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Synthesis and Diels–Alder Reactivity of Substituted [4]Dendralenes

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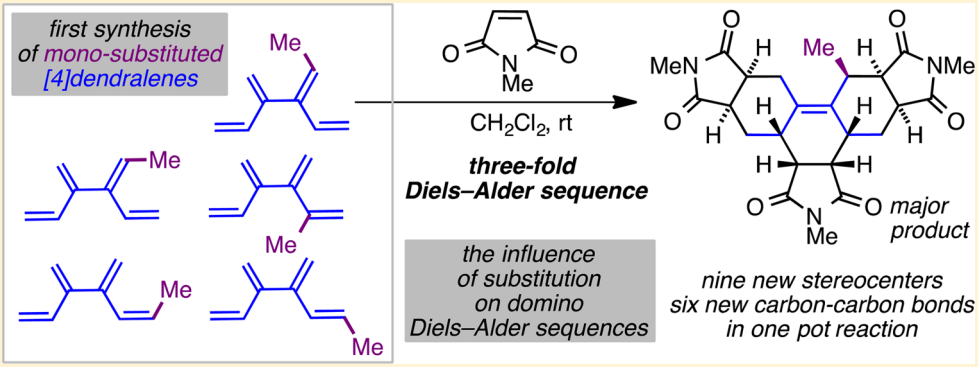
Supporting Information



ABSTRACT: The first synthesis of all five possible monomethylated [4]dendralenes has been achieved via two distinct synthetic strategies. The Diels–Alder chemistry of these new dendralenes (as multidienes) with an electron poor dienophile, *N*-methylmaleimide (NMM), has been studied. Thus, simply upon mixing the dendralene and an excess of dienophile at ambient temperature in a common solvent, sequences of cycloadditions result in the rapid generation of complex multicyclic products. Distinct product distributions are obtained with differently substituted dendralenes, demonstrating that dendralene substitution influences the pathway followed, when a matrix of mechanistic possibilities exists. Dendralene site selectivities are traced to electronic, steric and conformational effects, thereby allowing predictive tools for applications of substituted dendralenes in future synthetic endeavors.

INTRODUCTION

Dendralenes are acyclic, branched oligo-alkenes that have only recently become available through synthesis.[1] Dendralenes serve as multi-1,3-butadienes and possess the unique ability to participate in diene-transmissive Diels–Alder[2] reaction sequences.[3,4] Such processes rapidly generate complex polycyclic frameworks, and are beginning to feature in remarkably short step count total synthesis.[5] As depicted in Scheme 1, the first cycloaddition to the terminal site of a dendralene "transmits" olefinic character to a new site that is also conjugated to a pre-existing olefin on the dendralene framework. If this new 1,3-butadiene group can adopt an *s-cis* conformation, a second cycloaddition with either the same or a different dienophile can occur.

In principle, if successive cycloadditions occur at the 1,3-butadiene termini of the cross-conjugated chain, an [*n*]-dendralene can participate as diene in a maximum of ($n - 1$) diene-transmissive Diels–Alder cycloaddition reactions. [3]-Dendralenes, therefore, can undergo two cycloadditions, [4]dendralenes can undergo three cycloadditions, and so forth (Scheme 1).

Until now, studies into the Diels–Alder reactivity of *substituted* branched oligo-olefins have been limited to [3]-dendralene systems. With both the parent unsubstituted [3]dendralene and symmetrically multisubstituted systems (i.e., those carrying the same groups on both sides of the central C=C bond), the two 1,3-butadiene units are equivalent and there is no issue of site selection in the first cycloaddition event with a dienophile. With unsymmetrically substituted [3]dendralenes, different constitutional isomers can result from initial addition to the two dissimilar 1,3-butadiene sites. For target synthesis applications, it is imperative that the outcomes of these reactions can be predicted, and exploratory investigations have led to simple predictive guidelines (Figure 1).

With unsubstituted [4]dendralene (and its symmetrically multisubstituted analogues), diene-transmissive Diels–Alder sequences are more complex, since two different diene sites are available for both the first and second cycloaddition events (Scheme 2). With an excess of the electron poor dienophile *N*-methylmaleimide (NMM), for example, the parent [4]-dendralene (**1**) undergoes an initial Diels–Alder reaction favoring the terminal diene site, generating terminal mono-

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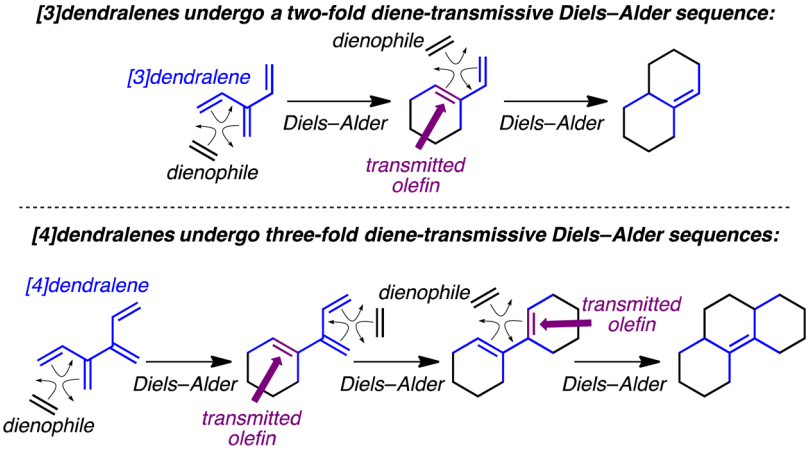
Scheme 1. Diene-Transmissive Diels–Alder Cycloaddition Sequences of [3]- and [4]Dendralene with the Prototypical Olefinic Dienophile



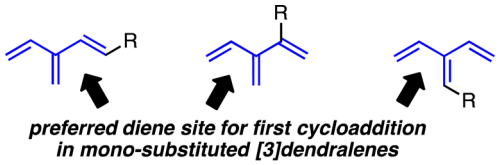


Figure 1. Site selection in dienophile additions to monosubstituted [3]dendralenes.

adduct **2**.[3] The minor monoadduct **3**, resulting from addition to the internal diene site, is inert toward further reaction at ambient temperature. Terminal monoadduct **2**, an unsymmetrically substituted [3]dendralene, is a more reactive diene than its progenitor [4]dendralene (**1**), hence is not isolated and undergoes a second cycloaddition. Of the two available diene sites in monoadduct **2**, a slight preference is seen for the semicyclic diene site, and two *endo*-mode bis-adducts **4** and **5** are generated, the former being the major product from the reaction. Diastereomeric bis-adducts **4** and **5** are the result of addition to the two distinct π-diastereofaces of the semicyclic diene of monoadduct **2**, with the former generated in high selectivity over the latter since it results from addition to the less sterically encumbered face. The transmitted 1,3-butadiene residue of **4** and **5** is unreactive toward further reaction with the dienophile under the reaction conditions since it cannot readily adopt the requisite *s-cis* conformation. Monocycloadduct **2** also undergoes Diels–Alder reaction to a substantial degree at the acyclic diene site, delivering two diastereomeric *terminal–terminal* bis-adducts **6** and **7**, both of which undergo a third—and final—cycloaddition at the newly transmitted 1,3-butadiene site to give two diastereomeric tris-adducts **8** and **9**. These two diastereomeric triple adducts are generated in a 1:1 ratio, which are the result of *endo*-stereoselective additions to the two *terminal–terminal* bis-adducts **6** and **7**, one of which is a *meso*-isomer (which has one unblocked π-diastereoface) and the other a chiral C_2 symmetric structure (with equivalent π-diastereofaces). We can deduce that the *terminal–terminal* bis-adducts **6** and **7** are formed in equal amounts, perhaps not too surprisingly when the substantial distance between the terminal diene site and *cis*-fused bicyclic ring section of monoadduct **2** are taken into account, in addition to the expected conformational freedom about the bond connecting the terminal diene of **2** with the bicycle.

Evidently, target synthesis applications of diene-transmissive multifold cycloadditions involving [4]dendralene will require substituents to be present in the multicyclic products. Such groups would, most efficiently, be incorporated into the precursor [4]dendralene framework. In light of the experience gained with substituted [3]dendralenes (Figure 1), two points are clear: (a) unsymmetrically substituted [4]dendralenes have more multifold cycloaddition pathways available to them than does the parent system (Scheme 2), since unsymmetrical substitution removes degeneracy from the terminal diene sites; and (b) the presence of a substituent is likely to have a strong steering influence upon the site selectivity of the initial cycloaddition (and perhaps subsequent ones). Since there are no reports in the literature on the site selectivity of cycloadditions to any unsymmetrically substituted [4]-dendralene, we elected to study all five possible monosubstituted-[4]dendralenes, **10**–**14** (Figure 2). We chose the methyl group as substituent due to its small size and relatively mild electronic influence.

This project mandated the development of new approaches for polyene synthesis, since there are no general methods for syntheses of substituted [4]dendralenes in the literature.

RESULTS AND DISCUSSION

Dendralene Synthesis. Upon a thorough review of the literature, it became abundantly clear that, while several significant contributions have been made, no general synthetic methods are available for substituted [4]dendralene synthesis. Thus, *fully substituted* [4]dendralenes have been prepared by multifold [2 + 2] cycloaddition/ring opening sequences between tetracyanoethylene and conjugated oligo-alkynes by Diederich[6] and Shoji,[7] with a related process involving cumulenes recently described by Tykwinski.[8] Highly substituted 1,3-dithiole-containing [4]dendralenes have been prepared as electron donors by several groups,[9] in studies based upon a pioneering Wittig approach by Sugimoto and Yoshida,[10] and Talpur et al.[11] Several isolated reports of dimerizations affording C_2 symmetric multisubstituted [4]-dendralenes have also appeared.[12] The thermal [3,3]-sigmatropic rearrangement of 1,4-bisallenes, described by Mukai as an unwanted side reaction,[13] has the potential to be a more general route to [4]dendralenes, as does Lee's 2-fold intramolecular metathesis/elimination approach.[14] The electrocyclization of tetravinylethylene is a very effective way to

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Scheme 2. Diene-Transmissive Diels–Alder Cycloaddition Sequences of [4]Dendralene (1) with the Dienophile *N*-Methylmaleimide (NMM)[3]

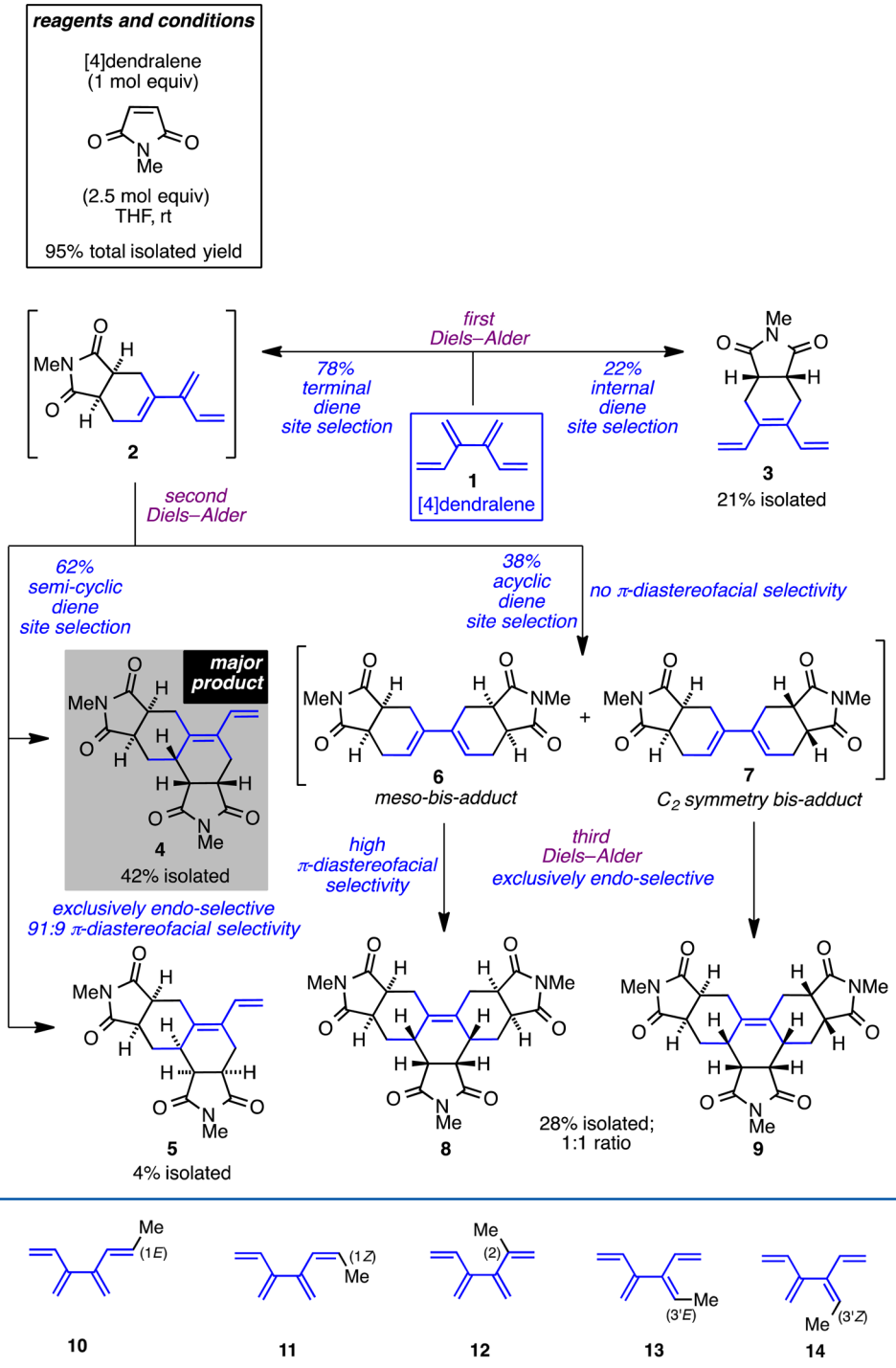

Figure 2. Five possible [4]dendralene structures carrying a methyl substituent.

prepare a specific subclass of cyclic [4]dendralenes,[15] but it lacks the ability to generate acyclic structures. Cross-couplings have been utilized by ourselves[16,17] and Shimizu and Hiyama[18] for a limited number of [4]dendralene substitution patterns. Herein we extend the cross-coupling methodology to a broader range of dendralene substitution patterns. We also introduce a complementary approach, involving a 2-fold Claisen rearrangement, to access dendralenes with substitution patterns that are presently inaccessible by cross-coupling reactions.

We considered several different routes for the preparation of these substituted [4]dendralenes. The unsubstituted hydrocarbon **1** is best prepared through a Kumada–Tamao–Corriu[19] type cross-coupling reaction between chloroprene and its corresponding Grignard reagent **15**. Had the requisite *substituted* 1,3-butadiene partners been readily accessible then we would have followed a similar pathway to the monomethylated [4]dendralenes. Disappointingly, this was not the case. In fact, there is a severe shortage of practical synthetic

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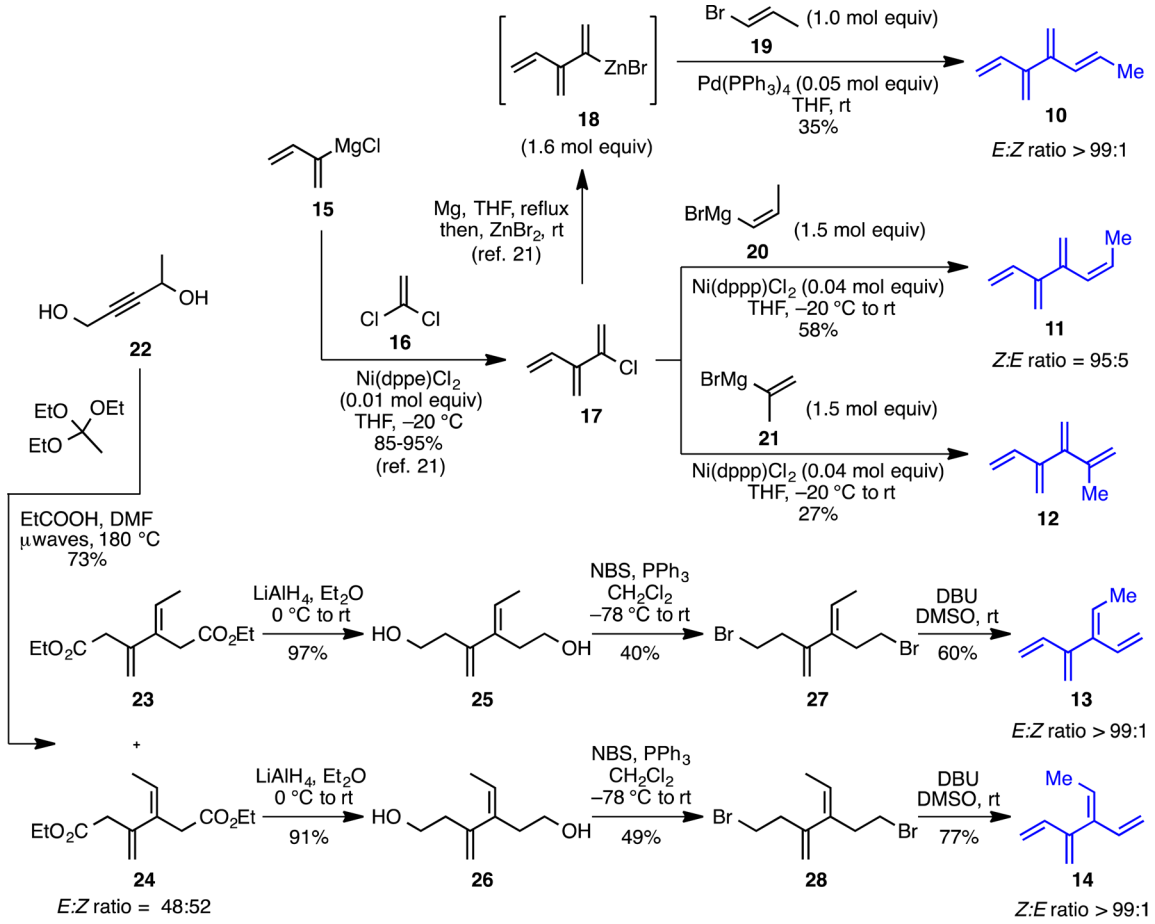
Scheme 3. Syntheses of the Five Mono-Methyl-Substituted-[4]Dendralenes



routes to useful 1,3-butadiene coupling partners in the literature, which represents an opportunity for future synthetic invention. We ultimately elected to prepare the five targets through serviceable approaches based upon solid literature precedent. Two distinct pathways were ultimately adopted (Scheme 3): the three congeners substituted at the terminal C=C bond (**10**, **11** and **12**) were prepared by Kumada–Tamao–Corriu or Negishi[20] cross-coupling reactions between 2-chloro[3]dendralene (**17**)[21] (or its corresponding organozinc species **18**[21]) with the requisite (and known[22]) propenyl-coupling partner **19**, **20**[23] and **21**.[24] The two derivatives that are methyl-substituted at the internal C=C bond of [4]-dendralene, **13** and **14**, were accessed by double HBr elimination of dibromides **27** and **28**.[25] The dibromides were accessed from the corresponding diols **25** and **26** through 2-fold Appel reactions.[26] The diols, in turn, were the products of 2-fold reductions of the diesters **23** and **24**, which were the readily separated diastereomeric products of a 2-fold[27] Johnson–Claisen rearrangement[28] of pent-2-yne-1,4-diol (**22**).

In stark contrast to the parent [3]dendralene, which rapidly decomposes through Diels–Alder dimerization at ambient temperature,[16] the parent [4]dendralene **1** can be stored neat on the bench without decomposition over extended time periods.[3] The monomethylated [4]dendralenes **10**–**14** were also sufficiently stable to be handled neat at room temperature without appreciable decomposition over several minutes and were stored neat in a −20 °C freezer without significant decomposition over several months.

Diels–Alder Reactions. In order to allow a direct comparison between the cycloaddition behaviors of the methyl-substituted [4]dendralenes with the parent unsubstituted hydrocarbon **1**,[29] the new tetraenes were exposed to the same dienophile, *N*-methylmaleimide (NMM). (For the reaction between [4]dendralene (**1**) and NMM, see Scheme 2.) NMM has many positive attributes as a model dienophile, including commercial availability, adduct stability toward purification, adduct crystallinity to facilitate structure determination through single crystal X-ray analysis, and predictable *endo*-stereoselection in Diels–Alder reactions with substituted 1,3-butadienes. To emphasize this last point, all cycloadditions reported herein were found to proceed with the exclusive formation of the *endo*-cycloadduct.

When 1*E*-methyl[4]dendralene (**10**) was treated with an excess[30] (3 mol equiv) of NMM at room temperature, five different products were formed (Scheme 4): a single internal monoadduct **29** in 14% yield, two bis-adducts **32** and **33** in 7% and 48% yields, both as single diastereomers, and two diastereomeric tris-adducts **36** and **37** in a 1:1 ratio (20% yield).[31] Upon the basis of this product distribution we can determine that the first cycloaddition reaction proceeds with ca. 84:16 site selectivity in favor of the two, dissimilar, terminal diene sites (i.e., **30**+**31**:**29** = 84:16). It is not possible to resolve the site selectivity of the two different terminal diene sites from the first Diels–Alder event, since both monoadducts **30** and **31** can, in principle, give rise to the tris-adducts **36** and **37**, by way of diastereomeric bis-adducts **34** and **35**. Assuming a worst-case scenario, that is tris-adducts **36** and **37** result exclusively from

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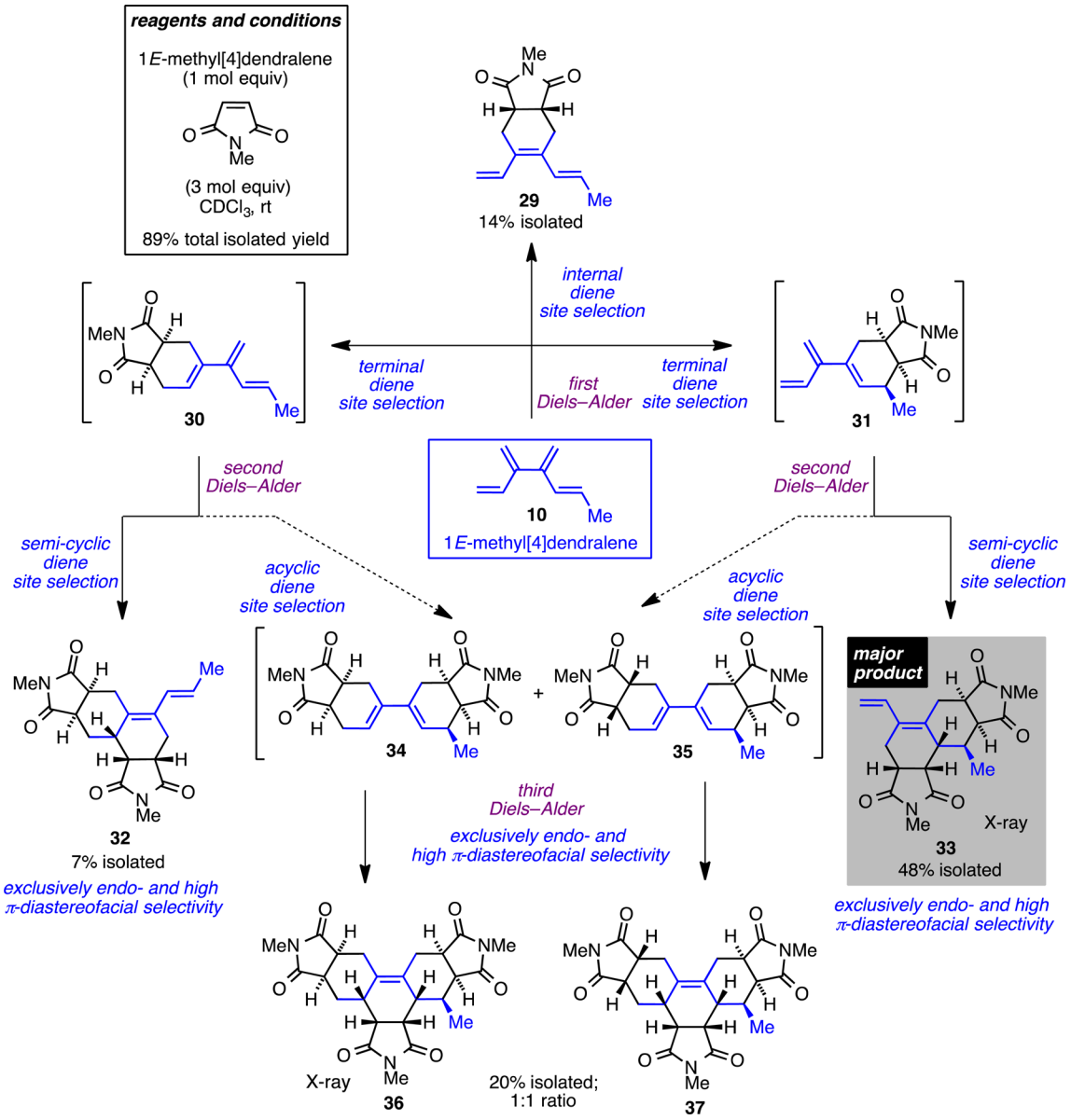
Scheme 4. Diels–Alder Reaction of 1*E*-Methyl[4]dendralene (10) with an Excess of NMM at Room Temperature



monoadduct **30**, we can deduce that the methyl-substituted terminal diene site is favored over the unsubstituted diene terminus by at least ca. 2:1. Bis-adduct **33**, the major product of the reaction, can only be formed from an initial addition to the more substituted terminal 1,3-butadiene site and a second addition to the semicyclic diene site of monoadduct **31**. The stereochemistry of this product reveals two successive *endo*-mode cycloadditions, with the second Diels–Alder event (**31** → **33**) proceeding with complete π-diastereofacial selectivity. This enhancement relative to the unsubstituted [4]dendralene (cf. Scheme 2, **2** → **4** + **5**) is presumably due to the additional steric blocking influence brought to bear by the methyl group. (The lack of detection of a minor diastereomer from the pathway **30** → **32** is presumably due to the very small amount of such a product being formed.)

Mirroring the sequence for the unsubstituted [4]dendralene **1**, the minor pathway for the second Diels–Alder reaction proceeds with a lack of π-diastereofacial selectivity, delivering *terminal–terminal* bis-adducts **34** and **35** in equal measure, which ultimately give rise to tris-adducts **36** and **37** in a 1:1 ratio through highly stereoselective final additions. The presence of the *C*-methyl group in *syn-terminal–terminal* bis-adduct **34** would be expected to reinforce the already strong (cf. Scheme 2, **6** → **8**) preference for dienophile approach from the bottom face during the third cycloaddition, thus forming tris-adduct **36** exclusively. In the case of *anti-terminal–terminal* bis-adduct **35**, the *C*-methyl group directs approach from the face of the diene opposite to it, thereby generating tris-adduct **37** in high selectivity.

Overall, the product distribution obtained from reaction of 1*E*-methyl[4]dendralene (**10**) with NMM correlates closely with that of the parent [4]dendralene (**1**). Similar yields of analogous products are obtained, in spite of the additional complexity brought to bear on the system by the methyl substituent. Overall, the presence of the *outside* methyl substituent at C1 only marginally increases the terminal site selectivity of the first Diels–Alder reaction (compare the *terminal*:*internal* ratio of ca. 78:22 for **1** with ca. 84:16 for **10**).

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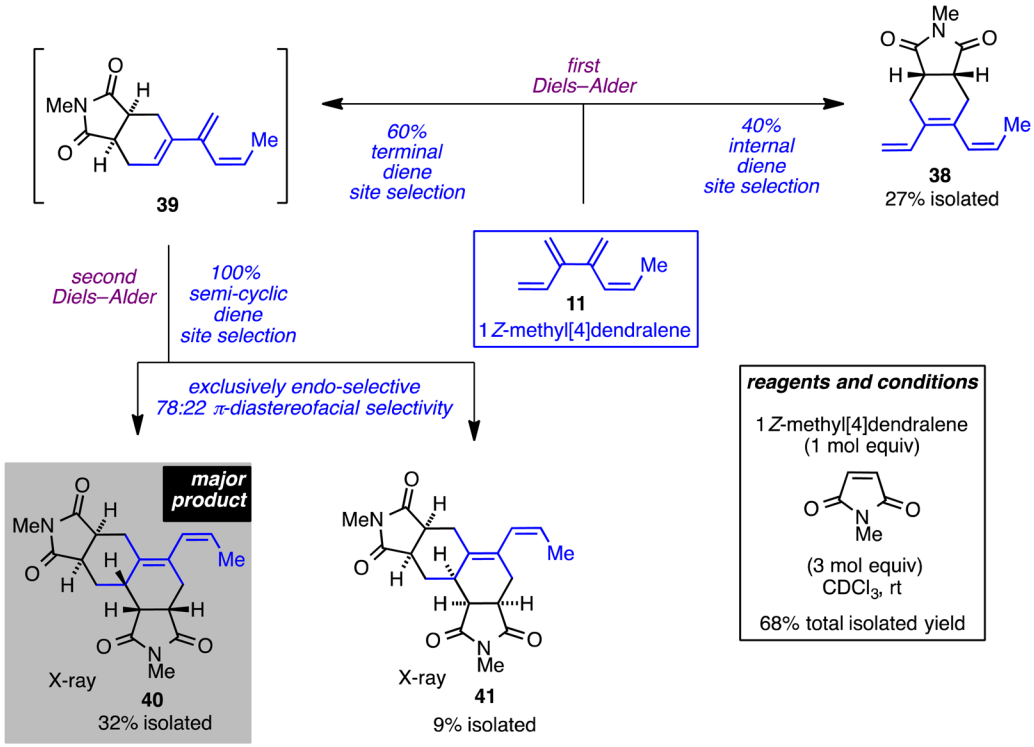
Scheme 5. Diels–Alder Reaction of 1*Z*-Methyl[4]dendralene (11) with an Excess of NMM at Room Temperature



The significant preference (at least 2:1) for the 1*E*-methyl-substituted butadiene terminus over the unsubstituted one is interesting, in light of the very mild influence of the methyl group. We presume that more activating 1*E*-substituents will give a much stronger preference for this site.

Exposure of 1*Z*-methyl[4]dendralene (**11**) to an excess[30] (3 mol equiv) of NMM at room temperature gave three products: internal monoadduct **38** in 27% yield, and two diastereomeric bis-adducts **40** and **41** in 32% and 9% yields, respectively (Scheme 5).[32] From this product distribution it is evident that the presence of the *inside*-methyl substituent prevents cycloaddition to the more substituted terminal diene site. Of the two remaining diene sites, we can deduce a ca. 60:40 site selectivity in favor of the less substituted *terminal* diene site, which is consistent with the *terminal*:*internal* ratio of 78:22 ratio observed with [4]dendralene (**1**) (Scheme 2). ([4]Dendralene (**1**) has two degenerate unsubstituted terminal diene sites and one internal site, whereas 1*Z*-methyl[4]dendralene (**11**) has one of each.) The *inside*-methyl substituent blocks addition to the acyclic diene site of monoadduct **39**, hence only bis-adducts **40** and **41** resulting from a second Diels–Alder reaction to the semicyclic diene site of **39** are seen. The π-diastereofacial selectivity of this second cycloaddition favors *anti*-bis-adduct **40**, qualitatively consistent with previous findings, albeit with slightly diminished selectivity in this case.

Thus, 1*Z*-methyl[4]dendralene (**11**) delivers significantly fewer products than both the parent system and the 1*E*-substituted congener, due to the blocking influence of the *inside* methyl substituent, which prevents the formation of tris-adducts. Evidently, this substitution alone will not be enough to engender synthetic utility upon the system, since two products are formed in roughly equal amounts in this reaction. Nevertheless, if terminal *Z*-substituents were present at both ends of the structure, we can safely predict the exclusive formation of the internal monoadduct.

When 2-methyl[4]dendralene (**12**) was treated with an excess[30] (3 mol equiv) of NMM at room temperature, four products were isolated: internal monoadduct **42** in 3% yield, and three bis-adducts **45**, **46**, and **47** in 26, 27, and 14% yields, respectively (Scheme 6).[32] It is clear that the presence of the methyl substituent at C2 has the effect of disfavoring the initial addition to the internal diene site. This is, presumably, a conformational effect, inasmuch as the methyl substituent either (a) disfavors the *s-cis* conformation of the internal diene through steric effects (Scheme 6, dashed box), and/or, as a result of this steric clash, (b) blocks dienophile approach due to the vinyl or 2-propenyl substituents being rotated out of the plane of the internal *cisoid* diene. Disappointingly, the site selectivity between the two dissimilar terminal diene sites cannot be determined, since it is not possible to establish the order of cycloaddition events leading to *terminal–terminal* bis-adducts **46** and **47**. Thus, both putative monoadducts **43** or **44** could, in principle, give rise to *terminal–terminal* bis-adducts **46** and **47**. Only monoadduct **43** can, however, give rise to bis-adduct **45** and, consistent with results described herein for the other substrates, the π-diastereofacial selectivity of this second Diels–Alder addition to the semicyclic diene site of monoadduct **43** is high. If regioisomeric monoadduct **44** is generated, then it must undergo a second addition exclusively to the remaining terminal diene site, a conclusion that seems reasonable in light of the presence of the *inside* methyl substituent, which would disfavor the *s-cis* conformation of the semicyclic diene of **44**. That the *terminal–terminal* bis-adduct **46** is preferred over its diastereomer **47** is interesting, since it indicates a moderate level of π-diastereofacial selectivity in the cycloaddition to the acyclic diene site(s) of monoadducts **43**/**44**. The lack of tris-adducts from *terminal–terminal* bis-adducts **46** and **47** is presumably, once again, the result of a disfavored *s-cis* conformation due to the presence of an *inside* methyl group.

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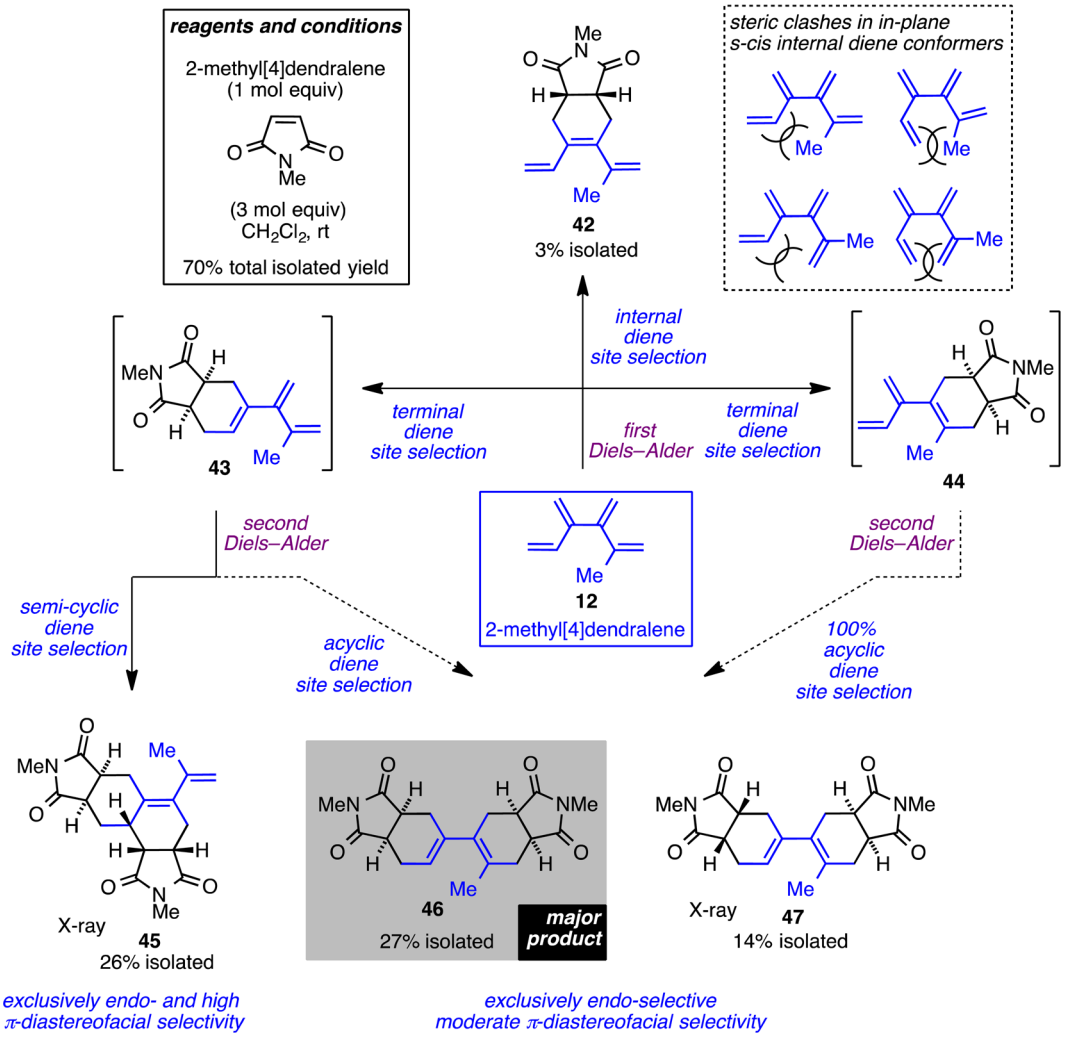
Scheme 6. Diels–Alder Reaction of 2-Methyl[4]dendralene (12) with an Excess of NMM at Room Temperature



In terms of future synthetic applications, the most important—and surprising—observation with 2-methyl[4]-dendralene (**12**) is that addition to its internal diene site is disfavored. A more detailed analysis of the experimental findings is thwarted by an inability to attribute products to specific pathways. Nonetheless, a significant hurdle toward future applications is that the 2-methyl substituent (and presumably other groups in this position) leads to the formation of different regioisomeric bis-adducts in significant amounts.

Exposure of 3′*E*-methyl[4]dendralene (**13**) to an excess[30] (3 mol equiv) of NMM at room temperature resulted in three products: internal monoadduct **48** in 42% yield, and diastereomeric bis-adducts **50** and **51** in 45% and 3% yields (Scheme 7).[31] The impact of the 3′-methyl substituent is clear from the first cycloaddition reaction, with no addition occurring to the terminal diene site to which it is attached, and addition to the remaining internal and terminal sites occurring in roughly equal measure. The presence of the *outside* methyl group leads to a modest enhancement upon the reactivity of the internal diene site of **13**, as evidenced by the increased quantity of the internal adduct (*terminal*:*internal* ratio = 53:47) relative to 1*Z*-methyl[4]dendralene (**11**) (Scheme 5, *terminal*:*internal* ratio = 60:40), a substrate which also has only one reactive internal and terminal diene but lacks a methyl substituent on either. While the internal monoadduct **48** is inert toward further reaction, terminal monoadduct **49** undergoes a highly site-selective and stereoselective cycloaddition reaction with more dienophile. Again, the methyl substituent of putative monoadduct **49** blocks addition to the acyclic diene site, hence steering the reaction path to bis-adducts **50** and **51**, with a strong π-diastereofacial selectivity in favor of the former, for reasons discussed in previous cases.

Hence, only two compounds (**48**+**50**) account for 87% of the isolated yield in the Diels–Alder reaction of 3′*E*-methyl[4]dendralene (**13**) with NMM. These two products are, however, the result of dienophile additions to two different diene sites in the precursor.

Reaction of 3′*Z*-methyl[4]dendralene (**14**) with an excess[30] (3 mol equiv) of NMM at room temperature delivered a mixture of five products: two diastereomeric bis-adducts **54** and **55** in 11% and in 8% yields and three diastereomeric tris-adducts **58**, **59** and **60** in 23, 18, and 10% yields, respectively (Scheme 8).[33] Unsurprisingly, none of the internal mono-adduct is observed from this reaction, presumably due to the *inside*-methyl substituent attached to the internal 1,3-butadiene unit of **14**. The first cycloaddition, therefore, proceeds with complete site selectivity in favor of the two terminal diene sites. As was the case with 2-methyl[4]dendralene (**12**) (Scheme 6), it is not possible to determine the selectivity for one of these

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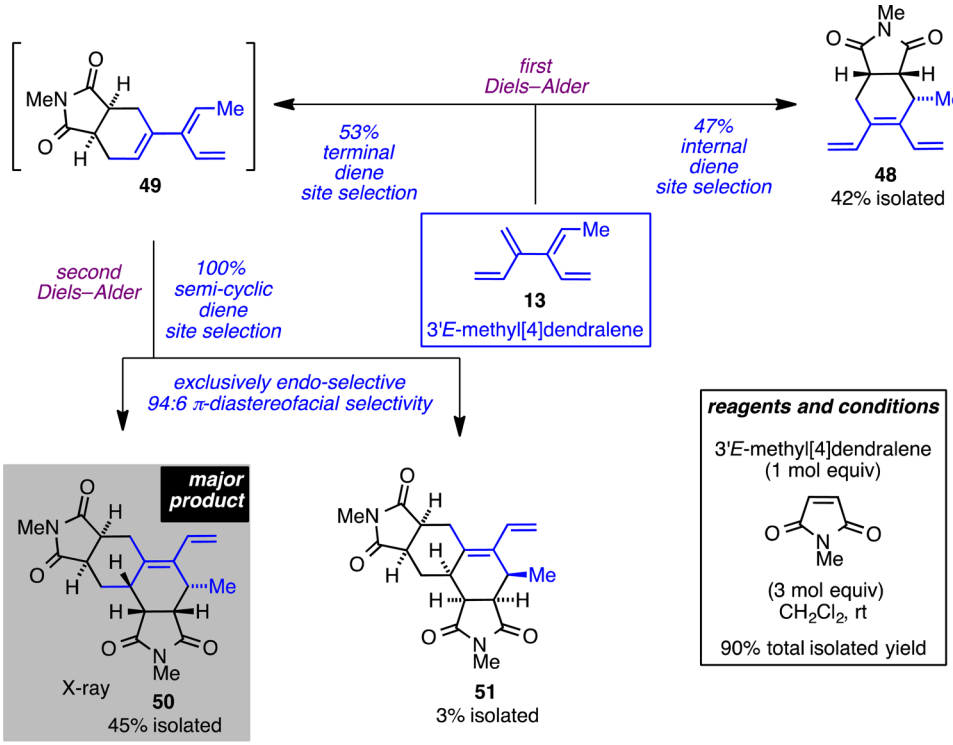
Scheme 7. Diels–Alder Reaction of 3′*E*-Methyl[4]dendralene (13) with an Excess of NMM at Room Temperature



terminal sites over the other, since the three tris-adducts **58**, **59** and **60** can, in principle, be derived from either of the two monoadducts, **52** or **53**. It is certain that addition occurs to the more substituted terminal diene site to generate monoadduct **52**, since two diastereomeric products (**54** and **55**) of addition to the semicyclic diene site of **52** are isolated. What is curious about this cycloaddition to the semicyclic diene site of **52** is its low level of π-diastereofacial selectivity. The methyl substituent would be expected to reinforce the preference for diastereomer **54**, by further shielding dienophile approach to the concave face of **52** (cf. **31** → **33**, Scheme 4). Consistent with this finding (but also surprising) is the relatively mild π-diastereofacial selectivity seen in the conversion of putative *anti-terminal–terminal* bis-adduct **57** into tris-adducts **59** and **60**. Not surprisingly, the diastereomeric *syn-terminal–terminal* bis-adduct **56** forms tris-adduct **58** exclusively. If monoadduct **53** is formed, then it reacts exclusively at the other terminal diene site to form *terminal–terminal* bis-adducts **56** and **57** and not at the semicyclic diene site, again due to the presence of the *inside*-methyl substituent.

SUMMARY AND CONCLUSIONS

In summary, two distinct synthetic strategies have been devised in order to access all five possible monomethylated [4]-dendralenes. Applications and extensions of these synthetic pathways can be envisioned for the preparation of other monosubstituted, as well as multisubstituted [4]dendralenes. These syntheses also serve as a stepping stone toward the synthesis of the as yet unknown monosubstituted higher [*n*]dendralenes (i.e., $n > 4$).

An exploratory investigation into the cycloaddition chemistry of these hydrocarbons has demonstrated that, in comparison with the unsubstituted [4]dendralene, each of the five possible monomethylated [4]dendralenes behaves differently on reaction with a dienophile. Thus, competing and complex sequences of cycloaddition reactions give rise to different distributions of mono-, bis- and tris-addition products. These reactions could not be easier to carry out, since they involve simply mixing the tetraene hydrocarbon with the dienophile at ambient temperature in a common solvent, yet they bring about some of the most striking examples of rapid complexity generation, with three new carbocycles, six new C–C bonds, and nine new stereocenters being generated.

Analysis of the outcomes of the Diels–Alder reactions of the five different substituted [4]dendralenes and comparisons with prior findings with the unsubstituted hydrocarbon has allowed the identification of recurring themes and the attribution of specific reactivity to substituent location. Some of our observations were predictable on the basis of known findings with substituted 1,3-butadienes.[34] Thus, the presence of an *inside*-methyl substituent on a 1,3-butadiene portion of the dendralene completely prevents Diels–Alder reaction at that site, whereas an *outside*-methyl substituent on a 1,3-butadiene unit leads to a moderate reactivity increase.[35] In this respect, the dendralene behaves as if it were simply a mixture of different substituted dienes. Other influences are less predictable, as exemplified by the case of the 2-methyl substituent, which inhibits dienophile addition to the adjacent, *internal* site in a [4]dendralene (**12**, Figure 3), whereas the same substituent promotes addition to the adjacent site in a [3]dendralene (Figure 1).

In all cases, an initial Diels–Alder addition of a dienophile to the internal site of a [4]dendralene results in formation of a product that resists further reaction at ambient temperature. Boosting the yield of the internal adduct is of interest since it will allow the rapid, high yield construction of downstream products. For example, 6π-electrocyclization of the internal adduct has been demonstrated previously with the parent [4]dendralene, along with cycloaddition to the resulting 1,3-cyclohexadiene structure, as has direct dienophile addition to

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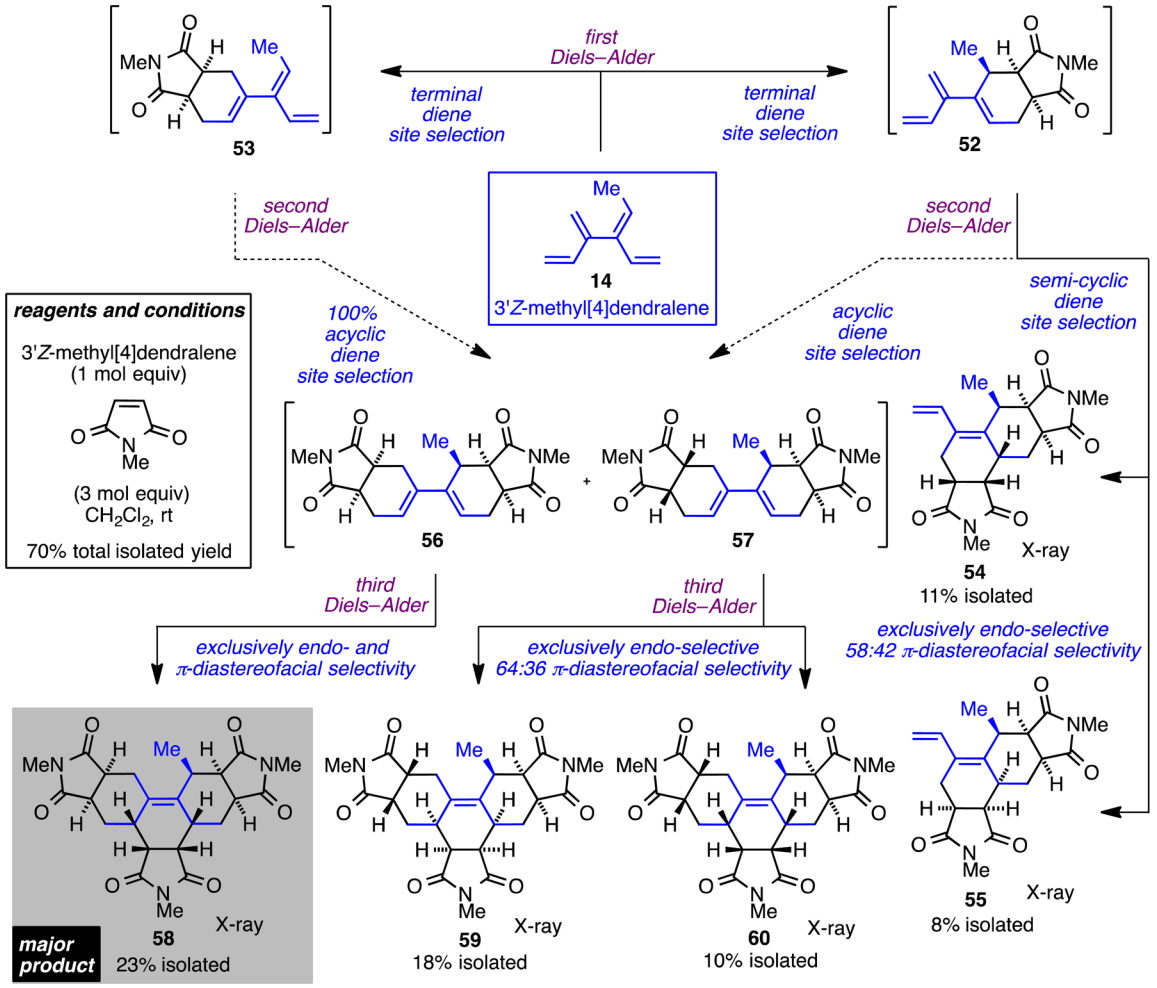
Scheme 8. Diels–Alder Reaction of 3′*Z*-Methyl[4]dendralene (14) with an Excess of NMM at Room Temperature



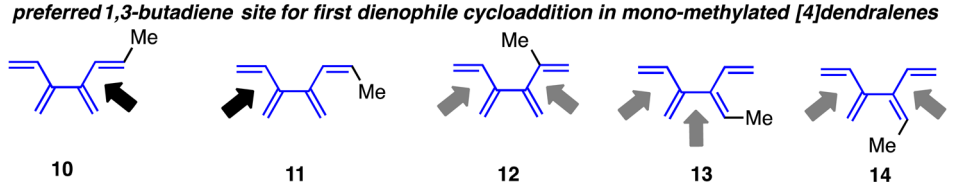


Figure 3. Site selection in dienophile additions to monosubstituted [4]dendralenes (darker shading indicates stronger selectivity).

the internal adduct under high pressure conditions.[3] Similar processes can be envisioned with the substituted systems.

An initial dienophile addition to a terminal 1,3-butadiene site gives rise to a substituted [3]dendralene, which can in turn react with another dienophile at either the acyclic or semicyclic diene site. A third Diels–Alder addition occurs to the product of addition to the acyclic site but, at ambient temperature, the semicyclic addition product does not react on. (Further addition is possible, however, under high pressure.[3]) The presence of a methyl group blocks reaction as an *inside*-substituent and mildly enhances reactivity as an *outside*-substituent. In general, the π-diastereofacial selectivities of these reactions are predictable through consideration of steric effects.

The purpose of this work was to develop ways to prepare substituted [4]dendralenes and to document their Diels–Alder reactivity, in the hope of promoting synthetic applications. The reactions described herein are of marginal direct use in total synthesis due to their propensity to generate complex mixtures. These findings do, however, form the foundations for directed, future studies toward specific product structures. The methyl substituent is neither a particularly sterically bulky group, nor is it strongly electron donating. For these reasons, it is likely that other substituents will exhibit higher selectivities. Thus, larger groups and those with more potent electronic characteristics will have a much greater influence, and the deployment of multiple substituents that operate cooperatively are likely to deliver significantly more selective domino cycloaddition sequences. The deployment of catalysts can also influence the site selectivity of Diels–Alder processes.[3] It is most likely the case that a combination of these tactics will be ultimately successful in achieving the highest level of control in multicycloaddition sequences to dendralenes. This work serves to highlight the significant challenges that need to be met, in order for these extraordinarily step economic processes to be applied in total synthesis.

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EXPERIMENTAL SECTION

General Methods. See the Supporting Information.

*Chloroprene (**62**).*[36] The title compound **62** was prepared following the patented procedure.[36]

*Buta-1,3-dien-2-ylmagnesium chloride (**15**).*[37] The title compound **15** was prepared following modification of the procedure reported by Nunomoto and Yamashita.[37]

*2-Chloro[3]dendralene (**17**).*[21] The title compound **17** was prepared following modification of the published procedure.[21]

*(3-Methylenepenta-1,4-dien-2-yl)magnesium chloride (**63**).*[21] The title compound **63** was prepared following modification of the published procedure.[21] A 3-necked round bottomed flask equipped with a condenser and dropping funnel was charged with oven-dried magnesium powder (3.7 g, 0.15 mol, 2.9 mol equiv) and flushed with argon for 1 h. To this was added THF (45 mL) followed by portionwise addition of 1,2-dibromoethane (1.8 mL, 21 mmol, 0.40 mol equiv) (***Caution!*** *Exothermic*). After refluxing had subsided, $ZnBr_2$ (0.59 g, 2.6 mmol, 0.050 mol equiv) was added and the sides of the reaction flask were rinsed with THF (5.0 mL). The reaction mixture was then heated to reflux and a solution of 2-chloro[3]dendralene (**17**) (6.0 g, 26% (w/w) solution in THF, 53 mmol, 1.0 mol equiv) and 1,2-dibromoethane (2.8 mL, 32 mmol, 0.60 mol equiv) in THF (40 mL) was added dropwise over 30 min. After the addition was complete, the reaction mixture was stirred at reflux for a further 10 min. The title compound **63** was obtained as a dark black solution (0.10 L, 0.22 M solution in THF, 22 mmol, 42%) and was used immediately in the next reaction.

*1E-Methyl[4]dendralene (**10**).* A freshly prepared solution of (3-methylenepenta-1,4-dien-2-yl)magnesium chloride (**63**) (25 mL, 0.16 M solution in THF, 4.0 mmol, 1.6 mol equiv) was added slowly into a stirred solution of $ZnBr_2$ (0.92 g, 4.1 mmol, 1.6 mol equiv) and THF (5.0 mL) at 0 °C. Once the addition was complete, the reaction mixture was allowed to warm to 25 °C and stirred for a further 20 min. To this was added 1*E*-bromopropene (**19**) (0.22 mL, 2.6 mmol, 1.0 mol equiv) followed by addition of $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol, 0.050 mol equiv) and the reaction mixture was stirred at 25 °C for 16 h with the exclusion of light. The resulting solution was poured into water (0.15 L), stirred for 15 min and petroleum ether (30−40 °C) (0.15 L) was added. The organic phase was separated and aqueous phase was then extracted with petroleum ether (30−40 °C) (2 × 0.10 L). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure (50 mbar, 0 °C). Purification by flash column chromatography (SiO_2, petroleum ether (30−40 °C)) gave the title compound **10** (0.11 g, 0.92 mmol, 35%) as a colorless oil. R_f 0.56 (petroleum ether (30−40 °C)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (ddd, J = 17.4, 10.5, 0.8 Hz, 1H), 6.13 (ddd, J = 15.5, 1.9, 0.7 Hz, 1H), 5.65 (dq, J = 15.6, 5.0 Hz, 1H), 5.24−5.14 (m, 2H), 5.12−5.01 (m, 3H), 4.89 (dd, J = 2.2, 0.8 Hz, 1H), 1.74 (ddt, J = 6.7, 1.5, 0.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5 (C), 146.4 (C), 137.7 (CH), 132.1 (CH), 128.5 (CH), 117.4 (CH_2), 116.5 (CH_2), 115.0 (CH_2), 18.2 (CH_3) ppm; IR (thin film) ν_{max} = 3083, 2954, 2923, 2852, 1635, 1456 cm^{-1}; LRMS (70 eV, EI) m/z (%) 120 ([M]$^{+\bullet}$, 15%), 105 (100), 91 (44), 79 (34); HRMS calc for C_9H_{12} [M]$^{+\bullet}$ 120.0939, found 120.0938.

*(Z)-Prop-1-en-1-ylmagnesium bromide (**20**).*[22] The title compound **20** was prepared following the procedure reported by Prieto et al.[22]

*1Z-Methyl[4]dendralene (**11**).* To a stirred solution of 2-chloro[3]-dendralene (**17**) (3.6 g, 32 mmol, 1.0 mol equiv) and Ni(dppp)Cl_2 (0.69 g, 1.3 mmol, 0.040 mol equiv) in THF (12 mL) at −20 °C was added dropwise a solution of (*Z*)-prop-1-en-1-ylmagnesium bromide (**20**) (0.24 L, 0.20 M solution in THF, 47 mmol, 1.5 mol equiv) over 25 min. The reaction mixture was then allowed to warm to 25 °C and stirred for 2.5 h. The resulting solution was poured into a mixture of ice-cold petroleum ether (30−40 °C) (0.60 L) and water (0.60 L) and stirred for 15 min before a solution of aqueous HCl (40 mL, 1.0 M) was added. The organic phase was separated, washed with a solution of saturated aqueous $NaHCO_3$ (0.10 L) followed by brine (0.10 L), dried over $MgSO_4$, filtered, and concentrated under reduced pressure (45 mbar, 0 °C). Purification by flash column chromatography (SiO_2, petroleum ether (30−40 °C)) afforded the title compound **11** (2.2 g, 18 mmol, 58%) as a colorless oil along with a small amount of the *E* isomer **10** and homocoupled byproduct **65** (**11**:**10**:**65** = 87:6:7 ratio). R_f 0.57 (petroleum ether (30−40 °C)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (ddd, J = 17.3, 10.7, 0.9 Hz, 1H), 5.99 (ddt, J = 11.6, 3.0, 1.7 Hz, 1H), 5.61 (dq, J = 11.6, 7.0 Hz, 1H), 5.31 (dd, J = 17.4, 1.7 Hz, 1H), 5.21 (d, J = 2.3 Hz, 1H), 5.17−5.08 (m, 4H), 1.74 (dd, J = 7.1, 1.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7 (C), 144.0 (C), 137.3 (CH), 129.8 (CH), 127.3 (CH), 117.4 (CH_2), 116.6 (CH_2), 115.7 (CH_2), 14.5 (CH_3) ppm; IR (thin film) ν_{max} = 3087, 3012, 2916, 1801, 1633, 1593, 1439 cm^{-1}; LRMS (70 eV, EI) m/z (%) 120 ([M]$^{+\bullet}$, 17%), 108 (3), 105 (100); HRMS calc for C_9H_{12} [M]$^{+\bullet}$ 120.0939, found 120.0944.

*Prop-1-en-2-ylmagnesium bromide (**21**).*[38] The title compound **21** was prepared following modification of the procedure reported by Slater et al.[38] 2-Bromopropene (**66**) (1.5 mL, 17 mmol, 1.0 mol equiv) was added to a stirred mixture of oven-dried magnesium powder (0.44 g, 18 mmol, 1.1 mol equiv) in degassed THF (25 mL) at 25 °C (***Caution!*** *Exothermic*). After the addition was complete, the reaction mixture was heated to 40 °C and stirred for 75 min. The title compound **21** was obtained as pale yellow solution (25 mL, 0.39 M solution in THF, 9.8 mmol, 57%).

*2-Methyl[4]dendralene (**12**).* To a stirred solution of 2-chloro[3]-dendralene (**17**) (0.50 g, 4.4 mmol, 1.0 mol equiv) and Ni(dppp)Cl_2 (95 mg, 0.14 mmol, 0.04 mol equiv) in THF (2.0 mL) at −20 °C was added dropwise a solution of prop-1-en-2-ylmagnesium bromide (**21**) (17 mL, 0.39 M solution in THF, 0.66 mmol, 1.5 mol equiv) over 7 min. The reaction mixture was allowed to warm to 25 °C and stirred for 2 h. The resulting mixture was poured into a stirred mixture of ice-cold petroleum ether (30−40 °C) (60 mL) and water (40 mL) and stirred for 15 min before a solution of aqueous HCl (10 mL, 1.0 M) was added. The organic phase was separated and washed with a solution of saturated aqueous $NaHCO_3$ (20 mL) followed by brine (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure (45 mbar, 0 °C). Purification by flash column chromatography (SiO_2, petroleum ether (30−40 °C) afforded the title compound **12** (0.14 g, 1.2 mmol, 27%) as a colorless oil. R_f 0.66 (petroleum ether (30−40 °C)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (dd, J = 17.3, 10.5 Hz, 1H), 5.30−5.27 (m, 1H), 5.23−5.20 (m, 1H), 5.16−5.09 (m, 1H), 5.08−4.98 (m, 5H), 1.96−1.94 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7 (C), 148.7 (C), 141.8 (C), 138.2 (CH), 117.7 (CH_2), 116.3 (CH_2), 116.1 (CH_2), 114.4 (CH_2), 20.3 (CH_3) ppm; IR (thin film) ν_{max} = 3092, 3006, 2974, 2948, 1586, 1458, 1440 cm^{-1}; LRMS (70 eV, EI) m/z (%) 120 ([M]$^{+\bullet}$, 12%), 119 (31), 115 (13), 107.1 (100); HRMS calc for C_9H_{12} [M]$^{+\bullet}$ 120.0939, found 120.0939.

*Pent-2-yne-1,4-diol (**22**).*[39] The title compound **22** was prepared following the procedure reported by Takahashi and Matsumoto.[40]

*(E)-Diethyl-3-ethylidene-4-methylenehexanedioate (**23**) and (Z)-Diethyl-3-ethylidene-4-methylenehexanedioate (**24**).* The title compounds **23** and **24** were prepared following modification of the procedure reported by Srikrishna and Nagaraju.[41] A microwave reactor vial was charged with a solution of pent-2-yne-1,4-diol (**22**) (1.7 g, 17 mmol, 1.0 mol equiv), triethyl orthoacetate (25 g, 0.15 mol, 9.1 mol equiv) and propionic acid (0.63 g, 8.5 mmol, 0.52 mol equiv) in dry DMF (30 mL). The reaction mixture was heated to 180 °C using microwave irradiation (300 W) for 25 min. The resulting mixture was diluted with Et_2O (60 mL) and washed with a solution of aqueous HCl (1.0 M) followed by a solution of aqueous LiCl (5% (w/w) in water). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc:hexane (5:95)) gave the title compound **23** (1.4 g, 5.8 mmol, 35%) as a yellow oil and the title compound **24** (1.5 g, 6.3 mmol, 38%) as a yellow oil.

*(E)-Diethyl-3-ethylidene-4-methylenehexanedioate (**23**).* R_f 0.37 (EtOAc:hexane (10:90)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (q, J = 6.7 Hz, 1H), 5.20 (s, 1H), 5.04 (s, 1H), 4.13 (dtd, J = 7.8, 6.8, 2.4 Hz, 4H), 3.33 (s, 2H), 3.28 (s, 2H), 1.77 (d, J = 6.9 Hz, 3H), 1.23 (tt, J = 7.1, 0.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 171.4

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(C), 140.8 (C), 132.4 (C), 126.7 (CH), 115.0 (CH_2), 60.7 (CH_2) (two coincident signals), 40.7 (CH_2), 33.9 (CH_2), 14.6 (CH_3), 14.2 (CH_3) (two coincident signals) ppm; IR (thin film) ν_{max} = 3096, 2982, 2938, 1732, 1610, 1446 cm^{-1}; LRMS (70 eV, EI) *m/z* (%) 240 ($[M]^{+\bullet}$, 42%), 225 (6), 194 (72), 166 (58), 93 (100); HRMS calc for $C_{13}H_{20}O_4$ $[M]^+$ 240.1362, found 240.1357.

*(Z)-Diethyl-3-ethylidene-4-methylenehexanedioate (**24**).* R_f 0.43 (EtOAc:hexane (10:90)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (qt, *J* = 6.9, 1.3 Hz, 1H), 5.21 (q, *J* = 1.5 Hz, 1H), 4.98 (d, *J* = 1.8 Hz, 1H), 4.09 (qd, *J* = 7.0, 1.5 Hz, 4H), 3.16 (d, 2H), 3.10 (t, *J* = 1.2 Hz, 2H), 1.69 (dt, *J* = 8.6, 1.0 Hz, 3H), 1.22 (td, *J* = 7.2, 1.9 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (C), 171.0 (C), 139.1 (C), 134.1 (C), 127.1 (CH), 118.8 (CH_2), 60.7 (CH_2), 60.6 (CH_2), 42.3 (CH_2), 41.2 (CH_2), 14.9 (CH_3), 14.3 (CH_3), 14.2 (CH_3) ppm; IR (thin film) ν_{max} = 3086, 2983, 2938, 1737, 1634, 1446 cm^{-1}; LRMS (70 eV, EI) *m/z* (%) 240 ($[M]^{+\bullet}$, 40%), 225 (12), 194 (78), 166 (68), 93 (100); HRMS calc for $C_{13}H_{20}O_4$ $[M]^{+\bullet}$ 240.1362, found 240.1362.

*(E)-3-Ethylidene-4-methylenehexane-1,6-diol (**25**).* A solution of (*E*)-diethyl 3-ethylidene-4-methylenehexanedioate (**23**) (4.7 g, 20 mmol, 1.0 mol equiv) in dry Et_2O (60 mL) was slowly added into a stirred suspension of $LiAlH_4$ (1.5 g, 39 mmol, 2.0 mol equiv) in dry Et_2O (40 mL) at 0 °C. The resulting mixture was stirred for 30 min and then allowed to warm to 25 °C and stirred further overnight. The resulting reaction mixture was cooled to 0 °C and carefully quenched by dropwise addition of water (25 mL) followed by addition of Et_2O (25 mL). The resulting mixture was then stirred at 25 °C for 1 h. The resulting reaction mixture was poured into a stirred saturated solution of aqueous NH_4Cl (0.10 L) before a solution of aqueous HCl (1.0 M, 0.10 L) was added. The organic phase was separated and the aqueous layer was extracted with Et_2O (4 × 0.10 L). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc:hexane (70:30)) gave the title compound **25** (3.0 g, 19 mmol, 97% yield) as a yellow oil. R_f 0.32 (EtOAc:hexane (70:30)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (q, *J* = 6.9 Hz, 1H), 5.11−5.09 (m, 1H), 4.99−4.97 (m, 1H), 3.68 (td, *J* = 6.4, 5.1 Hz, 4H), 2.59 (t, *J* = 6.6 Hz, 2H), 2.54 (td, *J* = 6.2, 1.0 Hz, 2H), 1.96 (br s, 2H), 1.76 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1 (C), 135.8 (C), 124.9 (CH), 113.1 (CH_2), 61.5 (CH_2), 61.2 (CH_2), 37.8 (CH_2), 31.0 (CH_2), 14.2 (CH_3) ppm; IR (thin film) ν_{max} = 3329, 2954, 2883, 1458, 1042 cm^{-1}; LRMS (70 eV, EI) *m/z* (%) 156 ($[M]^{+\bullet}$, 12%), 141 (11), 125 (36), 111 (69), 97 (100); HRMS calc for $C_9H_{16}O_2$ $[M]^{+\bullet}$ 156.1150, found 156.1150.

*(E)-6-Bromo-3-(2-bromoethyl)-4-methylenehex-2-ene (**27**).* *N*-Bromosuccinimide (5.3 g, 30 mmol, 2.0 mol equiv) was added portionwise to a stirred mixture of (*E*)-3-ethylidene-4-methylenehexane-1,6-diol (**25**) (2.3 g, 15 mmol, 1.0 mol equiv) and triphenylphosphine (7.8 g, 30 mmol, 1.0 mol equiv) in CH_2Cl_2 (0.10 L) at −78 °C. The reaction mixture was then allowed to warm to 25 °C and stirred overnight. The resulting mixture was poured into petroleum ether (30−40 °C) (0.10 L) and stirred for 30 min, filtered and concentrated under reduced pressure (45 mbar, 0 °C). The resulting mixture was again diluted with petroleum ether (30−40 °C) (0.10 L), filtered and concentrated under reduced pressure (45 mbar, 0 °C). Purification by flash column chromatography (SiO_2, petroleum ether (30−40 °C)) gave the title compound **27** (1.6 g, 5.7 mmol, 40% yield) as a colorless oil. R_f 0.56 (petroleum ether (40−60 °C)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (q, *J* = 7.0 Hz, 1H), 5.09 (s, 1H), 4.99 (s, 1H), 3.43 (t, *J* = 7.5 Hz, 2H), 3.35 (t, *J* = 7.9 Hz, 2H), 2.81 (dt, *J* = 15.4, 7.9 Hz, 4H), 1.77 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3 (C), 136.0 (C), 125.3 (CH), 113.2 (CH_2), 37.9 (CH_2), 31.6 (CH_2), 31.4 (CH_2), 30.8 (CH_2), 14.3 (CH_3) ppm; IR (thin film) ν_{max} = 3090, 2967, 2919, 2857, 1439 cm^{-1}; LRMS (70 eV, EI) *m/z* (%) 284 ($[M^{81}Br^{81}Br]^{+\bullet}$, 26%), 282 ($[M^{81}Br^{79}Br]^{+\bullet}$, 48%), 280 ($[M^{79}Br^{79}Br]^{+\bullet}$, 27%), 203 (99), 201 (100), 121 (74); HRMS calc for $C_9H_{14}{}^{81}Br_2$ $[M]^{+\bullet}$ 283.9421, found 283.9420; calc for $C_9H_{14}{}^{81}Br^{79}Br$ $[M]^{+\bullet}$ 281.9442, found 281.9424; $C_9H_{14}{}^{79}Br_2$ $[M]^{+\bullet}$ 279.9462, found 279.9461.

*3′E-Methyl[4]dendralene (**13**).* 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (3.5 g, 23 mmol, 6.4 mol equiv) was added dropwise into a stirred solution of (*E*)-6-bromo-3-(2-bromoethyl)-4-methylenehex-2-ene (**27**) (1.0 g, 3.6 mmol, 1.0 mol equiv) in anhydrous DMSO (3.0 mL) at 25 °C and stirred for 15 min. The resulting reaction mixture was then subjected to vacuum distillation at 65 mbar for 2 h and then at 20 mbar for a further 2 h (trap at −78 °C). The title compound **13** (0.26 g, 2.2 mmol, 60%) was isolated from the receiving flask as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.41 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.56−5.47 (m, 1H), 5.24−4.97 (m, 6H), 1.83 (d, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4 (C), 138.5 (C), 138.1 (CH), 131.7 (CH), 127.0 (CH), 117.8 (CH_2), 116.3 (CH_2), 116.2 (CH_2), 13.4 (CH_3) ppm; IR (thin film) ν_{max} = 3090, 3016, 2918, 1597, 1586 cm^{-1}; LRMS (70 eV, EI) *m/z* (%) 120 ($[M]^{+\bullet}$, 10%), 119 (26), 105 (31), 78 (86), 63 (100); HRMS calc for C_9H_{11} $[M^{+\bullet}-H]$ 119.0861, found 119.0857; calc for C_8H_9 $[M^{+\bullet}-CH_3]$ 105.0704, found 105.0702.

*(Z)-3-Ethylidene-4-methylenehexane-1,6-diol (**26**).* A solution of (*Z*)-diethyl-3-ethylidene-4-methylenehexanedioate (**24**) (4.3 g, 18 mmol, 1.0 mol equiv) in dry Et_2O (60 mL) was slowly added into a stirred suspension of $LiAlH_4$ (1.4 g, 36 mmol, 2.0 mol equiv) in dry Et_2O (40 mL) at 0 °C. The reaction mixture was stirred for 30 min and then allowed to warm to 25 °C and stirred further overnight. The resulting reaction mixture was cooled to 0 °C and carefully quenched by dropwise addition of water (25 mL) followed by addition of Et_2O (25 mL). The resulting mixture was then stirred at 25 °C for 1 h. The resulting reaction mixture was poured into a stirred saturated solution of aqueous NH_4Cl (0.10 L) before a solution of aqueous HCl (1.0 M, 0.10 L) was added. The organic phase separated and the aqueous layer was extracted with Et_2O (4 × 0.10 L). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc:hexane (70:30)) gave the title compound **26** (2.5 g, 16 mmol, 91% yield) as a yellow oil. R_f 0.26 (EtOAc:hexane (70:30)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (q, *J* = 6.9 Hz, 1H), 5.11 (d, *J* = 1.3 Hz, 1H), 4.81 (d, *J* = 2.3 Hz, 1H), 3.62 (dt, *J* = 13.2, 6.3 Hz, 4H), 2.42 (br s, 2H), 2.38 (t, *J* = 6.5 Hz, 2H), 2.32 (t, *J* = 6.3 Hz, 2H), 1.63 (d, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 138.5 (C), 124.1 (CH), 115.9 (CH_2), 60.9 (CH_2), 60.8 (CH_2), 39.6 (CH_2), 38.6 (CH_2), 14.7 (CH_3) ppm; IR (thin film) ν_{max} = 3339, 2936, 2882, 1441, 1045 cm^{-1}; LRMS (70 eV, EI) *m/z* (%) 156 ($[M]^{+\bullet}$, 4%), 138 (10), 126 (36), 111 (71), 97 (100); HRMS calc for $C_9H_{16}O_2$ $[M]^{+\bullet}$ 156.1150, found 156.1150.

*(Z)-6-Bromo-3-(2-bromoethyl)-4-methylenehex-2-ene (**28**).* *N*-Bromosuccinimide (1.1 g, 6.4 mmol, 2.0 mol equiv) was added portionwise to a stirred mixture of (*Z*)-3-ethylidene-4-methylenehexane-1,6-diol (**26**) (0.50 g, 3.2 mmol, 1.0 mol equiv) and triphenylphosphine (1.7 g, 6.4 mmol, 2.0 mol equiv) in CH_2Cl_2 (20 mL) at −78 °C. The reaction mixture was then allowed to warm to 25 °C and stirred overnight. The resulting mixture was poured into petroleum ether (30−40 °C) (30 mL) and stirred for 30 min, filtered and concentrated under reduced pressure (45 mbar, 0 °C). The resulting mixture was again diluted with petroleum ether (30−40 °C) (30 mL), filtered and concentrated under reduced pressure (45 mbar, 0 °C). Purification by flash column chromatography (SiO_2, petroleum ether (30−40 °C)) gave the title compound **28** (0.44 g, 1.6 mmol, 49% yield) as a colorless oil. R_f 0.46 (petroleum ether (40−60 °C)); ^1H NMR (300 MHz, $CDCl_3$) δ 5.50 (q, *J* = 6.8 Hz, 1H), 5.17 (d, *J* = 1.6 Hz, 1H), 4.91 (d, *J* = 1.9 Hz, 1H), 3.39 (t, *J* = 7.3 Hz, 2H), 3.35 (t, *J* = 7.3 Hz, 2H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.59 (t, *J* = 7.3 Hz, 2H), 1.67 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7 (C), 137.7 (C), 125.8 (CH), 117.3 (CH_2), 39.4 (CH_2), 38.6 (CH_2), 31.6 (CH_2), 30.5 (CH_2), 14.8 (CH_3) ppm; IR (thin film) ν_{max} = 3080, 2965, 2937, 2916, 2857, 1443, 1431 cm^{-1}; LRMS (70 eV, EI) *m/z* (%) 284 ($[M^{81}Br^{81}Br]^{+\bullet}$, 17%), 282 ($[M^{81}Br^{79}Br]^{+\bullet}$, 34%), 280 ($[M^{79}Br^{79}Br]^{+\bullet}$, 18%), 203 (91), 201 (94), 121 (66), 93 (100); HRMS calc for $C_9H_{14}{}^{81}Br_2$ $[M]^{+\bullet}$ 283.9421, found 283.9436; calc for $C_9H_{14}{}^{81}Br^{79}Br$ $[M]^{+\bullet}$ 281.9442, found 281.9445; calc for $C_9H_{14}{}^{79}Br_2$ $[M]^{+\bullet}$ 279.9462, found 279.9462.

*3′Z-Methyl[4]dendralene (**14**).* 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.8 g, 12 mmol, 6.4 mol equiv) was added dropwise into a stirred solution of (*Z*)-6-bromo-3-(2-bromoethyl)-4-methylenehex-2-

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ene (**28**) (0.50 g, 1.8 mmol, 1.0 mol equiv) in anhydrous DMSO (2.5 mL) at 25 °C and stirred for 15 min. The resulting reaction mixture was then subjected to vacuum distillation at 65 mbar for 2 h and then at 20 mbar for a further 2 h (trap at −78 °C). The title compound **14** (0.17 g, 1.4 mmol, 77%) was isolated from the receiving flask as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, J = 10.5, 6.4 Hz, 1H), 6.38 (dd, J = 10.7, 6.6 Hz, 1H), 5.75 (q, J = 6.9 Hz, 1H), 5.39 (d, J = 2.3 Hz, 1H), 5.11−4.87 (m, 5H), 1.61 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 139.9 (C), 139.1 (CH), 137.0 (CH), 128.3 (CH), 118.9 (CH_2), 115.9 (CH_2), 112.9 (CH_2), 14.8 (CH_3) ppm; IR (thin film) ν_{max} = 3089, 3004, 2914, 1583 cm^{-1}; LRMS (70 eV, EI) m/z (%) 120 ([M]$^{+\bullet}$, 4%), 78 (84), 63 (100); HRMS calc for C_9H_{12} [M]$^{+\bullet}$ 120.0939, found 120.0938.

*Reaction between 1E-Methyl[4]dendralene (**10**) and NMM.* A solution of 1*E*-methyl[4]dendralene (**10**) (66 mg, 0.55 mmol, 1.0 mol equiv) and NMM (0.18 g, 1.6 mmol, 3.0 mol equiv) in $CDCl_3$ (1.9 mL) was stirred for 21 h at room temperature. The solvent was then removed under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc:hexane (35:65 to 75:25)) gave the compound **29** (18 mg, 0.076 mmol, 14%) as a colorless oil, **32** (14 mg, 0.041 mmol, 7%) as a colorless oil, **33** (91 mg, 0.27 mmol, 48%) as a colorless solid, and a mixture of compounds **36** and **37** (70 mg). Further purification of the mixture of **36** and **37** by flash column chromatography (SiO_2, EtOAc:hexane (90:10)) afforded compound **36** (24 mg, 0.054 mmol, 10%) as a colorless solid and **37** (24 mg, 0.053 mmol, 10%) as a colorless oil.

*Monoadduct **29**.* R_f 0.36 (EtOAc:hexane (50:50)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (dd, J = 17.3, 11.0 Hz, 1H), 6.56 (dd, J = 15.5, 1.8 Hz, 1H), 5.86 (dq, J = 15.6, 6.7 Hz, 1H), 5.31 (d, J = 17.3 Hz, 1H), 5.09 (d, J = 11.0 Hz, 1H), 3.18−3.07 (m, 2H), 3.00−2.91 (m, 2H), 2.90 (s, 3H), 2.30 (dt, J = 14.3, 6.4 Hz, 2H), 1.82 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7 (C) (two coincident signals), 132.8 (C), 131.9 (CH), 130.0 (C), 126.9 (CH), 126.8 (CH), 113.6 (CH_2), 39.5 (CH) (two coincident signals), 25.3 (CH_2), 25.0 (CH_3), 24.1 (CH_2), 19.0 (CH_3) ppm; IR (thin film) ν_{max} = 2931, 1702, 1438, 1384, 1285, 1096 cm^{-1}; LRMS (70 eV, EI) m/z (%) 231 ([M]$^{+\bullet}$, 100%), 216 (67), 145 (65), 131 (91); HRMS calc for $C_{14}H_{17}NO_2$ [M]$^{+\bullet}$ 231.1259, found 231.1255.

*Bis-adduct **32**.* R_f 0.13 (EtOAc:hexane (50:50)); ^{1}H NMR (800 MHz, $CDCl_3$) δ 6.27 (d, J = 15.6 Hz, 1H), 5.78 (dq, J = 15.8, 6.6 Hz, 1H), 3.21 (ddd, J = 9.6, 5.7, 2.6 Hz, 1H), 3.18 (dd, J = 15.0, 2.2 Hz, 1H), 3.13 (ddd, J = 9.6, 6.3, 2.2 Hz, 1H), 3.11−3.05 (m, 2H), 3.00 (dd, J = 8.7, 5.5 Hz, 1H), 2.92 (s, 3H), 2.86 (s, 3H), 2.76 (ddd, J = 14.1, 13.4, 5.6 Hz, 1H), 2.38 (ddd, J = 14.2, 4.9, 2.6 Hz, 1H), 2.20−2.16 (m, 1H), 2.16−2.11 (m, 1H), 1.99−1.93 (m, 1H), 1.77 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 180.1 (C), 179.7 (C), 179.0 (C), 178.0 (C), 131.8 (C), 128.8 (C), 126.8 (CH), 126.4 (CH), 43.5 (CH), 39.9 (CH), 39.5 (CH), 39.0 (CH), 34.4 (CH), 25.2 (CH_2), 25.1 (CH_3), 25.0 (CH_3), 23.9 (CH_2), 23.6 (CH_2), 18.7 (CH_3) ppm; IR (thin film) ν_{max} = 2944, 1773, 1694, 1436, 1384, 1283, 1020 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 315 (9), 301 (7), 256 (12), 242 (13), 216 (18); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1582.

*Bis-adduct **33**.* An analytic sample of **33** was obtained by recrystallization from EtOAc/hexane to give colorless needles, mp 163−165 °C; R_f 0.19 (EtOAc:hexane (50:50)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (dd, J = 17.2, 11.0 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.09 (d, J = 11.0 Hz, 1H), 3.27 (dd, J = 8.7, 5.4 Hz, 1H), 3.22−3.01 (m, 5H), 3.00−2.91 (m, 1H), 2.87 (s, 3H), 2.85 (s, 3H), 2.24−2.12 (m, 1H), 2.00−1.86 (m, 2H), 1.56 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4 (C), 178.9 (C), 178.5 (C), 177.5 (C), 132.4 (C), 132.1 (C), 131.4 (CH), 115.0 (CH_2), 44.2 (CH), 41.5 (CH), 40.5 (CH), 40.4 (CH), 39.8 (CH), 29.2 (CH), 24.9 (CH_3), 24.8 (CH_3), 24.1 (CH_2), 24.1 (CH_2), 16.3 (CH_3) ppm; IR (KBr disc) ν_{max} = 2963, 1770, 1693, 1438, 1385, 1285, 1094 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 327 (6), 313 (12), 257 (15), 112 (42); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1584.

*Tris-adduct **36**.* An analytic sample of **36** was obtained by recrystallization from EtOAc/hexane to give colorless needles, mp 255−257 °C; R_f 0.20 (EtOAc, 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22 (dd, J = 8.6, 5.9 Hz, 1H), 3.19−3.07 (m, 3H), 3.04−2.91 (m, 5H), 2.90 (s, 6H), 2.86 (s, 3H), 2.65 (ddd, J = 14.1, 13.4, 5.4 Hz, 1H), 2.35 (ddd, J = 14.3, 5.0, 2.5 Hz, 1H), 2.16−2.05 (m, 2H), 2.03−1.91 (m, 1H), 1.85−1.74 (m, 1H), 1.54 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7 (C), 178.5 (C), 178.4 (C), 178.3 (C), 177.0 (C), 176.6 (C), 130.8 (C), 130.8 (C), 44.4 (CH), 43.4 (CH), 40.8 (CH), 40.6 (CH), 40.3 (CH), 39.2 (CH), 38.8 (CH), 33.7 (CH), 29.0 (CH), 25.0 (CH_3), 24.9 (CH_3), 24.8 (CH_3), 24.7 (CH_2), 24.4 (CH_2), 23.1 (CH_2), 16.5 (CH_3) ppm; IR (KBr disc) ν_{max} = 2961, 2948, 2842, 1770, 1695, 1435, 1383, 1286 cm^{-1}; LRMS (70 eV, EI) m/z (%) 453 ([M]$^{+\bullet}$, 100%), 438 (7), 342 (33), 256 (14), 112 (39); HRMS calc for $C_{24}H_{27}N_3O_6$ [M]$^{+\bullet}$ 453.1900, found 453.1905.

*Tris-adduct **37**.* R_f 0.31 (EtOAc 100%); ^{1}H NMR (800 MHz, $CDCl_3$) δ 3.27 (dd, J = 8.5, 5.6 Hz, 1H), 3.17 (ddd, J = 9.4, 6.2, 2.0 Hz, 1H), 3.08 (dd, J = 9.5, 5.2 Hz, 1H), 3.05 (dd, J = 8.5, 6.0 Hz, 1H), 3.01−2.97 (m, 2H), 2.99 (s, 3H), 2.96−2.89 (m, 1H), 2.86 (s, 3H), 2.84 (s, 3H), 2.71−2.64 (m, 2H), 2.35 (dt, J = 13.8, 4.6 Hz, 1H), 2.26 (q, J = 13.1 Hz, 1H), 2.21−2.14 (m, 2H), 1.84−1.76 (m, 2H), 1.55 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 179.3 (C), 178.7 (C), 178.6 (C), 178.3 (C), 176.7 (C), 176.6 (C), 132.2 (C), 129.8 (C), 44.3 (CH), 43.3 (CH), 41.1 (CH), 41.0 (CH), 40.7 (CH), 40.0 (CH), 39.5 (CH), 36.8 (CH), 29.5 (CH), 24.9 (CH_2), 24.9 (CH_3), 24.9 (CH_3), 24.8 (CH_3), 24.4 (CH_2), 23.8 (CH_2), 16.1 (CH_3) ppm; IR (thin film) ν_{max} = 2946, 1770, 1694, 1435, 1383, 1285 cm^{-1}; MS (70 eV, EI) m/z (%) 453 ([M]$^{+\bullet}$, 100%), 438 (5), 368 (7), 342 (73), 256 (26), 112 (48); HRMS calc for $C_{24}H_{27}N_3O_6$ [M]$^{+\bullet}$ 453.1900, found 453.1908.

*Reaction of 1Z-Methyl[4]dendralene (**11**) with NMM.* A solution of 1*Z*-methyl[4]dendralene (**11**) (in 95:5 ratio *Z*:*E* mixture) (0.10 g, 0.86 mmol, 1.0 mol equiv) and NMM (0.29 g, 2.6 mmol, 3.0 mol equiv) in $CDCl_3$ (3.0 mL) was stirred for 21 h at room temperature. The solvent was then removed under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc:hexane (25:75 to 60:40) afforded compounds **38** (52 mg, 0.22 mmol, 27%) as a colorless oil, **40** (90 mg, 0.26 mmol, 32%) as a colorless solid, **41** (24 mg, 0.070 mmol, 9%) as a colorless solid. Analytical sample of compound **38** was obtained by a reversed phase HPLC (t_R = 16.2 min, XBridge C18 column, 5 μm, 4.6 × 150 mm, eluting with THF:H_2O (25:75), flow rate = 1 mL/min).

*Monoadduct **38**.* R_f 0.42 (EtOAc:hexane (50:50)); ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) 6.45 (dd, J = 17.5, 10.9 Hz, 1H), 5.92−5.82 (m, 1H), 5.59 (dq, J = 11.4, 7.0 Hz, 1H), 5.30 (d, J = 17.5 Hz, 1H), 5.05 (d, J = 10.9 Hz, 1H), 3.24−3.07 (m, 2H), 3.00 (dd, J = 14.9, 2.9 Hz, 1H), 2.91 (s, 3H), 2.64 (dd, J = 15.0, 2.8 Hz, 1H), 2.50−2.37 (m, 1H), 2.33−2.18 (m, 1H), 1.45 (dd, J = 7.0, 1.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8 (C), 179.7 (C), 134.4 (CH), 133.6 (C), 131.7 (C), 128.2 (CH), 127.7 (CH), 112.9 (CH_2), 39.6 (CH), 39.6 (CH), 29.8 (CH_2), 25.1 (CH_3), 23.4 (CH_2), 15.0 (CH_3) ppm; IR (thin film) ν_{max} = 2932, 1772, 1697, 1433, 1381, 1286 cm^{-1}; LRMS (70 eV, EI) m/z (%) 231 ([M]$^{+\bullet}$, 94%), 230 (99), 216 (100), 145 (66), 131 (94); HRMS calc for $C_{14}H_{17}NO_2$ [M]$^{+\bullet}$ 231.1259, found 231.1254.

*Bis-adduct **40**.* An analytic sample of **40** was obtained by recrystallization from dichloromethane/hexane to give colorless prism, mp 152−154 °C; R_f 0.14 (EtOAc:hexane (50:50)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J = 11.4 Hz, 1H), 5.51 (dq, J = 11.3, 6.9 Hz, 1H), 3.22 (ddd, J = 9.7, 5.6, 2.6 Hz, 1H), 3.12−2.98 (m, 3H), 2.93 (s, 3H), 2.85 (s, 3H), 2.83−2.70 (m, 2H), 2.63 (dd, J = 14.2, 1.6 Hz, 1H), 2.38 (ddd, J = 14.1, 4.7, 2.6 Hz, 1H), 2.25−2.01 (m, 3H), 1.33 (dd, J = 6.9, 1.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2 (C), 179.6 (C), 179.1 (C), 178.0 (C), 131.3 (C), 130.7 (C), 127.5 (CH), 127.0 (CH), 43.6 (CH), 39.8 (CH), 39.3 (CH), 39.1 (CH), 33.9 (CH), 29.5 (CH_2), 25.7 (CH_2), 25.0 (CH_3), 24.9 (CH_3), 23.8 (CH_2), 14.6 (CH_3) ppm; IR (thin film) ν_{max} = 2951, 1772, 1692, 1436, 1383, 1283, 1020 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 327 (9), 313 (2), 301 (2), 256 (9), 242 (10), 216 (12); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1584.

*Bis-adduct **41**.* An analytic sample of **41** was obtained by recrystallization from EtOAc/hexane to give colorless needles, mp 217−219 °C; R_f 0.09 (EtOAc:hexane (50:50)); ^{1}H NMR (800 MHz,

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$CDCl_3$) δ 5.81 (d, J = 11.4 Hz, 1H), 5.54 (dq, J = 11.3, 6.9 Hz, 1H), 3.16 (t, J = 7.6 Hz, 1H), 3.10 (dd, J = 8.7, 5.4 Hz, 1H), 3.00 (s, 3H), 2.85 (s, 3H), 2.84−2.75 (m, 3H), 2.71 (d, J = 14.5 Hz, 1H), 2.45−2.38 (m, 2H), 2.38−2.34 (m, 1H), 2.33−2.29 (m, 1H), 1.91−1.84 (m, 1H), 1.39 (dd, J = 7.0, 1.7 Hz, 3H) ppm; ^{13}C NMR (200 MHz, $CDCl_3$) δ 179.2 (C), 179.1 (C), 179.0 (C), 177.8 (C), 132.1 (C), 130.3 (C), 127.7 (CH), 127.2 (CH), 43.7 (CH), 40.3 (CH), 40.1 (CH), 39.0 (CH), 36.8 (CH), 29.7 (CH_2), 25.5 (CH_2), 25.2 (CH_2), 25.0 (CH_3), 24.9 (CH_3), 14.7 (CH_3) ppm; IR (thin film) ν_{max} = 2951, 1775, 1699, 1691, 1437, 1384, 1284, 1027 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 327 (2), 313 (2), 300 (8), 257 2(9), 242 (13), 216 (15); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1579.

*Reaction of 2-Methyl[4]dendralene (**12**) with NMM.* A solution of 2-methyl[4]dendralene (**12**) (0.41 g, 3.4 mmol, 1.0 mol equiv) and NMM (1.1 g, 10 mmol, 3.0 mol equiv) in CH_2Cl_2 (4.0 mL) was stirred at room temperature for 14 h. The solvent was then removed under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc:hexane (40:60 to 60:40)) afforded compounds **42** (22 mg, 0.095 mmol, 3%) as a colorless oil, **45** (0.16 g, 0.47 mmol, 26%) as a colorless solid, **47** (88 mg, 0.26 mmol, 14%) as a colorless solid and **46** (0.17 g, 0.49 mmol, 27%) as a colorless oil. Analytical sample of compound **47** was obtained by a reversed phase HPLC (t_R = 16.5 min, Altima C18 column, 5 μm, 10 × 250 mm, eluting with CH_3CN:H_2O (30:70), flow rate = 4.7 mL/min).

*Monoadduct **42**.* R_f 0.74 (EtOAc:hexane (75:25)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (dd, J = 17.6, 11.0 Hz, 1H), 5.27 (d, J = 17.6 Hz, 1H), 5.04−4.95 (m, 2H), 4.57 (dd, J = 1.5, 0.7 Hz, 1H), 3.20−3.07 (m, 2H), 3.03−2.97 (m, 1H), 2.91 (s, 3H), 2.67 (dd, J = 15.0, 2.5 Hz, 1H), 2.37 (dd, J = 15.0, 6.3 Hz, 1H), 2.18 (dd, J = 14.2, 5.2 Hz, 1H), 1.74−1.70 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7 (C), 179.5 (C), 143.2 (C), 139.7 (C), 134.0 (CH), 130.3 (C), 115.6 (CH_2), 112.7 (CH_2), 39.6 (CH), 39.6 (CH), 28.6 (CH_2), 24.9 (CH_3), 23.3 (CH_2), 21.6 (CH_3) ppm; IR (thin film) ν_{max} = 3087, 2955, 2914, 2853, 1693, 1434 cm^{-1}; LRMS (70 eV, EI) m/z (%) 231 ([M]$^{+\bullet}$, 74%), 230 (100), 216 (49), 131 (57), 119 (59); HRMS calc for $C_{14}H_{17}NO_2$ [M]$^{+\bullet}$ 231.1259, found 231.1257.

*Bis-adduct **45**.* An analytic sample of **45** was obtained by recrystallization from EtOAc/hexane to give colorless needles, mp 186−188 °C; R_f 0.39 (EtOAc:hexane (75:25)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (dq, J = 3.0, 1.5 Hz, 1H), 4.44 (dd, J = 2.1, 0.9 Hz, 1H), 3.21 (ddd, J = 9.2, 5.5, 2.5 Hz, 1H), 3.15−3.04 (m, 3H), 3.00 (dd, J = 8.6, 5.1 Hz, 1H), 2.93 (s, 3H), 2.89 (s, 3H), 2.79 (ddd, J = 6.9, 6.9, 2.9 Hz, 1H), 2.65 (dd, J = 14.5, 1.4 Hz, 1H), 2.36 (ddd, J = 14.1, 4.9, 2.5 Hz, 1H), 2.23−1.97 (m, 3H), 1.63 (dd, J = 1.4, 0.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1 (C), 179.5 (C), 179.1 (C), 177.9 (C), 142.6 (C), 137.8 (C), 128.7 (C), 114.1 (CH_2), 43.3 (CH), 39.9 (CH), 39.6 (CH), 39.1 (CH), 33.8 (CH), 28.6 (CH_2), 24.9 (CH_2), 24.9 (CH_3), 24.7 (CH_3), 23.5 (CH_2), 21.7 (CH_3) ppm; IR (KBr disc) ν_{max} = 3075, 2960, 2946, 1687, 1435, 1384 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 242 (12), 231 (9), 112 (21); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1579.

*Bis-adduct **46**.* R_f 0.42 (EtOAc:hexane (75:25)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45−5.37 (m, 1H), 3.10−2.99 (m, 4H), 2.92 (s, 3H), 2.86 (s, 3H), 2.64 (ddd, J = 15.2, 7.2, 1.8 Hz, 1H), 2.53−2.38 (m, 3H), 2.20−2.04 (m, 4H), 1.54−1.51 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1 (C), 179.9 (C), 179.8 (C), 179.5 (C), 138.7 (C), 132.4 (C), 130.2 (C), 124.5 (CH), 39.9 (CH), 39.7 (CH), 39.4 (CH), 39.4 (CH), 30.8 (CH_2), 27.9 (CH_2), 26.9 (CH_2), 24.9 (CH_3), 24.9 (CH_3), 24.4 (CH_2), 20.4 (CH_3) ppm; IR (thin film) ν_{max} = 3057, 2949, 2849, 1774, 1694, 1434 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 242 (7), 112 (19); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1581.

*Bis-adduct **47**.* An analytic sample of **47** was obtained by recrystallization from EtOAc/hexane to give colorless needles, mp 185−187 °C; R_f 0.36 (EtOAc:hexane (75:25)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54−5.47 (m, 1H), 3.14−3.01 (m, 4H), 2.96 (s, 6H), 2.70 (ddd, J = 15.2, 7.1, 2.0 Hz, 1H), 2.54 (dtd, J = 14.7, 8.9, 2.1 Hz, 3H), 2.29−2.12 (m, 4H), 1.65 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2 (C), 180.0 (C), 179.8 (C), 179.7 (C), 139.6 (C), 132.2 (C), 130.8 (C), 124.3 (CH), 39.9 (CH), 39.8 (CH), 39.2 (CH), 39.1 (CH), 30.9 (CH_2), 28.2 (CH_2), 27.4 (CH_2), 25.1 (CH_3), 25.0 (CH_3), 24.3 (CH_2), 21.0 (CH_3) ppm; IR (KBr disc) ν_{max} = 3026, 2944, 2848, 1769, 1963, 1439 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 242 (8), 112 (26); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1580.

*Reaction of 3′E-Methyl[4]dendralene (**13**) with NMM.* A solution of 3′*E*-methyl[4]dendralene (**13**) (0.21 g, 1.8 mmol, 1.0 mol equiv) and NMM (0.58 g, 5.2 mmol, 3.0 mol equiv) in CH_2Cl_2 (7.5 mL) was stirred at room temperature overnight. The solvent was then removed under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc:hexane (30:70)) afforded compound **48** (0.17 g, 0.74 mmol, 42%) as a colorless oil, compound **50** (0.27 g, 0.79 mmol, 45%) as a colorless solid, and compound **51** (16 mg, 0.047 mmol, 3%) as a colorless solid.

*Monoadduct **48**.* R_f 0.78 (EtOAc:hexane (50:50)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (dd, J = 17.5, 11.1 Hz, 1H), 6.88 (dd, J = 15.8, 9.6 Hz, 1H), 5.37 (d, J = 11.0 Hz, 1H), 5.31 (d, J = 10.9 Hz, 1H), 5.21 (d, J = 2.7 Hz, 1H), 5.17 (d, J = 2.7 Hz, 1H), 3.38 (p, J = 7.1 Hz, 1H), 3.15−2.94 (m, 3H), 3.02 (s, 3H), 2.38−2.24 (m, 1H), 0.89 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4 (C), 178.8 (C), 138.1 (C), 132.6 (CH), 131.4 (C), 131.3 (CH), 114.5 (CH_2), 114.4 (CH_2), 43.3 (CH), 38.3 (CH), 29.8 (CH), 24.7 (CH_3), 21.9 (CH_2), 13.8 (CH_3) ppm; IR (thin film) ν_{max} = 3090, 2970, 2941, 1775, 1697, 1433, 1382 cm^{-1}; LRMS (70 eV, EI) m/z (%) 231 ([M$^{+\bullet}$], 25%), 230 (100), 216 (5), 204 (8), 145 (48); HRMS calc for $C_{14}H_{16}NO_2$ [M$^{+\bullet}$−H] 230.1181, found 230.1180.

*Bis-adduct **50**.* An analytic sample of **50** was obtained by recrystallization from dichloromethane/petroleum ether (40−60 °C) to give colorless needles, mp 182−184 °C; R_f 0.27 (EtOAc:hexane (50:50)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08−5.93 (m, 1H), 5.24 (dd, J = 11.2, 2.1 Hz, 1H), 4.89 (dd, J = 17.6, 2.1 Hz, 1H), 3.28−3.18 (m, 2H), 3.10 (ddd, J = 9.7, 6.4, 2.1 Hz, 1H), 2.99 (dd, J = 8.4, 5.3 Hz, 1H), 2.94 (s, 3H), 2.92−2.85 (m, 1H), 2.84 (s, 3H), 2.78 (dd, J = 13.3, 5.5 Hz, 1H), 2.39 (ddd, J = 14.1, 5.0, 2.5 Hz, 2H), 2.28−2.17 (m, 1H), 2.16−2.03 (m, 1H), 1.39 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2 (C), 179.7 (C), 177.6 (C), 177.1 (C), 138.0 (C), 132.3 (CH), 130.5 (C), 119.8 (CH_2), 45.4 (CH), 44.0 (CH), 39.6 (CH), 39.0 (CH), 34.2 (CH), 34.0 (CH), 25.5 (CH_2), 25.1 (CH_3), 24.7 (CH_3), 23.4 (CH_2), 14.9 (CH_3) ppm; IR (KBr disc) ν_{max} = 3093, 2934, 2946, 1769, 1697, 1433 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 257 (12), 230 (9), 112 (37); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1573.

*Bis-adduct **51**.* Colorless solid, mp 166−168 °C; R_f 0.20 (EtOAc:hexane (50:50)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15−6.01 (m, 1H), 5.28 (dd, J = 11.1, 2.1 Hz, 1H), 4.82 (dd, J = 17.5, 2.1 Hz, 1H), 3.26 (dd, J = 14.7, 6.4 Hz, 1H), 3.07 (dd, J = 8.4, 4.8 Hz, 1H), 3.03−2.96 (m, 1H), 3.00 (s, 3H), 2.86−2.72 (m, 3H), 2.83 (s, 3H), 2.62−2.48 (m, 1H), 2.46−2.30 (m, 2H), 2.05−1.89 (m, 1H), 1.45 (d, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2 (C), 179.1 (C), 177.4 (C), 177.0 (C), 136.9 (C), 132.5 (C), 132.3 (CH), 120.1 (CH_2), 45.7 (CH), 44.2 (CH), 40.0 (CH), 39.5 (CH), 36.9 (CH), 34.3 (CH), 25.2 (CH_2), 25.1 (CH_2), 24.9 (CH_3), 24.6 (CH_3), 15.0 (CH_3) ppm; IR (KBr disc) ν_{max} = 3081, 2938, 2849, 1770, 1696, 1435 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 327 (6), 313 (11), 257 (19), 112 (45); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1577.

*Reaction of 3′Z-Methyl[4]dendralene (**14**) with NMM.* A solution of 3′*Z*-methyl[4]dendralene (**14**) (0.42 mg, 3.5 mmol, 1.0 mol equiv) and NMM (1.2 g, 11 mmol, 3.0 mol equiv) in CH_2Cl_2 (15 mL) was stirred at room temperature overnight. The solvent was then removed under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc:hexane (30:70)) afforded compound **54** (0.13 g, 0.38 mmol, 11%) as a colorless solid, compound **55** (95 mg, 0.28 mmol, 8%) as a colorless solid, compound **58** (0.37 g, 0.82 mmol, 23%) as a colorless solid, compound **59** (0.28 g, 0.62 mmol, 18%) as a colorless solid, compound **60** (0.16 g, 0.35 mmol, 10%) as a colorless solid. Analytical samples of tris-adducts **58**, **59**, and **60** were isolated by a reversed phase HPLC (retention times: for **58**, t_R = 9.1 min; for **59**, t_R = 12.5 min; for **60**, t_R = 11.3 min, Altima C18 column, 5 μm, 4.6 × 250

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mm, eluting with CH_3CN:H_2O (30:70) to CH_3CN (100%), flow rate = 1.0 mL/min).

Bis-adduct **54**. An analytic sample of **54** was obtained by recrystallization from dichloromethane/petroleum ether (40−60 °C) to give colorless needles, mp 173−175 °C; R_f 0.56 (EtOAc:hexane (70:30)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (dd, J = 17.2, 11.0 Hz, 1H), 5.36 (d, J = 17.2 Hz, 1H), 5.13 (dd, J = 10.9, 1.1 Hz, 1H), 3.67 (q, J = 9.9 Hz, 1H), 3.48 (p, J = 7.2 Hz, 1H), 3.26−3.09 (m, 3H), 2.98 (s, 3H), 2.86 (s, 3H), 2.74−2.63 (m, 2H), 2.56 (dd, J = 9.6, 5.8 Hz, 1H), 2.30 (ddd, J = 15.2, 10.6, 8.4 Hz, 1H), 2.03 (dd, J = 15.4, 6.8 Hz, 1H), 0.88 (d, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0 (C), 178.9 (C), 178.9 (C), 178.8 (C), 137.3 (C), 131.1 (CH), 130.4 (C), 115.1 (CH_2), 46.1 (CH), 43.2 (CH), 40.4 (CH), 35.9 (CH), 34.0 (CH), 30.7 (CH), 25.0 (CH_3), 24.6 (CH_3), 24.2 (CH_2), 22.2 (CH_2), 17.1 (CH_3) ppm; IR (KBr disc) ν_{max} = 3080, 2926, 2842, 1773, 1690, 1435 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 324 (65), 112 (74); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1579.

Bis-adduct **55**. An analytic sample of **55** was obtained by recrystallization from dichloromethane/petroleum ether (40−60 °C) to give colorless prism, mp 164−166 °C; R_f 0.31 (EtOAc:hexane (70:30)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (dd, J = 17.0, 11.0 Hz, 1H), 5.39 (d, J = 17.2 Hz, 1H), 5.15 (d, J = 10.8 Hz, 1H), 3.58 (p, J = 7.3 Hz, 1H), 3.31−3.17 (m, 2H), 3.11 (dd, J = 9.6, 4.8 Hz, 1H), 3.02 (s, 3H), 2.98−2.87 (m, 2H), 2.85 (s, 3H), 2.69−2.36 (m, 3H), 2.05 (dd, J = 14.8, 6.7 Hz, 1H), 0.80 (d, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4 (C), 178.8 (C), 178.3 (C), 177.7 (C), 138.2 (C), 131.2 (CH), 130.5 (C), 115.2 (CH_2), 43.7 (CH), 42.4 (CH), 40.2 (CH), 38.6 (CH), 36.8 (CH), 29.8 (CH), 28.7 (CH_3), 24.8 (CH_3), 24.1 (CH_2), 23.2 (CH_2), 17.6 (CH_3) ppm; IR (KBr disc) ν_{max} = 2925, 2853, 1768, 1695, 1435 cm^{-1}; LRMS (70 eV, EI) m/z (%) 342 ([M]$^{+\bullet}$, 100%), 257 (37), 112 (62); HRMS calc for $C_{19}H_{22}N_2O_4$ [M]$^{+\bullet}$ 342.1580, found 342.1582.

Tris-adduct **58**. An analytic sample of **58** was obtained by recrystallization from dichloromethane/petroleum ether (40−60 °C) to give colorless prism, mp 244−246 °C; R_f 0.34 (EtOAc:hexane (75:25)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (q, J = 9.9 Hz, 1H), 3.33−3.11 (m, 3H), 3.11−2.99 (m, 3H), 2.98 (s, 3H), 2.91 (s, 3H), 2.86 (s, 3H), 2.78 (dd, J = 13.9, 5.3 Hz, 1H), 2.67 (dd, J = 15.1, 9.7 Hz, 1H), 2.58−2.43 (m, 2H), 2.37 (ddd, J = 14.3, 4.8, 2.2 Hz, 1H), 2.32−2.13 (m, 2H), 2.06−1.90 (m, 1H), 0.77 (br s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8 (C), 179.8 (C), 179.5 (C), 178.7 (C), 178.1 (C), 177.1 (C), 135.8 (C), 129.1 (C), 45.7 (CH), 43.9 (CH), 43.4 (CH), 39.4 (CH), 38.9 (CH), 35.7 (CH), 34.0 (CH), 33.4 (CH), 31.2 (CH), 25.0 (CH_3), 24.9 (CH_3), 24.6 (CH_3), 24.3 (CH_2), 23.5 (CH_2), 21.6 (CH_2), 17.1 (CH_3) ppm; IR (KBr disc) ν_{max} = 2938, 2875, 2854, 1769, 1688, 1435 cm^{-1}; LRMS (70 eV, EI) m/z (%) 453 ([M]$^{+\bullet}$, 100%), 438 (13), 424 (8), 394 (7), 329 (17), 112 (40); HRMS calc for $C_{24}H_{27}N_3O_6$ [M]$^{+\bullet}$ 453.1900, found 453.1895.

Tris-adduct **59**. An analytic sample of **59** was obtained by recrystallization from dichloromethane/petroleum ether (40−60 °C) to give colorless prism, mp 231−233 °C; R_f 0.19 (EtOAc:hexane (75:25)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (p, J = 7.5 Hz, 1H), 3.29−3.20 (m, 1H), 3.20−3.11 (m, 1H), 3.07−3.05 (m, 3H), 2.99 (s, 3H), 2.90 (s, 3H), 2.97−2.76 (m, 3H), 2.83 (s, 3H), 2.42−2.32 (m, 4H), 2.24−2.15 (m, 1H), 2.02 (d, J = 11.7 Hz, 1H), 0.72 (d, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9 (C), 179.4 (C), 179.2 (C), 177.9 (C), 177.2 (C), 176.6 (C), 136.6 (C), 129.6 (C), 43.8 (CH), 43.8 (CH), 42.6 (CH), 39.5 (CH), 39.0 (CH), 38.8 (CH), 36.1 (CH), 33.9 (CH), 28.8 (CH), 25.1 (CH_3), 24.8 (CH_3), 24.7 (CH_3), 23.7 (CH_2), 23.6 (CH_2), 23.2 (CH_2), 17.8 (CH_3) ppm; IR (KBr disc) ν_{max} = 2924, 1771, 1694, 1435 cm^{-1}; LRMS (70 eV, EI) m/z (%) 453 ([M]$^{+\bullet}$, 100%), 424 (9), 342 (29), 329 (13), 112 (49); HRMS calc for $C_{24}H_{27}N_3O_6$ [M]$^{+\bullet}$ 453.1900, found 453.1900.

Tris-adduct **60**. An analytic sample of **60** was obtained by recrystallization from chloroform/petroleum ether (40−60 °C) to give colorless prism, mp 144−146 °C; R_f 0.21 (EtOAc:hexane (75:25)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (q, J = 9.6 Hz, 1H), 3.38−3.23 (m, 1H), 3.20−3.05 (m, 3H), 3.02 (s, 3H), 2.99 (s, 3H), 2.85 (s, 3H), 2.84−2.66 (m, 3H), 2.66−2.19 (m, 6H), 1.92 (t, J = 13.4 Hz, 1H), 0.92 (br s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9 (C), 178.7 (C) (two coincident signals), 178.6 (C), 178.1 (C), 176.9 (C), 134.4 (C), 130.8 (C), 46.0 (CH), 44.1 (CH), 43.5 (CH), 39.9 (CH), 39.5 (CH), 36.8 (CH), 35.9 (CH), 33.8 (CH), 31.4 (CH), 25.0 (CH_3), 25.0 (CH_3), 24.8 (CH_3), 24.6 (CH_2), 23.9 (CH_2), 21.7 (CH_2), 17.8 (CH_3) ppm; IR (KBr disc) ν_{max} = 2923, 2852, 1771, 1694, 1434 cm^{-1}; LRMS (70 eV, EI) m/z (%) 453 ([M]$^{+\bullet}$, 100%), 342 (57), 329 (7), 112 (65); HRMS calc for $C_{24}H_{27}N_3O_6$ [M]$^{+\bullet}$ 453.1900, found 453.1902.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02583.

Crystal data for compounds **33**, **36**, **40**, **41**, **45**, **47**, **50**, **54**, **55**, **58**, **59**, and **60** (CCDC nos. 1421657, 1421658, 1421659, 1421660, 1421661, 1421662, 1421663, 1421664, 1421665, 1421666, 1421667, and 1421668, respectively). (CIF)

^{1}H and ^{13}C NMR spectra for all new compounds, anisotropic displacement ellipsoid plots for above compounds. (PDF)

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Notes

The authors declare no competing financial interest.

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(23) The Kumada−Tamao−Corriu type cross-coupling reaction between 2-chloro[3]dendralene (**17**) and the Grignard reagent of 1*Z*-bromopropene (**20**) was performed on gram scale and gave a *Z*:*E* product ratio of 95:5. The *E*- and *Z*- isomers **10** and **11** could not be separated chromatographically.

(24) Several unsuccessful variations on the cross-coupling themes were trialed, and the most instructive observations are summarized here. Interestingly, whereas the generation of the Grignard reagent of 1*Z*-propenyl bromide (**20**) proceeded relatively smoothly and with stereoretention, formation of the Grignard reagent of 1*E*-propenyl bromide (**19**) was capricious, and significant geometrical isomerization was observed during its cross-coupling. (*E*/*Z* isomerization has previously been reported during cross-couplings of the Grignard reagents of *E*- and *Z*-propenyl bromides: Zembayashi, M.; Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1975**, *16*, 1719−1722). Switching the nucleophile and electrophile allowed the formation of **10** but not by way of Kumada−Tamao−Corriu type cross-coupling, or Suzuki−Miyaura cross-coupling. Only the Negishi method between **18** and **19** depicted in Scheme 3 gave the desired product **10** in appreciable yield. Intriguingly, an attempted Negishi cross-coupling between trienylzinc species **18** and 1*Z*-bromopropene failed.

(25) This final step is reminiscent of the final step in our gram-scale synthesis of the parent [3]dendralene: Bradford, T. A.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2010**, *75*, 491−494.

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(29) The outcomes of these reactions were found to exhibit no significant solvent dependence. Thus, in test experiments between unsubstituted [4]dendralene (**1**) and *N*-methylmaleimide (NMM) in THF, CH_2Cl_2 and $CDCl_3$ (both dried/base-treated and used as received), the variance in product ratios was less than 5%. Details of these experiments are provided in the Supporting Information.

(30) The Diels−Alder reaction between monomethyl-substituted [4]dendralenes and 1 mol equiv of *N*-methylmaleimide (NMM) at room temperature resulted in the generation of a complex mixture of monoadducts and bis-adducts along with unreacted starting material.

(31) The estimated product ratio based upon analysis of crude ^{1}H NMR spectra was very similar to isolated product ratios.

(32) The estimated product ratio based upon analysis of the ^{1}H NMR spectrum of the crude product mixture was similar but not identical to that based upon isolated product yields: crude product ratio (^{1}H NMR) for the Diels−Alder reaction of 1*Z*-methyl[4]dendralene (**11**): **38**:**40**:**41** = 41:43:16; percentage ratio based upon isolated yields = 40:47:13, respectively; for the Diels−Alder reaction of 2-methyl[4]dendralene (**12**): **42**:**45**:**46**:**47** = 8:26:37:29; percentage ratio based upon isolated yields = 4:37:39:20, respectively. We attribute this discrepancy to selective losses of **40** and **45** during chromatographic purification.

(33) The high complexity of the ^{1}H NMR spectrum of the crude product precluded the estimation of a crude product ratio.

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