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Practical Synthesis and Diels−Alder Chemistry of [4]Dendralene

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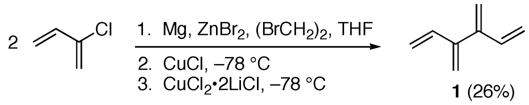
Acyclic cross-conjugated polyenes—the dendralenes—are fascinating compounds with enormous untapped potential in chemical synthesis.[1−4] As formulated by Hopf,[2−4] the Diels−Alder chemistry of [4]dendralenes should be multifaceted, with up to three dienophiles uniting with one molecule of the hydrocarbon, in principle, resulting in the very rapid assembly of functionalized polycyclic frameworks. Until now, the chemistry of [4]dendralene remains largely unexplored[5] since the hydrocarbon has not been available in synthetically useful amounts. Several ingenious routes to [4]-dendralene **1** have been developed, but only one provides more than a few milligrams of the hydrocarbon.[6−13] The exception is a patented procedure involving the dimerization of 4-chloro-1,2-butadiene.[14] Herein, we report an undemanding preparation of [4]-dendralene, employing standard laboratory equipment and methods based upon this early procedure. We show that the hydrocarbon undergoes a rich variety of domino cycloaddition reactions to form polycyclic systems, and we reveal methods to control the regiochemical outcomes of Diels−Alder reaction sequences involving [4]dendralene.

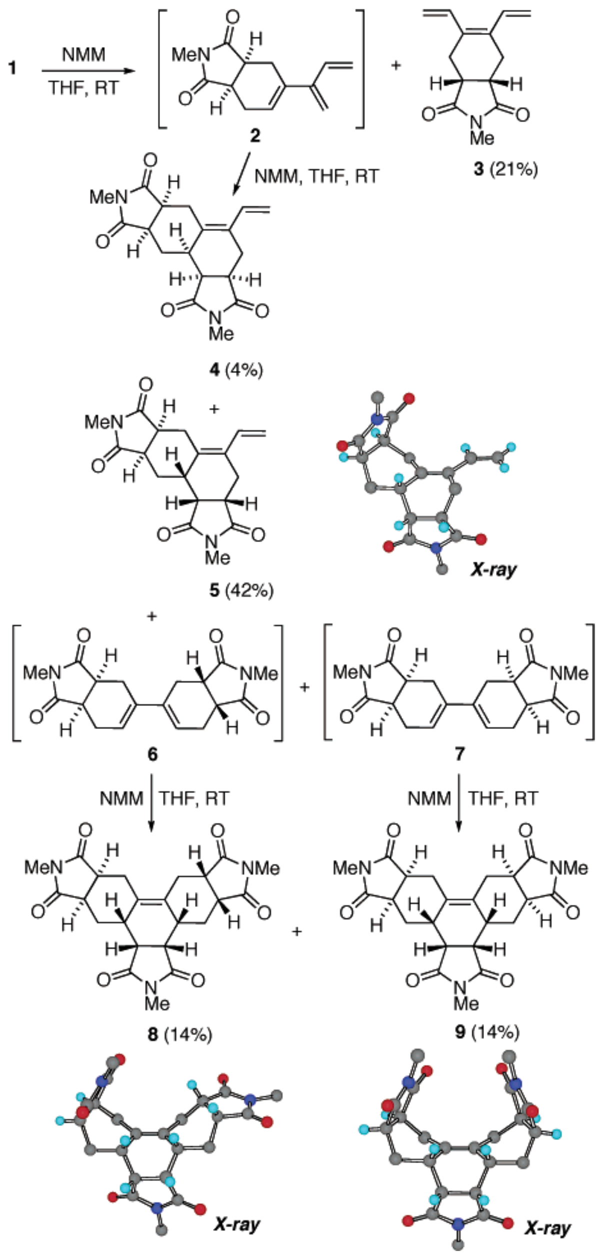
The synthesis of [4]dendralene **1** (Scheme 1) avoids protection, proceeds in one step, and uses the cheap and widely available starting material, chloroprene.[15] Thus, the chloroprene Grignard reagent[16] is converted into the organocopper species by the addition of anhydrous copper(I) chloride at −78 °C. Slow introduction of the oxidizing agent $CuCl_2•2LiCl$ at −78 °C[17] followed by aqueous workup and vacuum distillation affords [4]dendralene in 26% yield. We routinely prepare 10 g batches of [4]dendralene using this procedure. [4]Dendralene is considerably more stable than expected. Indeed, the hydrocarbon can be stored as a neat liquid at room temperature with minimal decomposition over several weeks!

Scheme 1. Practical Synthesis of [4]Dendralene **1**



[4]Dendralene reacts with an excess of *N*-methylmaleimide (NMM) under kinetically controlled conditions at room temperature in THF to furnish a mixture of five products: a single mono-adduct **3**, two diastereomeric bis-adducts **4** and **5**, and two diastereomeric tris-adducts **8** and **9** (Scheme 2).[18] The mono-adduct results from dienophile addition to the internal diene site of **1**; this compound does not undergo further reaction at room temperature. The other four products result from an initial cycloaddition to one of the two equivalent terminal diene sites of the hydrocarbon to give unsymmetrical [3]dendralene **2**, which reacts with more dienophile at each of the two available diene sites to yield four bis-adducts, two of which (**6** and **7**) are receptive toward a third cycloaddition. The two remaining bis-adducts **4** and **5** are inert toward further reaction at ambient temperature and pressure.

Scheme 2. Exhaustive Reaction of [4]Dendralene with NMM[a]



[a] Some hydrogens are omitted from X-ray crystal structures for clarity.

The second cycloaddition reaction involving mono-adduct **2** proceeds with ca. 5:3 site selectivity in favor of the semicyclic diene. Not surprisingly, this major pathway, which gives **4** and **5**, exhibits strong π-diastereofacial selectivity for dienophile approach to the convex face of semicyclic diene (i.e., to give **5**). The minor pathway flowing from mono-adduct **2** leads to bis-adducts **6** and **7**, which result from endo-mode additions to the acyclic diene site of **2**, a

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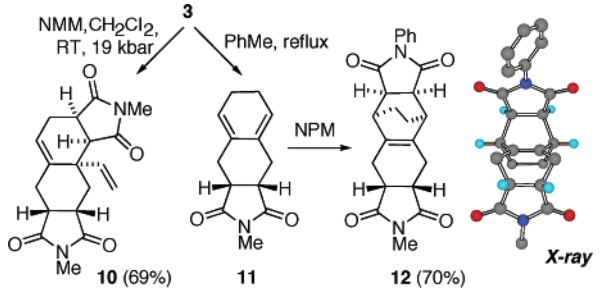
Scheme 3. Further Transformations of Mono-Adduct **3**



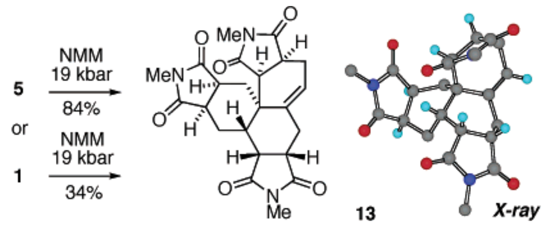
process which proceeds with no π-diastereofacial selectivity. Bis-adducts **6** and **7** undergo a third cycloaddition with NMM to give tris-adducts **8** and **9**, respectively. C_{2v} symmetric, chiral diene **6** can give only one endo-adduct, whereas achiral diene **7** can furnish two; only one is formed in the latter case, however, presumably for steric reasons.

Z-triene **3** can be coerced into direct cycloaddition with NMM under high pressure at ambient temperature to furnish tetracycle **10** as the major product (Scheme 3).[19] Alternatively, internal mono-adduct **3** undergoes a 6π-electrocyclization/cycloaddition cascade with *N*-phenylmaleimide (NPM) in refluxing toluene to give a single diastereomeric pentacycle **12** in 70% yield. In the absence of dienophile, electrocyclization product **11** is obtained in good yield.

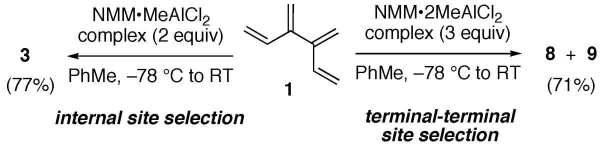
Furthermore, the major product from the exhaustive room temperature reaction between NMM and [4]dendralene, bis-adduct **5**, participates in a high yielding cycloaddition with NMM at ambient temperature at 19 kbar pressure to afford tris-adduct **13** (Scheme 4). The same product is accessible directly from [4]dendralene and NMM in a one-pot process in 34% isolated yield. This triple Diels−Alder sequence occurs in a domino “diene transmissive” sense: cycloadditions occur sequentially at diene residues from one end of the hydrocarbon to the other.[20]

Finally, essentially complete control over [4]dendralene site selectivity during the first and second cycloaddition events is achieved by simply premixing the dienophile with different amounts of simple Lewis acid promoters (Scheme 5). Thus, whereas the uncatalyzed reaction gives predominantly the products of an initial cycloaddition to the terminus of [4]dendralene (Scheme 2), high selectivity for **3**, the product of addition to the internal diene site, is obtained by premixing a 1:1 molar ratio of NMM and $MeAlCl_2$. With a 1:2 complex of the dienophile and Lewis acid, the first cycloaddition to **1** proceeds exclusively at the terminal diene site. Moreover, while the thermal cycloaddition of mono-adduct **2** with NMM proceeds preferentially through the semicyclic diene moiety to form **4** and **5**, this site selectivity is reversed with NMM•$2MeAlCl_2$ to give tris-adducts **8** and **9** as sole products. Investigations into the origin of this unusual reactivity profile are underway.

Scheme 4. Preparation of Tris-Adduct **13**



Scheme 5. Controlling the Cycloaddition Site Selectivity



This study demonstrates the rich cycloaddition chemistry of [4]dendralene. The extremely rapid assembly of structurally complex bridged and fused tricyclic systems common to natural products is a striking feature of this work. Thus, operationally simple one-flask sequences involving the union of four molecules, the construction of up to six new C−C bonds, and eight stereocenters has been demonstrated. Importantly, methods have been developed to steer precursors through the fascinating pathway of bond forming events such that any one of the many possible products can be obtained in high selectivity. The challenge now is to apply these very powerful complexity-generating sequences in target synthesis.

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Supporting Information Available: Synthetic details, crystallographic data, and NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hopf, H. In *Organic Synthesis Highlights V*; Schmalz, H.-G., Wirth, T., Eds.; Wiley-VCH: Weinheim, Germany, 2003; pp 419−427.
(2) Hopf, H. *Classics in Hydrocarbon Chemistry: Syntheses, Concepts, Perspectives*; Wiley-VCH: Weinheim, Germany, 2000.
(3) Hopf, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 705−707.
(4) Hopf, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 948−960.
(5) Bailey and Neilsen treated **1** with maleic anhydride and benzoquinone to give symmetrical bis-adducts (cf. **6** and **7**, Scheme 2), which resisted further reaction: Bailey, W. J.; Nielsen, N. A. *J. Org. Chem.* **1962**, *27*, 3088−3091. More recently, Hopf and Yildizhan exposed the hydrocarbon to dimethyl acetylenedicarboxylate to obtain a tris-adduct, which was isolated as the phenanthrene derivative upon oxidation.[1]
(6) Skattebøl, L.; Solomon, S. *J. Am. Chem. Soc.* **1965**, *87*, 4506−4513.
(7) Aufdermarsh, C. A., Jr. U.S. Patent 3264366, 1966; *Chem. Abstr.* **1966**, *65*, 107599.
(8) Grimme, W.; Rother, H. J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 505−506.
(9) Bee, L. K.; Everett, J. W.; Garratt, P. J. *Tetrahedron* **1977**, *33*, 2143−2150.
(10) Roth, W. R.; Scholz, B. P.; Breuckmann, R.; Jelich, K.; Lennartz, H. W. *Chem. Ber.* **1982**, *115*, 1934−1946.
(11) Buchan, C. M.; Cadogan, J. I. G.; Gosney, I.; Henry, W. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1785−1786. This paper describes a synthetic equivalent of the hydrocarbon.
(12) Brain, P. T.; Smart, B. A.; Robertson, H. E.; Davis, M. J.; Rankin, D. W. H.; Henry, W. J.; Gosney, I. *J. Org. Chem.* **1997**, *62*, 2767−2773.
(13) Fielder, S.; Rowan, D. D.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4331−4333.
(14) See ref 7. The patent describes two related approaches for the coupling of the Grignard reagent derived from 4-chloro-1,2-butadiene. No yields are reported, and no indication of product purity is provided.
(15) Chloroprene is not commercially available in Australia. We prepare it by the dehydrochlorination of 3,4-dichloro-1-butene with calcium hydroxide: Tassara, J.-P.; Baudoin, M. Eur. Pat. Appl. 94-202577, 1994; *Chem. Abstr.* **1994**, *122*, 290321.
(16) Nunomoto, S.; Yamashita, Y. *J. Org. Chem.* **1979**, *44*, 4788−4791.
(17) Thermal decomposition of the organocopper reagent (occurring at about −28 °C) affords [4]dendralene, but cleaner reactions were obtained with $CuCl_2$•2LiCl.
(18) As expected, all cycloadditions involving maleimide dienophiles were found to proceed exclusively through the endo-mode.
(19) This appears to be the first example of a *Z*-triene participating as a diene in a Diels−Alder reaction.
(20) This is the first example of a *double* diene-transmissive Diels−Alder sequence. For a review of diene-transmissive Diels−Alder reactions, see: Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176.

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