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Practical Synthesis and Reactivity of [3]Dendralene

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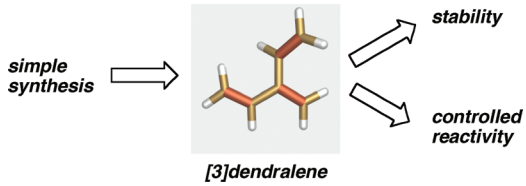
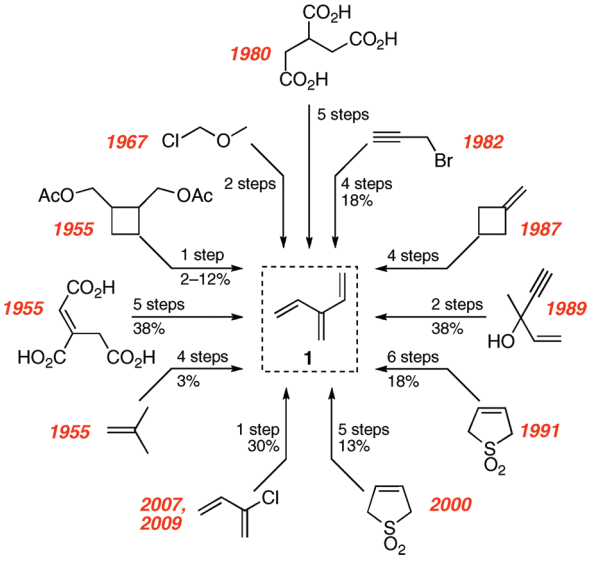


A convenient and high-yielding three-step synthesis of the simplest branched triene, [3]dendralene, has been devised. The synthesis is robust and operationally simple, requiring no chromatography and involving no protecting groups or specialized equipment, allowing the synthesis of the volatile hydrocarbon in pure, solvent free form on a multigram scale. The stability, dimerization when stored neat, and Diels−Alder reactivity of [3]dendralene—including double cycloaddition sequences and catalytic enantioselective variant—are reported.

Dendralenes are acyclic, branched oligo-alkenes with essentially untapped potential in synthesis.[1] We recently reported multigram scale synthetic preparations and characterizations of [4]-, [5]-, [6]-, [7]-, and [8]dendralenes, and we demonstrated that this family of fundamental hydrocarbons exhibit alternation in behavior.[2] In addition, we have shown that both [4]dendralene[3] and [5]dendralene[4] serve as precursors to polycyclic structures with natural product-like complexity, through their propensity to undergo domino sequences of pericyclic reactions. Herein we disclose a new synthetic route of the parent [3]dendralene **1** in solvent-free form. We identify the mode of decomposition of the hydrocarbon as a neat liquid, and its participation in new Diels−Alder reactions and domino Diels−Alder sequences.

For more than 50 years the synthesis of **1** focused on pyrolytic elimination methods (Scheme 1). The original preparation by Blomquist and Verdol involved the flow tube pyrolysis of a diacetate precursor at 485 °C.[5] A short time later, a significantly higher yielding procedure was reported by Bailey and Economy involving pyrolysis of a triacetate precursor at 540 °C,[6] which was later optimized (900 °C) by Trahanovsky.[7] The hydrocarbon has also been prepared by pyrolysis of 1,2-di(acetoxymethyl)cyclobutane at 450−485 °C;[8] through Hoffman elimination of a tris(trimethylammonium hydroxide) precursor at 180 °C/12 Torr;[9] by electrocyclic ring-opening of vinyl cyclobutene at 335 °C;[10]

SCHEME 1. Existing Synthetic Routes to the Simplest Acyclic, Branched Triene 1[a]



[a]Some yields are not disclosed in the original publications.

by acid-catalyzed elimination of a chloroether precursor at 140−160 °C;[11] and by pyrolysis of 3-vinyl-3-sulfolene at 550[12]

*To whom correspondence should be addressed: M.S.S., synthetic; M.N.P.-R., computational.

(1) Reviews: (a) Hopf, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 948–960. (b) Hopf, H. *Classics in Hydrocarbon Chemistry: Syntheses, Concepts, Perspectives*; Wiley-VCH: Weinheim, Germany, 2000; pp 253−260. (c) Hopf, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 705–707. (d) Hopf, H. In *Organic Synthesis Highlights V*; Schmalz, H.-G., Wirth, T., Eds.; Wiley-VCH: Weinheim, Germany, 2003; pp 419−427.

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(4) Bojase, G.; Payne, A. D.; Willis, A. C.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 910–912.

(5) Blomquist, A. T.; Verdol, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 81–83.

(6) Bailey, W. J.; Economy, J. *J. Am. Chem. Soc.* **1955**, *77*, 1133–1136.

(7) Trahanovsky, W. S.; Koeplinger, K. A. *J. Org. Chem.* **1992**, *57*, 4711–4716.

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(11) Marathon Oil Co., Findlay, Ohio. Synthesis of Polyene Derivatives. Netherlands Appl. NL6607062, Nov 25, 1966; *Chem. Abstr.* **1967**, *66*, 104644.

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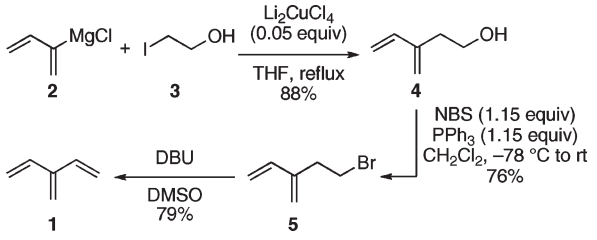
and 450 °C.[13] Hopf devised a route to **1** through the intermediacy of 2-ethynyl-1,3-butadiene, which in turn was prepared through both pyrolytic dehydration of an alcohol precursor over molecular sieves (300 °C)[14] and an ingenious rearrangement of an allenyne isomer (500 °C).[15]

Since these syntheses require somewhat specialized laboratory techniques and, in some cases, quite lengthy stepwise syntheses of precursors, we recently developed one-step, cross-coupling approaches to [3]dendralene **1** from commercially available starting materials (chloroprene and vinyl bromide) using standard laboratory methods.[16] Despite their simplicity and brevity, these recent approaches have the drawback that they allow access to the hydrocarbon only as a solution in THF. In light of the obvious need for solvent-free, multigram samples of the hydrocarbon, we devised a simple new route to [3]dendralene that employs standard laboratory equipment. The new preparation of [3]dendralene **1** is depicted in Scheme 2.

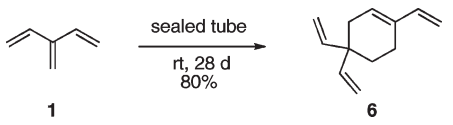
SCHEME 2. The New Synthesis of [3]Dendralene



This approach is conceptually similar to our earlier, one-step cross-coupling protocols in that it involves the union of two and four carbon fragments, namely **2** and **3**. The alcohol **4**, prepared according to the protocol described by Nunomoto,[17] and known[18] bromide **5**, can be stored over extended periods without significant decomposition. The triene-forming elimination step (**5** → **1**) is carried out by slow addition of DBU to a solution of the bromide in DMSO held at room temperature under a modest vacuum; the triene distills as it is formed and is collected in a cold trap (see the Experimental Section for details). We have prepared up to 5-g batches of the hydrocarbon of high (> 95%) purity in this manner. Due to the relatively unstable nature of the hydrocarbon when stored neat (vide infra), we prescribe the synthesis and storage of the bromide precursor **5** on large scale and the conversion of this compound into **1** as required. Nevertheless, when stored in ca. 1 M solutions in common organic solvents, **1** was found to undergo only slight (< 10%) decomposition over a one-month period in a −20 °C freezer.

Contrasting reports on the stability of **1** have been reported in the literature. Some have suggested that the hydrocarbon is too prone to polymerization for it to be synthetically useful[19] and another notes that the compound is stable and easily handled.[12] In fact, the perceived instability of the hydrocarbon has led to the development of synthetic equivalents of the triene.[19] To our knowledge, experimental findings relating to the propensity of **1** to undergo dimerization and/or polymerization have been reported in three papers. In the first,[5] **1** was reported to form a gelatinous mass on storage for 36 h at −5 °C and was also said to form a liquid dimer (structure not identified) on standing at room temperature for 2 days. The second report noted the dimerization of the hydrocarbon both during its formation through pyrolysis and distillation (structure not identified).[6] Trahanovsky[7] describes 0.1−0.4 M solutions of the hydrocarbon in benzene as reasonably stable at room temperature and a dimerization in these solutions over 22 h at 95 °C to produce a mixture of five compounds. This last report identifies **6** as the major dimer.[7] Since no data have been reported on the stability of the parent hydrocarbon as a pure compound, we placed neat samples of [3]dendralene in sealed glass ampules at 25 °C and its disappearance was monitored by ^{1}H NMR spectroscopy. Under these conditions, [3]dendralene has a half-life of ca. 10 h and undergoes a relatively clean dimerization to form Trahanovsky's [4+2] adduct **6** in 80% isolated yield after 4 weeks at room temperature (Scheme 3).

SCHEME 3. The Dimerization of [3]Dendralene



In principle, four distinct isomeric adducts may be formed, **6**−**9** (Scheme 4), which arise from permutations of the two aspects of regioselectivity, specifically site selectivity and orientational selectivity. Thus, either the inner (**I**) or outer (**O**) alkene site of **1** can function as the dienophile, and the dienophile and diene substituents can orient in either a "para" (**P**) or "meta" (**M**) sense in the product. The reason why **6** is the favored adduct may be nicely understood in terms of a straightforward qualitative mechanistic analysis advanced by Dewar et al.,[20] which is remarkably successful in predicting substituent effects on the regioselectivity of Diels−Alder reactions. In this analysis, the Diels−Alder transition state (TS) involving unsymmetrically substituted diene and dienophile components is highly asynchronous and has strong biradicaloid character. Consequently, it is permissible, for qualitative purposes, to approximate the biradicaloid TSs with the biradicals themselves, in which case, the most favored TS is predicted to be that which corresponds to the most stable biradical. Application of the Dewar analysis to the [3]dendralene dimerization leads to a comparison of the relative delocalization energies in the four TS biradical analogues **IP-Birad**, **IM-Birad**, **OP-Birad**, and **OM-Birad** (Scheme 4). **IP-Birad** is predicted to be the most stable species because it possesses a pair of delocalized pentadienyl radicals, whereas the others have either one (**IM-Birad** and **OP-Birad**) or two (**OM-Birad**) less stable allyl radicals.

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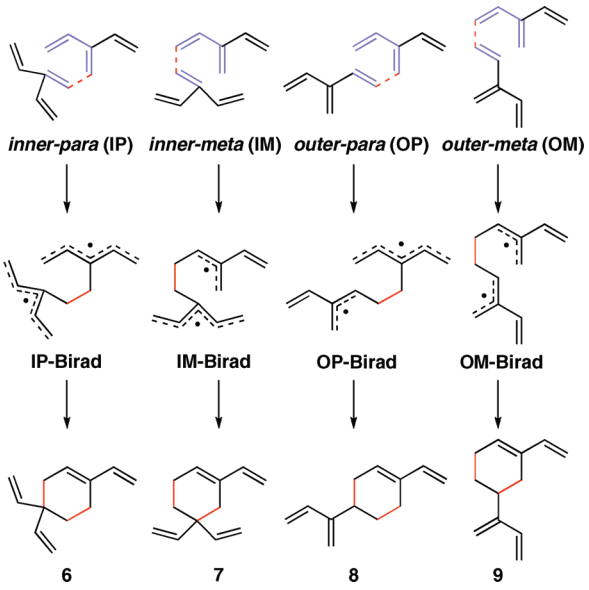
(21) This term was coined by Tsuge: Tsuge, O.; Wada, E.; Kanemasa, S. *Chem. Lett.* **1983**, *12*, 239–242.

SCHEME 4. Qualitative Dewar Mechanistic Analysis of the Dimerization of [3]Dendralene[a]



[a]The asynchronous, biradicaloid TSs may be approximated by the corresponding biradicals (**Birad** structures in center).

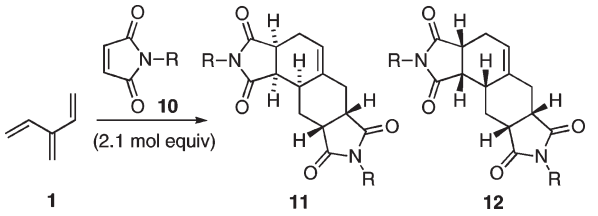
[3]Dendralene has been shown to undergo double (diene-transmisive)[21,22] cycloaddition reactions with maleic anhydride,[5,6] various quinones,[6,12] *N*-phenyl-1,2,4-triazoline-3,5-dione,[12] dimethylacetylenedicarboxylate,[12] and maleimide.[12] The stereoselectivity of the last of these transformations is the only one previously reported: a single diastereomer **11a** was reported from this reaction in 65% yield, with product stereochemistry assigned on the basis of NOE data. In our hands, under the reported conditions, an 87:13 mixture of two diastereomers is generated from the reaction of maleimide with [3]dendralene. The major diastereomer **11a** results from an *endo*-mode approach of the second maleimide dienophile to the less sterically encumbered π-diastereoface of the bicyclic monoadduct. As might be anticipated, the π-diastereofacial selectivity of this reaction is progressively improved in the dienophile series maleimide **10a** < *N*-methylmaleimide **10b** < *N*-phenylmaleimide **10c** < *N*-*tert*-butylmaleimide **10d** (Table 1). These reactions demonstrate that, despite its propensity to react as a dienophile in dimerization reactions, the hydrocarbon prefers to react with a more activated, electron poor dienophile.

[3]Dendralene has also been shown to undergo a single cycloaddition reaction with tetracyanoethylene in 92% yield, followed by a second addition with PTAD.[12] We find that maleimide dienophiles **10** also participate in selective monoadditions to [3]dendralene **1** in ca. 60−80% isolated yields by mixing stoichiometric amounts of the hydrocarbon and dienophile in toluene at ambient temperature (Scheme 5). Evidently, monoadducts of [3]dendralene **13** are less reactive toward dienophiles than is the triene.

With the less reactive dienophiles methyl and *tert*-butyl acrylate, methyl and ethyl methacrylate, and ethyl vinyl ketone, **14a**−**e**, Lewis acid activation also brings about

(22) For a review, see: Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167–176.

TABLE 1. DTDA Sequence of [3]Dendralene 1 with Maleimide Dienophiles 10



entry	R	product ratio **11**:**12**	isolated yield (%)
a	H	87:13	50[a]
b	Me	90:10	66
c	Ph	91[b]:9	91
d	*t*-Bu	96:4	80

[a]Yield over two steps: *N*-H-maleimide adducts were converted (K_2CO_3, MeI) into *N*-Me derivatives to assist isolation. [b]X-ray of **11c** in SI.

SCHEME 5. Selective Monocycloadditions of 1 with Maleimide Dienophiles 10

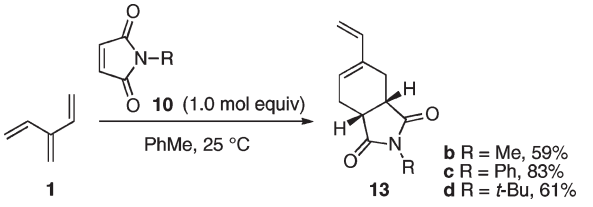
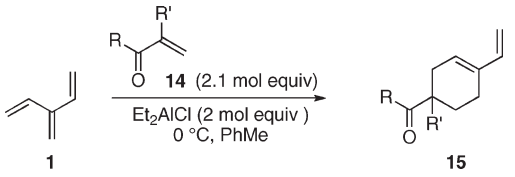


TABLE 2. Monoaddition Reactions of [3]Dendralene 1 with Unsymmetrical Dienophiles 14



entry	dienophile **14**	yield (%)
a	R = OMe, R′ = H	85
b	R = O*t*-Bu, R′ = H	46
c	R = OMe, R′ = Me	79
d	R = OEt, R′ = Me	75
e	R = Et, R′ = H	62

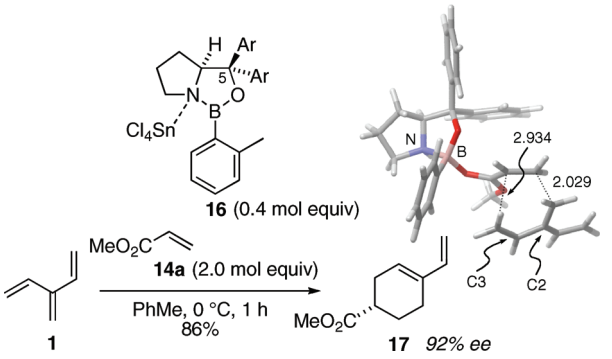
selective monoadditions to **1**, resulting in the formation of substituted semicyclic dienes **15**, even in the presence of excess dienophile (Table 2). In all cases, only the expected "para" regiosiomer was detected.

The successful extension of these findings into an enantioselective process is presented in Scheme 6, wherein **16**, a modified version[23] of Corey's oxazaborolidinium catalysts,[24] promotes the monocycloaddition of methyl acrylate **14a** to [3]dendralene **1**

(23) Catalyst **16**, carrying 3,5-dimethoxyphenyl groups, has been found to deliver higher enantioselectivities in Diels−Alder reactions than the corresponding phenyl and 3,5-dimethylphenyl systems introduced by Corey: Kwan, L. C. H.; Paddon-Row, M. N.; Sherburn, M. S.Unpublished results. Once again, we find $SnCl_4$ a useful Lewis acid activator of the oxazaborolidine (see ref 26).

(24) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117.

SCHEME 6. Enantioselective Oxazaborolidinium Cation-Catalyzed Diels–Alder Addition of [3]Dendralene 1 to Methyl Acrylate 14a and Model Transition Structure[a]

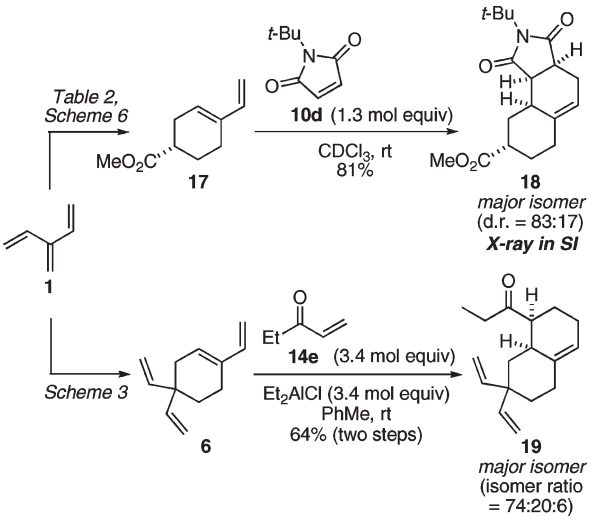


[a]This TS is based on the fully optimized TS for addition of butadiene to methyl acrylate, to which the additional vinyl group in [3]dendralene has been attached, without further optimization of the resulting structure. Ar = 3,5-dimethoxyphenyl.

to form adduct **17** in a respectable 86% yield and 92% ee. The absolute configuration of the major product **17** is assigned on the basis of the pre-TS model proposed by Corey et al.,[25] which has been verified by reliable quantum chemical calculations.[26,27] A model TS for this cycloaddition is depicted in Scheme 6. It is based on the B3LYP/6-32G(d)-optimized TS for addition of butadiene to methyl acrylate[27] and a vinyl group has been attached to the butadiene moiety at the "para" position with respect to the ester substituent. The marked bond-forming asynchronicity is clearly evident in the case of butadiene, one forming bond being advanced over the other by about 0.9 Å. Placement of the vinyl substituent at C2 of the diene will stabilize the developing cationic charge in the diene component in the TS, whereas attaching it at C3 will lead to little stabilization. This explanation of orientational selectivity in Lewis acid promoted reactions between **14** and **1** is analogous to that proposed above for [3]dendralene dimerization, except that in this case it is more appropriate to consider zwitterionic TS analogues rather than biradical ones.

In summary, a new synthesis of [3]dendralene has been developed. The approach allows access to solvent-free, multigram quantities of the pure hydrocarbon without the need for specialized equipment. The hydrocarbon undergoes relatively clean Diels–Alder dimerization at ambient temperature when stored neat. It also undergoes selective single and double cycloaddition reactions with a wide range of alkenic dienophiles under catalyzed and uncatalyzed conditions. These findings set the scene for applications of new DTDA additions in synthesis: proof-of-principle results are depicted in Scheme 7, which demonstrate the rapid stereoselective construction of functionalized decalin frameworks **18** and **19**.

SCHEME 7. Sequential DTDA Processes Involving [3]Dendralene 1



Experimental Section

[3]Dendralene (1). DBU (15.0 mL, 101 mmol, 3.2 equiv) was added dropwise to a stirred solution of 5-bromom-3-ethylene-pent-1-ene **5**[18] (5.0 g, 31 mmol, 1.0 equiv) in anhydrous DMSO (12.5 mL) at room temperature under nitrogen. The flask was equipped with a short path distillation apparatus and the receiver flask was cooled to −78 °C. After 15 min, a vacuum (60 mmHg) was applied for 1 h before increasing the vacuum (20 mmHg) for an additional hour. [3]Dendralene **1** was collected in the cold trap as a colorless oil (2.0 g, 79%). The hydrocarbon is stored as a 1 M PhMe or CH_2Cl_2 solution at −20 °C if not used immediately. Characterization data for **1** matched those previously reported.[13] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (2 H, dd, J = 17.4, 11.1 Hz), 5.41 (2 H, br d, J = 17.4 Hz), 5.15 (2 H, br d, J = 11.1 Hz), 5.15 (2 H, br s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9 (C), 115.8 (2 × CH), 115.6 (2 × CH_2), 110.5 (CH_2) ppm.

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Supporting Information Available: Experimental procedures and characterization data, including ^{1}H and ^{13}C NMR spectra, for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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