq), 179.4 (Cq), 178.3 (Cq), 131.9 (Cq), 131.6 (2×Cq), 128.8 (3×Cq), 128.2 (Cq), 122.8 (Cq), 86.6 (Cq), 84.2 (Cq), 46.3 (CH), 45.0 (CH), 40.9 (CH), 36.6 (CH), 33.8 (CH), 31.2 (CH₂), 29.7 (CH), 25.1 (CH₂), 24.7 (CH₂), 22.6 (CH₂), 19.4 (CH₃) ppm; IR (thin film): νmax = 3055, 2942, 2851, 1774, 1688 cm⁻¹; LRMS (ESI⁺): m/z (%): 417 ([M+H⁺]⁺, 100); HRMS (ESI⁺): calculated for C₂₅H₂₅O₄N: 417.1809; found: 417.1813.

The minor adduct 10 was isolated using 10% CH₂Cl₂ in EtOAc as a pale yellow solid (4 mg, 0.01 mmol, 13%). Rᵣ = 0.26 (100% EtOAc); m.p. 230 – 240 °C (decomposition, recrystallized by slow diffusion method from CH₂Cl₂ and diethyl ether). ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.06 (m, 5H), 4.26 (d, 3.7 Hz, 1H), 3.11 (brs, 2H), 3.06 – 2.76 (m, 4H), 2.76 – 2.51 (m, 4H), 2.53 – 2.26 (m, 2H), 2.20 (d, 3.7 Hz, 1H), 1.82 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 179.6 (Cq), 179.3 (Cq), 177.5 (Cq), 177.1 (Cq), 132.0 (Cq), 131.9 (2×Cq), 128.7 (Cq), 128.6 (3×Cq), 123.0 (Cq), 86.9 (Cq), 83.9 (Cq), 44.4 (CH), 44.3 (CH), 41.0 (CH), 39.2 (CH), 36.1 (CH), 31.0 (CH₂), 28.0 (CH), 24.9 (CH₂), 24.9 (CH₂), 23.7 (CH₂), 19.6 (CH₃) ppm; IR (thin film):...
**A General Synthesis of Dendralenes**

\[ \nu_{\text{max}} = 2919, 2849, 1773, 1695 \text{ cm}^{-1}; \text{LRMS (ESI+): m/z (%): 439 [M+Na]^+}, 100); 417 [M+H]^+, 60); \text{HRMS (ESI+): calculated for C}_2\text{H}_2\text{O}_2\text{N}_2: 417.1814; \text{found: 417.1815; calculated for C}_2\text{H}_2\text{O}_2\text{N}_2\text{Na}: 439.1634; \text{found: 439.1631.} \]

**2,8,10a-Trimethyl-6-(phenylethynyl)-3a,4,6,6a,9a,10,10a,10b-octahydroisoindolo[5,6-e]isoindole-1,3,7,9(2H,8H)-tetraone (9)**

1H NMR (400 MHz, C\text{D}_6): \( \delta \) 7.31 (brs, 2H), 6.91 (brs, 3H), 5.05 (d, \( J = 6.5 \text{ Hz} \), 1H), 3.65 (d, \( J = 5.1 \text{ Hz} \), 1H), 3.37 (q, \( J = 9.7 \text{ Hz} \), 1H), 2.91 (dd, \( J = 14.8, 9.0 \text{ Hz} \), 1H), 2.75 (s, 3H), 2.61 (s, 3H), 2.56 – 2.44 (m, 1H), 2.44 – 2.18 (m, 3H), 1.95 (d, \( J = 8.7 \text{ Hz} \), 1H), 1.84 (dd, \( J = 16.5, 8.9 \text{ Hz} \), 1H), 0.91 (s, 3H) ppm; \( ^{13}\text{C} \) NMR (100 MHz, C\text{D}_6): \( \delta \) 180.1 (Cq), 178.6 (Cq), 177.4 (Cq), 176.4 (Cq), 140.5 (Cq), 131.6 (2×CH), 128.8 (2×CH), 128.7 (CH), 122.9 (Cq), 122.5 (CH), 86.7 (Cq), 85.7 (Cq), 51.4 (CH), 45.1 (CH), 39.3 (CH), 37.3 (CH), 36.6 (Cq), 36.5 (CH), 32.4 (CH), 29.5 (CH), 24.7 (CH), 24.4 (CH), 24.0 (CH) ppm; IR (thin film): \( \nu_{\text{max}} = 3056, 2942, 2864, 1773, 1696, 1489 \text{ cm}^{-1}; \text{LRMS (ESI+): m/z (%): 439 [M+Na]^+}, 100), 417 ([M+H]^+, 20); \text{HRMS (ESI+): calculated for C}_2\text{H}_2\text{O}_2\text{N}_2\text{Na: 439.1628; found: 439.1612.} \)
X-ray Crystallography

Single crystal X-ray data for compounds were collected on a Supernova diffractometer using Cu Kα radiation, λ = 1.5418 Å and XCalibur with Mo Kα radiation, λ = 0.71073 Å radiation. Data reduction was performed using the CrysAlis PRO package. Structure solutions for all compounds were determined by ShelXT, and the structures refined using ShelXL in the OLEX2 program package.

1. Compound 4l-Z

\[ \text{C}_{21}\text{H}_{20}, \text{M} = 272.37, \text{T} = 150 \text{ K}, \text{monoclinic, space group P2}_1, \text{Z} = 2, a = 8.5944(1), b = 5.9312(1), c = 16.3498(2) \text{ Å}, \beta = 104.547(1)^\circ, V = 806.71(2) \text{ Å}^3, D_r = 1.121 \text{ Mg m}^{-3}, 3077 \text{ unique data (2} \theta_{\text{max}} = 147.4^\circ), 3018 \text{ with } I > 2\sigma(I); R = 0.045, Rw = 0.127, S = 1.07. \text{CCDC 1902664.} \]

2. Compound 4e-Z

\[ \text{C}_{21}\text{H}_{18}, \text{M} = 270.35, \text{T} = 294 \text{ K}, \text{orthorhombic, space group Pna2}_1, \text{Z} = 4, a = 10.9002(3), b = 20.0267(4), c = 7.6356(1) \text{ Å}, V = 1666.81(6) \text{ Å}^3, D_r = 1.077 \text{ Mg m}^{-3}, 3141 \text{ unique data (2} \theta_{\text{max}} = 145.4^\circ), 2705 \text{ with } I > 2\sigma(I); R = 0.051, Rw = 0.161, S = 1.03. \text{CCDC 1902662.} \]

3. Compound 3g
A General Synthesis of Dendralenes

4. Compound 3c

C_{14}H_{13}BrO, M = 315.20, T = 150 K, orthorhombic, space group P2_12_12_1, Z = 8, a = 5.79782(9), b = 7.59133(14), c = 63.3743(11) Å, V = 2789.30(8) Å³, D_x = 1.501 Mg m⁻³, 5656 unique data (2θ_{max} = 148.4°), 5612 with I > 2σ(I); R = 0.060, R_w = 0.131, S = 1.31. CCDC 1902663.

5. Compound 7

C_{25}H_{24}N_{2}O_{4}, M = 416.46, monoclinic, C2/c (No. 15), a = 21.8655(7) Å, b = 6.7309(2) Å, c = 29.0129(8) Å, β = 100.540(3)°, α = γ = 90°, V = 4197.9(2) Å³, T = 150.00(10) K, Z = 8, Z' = 1, μ(MoKα) = 0.090 mm⁻¹, 36549 reflections measured, 5529 unique (R_int = 0.0213) which were used in all calculations. The final wR² was 0.1174 (all data) and R was 0.0446 (I > 2σ(I)). CCDC 1922944.
6. Compound 10

\[ \text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_4, \quad M = 416.46, \quad \text{tetragonal, } I-4 \text{ (No. 82)}, \quad a = 18.1165(5) \text{ Å}, \quad b = 18.1165(5) \text{ Å}, \quad c = 12.8619(11) \text{ Å}, \quad \alpha = \beta = \gamma = 90^\circ, \quad V = 4221.4(4) \text{ Å}^3, \quad T = 150.00(10) \text{ K}, \quad Z = 8, \quad Z' = 1, \quad \mu(\text{CuK} \alpha) = 0.725 \text{ mm}^{-1}, \quad 12779 \text{ reflections measured, } 3605 \text{ unique } (R_{int} = 0.0488) \text{ which were used in all calculations. The final } wR_2 \text{ was 0.0871 (all data) and } R_1 \text{ was 0.0405 } (I > 2\sigma(I)). \quad \text{CCDC 1922943.} \]

7. Compound 9

\[ \text{C}_{25}\text{H}_{25.34}\text{N}_2\text{O}_{17}, \quad M = 419.53, \quad \text{monoclinic, } C2 \text{ (No. 5)}, \quad a = 22.1402(8) \text{ Å}, \quad b = 6.8047(2) \text{ Å}, \quad c = 14.2360(5) \text{ Å}, \quad \beta = 100.710(4)^\circ, \quad \alpha = \gamma = 90^\circ, \quad V = 2107.40(13) \text{ Å}^3, \quad T = 150.01(10) \text{ K}, \quad Z = 4, \quad Z' = 1, \quad \mu(\text{MoK} \alpha) = 0.091 \text{ mm}^{-1}, \quad 18911 \text{ reflections measured, } 5250 \text{ unique } (R_{int} = 0.0222) \text{ which were used in all calculations. The final } wR_2 \text{ was 0.0904 (all data) and } R_1 \text{ was 0.0355 } (I > 2\sigma(I)). \quad \text{CCDC 1922945.} \]
References

A General Synthesis of Dendralenes

\[
\text{Br} \quad \text{Br} \\
\text{C}_7\text{H}_{11}
\]

1f

400 MHz, CDCl₃
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

Br\_2Br
C\textsubscript{10}H\textsubscript{21}

1g

400 MHz, CDCl\textsubscript{3}
A General Synthesis of Dendralenes

2a

100 MHz, CDCl₃

\[ \text{Formula Image} \]

S78
A General Synthesis of Dendralenes

2b

100 MHz, CDCl₃
A General Synthesis of Dendralenes

2e
400 MHz, CD₆₂₆
A General Synthesis of Dendralenes

\[
\text{structure image}
\]

400 MHz, CDCl₃
A General Synthesis of Dendralenes

\[ \text{C}_5\text{H}_{11} \]

100 MHz, CDCl₃
A General Synthesis of Dendralenes

\[ \text{C}_{10}\text{H}_{21} \]

2g
100 MHz, CDCl₃
A General Synthesis of Dendralenes

\[ \text{Diagram of molecule} \]

2h
100 MHz, CDCl\textsubscript{3}
A General Synthesis of Dendralenes

400 MHz, CDCl$_3$

S93
A General Synthesis of Dendralenes

400 MHz, CDCl₃
A General Synthesis of Dendralenes

\[ \text{100 MHz, CDCl}_3 \]
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

$\text{NTos}$

2I

$400 \text{ MHz, CDCl}_3$
A General Synthesis of Dendralenes

2m
100 MHz, CDCl₃
A General Synthesis of Dendralenes

Me
Me
OMe
OMe
OMe
2o
400 MHz, CDCl₃
A General Synthesis of Dendralenes

Me
Me
OMe
OMe
OMe

2a
100 MHz, CDCl₃
A General Synthesis of Dendralenes

\[ \text{Me} \]

2p

100 MHz, CDCl\textsubscript{3}
A General Synthesis of Dendralenes

![Chemical structure and NMR spectrum](image-url)
A General Synthesis of Dendralenes

2r
400 MHz, CDCl₃
A General Synthesis of Dendralenes

400 MHz, CDCl₃
A General Synthesis of Dendralenes

2u
400 MHz, CDCl₃
A General Synthesis of Dendralenes

176 MHz, CD$_2$CN
A General Synthesis of Dendralenes

100 MHz, CDCl₃
$\text{3a}$

400 MHz, CDCl$_3$
A General Synthesis of Dendralenes

Br

3a

100 MHz, CDCl₃
A General Synthesis of Dendralenes

$\text{Me}$

Br

OMe

3b

400 MHz, CDCl$_3$
A General Synthesis of Dendralenes

171

S126
A General Synthesis of Dendralenes

3c
400 MHz, (CD$_3$)$_2$SO
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

3d
100 MHz, CDCl₃
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

400 MHz, CDCl₃

3f
A General Synthesis of Dendralenes

3 g
400 MHz, CDCl₃
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

Me\(\rightarrow\)Br
Me

3h
400 MHz, CDCl\(_3\)
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

![Chemical structure and NMR spectrum](image)
A General Synthesis of Dendralenes

\[ \text{3m} \]

400 MHz, CDCl\textsubscript{3}
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

Br
C_{10}H_{21}

30
400 MHz, CDCl$_3$
A General Synthesis of Dendralenes

\[
\begin{align*}
\text{Br} & \quad \text{C}_{10} \text{H}_{21} \\
3o & \\
100 \text{ MHz, CDCl}_3
\end{align*}
\]
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

$\text{Me}$

$\text{Br}$

$\text{O}$

$\text{Me}$

$3r$

400 MHz, CDCl$_3$
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

$4a-E$

$400$ MHz, CDCl$_3$
4a-Z
100 MHz, CDCl₃
A General Synthesis of Dendralenes

400 MHz, CDCl₃
A General Synthesis of Dendralenes

Me
Me

4b-Z
100 MHz, CDCl₃
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

$\text{Me}_3\text{C}$

$4\text{c-E}$

100 MHz, CDCl$_3$
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

\[ 4d-Z \]

400 MHz, CDCl₃
A General Synthesis of Dendralenes

4d-Z

100 MHz, CDCl₃
A General Synthesis of Dendralenes

Me

400 MHz, CDCl$_3$
A General Synthesis of Dendralenes

Me

4f-E

400 MHz, CDCl₃
A General Synthesis of Dendralenes

400 MHz, CDCl₃
A General Synthesis of Dendralenes

4g-Z
100 MHz, CDCl₃
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

[Chemical structure image]

100 MHz, (CD$_3$)$_2$SO
A General Synthesis of Dendralenes

Me

4l-Z

400 MHz, CDCl₃
A General Synthesis of Dendralenes

\[ \text{Me} \rightarrow \text{C}_{10} \text{H}_{21} \]

4k-E

100 MHz, CDCl\textsubscript{3}

S200
4k-Z
400 MHz, CDCl$_3$
A General Synthesis of Dendralenes

\[ \text{Me}_2C \text{C}_{10}H_{21} \]

100 MHz, CDCl\textsubscript{3}
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

$\text{Me}$

$\text{12}$

$400 \text{ MHz, CDCl}_3$

$S213$
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes

![Chemical structure](image)

10

CD$_2$Cl$_2$, 400 MHz

S217
A General Synthesis of Dendralenes
A General Synthesis of Dendralenes
Chapter Three:

Diene-Transmissive Diels–Alder Sequences with Benzynes
3 Diene-Transmissive Diels–Alder Sequences With Benzynes

**Prelude**

The work was published in the journal *Organic Letters*. The other authors listed on the manuscript are Michael S. Sherburn and Jas S. Ward. Jas S. Ward obtained the X-ray crystallographic studies upon samples provided by myself. The project, and the draft manuscript, was conceived and evolved in collaboration with Professor Michael S. Sherburn. All of the experimental work was conducted by myself.

This Chapter investigates the diene transmissive Diels–Alder (DTDA) reactivity of substituted [3]dendralenes with unstable dienophiles, benzynes. Reactions of dendralenes with benzynes have not been reported previously. Four different benzyne precursors were used in our studies, with the benzynes generated *in situ*. The cycloaddition reaction between benzyne and dendralenes gave a wide range substitution patterns, generating the mono adducts, 2-vinyl-1,4-dihydronaphthalenes, in moderate yields. The monoaadducts were then reacted with different dienophiles to generate new carbo- and hetero-annelated tetralins. The entire reaction sequence including benzyne generation, first Diels–Alder and the second Diels–Alder reactions could all be performed in one-pot. The tetralins were isolated in good yields and excellent π-diastereoselectivity for the second cycloaddition was observed.
Diene-Transmissive Diels–Alder Sequences with Benzynes
Josemon George, Jas S. Ward,* and Michael S. Sherburn*
Research School of Chemistry, Australian National University, Canberra, Australian Capital Territory 2601, Australia
Supporting Information

ABSTRACT: Diene-transmissive Diels–Alder (DTDA) sequences are extraordinarily powerful processes for the generation of fused bicyclic systems. Nonetheless, only stable dienophiles have previously been deployed. Herein we report DTDA sequences with a variety of substituted [3]dendralenes in the first study to deploy aryynes as dienophiles. We demonstrate the one-flask generation of complex, aromatic-ring-containing, multicyclic systems of relevance to medicinal chemistry. These synthetic operations provide numerous successful examples of the otherwise challenging and rarely reported intermolecular Diels–Alder reaction of acyclic 1,3-butadienes with aryynes, which is made possible due to the exalted reactivity of dendralenic dienes.

A cyclic sp²-rich hydrocarbon is an excellent precursor for the step-economic generation of multicyclic systems. Dendralenes are particularly prominent in this field because they serve as multidienes in interconnected sequences of [4 + 2] cycloadditions. The simplest cross-conjugated hydrocarbon, [3]dendralene, behaves as a double diene, reacting successively with two dienophiles in a so-called diene-transmissive Diels–Alder (DTDA) reaction sequence. In DTDA sequences of [3]dendralenes, the first [4 + 2] cycloaddition is generally faster than the second, which allows the use of two different dienophiles. Despite their obvious power and potential, DTDA sequences are by no means generalized processes because little in the way of dienophile variation has been investigated. Herein we deploy dendralenes for the first time in DTDA sequences with aryynes. In addition to significantly broadening the scope of the extraordinarily powerful (four covalent bonds, two rings formed) DTDA sequence, this investigation also demonstrates the rapid construction of novel, medicinal-chemistry-relevant structures.

Specifically, this work shows that a substituted [3]dendralene 1 undergoes an intermolecular Diels–Alder reaction with (a substituted) benzyne 2 to generate 2-vinyl-1,4-dihydronaphthalene 3, which, in turn, undergoes an intermolecular Diels–Alder reaction with a range of dienophiles 4 to furnish new carbo- and heteroannelated tetralins 5. Diverse substitution of the tricyclic framework is within reach using this approach, a feature made pertinent by the privileged position of these systems in medicinal chemistry (Figure 1). With diversely substituted [3]dendralenes available through a short and efficient two-step synthesis from aldehydes, we set about testing the feasibility of intermolecular cycloadditions to benzyne. Our confidence was fueled by the knowledge that [3]dendralenes are reactive dienes. Nonetheless, our

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Figure 1. Proposed two-fold Diels–Alder sequence and selected clinically used substances containing a carbo-/heteroannelated tetralin core.
enthusiasm was curtailed somewhat by the paucity of successful Diels–Alder reactions between benzynes and acyclic dienes.

Table 1. Aryne Additions to Internally-Substituted [3]Dendralenes 1 Generate 2-Vinyl-1,4-dihydronaphthalenes 3

<table>
<thead>
<tr>
<th>Aryne Additions</th>
<th>Yields (%)</th>
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<tbody>
<tr>
<td>Aryne Additions</td>
<td>Yields (%)</td>
</tr>
</tbody>
</table>


Scheme 1. Sequential 1,4-Nucleophilic Addition/Electrophilic Substitution of a 1,3-Butadiene

Unless otherwise specified, yields refer to isolated products from the n-BuLi method: To a solution of dendralene 1 and benzyne precursor 2c (1.0 mol equiv) in PhMe at 0 °C was added n-BuLi (1.2 mol equiv) dropwise over 5 min. **To a solution of dendralene 1 and benzyne precursor 2a or 2b (3.5 mol equiv) in MeCN at 23 °C was added CsF (6 mol equiv).** **To a solution of dendralene 1 and benzyne precursor 2a or 2b (2 to 3 mol equiv) in THF at −20 °C was added TBAF (3.5 mol equiv).** Procedure a was followed but with benzyne precursor 2d (3.0 mol equiv) and n-BuLi (3.2 mol equiv).

Table 2. One-Flask, Two-Fold Cycloadditions to Substituted [3]Dendralenes Involving First an Aryne, Then an Electron-Poor Alkene, Alkyne, or Azo-Compound Dienophile

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enthusiasm was curtailed somewhat by the paucity of successful Diels–Alder reactions between benzynes and acyclic dienes.
phenylpropenyl-lithium added Z
unprecedented result: None of the expected benzyne addition taken. One attempt involved the replacement of PhMe with elimination of CO
best performers, reports indicate: (a) 1,4-Disubstituted-1,3-butadienes are the
potential for further elaboration into multicyclic structures. In fact, we could locate only eight
diastereomeric products, in highly respectable yields, considering that up to six new stereocenters, four new covalent bonds, and a new oxetane ring system are generated in one operation.

Table 1 reports the results of (4 + 2) cycloadditions of in situ-generated benzynes, 1,6-dimethylbenzene, and 4,5-dimethoxybenzene with [3]dendralene 1a–h, which carry a single substituent at the internal carbon. In contrast with the most recent literature findings of acyclic diene–benzyn cycloadditions, for which the BDC method is superior, the acyclic diene units of substituted [3]dendralenes undergo the highest yielding reactions with n-BuLi/1,2-dihromobenzene and fluosodi/n-trimethylsilyl-benzene-1-trifluoromethane-sulfonate. Table 1 presents successful aryne additions to [3]dendralene carrying acyclic and cyclic allyl, alkenyl, and directly substituted aromatic substituents. The 2-vinyl-1,4-dihydrobenzene products 3 are poorly represented in the literature. This is surprising considering their significant potential for further elaboration into multicyclic structures.

We selected one set of conditions for aryne generation/cycloaddition based on those developed by Coe and coworkers, who report a 89% yield for a reaction between Coe and coworkers, who report a 89% yield for a reaction between

In summary, the formal analogy in the dienophile avoiding the side of the 2-vinyl-1,4-dihydrobenzene 3 that carries the substituents (R/R′) performed on a 100 g scale. Under the same conditions, [3]dendralenes gave modest yields by comparison, and hence optimization experiments were undertaken. One attempt involved the replacement of THF with MeCN as the solvent, which led to an intriguing and unprecedented result: None of the expected benzyn addition product of dendralene 1a was observed, but instead a product with two additional n-BuLi units and one less COeq bond, 6–Z, was isolated in ca. 20% yield. A 60% yield of this product was obtained in the absence of 1,2-dihromobenzene but with added bromobutane (Scheme 1). We presume that the nucleophilic addition of n-BuLi to either terminus of a 1,3-butadiene moiety of 1a generates the postulated lithium 7a or the phenylpropenyl-lithium 7b, which undergoes the nucleophile substitution of bromobutane. Organocuprates-initiated 1,4-addition polymerizations of dienes and dendralenes are known, but to our knowledge, 1,4-addition/substitution is without precedent for unsaturated hydrocarbons. Attempts to generalize these three-component, two C=C bond-forming process are underway.

A significant contributing factor to the relatively low isolated yields of 2-vinyl-1,4-dihydrobenzophanes 3 (Table 1) relates to difficulties with product isolation. The separation of target product 3 from unreacted dendralene 1 and benzyn side products was nontrivial, particularly when all were hydrocarbons. To circumvent this issue, we performed a second cycloaddition to semicyclic diene 3 with a nonhydrocarbon dienophile in the same reaction flask. We reasoned that the functionality in this double adduct would facilitate product isolation, hence simultaneously improving step economy and increasing isolated yields. The successful realization of this hypothesis is depicted in Table 2. Thus [3]dendralenes with the substituent types listed in Table 1, along with additional substituents carrying an internal, electron-poor aromatic ring (→ 5c) or an indole (→ 5g) and dendralenes with phenyle groups at the terminal sites (→ 5d, h), undergo one-flask DTDA sequences involving an aryne as the initial dienophile and N-methylmaleimide (NMM), N-phenylmaleimide (NPM), N-phenylmaleimide-2.5-diones (PTAD), or dimethylaminodicyclohexylamine (DMAD) as the representative second dienophile. The carbocyclic/lactam/lactone tetralin products of these three component reactions are isolated in highly respectable yields, considering that up to six new stereocenters, four new covalent bonds, and a new oxetane ring system are generated in one operation.

A similar approach using the TBAF/2-trimethylsilyl-benzene-1-trifluoromethane-sulfonate gave the best outcome in the one-flask process. For optimal yields, Kaki’s method[28] of TRAF workup was deployed in situ prior to the addition of the second dienophile to the reaction mixture, and an excess of the second dienophile was used. In most cases, the second cycloaddition proceeds with (within the limits of detection) complete α-diastereofacial selectivity, with the dienophile avoiding the side of the 2-vinyl-1,4-dihydrobenzene 3 that carries the substituents (R/R′), Table 2). Complete α-stereoselectivity is also seen in cases involving NMM as the dienophile. A final example, which extends the methodology to a more elaborate product structure, is depicted in Scheme 3. Thus the reaction of 2-vinyl-1,4-dihydrophthalene 3e with para-

In summary, the first Diels–Alder additions of arynes to dendralenes have been performed. These reactions have been sequenced with a second [4 + 2] cycloaddition in one operation to rapidly create complex multicyclic systems. This study significantly extends knowledge on aryne cyclodaddition chemistry to acyclic dienes, processes that are poorly represented in the literature. Evidently, the enhanced diene reactivity of dendralenes is a common theme to their success in benzynes–Diels–Alder additions. It is noteworthy that in contrast with 1,3-butadienes, dendralenes 1 provide reasonable yields from benzynes [4 + 2] cycloadditions irrespective of the presence or absence of terminal 1,3-butadiene substituents. The structures generated through this
new DTD sequence are suggestive of those found in biologically active compounds. In some cases, these new structures represent hybrids of natural products and drug molecules, which have obvious potential for exploitation outside of synthetic chemistry. Extensions of these studies to rheniumaromatically substituted dendrimers and applications of these concepts in target syntheses are underway.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orlett.9b02807.

Experimental procedures, characterisation data and nuclear magnetic resonance spectra, and cryotriblographic data for X-ray crystal structures (PDF)

**Accession Codes**

CCDC 1922951–1922955 contain the supplementary cryotlographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336033.

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**Author Contributions**

The manuscript was written through contributions of all authors. J.S.W. performed the X-ray structure analyses. All authors have given approval to the final version of the manuscript.

**Notes**

The authors declare no competing financial interest.

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**REFERENCES**


(17) The BDC method gives mixtures of single and two-fold addition products in lower yields than the other methods, with less recovery and no other discernible products. We attribute the poor mass balances of isolable products to polymer formation. Polyesters might be generated through acid-catalyzed depolymerisation from traces of acid remaining from the preparation of BDC, perhaps accelerated by the higher reaction temperatures used in this procedure.


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Reductive [4 + 1]-Cycloadditions Of Vinylidenes And Dienes.

Supporting Information

Diene-Transmissive Diels–Alder Sequences With Benzynes
Josemon George, Jas S. Ward, and Michael S. Sherburn
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General Methods

NMR Spectroscopy

$^1$H NMR spectra were recorded at 400 MHz using a Bruker AVANCE 400 spectrometer. Residual solvent peaks were used as an internal reference for $^1$H NMR spectra (CDCl$_3$ $\delta$ 7.26 ppm, CD$_2$Cl$_2$ $\delta$ 5.32 ppm, (CD$_3$)$_2$SO $\delta$ 2.50). Coupling constants ($J$) are quoted to the nearest 0.1 Hz. The assignment of proton signals was assisted by COSY, HSQC and HMBC experiments. $^{13}$C NMR spectra were recorded at 100 MHz using a Bruker AVANCE 400 spectrometer. Solvent peaks were used as an internal reference for $^{13}$C NMR spectra (CDCl$_3$ $\delta$ 77.16 ppm, CD$_2$Cl$_2$ $\delta$ 53.84 ppm, (CD$_3$)$_2$SO $\delta$ 39.52). Assignment of carbon signals was assisted by HSQC and HMBC experiments. The following abbreviations (or combinations thereof) are used to denote $^1$H NMR multiplicities: s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplet, t = triplet, m = multiplet.

Infrared Spectroscopy

IR spectra were recorded on a Perkin–Elmer UATR Two spectrometer as a thin film or solid.

Mass Spectrometry

Low-resolution EI mass spectra were recorded on a Finnigan Polaris Q ion trap mass spectrometer using electron impact (EI$^+$) ionization mode at 70 eV. High-resolution EI mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. Low-resolution ESI mass spectra were recorded on a ZMD Micromass spectrometer with Waters Alliance 2690 HPLC. High-resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) mass spectrometer.

Melting Points

Melting points were measured on a Stanford Research Systems Optimelt Automated Melting Point System and are uncorrected.

X-ray Crystallography

Single crystal X-ray data was collected on a SuperNova (Dual Source) diffractometer using a SuperNova (Cu) X-ray radiation source. Crystallographic structures were solved using CryoAlis PRO.
Experimental Procedures, Reagents, Chromatography and Glassware

Reactions were conducted under a positive pressure of dry nitrogen in oven dried glassware and at room temperature, unless specified otherwise. Anhydrous solvents were either obtained from commercial sources or dried according to the procedure outlined by Grubbs and co-workers.\cite{1} Commercially available chemicals were used as purchased, or where specified, purified by standard techniques. Analytical thin-layer chromatography was conducted with aluminum-backed silica gel 60 F<sub>254</sub> (0.2 mm) plates supplied by Merck, and visualized using UV fluorescence (λ<sub>max</sub> = 254 nm), or developed using KMnO<sub>4</sub> or p-anisaldehyde or phosphomolybdic acid followed by heating. Flash chromatography employed Merck Kiesegel 60 silica gel (230–400 mesh). Solvent compositions are given in (v/v). PS 40–60 °C refers to petroleum spirits, boiling point fraction 40–60 °C. The unsubstituted benzyne precursors, 1,2-dibromobenzene and 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate were purchased from Sigma–Aldrich and used as received. 1 M TBAF in THF and CsF were purchased from Sigma–Aldrich and used as received. Substituted dendralenes were synthesized as per the reported procedure.\cite{7}

Synthesis of Substituted Benzyne Precursors

1,2-Dibromo-4,5-dimethoxybenzene (2d)

\[ \begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
& \quad \text{CH}_2\text{Cl}_2 \\
& \quad 0 – 23 ^\circ\text{C}, 16\text{h} \\
& \quad \text{I}_2, \text{Br}_2 \\
\rightarrow \\
\text{MeO} & \quad \text{MeO} \\
\text{Br} & \quad \text{Br}
\end{align*} \]

1,2-Dibromo-4,5-dimethoxybenzene 2d was prepared according to the reported procedure by Sun and co-workers from 1,2-dimethoxybenzene (17.0 g, 123 mmol) as a white solid (20.8 g, 70.3 mmol, 57%) and characterization data was consistent with the literature.\cite{5}
3,6-Dimethoxy-2-trimethylsilyl-benzene-1-trifluoromethanesulfonate (2b)

The title compound was prepared in four steps as shown in the below scheme.

### 2,5-Dimethoxyphenol

2,5-Dimethoxyphenol was synthesised using a modified protocol from Michael and co-workers. A solution of 2,5-dimethoxybenzaldehyde (20.0 g, 120 mmol) in dry CH$_2$Cl$_2$ (40 mL) was added dropwise to a solution of m-CPBA (27.6 g, 160 mmol) in CH$_2$Cl$_2$ (160 mL) at 0 °C. The solution was heated to reflux with stirring for 16 hours. After cooling to room temperature, the solution was washed with saturated aqueous NaHCO$_3$ solution and saturated aqueous Na$_2$S$_2$O$_3$ and dried over MgSO$_4$. The solvent was removed under reduced pressure to give the crude ester as a yellow oil. This yellow oil was dissolved in MeOH (100 mL) and 10% NaOH was added (100 mL). The reaction mixture was stirred at 23 °C for 3h. The solution was acidified to pH 1 (6M HCl) and extracted with CH$_2$Cl$_2$ (200 mL) The solvent was removed under reduced pressure and purification by flash column chromatography (SiO$_2$, 10% EtOAc in PS 40–60) gave 2,5-dimethoxyphenol as a colorless oil (16.1 g, 104 mmol, 87%).
(2.5-Dimethoxyphenoxo)trimethylsilane

(2,5-Dimethoxyphenoxo)trimethylsilane was synthesised using a modified protocol from Castedo and co-workers.\textsuperscript{5} 2,5-Dimethoxyphenol (16.1 g, 104 mmol) and hexamethylsilazane (10.1 g, 13.1 mL, 63.0 mmol) were combined in a round bottom flask and heated to 70 °C for 45 minutes. The reaction mixture was cooled to room temperature and excess hexamethylsilazane was removed under reduced pressure to give the TMS ether in quantitative yield (23.5 g, 103 mmol, 99%).

(3,6-Dimethoxy-2-((trimethylsilyloxy)phenyl)trimethylsilane

The title compound was synthesised using a modified protocol from Castedo and co-workers.\textsuperscript{5} A solution of TMS ether (4.16 g, 18.4 mmol) in dry THF (25 mL) was added dropwise to a solution of freshly prepared LDA (2.16 g, 20.2 mmol) at −78 °C under N\textsubscript{2}. The solution was warmed to room temperature and stirred for two hours. The solution was then cooled to −78 °C and freshly distilled TMSCl (2.38 g, 2.80 mL, 22.0 mmol) was added dropwise. The solution was allowed to warm to 23 °C and stirred for 20h. The reaction mixture was quenched with saturated aqueous NH\textsubscript{4}Cl (5 mL) and extracted with Et\textsubscript{2}O (50 mL). The organic layer was dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure to give crude product as a colorless oil. The crude product was used without further purification.

3,6-Dimethoxy-2-trimethylsilyl-benzene-1-trifluoromethanesulfonate (2b)
Diene-Transmissive Diels–Alder Sequences With Benzyne

The title compound was synthesised using a modified protocol from Castedo and co-workers.\textsuperscript{5} n-BuLi (11.7 mL, 1.6 M, 18.6 mmol) was added dropwise to a solution of TMS ether (5.29 g, 17.7 mmol) in dry Et\textsubscript{2}O (190 mL) at 0 °C under N\textsubscript{2}. The solution was warmed to room temperature and allowed to stir for 4 hours. The solution was then cooled to 0 °C and triflic anhydride (10.0 g, 9.66 mL, 35.4 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 18 hours. The reaction mixture was quenched with saturated aqueous NH\textsubscript{4}Cl (70 mL) and the layers were separated. The aqueous layer was further extracted with Et\textsubscript{2}O (50 mL). The combined organic layer was dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure. Purification by flash column chromatography (SiO\textsubscript{2}, 33% CH\textsubscript{2}Cl\textsubscript{2} in PS 40–60) gave the product 2b as a pale brown solid (4.56 g, 12.7 mmol, 69% over two steps). m.p. 40 – 45 °C (CH\textsubscript{2}Cl\textsubscript{2}).

\textsuperscript{1}H NMR (400 MHz, (CD\textsubscript{3})\textsubscript{2}SO) \(\delta\) 7.26 (d, \(J = 9.0\) Hz, 1H), 7.03 (d, \(J = 9.0\) Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 0.32 (s, 9H) ppm; \textsuperscript{13}C NMR (100 MHz, (CD\textsubscript{3})\textsubscript{2}SO) \(\delta\) 157.6 (Cq), 144.4 (Cq), 141.6 (Cq), 122.1 (Cq), 118.4 (q, \(J = 321\) Hz, CF\textsubscript{3}) 115.3 (CH), 111.4 (CH), 56.1 (CH\textsubscript{3}), 56.1 (CH\textsubscript{3}), 0.64 (3×CH\textsubscript{3}) ppm; IR (thin film): \(v_{\text{max}}\) = 2946, 2904, 2841, 1574 cm\textsuperscript{-1}; LRMS (EI\textsuperscript{+}): m/z (%): 358 ([M\textsuperscript{+}], 18), 343 ([M–CH\textsubscript{3}\textsuperscript{+}], 58), 328 ([M–2×CH\textsubscript{3}\textsuperscript{+}], 58), 210 (100); HRMS (EI\textsuperscript{+}): calculated for C\textsubscript{12}H\textsubscript{17}O\textsubscript{5}F\textsubscript{3}SiS: 358.0518; found: 358.0519.


**General Method A: 1,2-Dibromide as the benzyne precursor**

\[\text{Br} \quad \text{Br} \quad \text{n-BuLi} \quad \text{Toluene, 0 °C} \quad \left[\begin{array}{c} \text{1} \\ \text{2} \end{array}\right] \quad \left[\begin{array}{c} \text{3} \end{array}\right] \quad \text{0 °C, 1h}\]

1,2-Dibromobenzene 2c (1.0 mol equiv) and dendralene 1 (1.0 mol equiv) were mixed in toluene (1.0 mL/0.1 g of dendralene) under N\textsubscript{2}. The reaction mixture was cooled to 0 °C and n-BuLi (1.2 mol equiv, 1.2 M – 1.5 M in hexane) was added dropwise over 5 minutes. The reaction mixture was stirred at 0 °C for 1h. The reaction mixture was quenched with saturated aqueous NH\textsubscript{4}Cl (1 mL/0.1 g dendralene) and the resulting heterogeneous solution was filtered through a plug of Celite and diluted with CH\textsubscript{2}Cl\textsubscript{2} (10 mL/0.1 g dendralene) and water (10 mL/0.1 g dendralene). The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (5 mL/0.1 g dendralene). The combined organic layer was
washed with saturated brine (5 mL/0.1 g dendralene), dried over Na₂SO₄ and concentrated under reduced pressure.

**General Method B:** 2-Trimethylsilyl-benzene-1-trifluoromethanesulfonate as the benzyne precursor and CsF as the fluoride source

\[
\begin{align*}
\text{OTf} & \quad \text{TMS} \quad \xrightarrow{\text{MeCN}} \quad \text{CsF} \quad \xrightarrow{23{^\circ}\text{C}, 24\text{h}} \quad \text{R}^2 \\
2a & \quad \text{R}^1 \quad \xrightarrow{1} \quad \text{R}^2 \\
& \quad \text{1} \\
& \quad \text{23° C, 24h} \\
& \quad \text{3}
\end{align*}
\]

2-Trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (1.5 mol equiv) and dendralene 1 (1.0 mol equiv) were dissolved in MeCN (1 mL/0.1 g of dendralene) under N₂. CsF (up to 6 mol equiv) was added and the reaction mixture was stirred at 23 °C for 24h. The reaction mixture was diluted with CH₂Cl₂ (10 mL/0.1 g dendralene) and water (10 mL/0.1 g dendralene) shaken well and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (5 mL/0.1 g dendralene). The combined organic layer was washed with saturated brine (5 mL/0.1 g dendralene), dried over Na₂SO₄ and concentrated under reduced pressure.

**General Method C:** 2-Trimethylsilyl-benzene-1-trifluoromethanesulfonate as the benzyne precursor and TBAF as the fluoride source

\[
\begin{align*}
\text{OTf} & \quad \text{TMS} \quad \xrightarrow{\text{THF}} \quad \text{TBAF} \quad \xrightarrow{-20^\circ\text{C to 0^\circ C}} \quad \text{R}^2 \\
2a & \quad \text{R}^1 \quad \xrightarrow{1} \quad \text{R}^2 \\
& \quad \text{0^\circ C, 1h} \\
& \quad \text{3}
\end{align*}
\]

2-Trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (2.0 – 3.0 mol equiv) and dendralene 1 (1.0 mol equiv) were dissolved in THF (1.0 mL/0.1 g of dendralene) under N₂. The reaction mixture was cooled to -20 °C and TBAF (up to 3.5 mol equiv, 1 M in THF) was added dropwise over 20 minutes. The resulting pale yellow reaction mixture was brought to 0 °C and stirred for 1h. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (1 mL/0.1 g dendralene). The resulting solution was diluted with CH₂Cl₂ (10 mL/0.1 g dendralene) and washed with water (10 mL/0.1 g dendralene). The aqueous layer was extracted with CH₂Cl₂ (5 mL/0.1 g dendralene). The combined organic layer was washed with saturated brine (5 mL/0.1 g dendralene), dried over Na₂SO₄ and concentrated under reduced pressure.
1-Phenyl-2-vinyl-1,4-dihyronaphthalene (3a)

Following General Method A, the reaction mixture containing dendrane 1a (73 mg, 0.46 mmol), 1,2-dibromobenzene 2c (56 µL, 0.46 mmol) and n-BuLi (0.46 mL, 1.2 M, 0.56 mmol) in toluene (0.75 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (5 g SiO₂, 100% PS 40–60) gave the mono DA adduct 3a as a colorless liquid (42 mg, 0.18 mmol, 39%). Rᵥ = 0.43 (100% PS 40–60).

Following General Method B, the reaction mixture containing CsF (233 mg, 1.54 mmol), dendrane 1a (40 mg, 0.26 mmol) and 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (93 µL, 0.38 mmol) in MeCN (1 mL) was stirred at 23 °C for 24h. After work up, purification by flash column chromatography (4 g SiO₂, 100% PS 40–60) gave the mono DA adduct 3a as a colorless liquid (24 mg, 0.103 mmol, 40%).

Following General Method C, the reaction mixture containing dendrane 1a (70 mg, 0.45 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.33 mL, 1.34 mmol) and TBAF (1.60 mL, 1 M, 1.57 mmol) in THF (2 mL) was stirred at 0 °C for 1h. After work up, purification by flash
column chromatography (4 g SiO\(_2\), 100% PS 40–60) gave the mono DA adduct 3a as a colorless liquid (62 mg, 0.27 mmol, 59%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.04 (m, 9H), 6.41 (dd, \(J = 17.6\) Hz, 1H), 6.26 (dd, \(J = 5.6\), 2.7 Hz, 1H), 5.21 (d, \(J = 17.6\) Hz, 1H), 4.98 (d, \(J = 10.9\) Hz, 1H), 4.91 (t, \(J = 2.8\) Hz, 1H), 3.75 (d, \(J = 22.0\) Hz, 1H), 3.56 (ddd, \(J = 22.0\), 5.2, 2.4 Hz, 1H) ppm; \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 145.4 (Cq), 138.9 (Cq), 138.1 (Cq), 137.8 (CH), 133.0 (Cq), 129.0 (CH), 128.8 (2×CH), 128.3 (CH), 127.7 (CH), 127.6 (2×CH), 126.6 (CH), 126.4 (CH), 126.1 (CH), 113.0 (CH\(_2\)), 46.3 (CH), 31.2 (CH\(_2\)) ppm; IR (thin film): \(v\) \(_{\max}\) = 3060, 3023, 2813, 1650, 1597, 1491 cm\(^{-1}\); LRMS (EI\(^+\)): m/z (%): 232\([\text{M}]^{+}\), 100, 217 (\([\text{M}–\text{CH}_3]\)^{+}, 50); HRMS (EI\(^+\)): calculated for C\(_{18}\)H\(_{16}\): 232.1252; found: 232.1252.

1-(4-Methoxyphenyl)-2-vinyl-1,4-dihyronaphthalene (3b)

Following General Method A, the reaction mixture containing dendralene 1b (62 mg, 0.33 mmol), 1,2-dibromobenzene 2c (40 µL, 0.33 mmol) and n-BuLi (0.32 mL, 1.23 M, 0.40 mmol) in toluene (0.75 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (4 g SiO\(_2\), 3% EtOAc in PS 40–60) gave the mono DA adduct 3b as a colorless liquid (35 mg, 0.13 mmol, 40%). R\(_f\) = 0.33 (5% EtOAc in PS 40–60).

Following General Method B, the reaction mixture containing dendralene 1b (75 mg, 0.40 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.12 mL, 0.48 mmol) and CsF (110 mg, 0.73 mmol) in MeCN (0.75 mL) was stirred at 23 °C for 24h. After work up, purification by flash
column chromatography (4 g SiO₂, 3% EtOAc in PS 40–60) gave the mono DA adduct 3b as a colorless liquid (40 mg, 0.15 mmol, 38%).

Following General Method C, the reaction mixture containing dendralene 1b (75 mg, 0.40 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.29 mL, 1.21 mmol) and TBAF (1.41 mL, 1 M, 1.41 mmol) in THF (0.75 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (5 g SiO₂, 3% EtOAc in PS 40–60) gave the mono DA adduct 3b as a colorless liquid (51 mg, 0.19 mmol, 49%).

1H NMR (400 MHz, CDCl₃) δ 7.31 –7.22 (m, 1H), 7.22 –7.06 (m, 5H), 6.77 (d, J = 8.7 Hz, 2H), 6.41 (dd, J = 17.6, 10.9 Hz, 1H), 6.25 (dd, J = 5.4, 2.6 Hz, 1H), 5.23 (d, J = 17.6 Hz, 1H), 5.00 (d, J = 10.9 Hz, 1H), 4.87 (t, J = 2.8 Hz, 1H), 3.79 –3.65 (m, 4H), 3.55 (ddd, J = 22.2, 5.6, 2.4 Hz, 1H) ppm; 13C NMR (100 MHz, CDCl₃) δ 158.1 (Cq), 139.2 (Cq), 138.3 (Cq), 137.9 (CH), 137.7 (Cq), 132.9 (Cq), 128.9 (CH), 128.4 (2×CH), 128.3 (CH), 127.6 (CH), 126.6 (CH), 126.0 (CH), 114.1 (2×CH), 113.0 (CH₃), 55.3 (CH₃), 45.3 (CH), 31.1 (CH₃) ppm; IR (thin film): ν_max = 3033, 3003, 2901, 1507 cm⁻¹; LRMS (EI⁺): m/z (%): 262([M]⁺, 21), 247 ([M–CH₃]⁺, 13), 154 ([M–CH₂]⁺, 100); HRMS (EI⁺): calculated for C₁₉H₁₈O: 262.1358; found: 262.1358.

1-(p-Tolyl)-2-vinyl-1,4-dihydronaphthalene (3c)

Following General Method A, the reaction mixture containing dendralene 1c (98 mg, 0.58 mmol), 1,2-dibromobenzene 2c (68 µL, 0.58 mmol) and n-BuLi (0.56 mL, 1.23 M, 0.69 mmol) in toluene (1 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography...
(5 g SiO₂, 1% EtOAc in PS 40–60) gave the mono DA adduct 3c as a colorless liquid (56 mg, 0.23 mmol, 39%). Rₚ = 0.40 (5% EtOAc in PS 40–60).

Following General Method C, the reaction mixture containing dendralene 1c (110 mg, 0.65 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.31 mL, 1.3 mmol) and TBAF (1.4 mL, 1 M, 1.4 mmol) in THF (2 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (7 g SiO₂, 1% EtOAc in PS 40–60) gave the mono DA adduct 3c as a colorless liquid (96 mg, 0.39 mmol, 60%).

¹H NMR (400 MHz, CDCl₃) δ 7.30 – 7.23 (m, 1H), 7.18 – 7.08 (m, 5H), 7.03 (d, J = 7.9 Hz, 2H), 6.40 (dd, J = 17.6, 10.9 Hz, 1H), 6.25 (dd, J = 5.4, 2.6 Hz, 1H), 5.22 (d, J = 17.6 Hz, 1H), 4.98 (d, J = 10.9 Hz, 1H), 4.88 (t, J = 2.9 Hz, 1H), 3.74 (d, J = 22.1 Hz, 1H), 3.54 (ddd, J = 22.1, 5.4, 2.2 Hz, 1H), 2.25 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 142.5 (Cq), 139.1 (Cq), 138.2 (Cq), 137.9 (CH), 135.9 (Cq), 132.9 (Cq), 129.5 (2×CH), 129.0 (CH), 128.2 (CH), 127.6 (CH), 127.4 (2×CH), 126.6 (CH), 126.0 (CH), 113.0 (CH₂), 45.8 (CH), 31.2 (CH₂), 21.1 (CH₃) ppm; IR (thin film): νmax = 3020, 2920, 1687, 1610, 1509 cm⁻¹; LRMS (EI⁺): m/z (%): 246([M⁺]+, 81), 231 ([M–CH₃]+, 96), 215 (100); HRMS (EI⁺): calculated for C₁₉H₁₈: 246.1409; found: 246.1407.

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Diene-Transmissive Diels–Alder Sequences With Benzynes
(S)-6,7-Dimethoxy-1-(p-tolyl)-2-vinyl-1,4-dihyronaphthalene (3d)

Following General Method A, the reaction mixture containing dendralene 1c (50 mg, 0.29 mmol), 1,2-dibromo-4,5-dimethoxybenzene 2d (260 mg, 0.881 mmol) and n-BuLi (0.69 mL, 1.37 M, 0.94 mmol) in toluene (1 mL) was brought from –20 °C to 0 °C and stirred for 1h. After work up, purification by flash column chromatography (10 g SiO$_2$, 6% EtOAc in PS 40–60) gave the mono DA adduct 3d as a colorless liquid (45 mg, 0.15 mmol, 51%). $R_f$ = 0.50 (10% EtOAc in PS 40–60).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13 (d, $J$ = 8.0 Hz, 2H), 7.04 (d, $J$ = 8.0 Hz, 2H), 6.69 (s, 1H), 6.64 (s, 1H), 6.38 (dd, $J$ = 17.6, 11.0 Hz, 1H), 6.27 – 6.15 (m, 1H), 5.21 (d, $J$ = 17.6 Hz, 1H), 4.97 (d, $J$ = 11.0 Hz, 1H), 4.77 (t, $J$ = 3.1 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.77 – 3.62 (m, 1H), 3.57 – 3.35 (m, 1H), 2.26 (s, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.8 (Cq), 147.5 (Cq), 142.9 (Cq), 138.1 (Cq), 137.9 (CH), 135.8 (Cq), 131.0 (Cq), 129.5 (2×CH), 127.5 (CH), 127.3 (2×CH), 124.7 (Cq), 112.9 (CH$_2$), 111.5 (CH), 110.8 (CH), 56.0 (2×CH$_3$), 45.5 (CH), 30.9 (CH$_2$), 21.1 (CH$_2$) ppm; IR (thin film): $\nu_{max}$ = 3000, 2932, 2833, 1737, 1610, 1508 cm$^{-1}$; LRMS (EI$^+$/): m/z (%): 306 ([M$^+$], 100), 291 ([M–CH$_3$]$^+$), 23, 275 ([M–OCH$_3$]$^+$), 16; HRMS (EI$^+$): calculated for C$_{21}$H$_{22}$O$_2$: 306.1620; found: 306.1619.

(5)-5,8-Dimethoxy-1-(4-methoxyphenyl)-2-vinyl-1,4-dihyronaphthalene (3e)
Following **General Method C**, the reaction mixture containing dendralene 1b (246 mg, 1.32 mmol), 3,6-dimethoxy-2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2b (947 mg, 2.64 mmol) and TBAF (4.00 mL, 1 M, 3.96 mmol) in THF (2.5 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (25 g SiO₂, 3% EtOAc in PS 40–60) gave the mono DA adduct 3e as a white solid (238 mg, 0.738 mmol, 56%). Rf = 0.50 (10% EtOAc in PS 40–60); m.p. 127 – 131 °C (CH₂Cl₂).

**1H NMR (400 MHz, CDCl₃)** δ 7.24 (d, J = 8.7 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 6.63 (s, 2H), 6.37 (dd, J = 17.6, 10.9 Hz, 1H), 6.17 (dd, J = 5.8, 2.4 Hz, 1H), 5.52 (dd, J = 17.6 Hz, 1H), 5.17 (t, J = 2.7 Hz, 1H), 4.97 (d, J = 10.9 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.59–3.59 (m, 1H), 3.43 (d, J = 23.2 Hz, 1H) ppm; **13C NMR (100 MHz, CDCl₃)** δ 157.7 (Cq), 150.9 (Cq), 150.8 (Cq), 138.8 (Cq), 137.7 (Cq), 137.2 (Cq), 129.8 (Cq), 129.3 (2×CH), 129.3 (2×CH), 121.5 (CH₂), 108.4 (CH), 107.4 (CH), 55.8 (CH₃), 55.7 (CH₃), 55.2 (CH₃), 38.8 (CH), 26.0 (CH₂) ppm; **IR (thin film):** νmax = 2998, 2934, 2833, 1607, 1507 cm⁻¹; **LRMS (ESI⁺):** m/z (%): 323 ([M+H]⁺, 35), 345 ([M+Na]⁺, 100); **HRMS (ESI⁺):** calculated for C₂₁H₂₃O₃: 323.1642; found: 323.1645.

1-Pentyl-2-vinyl-1,4-dihydronaphthalene (3f)

Following **General Method A**, the reaction mixture containing dendralene 1d (46 mg, 0.31 mmol), 1,2-dibromobenzene 2c (36 µL, 0.31 mmol) and n-BuLi (0.30 mL, 1.23 M, 0.37 mmol) in toluene (0.5 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (4 g SiO₂, 100% PS 40–60) gave the mono DA adduct 3f as a colorless liquid (22 mg, 0.10 mmol, 32%). Rf = 0.50 (100% PS 40–60).

**1H NMR (400 MHz, CDCl₃)** δ 7.22–7.12 (m, 4H), 6.42 (dd, J = 17.6, 10.9 Hz, 1H), 6.04 (dd, J = 5.8, 2.4 Hz, 1H), 5.28 (d, J = 17.6 Hz, 1H), 5.05 (d, J = 10.9 Hz, 1H), 3.76–3.69 (m, 1H), 3.52 (d, J = 21.3 Hz, 1H), 3.37 (dd, J = 21.2, 5.6 Hz, 1H), 1.72–1.49 (m, 2H), 1.33–1.04 (m, 6H), 0.82 (t, J = 6.9 Hz, 3H) ppm; **13C NMR (100 MHz, CDCl₃)** δ 140.1 (Cq), 139.7 (Cq), 137.9 (CH), 135.2 (Cq), 128.6 (CH), 127.8 (CH), 127.5 (CH), 125.9 (CH), 125.8 (CH), 111.1 (CH₂), 39.7 (CH), 36.2 (CH₂), 32.1 (CH₂), 31.3 (CH₂), 26.0 (CH₂), 22.8 (CH₂), 14.2 (CH₃) ppm; **IR (thin film):**
\[ \nu_{\text{max}} = 3021, 2954, 2856, \text{cm}^{-1} \]; LRMS (EI): m/z (%): 226([M]^+) 21, 155 ([M–C_{10}H_{21}]+, 100), 128 ([M–C_{12}H_{24}]+, 22); HRMS (EI): calculated for C_{17}H_{22}: 226.1722; found: 226.1727.

1-Decyl-2-vinyl-1,4-dihydronaphthalene (3g)

Following General Method A, the reaction mixture containing dendralene 1e (90 mg, 0.41 mmol), 1,2-dibromobenzene 2c (49 \( \mu \)L, 0.41 mmol) and \( n \)-BuLi (0.40 mL, 1.23 M, 0.49 mmol) in toluene (1 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (6 g SiO\(_2\), 100% PS 40–60) gave the mono DA adduct 3g as a colorless liquid (35 mg, 0.12 mmol, 29%); \( R_f = 0.50 \) (100% PS 40–60).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.24 – 7.10 (m, 4H), 6.43 (dd, \( J = 17.6, 10.9 \text{ Hz} \), 1H), 6.04 (dd, \( J = 5.7, 2.3 \text{ Hz} \), 1H), 5.28 (d, \( J = 17.6 \text{ Hz} \), 1H), 5.05 (d, \( J = 10.9 \text{ Hz} \), 1H), 3.77 – 3.63 (m, 1H), 3.52 (d, \( J = 21.2 \text{ Hz} \), 1H), 3.37 (dd, \( J = 5.9, 1.4 \text{ Hz} \), 1H), 1.76 – 1.47 (m, 2H), 1.35 – 1.05 (m, 16H), 0.88 (t, \( J = 6.9 \text{ Hz} \), 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 140.1 (Cq), 139.8 (Cq), 137.9 (CH), 135.2 (Cq), 128.6 (CH), 127.8 (CH), 125.9 (CH), 125.8 (CH), 111.1 (CH\(_2\)), 39.8 (CH\(_2\)), 36.3 (CH\(_3\)), 31.3 (CH\(_3\)), 29.9 (CH\(_3\)), 29.8 (CH\(_3\)), 29.8 (CH\(_3\)), 29.5 (CH\(_3\)), 26.3 (CH\(_3\)), 22.8 (CH\(_3\)), 14.3 (CH\(_3\)) ppm; IR (thin film): \( \nu_{\text{max}} = 2922, 2852, 1685, 1646, 1456 \text{ cm}^{-1} \); LRMS (EI): m/z (%): 296([M]^+) 14, 155 ([M–C_{10}H_{21}]+, 100), 128 ([M–C_{12}H_{24}]+, 100); HRMS (EI): calculated for C_{22}H_{32}: 296,2504; found: 296,2509.

1-Cyclohexyl-2-vinyl-1,4-dihydronaphthalene (3h)
Following **General Method A**, the reaction mixture containing dendralene 1f (49 mg, 0.30 mmol), 1,2-dibromobenzene 2c (36 µL, 0.30 mmol) and n-BuLi (0.29 mL, 1.23 M, 0.36 mmol) in toluene (0.6 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (4 g SiO₂, 100% PS 40–60) gave the mono DA adduct 3h as a colorless liquid (25 mg, 0.105 mmol, 35%). Rᵣ = 0.50 (100% PS 40–60).

1H NMR (400 MHz, CDCl₃) δ 7.18 – 7.13 (m, 4H), 6.44 (dd, J = 17.6, 10.9 Hz, 1H), 6.10 (dd, J = 6.2, 2.4 Hz, 1H), 5.25 (d, J = 17.6 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 3.59 (brs, 1H), 3.52 (d, J = 21.3 Hz, 1H), 3.32 (dd, J = 21.2, 6.0 Hz, 1H), 1.82 – 1.46 (m, 6H), 1.32 – 0.85 (m, 4H), 0.61 (qd, J = 12.9, 12.3, 4.0 Hz, 1H) ppm; 13C NMR (100 MHz, CDCl₃) δ 139.9 (Cq), 138.6 (CH), 137.9 (Cq), 136.2 (Cq), 129.6 (CH), 128.2 (CH), 127.7 (CH), 125.8 (CH), 125.3 (CH), 111.1 (CH), 46.1 (CH), 44.7 (CH), 32.5 (CH₂), 32.2 (CH₂), 28.8 (CH₃), 27.1 (CH₃), 26.7 (CH₃), 26.4 (CH₃) ppm; IR (thin film): vmax = 2922, 2850, 1678, 1646, 1448 cm⁻¹; LRMS (EI⁺): m/z (%): 238([M]+•, 25), 155 ([M–C₆H₁₁]+•, 96), 154 ([M–C₆H₁₂]+•, 100); HRMS (EI⁺): calculated for C₁₈H₂₂: 238.1722; found: 238.1722.

1-PHENETHYL-2-VINYL-1,4-DIHYDRONAPHTHALENE (3i)

Following **General Method A**, the reaction mixture containing dendralene 1g (102 mg, 0.55 mmol), 1,2-dibromobenzene 2c (66 µL, 0.55 mmol) and n-BuLi (0.54 mL, 1.23 M, 0.66 mmol) in toluene (1 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (6 g SiO₂, 100% PS 40–60) gave the mono DA adduct 3i as a colorless liquid (38 mg, 0.15 mmol, 27%). Rᵣ = 0.29 (100% PS 40–60).

1H NMR (400 MHz, CDCl₃) δ 7.29 – 7.17 (m, 6H), 7.17 – 7.11 (m, 1H), 7.08 (d, J = 7.0 Hz, 2H), 6.44 (dd, J = 17.6, 10.9 Hz, 1H), 6.08 (dd, J = 5.8, 2.4 Hz, 1H), 5.22 (d, J = 17.6 Hz, 1H), 5.04 (d, J = 10.9 Hz, 1H), 3.87 – 3.77 (m, 1H), 3.56 (d, J = 21.5 Hz, 1H), 3.42 (dd, J = 21.4, 5.7 Hz, 1H), 2.62 – 2.50 (m, 1H), 2.45 – 2.33 (m, 1H), 2.06 – 1.86 (m, 2H) ppm; 13C NMR (100 MHz, CDCl₃) δ 142.5 (Cq), 139.5 (Cq), 139.1 (Cq), 137.7 (CH), 135.2 (Cq), 128.6 (CH), 128.5 (2×CH), 128.4
(2CH), 128.0 (CH), 127.8 (CH), 126.1 (CH), 126.0 (CH), 125.8 (CH), 111.4 (CH), 39.4 (CH), 37.9 (CH), 32.3 (CH), 31.3 (CH) ppm; IR (thin film): νmax = 3084, 3061, 3024, 2920, 2856, 1646, 1604, 1494 cm⁻¹; LRMS (EI⁺): m/z (%): 260 ([M⁺]⁺, 4), 155 ([M-C₆H₅CH₂CH₂]⁺, 100), 128 ([M-C₁₀H₁₂]⁺, 29); HRMS (EI⁺): calculated for C₂₀H₂₀: 260.1565; found: 260.1571.

1-(Phenylenethynyl)-2-vinyl-1,4-dihyronaphthalene (3j)

Following General Method A, the reaction mixture containing dendralene 1h (78 mg, 0.43 mmol), 1,2-dibromobenzene 2c (51 µL, 0.43 mmol) and n-BuLi (0.35 mL, 1.5 M, 0.52 mmol) in toluene (1 mL) was stirred at 0 °C for 1h. After work up, purification by flash column chromatography (5 g SiO₂, 1% EtOAc in PS 40–60) gave the mono DA adduct 3j as a colorless liquid (39 mg, 0.15 mmol, 35%). Rf = 0.40 (5% EtOAc in PS 40–60).

¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, J = 7.2 Hz, 1H), 7.35 – 7.16 (m, 8H), 6.51 (dd, J = 17.6, 10.9 Hz, 1H), 6.12 (dd, J = 5.3, 2.8 Hz, 1H), 5.59 (d, J = 17.6 Hz, 1H), 5.21 (d, J = 10.9 Hz, 1H), 4.86 (t, J = 3.2 Hz, 1H), 3.69 (d, J = 22.1 Hz, 1H), 3.48 (ddd, J = 22.0, 5.2, 2.8 Hz, 1H) ppm;
¹³C NMR (100 MHz, CDCl₃) δ 137.0 (CH), 134.9 (2×Cq), 133.5 (Cq), 131.8 (2×CH), 129.1 (CH), 128.2 (CH), 128.2 (2×CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 126.8 (CH), 123.8 (CH₂), 113.1 (Cq), 90.9 (Cq), 80.7 (Cq), 31.9 (CH), 30.6 (CH₂) ppm; IR (thin film): νmax = 3059, 3020, 2962, 2856, 1657, 1597 cm⁻¹; LRMS (EI⁺): m/z (%): 256([M⁺]⁺, 65), 255 ([M-H]⁺, 72), 154 (100); HRMS (EI⁺): calculated for C₂₀H₁₆: 256.1252; found: 256.1253.
Twofold Cycloadditions to Substituted [3]Dendralenes

(rel)-(3aR,6R,11aR,11bS)-2-Methyl-6-phenyl-3a,4,6,11,11a,11b-hexahydro-1H-naphtho[2,3-e]isoindole-1,3(2H)-dione (5a)

Following General Method C, the reaction mixture containing dendralene 1a (95 mg, 0.61 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.44 mL, 1.8 mmol) and TBAF (2.1 mL, 2 M, 2.1 mmol) in THF (3 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO$_3$ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. N-Methylmaleimide 4a (405 mg, 3.65 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 10h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH$_2$Cl$_2$, then the filtrate was further diluted with CH$_2$Cl$_2$ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After work up, purification by flash column chromatography (20 g SiO$_2$, 25% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5a as a white solid (123 mg, 0.360 mmol, 59%). $R_f = 0.34$ (30% EtOAc in PS 40–60); m.p. 153 – 159 °C (10% EtOAc in hexane).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.32 (m, 2H), 7.32 – 7.24 (m, 2H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.16 – 7.07 (m, 3H), 6.79 (d, $J = 7.6$ Hz, 1H), 5.47 – 5.35 (m, 1H), 4.47 (s, 1H), 3.62 (dd, $J = 14.8$, 9.9 Hz, 1H), 3.23 (dd, $J = 8.5$, 6.7 Hz, 1H), 3.12 (t, $J = 7.6$ Hz, 1H), 3.02 (dd, $J = 14.8$, 6.2 Hz, 1H), 2.83 (s, 3H), 2.76–2.61 (m, 2H), 2.18 – 2.06 (m, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.8 (Cq), 178.3 (Cq), 178.3 (Cq), 143.8 (Cq), 139.4 (Cq), 139.3 (Cq), 138.0 (Cq), 130.2 (2×CH), 128.6 (2×CH), 128.1 (CH), 127.0 (CH), 126.7 (CH), 126.5 (CH), 126.4 (CH), 120.7 (CH), 51.5 (CH), 43.8 (CH), 40.4 (CH), 35.8 (CH), 31.3 (CH), 24.9 (CH$_2$), 24.7 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}}$ = 3029, 2951, 2851, 1772, 1696 cm$^{-1}$; LRMS (EI$^+$): m/z (%): 343 ([M$^+$], 100), 231 (79), 215 (60); HRMS (EI$^+$): calculated for C$_{23}$H$_{21}$NO$_2$: 343.1572; found: 343.1570.
(rel)-(3aR,6R,11aR,11bS)-2-Methyl-6-(p-tolyl)-3a,4,6,11,11a,11b-hexahydro-1H-naphtho[2,3-e]isoindole-1,3(2H)-dione (5b)

Following General Method C, the reaction mixture containing dendralene 1c (103 mg, 0.60 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.37 mL, 1.5 mmol) and TBAF (1.8 mL, 1 M, 1.8 mmol) in THF (2 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO₃ (120 mg) and Dowex 50WX8–400 resin (420 mg) were added and stirring was continued for 10 minutes. N-Methylmaleimide 4a (403 mg, 3.63 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 10h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH₂Cl₂, then the filtrate was further diluted with CH₂Cl₂ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO₂, 20% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5b as a colorless liquid (121 mg, 0.340 mmol, 56%). Rf = 0.33 (30% EtOAc in PS 40–60).

1H NMR (400 MHz, CDCl₃) δ 7.30 – 7.23 (m, 1H), 7.22 – 7.14 (m, 3H), 7.14 – 7.07 (m, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 7.6 Hz, 1H), 5.46 – 5.39 (m, 1H), 4.44 (s, 1H), 3.63 (dd, J = 14.8, 10.0 Hz, 1H), 3.23 (dd, J = 8.7, 6.5 Hz, 1H), 3.16 – 3.06 (m, 1H), 3.02 (dd, J = 14.8, 6.2 Hz, 1H), 2.83 (s, 3H), 2.75 – 2.61 (m, 2H), 2.37 (s, 3H), 2.17 – 2.06 (m, 1H) ppm; 13C NMR (100 MHz, CDCl₃) δ 179.8 (Cq), 178.3 (Cq), 143.9 (Cq), 139.5 (Cq), 138.0 (Cq), 136.6 (Cq), 136.2 (Cq), 130.1 (2×CH), 129.3 (2×CH), 128.0 (CH), 126.6 (CH), 126.4 (CH), 126.3 (CH), 120.4 (CH), 51.1 (CH), 43.8 (CH), 40.4 (CH), 35.9 (CH), 31.3 (CH₂), 24.8 (CH₃), 24.8 (CH₃), 21.2 (CH₃) ppm; IR (thin film): νmax = 3021, 2946, 2843, 1772, 1698 cm⁻¹; LRMS (El⁺): m/z (%): 357 ([M⁺]*, 100), 342 ([M–CH₃]⁺, 28); HRMS (El⁺): calculated for C₂₄H₂₃NO₂: 357.1729; found: 357.1729.
Following General Method C, the reaction mixture containing dendralene 1j (69 mg, 0.34 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.17 mL, 0.69 mmol) and TBAF (1.0 mL, 1 M, 1.0 mmol) in THF (1.5 mL) was stirred at 0 °C for 1 h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO$_3$ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. N-Methylmaleimide 4a (229 mg, 2.06 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 8 h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH$_2$Cl$_2$, then the filtrate was further diluted with CH$_2$Cl$_2$ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO$_2$, 25% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5c as a yellow solid (59 mg, 0.15 mmol, 44%). R$_f$ = 0.42 (50% EtOAc in hexane). 1H NMR (400 MHz, CDCl$_3$) δ 8.23 (d, J = 8.5 Hz, 2H), 7.39 – 7.23 (m, 4H), 7.15 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 7.5 Hz, 1H), 5.47 (s, 1H), 4.62 (s, 1H), 3.63 (dd, J = 14.9, 9.2 Hz, 1H), 3.32 – 3.23 (m, 1H), 3.21 – 3.13 (m, 1H), 3.00 (dd, J = 15.0, 6.4 Hz, 1H), 2.91 – 2.66 (m, 5H), 2.26 – 2.10 (m, 1H) ppm; 13C NMR (100 MHz, CDCl$_3$) δ 179.5 (Cq), 177.9 (Cq), 147.7 (Cq), 147.1 (Cq), 142.9 (Cq), 137.7 (Cq), 137.7 (Cq), 130.9 (2×CH), 128.7 (CH), 127.1 (CH), 126.7 (CH), 126.5 (CH), 123.8 (2×CH), 121.8 (CH), 51.3 (CH), 43.7 (CH), 40.2 (CH), 35.4 (CH), 31.1 (CH$_2$), 24.9 (CH$_2$), 24.6 (CH$_3$) ppm. IR (thin film): v$_{max}$ = 3071, 2947, 2848, 2254, 1772, 1691 cm$^{-1}$; LRMS (ESI$^+$): m/z (%) 389 ([M+1]$^+$, 20), 411 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calculated for C$_{23}$H$_{21}$N$_2$O$_4$: 389.1496; found: 389.1497.
Following General Method C, the reaction mixture containing dendralene 1b (55 mg, 0.30 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (215 mL, 0.886 mmol) and TBAF (1.0 mL, 1 M, 1.03 mmol) in THF (1.5 mL) was stirred at 0 °C for 1 h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO$_3$ (120 mg) and Dowex 50WX-8 res in (420 mg) and stirring was continued for 10 minutes. N-Methylemaleimide 4a (131 mg, 1.18 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 10 h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH$_2$Cl$_2$, then the filtrate was further diluted with CH$_2$Cl$_2$ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO$_2$, 25% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5d as a white solid (53 mg, 0.142 mmol, 48%). $R_f$ = 0.30 (40% EtOAc in PS 40–60); m.p. 169 – 173 °C (hexane:EtOAc, 8:2).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.29 – 7.24 (m, 1H), 7.19 (t, $J$ = 7.3 Hz, 1H), 7.10 (t, $J$ = 7.5 Hz, 1H), 7.05 (d, $J$ = 8.6 Hz, 2H), 6.90 (d, $J$ = 8.6 Hz, 2H), 6.78 (d, $J$ = 7.6 Hz, 1H), 5.46 – 5.36 (m, 1H), 4.42 (s, 1H), 3.83 (s, 3H), 3.63 (dd, $J$ = 14.7, 10.2 Hz, 1H), 3.23 (dd, $J$ = 8.6, 6.5 Hz, 1H), 3.12 (t, $J$ = 7.4 Hz, 1H), 3.02 (dd, $J$ = 14.8, 6.1 Hz, 1H), 2.84 (s, 3H), 2.76 – 2.59 (m, 2H), 2.16 – 2.04 (m, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 179.8 (Cq), 178.3 (Cq), 158.7 (Cq), 144.1 (Cq), 139.7 (Cq), 138.1 (Cq), 131.3 (2×CH), 131.2 (Cq), 128.0 (CH), 126.6 (CH), 126.4 (CH), 126.4 (CH), 114.0 (2×CH), 55.4 (CH$_3$), 50.6 (CH), 43.8 (CH), 40.4 (CH), 36.0 (CH), 31.4 (CH$_2$), 24.9 (CH$_2$), 24.8 (CH$_3$) ppm; IR (thin film): $\nu_{max}$ = 2946, 2835, 1772, 1694, 1611, 1511 cm$^{-1}$; LRMS (EI$^-$): m/z (%): 373 ([M]$^-$, 100), 358 ([M–CH$_3$]$^-$, 3), 342 ([M–OCH$_3$]$^-$, 22); HRMS (EI$^-$): calculated for C$_{24}$H$_{23}$NO$_3$: 373.1678; found: 373.1678.
Following General Method C, the reaction mixture containing dendralene 1d (61 mg, 0.41 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.25 mL, 1.0 mmol) and TBAF (1.2 mL, 1 M, 1.2 mmol) in THF (1.5 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO$_3$ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. N-Methylmaleimide 4a (271 mg, 2.44 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 10h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH$_2$Cl$_2$, then the filtrate was further diluted with CH$_2$Cl$_2$ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO$_2$, 15% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5e as a colorless liquid (69 mg, 0.20 mmol, 50%). $R_f$ = 0.66 (40% EtOAc in PS 40–60).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.24 – 7.18 (m, 1H), 7.18 – 7.12 (m, 2H), 7.08 – 7.01 (m, 1H), 5.71 – 5.60 (m, 1H), 3.41 (dd, $J$ = 15.1, 7.1 Hz, 1H), 3.23 – 3.04 (m, 4H), 2.84 – 2.70 (m, 4H), 2.68 – 2.57 (m, 1H), 2.16 – 2.00 (m, 1H), 1.77 – 1.60 (m, 2H), 1.45 – 1.18 (m, 6H); 13C NMR (100 MHz, CDCl$_3$) $\delta$ 179.9 (Cq), 177.9 (Cq), 143.2 (Cq), 140.1 (Cq), 137.4 (Cq), 128.6 (CH), 126.3 (CH), 126.0 (CH), 125.4 (CH), 118.5 (CH), 45.8 (CH), 43.9 (CH), 40.7 (CH), 35.2 (CH), 32.1 (CH$_2$), 31.4 (CH$_2$), 31.0 (CH$_2$), 27.7 (CH$_2$), 24.7 (CH$_3$), 24.2 (CH$_3$), 22.7 (CH$_2$), 14.2 (CH$_3$) ppm; IR (thin film): $\nu_{max}$ = 2952, 2928, 2855, 1773, 1696 cm$^{-1}$; LRMS (ESI$^+$): m/z (%): 338 ([M+1]$^+$, 42), 360 ([M+Na]$^+$, 100); HRMS (ESI$^+$): calculated for C$_{22}$H$_{28}$N$: 338.2111; found: 338.2111.
Following General Method C, the reaction mixture containing dendralene 1g (59 mg, 0.32 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.23 mL, 0.96 mmol) and TBAF (1.1 mL, 1 M, 1.1 mmol) in THF (1.5 mL) was stirred at 0 °C for 1 h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO$_3$ (120 mg) and Dowex 50WX–400 resin (420 mg) and stirring was continued for 10 minutes. N-Methylmaleimide 4a (231 mg, 1.91 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 10 h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH$_2$Cl$_2$, then the filtrate was further diluted with CH$_2$Cl$_2$ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO$_2$, 17% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5f as a colorless liquid (52 mg, 0.14 mmol, 44%). R$_f$ = 0.30 (30% EtOAc in PS 40–60).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.35 – 7.11 (m, 8H), 7.11 – 7.02 (m, 1H), 5.78 – 5.66 (m, 1H), 3.40 (dd, $J$ = 15.2, 6.8 Hz, 1H), 3.24 (t, $J$ = 6.7 Hz, 1H), 3.21 – 3.06 (m, 3H), 2.79 (ddd, $J$ = 15.3, 7.1, 2.0 Hz, 1H), 2.73 (s, 3H), 2.71 – 2.65 (m, 3H), 2.16 – 1.97 (m, 3H) ppm;

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 179.8 (Cq), 177.8 (Cq), 142.8 (Cq), 142.1 (Cq), 139.6 (Cq), 137.3 (Cq), 128.9 (CH), 128.5 (2×CH), 126.4 (CH), 126.2 (CH), 126.0 (CH), 125.5 (CH), 119.1 (CH), 45.5 (CH), 43.9 (CH), 40.6 (CH), 35.0 (CH), 34.1 (CH$_2$), 33.3 (CH$_2$), 31.0 (CH$_2$), 24.7 (CH$_3$), 24.1 (CH$_2$) ppm; IR (thin film): $\nu_{max}$ = 3023, 2928, 2851, 1772, 1696 cm$^{-1}$; LRMS (EI$^+$): m/z (%): 371 ([M$^+$]+, 47), 266 ([M–C$_3$H$_7$CH$_2$CH$_2$]$^+$, 100), 178 (31), 155 (57); HRMS (EI$^+$): calculated for C$_{25}$H$_{25}$NO$_2$: 371.1885; found: 371.1883.
Diene-Transmissive Diels–Alder Sequences With Benzynes

(re-(3aR,6aR,11aR,11bS)-2-Methyl-6-(1-tosyl-1H-indol-3-yl)-3a,4,6,11a,11b-hexahydro-1H-naphtho[2,3-e]isoindole-1,3(2H)-dione (5g)

Following General Method C, the reaction mixture containing dendralene 1i (91 mg, 0.26 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.16 mL, 0.65 mmol) and TBAF (0.78 mL, 1 M, 0.78 mmol) in THF (3 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO₃ (120 mg) and Dowex 50WX–400 resin (420 mg) and stirring was continued for 10 minutes. N-Methylmaleimide 4a (174 mg, 1.6 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 10 h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH₂Cl₂, then the filtrate was further diluted with CH₂Cl₂ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO₂, 30% EtOAc in PS 40–60) gave the double Diels-Alder adduct 5g as a white solid (63 mg, 0.12 mmol, 45%). Rf = 0.34 (40% EtOAc in PS 40–60); m.p. 157 – 161 °C (Et₂O:CH₂Cl₂, 5:5).

¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.39 (s, 1H), 7.28 – 7.15 (m, 4H), 7.12 (t, J = 7.4 Hz, 1H), 7.06 – 6.95 (m, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.53 (d, J = 7.7 Hz, 1H), 5.21 – 5.02 (m, 1H), 4.67 (s, 1H), 3.74 – 3.55 (m, 1H), 3.21 – 3.13 (m, 1H), 3.11 – 2.99 (m, 2H), 2.87 (s, 3H), 2.63 – 2.52 (m, 1H), 2.51 (dd, J = 15.2, 7.2 Hz, 1H), 2.32 (s, 3H), 2.08 – 1.88 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 179.7 (Cq), 178.3 (Cq), 145.1 (Cq), 141.4 (Cq), 138.1 (Cq), 137.3 (Cq), 136.1 (Cq), 135.1 (Cq), 130.0 (Cq), 127.7 (CH), 126.9 (2×CH), 126.7 (CH), 126.5 (CH), 126.4 (CH), 126.1 (CH), 124.8 (CH), 123.0 (CH), 121.9 (CH), 120.6 (Cq), 120.3 (CH), 114.3 (CH), 43.6 (CH), 42.5 (CH), 40.2 (CH), 36.2 (CH), 31.5 (CH₃), 25.0 (CH₃), 24.9 (CH₂), 21.7 (CH₃) ppm; IR (thin film): vmax = 3057, 2945, 2854, 1771, 1694 cm⁻¹; LRMS (ESI⁺): m/z (%): 537 ([M+H⁺]⁺, 8), 559 ([M+Na⁺]⁺, 100); HRMS (ESI⁺): calculated for C₃₂H₃₁N₂O₄S: 537.1843; found: 537.1843.
Following General Method C, the reaction mixture containing dendralene 1c (53 mg, 0.31 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.19 mL, 0.78 mmol) and TBAF (0.93 mL, 1 M, 0.93 mmol) in THF (2 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO₃ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. PTAD 4b (162 mg, 0.93 mmol) was added and the reaction mixture was stirred at 23 °C for 20h. The reaction mixture was filtered through a plug of Celite. The Celite pad was washed with 5 mL CH₂Cl₂, then the filtrate was further diluted with CH₂Cl₂ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO₂, 30% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5h as a white solid (83 mg, 0.20 mmol, 63%). Rᵢ = 0.60 (40% EtOAc in PS 40–60); m.p. 175–180 °C (hexane:EtOAc, 8:2).

¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.8 Hz, 2H), 7.41 – 7.33 (m, 1H), 7.25 – 7.17 (m, 3H), 7.10 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 7.2 Hz, 1H), 6.95 (t, J = 8.0 Hz, 2H), 6.06 (s, 1H), 4.98 (s, 1H), 4.83 – 4.68 (m, 1H), 4.35 (dd, J = 16.1, 4.3 Hz, 1H), 4.07 (dt, J = 16.1, 2.3 Hz, 1H), 3.72 (dd, J = 15.4, 5.9 Hz, 1H), 3.01 (dd, J = 15.3, 11.3 Hz, 1H), 2.32 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 152.6 (Cq), 151.6 (Cq), 141.0 (Cq), 137.8 (Cq), 136.8 (Cq), 136.4 (Cq), 134.0 (Cq), 131.3 (Cq), 130.1 (CH), 129.4 (3=CH), 129.3 (2=CH), 128.2 (CH), 128.2 (2=CH), 127.2 (2=CH), 125.6 (2=CH), 113.1 (CH), 52.3 (CH), 49.9 (CH), 43.3 (CH₂), 34.6 (CH₂), 21.1 (CH₃) ppm; IR (thin film): v_max = 3048, 3020, 2920, 2852, 2249, 1772, 1706 cm⁻¹; LRMS (ESI⁺): m/z (%): 422 ([M+H]⁺, 30), 444 ([M+Na]⁺, 100); HRMS (ESI⁺): calculated for C₂₇H₂₄N₃O₂: 422.1863; found: 422.1862.
(R)-Dimethyl (9aS,10R)-10-(4-methoxyphenyl)-3,9,9a,10-tetrahydroanthracene-1,2-
dicarboxylate (5i)

Following General Method C, the reaction mixture containing dendralene 1b (56 mg, 0.30 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.22 mL, 0.90 mmol) and TBAF (1.1 mL, 1 M, 1.05 mmol) in THF (1.5 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO₃ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. DMAD 4c (0.37 mL, 3.0 mmol) was added and the reaction mixture was heated under reflux for 20h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH₂Cl₂, then the filtrate was further diluted with CH₂Cl₂ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO₂, 8% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5i as a white solid (36 mg, 0.09 mmol, 30%). Rf = 0.26 (20% EtOAc in PS 40–60); m.p. 88–91 °C (hexane:EtOAc, 8:2).

¹H NMR (400 MHz, CDCl₃) δ 7.22 – 7.11 (m, 3H), 6.99 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.6 Hz, 2H), 5.83 (t, J = 3.4 Hz, 1H), 4.72 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.76 (s, 3H), 3.48 – 3.37 (m, 1H), 3.24 (dd, J = 16.0, 5.5 Hz, 1H), 3.16 (dd, J = 23.3, 7.0, 2.9 Hz, 1H), 2.99 (dd, J = 23.3, 6.5, 3.8 Hz, 1H), 2.79 (dd, J = 15.9, 12.2 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 168.7 (Cq), 168.2 (Cq), 158.3 (Cq), 137.8 (Cq), 137.8 (Cq), 137.2 (Cq), 136.9 (Cq), 135.8 (Cq), 131.5 (Cq), 130.2 (CH), 129.3 (2×CH), 128.9 (CH), 126.7 (CH), 126.6 (CH), 115.5 (CH), 113.8 (2×CH), 55.4 (CH₃), 52.4 (CH₃), 52.4 (CH₃), 52.1 (CH), 37.2 (CH₃), 33.0 (CH), 28.1 (CH₂) ppm; IR (thin film): v max = 3001, 2950, 2895, 2836, 2255, 1720 cm⁻¹; LRMS (EI⁺): m/z (%): 404 (M⁺¹, 11), 370 (41), 264 (70), 207 (100); HRMS (EI⁺): calculated for C₂₅H₂₄O₅: 404.1624; found: 404.1611.
Following General Method C, the reaction mixture containing dendralene 1k (74 mg, 0.22 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.13 mL, 0.55 mmol) and TBAF (0.66 mL, 1 M, 0.66 mmol) in THF (2.5 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO$_3$ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. N-Methylmaleimide 4a (121 mg, 1.10 mmol) was added and the reaction mixture was refluxed at 66 °C for 10h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH$_2$Cl$_2$, then the filtrate was further diluted with CH$_2$Cl$_2$ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO$_2$, 18% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5j as a white solid (62 mg, 0.12 mmol, 54%). $R_f = 0.49$ (30% EtOAc in PS 40–60); m.p. 191 – 195 °C (hexane:CH$_2$Cl$_2$, 9:1).

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, $J = 7.4$ Hz, 2H), 7.52 (t, $J = 7.5$ Hz, 2H), 7.45 – 7.39 (m, 1H), 7.35 – 7.15 (m, 5H), 7.14 – 7.03 (m, 4H), 6.98 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 7.3$ Hz, 1H), 6.72 (d, $J = 6.2$ Hz, 1H), 5.65 (s, 1H), 5.32 (d, $J = 11.6$ Hz, 1H), 4.67 (s, 1H), 3.87 (s, 3H), 3.62 – 3.51 (m, 1H), 3.18 (t, $J = 8.1$ Hz, 1H), 3.05 – 2.96 (m, 1H), 2.92 (d, $J = 11.4$ Hz, 1H), 2.85 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 178.0 (Cq), 175.9 (Cq), 158.9 (Cq), 145.5 (Cq), 141.4 (Cq), 140.5 (Cq), 140.0 (Cq), 139.5 (Cq), 132.3 (2×CH), 130.2 (2×CH), 129.9 (Cq), 129.2 (2×CH), 128.9 (2×CH), 128.4 (2×CH), 127.5 (CH), 127.1 (CH), 126.4 (CH), 126.3 (CH), 126.2 (CH), 126.1 (CH), 122.6 (CH), 114.3 (2×CH), 55.4 (CH$_3$), 50.5 (CH), 47.3 (CH), 45.2 (CH), 44.6 (CH), 43.3 (CH), 42.4 (CH), 24.8 (CH$_3$) ppm; IR (thin film): $v_{max} \approx 3057, 3031, 2956, 2925, 2856, 1771, 1694$ cm$^{-1}$; LRMS (ESI$^+$): m/z (%): 526 ([M+H]$^+$), 45, 548 ([M+Na]$^+$), 100; HRMS (ESI$^+$): calculated for C$_{36}$H$_{32}$NO$_3$: 526.2382; found: 526.2385.
Following **General Method C**, the reaction mixture containing dendralene 1k (94 mg, 0.28 mmol), 2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2a (0.17 mL, 0.69 mmol) and TBAF (0.83 mL, 1 M, 0.83 mmol) in THF (3 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO₃ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. PTAD 4b (146 mg, 0.833 mmol) was added and the reaction mixture was stirred at 23 °C for 16h. The reaction mixture was filtered through a plug of Celite. The Celite pad was washed with 5 mL CH₂Cl₂, then the filtrate was further diluted with CH₂Cl₂ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO₂, 20% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5k as an amorphous solid (91 mg, 0.15 mmol, 55%). Rf = 0.40 (40% EtOAc in PS 40–60).

$$\begin{align*}
\text{H NMR} & (400 \text{ MHz, CDCl}_3) \delta 7.53 (d, J = 7.1 \text{ Hz}, 2H), 7.44 (t, J = 7.4 \text{ Hz}, 2H), 7.41 - 7.30 \text{ (m, 8H), 7.30 - 7.18 (m, 5H), 7.17 - 7.11 (m, 3H), 7.00 (d, J = 7.8 \text{ Hz}, 1H), 6.92 (d, J = 8.7 \text{ Hz}, 2H), 5.88 (s, 1H), 5.34 (s, 1H), 5.05 (s, 1H), 5.02 (d, J = 10.5 \text{ Hz}, 1H), 4.68 (d, J = 10.5 \text{ Hz}, 1H), 3.84 (s, 3H) ppm; } \\
\text{C NMR} & \delta 158.9 (C\alpha), 155.0 (C\alpha), 148.7 (C\alpha), 141.0 (C\alpha), 139.0 (C\alpha), 138.9 (C\alpha), 137.0 (C\alpha), 136.6 (C\alpha), 135.3 (C\alpha), 131.4 (C\alpha), 130.4 (CH), 130.1 (CH), 130.0 (2×CH), 129.4 (2×CH), 129.1 (2×CH), 128.9 (2×CH), 128.9 (2×CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.8 (2×CH), 127.6 (CH), 127.3 (CH), 125.5 (2×CH), 119.4 (CH), 114.4 (2×CH), 114.4 (2×CH), 62.0 (CH), 55.5 (CH), 55.4 (CH), 54.5 (CH), 52.4 (CH) ppm; IR (thin film): \nu_{max} = 3062, 3028, 2836, 2252, 1778, 1720 \text{ cm}^{-1}; \text{LRMS (ESI)}: m/z (%) 590 ([M+H]^{+}, 100), 612 ([M+Na]^{+}, 65); \text{HRMS (ESI)}^+: \text{calculated for C}_{39}H_{31}N_{3}O_{3}Na: 612.2263; found: 612.2275.}
\end{align*}$$
(rel)-(3aR,6R,11aR,11bS)-7,10-Dimethoxy-6-(4-methoxyphenyl)-2-methyl-3a,4,6,11a,11b-hexahydro-1H-naptho[2,3-e]isoindole-1,3(2H)-dione (5l)

Following General Method C, the reaction mixture containing dendralene 1b (72 mg, 0.39 mmol), 3,6-dimethoxy-2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2b (277 mg, 0.773 mmol) and TBAF (1.2 mL, 1 M, 1.2 mmol) in THF (2 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO₃ (120 mg) and Dowex 50WX–400 resin (420 mg) and stirring was continued for 10 minutes. N-Methylmaleimide 4a (257 mg, 2.32 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 3h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The Celite pad was washed with 5 mL CH₂Cl₂, then the filtrate was further diluted with CH₂Cl₂ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO₂, 30% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5l as a white solid (83 mg, 0.19 mmol, 49%). Rf = 0.24 (40% EtOAc in PS 40–60); m.p. 173 – 175 °C (Et₂O:CH₂Cl₂, 9.8:0.2).

¹H NMR (400 MHz, CDCl₃) δ 6.90 (d, J = 8.5 Hz, 2H), 6.82 – 6.61 (m, 4H), 6.05 – 5.87 (m, 1H), 5.04 (s, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.68 (s, 3H), 3.24 – 2.98 (m, 3H), 2.90 – 2.82 (m, 1H), 2.82 – 2.73 (m, 1H), 2.70 (s, 3H), 2.62 (dd, J = 16.1, 7.7 Hz, 1H), 2.40 – 2.26 (m, 1H) ppm;

¹³C NMR (100 MHz, CDCl₃) δ 179.9 (Cq), 177.5 (Cq), 158.0 (Cq), 151.7 (Cq), 150.4 (Cq), 141.7 (Cq), 134.3 (Cq), 128.3 (2×CH), 128.3 (Cq), 127.1 (Cq), 120.4 (CH), 113.6 (2×CH), 108.7 (CH), 108.4 (CH), 56.2 (CH₂), 56.1 (CH₃), 55.3 (CH), 45.0 (CH), 43.5 (CH), 39.4 (CH), 31.5 (CH), 24.6 (CH₂), 24.5 (CH₃), 23.1 (CH₂) ppm; IR (thin film): v max = 2997, 2941, 2834, 2250, 1774, 1698 cm⁻¹; LRMS (ESI⁺): m/z (%): 456 ([M+Na]⁺, 100), 434 ([M+H]⁺, 15); HRMS (ESI⁺): calculated for C₂₆H₂₇NO₅Na: 456.1781; found: 456.1770.
Following General Method C, the reaction mixture containing dendralene 1d (82 mg, 0.55 mmol), 3,6-dimethoxy-2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2b (391 mg, 1.09 mmol) and TBAF (1.4 mL, 1 M, 1.4 mmol) in THF (2 mL) was stirred at 0 °C for 1 h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO₃ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. N-Methylmaleimide 4a (182 mg, 1.64 mmol) was added and the reaction mixture was heated under reflux at 66 °C for 4 h. The reaction mixture was cooled to 23 °C and filtered through a plug of Celite. The filtrate was further diluted with CH₂Cl₂ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO₂, 20% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5m as a white solid (124 mg, 0.312 mmol, 57%). Rf = 0.41 (40% EtOAc in PS 40–60); m.p. 113–117 °C (hexane:CH₂Cl₂, 9.5:0.5).

¹H NMR (400 MHz, CDCl₃) δ 6.76 – 6.49 (m, 2H), 5.76 – 5.58 (m, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.69 (dd, J = 9.4, 5.7 Hz, 1H), 3.39 – 3.27 (m, 1H), 3.18 – 3.11 (m, 1H), 3.10 – 3.02 (m, 1H), 2.96 – 2.84 (m, 2H), 2.77 – 2.63 (m, 4H), 2.31 – 2.15 (m, 1H), 1.84 – 1.44 (m, 1H), 1.44 – 1.31 (m, 1H), 1.31 – 1.14 (m, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 180.0 (Cq), 177.5 (Cq), 151.5 (Cq), 150.0 (Cq), 141.6 (Cq), 130.3 (Cq), 126.0 (Cq), 119.8 (CH), 108.0 (CH), 107.9 (CH), 56.2 (CH₃), 55.8 (CH₃), 44.1 (CH), 40.9 (CH), 39.8 (CH), 34.4 (CH₂), 31.7 (CH₂), 31.6 (CH), 27.5 (CH₂), 24.6 (CH₂), 24.1 (CH₂), 23.4 (CH₃), 22.7 (CH₃), 14.2 (CH₃) ppm; IR (thin film): v max = 2928, 2853, 1775, 1702, 1699, 1600 cm⁻¹; LRMS (EI⁺): m/z (%): 397 ([M]+•, 43), 326 ([M–C₅H₅]+•, 100); HRMS (EI⁺): calculated for C₂₅H₂₃NO₄: 397.2253; found: 397.2254.
Following General Method C, the reaction mixture containing dendralene 1d (74 mg, 0.49 mmol), 3,6-dimethoxy-2-trimethylsilyl-benzene-1-trifluoromethanesulfonate 2b (353 mg, 0.985 mmol) and TBAF (1.2 mL, 1 M, 1.2 mmol) in THF (2 mL) was stirred at 0 °C for 1h. Methanol (1 mL) was added to the reaction mixture, followed by CaCO$_3$ (120 mg) and Dowex 50WX8–400 resin (420 mg) and stirring was continued for 10 minutes. PTAD 4b (130 mg, 0.74 mmol) was added and the reaction mixture was stirred at 23 °C for 2h. The reaction mixture was filtered through a plug of Celite. The Celite pad was washed with 5 mL CH$_2$Cl$_2$. The filtrate was further diluted with CH$_2$Cl$_2$ (5 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. After work up, purification by flash column chromatography (10 g SiO$_2$, 15% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5n as a white solid (122 mg, 0.264 mmol, 54%). R$_f$ = 0.40 (30% EtOAc in PS 40–60); m.p. 158 – 161 °C (hexane:EtOAc, 9:1).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 1H), 5.76 (s, 1H), 4.92 – 4.83 (m, 1H), 4.31 (dd, J = 16.0, 4.5 Hz, 1H), 4.09 (d, J = 16.1 Hz, 1H), 3.81 (s, 3H), 3.79 – 3.65 (m, 5H), 2.55 (dd, J = 16.4, 10.7 Hz, 1H), 2.00 – 1.86 (m, 1H), 1.5 – 1.08 (m, 7H), 0.91 (t, J = 6.0 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.0 (Cq), 151.8 (Cq), 151.5 (Cq), 150.5 (Cq), 136.0 (Cq), 131.5 (Cq), 130.1 (Cq), 129.3 (2×CH), 128.2 (CH), 125.6 (2×CH), 123.0 (Cq), 113.3 (CH), 108.5 (CH), 107.7 (CH), 55.7 (CH$_3$), 49.5 (CH), 43.5 (CH$_2$), 43.1 (CH), 34.4 (CH$_2$), 31.5 (CH$_2$), 29.5 (CH$_3$), 27.6 (CH$_3$), 22.8 (CH$_3$), 14.3 (CH$_3$) ppm; IR (thin film): $\nu_{max}$ = 2950, 2928, 2855, 1774, 1710, 1600 cm$^{-1}$; LRMS (ESI)$^+$: m/z (%) = 462 ([M+H]$^+$, 75), 484 ([M+Na]$^+$, 100); HRMS (ESI)$^+$: calculated for C$_{27}$H$_{31}$N$_3$O$_4$Na: 484.2207; found: 484.2201.
Diene-Transmissive Diels–Alder Sequences With Benzynes

The reaction mixture containing the 2-vinyl-1,4-dihydnaphthalene 3d (39 mg, 0.13 mmol) and N-methylmaleimide 4a (18 mg, 0.17 mmol) in THF (1 mL) was heated under reflux for 16h. The reaction mixture was diluted with CHCl₃ (10 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (6 g SiO₂, 50% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5o as a white amorphous solid (41 mg, 0.10 mmol, 77%).

Rᵣ = 0.29 (50% EtOAc in PS 40–60).

¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, J = 7.8 Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H), 6.79 (s, 1H), 6.39 (s, 1H), 5.46 (brs, 1H), 4.40 (s, 1H), 3.89 (s, 3H), 3.68 (s, 3H), 3.43 (dd, J = 14.7, 9.2 Hz, 1H), 3.22 – 3.15 (m, 1H), 3.13 – 3.04 (m, 1H), 2.90 (dd, J = 14.8, 6.3 Hz, 1H), 2.81 (s, 3H), 2.75 – 2.62 (m, 2H), 2.20 – 2.07 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 179.8 (Cq), 178.2 (Cq), 147.4 (Cq), 147.4 (Cq), 143.8 (Cq), 137.0 (Cq), 136.5 (Cq), 131.3 (Cq), 129.9 (Cq), 129.7 (2×CH), 129.2 (2×CH), 120.2 (CH), 121.0 (CH), 111.0 (CH), 56.2 (CH₂), 56.1 (CH₃), 51.0 (CH), 43.6 (CH), 40.2 (CH), 35.3 (CH), 30.9 (CH₃), 24.8 (CH₃), 24.3 (CH₃), 21.2 (CH₃) ppm; IR (thin film): v_max = 2935, 2833, 1771, 1698, 1609 cm⁻¹; LRMS (ESI⁺): m/z (%): 418 ([M+H]⁺, 15), 440 ([M+Na]⁺, 100); HRMS (ESI⁺): calculated for C₂₆H₂₇NO₄: 418.2018; found: 418.2014; calculated for C₂₆H₂₇NO₄Na: 440.1838; found: 440.1841.
A reaction mixture containing the 2-vinyl-1,4-dihydronaphthalene 3d (39 mg, 0.13 mmol) and PTAD 4b (29 mg, 0.17 mmol) in THF (1 mL) was stirred at 23 °C for 1h. The reaction mixture was diluted with CH₂Cl₂ (10 mL) and water (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. After work up, purification by flash column chromatography (6 g SiO₂, 40% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5p as a white amorphous solid (54 mg, 0.11 mmol, 88%). Rₕ = 0.33 (50% EtOAc in PS 40–60).

1H NMR (400 MHz, CDCl₃) δ 7.62 – 7.31 (m, 5H), 7.10 (d, J = 7.6 Hz, 2H), 6.96 (d, J = 7.6 Hz, 2H), 6.65 (s, 1H), 6.47 (s, 1H), 6.05 (s, 1H), 4.89 (s, 1H), 4.69 (brs, 1H), 4.34 (d, J = 16.0 Hz, 1H), 4.06 (d, J = 16.2 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 3H), 3.62 (dd, J = 15.1, 5.7 Hz, 1H), 3.00 – 2.83 (m, 1H), 2.32 (s, 3H) ppm; 13C NMR (100 MHz, CDCl₃) δ 152.6 (Cq), 151.7 (Cq), 148.5 (Cq), 148.4 (Cq), 140.9 (Cq), 138.0 (Cq), 136.8 (Cq), 131.3 (Cq), 129.4 (2×CH), 129.3 (2×CH), 128.3 (CH), 128.1 (2×CH), 128.0 (Cq), 126.0 (Cq), 125.6 (2×CH), 112.7 (CH), 112.1 (CH), 111.3 (CH), 56.1 (CH₃), 56.0 (CH₃), 52.1 (CH), 49.9 (CH), 43.3 (CH₂), 34.2 (CH₂), 21.1 (CH₃) ppm; IR (thin film): νmax = 3002, 2935, 2853, 2252, 1771, 1705, 1609 cm⁻¹; LRMS (ESI⁺): m/z (%): 482 ([M+H]⁺, 10), 504 ([M+Na]⁺, 100); HRMS (ESI⁺): calculated for C₂₇H₂₂N₃O₄: 482.2074; found: 482.2074;
The reaction mixture containing the 2-vinyl-1,4-dihyronaphthalene 3e (80 mg, 0.25 mmol), benzoquinone 4d (70 mg, 0.65 mmol) and a crystal of BHT in THF (2 mL) was heated under reflux for 16h. The reaction mixture was cooled to 0 °C and methanol (1 mL), CeCl₃•7H₂O (185 mg, 0.500 mmol) and NaBH₄ (19 mg, 0.50 mmol) were added. The reaction mixture was stirred at 0 °C for 1 h then quenched with saturated aqueous NH₄Cl (2 mL) and diluted with water (10 mL) and CH₂Cl₂ (10 mL) shaken well and the layers were separated. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. After work up, purification by flash column chromatography (6 g SiO₂, 45% EtOAc in PS 40–60) gave the double Diels–Alder adduct 5q as a white solid (78 mg, 0.18 mmol, 72%). Rf = 0.36 (40% EtOAc in PS 40–60). m.p. 181–188 °C (hexane:EtOAc, 1:1).

¹H NMR (400 MHz, CD₂Cl₂) δ 6.96 (d, J = 8.4 Hz, 2H), 6.83 – 6.64 (m, 4H), 5.95 (s, 1H), 5.84 – 5.69 (m, 1H), 5.62 (d, J = 10.1 Hz, 1H), 4.94 (s, 1H), 4.42 – 4.23 (m, 2H), 3.82 (s, 3H), 3.73 (s, 3H), 3.66 (s, 3H), 3.61 (dd, J = 17.5, 5.9 Hz, 1H), 2.86 (brs, 1H), 2.69 (dd, J = 17.4, 9.9 Hz, 1H), 2.29 – 2.06 (m, 3H), 2.09 – 1.96 (m, 1H), 1.63 (d, J = 6.4 Hz, 1H), 1.51 (d, J = 5.6 Hz, 1H) ppm;

¹³C NMR (100 MHz, CD₂Cl₂) δ 158.3 (Cq), 151.4 (Cq), 150.9 (Cq), 141.9 (Cq), 136.0 (Cq), 130.9 (CH), 129.2 (CH), 129.1 (Cq), 128.5 (2×CH), 127.0 (Cq), 122.1 (CH), 113.7 (2×CH), 108.6 (2×CH), 70.4 (CH), 65.1 (CH₂), 56.2 (CH₂), 56.1 (CH₃), 55.5 (CH₃), 46.7 (CH), 39.4 (CH), 37.6 (CH), 33.2 (CH), 23.9 (CH₂), 23.4 (CH₂) ppm; IR (thin film): νmax = 3288, 2928, 2878, 2824, 1601 cm⁻¹; LRMS (ESI⁺): m/z (%): 457 ([M+Na]+, 100); HRMS (ESI⁺): calculated for C₂₇H₃₀O₅Na: 457.1991; found: 457.1989.
(rel)-(15S,4R,4aS,7S,12aS,12bR)-1,4,8,11-Tetramethoxy-7-(4-methoxyphenyl)-1,4,4a,5,7,12,12a,12b-octahydrotetraphene (9)

NaH (3 mg, 0.10 mmol) was dispensed in THF (0.5 mL) under N₂. The reaction mixture was cooled to 0 °C and a solution of diol 5q (20 mg, 0.05 mmol) in THF (0.5 mL) was added, followed by MeI (9 µL, 0.14 mmol) and stirring was continued at 23 °C for 48 h. The reaction mixture was quenched with saturated aqueous NH₄Cl (2 mL) and diluted with water (10 mL) and CH₂Cl₂ (10 mL), shaken well and the layers were separated. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. After work up, purification by flash column chromatography (4 g SiO₂, 40% EtOAc in PS 40–60) gave the product 9 as a white solid (16 mg, 0.03 mmol, 75%). Rᶠ = 0.47 (20% EtOAc in PS 40–60); m.p. 137 – 140 °C (hexane:EtOAc, 9:1).

¹H NMR (400 MHz, CDCl₃) δ 7.00 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 6.72 – 6.60 (m, 2H), 5.96 (d, J = 9.3 Hz, 1H), 5.86 (brs, 1H), 5.73 (d, J = 10.0 Hz, 1H), 4.94 (s, 1H), 3.82 (s, 4H), 3.75 (s, 4H), 3.63 (s, 3H), 3.38 (s, 3H), 2.98 (dd, J = 17.1, 6.0 Hz, 1H), 2.90 (s, 3H), 2.78 (brs, 1H), 2.63 (dd, J = 17.1, 9.8 Hz, 1H), 2.30 – 2.21 (m, 1H), 2.21 – 2.09 (m, 1H), 2.08 – 1.90 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 157.6 (Cq), 150.9 (Cq), 150.8 (Cq), 140.1 (Cq), 136.5 (Cq), 129.7 (Cq), 129.4 (CH), 128.3 (2×CH), 127.8 (Cq), 124.8 (CH), 120.8 (CH), 113.3 (2×CH), 107.6 (2×CH), 79.6 (CH), 73.5 (CH), 56.5 (CH₂), 56.4 (CH₂), 56.1 (CH₂), 55.7 (CH₂), 55.3 (CH₂), 46.4 (CH), 39.2 (CH), 34.6 (CH), 33.1 (CH), 23.4 (CH₂), 22.5 (CH₂) ppm; IR (thin film): νmax = 3028, 2929, 2901, 2831, 1602, 1506 cm⁻¹; LRMS (ESI⁺): m/z (%): 463 ([M+H]⁺, 10), 485 ([M+Na]⁺, 100); HRMS (ESI⁺): calculated for C₂₉H₂₅O₅: 463.2484; found: 463.2483, calculated for C₂₉H₂₅O₅Na: 485.2304; found: 485.2302.
$n$-BuLi addition to 3-phenyl[3]dendralene in the presence of 1,2-dibromobenzene

Following General Method A, $n$-BuLi (0.40 mL, 0.96 M, 0.38 mmol) was added to the reaction mixture containing dendralene 1a (54 mg, 0.35 mmol) and 1,2-dibromobenzene 2c (41 µL, 0.35 mmol) in THF (1.4 mL) at –20 °C over 10 minutes and brought to 23 °C slowly and stirring continued for 16h. After work up, purification by flash column chromatography (5 g SiO$_2$, 100% PS 40–60) gave the adduct 6Z as a colorless liquid (19 mg, 0.07 mmol, 20%) along with unreacted dendralene.

$n$-BuLi addition to 3-phenyl[3]dendralene in the presence of 1-bromobutane

$n$-BuLi (0.65 mL, 1.36 M, 0.89 mmol) was added to the reaction mixture containing dendralene 1a (63 mg, 0.40 mmol) and 1-bromobutane (87 µL, 0.81 mmol) in THF (1.5 mL) at 0 °C over 5 minutes and the reaction mixture was stirred at the same temperature for 2h. The reaction mixture was quenched by saturated aqueous NH$_4$Cl and extracted with CH$_2$Cl$_2$. The organic layer was washed with water, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude product as a mixture of geometrical isomers (dr = 7:3). Purification by preparative HPLC (Grace Altima C18 5µ 250×22 mm (P/N 81105), eluting with water/MeCN/2-propanol in 5:47.5:47.5 ratio) gave the major product 6Z ($t_R = 18.49$) as a colorless liquid (66 mg, 0.24 mmol, 60%) and the minor product 6E ($t_R = 16.97$) as a colorless liquid (18 mg, 0.067 mmol, 17%).

Major isomer 6Z. $R_f = 0.77$ (100% PS 40–60); $^1$H NMR (400 MHz, CD$_2$Cl$_2$) δ 7.28 (d, $J = 4.3$ Hz, 4H), 7.22 – 7.05 (m, 1H), 6.17 (dd, $J = 17.3$, 11.0 Hz, 1H), 5.71 (t, $J = 7.3$ Hz, 1H), 5.14...
Minor isomer 6E. Rf = 0.77 (100% PS 40–60); 1H NMR (400 MHz, CD2Cl2) δ 7.35 – 7.06 (m, 5H), 6.61 (dd, J = 17.6, 11.2 Hz, 1H), 5.61 (t, J = 7.4 Hz, 1H), 5.19 (d, J = 17.6 Hz, 1H), 5.00 (d, J = 11.2 Hz, 1H), 3.59 (t, J = 7.5 Hz, 1H), 2.25 (q, J = 7.4 Hz, 2H), 1.91 – 1.62 (m, 2H), 1.50 – 1.39 (m, 2H), 1.39 – 1.14 (m, 8H), 1.03 – 0.78 (m, 6H) ppm; 13C NMR (100 MHz, CD2Cl2) δ 145.9 (Cq), 139.1 (Cq), 133.8 (CH), 130.9 (CH), 128.4 (2×CH), 128.2 (2×CH), 126.1 (CH), 113.9 (CH2), 47.5 (CH), 35.3 (CH2), 32.0 (CH2), 30.6 (CH2), 30.1 (CH2), 28.0 (CH2), 23.2 (CH2), 23.0 (CH2), 14.3 (CH3), 14.3 (CH3) ppm; IR (thin film): vmax = 3086, 3062, 2956, 2927, 2857, 1598 cm⁻¹; LRMS (El⁺): m/z (%): 270[M⁺], 94, 213 ([M–C4H9]⁺, 78), 143 (100); HRMS (El⁺): calculated for C20H30: 270.2348; found: 270.2348.

Minor isomer 6E. Rf = 0.77 (100% PS 40–60); 1H NMR (400 MHz, CD2Cl2) δ 7.35 – 7.06 (m, 5H), 6.61 (dd, J = 17.6, 11.2 Hz, 1H), 5.61 (t, J = 7.4 Hz, 1H), 5.19 (d, J = 17.6 Hz, 1H), 5.00 (d, J = 11.2 Hz, 1H), 3.59 (t, J = 7.5 Hz, 1H), 2.25 (q, J = 7.4 Hz, 2H), 1.91 – 1.62 (m, 2H), 1.50 – 1.39 (m, 2H), 1.39 – 1.14 (m, 8H), 1.03 – 0.78 (m, 6H) ppm; 13C NMR (100 MHz, CD2Cl2) δ 145.9 (Cq), 139.1 (Cq), 133.8 (CH), 130.9 (CH), 128.4 (2×CH), 128.2 (2×CH), 126.1 (CH), 113.9 (CH2), 47.5 (CH), 35.3 (CH2), 32.0 (CH2), 30.6 (CH2), 30.1 (CH2), 28.0 (CH2), 23.2 (CH2), 23.0 (CH2), 14.3 (CH3), 14.3 (CH3) ppm; IR (thin film): vmax = 3086, 3062, 2956, 2927, 2857, 1598 cm⁻¹; LRMS (El⁺): m/z (%): 270[M⁺], 94, 213 ([M–C4H9]⁺, 78), 143 (100); HRMS (El⁺): calculated for C20H30: 270.2348; found: 270.2348.
X-Ray Crystallography

Single crystal X-ray data for compounds were collected on a Supernova diffractometer using Cu Ka radiation, \( \lambda = 1.54184 \) Å except for compound 9 that used Mo Ka radiation, \( \lambda = 0.71073 \) Å. Data reduction was performed using the CrysAlis PRO package. Structure solutions for all compounds were determined by ShelXT, and the structures refined using ShelXL in the OLEX2 program package.

1. Compound 5d

C\textsubscript{24}H\textsubscript{23}NO\textsubscript{3} (\( M = 373.43 \) g/mol): monoclinic, space group \( P2_1/n \) (no. 14), \( a = 8.71981(10) \) Å, \( b = 9.17689(10) \) Å, \( c = 23.8890(3) \) Å, \( \beta = 93.4208(11)^\circ \), \( V = 1908.21(4) \) Å\textsuperscript{3}, \( Z = 4 \), \( T = 150.00(10) \) K, \( \mu(\text{CuK\textalpha}) = 0.683 \) mm\textsuperscript{-1}, \( D_{\text{calc}} = 1.300 \) g/cm\textsuperscript{3}, 37421 reflections measured (7.4144° \( \leq 2\theta \leq 147.597^\circ \)), 3868 unique (\( R_{int} = 0.0396 \)) which were used in all calculations. The final \( R_1 \) was 0.0355 (\( I > 2\sigma(I) \)) and \( wR_2 \) was 0.0934 (all data). CCDC 1922955.

2. Compound 5g

C\textsubscript{32}H\textsubscript{28}N\textsubscript{2}O\textsubscript{4}S (\( M = 536.62 \) g/mol): monoclinic, space group \( C2/c \) (no. 15), \( a = 10.6976(2) \) Å, \( b = 24.7999(3) \) Å, \( c = 21.9739(4) \) Å, \( \beta = 103.752(2)^\circ \), \( V = 5662.55(17) \) Å\textsuperscript{3}, \( Z = 8 \), \( T = 149.99(10) \) K, CCDC 1922955.
\[ \mu(\text{CuK}_{\alpha}) = 1.332 \text{ mm}^{-1}, \text{Dcalc} = 1.259 \text{ g/cm}^3, \] 19587 reflections measured (7.128° ≤ 2θ ≤ 147.68°), 5674 unique (\(R_{int} = 0.0290\)) which were used in all calculations. The final \(R_1\) was 0.0512 (\(I > 2\sigma(I)\)) and \(wR_2\) was 0.1397 (all data). CCDC 1922954.

3. Compound 5j

C_{36}H_{31}NO_3 (M = 525.62 g/mol): triclinic, \(P\)-1 (No. 2), \(a = 12.7985(3)\) Å, \(b = 14.6201(3)\) Å, \(c = 16.1015(3)\) Å, \(\alpha = 102.171(2)^\circ\), \(\beta = 103.096(2)^\circ\), \(\gamma = 102.187(2)^\circ\), \(V = 2760.45(11)\) Å\(^3\), \(T = 150.01(10)\) K, \(Z = 4\), \(Z' = 2\), \(\mu(\text{CuK}_{\alpha}) = 0.629 \text{ mm}^{-1}\), 60801 reflections measured, 11099 unique (\(R_{int} = 0.0424\)) which were used in all calculations. The final \(wR_2\) was 0.1065 (all data) and \(R_1\) was 0.0399 (\(I > 2\sigma(I)\)). CCDC 1922951.

4. Compound 5l

C_{26}H_{27}NO_5 (M = 433.48 g/mol): triclinic, space group \(P\)-1 (no. 2), \(a = 6.1902(3)\) Å, \(b = 12.4868(6)\) Å, \(c = 14.2390(5)\) Å, \(\alpha = 89.146(4)^\circ\), \(\beta = 80.837(4)^\circ\), \(\gamma = 78.564(4)^\circ\), \(V = 1064.84(8)\) Å\(^3\), \(Z = 2\), \(T = 150.01(10)\) K, \(\mu(\text{CuK}_{\alpha}) = 0.760 \text{ mm}^{-1}\), \(\text{Dcalc} = 1.352 \text{ g/cm}^3\), 7316 reflections measured (7.224° ≤ 2θ ≤ 147.214°), 4208 unique (\(R_{int} = 0.0304\)) which were used in all calculations. The final \(R_1\) was 0.0513 (\(I > 2\sigma(I)\)) and \(wR_2\) was 0.1442 (all data). CCDC 1922953.
5. Compound 9

\[ \text{C}_{29}\text{H}_{34}\text{O}_{5} \quad (M=462.56) \]

triclinic, \( P-1 \) (No. 2), \( a = 8.4029(5) \, \text{Å}, \ b = 12.8926(10) \, \text{Å}, \ c = 12.9902(8) \, \text{Å}, \]
\( \alpha = 63.249(7)^\circ, \ \beta = 88.299(5)^\circ, \ \gamma = 75.429(6)^\circ, \ V = 1210.56(16) \, \text{Å}^3, \]
\( T = 150.00(10) \, \text{K}, \ Z = 2, \ Z' = 1, \ \mu(\text{MoK} \alpha) = 0.085 \, \text{mm}^{-1}, \]
26071 reflections measured, 5886 unique \( (R_{int} = 0.0329) \) which were used in all calculations. The final \( wR_2 \) was 0.1325 (all data) and \( R_1 \) was 0.0525 \( (I > 2\sigma(I)) \). CCDC 1922952.
References

6. Agilent Crystals PRO. Agilent Technologies Ltd, Yarnton, Oxfordshire, England, **2014**.
Diene-Transmissive Diels–Alder Sequences With Benzynes

3a
100 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes

$^{3g}$

$^{13}C_10H_{21}$

400 MHz, CDCl$_3$
Diene-Transmissive Diels–Alder Sequences With Benzynes

3h
400 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes

300 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes

$100 \text{ MHz, } \text{CDCl}_3$
Diene-Transmissive Diels–Alder Sequences With Benzynes

5a
100 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes
Diene-Transmissive Diels–Alder Sequences With Benzynes

5c
100 MHz, CDCl₃

$\text{MeN=O}$

$\text{O=\text{H}}$

$\text{H}$

$\text{H}$

$\text{H}$

$\text{H}$

$\text{NO}_2$

$\text{H}$

$\text{H}$

$\text{NO}_2$

$\text{H}$

$\text{H}$

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$\text{H}$

$\text{H}$

$\text{H}$

$\text{NO}_2$
Diene-Transmissive Diels–Alder Sequences With Benzynes

5d
100 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes

$\text{MeN}$

$\text{O}$

$\text{O}$

$\text{C}_6\text{H}_{13}$

$\text{Se}$

$100 \text{ MHz}, \text{CDCl}_3$
Diene-Transmissive Diels–Alder Sequences With Benzynes
Diene-Transmissive Diels–Alder Sequences With Benzynes

5g
400 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes

Figure 5g
100 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes

$\text{PhN} = \text{N}$

$\text{O}$

$\text{N}$

$\text{N}$

$\text{Me}$

5h

100 MHz, CDCl$_3$
Diene-Transmissive Diels–Alder Sequences With Benzynes

[Chemical structure diagram with 1H NMR spectrum]

100 MHz, CDCl$_3$
Diene-Transmissive Diels–Alder Sequences With Benzynes

\[
\text{Structure:}
\]

\[
\text{NMR spectrum: 400 MHz, CDCl}_3
\]
Diene-Transmissive Diels–Alder Sequences With Benzynes

5a
400 MHz, CDCl₃

MeN
O

H
H

MeO
O

Me

50 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes

400 MHz, CDCl₃
Diene-Transmissive Diels–Alder Sequences With Benzynes
Diene-Transmissive Diels–Alder Sequences With Benzynes

100 MHz, CD$_2$Cl$_2$
Chapter Four:

Diene-Transmissive Enantioselective Diels–Alder Reactions and Sequences Involving Substituted Dendralenes
4 Diene-Transmissive Enantioselective Diels–Alder Reactions and Sequences involving Substituted Dendralenes

Prelude

The work was published in the journal *Journal of Organic Chemistry*. The other author listed on the manuscript is Michael S. Sherburn. The project, and the draft manuscript, was conceived and evolved in collaboration with Professor Michael S. Sherburn. All of the experimental work was conducted by myself. Dr Anthony C. Willis performed the X-ray structure analysis and is acknowledged in the manuscript. In this chapter we discuss the organocatalysed, enantioselective Diels–Alder reactions of substituted [3]dendralenes.

MacMillan and co-workers (K. A. Ahrnedt, C. J. Borths, D. W. C. MacMillan., *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244) showed that chiral imidazolidinones are excellent organocatalysts for promoting the Diels–Alder reaction between a diene and certain α,β-unsaturated aldehydes to generate an adduct in good yield and excellent enantioselectivity. Our optimised reaction conditions worked well on a wide selection of substituted [3]dendralenes. The catalyst-promoted Diels–Alder reaction yielded the monoadducts in very good enantioselectivities (up to $er = 99:1$). Moderate to good yields were obtained with high regioselectivity and good diastereoselectivity. The enantiomerically enriched mono adducts were then subjected to a second Diels–Alder reaction with a different dienophile yielding the double adduct with high diastereoselectivity and yield. This method allowed us to synthesise complex molecules with high enantioselectivity. Finally, we have also shown that the entire reaction sequence can be conducted in a single pot.
DIENE-TRANSMISSIVE ENANTIOSELECTIVE DIELS–ALDER REACTIONS AND SEQUENCES INVOLVING SUBSTITUTED DENDRALENES

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ABSTRACT: Readily available and stable substituted [3]dendralenes undergo highly chemo- and regio- diastereoselective Diels–Alder reactions with acrolein to form enantiomERICALLY enriched cycloadducts. These monocycloadducts carry semicyclic dienes that undergo a second, substrate-controlled diastereoselective Diels–Alder reaction with a different dienophile to form 2-fold cycloadducts. Overall, annulated, functional group rich, chiral oligo-alkenes were accessed in one-pot operations that significantly extend the preparative value of diene-transmissive Diels–Alder sequences since they offer products of regio- and stereochemistry complementary to those generated from the parent, unsubstituted [3]dendralene.

INTRODUCTION

Until the turn of this century, relatively few acyclic, branched oligo-alkenes were known, a fact that can be attributed to the prevailing dogma, which would have researchers falsely believe oligo-alkenes were known, a fact that can be attributed to the exploratory nature, pertains to the chemical reactivity that arises from their acyclic, branched, π-bond-rich structure. Since every individual π-bond in a polymer can be used to form two new π-bonds through an addition process, structural complexity is rapidly created as a result of multifold $sp^3-C \rightarrow sp^3-C$ conversions. Many types of additions to a polyene can be envisaged, but in terms of target-relevant complexity generation, the Diels–Alder (DA) reaction is unmatched. This dominance is boosted in branched polyenes, since 1,3-butadiene reactivity in dendralenes can be sequenced. Thus, so-called diene-transmissive Diels–Alder (DTDA) sequences (Scheme 1), which were originally developed predominantly by the Tsuge and Fallis laboratories, are uniquely powerful events in which a minimum of four new covalent bonds and a new bicyclic ring system are generated. When two C=C dienophiles are used, a Δ[9]octalin ring system 6 is produced by way of semicyclic dione intermediate 8. When the oxidized, reduced, and heteroatom-containing derivatives and analogues of octalin 6 are considered, which are accessible by way of simple manipulations of DTDA adducts, or from related hetrodendralenic precursors and/or heterodienophiles, many natural product and medicinal chemistry target-relevant precursores are envisaged, for example, the synthesis of various hetrodendralenic and dimeric octalin building blocks are accessed in one-pot operations that significantly extend the preparative value of diene-transmissive Diels–Alder sequences since they offer products of regio- and stereochemistry complementary to those generated from the parent, unsubstituted [3]dendralene.
Enantioselective DTDA structures are within reach through a sequence which is rarely superseded in terms of atom and step economy. A substantial body of important work has been published on DTDA sequences,\(^1\),\(^2\) and their strategic value in total synthesis is gaining momentum.\(^1\) Nevertheless, fundamental questions remain about how to best interpret and deploy the uncommon power of a DTDA sequence. The question of enantioselective synthesis is the most pertinent of these and is the topic of the present work. Thus, of the dozens of publications describing DTDA sequences, only two papers report enantioselective DA reactions of dendralenes.\(^4\),\(^16\) As shown in Scheme 2, both papers describe examples involving unsubstituted [3]dendralene, which is an exceptionally reactive DA diene.

In the first of these previous investigations,\(^1\) [3]dendralene 1 underwent an enantioselective cycloaddition with methyl acrylate 7 catalyzed by a modified Corey oxazaborolidinium catalyst 8 to give monoadduct 9 in good yield and enantioselectivity. High catalyst loadings were required for this reaction, which is a weakness of the method.\(^1\) Nonetheless, the monoadduct 9 went on to react with N-tert-butylmaleimide 10 to give enantioenriched product 11 in good yield.

In the other previous study,\(^1\) [3]dendralene 1 was reacted with acrolein and \(E\)-\(\beta\)-monosubstituted acroleins 12 with MacMillan organocatalyst 13\(^1\) to give, following in situ hydride reduction of the formyl group, enantioenriched monoadducts 14. Enantioselectivities were uniformly good, but product epimerization to the cis-isomer was occasionally observed.\(^1\)

In both previous cases, the same sense of orientational regioselectivity was observed, in that the expected "para" cycloadduct (i.e., the 1,4-disubstituted cyclohexene product, viz. 9 and 14) was the only observed product. [3]Dendralene 1 has two identical 1,3-butadiene groups. Since neither carries a substituent at C1 or C4, it is not possible to determine whether the reaction forming products 9 and 14 proceeded through an endo- or exo-mode of addition.

The present work aimed to demonstrate that substituted dendralenes 3 are sufficiently reactive to participate in catalytic enantioselective DTDA sequences, in order to generate functionality-enriched and enantioenriched products.

### RESULTS AND DISCUSSION

In light of the relative ease of carrying out organocatalyzed reactions (Scheme 2, 1 \(\rightarrow\) 14 vs 1 \(\rightarrow\) 9) and the likelihood that the conditions required for such reactions would be compatible with a second cycloaddition, hence permitting one flask transformations (Scheme 2, 3 \(\rightarrow\) 18), we selected this approach over the chiral Lewis acid method. Our previous experience\(^1\) with [3]dendralene 1 (Scheme 2) told us that acrolein 15 was the most reactive dienophile for reactions promoted by organocatalyst 13. Since substituted [3]-dendralenes 3 are significantly less reactive as dienes than...
the parent [3]dendralene 1, we therefore focused attention upon acrolein 15 as the first dienophile. We were concerned that the decreased reactivity of substituted [3]dendralenes 3 in an initial cycloaddition might impact upon chemoselectivity in that semicyclic diene monoadduct 16 could, in principle, react a second time, particularly with an excess of the dienophile (5 molar equiv was routinely used). These fears turned out to be unwarranted, with monoselectivity seen in all cases. Evidently, the semicyclic diene of the monoadduct is significantly less reactive than the starting substituted dendralene. Interestingly, the presence of a conjugating substituent R (alkenyl, alkynyl, aryl, heteroaryl) in precursor 3 causes a complete reversal in orientational regioselectivity with acrolein 15, relative to the parent [3]dendralene 1 to produce monoadduct 16, which in turn reacts with separate C=C and N=N dienophiles 17 to form octalins and diazaoctalins with good chemo-, diastereo-, and enantioselectivities.

<table>
<thead>
<tr>
<th>Table 1. Enantioselective Organocatalyzed Diels−Alder Reactions of Substituted Dendralenes</th>
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<tr>
<td>The Journal of Organic Chemistry</td>
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<tr>
<td>Article</td>
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<tr>
<td>DOI: 10.1021/acs.joc.9b02296</td>
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<td>J. Org. Chem. 2019, 84, 14712−14723</td>
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Table 1 depicts the results of organocatalyzed reactions between 13 variously substituted [3]dendralenes S and acrolein 15, which highlights the strong performance of these systems throughout a range of substitution patterns.

Thus, phenyl and substituted phenyl groups (3a-d, 3k, 3m) are tolerated at the internal alkene of [3]dendralene, as are alkynyl (3e, 3f, 3j), alkyl (3k), and heteroaryl groups (16g, 16h). Methyl substituents are also allowed as substituents on one (3i−k) or both (16l, 16m) of the terminal alkene. In some cases, it was necessary to reduce the formyl group of the initial cycloadduct 19 into primary alcohol 16 before isolation, since significant epimerization occurred otherwise, resulting in low diastereomer ratios. In five other cases, however, the aldehyde could be isolated directly. In all
cases, enantiomer ratios were respectable, as determined by chiral HPLC or UPC2 by comparison with a racemic sample. In every case, the major product was the cis-diastereomer, resulting from an endo-mode addition of the dienophile to the diene but with orientational regioselectivity between the dienophile and the dendralene opposite to that seen in the parent case (Scheme 2). This assignment was based upon COSY and NOE NMR experiments performed on all major products, which were accompanied by a single-crystal X-ray analysis of cis-cycloadduct 16d. This crystal structure also confirmed the absolute configuration of the major product, which was as expected from previous related work.16,18

The cis-diastereomer can be easily identified from a $J = 4.4-4.9$ Hz coupling constant between the two stereocenter hydrogens; the trans-diastereomer has a vanishingly small coupling constant between the same two protons. A minor question over the origin of at least some of the minor, trans-diastereomer remains: while we observed epimerization of the endo-cycloadduct under the reaction conditions and/or on isolation,16 some of this material might also be generated through an exo-mode addition, since endo vs exo selectivity is not strong in some reported DA reactions.17

Not every substituted dendralene that we tested turned out to be effective in this organocatalyzed process. A list of unsuccessful structures is depicted in Figure 2.

Thus, allyl substitution at the internal alkene of [3]-dendralene, as in compounds 3n and 3o, leads to a significant reduction in rate, to such an extent that the organocatalyzed process becomes prohibitively slow. A strongly electron-efficient aromatic substituent, as in 3p, has a similar rate-retarding influence. Trisubstituted dendralene 3q with a (usually reactive, cf. 3c) 4-methoxyphenyl group, but also an E-phenyl group at one of the C=C terminal sites and a branching methyl at the other, is similarly unreactive. Interestingly, trisubstituted [3]dendralene 3r is reactive but furnished a mixture of four (nonenantionic) monoadducts, which we attribute to cis- and trans-diastereomeric forms of the two possible orientational regioselective addition modes to the E,E-1,3-butadiene group of the dendralene.

The switch in orientational regioselectivity in DA reactions with acrolein from the parent [3]dendralene 1 to the substituted species 3 can be rationalized by approximating the highly polarized, asynchronous, but concerted DA transition states (TS) to the discrete cationic intermediates themselves (Scheme 3). This classical interpretation was discussed eloquently in Dewar’s rationale for a qualitative biradicaloid mechanistic interpretation,21 which is more useful in cases where diene and dienophile lack an electron donor and acceptor, respectively. Thus, the vinyliminium dienophile can dock with the dendralene in two orientations but dominates the asynchronous transition state of the TS in both cases by causing a shorter developing bond at its dienophilic terminus. With the parent [3]-dendralene 1, the observed product 22 is formed from the DA TS 20-int with pentadienyl cation character (21-int), since the alternative pathway 2b-term would involve a TS with...
significantly less stable allyl cation character (21-term). In cases with [3]dendralenes carrying substituents at the internal C=C bond, two factors contribute to the preference for a reversed orientational regioselectivity; hence, the formation of products such as 19a, instead of the alternative 26. First, if the dendralene substituent is conjugating, then it will lead to a greater stabilization (25-term vs 25-int) of the polarized asynchronous TS from advanced terminal bond formation (24-term). Additionally, a TS with advanced internal bond formation (24-int) would be expected to engender destabilizing steric strain, since the substituent (the phenyl group in this case) is attached to the end of the diene with a short TS developing bond. This interpretation explains why all successful examples of DA reactions of substituted dendralenes conducted in this study involved conjugating substituents that are not electron withdrawing.

Scheme 4 depicts the outcomes of four separate one flask operations in which, following the first, catalyst controlled enantioselective cycloaddition, a second dienophile is added. In each case, within the limits of detection,[34] only one diastereomer is generated from the second DA reaction involving either N-methylmaleimide (NMM) 27 or N-
phenylhydrazolinedione (PTAD) 29, presumably on account of the steric impediment to approach of the dienophile to the z-diastereoface of the semicyclic donor carrying the two substituents. In the case of NSM 27 additions, as expected, only one of the cycloaddition products 28 and 34 were observed.

The final example of a DTDA sequence in Scheme 4 involves two cycloadditions that were performed in separate flasks and emphasizes the ability to rapidly generate enantioselectively enriched multicyclic systems that are rich in both stereocenters and functionality, in short order from simple acyclic building blocks. Thus, enantoienriched triacrylic triol 34, with seven stereocenters, is generated efficiently from three simple achiral components: acrolein, p-hydroxyacetophenone, and dendralene 3g. The last of these components is accessible in only two steps from inexpensive commercial precursors.

DTDA products 28 and 31 share the same tricyclic ring system with the pyranpyrones, recently isolated cytostatic mycobacterial metabolites.22 The bicyclic [4.4.0] decane ring system generated by the DTDA sequence of a [3]dendralene and two carbon-based dienophiles is one of the most common frameworks in natural products and their derived medicinal agents, either as a standalone bicyclic unit, as in mycormycins, or as a subunit in countless steroids and other molecules. DTDA adduct 34 contains a tricyclic ring system that maps onto substructural portions of steroids, kauranes, and specific notable compounds including taxolactone, norrosthree, and helicopindole E. Adducts of transdendralenes have many synthetic possibilities.23

**Conclusion**

This work shows for the first time that substituted [3]dendralenes undergo catalyst-controlled enantioselective DA reactions with a dienophile and that the enanitorriched products of these processes undergo substrate-controlled dendralene DA reactions with a second dienophile. Overall, chiral polyolefinic products containing a Δ1(9)-octalin moiety, in short order from simple acyclic building blocks, that this alternative approach to dendralene synthesis of a useful, chiral aldehyde, combined with convenient step- and atom economic enantioselective methods to build value into them, we are confident that this alternative approach Δ1(9)-octalin building block.22 With expanding access to stable [3]dendralenes, with seven stereocenters, is generated efficiently from three simple achiral components: acrolein, p-hydroxyacetophenone, and dendralene 3g. The last of these components is accessible in only two steps from inexpensive commercial precursors.

**Experimental Section**

General Methods. 1H NMR spectra were recorded at 400 MHz using a Bruker AVANCE 400 spectrometer. Residual solvent peaks were used as an internal reference for 1H NMR spectra (CDCl3, δ 7.26 ppm, CD2Cl2, δ 3.52 ppm, CD3OD, δ 3.31 ppm). Coupling constants (J) are quoted to the nearest 0.1 Hz. The assignment of proton signals was assisted by HMQC and HMBC experiments. The following abbreviations (or combinations thereof) are used to denote H NMR multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet. High-performance liquid chromatography was carried out with a Waters 600 Controller, a Waters 717 Plus autosampler and a Waters 2996 photodiode array detector, controlled with Empower Pro 2 software. Infrared spectra were recorded on a Perkin-Elmer UATR spectrometer as a thin film or solid. Low-resolution EI mass spectra were recorded on a Finnigan Polaris Q ion trap mass spectrometer using electron impact (EI) ionization mode at 70 eV. High-resolution EI mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. Low-resolution ESI mass spectra were recorded on a ZMD Micromass spectrometer with Waters Alliance HPLC. High-resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. Melting points were measured on a Stanford Research Systems Optimized Automated Melting Point System and are uncorrected.

Analytical thin-layer chromatography was conducted with aluminum-backed silica gel 60 F254 (0.2 mm) plates supplied by Merck, visualized using UV fluorescence (λmax = 254 nm), or developed using KMnO4, or p-anisidine or phosphomolybdic acid followed by heating. Flash chromatography employed Merck Kieselgel 60 silica gel (230–400 mesh). Infrared spectra were recorded in the (v/v) region at 100 MHz using a Bruker AVANCE 400 spectrometer. Residual solvent peaks were used as an internal reference for 1H NMR spectra (CDCl3, δ 7.26 ppm, CD2Cl2, δ 3.52 ppm, CD3OD, δ 3.31 ppm). Coupling constants (J) are quoted to the nearest 0.1 Hz. The assignment of proton signals was assisted by HMQC and HMBC experiments. The following abbreviations (or combinations thereof) are used to denote H NMR multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet. High-performance liquid chromatography was carried out with a Waters 600 Controller, a Waters 717 Plus autosampler and a Waters 2996 photodiode array detector, controlled with Empower Pro 2 software. Infrared spectra were recorded on a Perkin-Elmer UATR spectrometer as a thin film or solid. Low-resolution EI mass spectra were recorded on a Finnigan Polaris Q ion trap mass spectrometer using electron impact (EI) ionization mode at 70 eV. High-resolution EI mass spectra were recorded on a VG Autospec mass spectrometer operating at 70 eV. Low-resolution ESI mass spectra were recorded on a ZMD Micromass spectrometer with Waters Alliance HPLC. High-resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. Melting points were measured on a Stanford Research Systems Optimized Automated Melting Point System and are uncorrected. Single crystal X-ray data were collected on a SuperNova (Dual Source) diffractometer using a SuperNova (Cu) X-ray radiation source. Crystallographic structures were solved using CrysAlis PRO. Reactions were conducted under a positive pressure of dry nitrogen and at room temperature, unless specified otherwise. Commercially available chemicals were used as purchased, or where specified, purified by standard techniques. Microwave-assisted reactions were conducted under positive pressure of dry nitrogen and at room temperature, unless specified otherwise. Commercially available chemicals were used as purchased, or where specified, purified by standard techniques.
isolated directly (method A) or the crude was reduced (method B) before isolation.

General Method A. The crude reaction mixture was diluted with water (3 mL, 0.1 g dendralene) and extracted into CHCl₃ (10 mL, 0.1 g of dendralene). The organic and aqueous layers were separated, and the aqueous layer was further extracted with CHCl₃ (3 mL, 0.1 g of dendralene) × 3. The combined organic layer was washed with saturated brine (3 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure.

General Method B. The crude reaction mixture was treated with a solution of NaBH₄ (10 mmol) in THF (0.1 g dendralene) at 0 °C and stirred for 10 min. A solution of sodium borohydride (154 mg, 4.05 mmol) in MeCN/H₂O (1 mL/min) was added dropwise at 0 °C and stirring was continued at the same temperature for 10 min. Workup afforded the crude material as a mixture of diastereomers (dr = 81:19). Purification by flash column chromatography (3 g silica; 6% EtOAc in PE) gave the major diastereomer alcohol 3ta as a colorless oil (46 mg, 0.22 mmol, 46%): [α]_D = +174 (c 0.15, CHCl₃), 183 (\([M+\text{•}]\) max 297, 242 (\([M+\text{•}]\) max 292), 164, 138, 108, 90 cm⁻¹). HRMS (EI) m/z: [M+H]⁺ 238.1128 (calcd for C₁₄H₂₁O₃ 238.1126).

(1R, 2R, 4R)-4-Methyl-6-vinyl-1,2,3,4-tetrahydro-1,1-biphenyl-2-yl)methanol (16a). Following general method B, the reaction mixture containing dendralene 3a (75 mg, 0.47 mmol), (J- MacMillan's catalyst (54 mg, 0.093 mmol), and sodium borohydride (0.16 mol, 2.5 mmol) in MeCN/H₂O (0.75 mL) was stirred at 0 °C for 10 min. A solution of sodium borohydride (150 mg, 3.80 mmol) in THF/H₂O/MeOH (1 mL) was added dropwise at 0 °C, and stirring was continued at the same temperature for 10 min. Workup afforded the crude material as a mixture of diastereomers (dr = 81:19). Purification by flash column chromatography (3 g silica; 6% EtOAc in PE) gave the major diastereomer alcohol 16a as a colorless oil (72 mg, 0.30 mmol, 47%): [α]_D = 0.40 (40% EtOAc in PE), \([\alpha]_D = +257 (c 0.900, CHCl₃), 74 \text{ %}\) for C₂₀H₂₄O₂, calculated for C₂₀H₂₄O₂ 336.4). HRMS (EI) m/z: [M+H]⁺ 289.1514 (calcd for C₂₀H₂₄O₂ 289.1513), 109.1 (74 % (M-OH)⁺, HRMS (EI) m/z 109.0 (74 % (M-OH)⁺), 108.0 (74 % (M-OH)⁺, 107.0 (74 % (M-OH)⁺).}

The crude reaction mixture containing dendralene 15 (50 mg, 0.28 mmol), (J-MacMillan's catalyst (10 mg, 0.017 mmol), and sodium borohydride (154 mg, 3.80 mmol) in THF/H₂O/MeOH (1 mL) was added dropwise at 0 °C and stirring was continued at the same temperature for 10 min. Workup afforded the crude material as a mixture of diastereomers (dr = 81:19). Purification by flash column chromatography (4 g silica; 10% EtOAc in PE) gave the major diastereomer alcohol 3b as a colorless oil (72 mg, 0.30 mmol, 47%): [α]_D = 0.900 (40% EtOAc in PE), \([\alpha]_D = +257 (c 0.900, CHCl₃), 74 \text{ %}\) for C₂₀H₂₄O₂, calculated for C₂₀H₂₄O₂ 336.4). HRMS (EI) m/z: [M+H]⁺ 289.1514 (calcd for C₂₀H₂₄O₂ 289.1513), 109.1 (74 % (M-OH)⁺, HRMS (EI) m/z 109.0 (74 % (M-OH)⁺, 108.0 (74 % (M-OH)⁺, 107.0 (74 % (M-OH)⁺).}

The crude reaction mixture containing dendralene 15 (50 mg, 0.28 mmol), (J-MacMillan's catalyst (10 mg, 0.017 mmol), and sodium borohydride (154 mg, 3.80 mmol) in THF/H₂O/MeOH (1 mL) was added dropwise at 0 °C and stirring was continued at the same temperature for 10 min. Workup afforded the crude material as a mixture of diastereomers (dr = 81:19). Purification by flash column chromatography (4 g silica; 10% EtOAc in PE) gave the major diastereomer alcohol 3b as a colorless oil (72 mg, 0.30 mmol, 47%): [α]_D = 0.900 (40% EtOAc in PE), \([\alpha]_D = +257 (c 0.900, CHCl₃), 74 \text{ %}\) for C₂₀H₂₄O₂, calculated for C₂₀H₂₄O₂ 336.4). HRMS (EI) m/z: [M+H]⁺ 289.1514 (calcd for C₂₀H₂₄O₂ 289.1513), 109.1 (74 % (M-OH)⁺, HRMS (EI) m/z 109.0 (74 % (M-OH)⁺, 108.0 (74 % (M-OH)⁺, 107.0 (74 % (M-OH)⁺).}
The racemate was synthesized in a similar manner using racemic catalyst.

(18R,2S)-2-(Phenylmethyl)-3-hydroxy-3-oxo-1-carbodihyde [19]. Following general method A, the racemic mixture containing dendralene-3 (21 mg, 0.71 mmol), and acrolein (32.2 mg, 0.44 mmol) in MeCN/H_2O (1:2 mL) was stirred at 50 °C for 16 h. Workup afforded the crude material as a mixture of diastereomers (90:10). Purification by flash column chromatography (5 g SiO_2, 5% EtOAc in PE) gave the major diastereomer dihydroalkyne 106 as a colorless oil (98 mg, 0.29 mmol, 66%). IR (thin film): 3357, 2921, 1639, 1588, 1576, 1096 cm^{-1}; HRMS (ESI) m/z: [M+H]^+ 252.2160 (24), 251.2180 (24) ppm; LRMS (EI) m/z: 252 (M, 24), 251 (M, 24) ppm. The racemate was synthesized in a similar manner using racemic catalyst.

(18S,2R)-2-(Phenylmethyl)-3-hydroxy-3-oxo-1-carbodihyde [19]. Following general method A, the racemic mixture containing dendralene-3 (21 mg, 0.71 mmol), and acrolein (32.2 mg, 0.44 mmol) in MeCN/H_2O (1:2 mL) was stirred at 50 °C for 16 h. Workup afforded the crude material as a mixture of diastereomers (90:10). Purification by flash column chromatography (5 g SiO_2, 5% EtOAc in PE) gave the major diastereomer dihydroalkyne 106 as a colorless oil (98 mg, 0.29 mmol, 66%). IR (thin film): 3357, 2921, 1639, 1588, 1576, 1096 cm^{-1}; HRMS (ESI) m/z: [M+H]^+ 252.2160 (24), 251.2180 (24) ppm; LRMS (EI) m/z: 252 (M, 24), 251 (M, 24) ppm. The racemate was synthesized in a similar manner using racemic catalyst.
Following general method A, the reaction mixture containing dendralene (27 mg, 0.060 mmol) was purified by flash column chromatography (8 g silica, 30% EtOAc in PE) to give the major dendralene alcohol (9 mg, 0.040 mmol, 67%). Rf = 0.75 (30% EtOAc in PE); [α]D = +252 (c = 1.50, CHCl3). *H NMR (400 MHz, CDCl3): δ = 7.32 (d, 0.5 Hz, 1H), 7.25 (4.5 Hz, 1H), 2.46 (s, 3H), 2.31 (s, 3H), 1.04 (d, 6.8 Hz, 3H), 0.86 (t, 7.2 Hz, 3H), 0.98 (q, 7.3 Hz, 2H), 0.92 (s, 6H), 0.88 (d, 6.5 Hz, 3H), 0.84 (d, 6.6 Hz, 3H), 0.81 (d, 6.3 Hz, 3H), 0.79 (s, 3H). *C NMR (100 MHz, CDCl3): δ = 136.4 (Cq), 137.0 (Cq), 129.9 (CH), 125.3 (CH2), 119.4 (CH), 115.9 (CH), 111.3 (CH), 110.5 (CH), 29.7 (CH3), 24.7 (CH3), 18.5 (CH3), 14.7 (CH3), 14.5 (CH3), 14.4 (CH3). HRMS (ESI−) m/z [M−H]+ calecd for C22H36O6Si, 419.2163, found 419.2172. The racemate was synthesized in a similar manner using racemic catalyst. *[CS2H2D2, 1.2,3,4-tetrahydro-(1,1-biphenyl)-2-yl]methanol (15e). Following general method B, the reaction mixture containing dendralene (3 mg, 0.040 mmol), (S)-MacMillan's catalyst (27 mg, 0.03 mmol) and acrolein (0.31 mL, 3.2 mmol) in MeCN/H2O (0.5 mL) was added dropwise at 0 °C, and stirring was continued at the same temperature for 10 min. Workup afforded the crude material as a mixture of diastereomers (dr = 95:5). Purification by flash column chromatography (10 g silica, 30% EtOAc in PE) gave the major dendralene alcohol (2 mg, 0.006 mmol, 62%). Rf = 0.93 (30% EtOAc in PE); [α]D = +246 (c = 1.50, CHCl3). *H NMR (400 MHz, CDCl3): δ = 7.32 (d, 4.5 Hz, 1H), 7.25 (4.5 Hz, 1H), 2.46 (s, 3H), 2.31 (s, 3H), 1.04 (d, 6.8 Hz, 3H), 0.86 (t, 7.2 Hz, 3H), 0.98 (q, 7.3 Hz, 2H), 0.92 (s, 6H), 0.88 (d, 6.5 Hz, 3H), 0.84 (d, 6.6 Hz, 3H), 0.81 (d, 6.3 Hz, 3H), 0.79 (s, 3H). *C NMR (100 MHz, CDCl3): δ = 136.4 (Cq), 137.0 (Cq), 129.9 (CH), 125.3 (CH2), 119.4 (CH), 115.9 (CH), 111.3 (CH), 110.5 (CH), 29.7 (CH3), 24.7 (CH3), 18.5 (CH3), 14.7 (CH3), 14.5 (CH3), 14.4 (CH3). HRMS (ESI−) m/z [M−H]+ calecd for C22H36O6Si, 419.2163, found 419.2172. Rf = 0.93 (30% EtOAc in PE); [α]D = +246 (c = 1.50, CHCl3). *H NMR (400 MHz, CDCl3): δ = 7.32 (d, 4.5 Hz, 1H), 7.25 (4.5 Hz, 1H), 2.46 (s, 3H), 2.31 (s, 3H), 1.04 (d, 6.8 Hz, 3H), 0.86 (t, 7.2 Hz, 3H), 0.98 (q, 7.3 Hz, 2H), 0.92 (s, 6H), 0.88 (d, 6.5 Hz, 3H), 0.84 (d, 6.6 Hz, 3H), 0.81 (d, 6.3 Hz, 3H), 0.79 (s, 3H). *C NMR (100 MHz, CDCl3): δ = 136.4 (Cq), 137.0 (Cq), 129.9 (CH), 125.3 (CH2), 119.4 (CH), 115.9 (CH), 111.3 (CH), 110.5 (CH), 29.7 (CH3), 24.7 (CH3), 18.5 (CH3), 14.7 (CH3), 14.5 (CH3), 14.4 (CH3). HRMS (ESI−) m/z [M−H]+ calecd for C22H36O6Si, 419.2163, found 419.2172. Enantioselective DTDA of 386
MeCN/H catalyst (36 mg, 0.096 mmol), and acrolein (160 containing dendralene reaction mixture containing dendralene cinnoline-8-carbaldehyde (32).

2.62 (m, 2H), 2.37

128.4 (2

\times

2

8

H

2

J

1.43 (m, 1H) ppm; IR (thin

\nu_{\text{max}}

5.91 (s, 1H), 5.84 (s, 1H), 5.79

HRMS (ESI-TOF) m/z [M + H] + Hf calculated for C31H39NO4, 533.2798, found 533.2792.

MeCN/H2O (1:0 mL) was stirred at 0 °C for 16 h. FT-IR 29 (81 mg, 0.08 mmol, 2 mole equiv) was added to the reaction mixture and stirred at 23 °C for 16 h. Workup afforded the crude material as a mixture of diastereomers (dr = 80:20). Purification by flash column chromatography (σ 50%, 25% EtOAc in PE) gave the aldehyde 30 as a colorless oil (45 mg, 0.11 mmol; 47%). Rf = 0.40 (50% EtOAc in PE; [α]D = −175° (c = 100, CHCl3).

H NMR (400 MHz, CDCl3) δ 6.06 (s, 1H), 7.60–7.36 (m, 4H), 7.31–7.14 (m, 4H), 6.47 (d = 1.58 H, H), 6.13 (d = 1.58, 7.1 H, H), 5.46 (d = 1.57, 7.18 H, H), 4.21 (d = 1.63, 5.3 H, H), 4.07 (d = 1.63, 2.8 H, H), 3.95–3.88 (m, 1H), 2.76–2.65 (m, 2H), 2.55 (d = 1.29, 4.3 H, H), 2.15–2.03 (m, 1H), 1.97–1.92 (m, 1H), 1.36–1.45 (m, 1H) ppm; 13C NMR {σ 100 MHz, CDCl3} δ 20.2 (CH), 152.4 (Cq), 151.8 (Cq), 137.6 (Cq), 134.6 (CH), 133.1 (Cq), 129.3 (2 × Cq), 128.9 (2 × CH), 128.3 (CH), 128.2 (CH), 126.5 (2 × CH), 126.2 (2 × CH), 124.7 (CH), 118.6 (Cq), 54.4 (Cq), 51.1 (CH), 46.9 (CH), 41.3 (CH), 29.7 (CH), 20.3 (CH) ppm; IR (thin film) ν (κ = 29, 2524, 2377, 1701, 1797 cm−1; IRMS (ESI) m/e 468 (100), 430 (M + Na)+, 406 (M + Na)+, 401 (M + H) + Hf, 395 (M + Na)+, 385 (M + H)+, 380 (M + Na)+, 375 (M + H)+, 370 (M + Na)+, 366 (M + H)+, 360 (M + Na)+, 353 (M + H)+, 350 (M + H)+, 348 (M + Na)+). CRMDH (ESI+TOF) m/z [M + H] + Hf calculated for C35H39NO5, 559.2818, found 559.2814.

2.72 (m, 5H), 1.76–1.62 (m, 7H). Workup afforded the crude material as a mixture of diastereomers (dr = 80:20). Purification by flash column chromatography (σ 50%, 25% EtOAc in PE) gave the aldehyde 31 as a colorless oil (52 mg, 0.14 mmol; 46%). Rf = 0.30 (40% EtOAc in PE; [α]D = −170° (c = 100, CHCl3).

H NMR (400 MHz, CDCl3) δ 7.30–7.15 (m, 2H), 7.15–7.07 (m, 2H), 5.41 (d = 5.08, H), 3.19 (d = 4.1 H, H), 1.21–1.13 (m, 2H), 0.80–0.72 (m, 5H), 0.61–0.53 (m, 5H) ppm; 13C NMR {σ 100 MHz, CDCl3} δ 150.8 (Cq), 137.2 (Cq), 128.3 (Cq), 127.8 (Cq), 124.9 (CH), 118.5 (Cq), 54.8 (Cq), 51.4 (Cq), 46.9 (CH), 41.4 (CH), 35.5 (CH), 29.7 (CH), 20.3 (CH) ppm; IR (thin film) ν (κ = 29, 2924, 2852, 2773, 1701, 1797 cm−1; IRMS (ESI) m/e 464 (100), 430 (M + Na)+, 406 (M + H)+, 401 (M + Na)+, 395 (M + Na)+, 385 (M + H)+, 380 (M + Na)+, 375 (M + H)+, 370 (M + Na)+, 359 (M + H)+, 358 (M + Na)+, 348 (M + Na)+). CRMDH (ESI+TOF) m/z [M + H] + Hf calculated for C35H39NO5, 559.2818, found 559.2814.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b02296.

NMR spectra and HPLC chromatograms (PDF)

Crystallographic data for the X-ray crystal structure of 1d (CIF)

Access Codes

CCDC 1494192 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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ORCID

© 2018 Michael S. Sherburn: 100000-0000-0773-0752

Notes

The authors declare no competing financial interest.
REFERENCES


(2) Whyte, S. Why some polynuclear compounds are heat, light, oxygen, or acid sensitive, to account for this behavior to all such compounds as an overgeneralization.


(15) For reviews of DTDA sequences, see ref 3.


(17) For further details on the application of this methodology, see ref 11.


(22) The complexity of the crude product mixtures from these one-pot reactions only permits us to quote diastereomer ratios of >80:20 for three cases (30, 31 and 32). Our inability to isolate other diastereomeric products makes us confident that selectivities are higher than these minimum values.


Supporting Information

Diene-Transmissive Enantioselective Diels–Alder Reactions
and Sequences Involving Substituted Dendralenes
Josemon George, Michael S. Sherburn*
Contents

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Thermal Ellipsoid Plot .................................................. S4
References ................................................................. S5
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HPLC Spectra ............................................................. S46-S58
X-Ray Crystallography

Single crystal X-ray data for 16d was collected on a Supernova diffractometer using Cu Kα radiation, $\lambda = 1.54184$ Å. Data reduction was performed using the CrysAlis PRO package. Structure solution and refinement used the CRYSALS program package.

Crystal data and ellipsoid plot for compound 16d

The sample for X-ray crystallography was prepared by recrystallizing from n-hexane:EtOAc (9:1) as colorless plates (crystal dimensions $0.29 \times 0.21 \times 0.07$ mm).

Crystal data: $C_{18}H_{24}O_4$ (M=304.39 g/mol); monoclinic, space group $P2_1$, $a = 7.1640(1)$ Å, $b = 10.8451(1)$ Å, $c = 10.6270(1)$ Å, $\beta = 103.8053(14)^\circ$, $V = 801.81(2)$ Å$^3$, $Z = 2$, $T = 150$ K, $\mu$ (CuKα) = 0.71 mm$^{-1}$, $D_x = 1.261$ Mg m$^{-3}$, 12636 reflections measured, 2850 unique (Rint = 0.018) which were used in all calculations. The final $wR_2$ was 0.063 (all data) and $R1$ was 0.024 (I > 2σ(I)). CCDC 1944916. The anisotropic displacement ellipsoid plot of 16d is depicted in Figure S1.
Figure S1: Anisotropic displacement ellipsoid plot of 16d. Ellipsoids exhibit 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
References for the X-Ray Crystallographic Analysis

2. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J.
Enantioselective DTDA

Minor diastereomer of 16a
400 MHz, CDCl₃
Minor diastereomer of 16a
100 MHz, CDCl₃
Enantioselective DTDA

HO

OMe

16c

400 MHz, CDCl₃
Enantioselective DTDA
Enantioselective DTDA
Enantioselective DTDA

101
400 MHz, CDCl₃
Enantioselective DTDA

19f
100 MHz, CDCl₃
Enantioselective DTDA
Enantioselective DTDA

[Chemical structure and NMR spectra with annotations]
Enantioselective DTDA

400 MHz, CDCl$_3$

![Chemical Structure](image)
Enantioselective DTDA
Enantioselective DTDA

10j
100 MHz, CDCl₃
Enantioselective DTDA
Enantioselective DTDA
Minor diastereoisomer of 19k
400 MHz, CDCl₃
Enantioselective DTDA

Minor diastereoisomer of 19k
100 MHz, CDCl₃
Enantioselective DTDA
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Enantioselective DTDA
Enantioselective DTDA

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Enantioselective DTDA

30
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Enantioselective DTDA

100 MHz, CDCl₃
Enantioselective DTDA

400 MHz, C₆D₆
Enantioselective DTDA

![Chemical Structure](image)

32
100 MHz, C₆D₆

S43
Enantioselective DTDA

34
700 MHz, CD$_2$OD

S44
Enantioselective DTDA

$\text{HO}$

$\text{H}$

$\text{H}$

$\text{OH}$

$\text{34}$

$175 \text{ MHz, CD}_2\text{OH}$
Enantioselective DTDA

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Peak Name | RT (min) | Area (umol) | % Area | Height (umol)
---|---|---|---|---
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Enantioselective DTDA

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Enantioselective DTDA
Enantioselective DTDA

![Chemical Structure](image)

![Chromatogram 1](image)

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S54
Enantioselective DTDA
Chapter Five:

Conclusions

and

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The goal of modern synthesis is to create a complex molecule of interest from simple starting materials in an efficient manner. Such a synthesis should be efficient with respect to time, resources, atom- and step economy. We identified the potential of substituted [3]dendralenes as intermediates in efficient syntheses. Specifically, we exploited the ability of dendralenes to permit diene transmissive Diels–Alder reaction sequences to generate complex molecules rapidly.

The synthetic work presented in chapter two details a highly efficient synthesis of substituted dendralenes. Our synthetic effort to make the dendralene is noteworthy due to the following aspects, (1) It doesn’t require expensive starting materials and reagents (2) No unstable intermediates are involved (3) Bench-stable products are formed. Above all, this method of making substituted dendralenes is superior to the existing methods. No other methods in the literature can generate both diastereomers of a dendralene in high selectivity and yield. This methodology has allowed us to synthesise a variety of complex molecules and we have shown this through the efficient synthesis of different octalin ring systems (2 or 3) from different diastereomers of the dendralenes (1Z or 1E)

Scheme 1: Synthesis of diastereomeric dendralenes and constitutional isomers of their double Diels–Alder adducts
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Future work should focus on the use of this methodology for the synthesis of other hydrocarbon compounds. Our group has already extended this methodology to the synthesis of tetravinyl ethylene (TVE) and tetraethynylene ethylene (TEE) hybrid systems. Accessing such building blocks selectively and in large quantities opens the door for synthetic chemists to investigate new reactivities and properties associated with such compounds. Another future application of this methodology is to apply it to the total synthesis of a target molecule or natural product. A number of natural products have already been identified wherein we can apply this methodology. Work in this area is ongoing in the group.

In chapter three we discuss the development of the first reported Diels–Alder reactions of dendralenes with unstable dienophiles, benzyynes to generate fused bicycles, 2-vinyl-1,4-dihydronaphthalenes. These mono Diels–Alder adducts can then be subjected to a second Diels–Alder reaction to make tricyclic and tetracyclic core structures that resemble medicinally important structural motifs. These complex polycyclic structures are developed in just four steps, starting from commercially available, simple aldehydes. The two diene transmissive Diels–Alder reactions are performed in a one-pot fashion, avoiding work up and purification. Furthermore, an unprecedented, new type of a reactivity of dendralenes in the presence of $n$-BuLi and an electrophile is also reported and studies regarding this are ongoing.

Our observations of Diels–Alder reactivity between dendralenes and benzyynes are beneficial to future expeditions in synthetic organic chemistry. So far, only three methods of benzyne generation in the presence of dendralene have been investigated. Finding other methods to generate benzyynes is a potential option for future studies. In our presented work, we used benzyynes as the dienophiles in only the first Diels–Alder reaction and a future study could focus on using benzyynes in only the second Diels–Alder reaction or benzyynes as the dienophile for both of the Diels–Alder reactions (Scheme 2). Based on the power of this methodology to generate tricyclic and tetracyclic compounds and the presence of these structural motifs in numerous natural products, this methodology would be an ideal candidate for use in total synthesis.
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Chapter four revealed that we can make enantioenriched polycyclic structures from acyclic, achiral compounds, [3]dendralenes. The use of MacMillan’s organocatalyst allowed for the generation of enantioenriched monoadducts with a wide variety of substitution patterns (Scheme 3). Furthermore, the employment of a substrate-controlled second Diels–Alder reaction generated complex structures in good enantioselectivity and yield. Work is currently ongoing with other organocatalysts been screened and a wider variety of dienophiles been explored.

The three projects outlined in this thesis disclose the efficient synthesis of complex, multicyclic structures from synthetically important building blocks, dendralenes in a step- and atom economic manner. Investigation into the use of substituted [3]dendralenes in the synthesis of natural products and target molecules are only just beginning. Our methods for substituted [3]dendralene synthesis and preliminary reactivity studies pave the way for others to implement these versatile compounds in their step and atom economic syntheses.